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The *International Journal of Medical Students* (IJMS) is a peer-reviewed open-access journal created to share the scientific production and experiences of medical students and recently graduated physicians worldwide.

International Journal of Medical Students
Year 2020 - Volume 8 - Issue 3

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The *International Journal of Medical Students* (IJMS) is a peer-reviewed, open-access journal created to share the scientific production and experiences of medical students and recently graduated physicians worldwide. Our objective is to be the primary diffusion platform for medical students, using standards that follow the process of scientific publication.

The Journal receives contributions and unpublished manuscripts of Original Articles, Short Communications, Reviews, and Case Reports, which are reviewed by experts (Peer-Reviewers) who have previously published similar research. In addition, the Journal accepts Interviews, Experiences, and Letters reviewed by the Editorial Team. This supports the quality and validity of the publications. The time between submission and final publication in most cases has been two to four months depending on the diligence of Peer-Reviewers and Authors.

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IJMS INTERNATIONAL JOURNAL of MEDICAL STUDENTS

Editorial

A Grain of Sand in the Ocean: Training New Generations of Editors, Reviewers, and Medical Scientists

Francisco J. Bonilla-Escobar,[1] Annora A. Kumar,[2] Georgiana Farrugia-Bonnici,[3] Paul MacDaragh Ryan,[4] Mihnea-Alexandru Găman.[5]

Since its conception, the *International Journal of Medical Students (IJMS)* has aimed to train the next generation of medical scientists and medical editors.[1,2] Besides being the main platform of scientific publications for medical students and recently graduated physicians, the *Journal* has become a stage for the training of medical editors, reviewers, and scientists of tomorrow.[3] In the short history of the *Journal*, we have had more than 300 medical students involved in the editorial process including activities such as promoting the *Journal*, reviewing articles, copyediting, proofreading, and diagramming. All of this would not have been possible without our founders, who aimed to create this productive environment towards increasing visibility of medical students' publications,[1] whilst maintaining the highest quality[2,4-6] and allowing open-access, all without article publishing charge or a readers fee (diamond open-access).

In this historic last issue of 2020, we acknowledge the work of medical students all around the globe who are part of our way out of this pandemic,[7] scientists that worked around this issue to help us understand the problem and solve its challenges, and to healthcare workers for their care and resilience during the difficult situations that they have been exposed to over the past months. This pandemic has been one of the hardest tests for the medical profession in our generation. However, their values, highlighted in an interview published in the *Journal* two years ago, give us an answer of what was going to happen: "*In every crisis, the answer to new challenges is to deliver the best care possible while also carrying out investigative work to push back the boundaries of science and improve medicine*".[8] It is now time to move into a better tomorrow where all of the lessons that 2020 has left us can be used to help us to grow stronger as one humanity.

In the last issue of the year, we are publishing analyses of local and global data,[9] one at national level in Mexico; going from COVID-19[9,10] to oncology,[11] medical education,[12] internet addiction,[13] screening information readability,[14] and hypertension.[15] Furthermore, this issue includes updates on cancer immunotherapy[16] and glucose-6-phosphate dehydrogenase deficiency.[17] In addition, you will find reports of cases about a challenging anesthetic case,[18] polysensitivity to unrelated drugs,[19] and an oncological patient with a atypical lymphatic drainage.[20] As in previous issues,[21-56] we are sharing the experiences of medical students and recently graduated physicians around the globe. COVID-19 experiences have not stopped being submitted and we are proud to publish these novel perspectives from around the world. This issue encompasses the experiences of medical students working side-by-side with healthcare providers battling against the pandemic,[57,58] lessons arising from the challenges of leading a free-clinic,[59] and strategies to promote mental health,[60] and learning opportunities during this time.[61] Furthermore, we highlight the experience of a cornea harvester's history and the lessons that can be learned from it.[62] Finally, as we encourage readers to submit their comments to *IJMS* as Letters to the Editor, we have had comments on two previously published articles,[63-67] as well as comments on COVID-19 relapse vs. reinfection,[68] online open book examinations for medical students,[69] and a call for action for a group of first responders: firefighters.[70]

One of the lessons gleaned from the COVID-19 pandemic is discussed by MacArthur et al., where the authors assess the way in which the COVID-19 pandemic has exacerbated existing gender inequalities within research; specifically, the lower rates of women submitting articles during the pandemic compared to men.[71] This is of particular interest as the gender gap in medical school has been declining in recent years. Countries including the United States, United Kingdom, and Australia have seen female medical student admissions outnumber male admissions for the first time in history.[72-74] Nevertheless, amidst a 21st century backdrop of increasing (albeit imperfect) gender equity and fourth-wave feminism,[75] this editorial provides a timely reminder that female success in the medical profession goes beyond medical school acceptance. Once women are accepted into medical school, they still face the remnants of an once male-dominated field.[76,77] For all genders, success in this field becomes more complicated during a pandemic — and research involvement is a large part of this success. In addition to the positive implications that publishing research has on one's career, student research must not be overlooked as an influential form of advocacy. Research is a channel through which medical students can project their voices and promote discussion towards change regarding medical curriculum, research accessibility, research options, and mentoring.

The history of medicine and medical research has been irrevocably marked by gender, racial, and socioeconomic discrimination. In the wake of COVID-19 intensifying existing inequalities, MacArthur et al. ultimately reinforce the need to work strategically, taking an intersectional approach to prevent these inequalities.[71] In addition to being committed to tackling these inequalities, the Executive Committee of the *Journal* is striving to identify and engage female doctors and researchers in editorial and leadership roles within the *Journal*. One recent example of this is the Communications and Public Relations Committee (CPR-C), which is lead by Dr. Georgiana Farrugia-Bonnici. As of December 17th 2020, the *IJMS* CPR-C boasts three Regional Ambassadors for Europe, Africa, and America with two women occupying those positions, as well as 40% (10/25) women as official Ambassadors. The CPR-C strives to work together as a team in order to benefit the *IJMS* by boosting social media presence, and spreading positive messages about the *Journal* amongst medical students enrolled in different universities worldwide, ultimately aiming to inform medical students about the numerous opportunities for growth that are offered within the *Journal*.

Affiliations:

[1] MD, MSc, PhD(c). Department of Ophthalmology, University of Pittsburgh, Pittsburgh, USA. Universidad del Valle, Cali, Colombia. Science to Serve the Community Foundation, SCISCO Foundation / Fundación SCISCO. Editor in Chief, International Journal of Medical Students (*IJMS*). Address: 1400 Locust St, Pittsburgh, PA, USA. Email: fjbonillaescobar@gmail.com

[2] Medical student. The University of Western Australia, Perth, Australia.

[3] BSc (Hons). Rad, M.D., MSc FM. University of Malta, Malta.

[4] MB BCh BAO PhD. Cork University Hospital, University College Cork, Cork, Ireland. Deputy Editor, *IJMS*.

[5] MD, PhD student. "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania. Department of Hematology, Center of Hematology and Bone Marrow Transplantation, Fundeni Clinical Institute, Bucharest, Romania. Scientific Editor, *IJMS*.

Nevertheless, the path to gender equity is still long and arduous. Although we are committed to gender inclusion, we have seen the same pattern of higher proportions of men enrolled in the *Journal* over time. We hope that this editorial also serves as a call for new applicants to all different positions in the *Journal*.

Finally, there are some changes in the *Journal* that are worth mentioning. Since all reviewers have had the chance to confirm their review records on Publons, we will be publishing our last acknowledgement of peer-reviewers this year. Additionally, we have encouraged all of our team members to complete and graduate from the course provided by the Publons Academy and become a certified peer-reviewer with the aim of increasing the quality of our work. Nonetheless, we will not finish a tradition without starting a new one. The "**IJMS Student Editors of the Year**" will be given to a Student Editor who has been enrolled in the *Journal* for over a year and has demonstrated passion for the work that we do by exhibiting the spirit of collaboration, participation in the *Journal* activities, and the highest grade of commitment to the work that we publish. This year, we are recognizing *Madeleine J. Cox* from the University of New South Wales, Sydney, Australia, and *Nikoleta Tellios* from the University College Cork, Ireland as the *IJMS* Student Editors of the Year. We also make a special mention for *Adnan Mujanovic* from the University of Tuzla Medical Faculty, Bosnia and Herzegovina, *Ciara Egan* from the Humanitas University, Milan, Italy, *Leah Komer* from the University College Cork, Ireland, and *Sohaib Haseeb* from James Cook University, Townsville, Queensland, Australia, for their commitment to the *Journal* activities, dedication, and detailed revisions of the work being published in the issue 3, volume 8 of 2020, of the *IJMS*.

The publication of this issue would not have been possible without the hard work of all the members of our Editorial Team, with whom we are deeply thankful for. New things are around the corner for all of us, and we hope for the best in the incoming year.

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Editorial

Pre-Existing Social Conditions: A Call to Prevent the Perpetuation of Gender Inequalities in Research Production during COVID-19

Kelly Rhea MacArthur,[1] Madeleine J. Cox,[2] Ciara Egan,[3] Leah Komer.[4]

The coronavirus disease 2019 (COVID-19) global pandemic continues to influence a vast array of aspects in our material, psychological, and social lives. The area of academic publishing does not seem to be an exception. Emerging evidence reveals that there are changing patterns in scientific endeavors, including an exponential increase in the number of COVID-19 related manuscripts submitted to academic journals for peer review.[1] Among these documented changing patterns, of note are the gender discrepancies, with women producing significantly less research than men, including article submissions, pre-prints, and publications, since the initial COVID-19 outbreak in early 2020.[2-5] For example, in one interesting and sophisticated statistical examination, Squazonni and colleagues[1] calculated the change in submissions during the initial quarantine period using the individual as the unit of analysis. They found that, while article submissions increased for everyone, they did so at a significantly higher rate among men. And, in three out of four different academic disciplines including *Health & Medicine*, there was an interaction effect between gender and seniority, with women in more advanced stages of their career being negatively impacted the most in terms of article submission rates. While these patterns have been noted across different disciplines, but to differing degrees,[6] it is of particular interest here how gender inequality in research production may have long-lasting effects on the careers of current medical students.

The global pandemic has increased the demand for systematic studies on our changing society. Medical students are responding accordingly,[7] however, this may have exacerbated existing gender inequalities. In contemplating what academic journals' responsibilities are, it is beneficial to consider the possible underlying societal causes of these gender inequalities. That is, gender inequalities in research production can be considered a natural and expected extension of larger societal patterns that existed long before the pandemic.[8] In trying to disentangle the causes and effects of COVID-19 on gender inequality in academic publishing, it is useful to consider at least three intersecting and pre-existing social conditions, all of which research has identified in the field of medicine: 1) the unequal division of labor both at home and work; 2) women's lower well-being compared to men; and 3) men's greater representation in science, technology, engineering, and mathematics (STEM) fields.

The first consideration regarding the well-documented unequal division of domestic labor begs the question: For those who have been stuck at home, what exactly are they doing, and are these activities related to the differential rates of article submissions? Recent research suggests that, yes, women and men have not been spending their time in the same ways during the pandemic. For example, in an analysis of change in paid work hours, among those who were fortunate enough to continue employment during the original lockdown period, Collins and colleagues[9] found that women, and in particular mothers of young children, had reduced their work hours significantly more so than men/fathers. These findings of a "motherhood penalty"[10] are neither new nor surprising and suggest that the well-documented historical pattern of women's disproportionate contribution to home and childcare duties[11] has worsened with the pandemic, particularly regarding new homeschooling responsibilities.[12] In turn, women's greater domestic labor roles are likely a contributing factor to female medical students' lower rates of academic publishing during the pandemic.[13]

It is well established that women consistently report greater levels of psychological distress compared to men,[14] which is the second gendered pattern that existed long before COVID-19, but nonetheless may have been magnified by the pandemic and, in turn, affected rates of academic publishing. The viral pandemic has provoked many anxieties and uncertainties, which may have a greater burden on women, therefore, making it difficult to conduct research. This may be especially true since isolation and loneliness from quarantining and physical distancing regulations are likely to produce a public health crisis unparallel to anything we have seen before.[15] Furthermore, we should expect medical students to be particularly susceptible to these adverse effects, since they are already at an increased risk of psychological distress arising from the demands of medical school, including professional burnout,[16,17] depression and anxiety,[18-20] low life satisfaction,[21] alcohol/substance misuse,[22] suicidal ideation,[23] and suicide.[24] Early reports suggest that the well-being of medical students has suffered as a result of the pandemic and—again, not surprisingly—female medical students seem to be particularly vulnerable.[25-27]

[1] PhD. Associate Editor International Journal of Medical Students (IJMS). Associate Professor of Sociology, Department of Sociology & Anthropology, University of Nebraska Omaha. Adjunct Faculty, Department of Psychiatry, University of Nebraska Medical Center, Nebraska, United States.
[2] BMedSc, BSc(Hons), MD student, MScMed (SRH) student. University of New South Wales, Sydney, Australia. University of Sydney, Sydney, Australia. Student Editor IJMS.
[3] BSc, Medical Student, Humanitas University, Humanitas Research Hospital, Milan, Italy. Student Editor IJMS.
[4] BSc (Hons), Medical Student, School of Medicine University College Cork, Cork, Ireland. Student Editor IJMS.

About the Author: *Kelly MacArthur is a medical sociologist with publications in the areas of medical student well-being, the effects of loneliness on health, health disparities, and quantitative methods/statistics. Madeleine Cox is a final year medical student. She is passionate about reproductive endocrinology and infertility with publications and internationally recognized prizes in the field of polycystic ovary syndrome (PCOS). She is a UNSW Faculty Dean's award recipient, holds a University Blue and is a founding member of the Australasian council of undergraduate research (ACUR). Ciara Egan is a fourth-year medical student in a six-year program. She holds a dual Bachelor's Degree in Biology and Nutrition, and is part of the Excellence in Research Track at Humanitas, a 3-year program to train future physician-scientists. Leah Komer is currently a final year medical student; she was awarded the 2020 John Renner Award from the American Academy of Addiction Psychiatry for her achievements and pursuit of excellence in the field of Addiction Psychiatry.*

Correspondence:
Kelly Rhea MacArthur, PhD
Address: 6001 Dodge St. Omaha, NE 68182, United States
Email: kmacarthur@unomaha.edu

A third related possible explanation for men's greater productivity in academic publishing since the initial COVID-19 outbreak is their disproportionate representation in STEM fields, making men especially prime to conduct COVID-19 related research. Presently, women are significantly underrepresented in STEM globally.[28] Thus, more men may have been in a superior position to readily apply their research to be COVID-19 specific. There is some evidence to support this claim in which analyses on COVID-19 related studies show that men are indeed submitting and publishing more in this specific area than are women.[1,5,29]

Unfortunately, lessened research productivity during medical school may have cumulative effects that disadvantage women's careers long-term. It is well understood that published research during medical school improves residency applications, thus, increasing chances of acceptance into highly competitive programs.[30-33] This is confirmed by the results of the *2020 National Residency Match Program*. For both MD and DO US students in most specialties, matched students had a higher number of research experiences and publications compared to unmatched students.[34,35] Although there is heterogeneity in the application for specialty programs worldwide, a unifying trend seen internationally is the benefit of publishing research during one's own medical career.

Beyond increasing the quality of an individual's residency application, research conducted during medical school assists in identifying future physician-scientists. The career of a physician-scientist is unfortunately a declining population globally, with many medical education programs attempting to address this through compulsory research courses.[36-38] Therefore, since the onset of this pandemic, the decline of published research by female medical students threatens women's careers.[39] As a society, we are at risk of reversing the diligent work achieved to improve gender equality in the fields of science and medicine and are at a crucial point where promoting and providing opportunities for the development of women physician-scientists is necessary to avoid this risk.

The COVID-19 pandemic has dramatically increased the amount of academic publishing over the past year. Pre-pandemic, the research community expressed the importance and intentions to address its own gender disparities.[40-42] However, in a world of a viral pandemic and traditional social structures, STEM research has not successfully fulfilled its objectives. Female medical students, even those who excel in their academic pursuits, are at a significant disadvantage of publishing research and risk the glass ceiling effect once they graduate.[43] This may be due to COVID-19 exacerbating the unequal expectations of domestic duties for females, higher risk of psychological distress in women, and overall fewer scientific contributions by women in the field of science and medicine.

So, what are journals' responsibilities, especially a journal that is explicitly committed to highlighting medical students' experiences and advancing their careers by giving them an outlet for scientific publication? Although a single journal cannot completely reverse the profound societal gender inequalities that currently exist; an individual journal can provide attention to these discussed patterns, recognize their own short-comings, and actively work towards inclusion and equality throughout their scientific endeavors. While "pre-existing conditions"—the social, economic, political, and historical forces discussed above— have led us to the gender inequalities we experience today, *The International Journal of Medical Students* (IJMS) is committed to acknowledging these gender inequalities and preventing their perpetuation among the next generation of future doctors and physician-scientists.

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Original Article

SARS-CoV-2 Infection Among Healthcare Workers in Tijuana, Mexico: A Cross-Sectional Study

José Adrián Yamamoto-Moreno,[1] Cecilia Pineda-Aguilar,[1] Samuel Ruiz-Pérez,[2] Gloria Liliana Gortarez-Quintana,[2] Marco Antonio Ruiz-Dorado.[3]

Abstract

Background: Healthcare workers (HCW) are a high-risk group for contraction of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The aim of this study was to estimate the effect size of being a HCW and acquiring coronavirus disease 2019 (COVID-19) at the Mexican Institute of Social Security (IMSS) in Tijuana, Mexico. **Methods:** A cross-sectional study of the Epidemiologic Surveillance Online Notification System database was conducted, including entries from Tijuana City between March 11, 2020 to May 1, 2020. Multiple imputation was performed for SARS-CoV-2 RT-PCR result where data was missing. Prevalence odds ratios (POR) were calculated to estimate the effect size of HCWs contracting COVID-19 compared to the general population (GP). **Results:** From a total of 10,216 entries, 6,256 patients were included for analysis. HCW status was significantly associated with higher odds of acquiring COVID-19, (POR=1.730, 95% Confidence Interval [95%CI]=1.459;2.050). Nurses had double odds (POR=2.339, 95%CI=1.804;3.032) than the GP. Physicians had a POR=1.828 (95%CI=0.766;1.380). Resident physician status was double the likelihood of the GP (POR=2.166, 95%CI=0.933;5.025). Meanwhile, being an intern had a protective factor (POR=0.253, 95%CI=0.085;0.758). Among medical specialties, emergency medicine had the highest exposure-effect association, followed by anesthesiologists. **Conclusion:** HCW had up to 73% increased odds of acquiring COVID-19 than the GP in Tijuana, Mexico. Nurses were the group with the highest likelihood out of all HCW, as a result of prolonged and close contact with patients. Emergency medicine and anesthesiology were the medical specialties with the highest odds of infection because they frequently perform aerosol-generating procedures.

Key Words: COVID-19; Coronavirus; SARS-CoV-2; Health personnel; Healthcare workers (Source: MeSH-NLM).

Introduction

Healthcare workers (HCW) are a high-risk population for acquiring COVID-19. [1-2] Viral transmission has multiple pathways, the most studied being through respiratory droplets, with increased estimates of transmission of SARS-CoV-2 compared to influenza.[3,4] For HCW, the workplaces at greater risk of infection are the respiratory and infectious disease departments, the ICU, and the operating room, given the prolonged times exposed to patients and the performance of aerosol-generating procedures.[5,6] On January 2020, Category A specifications for control and prevention of infection measures were recommended by Chinese Centers for Disease Control and Prevention as their country was the first to experience the pandemic, even though COVID-19 was considered a Group B infectious disease by the World Health Organization.[7,8] These measures focus on preventing transmission primarily through respiratory droplets during the execution of high-risk procedures such as endotracheal intubation, extubation, non-invasive ventilation, CPR, bronchoscopy, surgery, and autopsies.[9]

However, many asymptomatic and mild cases, which are still infectious, continue to seek medical attention for other health problems at primary care clinics and emergency departments, contributing to the increase in the number of cases.[4,10] Taking this into consideration, primary care and emergency physicians are considered to be most at risk for acquiring SARS-CoV-2 infection, from subclinical to some symptomatic cases.[11,12] Furthermore, different modes of viral transmission are still being researched, with new recommendations on the management and handling of fecal matter[13] and corpses of confirmed COVID-19 cases.[14] Although vertical transmission has not been demonstrated, there has been reports of pregnant women admitted with suspected COVID-19 at the end of gestation giving birth to newborns with positive SARS-CoV-2 test results.[15]

As a result of the uncertainty regarding disease transmission, severity, and mortality, access to some resources, such as face masks, sanitizers, and thermometers were soon scarce. At present, actions are being enforced to minimize the risks in the workplace with measures such as filtering at entry points, sanitizing hospitals, and continually providing personal protecting equipment (PPE) to the medical staff. Despite this, many HCWs in Mexico still feel vulnerable and question whether the PPE with which they are provided is sufficient.[9] In other countries, HCW screening has been proposed, as they are considered amplifiers of nosocomial and community transmission.[6]

Regardless, the measures implemented have not been sufficient to contain the escalating number of cases. COVID-19 outbreaks have been reported all across Mexico, and several hospitals have notified of outbreaks internal to the hospital involving HCWs.[9] The increase in the number of cases among the general population (GP) has also been reflected in HCWs,[2,16,17] with sustained rises of confirmed cases. On April 24, 2020, 1,934 HCWs had a positive RT-PCR result for SARS-CoV-2, which represented 15% of the total (12,872) confirmed cases up to that day. The affected HCWs were distributed as follows: 47% physicians, 35% nurses, 15% other HCWs, 1% dentists and 1% laboratory staff, with as many as 4,148 HCWs temporarily removed from the workforce due to infection.[18]

Thus, the aim of this study was to estimate the effect size of being a HCW and acquiring COVID-19 at the Mexican Institute of Social Security (IMSS) in Tijuana, a US-border city in Mexico. As secondary analyses, risk estimates were stratified by HCW categories, by physician hierarchies, and by medical specialties.

[1] MD, Universidad Autónoma de Baja California, Facultad de Medicina y Psicología; Instituto Mexicano del Seguro Social, H. Gineco-Obstetricia y Unidad de Medicina Familiar No. 7, Tijuana, México.
[2] Medical student, Universidad Autónoma de Baja California, Facultad de Medicina y Psicología, Tijuana, Mexico.
[3] Internal medicine specialist, Instituto Mexicano del Seguro Social, Hospital de Gineco-Obstetricia y Unidad de Medicina Familiar No. 7, Tijuana, México.

About the Author: *José Adrián is a recently graduated physician from a 7-year program at Universidad Autónoma de Baja California in México. He was awarded the Carlos Slim Foundation scholarship for excellence in Medicine and served as National Officer of Medical Publications in Asociación Mexicana de Médicos en Formación (AMMEF) from 2019-2020.*

Correspondence:
José Adrián Yamamoto-Moreno
Address: Tijuana, México.
Email: adrian.yamamoto@uabc.edu.mx

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Methods

Study Design

A cross-sectional database study was conducted using data from the IMSS's Epidemiologic Surveillance Online Notification System (SINOLAVE), an internal network database that includes the records of COVID-19 suspected cases reported from different IMSS centers in Mexico. As this was secondary research from an institutional database, it was exempt from IRB review at IMSS.

Data Source

The data for the study was extracted on May 11, 2020 and it corresponded to the entries recorded from March 11, 2020 to May 1, 2020. The data extraction criteria from SINOLAVE database were subset records from the Baja California delegation, including healthcare units from "all regimes". Additional information about specific occupations of patients identified as HCWs was manually obtained through social security number (SSN) from electronic medical records before concealing subject identities for further analysis.

Data Type

The SINOLAVE database consists of the following items: patient SSN, registry date, symptoms onset date, occupation and employer, clinical history including presence or absence of signs and symptoms, personal medical history (including chronic disease, tobacco smoking, alcohol consumption and pregnancy status, as well as history of travel and contact with COVID-19 cases and/or animals), results from RT-PCR for SARS-CoV-2 from nasopharyngeal or oropharyngeal swabs or specimens from lower respiratory tract secretions, treatment, and outcomes from primary and secondary healthcare systems.

Participants

The database was filtered to only include patients of all ages registered in Tijuana, Mexico, which corresponded to those notified from primary care centers number 7, 18, 19, 27, 33, 34, 35 and 36, and secondary care centers number 1 and 20. Individuals without complete personal and clinical history were excluded and duplicated or triplicated entries were eliminated. The first chronological record or the one that fulfilled severe acute respiratory infection (SARI) criteria was kept if records were registered twice at the same healthcare level. If duplicates were reported by different healthcare levels, the entry kept was from the highest healthcare level that included a reported laboratory test result. Data was recorded in a way that the identity of the human subjects could not be ascertained.

Variables

Patients whose registered occupation was "physician", "nurse", "laboratory staff", "dentist" or "other HCW", along with being enrolled as "IMSS employee" were defined as HCWs. Other IMSS employees with entries of different occupations from the ones previously mentioned, were reclassified as "other HCW". The remainder of patients who did not satisfied the above-mentioned criteria were defined as GP.

Additional categories were assigned within the physician subgroup by hierarchy position and medical specialty. The former divides the patient into three groups: "attending physician", "resident physician" and "intern". In the latter, groups by medical specialty were classified by combining attending physicians and residents from the same area, including "anesthesiology"; "surgery"; "OB-GYN"; "internal medicine"; "primary care medicine", which includes family medicine and general practitioners; "emergency medicine"; and "other specialties", which includes physicians in executive positions, intensive care medicine, orthopedics, pediatrics, occupational medicine, and physical medicine and rehabilitation.

Regarding outcomes, patients with at least one positive RT-PCR test for SARS-CoV-2 were considered confirmed COVID-19 cases and patients with a negative result were considered non-COVID-19 cases.

Statistical Analysis

Multiple imputation with logistic linear regression was performed. A total of 99 imputations were created using multiple imputation under the missing at random (MAR) assumption for entries where a RT-PCR for SARS-CoV-2 result was missing. Age, gender, occupation, IMSS employee, signs and symptoms, personal medical history and contact with suspect cases were considered predictors of missingness and defined as auxiliary variables for imputation before the analysis was conducted.

The mode value from the multiple imputation was assigned to registries with missing information, obtaining the following two sets of data: the complete-case analysis, excluding participants without a RT-PCR result (Analysis 1) and an alternative data set incorporating multiple imputation data including all of the patients (Analysis 2).

For the analysis of the relationship between HCW and COVID-19 case status, crude prevalence odds ratios (POR) were calculated with 95% confidence intervals (95%CI) and the χ^2 test was used in the bivariate analysis, in addition to Yates correction. The Mantel-Haenszel test was used to control for confounding, stratifying by age, gender, and history of chronic disease, as no other demographic data was included in the database. Statistical analysis for each set of data was conducted using IBM SPSS Statistics 25 and Stata 15. Statistical significance was considered as a *P*-value < 0.05. An alternative statistical analysis using Rubin's rules for pooling multiple imputation results and binomial logistic regression to estimate the effect size of being a HCW and acquiring COVID-19 is included in the following link: http://ijms.info/IJMS/article/view/625/Supplementary_Material

Results

From a total of 10,216 entries in the SINOLAVE registry, data from 6,256 patients was analyzed after eliminating 3,960 cases that failed to meet the inclusion criteria (3,858 were records from outside of Tijuana City, 72 were repeated, and 30 had missing data, see ***Figure 1***). Only 897 (14.33%) patients from the 6,256 included had at least one RT-PCR test for SARS-CoV-2, thus it was possible to classify them as a COVID-19 case or a non-case for Analysis 1. On the other hand, multiple imputation was performed on data from 5,359 (85.66%) subjects to complete Analysis 2, which included all the patients involved in this study.

Mean age for Analysis 1 was 45 years (SD 13), with a minimum of 0 to a maximum of 88 years of age (***Table 1***). Analysis 2 showcased a mean age of 39 years (SD 19), with an age range of 0 to 97 years. The most represented age group was 40 to 59 years (47.05%) in Analysis 1, and for Analysis 2 it was 16 to 39 years (52.40%). There were slightly more males than females included in both analyses, with 493 (54.96%) vs. 404 (45.04%) in Analysis 1, and 3,190 (50.99%) vs. 3,066 (49.01%) in Analysis 2, respectively. While the Analysis 2 group included 5,634 patients (90.06%) from the GP and only 622 HCWs (9.94%), the Analysis 1 group was composed of 653 members (72.80%) of the GP and 244 HCWs (27.20%). A confirmatory test was performed on 36.01% of HCW suspect cases and only 11.59% of the GP. A history of chronic disease was more common in the Analysis 1 group with 39.69%, compared to 28.84% in Analysis 2. The most prevalent chronic diseases among HCW were hypertension (17.4%), obesity (11.9%), and asthma (8.2%), whereas in the GP they were hypertension (18.1%), obesity (13.4%), and diabetes (11.6%). A similar proportion of smokers were involved in both groups with 4.1% vs. 4.7% in HCW and GP, respectively.

Figure 1. Flowchart of the Study.

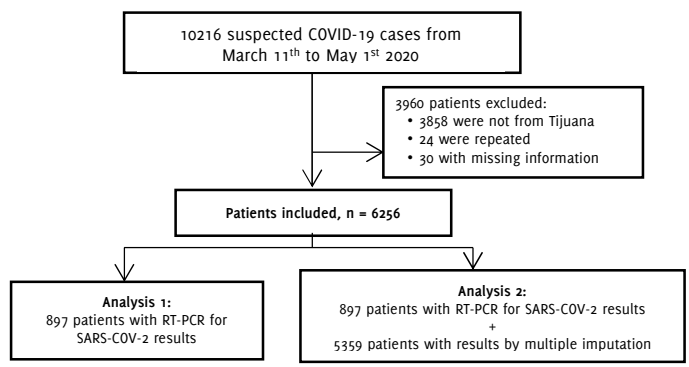


Table 1. Demographic Characteristics of Study Subjects.

Variables	Analysis 1			Analysis 2 (Multiple Imputation)		
	COVID-19 case *n* = 558	COVID-19 non-case *n* = 339	Total *n* = 897	COVID-19 case *n* = 3,103	COVID-19 non-case *n* = 3,153	Total *n* = 6,256
Gender, n (%)						
Male	326 (58.42)	167 (49.26)	493 (54.96)	1,770 (57.04)	1,420 (45.04)	3,190 (50.99)
Female	232 (41.58)	172 (50.74)	404 (45.04)	1,333 (42.96)	1,733 (54.96)	3,066 (49.01)
Age, years (standard deviation)						
Mean	47 (14)	41 (16)	45 (16)	42 (13)	36 (12)	39 (19)
Range	7-87	0-88	0-88	0-97	0-91	0-97
Age groups, n (%)						
0 to 5 years	0 (0.00)	13 (3.83)	13 (1.45)	2 (0.06)	36 (1.14)	38 (0.61)
6 to 15 years	4 (0.72)	6 (1.77)	10 (1.11)	9 (0.29)	36 (1.14)	45 (0.72)
16 to 39 years	170 (30.47)	142 (41.89)	312 (34.78)	1,329 (42.83)	1,949 (61.81)	3,278 (52.40)
40 to 59 years	283 (50.72)	139 (41.00)	422 (47.05)	1,476 (47.57)	1,034 (32.79)	2,510 (40.12)
>60 years	101 (18.10)	39 (11.50)	140 (15.61)	287 (9.25)	98 (3.11)	385 (6.15)
Healthcare workers, n (%)						
Yes	136 (24.37)	108 (31.86)	244 (27.20)	384 (12.38)	238 (7.55)	622 (9.94)
No	422 (75.63)	231 (68.14)	653 (72.80)	2,719 (87.62)	2,915 (92.45)	5,634 (90.06)
History of chronic disease, n (%)						
Yes	228 (40.86)	128 (37.76)	356 (39.69)	946 (30.49)	858 (27.21)	1,804 (28.84)
No	330 (59.14)	211 (62.24)	541 (60.31)	2,157 (69.51)	2,295 (72.79)	4,452 (71.16)

Of all HCWs included (***Table 2***), physicians represented the largest subgroup within Analysis 1 with 96 subjects (39.34%), followed by nurses and other HCWs with 80 (32.79%) and 66 (27.05%), respectively. However, nurses represented the largest subgroup among HCWs within Analysis 2 with 236 subjects (37.94%), followed by other HCWs with 208 (33.44%), and physicians with 173 (27.81%). Likewise, within the doctors' subgroup in both Analyses 1 and 2, 41 (58.57%) and 80 (63.49%) were attending physicians; 18 (25.71%) and 26 (20.63%) were residents; and 11 (15.71%) and 20 (15.87%) were interns, respectively.

From a total of 173 physicians (***Table 3***) it was possible to identify the area of specialty or job position of only 126 subjects (72.8%) through a hospital records search. In both sets of analyses, the specialty with the largest representation was internal medicine. However, subtracting resident physicians, that respectively account for 30.51% and 24.52% in Analyses 1 and 2, from their respective specialties showcased that interns were the largest subset among the doctors' subgroup.

The association between being a HCW and a COVID-19 confirmed case was statistically significant, both in Analysis 1 (χ^2=5.947, df=1, *P*=0.015), and Analysis 2 (χ^2=40.692, df=1, *P*<0.001), but the direction of risk is contrary according to each analysis. In Analysis 1, the POR=0.689 (95%CI 0.511, 0.930), whilst in Analysis 2, POR=1.730 (95%CI 1.459, 2.050). The GP was used as referent for analysis. Stratifying by age group, the statistical significance of the Analysis 1 was lost (POR=0.757; 95%CI 0.551, 1.040; χ^2_{MH}=3.566, df=1, *P*=0.168) It was identified that only the age group of 40 to 59 years maintained a statistically significant association (POR=0.550; 95%CI 0.349, 0.869; χ^2_{MH}=6.668, df=1, *P*=0.010). In this same analysis, there was no change in statistical significance after adjusting by gender (POR=0.728; 95%CI 0.537, 0.986; χ^2_{MH}=3.880, df=1, *P*=0.049), but higher odds were observed after adjusting by history of chronic disease (POR=1.451; 95%CI 1.075, 1.956; χ^2_{MH}=5.967, df=1, *P*=0.015). A slight increase in size effect was observed in Analysis 2 after adjusting by age group (POR=1.857; 95%CI 1.563, 2.206; χ^2_{MH}=51.050, df=1, *P*<0.001) and gender (POR=1.897; 95%CI 1.596, 2.254; χ^2_{MH}=53.552, df=1, *P*<0.001), whereas adjusting by history of chronic disease rendered lower odds (POR=0.578; 95%CI 0.488, 0.685; χ^2_{MH}=40.692, df=1, *P*<0.001).

Nurses were the HCW subgroup with the highest odds of acquiring COVID-19 (***Figure 2***), with a POR=2.339 (95%CI 1.804, 3.032) compared to the GP in Analysis 2, and POR=1.210 (95%CI 0.640, 1.628) in Analysis 1. In addition, other HCWs had a POR=1.765 (95%CI 1.336, 2.330) in Analysis 2, whereas in Analysis 1 this was not statistically significant (OR=0.689; 95%CI 0.511, 0.930). On the other hand, physicians showcased a protective factor in Analysis 1 (POR=0.557; 95%CI 0.365, 0.851) and a small excess in effect size compared to the GP in Analysis 2 (POR=1.028; 95%CI 0.766, 1.380). No change in statistical significance observed after stratifying by gender, age group, and history of chronic disease. It was not possible to estimate the association and individual risk of dentists and laboratory staff for COVID-19 given the low number of subjects in these subgroups.

Within the different physician hierarchies (***Figure 3***), it was found that interns had a POR=0.345 (95%CI 0.099, 1.179) and POR=0.253 (95%CI 0.085, 0.758) in Analyses 1 and 2, respectively. Meanwhile, residents had a higher likelihood of acquiring COVID-19 than the GP in both analyses (Analysis 1: POR=1.593; 95%CI 0.563, 4.510; Analysis 2: POR=2.166; 95%CI 0.933, 5.025). On the other hand, attending physicians showcased a POR=0.561 (95%CI 0.290, 1.083) in Analysis 1, and POR=1.320 (95%CI 0.841, 2.070) in Analysis 2. Adjusting by gender, age group and history of chronic disease showed no difference in statistical significance.

Further analysis was conducted to estimate the risk attached to each medical specialty included in this study compared to that of the cluster of physicians (***Figure 4***). It was observed that emergency medicine had the highest odds for contracting COVID-19 among medical specialties (Analysis 1: POR=8.828; 95%CI 1.040, 74.934; Analysis 2: POR=4.071; 95%CI 1.090, 15.208), followed by anesthesiology (Analysis 1: POR=1.943; 95%CI 1.452, 2.447; Analysis 2: POR=2.806; 95%CI 0.544, 14.466). Surgeons (Analysis 1: POR=1.084; 95%CI 0.298, 3.946; Analysis 2: POR=1.963; 95%CI 0.734, 5.247) and primary care physicians (Analysis 1: POR=1.563; 95%CI 0.343, 7.112; Analysis 2: POR=1.200; 95%CI 0.391, 3.680) also showed increased odds compared to that of all doctors. The

Table 2. Frequency of Healthcare Workers by Category.

Category, n (%)	Analysis 1 (*n*=244)	Analysis 2 (*n*=622)
Nurses	80 (32.79)	236 (37.94)
Other healthcare workers[a]	66 (27.05)	208 (33.44)
Physicians	96 (39.34)	173 (27.81)
Interns[b]	11 (15.71)[c]	20 (15.87)[c]
Residents[b]	18 (25.71)[c]	26 (20.63)[c]
Attendings[b]	41 (58.57)[c]	80 (63.49)[c]
Laboratory staff	1 (0.41)	3 (0.48)
Dentists	1 (0.41)	2 (0.32)

Legend: [a] Includes stretcher-bearers, cleaning staff, ambulance drivers, receptionists and others. [b] Includes only those with identified hierarchy. [c] Percentage calculated from the total of physicians with identified hierarchy (Analysis 1: *n*=70, Analysis 2: *n*=126).

Figure 2. Unadjusted Prevalence Odds Ratios (POR) and 95% Confidence Intervals (95%CI) for COVID-19 According to Healthcare Worker Category.

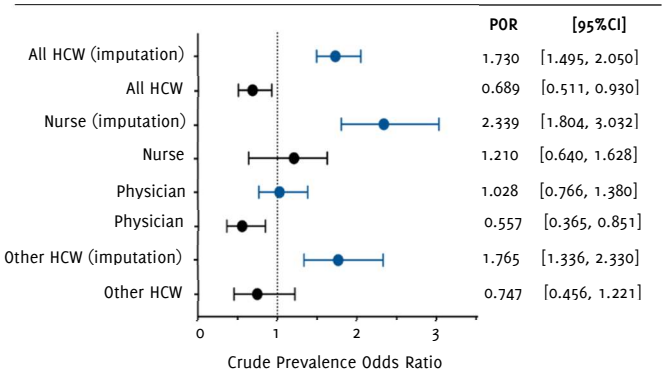


Figure 3. Unadjusted Prevalence Odds Ratios (POR) and 95% Confidence Intervals (95%CI) for COVID-19 According to Medical Hierarchy.

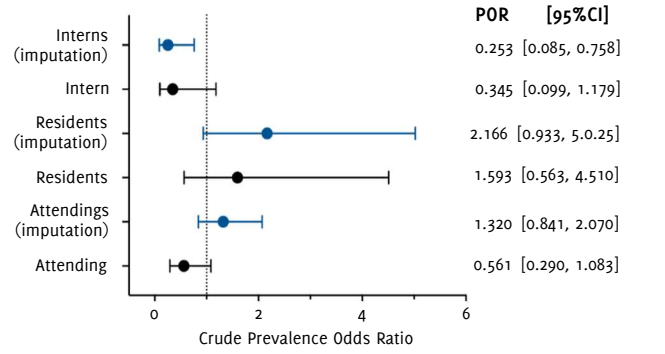
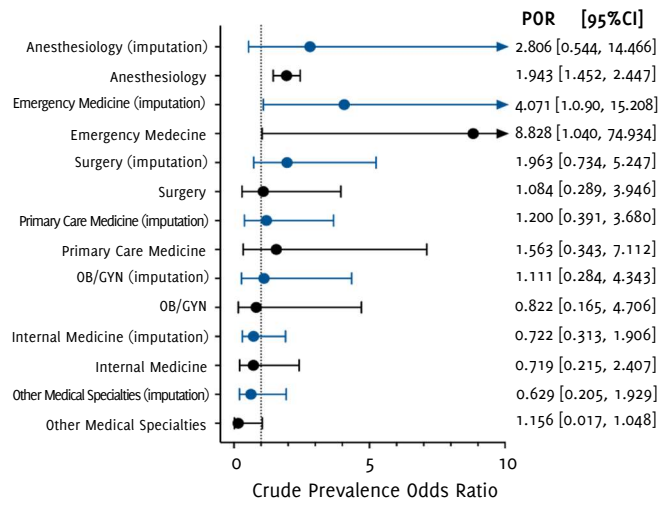


Figure 4. Unadjusted Prevalence Odds Ratios (POR) and 95% Confidence Intervals (95%CI) for COVID-19 by Medical Specialty.



internal medicine specialists had a possible protective factor (Analysis 1: POR=0.71; 95%CI 0.215, 2.407; Analysis 2: POR=0.722; 95%CI 0.313, 1.906). Likewise, all other medical specialties, which for this analysis included intensive care physicians, pediatricians, and physicians in executive positions had a lower likelihood of acquiring COVID-19 (Analysis 1: POR=0.629; 95%CI 0.205, 1.929; Analysis 2: POR=0.156; 95%CI 0.017, 1.048). On the other hand, OB-GYN was shown to have conflicting effect size estimates (Analysis 1: POR=0.822; 95%CI 0.165, 4.706; Analysis 2: POR=1.111; 95%CI 0.284, 4.343).

Table 3. Frequency of Physicians by Declared Medical Specialty.

Medical specialty[a], n (%)	Analysis 1 (*n*=70)	Analysis 2 (*n*=126)
Internal medicine	13 (18.57)	23 (18.25)
Surgery	11 (15.71)	20 (15.87)
Interns[b]	11 (15.71)	20 (15.87)
Primary care	8 (11.43)	14 (11.11)
Emergency medicine	9 (12.86)	14 (11.11)
Gynecology & Obstetrics	6 (8.57)	9 (7.14)
Anesthesiology	2 (2.86)	8 (6.35)
Pediatrics[c]	1 (1.43)	5 (3.97)
Physicians in executive positions[c]	4 (5.71)	4 (3.17)
Orthopedics[c]	1 (1.43)	4 (3.17)
Intensive care[c]	2 (2.86)	3 (2.38)
Occupational medicine[c]	1 (1.43)	1 (0.79)
Physical medicine and rehabilitation[c]	1 (1.43)	1 (0.79)

Legend: [a] Represents the sum of attendings and residents of the same specialty. [b] Do not represent a specific medical specialty; they are rotating medical staff. [c] These make up the group "all other medical specialties" combined.

Discussion

In this study, HCWs had 73% higher odds of acquiring COVID-19 than the GP. A disparity in the number of COVID-19 confirmatory tests was observed, since the HCW cluster was tested at least three times more (36.01%) than the GP (11.59%). Therefore, multiple imputation was performed to reduce the bias generated by the lack of confirmatory test results. Comparing between HCW categories, nurses were identified as the group with highest likelihood of acquiring COVID-19, with nearly double the odds of the GP. Conversely, the physician subgroup showcased a statistically significant protective factor in one of the analyses. However, using Analysis 2, it demonstrated only an additional 2.8% increase in odds from the GP, without statistical significance. Analyzing the physicians cluster by hierarchy, the group with the largest effect size estimate was resident physicians, with approximately 50% to 60% higher odds than GP in both analyses, but neither were statistically significant. On the contrary, interns showcased a potential protective factor compared to the GP. Finally, emergency medicine held the largest effect size among the medical specialties included in this study. A four- to eight-fold increase in odds compared to the all the other medical specialties was observed, and although statistically significant, wide confidence intervals were estimated. Anesthesiology followed as the second medical specialty with the highest likelihood of infection, by nearly double the estimate, but also with wide confidence intervals. In contrast, internal medicine posed a possible protective factor, with a close to 30% decreased likelihood of contracting COVID-19 than the rest of physicians; however, this finding was not statistically significant in either analysis.

Among all confirmed cases of COVID-19, HCWs represent nearly a quarter of the patients in Analysis 1 and only 7.55% in Analysis 2. In this study, HCWs were demonstrated to have roughly 73% higher odds of acquiring COVID-19 than the GP. This can be explained by HCW having direct or indirect contact with multiple patients and their surroundings, sometimes in confined areas.[17,19] Thus, HCW may experience a greater exposure to the virus, both chronologically and quantitively, than the GP. Even though infection prevention protocols were established according to HCW categories and tasks from the start of the pandemic, these measures were mostly focused on droplet and contact transmissions.[20] However, as recently reported, SARS-CoV-2 transmissibility can be heterogeneous[21,22] and the ability to appropriately don and doff PPE varies widely between each individual worker and by level of training.[1,23] Age was found to be a possible confounding factor in one of the analyses, this can be attributed to the fact that most HCW included in this study were in the age group of 40 to 59 years. Although this phenomenon was not seen in Analysis 2. Therefore, being an HCW —independently of category, despite the use of PPE, and other protective measures— represents a major risk of acquiring COVID-19.

Although it was not possible to calculate the effect size estimate for every individual category included under the term HCW, nurses were identified as the group with the highest likelihood for acquiring COVID-19. This phenomenon has been previously described by Chen et al.[24] during the 2009 influenza pandemic in Singapore, while other authors[25] have found that nurses have a greater COVID-19 mortality rate compared to physicians in Italy, Brazil, Spain and France. This could be attributed to multiple factors, such as the type and length of interventions carried out by nurses and having more frequent and closer contact with patients for extended periods of time compared to, for example, physicians.[26,27] Therefore, they are subjected to a greater exposure than the rest of the healthcare workforce. Additionally, it should be considered that nurses are the largest group of all the HCWs in this study population. Because of this, they may also have higher probabilities of coming into contact with infected colleagues in the workplace. On the other hand, physicians were subjected to a smaller effect size, and even appeared to have a degree of protection in Analysis 1. This could be explained considering the diversity within medical specialties, including the heterogeneity of procedures they perform and the PPE recommended for each group. A similar situation emerged when analyzing the odds of other HCWs, which included a vast range of job positions such as physicians in executive roles, social workers, receptionists, stretcher-bearers, ambulance drivers, cleaning staff, among others; each one of them with a different level of occupational exposure and PPE usage requirements.[7,28]

Comparing hierarchy roles among physicians, residents were the group of doctors with the highest odds of acquiring COVID-19 compared to the GP. Although resident physicians essentially partake in the same activities as their attendings, the workload is not comparable. The long working hours and greater frequency of contact with patients[29,30] appears to increase the risk of exposure to infected patients in this group. Moreover, residency training for physicians is a well-established stressful experience, which may contribute to a compromised immune system.[31,32] Conversely, interns usually execute tasks of a slightly lesser complexity but under the same working conditions as residents. However, in Mexico they are still considered medical students and therefore most of them were withdrawn from COVID-19 high-risk areas[33] and, in addition to being younger than the rest of physicians, this could have contributed to lower odds of contracting COVID-19 for this group.

Analyzing the differences in effect size estimates between medical specialties, emergency medicine physicians had the highest odds for COVID-19. This coincides with the results published by Whiteside et al.,[34] in which emergency department and primary care personnel infection risk was greater than that of other areas. This could be explained considering that emergency rooms are primary points of entry to any other department in most hospitals. Despite the implementation of entry-point filters for patients with respiratory symptoms and COVID-19 suspect cases, emergency physicians are still exposed to many patients seeking urgent medical attention for other reasons while possibly being asymptomatic carriers of SARS-CoV-2,[35] and even perform resuscitation maneuvers in severely ill patients, some of whom could be potential COVID-19 cases. Moreover, patients gathering in emergency rooms is commonplace in Mexico, compromising the implementation of infection control and prevention measures required to limit disease transmission. Not surprisingly, the second medical specialty with highest odds was anesthesiology, as they perform aerosol-generating procedures on a regular basis,[36] and consequently have a greater exposure to viral particles. In contrast, other medical specialties showcased a protective factor, such as internal medicine and OB-GYN, although neither had statistically significant results. However, it is necessary to further investigate if different, or even more stringent measures—such as indiscriminate use of PPE and implementation of multiple filter systems for patients—are being taken that could explain this phenomenon.

The limitations of this study are inherent to the design itself, considering that the data used was not specifically generated with the intention of answering our research question. Errors in categorization could have been made due to not having complete information on the occupation from all participants. Likewise, lack of information about HCW type of contact with patients, working hours, and frequency of exposure did not allow for further analysis to meaningfully compare different patterns between HCW categories. These results are based on data from a public healthcare system in one city in northern Mexico and thus is not necessarily internationally generalizable. It should be noted that POR is not an estimation of risk and therefore these results are to be cautiously interpreted, as they could overestimate the effect size if an approximation to risk is to be inferred. Multiple imputation helped avoid further reduction of our study population and mitigated the bias from missing data. Nevertheless, using this method for analysis showcased some opposing results that could be explained by a number of factors. Primarily, multiple imputation using the MAR assumption implies a random distribution of attributes under the premise that missing data depends on the observed data and not on the values of the missing data, whereas RT-PCR results in Analysis 1 were obtained by testing individuals according to clinical judgement and hospital policies and resources. As a result, characteristics such as the auxiliary variables used for imputation contribute to predict missing data, but with limitations such as complete medical records and individual hospital policies and procedures for testing were not included in the database. Therefore, the distribution of cases could differ from actuality in both analyses. Likewise, results regarding medical specialties should be interpreted cautiously, as the number of participants included was low, resulting in wide confidence intervals. Finally, our study also takes into consideration the non-occupational risk to which HCWs are also exposed to outside the workplace, for instance the analyses used the GP as referent.

Conclusion

In this cross-sectional database study, it was demonstrated that HCWs have higher odds of acquiring COVID-19 than the GP among IMSS users in Tijuana, Mexico. Nurses were the HCW group with the highest likelihood of acquiring SARS-CoV-2 infection. Regarding physician hierarchy, residents had the biggest effect estimate. On the other hand, interns, who were removed from COVID-19 high-risk areas, showcased a protective factor. Moreover, among medical specialties included in this study, emergency medicine and anesthesiology have the highest odds for contracting COVID-19, likely owing to the frequent execution of aerosol-generating procedures. In addition, medical specialties assumed to be more exposed to confirmed COVID-19 cases, such as internal medicine, or departments where more thorough infection control practices are systematically applied, such as OB-GYN, had a possible protective factor. Complementary studies are required to confirm our findings including a bigger and more open population, and even a follow-up of this study population, considering risk factors associated with each HCW category. It is essential to perform local and nation-wide research in order for health authorities to endorse evidence-based preventive protocols aimed at protecting and supporting the workforce that is currently sustaining healthcare systems during the crisis.

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Conflict of Interest Statement & Funding

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Author Contributions

Conceptualization: JY, CP, SR & MR. Methodology: JY, CP & SR. Validation: JY, GG & MR. Formal Analysis: SR. Investigation: JY, CP & SR. Resources: JY & CP Data Curation & Writing – Original Draft: JY, CP, SR & GG. Writing – Review & Editing: JY, CP, GG & MR. Visualization: JY, GG. Supervision: JY, CP. Project Administration: JY, CP, & MR.

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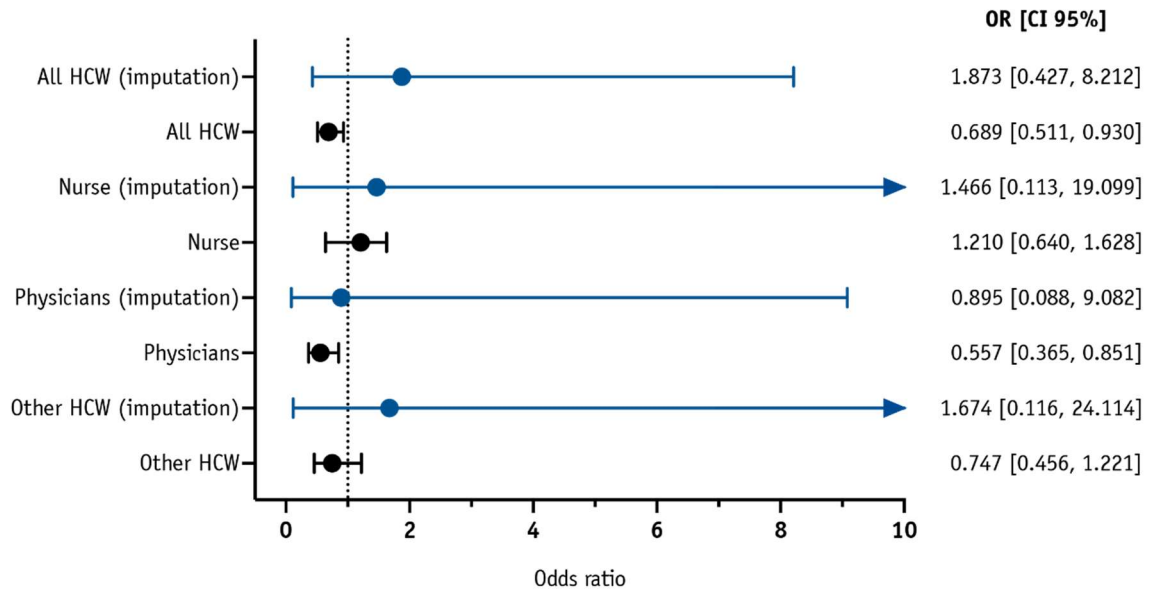
Supplementary Material

SARS-CoV-2 Infection Among Healthcare Workers in Tijuana, Mexico: A Cross-Sectional Study

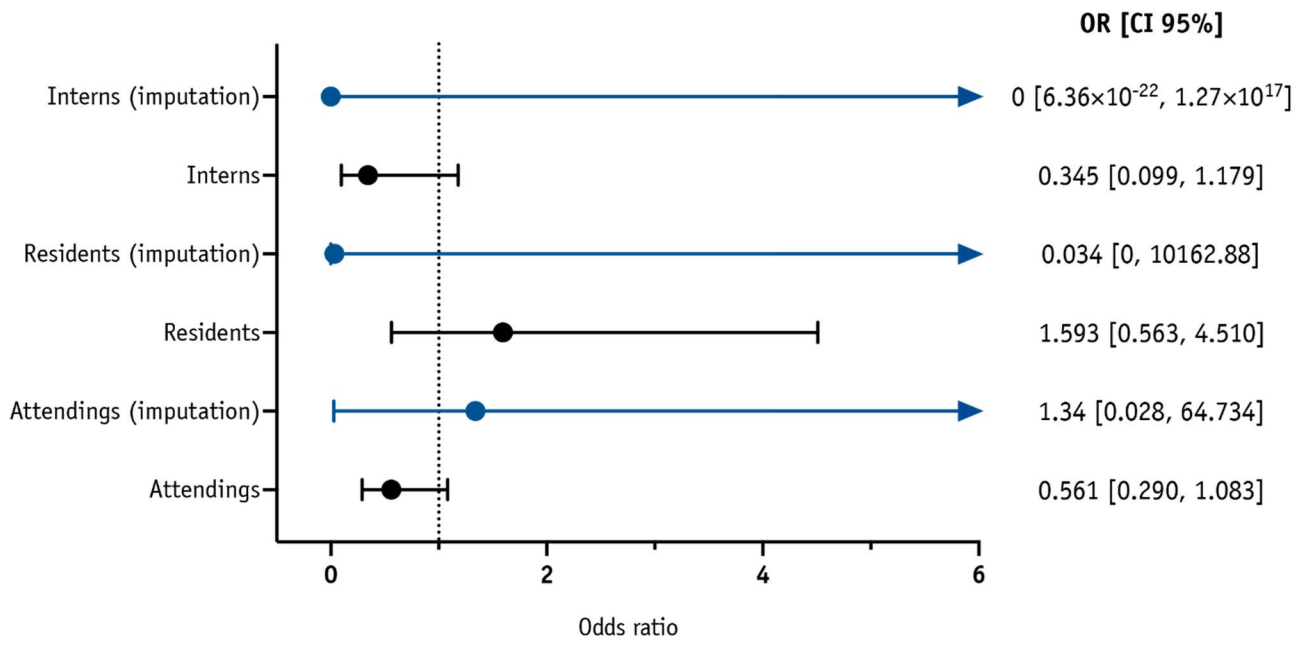
Supplementary Table 1. Demographic Characteristics of Study Subjects.

Variables	Analysis 1			Analysis 2 (pooled multiple imputation)		
	COVID-19 case *n* = 558	COVID-19 non-case *n* = 339	Total *n* = 897	COVID-19 case *n* = 3,263	COVID-19 non-case *n* = 2,993	Total *n* = 6,256
Gender, n (%)						
Male	326 (58.42)	167 (49.26)	493 (54.96)	1,775 (54.40)	1,415 (47.30)	3,190 (50.99)
Female	232 (41.58)	172 (50.74)	404 (45.04)	1,488 (45.60)	1,577 (52.70)	3,066 (49.01)
Age, years (standard deviation)						
Mean	47 (14)	41 (16)	45 (16)	41 (13)	37 (13)	39 (13)
Range	7-87	0-88	0-88	0-97	0-97	0-97
Age groups, n (%)						
0 to 5 years	0 (0.00)	13 (3.83)	13 (1.45)	6 (0.18)	32 (1.07)	38 (0.61)
6 to 15 years	4 (0.72)	6 (1.77)	10 (1.11)	16 (0.49)	29 (0.97)	45 (0.72)
16 to 39 years	170 (30.47)	142 (41.89)	312 (34.78)	1,518 (46.52)	1,760 (58.80)	3,278 (52.40)
40 to 59 years	283 (50.72)	139 (41.00)	422 (47.05)	1,461 (44.77)	1,049 (35.05)	2,510 (40.12)
>60 years	101 (18.10)	39 (11.50)	140 (15.61)	262 (8.03)	123 (4.11)	385 (6.15)
Healthcare workers, n (%)						
Yes	136 (24.37)	108 (31.86)	244 (27.20)	353 (10.82)	269 (8.99)	622 (9.94)
No	422 (75.63)	231 (68.14)	653 (72.80)	2,910 (89.18)	2,724 (91.01)	5,634 (90.06)
History of chronic disease, n (%)						
Yes	228 (40.86)	128 (37.76)	356 (39.69)	998 (30.59)	806 (26.93)	1,804 (28.84)
No	330 (59.14)	211 (62.24)	541 (60.31)	2,265 (69.41)	2,187 (73.07)	4,452 (71.16)

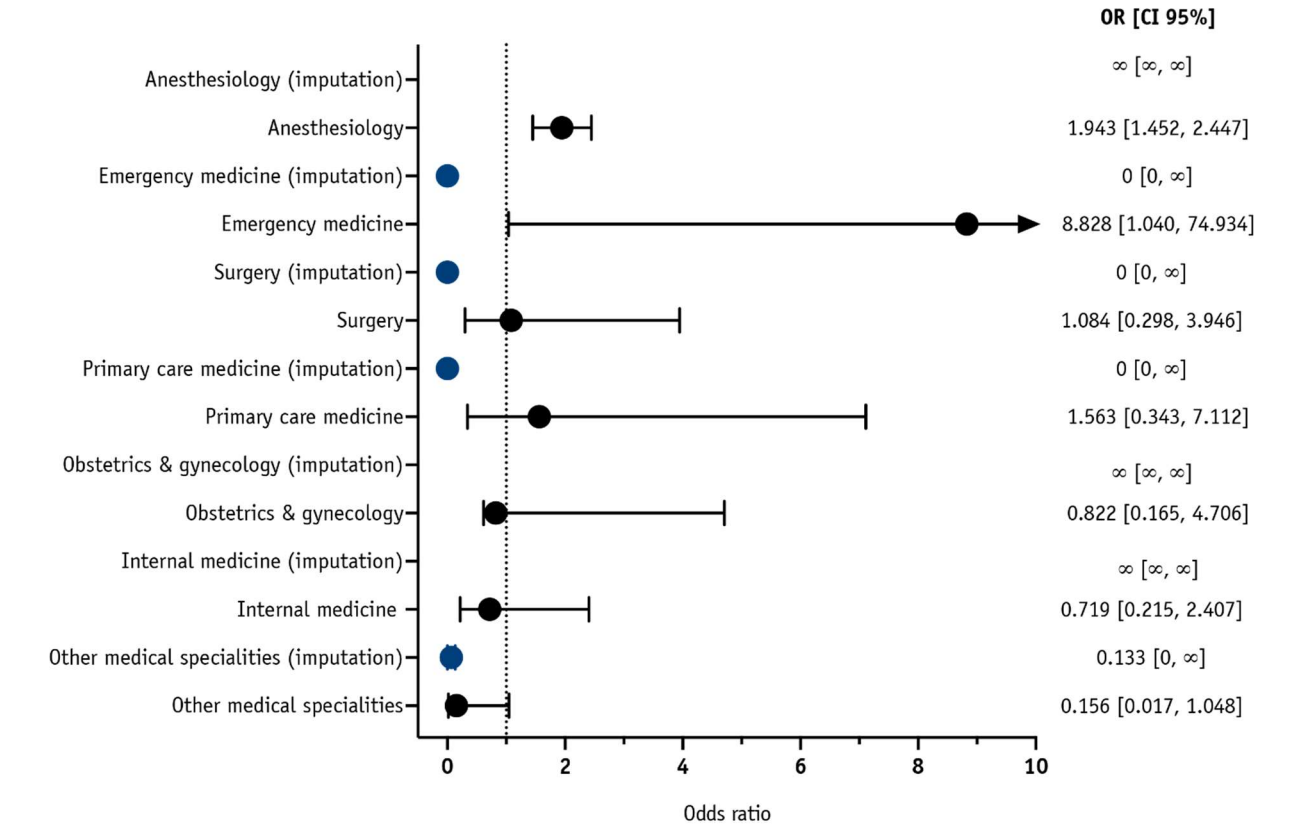
Supplementary Figure 1. Unadjusted Odds Ratios for COVID-19 According to Healthcare Worker Category



Supplementary Figure 2. Unadjusted Odds Ratios for COVID-19 According to Medical Hierarchy.



Supplementary Figure 3. Unadjusted Odds Ratios for COVID-19 by Medical Specialty.



Supplementary Table 2. Statistical Analysis Using Binomial Logistic Regression from Pooled Multiple Imputation Data

Category	*P-value*	Odds ratio (OR)	95%CI Lower bound	95%CI Higher bound
Effect size of being a HCW for acquiring COVID-19 (GP as referent)				
All hcw	0.404	1.873	0.427	8.212
Adjusted for sex	0.096	1.485	0.932	2.366
Adjusted for age	0.039	0.976	0.054	0.999
Adjusted for history	0.137	0.693	0.427	1.124
Effect size for acquiring COVID-19 by HCW category (All HCW as referent)				
Nurses	0.77	1.466	0.113	19.099
Adjusted for sex	0.233	1.801	0.684	4.743
Adjusted for age	0.316	0.98	0.942	1.019
Adjusted for history	0.094	0.513	0.235	1.119
Physicians	0.926	0.895	0.088	9.082
Adjusted for sex	0.171	1.687	0.798	3.564
Adjusted for age	0.198	0.977	0.942	1.012
Adjusted for history	0.801	1.11	0.492	2.507
Other hcw	0.705	1.674	0.116	24.114
Adjusted for sex	0.172	1.684	0.796	3.562
Adjusted for age	0.286	0.978	0.939	1.019
Adjusted for history	0.31	0.645	0.277	1.505
Effect size for acquiring COVID-19 by HCW category (GP as referent)				
Nurses	0.936	1.101	0.104	11.617
Adjusted for sex	0.153	1.894	0.788	4.554
Adjusted for age	0.309	0.981	0.944	1.018
Adjusted for history	0.144	0.572	0.271	1.21
Physicians	0.85	0.802	0.081	7.98
Adjusted for sex	0.169	1.662	0.806	3.429
Adjusted for age	0.19	0.976	0.941	1.012
Adjusted for history	0.661	1.193	0.542	2.628
Other hcw	0.644	1.848	0.136	25.059
Adjusted for sex	0.162	1.691	0.809	3.538
Adjusted for age	0.215	0.975	0.937	1.015
Adjusted for history	0.305	0.647	0.281	1.49
Effect size for acquiring COVID-19 by medical hierarchy (physicians as referent)				
Interns	0.54	0.000009	6.37E-22	1.27652E+11
Adjusted for sex	0.999	0.003	0	.
Adjusted for age	0.53	1.587	0.375	6.718
Adjusted for history	0.999	426.964	0	.
Residentes	0.6	0.034	0	10162.88
Adjusted for sex	0.982	1.027	0.107	9.87
Adjusted for age	0.708	1.081	0.719	1.624
Adjusted for history	0.899	1.177	0.094	14.802
Attendings	0.882	1.34	0.028	64.734
Adjusted for sex	0.354	1.751	0.535	5.733
Adjusted for age	0.161	0.951	0.887	1.02
Adjusted for history	0.477	1.612	0.432	6.024
Effect size for acquiring COVID-19 by medical hierarchy (All HCW as referent)				
Interns	0.54	0	0	1.27652E+11
Adjusted for sex	0.999	0.003	0	.
Adjusted for age	0.53	1.587	0.375	6.718
Adjusted for history	0.999	426.964	0	.
Residentes	0.6	0.034	0	10162.88
Adjusted for sex	0.982	1.027	0.107	9.87
Adjusted for age	0.708	1.081	0.719	1.624
Adjusted for history	0.899	1.177	0.094	14.802
Attendings	0.844	1.483	0.029	75.798
Adjusted for sex	0.362	1.748	0.525	5.822
Adjusted for age	0.155	0.951	0.887	1.019
Adjusted for history	0.519	1.544	0.413	5.777
Effect size for acquiring COVID-19 by medical hierarchy (GP as referent)				
Interns	0.54	0	0	1.27652E+11
Adjusted for sex	0.999	0.003	0	.
Adjusted for age	0.53	1.587	0.375	6.718
Adjusted for history	0.999	426.964	0	.
Residentes	0.6	0.034	0	10162.88
Adjusted for sex	0.982	1.027	0.107	9.87
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Adjusted for age	0.161	0.951	0.887	1.02
Adjusted for history	0.477	1.612	0.432	6.024
Effect size for acquiring COVID-19 by medical specialty (GP as referent)				
Anesthesiology	0.993	.	.	.
Adjusted for sex	0.998	0.000	0.000	.
Adjusted for age	0.992	0.000	0.000	.
Adjusted for history	0.996	1.352E+93	0.000	.
Emergency	0.999	0.000	0.000	.
Adjusted for sex	0.999	572.527	0.000	.
Adjusted for age	0.755	1.054	0.758	1.464
Adjusted for history	-1375.951	28359749.810	0.000	.
Surgery	151148.918	0.000	.	0
Adjusted for sex	3356828.370	0.000	.	0
Adjusted for age	0.264	0.000	.	0
Adjusted for history	5703.153	0.000	.	0
Primary care	718318191158.345	0.000	.	0.000
Adjusted for sex	3.867	0.000	.	0.000
Adjusted for age	0.568	0.000	3.5796E+196	0.000
Adjusted for history	0.001	0.000	.	0.000
Ob-gyn	-7004735051268220	151148.918	0.000	.
Adjusted for sex	0.999	3356828.370	0.000	.
Adjusted for age	0.999	0.264	0.000	.
Adjusted for history	-11477835663185500	5703.153	0.000	.
Internal med	-7004735051268220	151148.918	0.000	.
Adjusted for sex	0.999	3356828.370	0.000	.
Adjusted for age	0.999	0.264	0.000	.
Adjusted for history	-11477835663185500	5703.153	0.000	.
Others	1.000	0.133	0.000	.
Adjusted for sex	0.657	1.875	0.116	30.192
Adjusted for age	0.494	0.949	0.818	1.102
Adjusted for history	1.000	5.740	0.000	.
Effect size for acquiring COVID-19 by medical specialty (All HCW as referent)				
Anesthesiology				
Adjusted for sex	The parameter covariance matrix cannot be calculated, SPSS ignores the statistics			
Adjusted for age				
Adjusted for history				
Emergency	1.000	0.000	0.000	.
Adjusted for sex	0.999	572.527	0.000	.
Adjusted for age	0.755	1.054	0.758	1.464
Adjusted for history	-1375.951	28359749.810	0.000	.
Surgery	1.000	5.538	0.000	.
Adjusted for sex	1.000	0.000	0.000	.
Adjusted for age	0.615	0.931	0.706	1.229
Adjusted for history	1.000	579.528	0.000	.
Primary care	0.999	718318191158.345	0.000	.
Adjusted for sex	1.000	3.867	0.000	.
Adjusted for age	0.999	0.568	0.000	3.57969836E+196
Adjusted for history	0.999	0.001	0.000	.
Ob-gyn	-7004735051268220	151148.918	0.000	
Adjusted for sex	0.999	3356828.370	0.000	.
Adjusted for age	0.999	0.264	0.000	.
Adjusted for history	-11477835663185500	5703.153	0.000	.
Internal med	1.000	0.000	0.000	.
Adjusted for sex	0.735	1.435	0.177	11.610
Adjusted for age	0.925	1.005	0.904	1.117
Adjusted for history	1.000	2025.182	0.000	.
Others	1.000	0.133	0.000	.
Adjusted for sex	0.657	1.875	0.116	30.192
Adjusted for age	0.494	0.949	0.818	1.102
Adjusted for history	1.000	5.740	0.000	.
Effect size for acquiring COVID-19 by medical specialty (physicians as referent)				
Anesthesiology				
Adjusted for sex	The parameter covariance matrix cannot be calculated, SPSS ignores the statistics			
Adjusted for age				
Adjusted for history				
Emergency	0.998	0.000	0.000	.
Adjusted for sex	0.999	1115632.547	0.000	.
Adjusted for age	0.849	1.037	0.710	1.516
Adjusted for history	1.000	16995783.010	0.000	.
Surgery	1.000	5.538	0.000	.
Adjusted for sex	1.000	0.000	0.000	.
Adjusted for age	0.615	0.931	0.706	1.229
Adjusted for history	1.000	579.528	0.000	.

Primary care	0.999	718318191158.345	0.000	.
Adjusted for sex	1.000	3.867	0.000	.
Adjusted for age	0.999	0.568	0.000	3.57969836E+196
Adjusted for history	0.999	0.001	0.000	.
Ob-gyn	-7004735051268220	151148.918	0.000	.
Adjusted for sex	0.999	3356828.370	0.000	.
Adjusted for age	0.999	0.264	0.000	.
Adjusted for history	-11477835663185500	5703.153	0.000	.
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Adjusted for history	1.000	2025.182	0.000	.
Others	1.000	0.133	0.000	.
Adjusted for sex	0.657	1.875	0.116	30.192
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Adjusted for history	1.000	5.740	0.000	.

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Original Article

Knowledge, Attitude, and Practices Associated with COVID-19 Among School Students in Bharatpur, Chitwan District of Nepal

Deepak Subedi,[1,2] Suman Bhandari,[1] Asmita Gaire,[1] Milan Kandel,[2] Sanju Subedi,[3] Surendra Karki.[4]

Abstract

Background: The virus causing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has reached pandemic proportions. Understanding people's perceptions of the disease will provide tools to improve strategies to limit its transmission. This study aims to assess the knowledge, attitude, and practices (KAP) associated with the disease among high school students. **Methods:** Cross-sectional study conducted among secondary level students (grade 8th and 9th) in an urban high-school at Bharatpur, Chitwan, Nepal to assess KAP using a pre-tested questionnaire. Data were analyzed using Epi Info 7.2.3.1. **Results:** We collected 101 surveys (response rate 100%). Most of the students were found to be knowledgeable about the timeline of the first outbreak (92.08%), and nearly three-fourths of participants knew about hand-washing for 20 seconds (73.27%). Information about the presence of the disease in Nepal (50.50%), its causative agent (65.53%), and symptoms (57.43%) showed that there is a knowledge gap among participants. Most of the participants were found to have a positive attitude towards the prevention and control of the disease. The majority of the respondents reported using face mask (77.23%) and adopting hand-washing measures (79.21%) as preventive strategies. The majority of the students were highly concerned about the disease. **Conclusion:** Secondary level students of Chitwan, Nepal were found to have fair knowledge and understanding of the disease, showed a moderately positive attitude towards preventive measures, and reported appropriate preventive practices against the disease. It is recommended that a similar study with a wider population be conducted to assess KAP of Nepalese people towards SARS-CoV-2.

Key Words: Health Knowledge, Attitudes, Practice; COVID-19; SARS-CoV-2; Students (Source: MeSH-NLM).

Introduction

Several cases of pneumonia of unknown etiology and origin was reported on December 31, 2019, in Wuhan City, Hubei province in China.[1] Patients with clinical symptoms of dry cough, dyspnea, and fever presented with a positive travel history to Wuhan's Huanan Seafood Wholesale Market.[2] On January 7, 2020, the causative agent for this unknown disease was identified as a novel type of coronavirus, and on February 11, 2020, the International Committee on Taxonomy of Viruses (ICTV) named it as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[3] Later, the World Health Organization (WHO) announced "COVID-19" as the name of the disease on February 11, 2020.[3] On January 30, 2020, the WHO declared this epidemic as a Public Health Emergency of International Concern (PHEIC) under International Health Regulation (2005).[4] On March 11, 2020, the WHO declared the COVID-19 outbreak as a pandemic.[5] By Mid-September of 2020, this disease had spread to over 216 countries and territories across the world infecting more than twenty nine million people and nearly a million deaths. As the disease is still evolving, the magnitude of the infection and death are yet to be known.[6]

Nepal is no exception to this global threat. Nepal is particularly vulnerable as it borders with China from where the infection started and India where the disease is rapidly spreading.[7] Likewise, thousands of Nepalese migrant workers are scattered throughout the world, including Gulf countries, European nations, USA, and Australia, who are struggling with COVID-19. In the Global Health Security Index, Nepal ranks 111th among 195 countries and does not have adequate human and medical resources and weak health system to act upon such a medical emergency.[8] As expected, the COVID-19 virus entered Nepal and the first case was confirmed on January 23, 2020[9] in a 32-year-old male Nepalese student who returned from Wuhan, China on January 13, 2020.[10] The second case was detected on March 22, 2020 in a Nepalese female who returned to Nepal on March 17, 2020 from France via Doha, Qatar.[11] After that, more than 64,000 confirmed cases and over 400 deaths have been identified until September 20, 2020.[12]

A study on knowledge, attitude, and practices (KAP) to understand the perception and behavior of people during an infectious disease outbreak can be pivotal to improve awareness and communication efforts by clinicians and public health officials.[13] This study was undertaken to assess the knowledge, attitude, and practices associated with COVID-19 preventive measures among high school students in the Chitwan district of Nepal.

Methods

Study Design, Sample Size, and Sampling Protocol

This is a cross-sectional study conducted using a pre-tested and structured questionnaire among 101 students of grade 8 and 9 in one of the urban schools at Bharatpur, Chitwan district, during the second week of March 2020. There was no sample size calculation as we surveyed all the students in the two grades (response rate 100%).

[1] Bachelor of Veterinary Science and Animal Husbandry (BVSc & AH). Paklihawa Campus, Institute of Agriculture and Animal Science, Tribhuvan University, Rupandehi, Nepal.
[2] New Hope Agrobusiness Nepal Private Limited, Bharatpur, Chitwan, Nepal.
[3] Bachelor of Public Health (BPH). Chitwan Medical College, Tribhuvan University, Chitwan, Nepal.
[4] PhD, Epidemiology. Department of Epidemiology and Public Health, Himalayan College of Agriculture Sciences and Technology, Kirtipur, Kathmandu, Nepal.

About the Author: *Deepak Subedi is a recent graduate of Bachelor of Veterinary Science and Animal Husbandry (BVSC & AH) from the Institute of Agriculture and Animal Science, Tribhuvan University, Rupandehi, Nepal. He is a registered veterinarian (NVC Reg No. 1301) under Nepal Veterinary Council and currently working in New Hope Agrobusiness Nepal Private Limited, Bharatpur, Chitwan, Nepal as a poultry technical executive. He is the founder president of Creative Veterinary Student Association, Nepal, and the recipient of the most inspirational Tunza Eco Generation Ambassador of the 21st Eco-generation Regional Ambassadors.*

Correspondence:
Deepak Subedi
Address: Siddarthanagar, Rupandehi, Lumbini Province, 32900, Nepal.
Email: subedideepu26@gmail.com

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Questionnaire Design and Administration

The questionnaire was prepared by the authors to understand the situation of COVID19 in Nepal and the target population. The survey was validated by pretesting it with 10% (n=10) of the students. At first, the school was purposively selected and the study was explained to the teachers and school principals. They agreed to conduct the survey among their students. The survey was self-administered and if there were questions about an item, the research team addressed them in the student's native language.

The following information was collected: demographic profile of the students such as age and sex; knowledge about COVID-19 including cause, signs and symptoms, mode of transmission, incubation period, vaccination and treatment; information related to the outbreak and the situation in Nepal, attitudes and perceptions towards the disease, its prevention, and control measures were assessed. In addition, participant's perception of government actions and precautions to be followed by the infected person were assessed through twelve statements with choices given as "strongly agree", "agree", "neutral", "disagree", or "strongly disagree". The questions were close-ended. Questions were designed in English but asked in the Nepali language. After the questionnaire was filled, an awareness session was conducted on COVID-19 for an hour by veterinary interns. Ethical approval of the study was obtained from the Institutional Review Committee at Chitwan Medical College (CMC-IRC/077/078). Informed consent was obtained from the students under the supervision of teachers and after institutional approval was granted. Data were anonymized and analyzed at an aggregated level.

Table 1. Knowledge and understanding of students about COVID-19.

Characteristics	Frequency (%)	95% CI
Have your family members or relatives abroad suffered from COVID-19?, Yes	2 (1.98)	0.24-6.97
Have you heard of COVID-19?, Yes	68 (67.33)	57.28-76.33
Have there been any cases of COVID-19 in Nepal?, Yes	51 (50.50)	40.36-60.60
What is the cause of COVID-19?		
Virus	73 (72.28)	62.48-80.72
Bacteria	9 (8.91)	4.16-16.24
Both	8 (7.82)	3.48-15.01
None	3 (2.97)	0.62-8.44
All	8 (8.792)	3.48-15.01
From where did you learn about the COVID-19 for the first time?		
Family	6 (5.94)	2.21-12.48
Friends/Relatives	5 (4.95)	1.63-11.18
Newspaper	2 (1.98)	0.24-6.97
Radios	5 (4.95)	1.63-11.18
School	2 (1.98)	0.24-6.97
Social Media	70 (69.31)	59.34-78.10
Teachers	2 (1.98)	0.24-6.97
Television	9 (8.91)	4.16-16.24
Do you think COVID-19 is a fatal disease?, Yes	59 (58.42)	48.18-68.14
What is coronavirus disease 2019 (COVID-19)?		
Respiratory illness	66 (65.53)	55.23-74.4
Gastrointestinal illness	1 (0.99)	0.03-5.40
All	10 (9.90)	4.85-17.46
Not sure	24 (23.76)	15.86-33.26
Do you fear to go to the public areas due to COVID-19?, Yes	46 (45.54)	35.69-55.76
Which group of people are at higher risk of getting very sick from this illness?		
Children	8 (7.92)	3.48-15.01
Old People	27 (26.73)	18.41-36.46
People with chronic medical conditions, heart and lung disease and diabetes	22 (21.78)	14.18-31.10
People with a weak immune system	44 (43.56)	33.72-53.80
Had you heard about Coronavirus before it became epidemic?, Yes	25 (24.75)	16.70-34.33
Have you heard about MERS and SARS?, Yes	32 (31.68)	22.78-41.69
How long should we wash our hands with soap water?		
At least 20 seconds	74 (73.27)	63.54-81.59
For 7 seconds	13 (12.87)	7.04-21.00
Less than 7 seconds	4 (3.96)	1.09-9.83

Data Management and Analysis

Collected data were entered in Microsoft Excel 2016, and statistical analysis was conducted using Epi Info 7.2.3.1 developed by the Center for Disease Control of the United States. Means and standard deviations (SD) were calculated for continuous variables, while frequencies and percentages with 95% confidence intervals (95%CI) were calculated for categorical responses.

Results

A total of 101 students (58 male and 43 female) participated in the survey. The mean age of the respondents was 14.8 years (Range 13-17 years). The survey showed that 67.3% of respondents had heard about COVID-19. The majority of the respondents (73.3%) were aware that COVID-19 is a viral infection while 8.9% of students thought it was caused by bacteria and 7.8% of students believed that it is caused by both virus and bacteria. More than two-thirds of the participants (69.3%) first came to know about COVID-19 from social media, while 8.9% heard from television and 5.9% from family members. Half of the participants (50.5%) were aware that a case of COVID-19 was also detected in Nepal. The majority (92.1%) were aware that this disease started in Wuhan, China.

Two participants had family members/relatives abroad who were infected with COVID-19. More than half of the participants considered it a fatal disease (58.4%) with respiratory signs (65.5%). The majority of students (54.5%) responded that they do not fear to go outside in public areas. Above 40% respondents (43.6%) believed that people with a weak immune system are at high risk of the disease, while 26.7%

Table 1 (continuation)

Characteristics	Frequency (%)	95% CI
How can COVID-19 be transmitted?		
From infected animal to healthy human (Zoonotic Disease)	25 (24.75)	16.70-34.33
From carrier human to healthy human	2 (1.98)	0.24-66.97
From infected human to healthy human	19 (18.81)	11.72-27.81
From carrier animal to healthy human	4 (3.96)	1.09-9.83
Both 1 & 2	16 (15.84)	9.33-24.45
All	29 (28.71)	20.15-38.57
Not Sure	6 (5.94)	2.21-12.48
What is the incubation period for COVID-19?		
14-21 days after exposure	9 (8.91)	4.16-16.24
1-7 days after exposure	19 (18.81)	11.72-27.81
2-14 days after exposure	28 (27.72)	19.28-37.52
Not Sure	45 (44.55)	34.66-54.78
Having a family pet increases your risk of contracting COVID-19, do you agree?		
Strongly Agree	18 (17.82)	10.92-26.70
Agree	19 (18.81)	11.72-27.81
Neutral	40 (39.60)	30.01-49.83
Disagree	16 (15.84)	9.33-24.25
Strongly Disagree	8 (7.92)	3.48-15.01
Is COVID-19 the same as common cold/flu?, Yes	51 (50.50)	40.36-60.60
What are the symptoms of COVID-19?		
Cough	9 (8.91)	4.16-16.24
High Temperature	4 (3.96)	1.09-9.83
Runny Nose	10 (9.90)	4.85-17.46
Shortness of Breath	3 (2.97)	0.62-8.44
Sneezing	5 (4.95)	1.63-11.88
Both high temperature and shortness of breath	12 (11.88)	6.29-19.83
All	58 (57.43)	47.19-67.21
Is there a specific antiviral treatment for COVID-19?, Yes	8 (7.92)	3.84-15.01
Is there a vaccine against COVID-19?, Yes	27 (26.73)	18.41-36.46
Where did the COVID-19 outbreak occur?		
Beijing, China	2 (1.98)	0.24-6.97
Shanghai, China	3 (2.97)	0.62-8.44
Shenzhen, China	3 (2.97)	0.62-8.44
Wuhan, China	93 (92.08)	84.99-96.52
Have you ever heard about term zoonosis? Yes	32 (31.68)	22.78-41.69

believed older people are at higher risk. A large part of the respondents (73.3%) was aware that the duration of the hand-washing should be at least 20 seconds to prevent the disease. Around one-third (28.7%) students believed that COVID-19 could be transmitted through infected animal to healthy human, carrier human to a healthy human, infected human to healthy human or carrier animal to healthy human. Nearly 40% respondents (39.6%) were neutral regarding the increasing risk of disease having pet animals in the home, while 17.8% strongly agreed, 18.8% agreed, 15.8% disagreed and 7.9% strongly disagreed. The majority of the respondents (59.4%) were not sure about treatment, and the 41.6% believed there is no vaccination of the disease (***Table 1***). Majority of the students believed that COVID-19 could be transmitted through the animal source (87.1%), contact with infected people who had no symptoms (53.5%), touching of contaminated surfaces (75.2%), infected droplets (96.0%), contaminated food and water (77.2%), contaminated fomites (64.4%), physical contact with an infected person (84.1%) and bite of the mosquito (50.5%) (***Table 2***).

Students' attitude regarding prevention and control of COVID-19 were found generally positive. More than half of the students strongly agreed to avoid contact with unhealthy people (57.4%), boosting immunity (52.5%), following hygienic practices (59.4%), use of proper medical service (53.5%), quarantine (51.5%) and hand wash with soap and water (59.4%) as prevention and control of the disease. Less than half of the respondents strongly agreed, avoiding touching of eyes, nose, and mouth with unwashed hands (39.6%), awareness (46.5%), education (46.5%), practice food safety (49.5%) and use of hand sanitizer (37.6%) for prevention and control. In total, 31.7% strongly agreed, 33.7% agreed, 24.8% were neutral, 5.9% disagreed and 3.9% strongly disagreed regarding unprotected contact with live wild or farm animals. 23.8% strongly agreed, 12.9% agreed, were neutral 28.7%, 19.8% disagreed and 14.9% strongly disagreed to avoid contact with healthy people for the prevention and control COVID-19 (***Table 3***).

Little above 50% of the students (52.5%) were adopting a high level of precautions, while 24.8% were following minimal precautions, 11.9% did not follow any precautions, and 10.9% believed in supernatural power to fight against COVID-19. More than half of the respondents (52.5%) stopped eating meat products; 60.4% were avoiding normal activities; and 73.3% were avoiding frequent touching of mouth, eye, and nose. A large number of students (77.2%) were reported using a face mask and adopting hand-washing measures (79.2%) to be protected from the COVID-19. The vast majority of the students (81.2%) were covering mouth and nose with a tissue while sneezing and using tissue paper while coughing (70.3%) and disposing of it in the trash after its use (***Table 4***).

More than half of the students (57.4%) strongly agreed that the government should restrict travel, isolate positive cases (34.7%), close the educational institutions if positive cases increases (47.5%), and restrict people arrival from the infected areas (46.5%). Likewise, one-third of the study population (38.6%) agreed on the isolation of positive cases. Less than half of the population (41.6%) strongly agreed, 15.8% agreed, while 20.8% were neutral and 14.9% strongly disagree on staying at home during a pandemic. (***Table 5***). The majority of the students strongly agreed on covering mouth and nose while cough and sneeze (63.4%) and seeking medical services (65.3%) if they are sick. Less than half of the respondents (41.68%) strongly agreed and 38.6% agreed to follow cleanliness and disinfection of frequently touched objects and surfaces. Almost half of the students (51.5%) strongly disagreed on travel of sick people (***Table 6***).

Table 2. Students' knowledge about transmission of COVID-19.

Characteristics, response	Frequency (%)	95% CI
Animal Source, Yes	88 (87.13)	79.00-92.96
Contact with infected people who had no symptom, Yes	54 (53.47)	43.27-63.45
Touching of contaminated surfaces, Yes	76 (75.25)	65.67-83.30
Infected droplets, Yes	97 (96.04)	90.17-98.91
Contaminated food and water, Yes	78 (77.23)	67.82-84.98
Contaminated fomites, Yes	65 (64.36)	54.21-73.64
Physical contact with an infected person, Yes	85 (84.14)	75.55-90.67
Bite of mosquito, Yes	51 (50.50)	40.36-60.60

Discussion

This is the first KAP study towards COVID-19 among Nepalese students to the best of our knowledge. This study found that there is a significant knowledge gap related to COVID-19 among high-school students in Chitwan, Nepal and fair proportion of students were aware regarding the protective measures they need to take to prevent the spread of the disease. The finding showed that a good proportion of students need awareness regarding knowledge, their attitudes and practices.

This study shows that more than 72% of students were aware that virus is the causative agent for the COVID-19. In a similar survey conducted among high school students in Nepal on avian influenza, 52.5% of students had correctly answered virus as the cause of the disease.[14] This shows that though this disease is relatively new, even good number of high school students are already aware of this. In our study, the majority of the students had general knowledge about COVID-19 like first outbreak, cases in Nepal, type of disease symptoms, and hand wash duration. This shows that most of them had good knowledge of the disease which might be due to the increased access to social media, from where 69.3% of responded acquired information on COVID-19. Consistent with our study, social media was the most pursued platform (74.8%) to acquire COVID-19 information among the young adults of Karachi, India.[15] In a study conducted in China, the mean knowledge score was 90%,[16] which makes sense as this disease started in China and awareness level among Chinese was higher. In a web-based cross-sectional study among Nepalese people conducted by Singh et al., 2020, knowledge score was 10.0 (±3.0 IQR) and only half participants knew about quarantine concept and safe distance to prevent disease transmission.[17]

Only one-third of students correctly responded on the incubation period of the disease which indicates though they have heard the name of the disease and causative agent, their depth of knowledge is limited. As the knowledge of incubation period is important from public health point of view and limited knowledge observed among students, it warrants for increased awareness program among the students who are also major source of information in several households in low-income countries like Nepal. In our study, 32.67% students knew that there was no specific treatment for COVID-19, while 59.41% were not sure about treatment. In a study among Italian undergraduate students, 70% respondents suggested there was no treatment of COVID-19.[18]

Our study also showed that majority of students had never heard about term zoonosis. As more than 70% of infectious disease in humans originate in animal population, mostly wildlife, it would be helpful to include one lesson on zoonotic diseases in the high-school curriculum. The majority of students were knowledgeable on disease transmission routes such as touching of contaminated surfaces, infected droplets, contaminated fomites and physical contact with an infected person. Similar to our study, majority of young adults of Karachi were knowledgeable in source of transmission and preventive measure.[15]

This knowledge level shall be helpful if the disease spreads to their community. A large portion of the student believed COVID-19 could be transferred through the animal source, and half of them were avoiding meat products. In the study of Singh et al., 70% participants responded that restricting consumption of poultry and other meat can prevent the

Table 3. Students' attitudes toward preventive measures and control of COVID-19.

Characteristics	Frequency (%)	95% CI
Avoid unprotected contact with live wild or farm animals		
Strongly Agree	32 (31.68)	22.78-41.69
Agree	34 (33.66)	24.56-43.75
Neutral	25 (24.75)	16.70-34.33
Disagree	6 (5.94)	2.21-12.48
Strongly Disagree	4 (3.96)	1.09-9.83
Avoid contact with healthy people		
Strongly Agree	24 (23.76)	15.86-33.26
Agree	13 (12.87)	7.04-21.00
Neutral	29 (28.71)	20.15-38.57
Disagree	20 (19.80)	12.54-28.91
Strongly Disagree	15 (14.85)	8.56-23.31
Avoid contact with unhealthy people		
Strongly Agree	58 (57.43)	47.19-67.21
Agree	19 (18.81)	11.72-27.81
Neutral	16 (15.84)	9.33-24.45
Disagree	5 (4.95)	1.63-11.18
Strongly Disagree	3 (2.97)	0.62-8.44
Avoid touching your eyes, nose, and mouth with unwashed hands		
Strongly Agree	40 (39.60)	30.01-49.83
Agree	31 (30.69)	21.90-40.66
Neutral	24 (23.76)	15.86-33.26
Disagree	4 (3.96)	1.09-9.83
Strongly Disagree	2 (1.98)	0.24-6.97
Awareness		
Strongly Agree	47 (46.53)	36.55-56.73
Agree	26 (25.74)	17.56-35.40
Neutral	16 (15.84)	9.33-24.45
Disagree	9 (8.91)	4.16-16.24
Strongly Disagree	3 (2.97)	0.62-8.44
Boosting Immunity		
Strongly Agree	53 (52.48)	42.30-62.51
Agree	20 (19.80)	12.54-28.91
Neutral	24 (23.76)	15.86-33.26
Disagree	3 (2.97)	0.62-8.44
Strongly Disagree	1 (0.99)	0.62-8.44
Early diagnosis and treatment		
Strongly Agree	34 (33.66)	24.56-43.75
Agree	36 (35.64)	26.36-45.79
Neutral	19 (18.81)	11.72-27.81
Disagree	5 (4.95)	1.63-11.18
Strongly Disagree	7 (6.93)	2.83-13.76
Education		
Strongly Agree	47 (46.53)	36.55-56.73
Agree	22 (21.78)	14.18-31.10
Neutral	20 (19.80)	12.54-28.91
Disagree	10 (9.90)	4.85-17.46
Strongly Disagree	2 (1.98)	0.24-6.97
Following hygienic practices		
Strongly Agree	60 (59.41)	49.18-69.07
Agree	20 (19.80)	12.54-28.91
Neutral	11 (10.89)	5.56-18.65
Disagree	7 (6.93)	2.83-13.76
Strongly Disagree	3 (2.97)	0.62-8.44
Isolation		
Strongly Agree	28 (27.72)	19.28-37.52
Agree	36 (35.64)	26.36-45.79
Neutral	29 (28.71)	20.15-38.57
Disagree	6 (5.94)	2.21-12.48
Strongly Disagree	2 (1.98)	0.24-6.97

Table 3. (continuation).

Characteristics	Frequency (%)	95% CI
Lockdown		
Strongly Agree	30 (29.70)	21.02-39.61
Agree	27 (26.73)	18.41-36.46
Neutral	32 (31.68)	22.78-41.69
Disagree	8 (7.92)	3.48-15.01
Strongly Disagree	4 (3.96)	1.09-9.83
Proper medical service		
Strongly Agree	54 (53.47)	43.27-63.45
Agree	18 (17.82)	10.92-26.70
Neutral	19 (18.81)	11.72-27.81
Disagree	6 (5.94)	2.21-12.48
Strongly Disagree	4 (3.96)	1.09-9.83
Monitoring and Surveillance		
Strongly Agree	31 (30.69)	21.90-40.66
Agree	32 (31.68)	22.78-41.69
Neutral	28 (27.72)	19.28-37.52
Disagree	5 (4.95)	1.63-11.80
Strongly Disagree	5 (4.95)	1.63-11.18
Practice food safety		
Strongly Agree	50 (49.50)	39.40-59.64
Agree	28 (27.72)	19.28-37.52
Neutral	17 (16.83)	10.12-25.58
Disagree	5 (4.95)	1.63-11.18
Strongly Disagree	1 (0.99)	0.03-5.39
Quarantine		
Strongly Agree	52 (51.49)	41.33-61.55
Agree	30 (29.70)	21.02-39.61
Neutral	16 (15.84)	9.33-24.45
Disagree	0	0
Strongly Disagree	3 (2.97)	0.62-8.44
Use alcohol-based sanitizer		
Strongly Agree	38 (37.62)	28.18-47.82
Agree	19 (18.81)	11.72-27.81
Neutral	30 (29.70)	21.02-39.61
Disagree	7 (6.93)	2.83-13.76
Strongly Disagree	7 (6.93)	2.83-13.76
Sealing the territory		
Strongly Agree	31 (30.69)	21.90-40.66
Agree	33 (32.67)	23.67-42.72
Neutral	24 (23.76)	15.86-33.36
Disagree	7 (6.93)	2.83-13.76
Strongly Disagree	6 (5.94)	2.21-12.48
Stopping international flights		
Strongly Agree	37 (36.63)	27.27-46.81
Agree	30 (29.70)	21.02-39.61
Neutral	21 (20.79)	13.36-30.01
Disagree	8 (7.92)	3.48-15.01
Strongly Disagree	5 (4.95)	1.63-11.18
Wash your hands with soap and water		
Strongly Agree	60 (59.41)	49.18-69.07
Agree	21 (20.79)	13.36-30.01
Neutral	13 (12.87)	7.04-21.00
Disagree	4 (3.96)	1.09-9.83
Strongly Disagree	3 (2.97)	0.62-8.44

spread of COVID-19.[17] Though there is no scientific evidence that domestic animals play any role in SARS-CoV-2 transmission, the fake news circulating in social media that the disease may be transmitted by eating meat might have contributed to this misconception. This has caused huge losses in the livestock industy upon which the livelihood of tens of thousands of people depends on. This shows that government needs to convince people that eating meat of domestic animal is safe. More than half of the students believed mosquitoes can transfer COVID-19 which may be due to a recent outbreak of dengue, mosquito-borne disease, in Chitwan district.[19]

The attitude of school students toward prevention and control suggests that the majority of them had positive attitude towards the precautionary measures they need to take to protect themselves from the disease. The majority of the students strongly agreed to avoid contact with unhealthy people, boosting immunity, following hygienic

Table 4. The practice of students toward COVID-19.

Characteristics	Frequency (%)	95% CI
Precautions		
Believing God	11 (10.89)	5.56-18.65
Taking a High Level of Precautions	53 (52.48)	42.30-62.51
Taking Minimal precaution	25 (24.75)	16.70-34.33
Taking No Precaution	12 (11.88)	6.29-19.83
Acquiring meat products		
Yes	48 (47.52)	37.49-57.70
No	53 (52.48)	42.30-62.52
Avoiding normal activities during flu-like symptoms		
Yes	61 (60.40)	50.17-69.99
No	40 (39.60)	30.01-49.83
Avoiding frequent touching of mouth, eye, and nose		
Yes	74 (73.27)	63.54-81.59
No	27 (26.73)	18.41-36.46
Using a face mask		
Yes	78 (77.23)	67.82-84.98
No	23 (22.77)	15.02-32.18
Frequent hand washing		
Yes	80 (79.21)	67.82-84.98
No	21 (20.77)	15.02-32.18
Covering mouth and nose with a tissue while sneezing and coughing		
Yes	82 (81.19)	72.18-88.28
No	19 (18.18)	11.72-27.18
Disposal of tissue into the trash after its use		
Yes	71 (70.30)	60.39-78.98
No	30 (29.70)	21.02-39.61

Table 5. Concerns of students on the COVID-19 outbreak.

Characteristics	Frequency (%)	95% CI
The government should restrict travel from and to the areas of the disease		
Strongly Agree	58 (57.43)	47.19-67.21
Agree	19 (18.81)	11.72-27.81
Neutral	14 (13.86)	7.79-22.16
Disagree	4 (3.96)	1.09-9.83
Strongly Disagree	6 (5.94)	2.21-12.48
The government should isolate positive cases		
Strongly Agree	35 (34.65)	25.46-44.77
Agree	39 (38.61)	29.09-48.82
Neutral	17(16.83)	10.12-25.58
Disagree	3 (2.97)	0.62-8.44
Strongly Disagree	7 (6.93)	2.83-13.76
The government should be ready to close the educational institutions if the positive cases increases		
Strongly Agree	48 (47.52)	37.49-57.70
Agree	25 (24.75)	16.70-34.33
Neutral	18 (17.82)	10.92-26.70
Disagree	6 (5.94)	2.21-12.48
Strongly Disagree	4 (3.96)	1.09-9.83
The government should stop inviting people from areas where the disease is frequent		
Strongly Agree	47 (46.53)	36.55-56.73
Agree	27 (26.73)	18.41-36.46
Neutral	13 (12.87)	7.04-21.00
Disagree	5 (4.95)	1.63-11.18
Strongly Disagree	9 (8.91)	4.16-16.24
We should avoid leaving home		
Strongly Agree	42 (41.58)	31.86-51.82
Agree	16 (15.84)	9.33-24.45
Neutral	21 (20.79)	13.36-30.01
Disagree	7 (6.93)	2.83-13.76
Strongly Disagree	15 (14.85)	8.56-23.31

practices, use of proper medical service, quarantine, and hand wash with soap and water as the preventive measure of the disease. Consonant to our study, majority of the respondents had positive perception towards universal preventive measure of COVID-19 in the study of Singh et al., 2020.[17]

Table 6. Concerns of students on measures to be applied by a COVID-19 infected person.

Characteristics	Frequency (%)	95% CI
Clean and disinfect frequently touched objects and surfaces		
Strongly Agree	42 (41.58)	31.86-51.82
Agree	39 (38.61)	29.09-48.82
Neutral	6 (5.94)	2.21-12.48
Disagree	13 (12.87)	7.04-21.00
Strongly Disagree	1 (0.99)	0.03-5.39
Cover a cough or sneeze with a tissue		
Strongly Agree	64 (63.37)	53.19-72.73
Agree	14 (13.86)	7.78-22.16
Neutral	19 (18.81)	11.72-27.81
Disagree	2 (1.98)	0.24-6.97
Strongly Disagree	2 (1.98)	0.24-6.97
Throw the tissue in the trash after using it		
Strongly Agree	43 (42.57)	32.79-52.81
Agree	33 (32.67)	23.67-42.72
Neutral	12 (11.88)	6.29-19.83
Disagree	12 (11.88)	6.29-19.83
Strongly Disagree	1 (0.99)	0.03-5.39
Follow medical services		
Strongly Agree	66 (65.35)	55.23-74.54
Agree	13 (12.87)	7.04-21.00
Neutral	8 (7.92)	3.48-15.01
Disagree	7 (6.93)	2.83-13.76
Strongly Disagree	7 (6.93)	2.83-13.76
Make a group of sick people and travel		
Strongly Agree	11 (10.89)	5.56-18.65
Agree	15 (14.85)	8.56-23.31
Neutral	16 (15.84)	9.33-24.45
Disagree	7 (6.93)	2.83-13.76
Strongly Disagree	52 (51.49)	41.33-61.55
Stay self-isolated		
Strongly Agree	57 (56.44)	46.20-66.28
Agree	18 (17.82)	10.92-26.70
Neutral	20 (19.80)	12.54-28.91
Disagree	4 (3.96)	1.09-9.83
Strongly Disagree	2 (1.98)	0.24-6.97

The outbreak was rapidly spreading all over the world, and Nepal had only one recovered positive case when the survey was conducted. Many people were concerned about disease, they tried to acquire more knowledge about the disease through sources including social media. Online news was broadcasting about do's and don'ts of the disease. The reason for this observation might be associated with increased access of students to social media such as Facebook through smartphones.

In this study, the majority of the students claimed they were taking high precautions against COVID-19 which indicates practice level was satisfactory. The majority of them were using face masks (77.23%), a large portion of them claimed of regular hand-wash (79.21%) and were avoiding frequent touching of mouth, eye, and nose. However, it is not certain if they have been practicing it or not in real life. In a study among social media users in Jammu and Kashmir, India 87% participants reported washing hands with soap and water regularly and 73% reported wearing mask regularly.[20] In a study among medical students of Iran, 96.7% were washing hand more often, 93.8% decreased the use of public transportation, and 97.1% were avoiding coughing around people.[21] However, in a study among public of Malaysia, only 51.2% participants were wearing mask and 87.8% were practicing hand washing.[22]

Knowledge governs toward a positive attitude of the individual and their practices, but not always. Sometime fear may also play a crucial role as more than half think COVID-19 is a fatal disease, and 45.5% of students were already in fear to go in public areas. The majority of the students were highly concerned about the disease, (***Table 5***) and also most of them were aware of precautions need to be taken by an infected person (***Table 6***).

The limitations of this study are the relatively small sample size and the coverage of only one school. This was mainly due to the imposition of lockdown by the Government of Nepal on the second day of the survey, which restricted movement to survey students from other schools. As the sample size is relatively small, it may underestimate or overestimate the knowledge, attitudes, and practices among high school students.

Conclusion

This study showed that the secondary level students had basic understanding of COVID-19, had a moderately positive attitude towards preventive measures, and a good proportion of participants were adopting appropriate practices and were concerned toward the COVID-19 outbreak. There were some fundamental gaps in knowledge and attitudes among the students indicating the necessity of awareness campaigns. Furthermore, it is suggested to conduct a study in wider population including rural areas, people from different age group and education level to assess knowledge, attitude and practice toward the COVID-19 in Nepal.

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Author Contributions

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Original Article

The Negative Correlation of Spice Intake and Colorectal Cancer: A Statistical Analysis of Global Health Databases

Shinjit Mani,[1] Nathan Pramanik,[1] Deeksha Rao,[1] Stuti Sharma,[1] Timur R. Akhmetov.[2]

Abstract

Background: Colorectal Cancer (CRC) has multiple risk factors and depends highly on diet. Positive associations of red meat and processed meat intake and CRC have been proven, but no research has been conducted on the relation of spice intake and CRC risk. Various in-vitro studies have demonstrated the anticancer activity of chemicals present in spices, which is the main driving force for our statistical analysis. **Methods:** We analyzed Global Burden of Disease (GBD) database, Food and Agricultural Organization of United Nations (FAO) database, and Global Dietary Database (GDD) using Pearson correlation statistics to find any significant correlation, mainly between spice intake and CRC risk. Data from 1990 to 2013 of 100 countries was collected for the analysis. Twenty-three-year average values (±SD) were calculated for CRC risk, spice, red meat, processed meat, vegetable, and fruit intake. CRC risk is taken as dependent variable whereas all other were independent variables. All variables were analyzed using Pearson correlation analysis. Results with $p<0.05$ were further analyzed using regression analysis. **Results:** Pearson correlation showed that spice intake had a significant negative correlation ($r= -0.301$, $p=0.002$) whereas red meat ($r= 0.722$, $p<0.001$) and processed meat ($r= 0.339$, $p<0.001$) had a significant positive correlation with CRC risk. **Conclusion:** Significant negative correlation between spice intake and CRC risk indicates that higher spice intake can be preventive against cancer and possibly decrease the risk of colorectal cancer in populations with higher CRC risk.

Key Words: Spices; Colorectal Cancer; Red Meat (Source: MeSH-NLM).

Introduction

Colorectal Cancer (CRC) is the second most prevalent cancer in the world both in males and females according to the Global Burden of Disease database.[1] The highest prevalence is seen among countries in Europe, North America, and West Pacific region.[1] Such global distribution is related to the fact that CRC risk is highly dependent on dietary factors. Red meat is defined as "Meat from mammals", and processed meat is defined as "Meat preserved by smoking, curing or salting, or adding of chemical preservatives".[2] The positive relation between red meat and processed meat intake and CRC has already been proven.[3] Polycyclic aromatic hydrocarbons, heterocyclic aromatic amines, and N-nitroso compounds are carcinogens found to be present in red meat and processed meat are responsible for the malignant transformation of glandular epithelial cells, which line the colon and rectum.[4] Some studies suggested positive impact of vegetable and fruit intake to deter the risk of CRC.[5] But the studies that were done so far to explore the relation of spice intake with CRC have shown conflicting results.[6-24]

Spices are defined as "Aromatic vegetable substances, used to give special flavor to food".[6] Some studies have shown high spicy food intake is related to an increased CRC risk,[7-10] whereas other in-vitro studies explored the possibility of finding novel active biochemical substances with cancer preventive actions in spices.[11-24] It was found that polyphenols are abundant in spices.[11] Polyphenols are known to prevent carcinogenesis by inhibiting cytochrome P450, which prevents DNA damage by various mechanisms such as direct radical scavenging and modulation of phase II metabolizing enzymes, and can also induce mechanism of apoptosis in the event of DNA damage.[11,12] Gingerol (Ginger) and Thumoquinone (Black cumin/ *Nigella Sativa*) are other types of polyphenols that have chemoprotective actions, which are currently being explored by researchers. Thymoquinone is known to upregulate the miR-34a and downregulate Rac1 expression, decreases NF-kB and IKKα/β phosphorylation, and can decrease the activity of ERK1/2 and PI3K.[13] Gingerol, on the other hand, shows anti proliferative, cytotoxic, and antitumor activity by regulating various cellular mechanisms, such as Bax/Bcl2, TNF-α, Nrf2, p65/NF-κB, SAPK/JNK, caspases-3, caspase-9, and p53.[14,15] Turmeric is a spice extensively used in curries, which contains at least 25 active chemical substances, such as Curcumine and Turmerone, that have antioxidant, neuroprotective, cytotoxic, anti-inflammatory, antiangiogenic, antitumor activities.[16,17] Among all these, Curcumine is one of the most effective bioactive substance studied extensively so far. Curcumin can induce apoptosis in response to cell damage by various mechanisms such as downregulating COX-2, NF-kB, PI3K-AKT, and by upregulating DR5, Fas ligand, P53, P38.[18-20] It also inhibits metastasis by microRNA expression regulation, and an autophagy modulator by itself.[21,22] Other than that, coriander and cinnamon were also found to have anticancer activities.[23,24] Among the spices, Capsaicin is an exception, which is known to be tumerogenic. Capsaicin is widely found in paprika, pimento, chili, jalapenos. The carcinogenic properties are mediated through EGFR and TRPV1 pathway, to increase COX2 and induce inflammation.[25] Arguably, a low to moderate dose of capsaicin showed anticancer activity is some preclinical studies,[25,26] thus the results are conflicting.

[1] Medical Student. Department of General Medicine, Faculty of Foreign Students, Kazan State Medical University, Kazan, Russian Federation.
[2] MD. PhD. Associate Professor, Department of General Pathology, Kazan State Medical University, Kazan, Russian Federation

About the Author: *Shinjit Mani is currently a fifth-year medical student at Kazan State Medical University, Kazan, Russia of a total six-year program. He completed this particular research work under the supervision of Asso. Prof. T.R. Akhmetov, at the Department of Pathology of Kazan State Medical University in 2019. Currently he is working in a preclinical laboratory-based cancer research program under the supervision of Prof. Sergei Boichuk. He was chosen for the "Board of Honor 2019" by the university for his success in studies and research work.*

Correspondence:
Shinjit Mani
Address: Ulitsa Butlerova 49, Kazan, Russian Federation
Email: shinjit.mani@gmail.com

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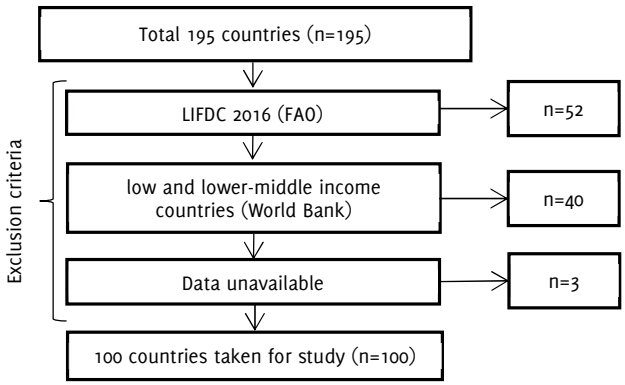
In real world data, South Asian countries with high spice intake were seen to have lesser rates of CRC.[1] For this to be true, spice intake should have some protective effect against CRC. However, no research has been conducted on the relation of spice intake and CRC on a global scale. The contrast between research data and real-world data, and the results of previous in-vitro studies were the driving force behind this statistical analysis. Thus, we collected data from three global health databases on CRC incidence per 100,000 and five possible dietary factors, which may be responsible to modify the risk of CRC, and analyzed them to gain a global perspective of the CRC risk and its relation to diet. The aim of the analysis was to determine if there was a significant correlation between the selected dietary factors and CRC risk.

Methods

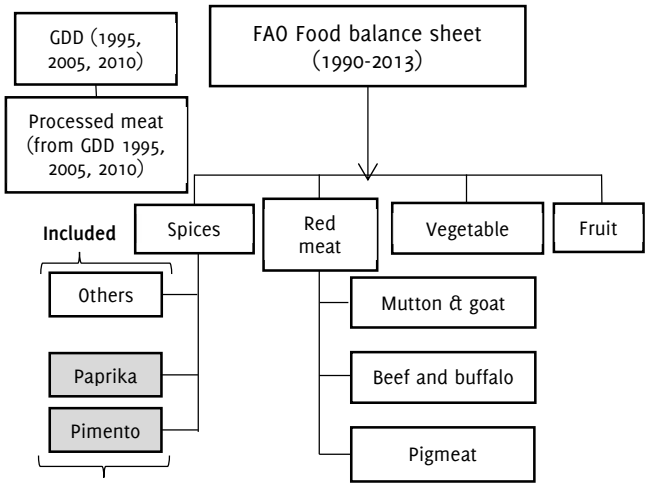
In total, three databases were considered for this analysis, the Global Burden of Disease (GBD) database for data on CRC,[1] Food and Agricultural Organization of United Nations (FAO) database,[27] and Global dietary database (GDD).[28] Out of 195 countries, data from 100 countries was used. We excluded the countries listed in Low Income Food Deficit Countries (LIFDC) by Food and Agricultural Organization of United Nations (n=52),[29] and also the low and lower-middle income countries as per World Bank Criteria (n=40).[30] Further, the countries with incomplete data were excluded (n=3). This resulted in 100 countries for statistical analysis, as shown in ***Figure 1A***. This analysis considers populations of all ages and both males and females. A total of 95 countries (mainly LIFDC, low and lower-middle income countries) were excluded from the analysis because they had extremely low intake of the dietary factors that were selected for analysis. Including such countries with very low intake of all dietary components carries the risk of a bias in the results. Thus, the above-mentioned criteria were used to exclude LIFDC and low and lower middle-income countries **(*Figure 1A*)**.

We included data from 1990 to 2013 for CRC incidence and all dietary factors except for the processed meat intake, for which data was only available for the years 1990, 2005, and 2010 from GDD. The five dietary factors which included were spice, red meat, processed meat, vegetable and fruit intake (***Figure 1B***). These dietary factors were chosen based on previous research.[31] Data for all dietary factors (except processed meat) was collected from the food balance sheet of FAO database. The unit for food intake was "kilogram per annum" as shown in ***Figure 1C***. Data on three categories of spices were available on FAO database i.e. 'Paprika', 'Pimento', 'Others'. Out of these 3 categories we took only the data from the category 'others'. Data for 'Paprika' and 'Pimento' was rejected as their carcinogenicity was proven previously with some conflicting results.[25] For red meat intake, we included data from categories 'Mutton & goat', 'Beef and buffalo', and 'Pigmeat'. For data of vegetable and fruit intake, we used the category 'Vegetables' and 'Fruits' from FAO food balance sheet. As an exception, data for processed meat was taken from the Global Dietary database, with the average data from the three years, 1990, 2005, and 2010, being used in the final calculation. All this data, except for processed meat intake, was further converted to average annual food intake using the formula as shown in ***Figure 1C***. "Average red meat/processed meat/spice/vegetable/fruit intake" corresponds to the mean value of 24 years of data. The data on CRC was collected from the Global Burden of Disease database by the unit "Rate of incidence per 100,000" and converted to "Average annual risk (%) of CRC" using the formula as shown in ***Figure 1C***. Graphical representation of the partial dataset is shown in ***Figure 2***. Primary scale was used to show the "CRC incidence per 100,000" using a bar graph with corresponding standard deviation (SD) and the secondary scale is used to show the food intake "kg/annum" using line chart with corresponding SDs. The complete dataset can be downloaded ***here***, it contains data on Average Annual Rate of CRC Incidence per 100,000 of all 100 countries, arranged in ascending order, along with the data of all other dietary factors with SD, and 95% confidence interval (CI). This data was used for final statistical analysis. In an exception to the country "Bermuda", the data on processed meat intake was supplemented by the data of "Latin America, Central Region" from GDD in place of original data, as the original data was missing when the database was accessed. The data of Average annual risk (%) of CRC is shown in ***Figure 3***, as a map, where Z score of -2 to +2 was used to identify the countries according to their CRC risk. To create the map, we used the website mapchart.net, and the template of the map with microstates. Four different color codes were used to identify the risks according to their Z-scores.

Figure 1. Methods:
1A. Inclusion-Exclusion Criteria Used for Selection of the Countries.



1B. Sets of the Data Related to Food Intake Collected from Different Global Databases.



Excluded, as **Capsaicin** could be carcinogenic

1C. Conversion of the Collected Data Into Average.

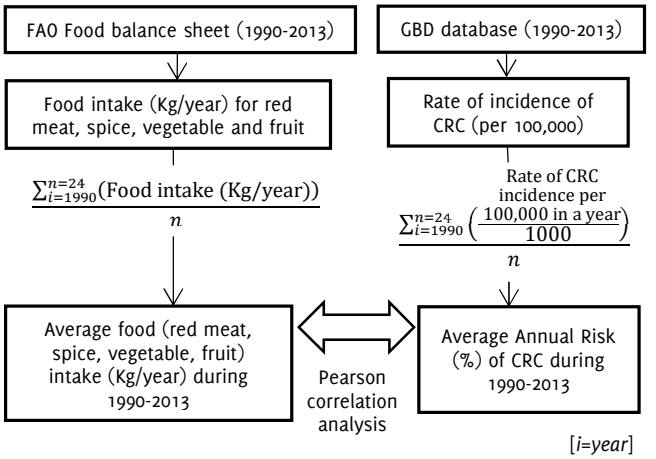


Figure 2. Data Visualisation According to The Ascending Order of Colorectal Cancer (CRC) Incidence and Food Intake Pattern. **A.** Red Meat and Processed Meat Intake (kg/annum) Plot Shows Increasing Trend of Intake Along with Increasing Cancer Risk. **B.** Graph Shows a Decreasing Trend of Spice Intake (Kg/annum) with Increasing CRC Incidence

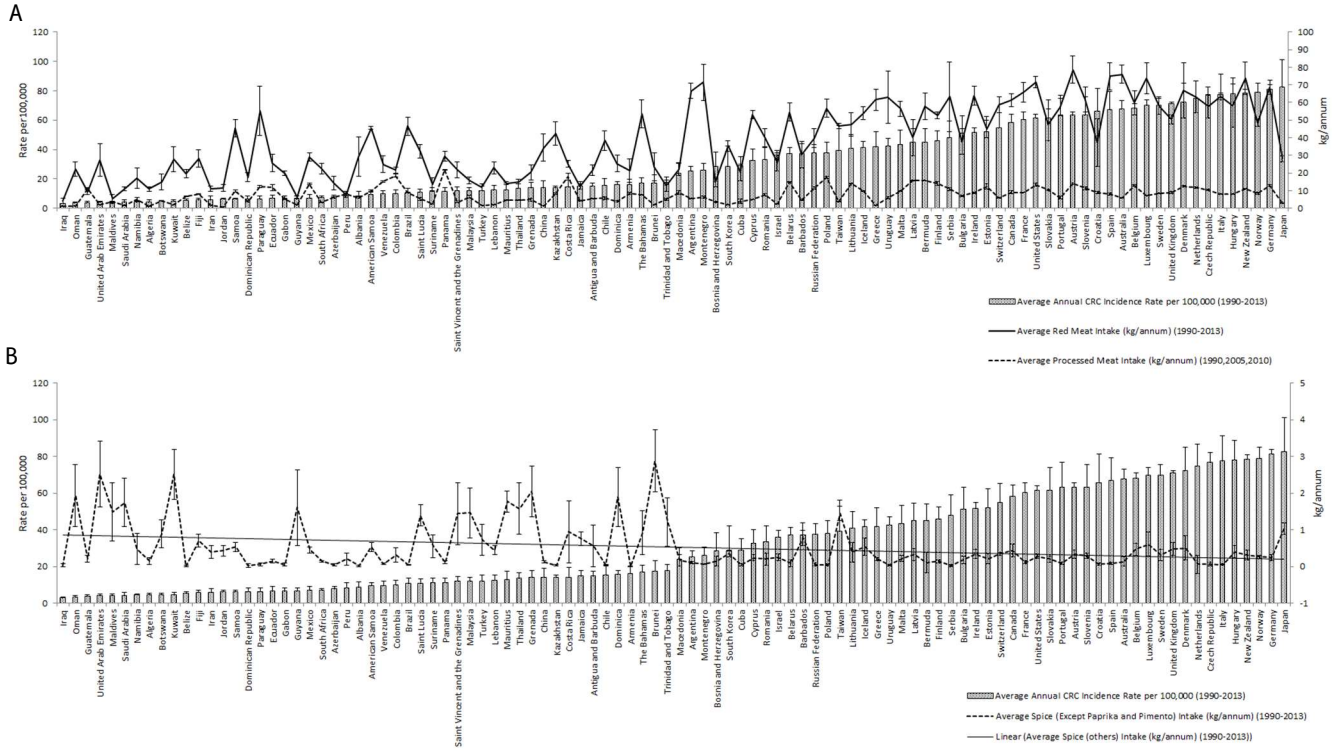
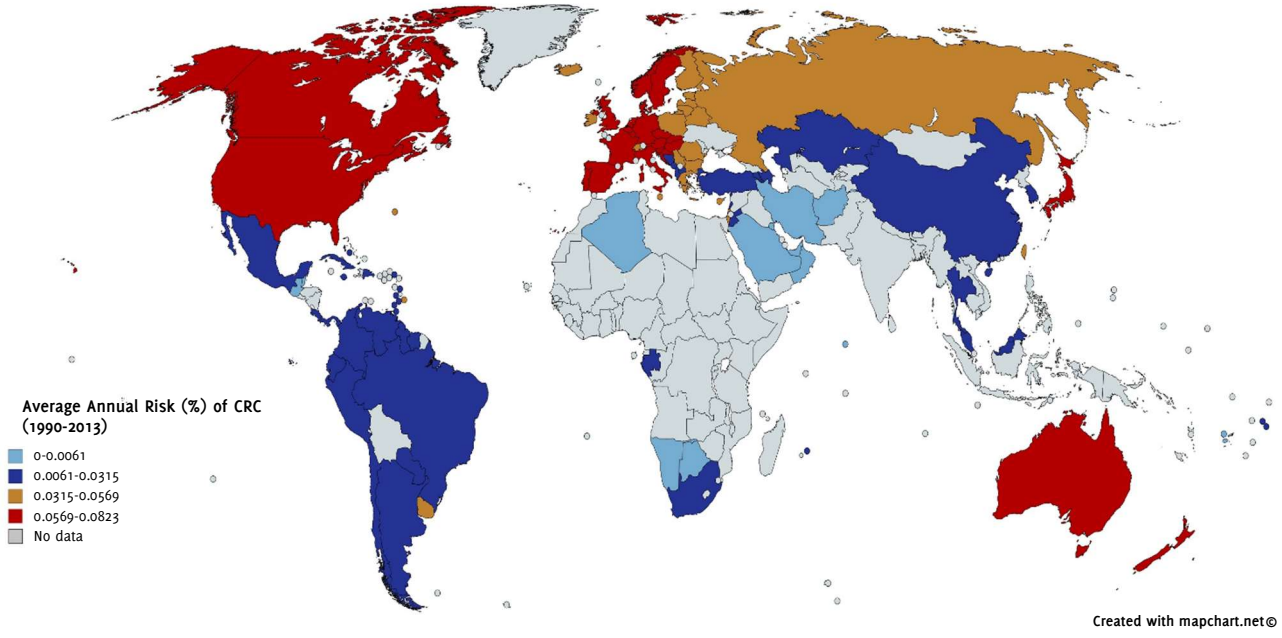


Figure 3. Average Annual Risk (%) of Colorectal Cancer (CRC) of the Selected Countries, 1990-2013.



We used IBM SPSS statistics v23 for all statistical analysis. Histograms with normal distribution curves were used to visualize the data distribution of all dietary factors. Boxplots were used to compare the data distribution among the variables. Average annual risk (%) of CRC was the dependent variable and the rest were taken as independent variables. All the variables were analysed using Pearson correlation analysis. A 95% CI of the Pearson correlation coefficient was calculated according to the formula of Fisher's transformation.[32] Scatter-dot plot was used to visualise the correlation statistics, using trend line and 95%CI of the correlation. The correlation results with $p<0.05$ were then analysed using forward and backward regression analysis for further confirmation. The data was also analysed using partial correlation analysis to determine any possible dependency between independent variables.

Table 1. Descriptive Statistics

Descriptive Statistics	Average Annual CRC Incidence Rate per 100,000 (1990-2013)	Average Red Meat Intake (kg/annum) (1990-2013)	Average Processed Meat Intake (kg/annum) (1990,2005,2010)	Average Spice (Except paprika and pimento) Intake (kg/annum) (1990-2013	Average Vegetable Intake (kg/annum) (1990-2013)	Average Fruit Intake (kg/annum) (1990-2013)
Mean	31.567	38.214	7.625	0.528	97.906	101.298
Median	20.996	36.250	7.135	0.285	89.617	95.118
Mode	N/A	45.571	7.994	0.473	11.713	166.083
Standard Deviation	25.424	20.829	4.607	0.634	55.362	48.019
Kurtosis	-1.113	-1.269	-0.066	2.739	0.437	4.994
Skewness	0.584	0.184	0.621	1.803	0.895	1.543
Range	79.505	74.545	20.854	2.870	249.170	307.264
Minimum	3.215	4.06	0.937	0.008	11.713	28.351
Maximum	82.720	78.605	21.791	2.878	260.882	335.615
Count	100	100	100	100	100	100

Results

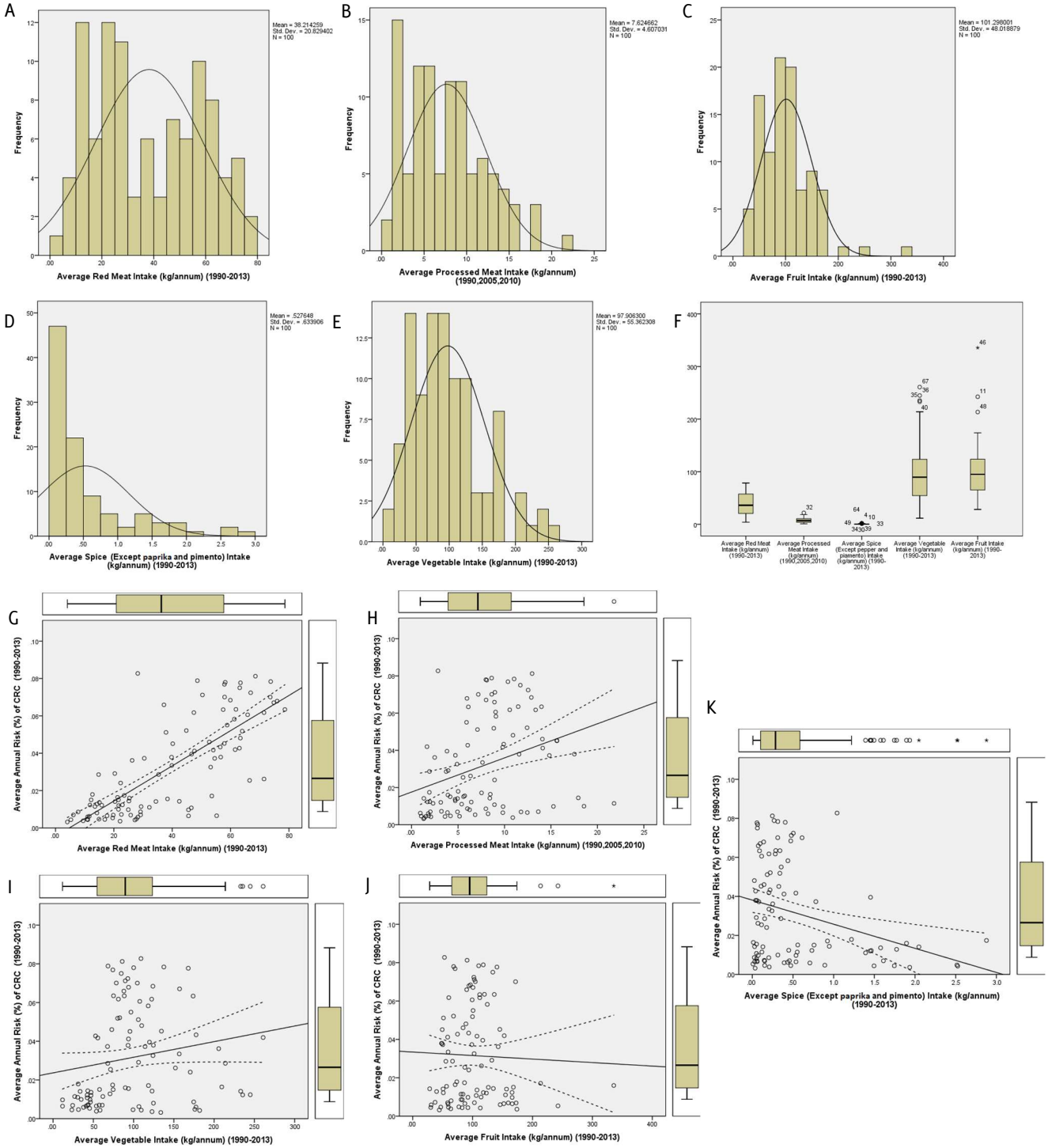
Overall, the result shows the dynamics of CRC risk and food intake along with their correlation. ***Figure 2A*** describes the data on red meat and processed meat on the background of CRC incidence rate per 100,000. There was higher red meat consumption among the countries with higher CRC incidences, such as Germany (81.24 per 100000; 60.53 kg/annum), New Zealand (78.36 per 100000; 73.73 kg/annum), Denmark (72.38 per 100000; 66.88 kg/annum) with exceptions such as Croatia (65.91 per 100000; 37.16 kg/annum), and Bulgaria (51.16 per 100000; 37.86 kg/annum). Some of the countries with low CRC incidence were found to have higher red meat intake, which is similar to the countries with high CRC risk, i.e. Paraguay (6.54 per 100000; 55.21 kg/annum), Samoa (6.46 per 100000; 44.57 kg/annum), Brazil (10.76 per 100000; 46.54 kg/annum). The reverse is also observed in the case of Japan, where the red meat and processed meat intake is relatively less (28.18 kg/annum; 2.83 kg/annum) with the highest CRC incidences (82.71 per 100000) among all the 100 countries. A positive was also observed between processed meat intake and CRC incidences. However, some countries such as Panama (11.46 per 100000; 21.79 kg/annum), Colombia (9.94 per 100000; 18.55 kg/annum), and Costa Rica (14.4 per 100000; 17.93 kg/annum) had higher processed meat intake but decreased CRC risk. Overall, the trend for both red meat and processed meat consumption is positive with increasing CRC incidence. The data plot in ***Figure 2B*** shows most of the countries with higher CRC incidences consume low spice i.e. Germany(81.24 per 100000; 0.24 kg/annum), Italy (77.70 per 100000; 0.056 kg/annum), Czech Republic (76.8 per 100000; 0.065 kg/annum), and the opposite was seen with the countries with low CRC incidences, with some exceptions, such as Iraq (3.21 per 100000; 0.034 kg/annum), Belize (5.34 per 100000; 0.007 kg/annum), Dominican Republic (6.51 per 100000; 0.029 kg/annum) and Gabon (6.90 per 100000; 0.057 kg/annum). Altogether, there is an inverse relation between spice consumption and CRC incidence. The data plot on vegetable and fruit intake is not shown, as the correlation was not significant.

The data on Average Annual Risk (%) of CRC in ***Figure 3*** clearly identified the countries of South East Asia, Middle East, North Africa and South America in a below average risk (0-0.0315%). The countries of Eastern Europe and Eurasia region have higher than average risk (0.0315-0.0569%). Most importantly, the countries of North America, Europe, and Oceania are identified with highest risk of CRC (0.0569-0.0823%). The color scheme is based on the Z-score of Average Annual Risk (%) of CRC, where blue indicates -2SD range from the mean, navy-blue indicates -1SD range from mean, brown indicates +1SD range from mean, and red indicates +2SD range from mean. The mean risk of CRC (±SD) is 0.0315 (±0.0254).

The descriptive statistics shows the mean, median, mode, standard deviation (SD), excess kurtosis, skewness, range, minimum, maximum, and count of all the variables (***Table 1***). Careful evaluation of Excess Kurtosis shows that the variables "Average Annual Risk (%) of CRC" (-1.11), "Average Red Meat Intake" (-1.26), and "Average Processed Meat intake" (-0.065) are platykurtic in nature with values less than 0. It is further explained using the histogram of the variable in ***Figure 4A***. The other three variables are leptokurtic, with an excess kurtosis value greater than 0. Among them "Average Spice Intake" and "Average Fruit Intake" has the highest excess kurtosis of 2.73 and 4.99. These same two variables are also observed to have high skewness (positive), with skewness values of 1.8 and 1.5. The data shows that the majority of the countries have a less than average spice (mean 0.527, mode 0.472) and fruit intake (mean 101.29, mode 166.08), while a minority has a very high intake. For further understanding, we plotted a histogram chart of all five dietary factors. As shown in ***Figure 4 A-E,*** the histogram shows bimodal distribution for the variable "Average Red Meat Intake", with the first one nearly at 20kg/annum and the other at 60kg/annum. This bimodal distribution is the reason of the low excess kurtosis value, as the distribution is spread widely on the tails side. Other variables had normal distributions with moderate to high positive skewness, and the mode value less than the mean values. The histogram of "Average Spice Intake" shows a very low mode value (0.472), which actually contributes to the skewness of the dataset. On the other hand, the boxplots (***Figure 4F***) provide a visual comparison between all five dietary factors. It accurately shows the range, first quartile, median, third quartile, and the outliers. The variables "Processed Meat Intake" (high 21.7, low 0.93) and "Average Spice Intake" (high 2.87, low 0.007) have relatively small range of values, thus for proper understanding, the boxplots are shown again in ***Figure 4H*** and ***Figure 4K***. It is important to understand that outliers that are shown in the graphs, are not excluded from the analysis, Despite being outside the range of (Q1-1.5*IQ) to (Q3+1.5*IQ) and are significant.

To determine the statistical significance, we used Pearson correlation analysis (***Table 2***). The results showed a significant positive correlation between CRC risk and red meat (r=+0.772, 2-tailed p<0.001, 95%CI .678 to .841) as well as processed meat (r=+0.332, 2-tailed p=0.001, 95%CI .145 to .496). A significant negative correlation was also found between CRC risk and spice intake (r=-0.301, 2-tailed p=0.002, 95%CI -.470 to -.111). Surprisingly, vegetable (r=0.176, 2-tailed p=0.080, 95%CI -.021 to .360) and fruit intake (r=-.035, 2-tailed p=0.733, 95%CI -.230 to .163) had no significant correlation with CRC. The scatter-dot plot for the visualization of the correlation analysis in ***Figure 4G-K*** shows the regression line with 95%CI which corresponds to the data given in the ***Table 2.*** Further investigation using linear regression analysis of the data showed the model fit or R^2 for red meat was highest (R^2=0.596) followed by processed meat (R^2=0.111) and spice intake (R^2=0.091). In forward and backward regression analysis (data not shown) we found that the predictive power of CRC risk is highest in "Average Red Meat Intake". The partial correlation (***Table 3***) was conducted to answer the question of interdependence of the dietary factors. As the results show,

Figure 4. Statistical Analysis of Data Sets. **A-E.** Histogram showing the normal distribution and the skewness of the data. **F.** Boxplots to compare between different dietary intake factors. **G-K.** Dot plot distribution, visualization of correlation analysis with 95%CI along with the corresponding boxplots.



"Average Red Meat Intake" had a significant positive partial correlation to CRC (0.727, p<0.001), while "Average Processed Meat Intake" (-0.035, p=0.735) and "Average Spice Intake" (-0.043, p=0.675) had no significant partial correlation.

Discussion

It is worth mentioning that the negative correlation between spice intake and CRC is a novel finding. The positive correlation of red meat and processed meat with CRC is in agreement with previous studies.[4] Different research has shown conflicting results regarding vegetable consumption and fruit consumption and their effect on CRC, where some showed a negative relation, others denied any relation at all.[31,33,34] In our research, we did not find any significant correlation. Data on spice intake shows high positive skewness with mode value much less than mean value, this confirms that the majority of the countries have less than average spice intake. Model fit (R^2) plays a major role in the

forward and backward regression, which explains the decreased predictive power by "Average Processed Meat Intake" and "Average Spice Intake". As per the data on partial correlation, red meat intake is found to be the major cause of CRC irrespective of the processed meat and spice intake, while processed meat intake has no significant influence on CRC by itself. And most importantly, spice intake does not influence CRC risk alone, the significant negative correlation is seen when red meat intake is considered. In conclusion, our results indicate that spice intake can have a beneficial effect among the population with high red meat intake, which may decrease the risk of CRC in the long term, but vegetable and fruit intake may not have any additional benefit to deter CRC risk. This new finding in this analysis agrees with the preclinical studies that demonstrated the anticancer properties of various spices.[5-19]

It is important to mention the limitations of this analysis. In the FAO database, there was no mention of any particular spices in the category 'others', which compromises the accuracy of the results to some extent. The other two categories 'Paprika' and 'Pimento' were not taken into the analysis. Previous studies suggested that high amounts of spicy food that are rich in chilies may cause chronic inflammation in gastrointestinal tract and in long term can trigger cancer, with some conflicting results claiming capsaicin in low doses can have anti-cancer activities.[25,26] Due to these conflicting results we did not consider

'Paprika' and 'Pimento' for the analysis. Recent data for every country as not available. Data of food intake later than the year 2013 was not available in FAO database, thus we took the data from 1990 to 2013 for our analysis. The GDD had the data only for the year 1995, 2005, 2010. These three years of data was used in calculation of processed meat intake, which may have limited the accuracy of the analysis. With more accurate data and a larger sample size the model fit of the data can be improved and enhance accuracy.

The risk of cancer can vary from population to population, depending on multiple factors from behavioral to biological. For instance, this is seen in Japan where despite high spice intake and low red meat intake, there is higher CRC risk, possibly due to their genetic predisposition for gastrointestinal cancer. This contrasts with Europe and North America, where high CRC risk is largely due to unhealthy dietary pattern containing high red meat.[35]

Thus, studies conducted within a particular population may not provide an exact picture of a disease or treatment. Therefore, an analysis using global databases is important. In recent years, global health has become an important topic of discussion. It is important to view disease as a global issue which needs a large-scale solution. It is not enough to improve individual health to create a sustainable future with a healthy population. To do so requires addressing the social, behavioral and dietary changes which can be implemented on a large scale within the population. The novel finding in this analysis is the negative correlation of spice intake and CRC risk. The most important question that arises from this data is: what is the adequate amount of spice intake that can help decrease the CRC risk? To answer this question, further research needs to be conducted, using different population groups with variable risks. Our results show that a simple addition of spice in the diet may be beneficial to the population where red meat intake is high, and provides an incentive to further explore the cancer preventive mechanism of the spices, and their use in the field of global health and cancer prevention.

Table 2. Results of Pearson Correlation Analysis.

	Average Risk (%) of CRC during the year 1990-2013 (n=100)			
	Pearson Correlation Statistics 'R' (P value - 2 tailed)	95% CI of correlation coefficient*	Regression analysis R square	Regression analysis Unstandardized coeff. (constant, B)
Average Spice Intake (kg/annum) (1990-2013)	-0.301 (0.002)	-0.470 to -0.111	0.091	(0.038, -0.012)
Average Red Meat Intake (kg/annum) (1990-2013)	0.772 (<0.001)	0.678 to 0.841	0.596	(-0.004, 0.001)
Average Processed Meat Intake (kg/annum) (1990, 2005, 2010)	0.332 (0.001)	0.145 to 0.496	0.111	(0.018, 1 0.002)
Average Vegetable Intake (kg/annum) (1990-2013)	0.176 (0.080)	-0.021 to 0.360	–	–
Average Fruit Intake (kg/annum) (1990-2013)	-0.035 (0.733)	-0.23 to 0.163	–	–

Table 3. Results of Partial Correlation Analysis.

	Average Risk (%) of CRC during the year 1990-2013 (n=100)	
	Partial Correlation	P value
Average Red Meat Intake (kg/annum) (1990-2013)	0.727	<0.001
(Controlling for spice and processed meat)	-0.035	0.735
Average Processed Meat Intake (kg/annum) (1990, 2005, 2010)	-0.043	0.675

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Original Article

From Student to Teacher: Medical Student Perceptions of Teaching Children and a Novel Application of the One Minute Preceptor

Laura Cline,[1] Muna Canales.[2]

Abstract

Background: As students progress through medical school, the student assumes teaching roles, but without formal training regarding how to teach. **Methods:** We administered surveys to 1st, 2nd and 4th year medical students asking about perceptions of teaching. The surveys were completed in the Fall (2019) and again in late Spring (2020). In the interim, students were given the opportunity to teach 5th graders during an outreach program. We gave the medical student volunteers a brief interactive session about the One Minute Preceptor (OMP) as a tool to teach the children. In the Spring survey, medical students who used the OMP were also asked about its utility in the pediatric setting. **Results:** Seventy-four students completed survey 1 and, of these, 51 completed the follow-up survey. Mean age was 24-27; 57% were female. Across both surveys, .70% were comfortable with and felt they understood their role as a teacher of trainees, peers, and patients. However, <50% felt they knew any teaching method or had a plan for improving teaching skills. All felt that teaching was an important medical skill. Six students completed OMP training and the outreach program. All felt the OMP was useful to teach key points, provide feedback, and involve the learner. They also all felt the OMP should be taught in medical school. **Conclusion:** Medical students believe it is important to learn teaching skills. The OMP may be a useful addition to the medical school curriculum to help medical students teach in doctor-patient settings across ages and group sizes.

Key Words: One Minute Preceptor; Teaching; Medical students; Curriculum (Source: MeSH-NLM).

Introduction

The average medical student spends over twenty years acquiring as much knowledge and skills as humanly possible. During medical training, the student's role completely shifts as they enter the clinical years and progress to residency. The student *becomes* the teacher. Through both positive and negative educational experiences, the student begins to form an idea of what makes a good teacher, though the student never *formally* learned how to become a teacher. One might argue that learning this skill is not necessary until residency begins, hence the plethora of resident as teacher programs throughout the USA as mandated by the Accreditation Council for Graduate Medical Education. The counter argument, however, is that during medical school, students are *informally* learning important history, physical, documentation, social, and emotional skills to be effective residents, so why not formally train them as teachers during medical school as well? Opportunities for teaching peers, younger classmates, other healthcare professionals, and patients are ubiquitous throughout medical school. Thus, the training of physicians as teachers could begin in medical school. Currently, however, it is unclear how medical students feel about the importance of having formal teaching training added to their curriculum. More importantly, the ideal framework to deliver efficient, effective training in clinical teaching is unclear.

One well known teaching model utilized to guide faculty and resident teachers is the One Minute Preceptor (OMP). This is a five-step method originally developed in 1992 with the primarily goal of improving effectiveness and efficiency in clinical teaching. The OMP is quick to learn and easily remembered as the following five steps: 1) get a commitment from the learner, 2) probe for supporting evidence, 3) teach general rules, 4) reinforce what's done well, 5) correct mistakes.[1] While there are many other teaching models in the medical education realm, the OMP was chosen in this study because it can be utilized in under five minutes and due to its wide use throughout the USA. This model has been extensively studied in various countries in a variety of specialties from family medicine to pediatrics, emergency medicine, internal medicine, psychiatry, and gynecology.[2] Results from residents and attending surveys of perceptions and use of the OMP show that it is felt to be useful for a) teaching efficiently and in a student-focused manner, b) focusing on specific and limited take home points, c) improving the teacher's ability to rate students' competencies, and d) increasing the teacher's teaching skills and confidence.[1,3-6] Furthermore, the OMP can be effectively applied to physician teachers at any level, given that the model is flexible to adaptation based on abilities of both teacher and student.[7] Once taught, the OMP is repeatedly used in teaching interactions and has been formally incorporated into several residency training curricula as part of the resident as teacher series.[1,3-6] From a learner perspective, medical students being taught by physicians using the OMP method prefer it over traditional clinical interactions, citing it as more interactive, intellectually inspiring, and effective.[8] However, to date there is no literature on *medical students* utilizing the OMP to *teach others*. Furthermore, studies have not explored the effectiveness of using the

[1] MD. Department of Medical Education, University of Florida College of Medicine, Gainesville, United States.
[2] MD, MSc. Department of Medicine, University of Florida College of Medicine; Geriatric Research Education and Clinical Center, Medical Service, Malcom Randall VA Medical Center, Gainesville, FL, United States.

About the Author: *Laura Cline received her M.D. degree in May 2020 from the University of Florida. She graduated with an Award of Distinction in the Medical Education Track after completing the capstone project described in this publication. She was also a member of Alpha Omega Alpha, Gold Humanism, and the 2020 recipient of the Judy Duff Memorial Award. She began residency training in pediatrics at the Medical College of Wisconsin.*

Correspondence:
Laura Cline
Address: 1600 SW Archer Rd, Gainesville, FL 32610, United States
Email: lauracline55@gmail.com

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OMP with groups of learners instead of one on one, as is commonly encountered during clinical settings, or with children as the learners.

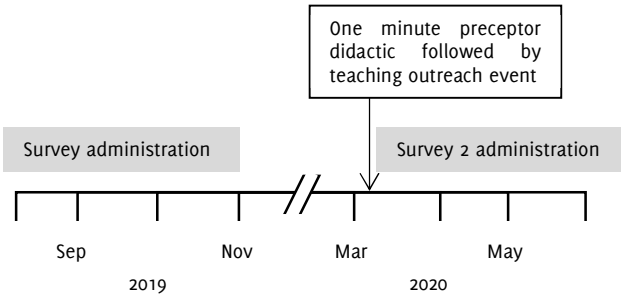
Therefore, given the need for expanding medical student education to include how to be an effective teacher, the strong support for the OMP's use in clinical teaching, and the notion that the model can be adapted to any level based on teacher and student abilities, we aim to teach medical students about the OMP and assess their perceptions on its use in teaching children and teaching in group settings. We will also determine medical students' background perspectives on teaching, including comfort level with teaching, motivating factors for participating in an outreach program to teach children, and their perceived importance of formal training to teach in their curriculum.

Methods

Overview

We performed a descriptive pre and post-intervention survey study of medical students to understand perspectives on teaching, drivers of motivation to teach and opinions regarding the effectiveness of the OMP as a teaching tool for them ***Figure 1***. This study was conducted over the 2019-2020 academic year at the University of Florida Medical School. The University of Florida Institutional Review Board approved this study under number 201902111 and participants provided written performed consent before enrolling in this study.

Figure 1. Flow of Study Events



Study Population

All members of the University of Florida College of Medicine Classes of 2020, 2022, and 2023 were given the option to participate in this before and after survey study. The class of 2021 was excluded due to their busy schedule and clinical obligations during their third-year clerkship experiences. There were 74 total participants, aging from 21-32, with students in all years of medical school (1,2,3 and 4).

Recruitment and Enrollment

We gave a short, in-person description of the project to medical students in the class of 2022 and 2023 at the beginning of one of their lectures in the Fall of 2019 *Figure 1*. The purpose, duration, risks, benefits, alternatives and security of data was discussed with the students and any questions were answered. We then told them to expect an email later in the day with a link to the electronic informed consent form. The same process was repeated, but completely in electronic form, for the class of 2020 due to their 4th year schedules being very spatially spread out. The students then were able to read about the study again as well as the consent form and, if they chose, electronically consent using Research Electronic Data Capture (Redcap). Following the consent process, students were immediately directed to Survey 1.

Intervention

The experimental group consisted of subjects who self-selected to participate in an annual outreach program. In this program, University of Florida medical students spend 3-4 hours teaching local 5th grade students at one school about the cardiovascular system during the Spring semester. The intervention was as follows: students were given the option to attend a brief (5-10 minute) pre-program presentation in which they could learn about and practice the OMP. The format of this presentation was designed based on literature that suggests a combination of video examples, didactic lecturing, active role playing, and discussion is helpful in teaching the OMP method to others. [3,11] The presentation began by emailing out two optional clinical teaching videos from YouTube—one reflecting a traditional approach and one reflecting the OMP approach. [12,13] Using the OMP method, the authors gave email prompts for the group of students to identify the differences between the two videos. For in-person instruction, on the morning of the teaching event, the medical students received a 5-minute didactic PowerPoint presentation on the OMP followed by brief review of an example of using the OMP in a clinical setting. [11, 14] Then, students participated in four active role-playing scenarios and scripts, of increasing difficulty, using relevant 5th grade cardiovascular examples to practice using the OMP. The medical students were then encouraged to use the OMP when teaching the cardiovascular lesson to the 5th grade students that day.

Measurements

Survey 1

Using REDCap's online survey platform, we asked medical students to rate their perceptions and comfort levels in teaching on a 5-point Likert scale (Survey 1) as in similar prior studies. [9,10] Survey 1 also gathered demographic information to help understand subject baseline characteristics that could influence their perceptions of teaching and desires to teach children. This survey was given immediately following recruitment and enrollment, at the beginning of the academic year *Figure 1*.

Survey 2

A few days after the intervention, a follow up survey (Survey 2) was administered to all of the subjects, both those who participated in the intervention (experimental group) and those who did not but completed Survey 1 (controls) *Figure 1*. This survey repeated the same questions on the self-assessment of teaching comfort and views to see if those naturally changed over time or improved with the OMP intervention. Further, for the experimental group, we asked about the effectiveness of the OMP preprogram PowerPoint, the use of teaching the OMP to all medical students, their ability to use OMP in group teaching, and the overall effectiveness for teaching students with the OMP using a Likert scale and questions from previous studies of OMP effectiveness. [4]

Analytic approach

Because only 6 students participated in the intervention, we proceeded with a descriptive approach. First, we summarized Survey 1 responses from overall respondents, regardless of completion of Survey 2 using counts and proportions for categories of demographics. We collapsed categories of Likert Scale responses into proportion responding agree/strongly agree vs neutral/disagree/strongly disagree due to skewed distribution of responses and for ease of presentation. We then created a table of similar data for those who only completed Survey 1 and those who completed both surveys to visually inspect for any large differences. Finally, we display changes in Survey 1 and Survey 2 responses between those who completed both surveys but did not participate in the intervention (controls) and those who did participate in the intervention (experimental).

Table 1. Survey 1 Demographic Data

	All participants completing Survey 1 (n=74)	Comparison Group: Completed Survey 1 and 2, did not participate in OMP and Outreach (n=45)	Experimental Group: Completed Survey 1 and 2, participated in OMP and Outreach (n=6)
Age (years)			
18-23	21 (28%)	13 (29%)	0 (0%)
24-27	40 (54%)	28 (62%)	3 (50%)
28-31	11 (15%)	3 (7%)	2 (33%)
32+	2 (3%)	1 (2%)	1 (17%)
Gender, n (%)			
Male	32 (43%)	16 (36%)	4 (67%)
Female	42 (57%)	29 (64%)	2 (33%)
Year in Medical School, n (%)			
MS 1	12 (16%)	8 (18%)	1 (17%)
MS 2	33 (45%)	18 (40%)	2 (33%)
MS 3	2 (3%)	0 (0%)	0 (0%)
MS 4	27 (36%)	19 (42%)	3 (50%)
Degree* (n)			
STEM	50	30	5
Arts/Humanities	6	3	1
Health Sciences	9	6	1
Social Sciences	18	12	1
Business	0	1	0
Has Children, n (%)	3 (4%)	0 (0%)	1 (17%)
Worked as Teacher, n (%)	10 (13%)	8 (18%)	0 (0%)
Worked in clinical setting with pediatric patients, n (%)	32 (43%)	20 (44%)	5 (83%)
Knows about OMP, n (%)	3 (4%)	2 (4%)	0 (0%)
Predicted Specialty, n (%)			
Pediatrics	11 (15%)	9 (20%)	1 (17%)
Family Medicine	4 (5%)	3 (7%)	1 (17%)
Other	59 (80%)	33 (73%)	4 (66%)

Legend: *MS=medical student; STEM=Science Technology Engineering and Math; OMP=One Minute Preceptor; *May add up to more than 74 due to option to choose multiple degree per participant.*

Results

Demographics

Seventy-four medical students consented and participated in the Survey 1, of which 69% (n=51) completed the follow up, Survey 2 ***Table 1***. Six of those 51 who completed both surveys self-selected to participate in the teaching outreach day where they learned about and used the OMP (experimental group). The remaining 45 participants are noted as the control group. The demographics, shown in ***Table 1***, illustrate the participants' amount of potential baseline exposure to teaching and working with children in past or future. Additionally, ***Table 1*** illustrates some demographic differences between the experimental and control group, most notably in the distributions of age, gender, and prior history professionally working with pediatric patients, which may influence the results presented later.

Perspectives on Teaching

Table 2 displays responses to Survey 1 questions about perspectives on teaching among all participants, and Survey 1 and 2 responses by experimental versus comparator group. Overall, there were no substantial differences in baseline (Survey 1) perspectives on teaching between the group that took only Survey 1 compared to those that completed both surveys (less than 15% in all categories). At baseline,

Table 2. Perspectives on Teaching at Baseline and Follow-Up

Statement, n (%)	All participants completing Survey 1 (n=74)	Comparison Group: Completed Survey 1 and 2, did not participate in OMP and Outreach (n=45)		Experimental Group: Completed Survey 1 and 2, participated in OMP and Outreach (n=6)	
		Survey 1	Survey 2	Survey 1	Survey 2
I understand my role in teaching younger/future medical students	62 (84%)	37 (82%)	39 (87%)	6 (100%)	6 (100%)
I understand my role in teaching my peers	53 (72%)	30 (67%)	38 (84%)	5 (83%)	5 (83%)
I understand my role in teaching patients	73 (99%)	44 (98%)	44 (98%)	6 (100%)	6 (100%)
I can apply at least 2 different teaching methods	34 (46%)	19 (42%)	39 (64%)	2 (33%)	4 (67%)
I can describe and evaluate the teaching methods I use	18 (24%)	9 (20%)	18 (40%)	2 (33%)	3 (50%)
I have a plan for improving my teaching skills	16 (22%)	9 (20%)	14 (31%)	1 (17%)	3 (50%)
I can help others become better teachers	28 (38%)	13 (29%)	14 (31%)	4 (67%)	6 (100%)
I am comfortable teaching younger/future medical students	58 (78%)	35 (78%)	36 (80%)	6 (100%)	6 (100%)
I am comfortable teaching my peers	51 (69%)	29 (64%)	35 (78%)	4 (67%)	5 (83%)
I am comfortable teaching patients	59 (80%)	35 (78%)	39 (87%)	6 (100%)	6 (100%)
I am comfortable teaching children	58 (78%)	34 (76%)	36 (80%)	6 (100%)	6 (100%)
People I teach would describe my skills as good	42 (57%)	25 (55%)	22 (49%)	5 (83%)	4 (67%)
Teaching is an important medical skill	74 (100%)	45 (100%)	45 (100%)	6 (100%)	6 (100%)
Developing teaching skills is important to professional development.	74 (100%)	45 (100%)	44 (98%)	6 (100%)	6 (100%)

›80% of participants felt comfortable with and understood their role in teaching future medical students, patients and peers though fewer felt confident about their role relative to teaching peers (72%). Less than half of participants felt they could apply at least 2 different teaching methods (46%, n=34) or help others become better teachers (38%, n=28), and even fewer (24%, n=18) felt they could describe and evaluate the methods they use or plan for improving their skills. Only 57% (n=42) of students felt that their teaching skills would be described as good. All students highly valued and believed that teaching is an important skill and is important for professional development.

When comparing experimental and control groups, at baseline more students in the experimental group felt they understood their role in teaching younger students (100% vs 82%) and peers (83% vs 67%). The experimental group also more frequently felt they could help others improve their teaching skills (67% vs 29%), were comfortable teaching younger students (100% vs 78%), patients (100% vs 78%) and children (100% vs 76%) and perceived their teaching skills as being good (83% vs 55%).

We found that, in general, over the course of an academic year medical student confidence in teaching increased ***Table 2***. More students in both the experimental and comparator groups had knowledge of and were able to apply multiple different teaching methods (increased 34% and 22% respectively), had plans for improving their own teaching strategies (increases 33% and 11% respectively), and were comfortable teaching peers (increased 16% and 14% respectively). More students in the comparator group increased their understanding of their role in teaching peers by the end of the year (67% to 84%), achieving a similar percent as the experimental group's baseline (83%). More students who learned about the OMP (the experimental group) felt comfortable helping others become better teachers by the end of the year (increased by 33%) compared to the control group whose perception on the same topic did not change. After the course of a year, fewer students in both the control and experimental group rated their self-perceived teaching skills as good (decreased by 6% and 16% respectively). Additionally, compared to their own perceptions at the beginning of the year, the students who learned the OMP (experimental group) had an increase in their ability and desire to help others become better teachers (67% to 100%). When the control group was asked this same question, their confidence in and desire to become better teachers were lower at baseline and did not change over the course of this year (29% to 31%).

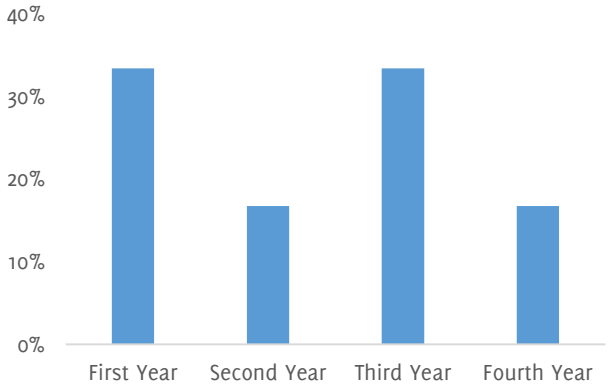
Perspectives on OMP

To understand if the experimental group liked or disliked the OMP, the group rated their level of agreement with a series of statements, resulting in ***Table 3***. 100% (n=6) found it was a useful method for teaching elementary school students, an effective and efficient teaching tool, and were overall satisfied with the teaching tool. When asked why it was effective, 100% (n=6) noted it was quick to use, 67% (n=4) noted its structure was helpful, and 50% (n=3) noted it being learner focused. Due to the nature of teaching 5th graders, the medical students had the opportunity to use the OMP in both individual and group settings. 67% (n=4) of the students said it was an effective tool in groups but when asked if it was easier to be used in groups or with individual students, 67% (n=6) said it is easier with individuals while the others said it worked equally well. Also, 83% (n=5) felt that initiating "ascertainment of commitment" from the learner was challenging to do in this setting. Nevertheless, 100% of the students said they will use the OMP when working with future children patients, future adult patients, and future students. All students in the experimental group stated that the OMP should be taught to medical students, saying it "is an easy, helpful way to explore a learner's thought patterns and guide them to a more beneficial pattern"; "provides a method for engaging a small audience"; and "if nothing else, it helps to orient towards a mindset that facilitates insight into teaching methods." ***Figure 2*** shows the results of when in the medical school curriculum students think they should learn the OMP.

Table 3. Usefulness of the OMP among those who completed the program (n=6)

Statement, n (%)	Very good /excellent, n (%)
Ability to ascertain commitment to learning from your student	1 (17%)
Ability to assess underlying reasoning of your learner	4 (67%)
Ability to assess fund of knowledge of your learner	4 (67%)
Ability to teach a few key points for students' future use	6 (100%)
Ability to provide positive feedback to the student to reinforce what was done well	6 (100%)
Ability to provide constructive feedback to the student	4 (67%)
Ability to involve student (s)	6 (100%)
Overall efficiency as a teaching tool	6 (100%)
Overall effectiveness as a teaching tool	6 (100%)
Overall satisfaction with OMP as a teaching tool	6 (100%)

Figure 2. Timing of OMP: Which year to Teach Medical Students the OMP



Discussion

We found that medical students place high value on their role as teachers in medicine, and subsequently desire to develop their teaching skills throughout their professional careers. However, they lack an armamentarium of teaching tools and do not have a plan for or understanding of how they will learn to teach. When we introduced a small group of medical students to the OMP, they found it to be a useful teaching strategy. They felt it was an effective method for teaching the pediatric population, suggesting a potential application of the OMP beyond traditional settings (older physician to younger physician/student). Finally, they thought the OMP should be taught to all medical students.

While medical students might not directly state their love of teaching as their motivation for pursuing medicine, teaching is intimately tied to the most cited rationale- the desire to help people. [16] These students have been in school long enough and likely understand the value of a good teacher and therefore aim to emulate those positive characteristics they have seen. Because of the busy nature of medicine, some knowledge is gathered from on-the-go teaching from residents or faculty; in fact, surveys have shown that the majority of medical students attribute about one third of what they have learned to resident teachers. [17] This cycle of acquiring knowledge from more

senior trainees and faculty inspires students to value their own role as teachers; indeed, studies show over 80% of medical students desire to teach students in their career. [17] Students in our study had similar values, with all students surveyed placing high value on the role of teaching in medicine and developing teaching skills throughout their professional careers. However, though there is a desire to learn how to teach as well as ample opportunity to practice teaching, instruction in formal teaching methods is not required as part of the medical school curriculum. Since the 1990s, there has been an increasing number of medical teaching electives offered, but none are mandatory. [17] While many may want to participate in such electives they may not do so due to pressure to take advanced electives in their specialty in order to compete for USA residency positions.

Despite the novel application of the OMP in our study, the medical students' impression of OMP was similar to that from existing literature on physician perspective on OMP utility in clinical teaching. Students found the OMP to be an effective, efficient, learner-centered teaching strategy for teaching children and teaching in groups. The OMP increased their ability to determine the student's fund of knowledge, provide feedback, and teach focused learning points. Not only did all of them think the method was applicable to teaching elementary aged students, they all planned to use it in future encounters teaching children. The alignment of our findings on with that of the literature, albeit a different application of the OMP, strengthens the validity of our results. Concordance with the literature also suggests that OMP may be practically used by medical students on alternative groups of learners during their medical school training. [7] Despite the non-clinical setting of this study, we believe we simulated the doctor-patient conversation by having medical students teach 5th graders about the cardiovascular system. While it is not an exact simulation of all teaching-based conversations during a patient encounter, it does mimic a common conversation when a physician explains physiology and mechanism of disease to a patient who does not understand complicated science. As such, the OMP has the potential to be utilized in settings beyond the traditional inter-professional "physician to student-learner" model. Indeed, it can be utilized in physician-patient teaching conversations to help patients, both pediatric and adult, better understand relevant complex health topics. More studies need to be done in order to further investigate this expanded use of the OMP.

The medical students who used the OMP unanimously stated it would be beneficial for all students to learn about the OMP at some point in the curriculum. Though the best time to teach the OMP is unclear, our study suggests a clear area of and desire for an addition to graduate medical education. Additionally, while we cannot make conclusions given the small sample size in the experimental groups, this study suggests that teaching medical students about the OMP may be correlated with an increased desire of the students to help *others* become better teachers. Generating a culture of medical students who are empowered to boost others' teaching skills may be a powerful added benefit to instructing medical students on teaching methods.

While our study provides fertile ground for future research, it has several important limitations. First, our experimental group sample size was small, limiting our findings to a descriptive nature. Similarly, the students in the experimental group were 100% comfortable teaching those younger than them at baseline, generating selection bias in this group. Also, this is a single center study, limiting external validity to other medical schools. In addition, the complexity of the intervention design as a blend of many new OMP contexts (medical students as teachers, children as students, group setting, simulating doctor-patient conversation) precludes commenting specifically on any one of these contexts. Ultimately, further studies are needed to boost the power and generalizability of these trends as well as gather more focused information on each use of the OMP. In addition, future studies should examine perspectives of the *learners* in these novel OMP application settings. In a study like ours, one could survey the 5th graders at the elementary school to see if they like the method and see if they retain more when learning from students who used the OMP model versus the traditional model. Nevertheless, our work paves the way for limitless opportunities to study an expanded role for the OMP as a teaching tool in medicine. For reference, the University of Florida College of Medicine is 48.7% male/ 51.3% female for the classes that participated in this study, showing an initially representative gender population self-selected to participate.

Conclusion

To summarize, the OMP is a method that is well-known and well-studied for aiding busy physicians in their "on-the-go" medical education efforts, but it has the potential to be much more than that for both faculty and medical students. Medical students value their role as a teacher in medicine and desire to learn teaching skills in their curriculum. The OMP or something similar, could be added into medical curricula to arm students as teacher, and to ignite a culture of more empowered physician teachers.

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Author Contributions

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Original Article

Internet Addiction and Its Relationship with Depression and Academic Performance: A Cross-Sectional Study at a Medical School in Pakistan

Farrukh Ansar,[1] Waqar Ali,[2] Adil Zareef,[3] Noman Masud,[1] Sawar Zahab,[1] Huma Iftekhar.[1]

Abstract

Background: Excessive Internet use may induce depression, influence relationships, and decrease academic performance. There is scarce information about Internet addiction in Pakistan. This study aimed to determine prevalence of Internet addiction and its relationship with depression and academic performance. **Methods:** A study based on a self-administered survey was carried out at a medical school in Peshawar, Pakistan. Participants were medical students (MBBS) and a non-randomized convenience sampling technique was utilized for data collection. We collected demographic information, last professional exam score, Internet addiction, and depression scores using the Young's Internet Addiction Test (YIAT) and the Beck's Depression Inventory (BDI), respectively. The analysis included binomial 95% confidence intervals (95% CI) estimations and linear and logistic regressions to assess variables relations. **Results:** We analyzed responses from 231 participants (380 students approached and 250 responded: response rate=65.79%, 19 excluded), 64.07% were male and the age average was 21±2 years. Profound and slight addiction to the Internet was found in 9.09% (95%CI=5.71-13.56) and 41.99% (95%CI=35.55-48.64) of students, respectively. Frequency of depression (mild-severe) was 59.74% (95%CI=53.11-66.12). Levels of Internet addiction and depression were found associated after adjusting by sex and age (β=0.27, R2=0.03, p-value=0.009). Internet addiction (OR=0.54, 95%CI=0.2-1.49, p-value=0.23) and depression (OR=0.62, 95%CI=0.36-1.09, p-value=0.10) were not significantly associated with low grades after adjusting by sex and age. **Conclusion:** More than half of the students are having excessive Internet usage which could result in despondency and academic performance deterioration. Internet addiction should be considered an emerging challenge and appropriate mitigation measures should be taken opportunely.

Key Words: Internet addiction disorder; Depression; Academic Performance; Medical Schools; Public health (Source: MeSH-NLM).

Introduction

Internet Addiction is described as unnecessary or inadequately controlled distractions, desires or practices regarding excessive Internet utilization and web access that lead to devitalizing or stressful behaviour.[1] The condition has attracted increasing attention in the popular media and among researchers. The problem is arising as a result of increased access to personal computers and Internet services.[2]

The problem of Internet dependence prevails around the world, but mostly in nations where Internet access and innovation are easily accessible.[3] Onset is reported to occur usually in the second and third decade of life.[4] Internet Addiction Disorder disturbs and affects the daily life of individuals by causing neurological problems, psychosomatic perturbation, and difficulty in social interactions.[5] Studies carried out in European and American regions have shown inclined pervasiveness rates especially among youngsters aged 18 to 25 years.[6] The possibility that risky use of Internet-based gadgets meets criteria for dependence, and hence ought to be included in the Diagnostic and Statistical Manual of Mental Disorders (DSM), was first proposed in 1996.[7] In 2013, Internet addiction was integrated in the latest version of DSM-5 under the name of Internet gaming disorder by the American Psychiatric Association.[8] After integration of Internet addiction in DSM-5, many researchers came forward and progress was made to understand and address this issue and currently, it is widely known as Internet Addiction Disorder.[3,9]

In this manner an assortment of frequently used criteria have been proposed and contemplated, some of which have been recognized and practiced. However, observational studies gave a conflicting set of criteria to characterize Internet Addiction Disorder.[10] Presently, many reliable and diagnostic tools are available for evaluation of Internet Addiction Disorder including Young's Internet Addiction Test,[11] the Problematic Internet Use Questionnaire[12] and the Compulsive Internet Use Scale.[3] There are various models available for the improvement and upkeep of Internet Addiction Disorder, for example; cognitive-behavioral model of problematic Internet use,[4] the Anonymity, Convenience, Escape (ACE) model,[13] Triple-A engine,[14] and a far-reaching model of the advancement and support of Internet fixation by Winkler and Dörsing.[15]

There is emerging proof that genetics may play an important role in addictive behaviour. The hereditary hypothesis states that individuals suffering from Internet Addiction Disorder do not have sufficient number of dopamine receptors or they have a deficiency of neurotransmitters, besides experiencing issues in distinctive degrees of joy in activities that many other people would find rewarding.[16]

Various studies have revealed that excessive Internet use is associated with mood disturbance and unhappiness.[5,9] In addition, it has been described that youths' dependence on the Internet has brought about many negative outcomes including academic disillusionment, poor

[1] Under Graduate Medical student MBBS. Northwest school of Medicine, affiliated with Khyber Medical University, Peshawar, Pakistan.
[2] MBSS, MPH, HTM, PhD. Northwest school of Medicine, affiliated with Khyber Medical University, Peshawar, Pakistan.
[3] MBSS, MPH. Assistant professor Community Medicine Department. Northwest school of Medicine, affiliated with Khyber Medical University, Peshawar, Pakistan.

About the Author: *Farrukh Ansar is currently 4th year MBBS student at Northwest School of Medicine, Peshawar, Pakistan of a 5-year MBBS program. The author is Bebras silver medalist and acting as a student editor at Northwest journal of student research (NJSR).*

Correspondence:
Farrukh Ansar
Address: Northwest school of Medicine, Phase V, Hayatabad, Peshawar.
Email: farrukhanser@gmail.com

Editor: Francisco J. Bonilla-Escobar
Student Editors: Leah Komer, Madeleine J. Cox
Copyeditor: Leah Komer
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family connections, weakened social life, and emotional and mental issues.[17] There is a comparative occurrence of depression among people dependent on the Internet and of Internet addiction among depressed patients. According to the American Psychiatric Association; depression is a common and serious medical illness that negatively affects how an individual feels, thinks and acts.[18] Depression may present as profound distress or sadness, sleep deprivation, loss of hunger, agitated state of mind, fractiousness, and destructive inclinations. Besides these, characteristics such as low self-esteem, a dread of dismissal and need for affirmation, can be observed in depressed individuals.[19] It is also suggested that depression may lead to excessive utilization of the Internet, and the interesting and appealing elements of the websites may induce Internet addiction.[20]

World Development Indicator shows that almost half of the world's population have Internet access and majority of the users are college and university students.[21] It has been indicated that university students are more prone to the pathological use of the Internet.[22] A meta-analysis has indicated that the frequency of Internet addiction among medical students is approximately five times higher than the general population which depicts that medical students fall under the high-risk category.[23] Researchers have suggested that modern gadgets, unstructured timetable, availability of online learning material, and less parental control can contribute towards a higher predominance of Internet addiction and its negative outcomes among medical students.[6] Estimating the prevalence of Internet addiction and depression among medical students can be valuable, and their relationship can give new evidence in this domain. Comorbid Internet-based life dependence and depression is a significant clinical challenge as the consequences of both conditions are worsened by the other.[12] Minimal studies are conducted in Pakistan regarding Internet addiction and its association with depression. Therefore, the current study is aimed to determine the Internet addiction prevalence among undergraduate students of a medical college and its relationship with depression and academic performance.

Methods

Study Design and Setting

This is a cross-sectional study based on a self-administered questionnaire using a convenience sampling strategy. It was conducted at Northwest School of Medicine, Peshawar, Pakistan. This School of Medicine is a private medical institution situated in the provincial Capital, Peshawar and affiliated with the largest medical university (Khyber Medical University) of the province Khyber-Pakhtunkhwa. Students belonging from different cultures and ethnicities pursue their medical education in this institute. This medical school was established in 2016 and offers a five-year Bachelor of medicine and Bachelor of surgery (MBBS) degree program. Currently, four academic years are operational (one through four). The data for the study was collected during the first week of February 2019. The Independent Ethics committee of Northwest General Hospital granted ethical approval for the study (Ref No: NwGH/EC/24).

Study Size

Openepi® software was used for sample size calculation, considering the entire population of college as 400, the calculated sample size with a confidence level of 95% and an error of 5% was 197.

Participants

Data was collected from the students of all years in the medical school. All participants were the students of MBBS. The participation of the students in the study was voluntary and non-randomized convenience sampling technique was utilized for data collection. Trained research assistants approached the students of each class at the end of a long class format (LCF) lecture and requested all present students to participate in the study. Students were encouraged to participate in the study by explaining the purpose and need of conducting this study. During filling of questionnaires, investigators were present besides the participants and helped them if they faced any equivocalness or needed any help; however, to overcome information bias, students were not permitted to discuss the questionnaire during the whole process. The academic score reported by the students was also verified by the students' affairs office. Only those students that signed the consent form and were willing to participate in the study were included in the study. Students aged less than 18 years or suffering from any acute or chronic mood disorder were not allowed to participate in the study. Exclusion criteria included questionnaires with incomplete or incoherent information, and on this basis, 19 forms were excluded. Data was collected in the 1st quarter of the academic year when students are not under stress and fear of final examinations, or other rigorous academic activities - so that the results could be fair and conclusive.

Variables

Data was collected through self-administered questionnaires comprising of 4 sections. The first section consisted of an informed consent form developed by World Health Organization Research Ethical Review Committee.[24] The next section was for demographics while the third and fourth sections comprised of Young's Internet Addiction Test (YIAT)[11] and Beck's Depression Inventory (BDI)[25], both are internationally recognized and have proven reliable. The YIAT is a 20-item questionnaire with 6 options on each question ranging from 0 to 5. The minimum conceivable score is 0, and the maximum is 100. According to developers' guidelines, individuals who acquire a score between 20-49 points are considered as normal users who have control over the Internet. Individuals who score in between 50-79 are experiencing slight Internet dependence while those who scored in the range 80-100 reflect severe Internet dependency.[11] For depression, BDI is the most widely accepted tool and it comprises of 21 items. Each question has options to be selected, and each option has a score ranging from 0 to 3. The lowest score is 0 while the highest score is 63. Based on the score obtained, there are six categories set by developers of the scale. A score of 1-10 is considered normal, 11-16 mild mood disturbance, 17-20 borderline clinical depression, 21-30 moderate depression, 31-40 severe depression, and over 40 is considered as extreme depression.[25] In the questionnaire, students were also asked to report their scores of the most recent professional examination in percentages. This annual professional examination practiced at the Northwest School of Medicine collects only scores of the final examination, and these are counted for promotion and earning a degree. So, the scores of professional examinations portray the academic performance of a student. However, for first-year medical students, the aggregate of Medical College Admission Test and Higher Secondary School final results were reported. Afterwards, the academic scores were categorized as low grades (those who scored less or equal than 75%) and high grades (those who scored more than 75%) to understand the association of academics with Internet addiction and depression.

Quantitative Variables and Statistical Analysis

The analysis was run using a 95% confidence interval and p-value set at 0.05 using Statistical Package for Social Science (SPSS) Version 16.0 IBM INC. Chicago, USA and Stata16 (StataCorp, TX). Categorical variables were described using frequencies and percentages while continuous variables were described using central tendency and dispersion measurements. Bivariate analysis included the use of Chi-squared test and the Pearson correlation test, for categorical variables. For continuous variables, t-test was used. To identify the relation and effect of covariables on Internet addiction scores we used simple and multivariate linear regressions.

Internet addiction was further categorized in two sections as highly internet dependent students (who scored 80-100 on YIAT) and non-internet dependent students (who scored 20-79). Depression was also categorized into two groups; non-depressed individuals (who scored 1-16 on BDI) and depressed individuals (who scored 17-63). Using simple logistic regression, we estimated the odds ratio (OR) and confidence

intervals to assess the association of the study variables with depression. Furthermore, we assessed the association of the study variables with medical students' latest final examination result scores. We firstly assessed the variables with simple logistic regressions and added them into a multivariate logistic model to identify the adjusted effect of the variables on grades.

Results

Socio-Demographic Characteristics

Out of 380 students invited to participate in the survey, 250 students filled the survey for a response rate of 65.79%. We excluded 19 (7.6%) surveys and our final population for analysis was 231 (92.4%) participants. Our study population comprised of 148 (64.07%) male and 83 (35.93%) female students. Participants' distribution according to academic year was 23.38% (54), 25.54% (59), 26.41% (61), and 24.67% (57) for first, second, third, and fourth year, respectively. The age of respondents ranged from 18 to 29 with a mean of 21±2 years. Female students were younger than male students (20.07±1.89 vs. 21.74±1.51, p-value=0.003). The academic scores ranged between 47% to 90% with a mean of 73.31±7.27% with no significant sex differences (p-value=0.97).

Frequency of Internet Addiction

The mean Internet addiction score using YIAT was found to be 50.52±18.80 (range 1-97). Our results show that 4.76% (n=11, 95%CI=2.40-8.36) of students spend less time on the Internet than normal users, 44.16% (n=102, 95%CI=37.64-50.82) were average Internet users, and 41.99% (n=97, 95%CI=35.55-48.64) were experiencing occasional or frequent problems because of the Internet (slight Internet addiction), whereas 9.09% (n=21, 95%CI=5.72-13.56) of students were categorized as severe Internet dependents. There was a statistically significant difference when comparing sex by level of Internet addiction; 45.95% of male students report a slight addiction compared to 34.94% of female students (p-value>0.05). High Internet addiction was found in 11.49% of male students and 4.82% in female students (p-value=0.043). The mean YIAT score in males was 53.41±18.26, while in females it was 45.37±18.74 (p-value=0.002).

Frequency of Depression

The mean Beck's-Depression-Inventory score was 20.09±12.1 and ranged between 0-55. According to Beck's Depression Inventory categorization, 27.71% (n=64, 95%CI=22.04-33.96) of students fell in the normal category, 16.88% (n=39, 95%CI=12.29-22.35) were suffering from mild mood disturbance, 7.79% (n=18, 95%CI=4.68-12.04) were found to be at borderline clinical depression, 23.81% (n=55, 95%CI=18.47-29.84) were suffering from moderate depression, 19.05% (n=44, 95%CI=14.19-24.71) fell in the category of severe depression, while 4.76% (n=11, 95%CI=2.4-8.36) of the students were identified as extremely depressed. There was no statistical difference when comparing sex and the categories of depression (p-value=0.06). The mean depression score was 20.19 ± 12.92 in males and 19.92±10.53 in female respondents (p-value=0.87).

Relationship Between Internet Addiction and Depression

Correlation between Internet addiction and depression was 0.164 (Pearson Correlation R) with a p-value 0.01. The simple linear regression model described that for each increase in the Internet addiction scorer there was an increase in the depression score (β=0.27, p-value=0.009, R^2=0.03, ***Figure 1***). Adjusting the model by age and sex, it was found that being male increased the Internet addiction levels (β=7.43, p-value=0.004) and did not change the net effect of depression over the addiction (β=0.25, p-value=0.01) but the relation of this characteristics explained only 7.6% of the variability in Internet addiction. Finally, the odds ratio (OR) of depression among those addicted to the Internet was 1.34 (95%CI=0.53-3.37, p-value=0.53), indicating an association with depression; however, the confidence interval crossed the null value and further adjustment was not appropriate given the sample size.

Table 1. Distribution of Internet Addiction and Depression Categories with Academic Performance (n = 231).

Characteristic	Students who scored ≤75%	Students who scored >75%	Total	p-value
Internet Addiction				0.026*
Less Internet users	2 (1.59%)	9 (8.57%)	11 (4.76%)	
Normal Internet users	51 (40.48 %%)	51 (47.6%)	102 (44.16%)	
Slight Internet Addiction	60 (47.62%)	37 (35.24%)	97(41.99%)	
High Internet Addiction	13 (10.32)	8 (7.62%)	21 (9.09%)	
Depression Categories				0.125*
Within normal limits	32 (25.40%)	32 (30.48%)	64 (27.71%)	
Mild mood disturbance	17 (13.49%)	22 (20.95%)	39 (16.88%)	
Borderline Clinical depression	7 (5.56%)	11 (10.48%)	18 (7.79%)	
Moderate depression	33 (26.19%)	22 (20.95%)	55 (23.81%)	
Severe depression	29 (23.02%)	15 (14.29%)	44 (19.05%)	
Extreme depression	8 (6.35%)	3 (2.86%)	11 (4.76%)	

Figure 1. Scatter plot and linear relation of Depression and Internet addiction scores.

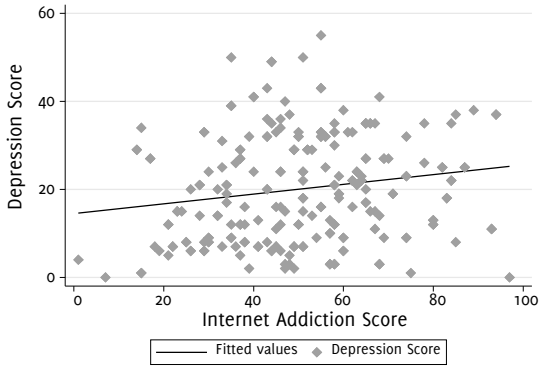

Figure 2. Scatter plot of the Internet addiction and Percentage of academic scores.

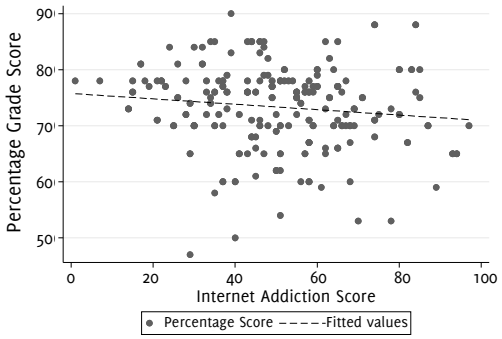

Table 2. Associated factors with low academic performance (low grades).

Characteristic	$_u$OR	95%CI	p-value	$_a$OR	95%CI	p-value
Internet addiction	0.71	0.28-1.80	0.479	0.54	0.19-1.48	0.234
Depression	0.60	0.35-1.01	0.0577	0.62	0.35-1.09	0.100
Sex	0.90	0.52-1.55	0.726	1.39	0.76-2.57	0.281
Age	0.62	0.50-0.75	<0.0001	0.59	0.48-0.73	<0.0001

Association of Academics with Internet Addiction and Depression

There was an inversely proportional relation between academic performance and Internet addiction, where each increase in the YIAT's score decreased the percentage academic score (β=-0.32, p-value=0.06, R^2=0.015; ***Figure 2***); however, it was not significant. Number of students who obtained a grade less than or equal to 75% were 54.55% while students who scored above 75% were 45.45%. ***Table 1*** shows the relationship between grades, Internet addiction (p-value=0.026) and depression (p-value=0.12). In the multivariate logistic regression analysis adjusted by sex and age (***Table 2***), it was found that Internet addiction (OR=0.54, 95%CI=0.2-1.49, p-value=0.23) and depression (OR=0.62, 95%CI=0.36-1.09, p-value=0.10) were associated with a score equal or below 75%; however, these findings were not statistically significant (Pseudo R^2=0.10).

Discussion

The global accessibility of better Internet service and availability of modern gadgets has raised the problem of Internet addiction. As Internet dependence is widely perceived as a mental health issue that might affect the lives of youngsters, it is important to watch out for its dominance and to initiate preventive and mitigation measures to keep control on this silent public health problem.[26] Few investigations are directed on the pervasiveness of Internet addiction in the subcontinent region which compelled us to establish the frequency of Internet addiction among students of a Medical school in Pakistan.

Various global investigations have shown that youngsters aged between 18 to 25 years have the highest chance of developing Internet dependence. Across the globe, the prevalence rates reported for Internet addiction vary widely (between 0.3% and 38%).[27] Systematic reviews in the United States and Europe have shown predominance rates fluctuating somewhere in between 1% and 8%.[5] Our study has demonstrated that Internet addiction among medical students was 9.09% (95%CI=5.71-13.56) while a local study has demonstrated that Internet addiction was found in 7.9% of medical students.[28] Investigators from India also revealed that the frequency of Internet addiction was discovered to be 6% at a dental college.[29] A middle-eastern study conducted on undergraduate medical students of Qassim University depicted that frequency of Internet-addicted students in their study sample was 12.4%.[30] These findings show the trend of having a high frequency of Internet addiction among medical students than the global average in the general population. Results from current investigation demonstrate that mean score of Internet addiction scale was higher in males than in females (p-value=0.043). A study from China bolsters our evidence by reporting the same trend.[31] Various review articles and meta-analyses have also shown that male students are more prone to developing Internet addiction than the counterpart gender.[28,32] Overall, our outcomes have indicated that predominance of web fixation in our study sample is marginally higher than the worldwide average and other local studies.

Beck Depression Inventory was used to determine depression among the respondents. According to Beck's Depression Inventory the respondents fall into six categories - normal students (29%), mild mood disturbance (16.5%), borderline clinical depression (7.8%) while students suffering from mild, moderate, and extreme depression were 24.4%, 17.1% and 4.6%, respectively. These figures give us an insight that at least 55.41% (n=128, 95%CI=48.75-61.93) students are suffering from depressive illness. Using Beck's Depression Inventory, a study from medical colleges of Iran also reported that 52% of the students were suffering from depression.[33] Another Turkish investigation reported that prevalence of depression was 39% in their study population. [34]

Literature review has demonstrated that depression and Internet Addiction Disorder happens together roughly twice as would be anticipated alone.[10] Both factors might be driven by shared fundamental psychological and social mechanisms. For example, nervousness hub actuation, rest aggravation, latent style of life, helpless dietary propensities, and ecological and social hazard factors.[35]

Research on depression and Internet addiction showed that the misuse of the Internet brings an interruption of the ordinary life of an individual and also affects the people around them, which was related to an increase in the frequency of depression.[36] Besides, in 2005 it was proposed that depression is the distal fundamental reason for Internet addiction.[37] A major scale investigation among undergraduate students found that Internet addiction was identified with indications of attention deficit hyperactivity disorder (ADHD) and burdensome disorders. However, it is conceivable that they may spend more time on the Internet and progress to addiction if the depression was not well treated.[38] Current investigation has demonstrated that Internet addiction and depression are correlated; Internet addicts suffered from more depression than average Internet users. The current study reported that odds ratio (OR) for depression with Internet addiction was 1.34 (95% CI=0.53-3.37) but without statistical significance. However, the multivariate logistic regression model exhibits that increase in YIAT scores resulted in decreased academic scores with a p-value of 0.06 which is close to the significance level. Still, we could identify an inverse relationship between internet addiction and academic performance. Similar but significant outcomes were found from an exploratory study led by Japanese researchers where it was found an OR of 2.8 (95% CI=2.4–3.3).[39] Another international study reported a statistically significant association between Internet addiction and depression with OR = 1.9 (95% CI= 1.3–2.7).[40] Correlation analysis also provided that there is positive association between Internet addiction and depression. same was reported by various national and international studies.[22,27] A reason why our results were not significant could be attributed to the sample size calculation which was planned to identify prevalence and not for multivariate analysis. Further research is required to shed light on this issue locally.

As manifested by various empirical studies, Internet addiction has a negative outcome on the academic performance of the students; more time spent online for non-educational purposes result in short attendance, distractive behaviour, lack of interest in studies, difficulty in grasping concepts, and cognitive decline which ultimately results in low grades.[42,43] The current study has explored that there was not a significant relationship between Internet addiction and academic performance given that Internet addiction (OR=0.54, 95%CI=0.2-1.49, p-value=0.23) was associated with low grades. However, multivariate logistic regression model show that increase in YIAT scores decreased the academic scores. These results cannot conclude that either academic performance is related with Internet addiction or not. However, results from other settings demonstrated significant results. They expressed that predominance of pathological web use was significantly higher in students with declining grades.[43] A recent investigation among dental students also revealed that there was a strong association (OR=6 95%CI=2.29-15.67) between scholastic grades and frequency of Internet addiction.[29] The possible reason for the discrepancy in these results with comparison to other investigations might be the study design we have used, which is a limitation of our study. However, the Pearson chi-squared test reveals that pervasiveness of Internet addiction was significantly higher in the group of students who obtained low grades in their final professional examination. Various other investigations likewise gave similar outcomes which are in accordance with our outcomes.[23,42,44]

Web fixation can likewise cause despondency, introversion, hopelessness and different other psychosocial conditions.[11] These variables seriously affect the daily life of an individual including important duties of daily routine like social interaction with peers, family and educational or employment supervisors.[28] Sometimes severe addiction can spawn permanent damage to career besides physical and emotional health. Moreover, web abuse may introduce youngsters towards pornographic addiction, non-ethical hacking, spamming, phishing, and intrusion into security networks which can no doubt endangers the integrity of personal health and finances, but can also lead to legal proceedings against the subject.[45] Some analysts have even cautioned that Internet addiction may turn into a twenty-first-century scourge and may bring a significant global public health issue.[46] All these statistics and analysis raise worries and concerns for educational experts and public health policymakers. The increasing inescapability of Internet addiction should be considered as an emerging public health problem, and proper mitigatory measures should be taken well ahead of time.

Limitations

Potential limitations of the current study may be its single centered nature as only students from one private medical school of Peshawar have been selected. One strength is that our participation rate increased our sample size above the one calculated to reach up to 97% confidence in the calculations. However, this sample cannot be considered as representative for all other medical colleges and multivariate analysis did not account for the calculation limiting the reliability of the regressions. Besides, the study design is also a limitation to the associations described, as the setting of the current study is a private sector medical school. Further research should be carried out at public sector medical colleges to compare the outcomes. The effect of factors like socioeconomic status, availability of better internet service and modern devices can also be studied to generate more specific outcomes.

Conclusion

In conclusion, it appears that in Pakistan, Internet addiction among young undergraduate medical students is an emergent as in this single-center study, 9.7% of the medical students fall under the category of high Internet addiction, whereas 42.2% students are encountering problems with Internet use which can be considered as slight Internet addiction. In the future, greater progression in the Information Technology sector will increase the availability of affordable and fast Internet services and will offer more efficient and captivating gadgets that can exacerbate the situation. It was likewise found that depression was more common in students who presented the attributes of Internet Addiction Disorder. Otherwise, academic performance of Internet-addicted students was significantly lower than normal Internet users. We recommend that Internet Addiction Disorder should be taken as a serious issue and awareness among masses should be raised regarding its consequences. Institutions should adopt preventive strategies to cope with this issue, and proper screening should be made mandatory at regular intervals of time to reveal the burden of this disorder. Those who are suffering from Internet Addiction Disorder or associated depression should be offered appropriate counseling and adequate referrals. Availability and accessibility of alternative healthy activities would be a valuable measure to protect the young generation from the negative impact of the Internet and further research is needed strengthening the study designs to identify associated factors but also evaluating the effect of interventions.

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Original Article

Pap Smear Readability on Google: An Analysis of Online Articles Regarding One of the Most Routine Medical Screening Tests

Mark J. Parry,[1] Travis S. Dowdle,[2] Jesse N. Steadman,[3] Tiffany R. Guerra,[1] Kim L. Cox.[4]

Abstract

Background: The Papanicolaou smear (Pap smear, Pap test) is one of the most routine screening tests performed in medicine. The development and widespread use of this test has brought a considerable decrease in the incidence of cervical cancer. Unfortunately, this disease process continues to convey significant morbidity and mortality. These persistent phenomena may be the result of inadequate compliance with routine Pap smear screening, in which limited education is thought to play a role, particularly among ethnic minority groups. **Methods:** A Google search using the phrase "pap smear" was performed and the first fourteen web addresses were analyzed using four standardized readability indices: the Flesh-Kinkaid Grade Level, the Simple Measure of Gobbledygook, the Gunning Fog Index and the Automated Readability Index. The average grade level readability was then compared to the American Medical Association recommendation that health care information should be written at a 5th or 6th grade reading level (i.e., ages 10-12 years). **Results:** The average grade-level readability values of the fourteen analyzed sites using the four aforementioned indices were 8.9, 8.8, 11.9, and 8.4, respectively. The mean readability of all four indices was 9.5. **Conclusion:** The grade-level readability of commonly accessed internet information regarding Pap smears is above the recommendation of the American Medical Association. Health care providers and website authors should be cognizant of this, as it may impact compliance. This is particularly important given that this routine healthcare test is recommended for nearly fifty percent of the world's population at various points throughout their lifetime.

Key Words: Papanicolaou test; health literacy; early detection of cancer; search engine; comprehension; reading (Source: MeSH-NLM).

Introduction

Introduced by George Papanicolaou in the first half of the 20th century, the Papanicolaou smear (Pap smear, Pap test) is an important screening method for cervical cancer.[1] The goal of a Pap smear is to identify cervical cells suspicious for pre-cancer or cancer.[2] To do this, a small number of cells are sampled from the patient's cervix by a health care provider. These cells are then prepared and evaluated microscopically for irregularities.[2] If abnormalities are identified, a diagnostic colposcopy with cervical biopsy is performed to better categorize the cervical changes, following which, an individualized treatment plan is designed based on the patient's findings.[2,3] Treatment may include destruction of the affected cells with extreme temperatures, removal of cervical tissue, or chemotherapy coupled with surgery or radiation.

The United States Preventive Services Task Force (USPSTF) recommends that women ages 21 to 29 receive a Pap test once every three years.[3] When a woman reaches the age of 30, recommended screening can be performed in one of three ways: a Pap test every three years, high-risk human papillomavirus (hrHPV) testing every five years or co-testing with both a Pap test and hrHPV testing every five years. hrHPV testing evaluates for oncogenic types of HPV.[2] Positive hrHPV testing, as with a positive Pap test, indicates an increased risk of developing cervical cancer.

Since its inception, the Pap smear has experienced widespread utilization and brought a substantial decline in the incidence of cervical cancer.[2] Unfortunately, this screening method continues to be underutilized. The American Cancer Society cites the 2018 median compliance rate with cervical cancer screening recommendations at 85% and estimates that in 2020 there will be 13,800 new cases of invasive cervical cancer diagnosed and 4,290 subsequent deaths within the United States (US).[2,4]

Various studies in the US have recognized limited education as a potential barrier to cervical cancer screening.[5-8] One study found that the number of women who correctly understood the term Pap smear was fewer than 10%.[9] This is especially true among Hispanic women who scored the lowest among all ethnic groups on a questionnaire measuring knowledge of Pap testing; this demographic is also significantly more likely to have never had a Pap test.[5,10,11] Data from the Centers for Disease Control and Prevention (CDC) indicates that Hispanics have the highest ratio of HPV-associated cervical cancer relative to other ethnicities, demonstrating a rate of 9 per 100,000 women.[12] While cultural factors including the fear of finding cancer and language barriers appear to play a role in this discrepancy, it is the lack of knowledge regarding cervical cancer screening that will be further explored here.[5]

In addressing the limited knowledge and relatively low screening rates of Pap smears among certain demographics, easy access to comprehendible patient-education material becomes vitally important.

[1] Texas Tech University Health Sciences Center – Paul L. Foster School of Medicine, El Paso, TX, United States
[2] Texas Tech University Health Sciences Center – School of Medicine, Lubbock, United States
[3] University of Utah – School of Medicine, Salt Lake City, UT, , United States
[4] Pocatello Women's Health Clinic – Pocatello, ID, , United States

About the Author: *Mark J. Parry is currently a 4th year medical student at the Paul L. Foster School of Medicine in El Paso, Texas (USA), which is a 4-year MD program.*

Correspondence:
Mark J. Parry
Address: 5001 El Paso Dr, El Paso, TX 79905, United States
Email: mark.parry@ttuhsc.edu

Editor: Paul MacDaragh Ryan & Paul Morgan
Student Editors: Nikoleta Tellios, Madeleine Jemima Cox, Najdat Bazarbashi, Andrew Thomas & Ciara Egan
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In the current era, the internet is a common source for this health information. A study performed in 2013 found that the majority of US adults reported searching online for health information in the past year with over one third of respondents attempting to "self-diagnose" a particular medical condition.[13] Among Internet search engines, Google is used most frequently, holding 86.86% of the global market share amongst all search engines.[14]

Google search data has shown how women react to important public health news, such as the Irish "CervicalCheck" scandal in 2018 when over 200 women were given incorrect Pap smear results.[15] After this information broke to the public, Google searches for "cervical check" and "cervical cancer" rose substantially, and the conduction of Pap smear tests increased by 40% in the subsequent weeks. Given the unpredictable nature of such public health crises, it is important that online health materials are periodically evaluated.

The American Medical Association (AMA) recommends health information be written at a US 5th or 6th grade reading level.[16] Therefore, the aim of this investigation was to evaluate the compliance of online reading material related to Pap smears with this recommendation. As few studies of this nature have been performed in the field of obstetrics and gynecology (OB/GYN), the effect of this work is expected to be particularly insightful to both providers and patients.[17-19] Expecting consistency with prior readability studies, the hypothesis of this work is that the grade-level readability of online material on Pap smears is written at a grade level greater than what is recommended by the AMA.[20-23]

Methods

Readability Indices

The readability of online health information has been evaluated in the past using standardized indices.[19-23] These metrics have been discussed in papers by the National Cancer Institute and the Centers for Medicare and Medicaid Services.[24,25] From these sources and further research on readability measures, four indices that each provide a grade-level readability were selected for this study.[19-28] Considered together, these provide a reliable average readability for written materials; each measures readability in a unique way. The indices utilized are described below:

1. Flesh-Kinkaid Grade Level (FKGL): This particular formula was originally validated for use by the armed forces in the US. It analyzes sentence length and word length to judge the grade-level readability of a given text.[23,26] This index has been used extensively in the past for the analysis of healthcare related literature.[27]
2. Simple Measure of Gobbledygook (SMOG): This is a validated index that uses a complex formula to measure the number of polysyllabic words inside a sample of 30 sentences.[18,26] It is one of the most well-suited tests for analyzing the readability of healthcare information.[27]
3. Gunning Fog Index (FOG): This measure was partially validated against an initial gold standard for analyzing readability: the McCall-Crabbs Passages.[26,27] It examines the total number of words as well as those words that are considered "complex" (three syllables or more). [23,26]
4. Automated Readability Index (ARI): This index was validated for use with Air Force technical material. It deviates slightly from the previously mentioned indices in that it also uses the number of characters per word in calculating a grade-level readability.[21,28]

Selection of Websites

The history and cache on the Google search engine within the Google Chrome browser were completely cleared and the phrase "pap smear" was searched on June 13, 2020 in the US state of Texas. Various permutations of the search term "pap smear" could be employed by patients depending on their background and life situation. In order to account for this variance, the authors agreed that the best method in determining an overall grade-level readability of patient materials related to Pap smears would be to query on the topic itself, rather than related keywords and phrases. To validate this decision, a review of data available from Google Trends—an application that charts relative interest over time for selected search queries—was conducted.[29] Four potential searches ("pap smear", "cervical cancer", "pap test" and "pelvic exam") were compared within the three categories of "Texas", "United States" and "Worldwide" to gain a sense of the relative popularity of the phrase "pap smear" within these regions.

With the chosen query of "pap smear," the first 14 uniform resource locator (URL) results, excluding educational videos and advertisements, were selected as the aggregate to be evaluated. The authors determined the quantity of inclusions from an analysis of a large dataset measuring search engine user behavior by a metric entitled click-through rate (CTR).[30] The website "Advanced Web Ranking" was used, which averages monthly Google CTR data from millions of keywords. Within the site, the categories "international" and "all devices" within the "year over year" grouping for the year 2019 were analyzed.[30]

CTR is a measure of the likelihood that a click will occur when an advertisement is placed at a given location in the query and has also been applied to URL results in Google searches.[30,31] To explain this further, the CTR value for the first position in a Google search query from 2019 was 34.07.[30] That is, the likelihood that a person clicks on the first link in a given Google search is just over one third. Looking at the first 14 URL results gives an aggregate CTR value of 98.90, making this an in-depth measure of the total material that a patient inquiring online for health information may view.

Evaluating Readability

The grade-level readability from the four aforementioned readability indices (FKGL, SMOG, FOG, ARI) was calculated using an online software from WebFX.[32] This is a verified online tool recommended for educators to guide their students.[33] The educational text from each website was first copied and pasted into a Microsoft Word document. All advertisements were deleted, tables were excluded, titles that were not entire sentences were omitted, and lists or bullet points were converted into written sentence form. In instances where complete sentences could not be established, these words were excluded from the data entry. The objective was to ensure that the text inputted into the program was as close to the actual value as possible. In one instance (the 13th result in our query; a page entitled "Pap test" from Wikipedia), the set of text was too large to be evaluated using the WebFX tool. To accommodate this, the text was divided into 10 sections of about 300 words each. The sections were then individually entered, after which an average of all 10 readability values in each of the 4 specific indices was obtained.

Once the 4 indices had been obtained for each of the 14 included URLs (***Table 1***), the values were averaged together in Microsoft Excel to give an aggregate grade-level readability of the online material from the selected query of "pap smear". The cutoff for grade-level readability was set at 6.3, in conjunction with the AMA's recommendation that healthcare information be written at a 5th or 6th grade reading level.[16] 6.3 was chosen in place of 6.0 because healthcare vernacular is inherently difficult to understand and a prior study found that the grade-level readability obtained by the FKGL would decrease by 0.3 if medical vocabulary were removed.[23,34]

Results

Google Trends data from the week of June 7-June 13, 2020 using the search term "pap smear" gave a popularity value in Texas, the United States and worldwide of 63, 58, and 57 respectively, where a value of 100 represents peak popularity (***Table 2***). The phrase "cervical cancer" had values of 40, 43, and 63. The expression "pap test" showed values of 10, 7, and 23 and "pelvic exam" received values of 5, 7, and 6.

Table 1. Comparison of Website URL Position in a Query Following a Google Search for "pap smear" and Average Grade-Level Readability as Determined Using Four Standardized Readability Indices.

Position in Query	Website URL	Average Grade-Level Readability
1	https://www.mayoclinic.org/tests-procedures/pap-smear/about/pac-20394841	10.3
2	https://www.healthline.com/health/pap-smear	8.9
3	https://medlineplus.gov/ency/article/003911.htm	8.3
4	https://www.womenshealth.gov/a-z-topics/pap-hpv-tests	7.6
5	https://www.cancer.gov/publications/dictionaries/cancer-terms/def/pap-smear	9.6
6	https://www.webmd.com/women/guide/pap-smear#1	6.4
7	https://www.medicinenet.com/pap_smear/article.htm#pap_smear_facts	12.7
8	https://kidshealth.org/en/teens/pap-smears.html	7.4
9	https://www.cancer.net/navigating-cancer-care/diagnosing-cancer/tests-and-procedures/pap-test	8.7
10	https://labtestsonline.org/tests/pap-smear	11.5
11	https://hhma.org/blog/pap-smear-guidelines/	7.7
12	https://my.clevelandclinic.org/health/diagnostics/4267-pap-test	11.5
13	https://en.wikipedia.org/wiki/Pap_test	12.6
14	https://www.medicalnewstoday.com/articles/311995	9.8

Table 2. "Interest Over Time" Values by Region for Four Different Search Terms Related to Cervical Cancer Screening using Google Trends Data Specific to the Week of June 7 – June 13, 2020, Peak Popularity for a Given Search is 100.

Search Term	Texas	United States	Worldwide
"pap smear"	63	58	57
"cervical cancer"	40	43	63
"pap test"	10	7	23
"pelvic exam"	5	7	6

The CTR data from 2019 showed that the click probability was much greater within the first seven results as compared to the second seven results (***Figure 1***). The subtotal CTR value for the first 7 URLs was 86.29 and the next 7 URLs accounted for 12.61, giving a total value of 98.90. Thus, the first 14 positions provide an aggregate of the vast majority of clicks that occur after a user inputs a query into a search engine.

The 14 sites were analyzed for readability using the FKGL, SMOG, FOG, and ARI with the average values being 8.9, 8.8, 11.9 and 8.4, respectively. Each individual URL together with its average grade-level readability is highlighted in (***Table 1***). These values ranged from 6.4 to 12.7. The URL that had the lowest average grade-level readability was from WebMD and the site with the highest average grade-level readability came from MedicineNet. Other websites analyzed that may be easily recognizable to the average health care consumer were: Mayo Clinic, Wikipedia, Cleveland Clinic and womenshealth.gov.

The total average grade-level readability taking into account all 4 indices was 9.5 (***Figure 2***). Considering the first seven URLs and the next seven URLs separately, the values were found to be 9.1 and 9.9, respectively. The trendline of average grade-level readability was slightly upward, indicating that the mean increases as one moves to the URLs appearing later in the queue.

Discussion

The grade-level readability of information from the popular search term "pap smear" obtained via a Google search is above what is recommended by the AMA. None of the URLs evaluated were below the chosen cutoff of 6.3 for grade-level readability. This is consistent with findings in other disciplines where the readability of healthcare information has been explored.[20-23] There appears to be a paucity of research on similar topics in OB/GYN, however.[17-19]

When evaluating the first seven URLs, the average grade-level readability is more than two grade levels above what is recommended. This could imply that a number of patients are not finding readable information online about a topic that is of significant importance to women worldwide. If a woman receives Pap smears as part of routine screening throughout her life with no abnormalities, the minimum number of tests she will undergo is 11, making screening for cervical cancer one of the most frequent of all routine female cancer screenings.[34,35] Thus, the potential relevance of this should not be ignored. Importantly, these findings may be particularly relevant for individuals with decreased health literacy or for those who speak English as a second language, given that Google Translate makes more errors in translating to another language when the original sentence is written at a higher grade level.[36,37]

It appears that the grade-level readability increases as one moves to the second page of results in the "pap smear" query performed. In this case, the limited data may suggest that the top-viewed websites possess more readable material for consumers. It is interesting to note, however, that the top "hit" in the query was from an article published by the Mayo Clinic with an overall grade-level readability of 10.3. This shows that while the readability of a particular domain certainly plays a role in determining which websites populate first in a given search engine, there are a host of other contributing factors. The particular set of strategies aimed at populating a link early in the search results is termed search engine optimization (SEO).[38]

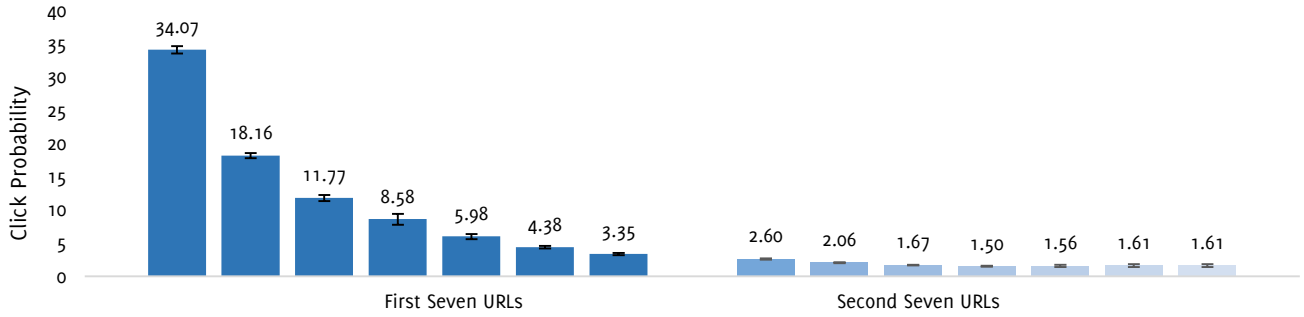
Other factors that play a part in SEO include: the website's recognized expertise on a particular topic, relevancy of the site to the question asked, the overall quality of the website's content, the navigability of the site, and the location in which the search was conducted.[38,39] Our analysis was not focused on the relationship between readability SEO, but rather analyzing the readability of websites that already had strong SEO ratings. Reassuringly, 3 of the first 8 URLs encountered are near the AMA's recommended grade-level readability level. This indicates that some of the information obtained via a Google search on Pap smears is being written at an appropriately readable level for patients.

Other websites may benefit from looking to such sites or involving patients and public partners as they prepare educational material for patients.

Limitations

One significant limitation of this study is that only a single query was used in searching. A single query was chosen instead of multiple queries as "pap smear" was considered to be a broad enough search to give a representative sample of the Internet information that exists on the topic. Based on Google Trends data from the week in which the search was performed, this appears justified. The popularity of "pap smear" superseded the other three search terms demonstrably in both regional and US locales. Within the "worldwide" category, the phrase "cervical cancer" was slightly more popular, though the difference was

Figure 1. Probability of Clicks Occurring in the First Seven URLs vs. The Following Seven URLs of a 2019 Google Search, A Total of Fourteen URLs Are Shown with a Cumulative CTR Value of 98.90, Error Bars Represent Standard Deviation Based on Monthly Data from 2019.



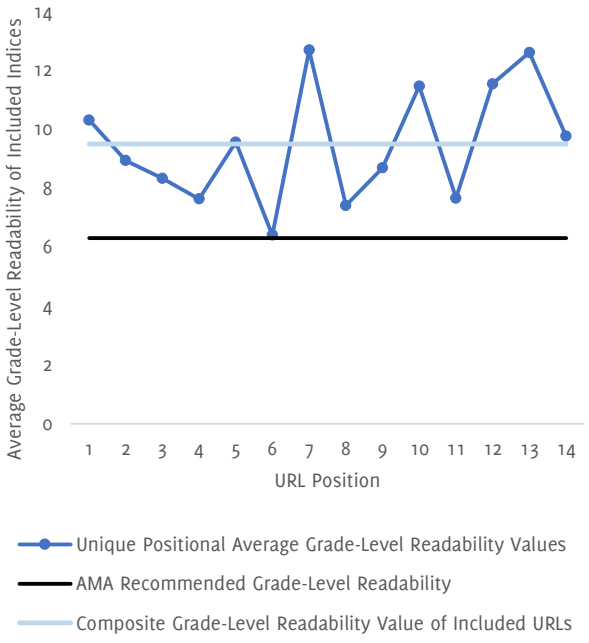
marginal at 63 for "cervical cancer" and 57 for "pap smear". Considering that Google uses location as one of the determining factors in which sites populate first following a search, the column for "Texas" (the location in which the search was performed) may be the most important.[39] This column showed "pap smear" to be favored by more than 20 points.

The usage of a single query factored into the decision to evaluate 14 URLs instead of 7. It was believed that this could facilitate the discovery of some of the articles that would have been moved further up the list of results in similar search queries. No more than 14 websites were deemed necessary based on current behavior of online users as shown in the 2019 CTR data.

Another limitation of this study is that the FOG index gave higher average values than the other indices. This is, however, consistent with other published studies.[18,20-23] This could be because the FOG is a unique metric for evaluating readability, which looks at the total number of words per sentence and how complex the words are. Medical terminology frequently employs the use of large, complex words as standard vernacular, which may help explain the higher value calculated by this index. Even if the FOG index was taken out of the analysis, the average grade-level readability would be 8.6, more than 2 grade levels above the AMA recommendation.

A final limitation is that this study did not consider additional reasons that vulnerable populations, such as Hispanic women, may have lower rates of cervical cancer screenings. This study was focused primarily on only one aspect of this complex issue: the grade-level readability of online materials on Pap smears. Other factors such as "fear of finding cancer", male physicians, and language barriers have been noted as significant obstacles and could be further explored.[5]

Figure 2. Grade-Level Readability Values for First 14 URLs in a Google Search for "pap smear" Compared to Superimposed Static Lines Representing the Composite Average Grade-Level Readability of All URLs and the Recommended Grade-Level Readability by the AMA.



Further Investigation

The current era is one in which YouTube is the second most popular social media platform, garnering 1.9 billion users in 2020.[40] In addition, the current COVID-19 pandemic has shifted much of school education to an online format and brought a huge uptick in the number of telehealth visits conducted.[41,42] With this, it could be argued that the importance of audiovisual learning has never been greater. In our study, six of the first seven sites and ten out of the fourteen total sites had a video or image that was accessible to the viewer. Using readability indices alone, there is no way to account for the added educational value that these resources may confer. Thus, further studies could be performed to assess the significance of audiovisual learning in patient education. While it has been found that in certain scenarios audiovisual materials may be helpful for patients, this has not been widely examined.[43,44] Factors within this domain that deserve further investigation include: the formulation of specific indices to measure the impact of audiovisual learning, the percentage of various cohorts that are audiovisual learners, and the potential impact of such findings on screening exam discrepancies amongst groups (such as ethnic minorities).

Another area deserving further investigation exists. There appears to be a tendency for patients to misjudge an abnormal Pap smear (one showing precursor lesions with malignant potential) as being consistent with a diagnosis of cervical cancer. One study found that nearly 1/3 of individuals who were asked the true-false question, "If you have an abnormal result on the Pap test: It means you have cancer" answered either incorrectly or "don't know".[11] This is worth exploring given the potential for physician confusion and patient mistreatment as a result of this inadequate understanding. This would seem especially pertinent in patients where some form of treatment for a precancerous lesion (such as loop electrosurgical excision procedure (LEEP) or cryotherapy) is required.

Finally, readability is only one aspect of patient education. An equally meaningful study could examine the accuracy of the content contained on the most frequently viewed websites for the search term "pap smear." This could be accomplished by having a panel of experts blindly review each webpage and score them for correctness, thus providing a supplement to the important findings of the current study.

Conclusion

Medical information may be inherently difficult to understand. While the overall grade-level readability of articles discussing Pap smears via a Google search appears to be better than that of other healthcare readability papers, it still exceeds what is recommended by the AMA.[18, 20-22] This discrepancy is significant given that the Pap smear is a routine test recommended for nearly fifty percent of the population at various points throughout their lifetime. The findings of this study should guide healthcare providers and website authors alike to be more cognizant of the information that is transmitted online to patients with the ultimate goal of decreasing the grade-level readability to what is suggested by the AMA.

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Original Article

Hypertension Awareness, Treatment, and Control in Mexico: An Opportunistic Medical Student-led Blood Pressure Screening Campaign – A Cross-Sectional Study

José Adrián Yamamoto-Moreno,[1] Suzzette Anaís Navarro-Rodríguez,[2] Samuel Ruiz-Pérez,[3] Juan Carlos Godínez-Reyes,[4] Marvin Mendoza-Rojo.[5]

Abstract

Background: Hypertension remains a growing public health concern in Mexico. This study aims to describe hypertension awareness, treatment, control, and its associated factors in participants of an opportunistic, medical student-led blood pressure screening campaign in Mexico. **Methods:** A cross-sectional study using convenience sampling was performed, including participants aged 18 years and older from 15 Mexican states. Each participant completed a questionnaire about risk factors and had three blood pressure measurements taken. Hypertension was defined as ≥140/90 mmHg. Multiple imputation with linear regression was performed where data was missing. **Results:** From a population of 2,545 participants, 623 (24.5%) participants had hypertension. Of those with hypertension, 81.9% had a previous diagnosis of hypertension, and only 16.1% were not on medication at the time of screening; 61% were controlled, 21% were uncontrolled patients, and 18% were not aware they had hypertension. The largest proportion of uncontrolled cases (33%) were found in states with high marginalization, and the number of unaware hypertensives in very low marginalization states were double that of the national figure. More than half of the participants taking antihypertensive agents were on a single medication, achieving control in almost 8 in 10 patients. **Conclusion:** Most uncontrolled hypertensive patients in Mexico belong to marginalized states. These results could inform state legislative policy to help bridge healthcare gaps.

Key Words: Hypertension; Blood Pressure; Screening; Mexico (Source: MeSH-NLM).

Introduction

Hypertension is a chronic, controllable disease of multifactorial etiology, characterized by a sustained increase in blood pressure (BP) levels.[1] Its importance lies in the fact that it is the most common risk factor for the development of cardiovascular disease (CVD), which is the leading cause of death worldwide, generating approximately 10.5 million deaths per year.[2,3]

In high-income countries, an improvement in the awareness, treatment, and control of the disease has been observed.[4] Healthcare systems in countries with better control of hypertension such as the United States, Canada, South Korea, and Germany all have health education or health check-up programs.[5] However, in low and middle-income countries such as Brazil, China, India, Indonesia, Mexico, and South Africa, the results of disease prevention strategies have been less favorable, revealing a need to improve health services and prevention programs.[6]

In Latin America, 40% of the adult population suffers from hypertension. This can be attributed to considerable variations in hypertension awareness, treatment and control depending on race/ethnicity, sex, income, occupation, education, social position, psychosocial and behavioral factors, among other social aspects.[7] For example, people with a higher socioeconomic level are more likely to be physically inactive, with physical inactivity being one of the main risk factors for hypertension.[7] On the other hand, better adherence to treatment has been observed in people with a higher educational level.[8] Small studies have shown that the majority of people living with hypertension do not know the normal BP levels and that there is a correlation between body weight and elevated BP.[9]

Hypertension is still a growing public health concern in Mexico. The National Health and Nutrition Survey (ENSANUT) reported prevalence figures of 25.5%, of which 40.0% were not aware they had hypertension. Among those who were previously diagnosed with hypertension, 79.3% received pharmacological treatment, and only 45.6% were properly controlled.[10] An estimated increase of 151% is expected in the number of individuals needing care for hypertension by 2050 if further actions are not taken in Mexico.[8]

Several global campaigns have been devised to improve awareness and early detection of hypertension—such as the May Measurement Month (MMM)—a global screening intervention performed on an annual basis by the International Society of Hypertension (ISH). This campaign focuses on measuring BP among the general population and identifying risk and predisposing factors for the disease.[3,6] The 2019 intervention had a response from more than 100 countries, with a final count of 1,508,130 participants worldwide.[6]

[1] Physician, Universidad Autónoma de Baja California, Facultad de Medicina y Psicología, Tijuana, México.
[2] Medical student, Universidad de Sonora, Departamento de Medicina y Ciencias de la Salud, Hermosillo, México.
[3] Medical student, Universidad Autónoma de Baja California, Facultad de Medicina y Psicología, Tijuana, México.
[4] Medical student, Universidad de Guadalajara, Centro Universitario de Ciencias de la Salud, Guadalajara, México.
[5] Medical student, Universidad Autónoma de Chihuahua, Facultad de Medicina y Ciencias Biomédicas, Chihuahua, México.

About the Author: *José Adrián Yamamoto-Moreno is a recently graduated physician from a 7-year program at Universidad Autónoma de Baja California in México. He was awarded the Carlos Slim Foundation scholarship for excellence in Medicine and served as National Officer of Medical Publications in Asociación Mexicana de Médicos en Formación (AMMEF) from 2019-2020.*

Correspondence:
Jose Adrián Yamamoto-Moreno
.ress: Avenida Alvaro Obregon s/n, Nueva, 21100 Mexicali, B.C., Mexico
Email: adrian.yamamoto@uabc.edu.mx

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As an approach to addressing such problems in Mexico, the Asociación Mexicana de Médicos en Formación (AMMEF, the Mexican Association of Physicians in Training) took the initiative to perform an opportunistic BP screening campaign inspired by the MMM methodology.[3,6] The aim of this study was to describe hypertension awareness, treatment, control, and its associated factors in participants of an opportunistic medical student-led BP screening campaign in Mexico.

Methods

Study design and Participants

This was a cross-sectional study using convenience sampling. A detailed protocol was developed to be used for all entities in the country. The full protocol can be consulted at http://ijms.info/IJMS/article/view/639/Supplementary_Material. The eligibility criteria for participants were an age of 18 years and older, and consent to participate in the study according to local policies. Online and face-to-face training was provided for leaders of local screening teams distributed in 15 states of Mexico about the questionnaire application and standardized methodology for BP measurements. The screening was performed in Aguascalientes, Baja California, Chihuahua, Chiapas, Coahuila, Durango, Guanajuato, México, Nayarit, Nuevo León, Puebla, San Luis Potosí, Sonora, Veracruz and Zacatecas. Sites of screening were set up in hospital waiting rooms, public outdoor or indoor areas, nursing homes, schools, homes, and workplaces.

Data were collected from the beginning of June to the end of October 2019 by volunteer medical students using an automated electronic device or an aneroid sphygmomanometer with a stethoscope. Recommendations for the measurement of BP included three seated recordings taken on the left (preferably) or right arm with a one-minute gap between readings.

Questionnaire

The MMM questionnaire was created by the International Society of Hypertension (ISH); it consisted of 24 items with sociodemographic data; identification of risk factors; anthropometric and blood pressure measurements (https://maymeasure.com/ get-involved/downloadable-resources).

Variables

Hypertension was defined as a systolic blood pressure (SBP) ≥140 mmHg or a diastolic blood pressure (DBP) ≥90 mmHg in at least two of the readings. Cases were classified as "unaware hypertensive" (UAH) patients for those that satisfy the hypertension definition at screening but did not have a previous diagnosis or treatment; "controlled hypertensive" (CH) population for those with normal BP values at screening but with a previous diagnosis or treatment for hypertension; "uncontrolled hypertensive" (UCH) patients were those that complied hypertension criteria at screening and had a diagnosis and/or treatment for hypertension; "non-hypertensive" (NH) population were those that did not satisfy any of the previous conditions. A control group was established, including participants without hypertension who declared taking no medication or having clinical signs of diabetes, with no history of stroke, myocardial infarction (MI), gestational hypertension (GH), pregnancy at the time of screening, smoking, and alcohol drinking. Associated factors to changes in BP were considered to be fasting, history of stroke, history of MI, diabetes, pregnancy, history of GH, tobacco smoking, alcohol consumption, body mass index (BMI) and heart rate. Screening locations were classified according to Social Gap Index (SGI) emitted by the National Council for the Evaluation of Social Development Policy, which ranks federal entities on five levels based on access to education, health, basic services and housing, from lowest to highest level of social inequality.[11]

According to the SGI, marginalization is very low in Aguascalientes, Coahuila and Nuevo León; low in Baja California, Chihuahua, State of Mexico, Sonora and Zacatecas; middle in Durango, Guanajuato and Nayarit; high in Puebla and San Luis Potosí and very high in Chiapas and Veracruz.[11]

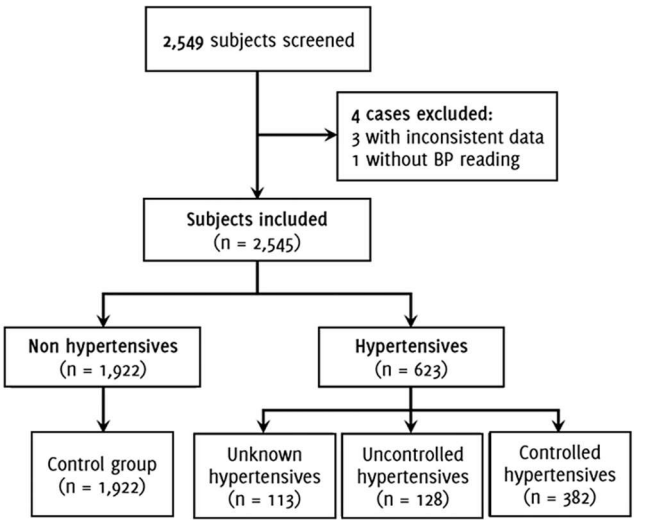
Statistical Analysis

Multiple imputation with linear regression was performed five times using the missing at random (MAR) assumption where data was missing for variables such as height, weight, and subsequent BP readings. Geographical localization, sex, medical history, SBP, and DBP measurements were used as indicators for multiple imputation. Missing values were replaced with the pooled imputed data, and the resulting dataset was tested for normality using the Kolmogorov-Smirnov test in a Monte Carlo simulation of 500 cases. For the analysis of attributable factors to changes in BP, mean SBP, and DBP of the control group were calculated, and used as reference All statistical analysis was performed using IBM SPSS Statistics for Windows (Armonk, NY) and began in June 2020.

Results

From a total of 2,549 entries, the study included 2,545 participants after eliminating 4 entries as shown in ***Figure 1***. Missing data was observed in 48 (1.80%) cases for height, 52 (2.04%) for weight, 800 (31.43%) for second BP reading, and 1,320 (51.47%) for third BP reading. An estimated error <2% in data distribution was observed after multiple imputation.

Figure 1. Study Flowchart.



Roughly half of the screenings were carried out in open public areas (53.8%), followed by hospitals and clinics (26.8%), closed public areas (12.5%), homes (5.1%), workplaces (1.0%), educational institutions (0.5%) and nursing homes (0.3%). From the total number of participants included, 53.6% were women (see ***Table 1***). Mean age was 41 years with a range from 18 to 91 years, with most participants in the 18 to 39 years age group, accounting for 50.6% of screened subjects. Almost a quarter (24.1%) of participants had a history of smoking, 57.7%declared having never or almost never consumed alcohol, 26.6% consumed alcohol between one and three times per month, and 15.3% at least once a week. Regarding diabetes, 6.9% of participants did not know if they had diabetes, whereas 11.4% declared having the diagnosis. Only 1.5% and 2.7% of participants had a history of stroke or MI, respectively. A history of GH was declared by 9.2% of women involved, and only 40 (1.6%) participants were pregnant at the time of screening.

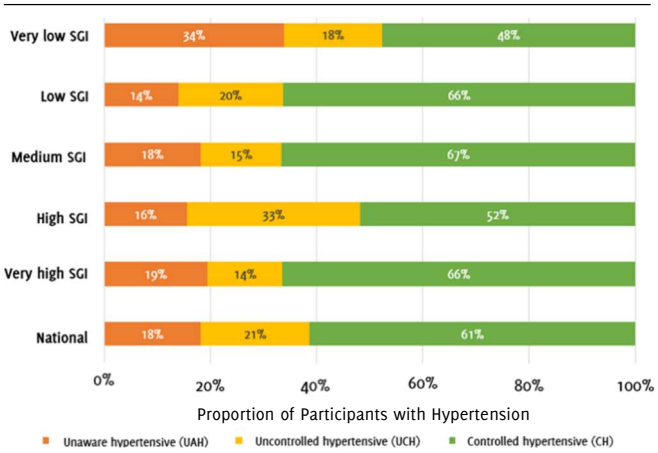
The state with the most participants was Chiapas (12.9%), followed by Puebla (12.8%) and Sonora (11.9%). On the other hand, states with the smallest screened samples were San Luis Potosí (1.0%), Nuevo León (1.1%), and Zacatecas (2.0%). The highest mean BP standardized for age and sex was that of Coahuila (SBP 130.13 mmHg, DBP 85.20 mmHg)

Table 1. Demographic Characteristics of Participants.

Variables	Hypertensive patients *n* = 623 (24.5%)	Non-hypertensive patients *n* = 1,922 (75.5%)	Total *n* = 2,545
Sex, n (%)			
Male	303 (48.6%)	878 (45.7%)	1,181 (46.4%)
Female	320 (51.4%)	1,044 (54.3%)	1,364 (53.6%)
Age, years (standard deviation)			
Mean	56 (15)	36 (16)	41 (73)
Range	18-90	18-91	18-91
Age group, n (%)			
18 to 39 years	94 (15.1%)	1,195 (62.2%)	1,289 (50.6%)
40 to 59 years	262 (42.1%)	531 (27.6%)	793 (31.2%)
≥60 years	267 (42.9%)	196 (10.2%)	463 (18.2%)
History of diabetes, n (%)			
Yes	173 (27.8%)	117 (6.1%)	290 (11.4%)
No	399 (64%)	1,674 (87.1%)	2,073 (81.5%)
Does not know	51 (8.2%)	131 (6.9%)	133 (6.9%)
History of smoking, n (%)			
Yes	163 (26.3%)	447 (23.4%)	610 (24.1%)
No	456 (73.7%)	1,460 (76.6%)	1,916 (75.9%)
Alcohol consumption, n (%)			
1 to 3 times per month	132 (21.2%)	546 (28.4%)	678 (26.6%)
At least once a week	89 (14.3%)	301 (15.7%)	390 (15.3%)
Never	401 (64.4%)	1,067 (55.5%)	1,468 (57.7%)
Not declared	1 (0.2%)	8 (0.4%)	9 (0.4%)
History of stroke, n (%)			
Yes	31 (5.1%)	6 (0.3%)	37 (1.5%)
No	571 (94.9%)	1,886 (99.7%)	2,457 (98.5%)
History of myocardial infarction, n (%)			
Yes	55 (9.2%)	13 (0.7%)	68 (2.7%)
No	543 (90.8%)	1,884 (99.3%)	2,427 (97.3%)
History of gestational pregnancy, n (%)			
Yes	73 (21.8%)	65 (5.6%)	138 (9.2%)
No	262 (78.2%)	1,104 (94.4%)	1,366 (90.8%)
Antihypertensive drugs usage, n (%)			
Yes	428 (68.7%)	0 (0.0%)	428 (68.7%)
No	195 (31.7%)	0 (0.0%)	195 (31.7%)
Aspirin usage, n (%)			
Yes	208 (33.5%)	244 (12.8%)	452 (17.9%)
No	412 (66.5%)	1,666 (87.2%)	2,078 (82.1%)
Statin usage, n (%)			
Yes	158 (25.5%)	38 (2%)	196 (7.8%)
No	462 (74.5%)	1,866 (98%)	2,328 (92.2%)

and the lowest that of Aguascalientes (SBP 110.75 mmHg, DBP 70.56 mmHg), as shown in ***Table 2***. Stratifying by the SGI, states with a low SGI had the most participants (33.7%), and those with very low SGI had least participation (11.2%). Mean BP standardized by age and sex was highest at high SGI (SBP 124.14 mmHg, DBP 82.29 mmHg) and lowest at

Figure 2. Proportion of Unaware, Uncontrolled and Controlled Hypertensives by Social Gap Index.



low SGI (SBP 121.14 mmHg, 78.64 mmHg), as can be seen in ***Table 3***. The number of identified cases of hypertension decreased by 1.25% and 3.57% with the second and third readings, respectively, and increased to 5.18% using the mean of the three readings, as shown in ***Table 4***.

National mean BP, considering all three readings, was 119.56 mmHg for SBP and 77.28 for DBP. Classifying participants by type of case, as previously described, it was found that 922 (75.5%) were NH and 623 (24.5%) participants had hypertension. Of those with hypertension, 510 (81.9%) subjects had a previous diagnosis of hypertension, and only 82 (16.1%) did not declare taking a pharmacological treatment at the time of screening; 397 (61%) were CH patients, 128 (21%) were UCH patients and 113 (18%) were UAH cases. The proportion of UAH patients in areas with a very high SGI was only 1% above the national figure; meanwhile those areas with a very low SGI doubled it (34% vs. 18%). States with a low SGI were the areas with the smallest number of cases of UAH (14%). A high SGI was found to have the highest number of UCH cases (33%), being the only group of states surpassing the national figure. On the other hand, areas with medium SGI had the largest proportion of CH cases (67%). In contrast, regions with a very low SGI had the smallest proportion of controlled patients, followed by the states with low SGI, 13% and 9% below the national figure, respectively, as shown in ***Figure 2***.

The most common medications among participants were antihypertensive drugs, such as angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), calcium channel blockers, diuretics, beta-blockers, and alpha-agonists, with 428 (16.8%) patients taking at least one of them, which accounted for 68.7% of hypertensive patients taking medication. Of these, 225 (52.6%) took one medication with 171 (76.0%) controlled, 145 (33.87%) took two medications and 98 (67.6%) were controlled, 42 (9.8%) took three antihypertensive drugs with 30 (71.4%) controlled, 10 (2.3%) took four different medications with 100% control rate, and 6 (1.42%) took five or more medications achieving BP control in 4 (66.7%). Aspirin was the second most used drug among hypertensive patients (33.5%), followed by statins (25.5%).

A polynomic (two degrees) model of the association between age and mean BP from all three readings, including patients not receiving pharmacological treatment, (***Figure 3***) showed an ascending linear trend for SBP in women, and an inverted U shape for DBP, with the largest increment in BP between 65 and 75 years of age. Meanwhile, both curves showed an inverted U shape for men with the highest BP levels between 50 and 60 years for SBP, and between 45 and 55 years for DBP. Men had an SBP higher than women up until 73 years, at which point trends are inverted. The same phenomenon was also observed for DBP at age 72.

Table 2. Mean Blood Pressure by State, before and after standardization by age and sex.

State	*n* (%)	SBP (mmHg)		DBP (mmHg)		Standardized by age and sex SBP (mmHg)		DBP (mmHg)	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
Aguascalientes	154 (6.1)	114.66	12.13	73.08	9.48	110.75	12.13	70.56	9.48
Baja California	160 (6.3)	121.64	14.07	75.64	11.06	119.57	14.07	74.67	11.06
Chihuahua	176 (6.9)	120.41	11.95	79.89	10.72	118.99	11.95	78.79	10.72
Chiapas	328 (12.9)	119.89	11.58	76.91	8.26	118.78	11.58	76.97	8.26
Coahuila	104 (4.1)	129.93	20.42	84.92	11.98	130.13	20.42	85.20	11.98
Durango	152 (6.0)	122.16	14.82	82.09	22.54	118.62	14.82	80.88	22.54
Guanajuato	151 (5.9)	114.71	7.99	75.44	5.06	114.21	7.99	75.34	5.06
México	167 (6.6)	119.65	14.58	78.52	10.71	118.27	14.58	77.99	10.71
Nayarit	178 (7.0)	120.04	11.91	79.55	9.33	118.64	11.91	78.88	9.33
Nuevo León	28 (1.1)	122.75	6.94	77.14	3.20	122.04	6.94	76.95	3.20
Puebla	327 (12.8)	124.43	14.36	76.64	8.05	123.13	14.36	76.33	8.05
San Luis Potosí	25 (1.0)	123.47	15.37	80.51	11.28	114.85	15.37	76.58	11.28
Sonora	304 (11.9)	122.71	14.60	80.93	12.02	120.82	14.60	79.73	12.02
Veracruz	240 (9.4)	121.85	15.54	76.13	11.42	120.81	15.54	76.04	11.42
Zacatecas	51 (2.0)	123.15	14.82	81.46	9.73	122.52	14.82	80.86	9.73

The control group was composed of 704 participants; their mean BP including all three readings was 114.52 mmHg for SBP and 75.14 mmHg for DBP. Analyzing for possible factors attributable to changes in BP, all variables except pregnancy, which decreased DBP by 1.5 mmHg, were associated with an increased mean difference (MD) in BP, as can be seen in ***Figure 4***. Factors with the most influence over SBP were history of MI (13.41 mmHg), diabetes (12.80 mmHg), and stroke (12.11 mmHg). The highest increase in DBP was observed in participants with a history of stroke (6.64 mmHg), diabetes (4.59 mmHg) and MI (3.47 mmHg). Tobacco smoking was shown to increase SBP by 7.25 mmHg and DBP by 3.37 mmHg, whereas alcohol drinking increased 4.06 and 7.06 mmHg for SBP and 2.21 and 2.50 mmHg for DBP in those who drank one to three times per month and at least once a week, respectively. Aside from medical history, fasting at the time of screening was the condition associated with the highest increase in SBP (10.36 mmHg); DBP only increased by 3.01 mmHg.

A proportional increase in BP and BMI was observed, with obese participants having an additional 13.54 mmHg in SBP and 8.11 mmHg in DBP. On the contrary, those considered underweight had a decrease of 0.43 mmHg in SBP and 4.92 mmHg in DBP compared with those in th control group, as shown in ***Figure 5***.

Figure 3. Change in Blood Pressure with Age and Sex from Linear Polynomic Model.

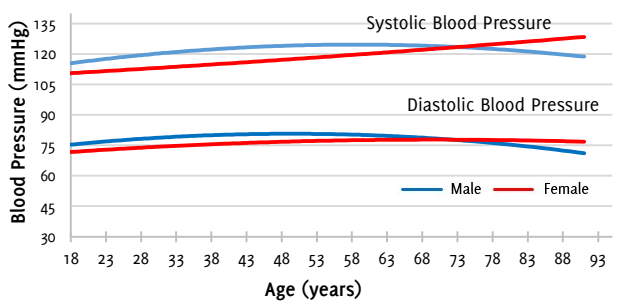
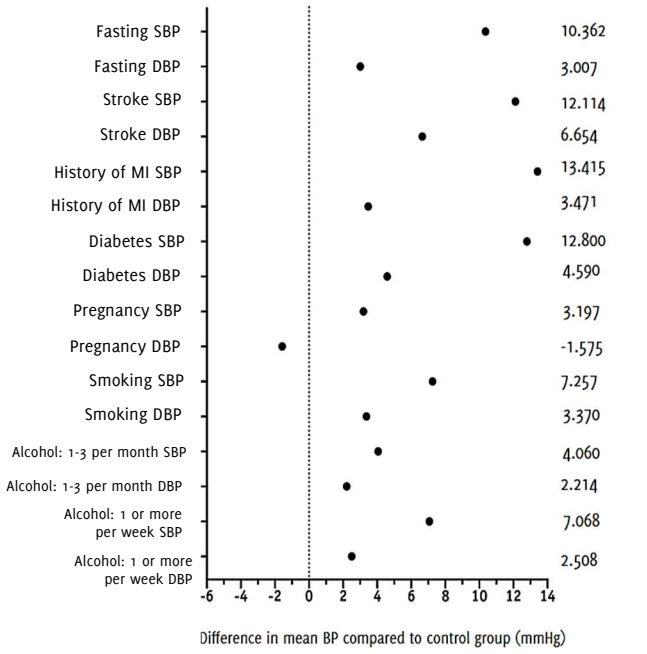


Figure 4. Change in Mean Systolic and Diastolic Blood Pressure Compared to Non-hypertensives for Associated Factors to Changes in Blood Pressure.



Comparing mean heart rate from all three BP readings, a similar phenomenon from that observed with BMI emerges, where the greater the heart rate, the higher the increase in BP. An increase of 16.68 mmHg in SBP and 10.79 mmHg in DBP were seen with heart rates ≥100 bpm. Meanwhile, when the heart rate is <60 bpm, DDB descends 0.73 mmHg (see ***Figure 6***) compared to the control group.

Table 3. Mean Blood Pressure by Social Gap Index, Before and After Standardization by Age and Sex.

Social Gap Index	n (%)	SBP (mmHg)		DBP (mmHg)		Standardized by age and sex			
						SBP (mmHg)		DBP (mmHg)	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
Very low[a]	286 (11.2)	118.90	17.81	76.51	12.16	122.84	17.81	79.01	12.16
Low[b]	858 (33.7)	119.82	14.02	78.32	11.34	121.14	14.02	78.64	11.34
Medium[c]	481 (18.9)	117.24	12.07	78.40	14.31	120.07	12.07	80.98	14.31
High[d]	352 (13.8)	122.55	14.57	76.34	8.30	124.14	14.57	82.29	8.30
Very high[e]	568 (22.3)	119.63	13.42	76.58	9.73	120.89	13.42	80.64	9.73

Legend: *[a] Includes Aguascalientes, Coahuila and Nuevo León; [b] Includes Baja California, Chihuahua, México, Sonora and Zacatecas; [c] Includes Durango, Guanajuato and Nayarit; [d] Includes Puebla and San Luis Potosí; [e] Includes Chiapas and Veracruz*

Table 4. Mean Blood Pressure by Social Gap Index, Before and After Standardization by Age and Sex.

Reading	SBP (mmHg)		DBP (mmHg)		Number with hypertension	Proportion of hypertension (%)
	Mean	SD	Mean	SD		
1	120.43	15.29	77.50	11.23	546	21.45
2	119.21	14.67	77.37	18.24	514	20.20
3	119.05	14.15	77.26	11.37	455	17.88
Mean of 1 and 2	119.82	14.50	77.43	12.74	450	17.68
Mean of 2 and 3	119.13	14.12	77.31	12.73	422	16.58
Mean of 1, 2 and 3	119.56	14.18	77.38	11.40	414	16.27

Figure 5. Change in Mean Systolic and Diastolic Blood Pressure Compared to Non-hypertensives, for Body Mass Index Category.

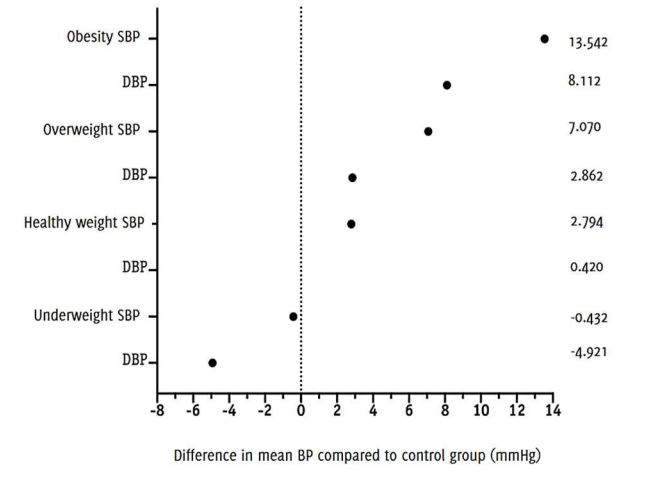
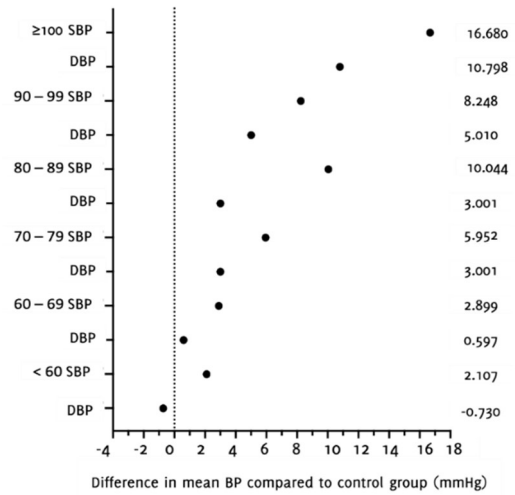


Figure 6. Change of Systolic and Diastolic Blood Pressure Compared to Non-hypertensives, for Heart Rate Range.



Discussion

In this study of over 2,500 adults in Mexico, it was observed that 24.5% were hypertensive, similar to the 25.5% reported by the ENSANUT 2016 study and lower compared to 73.0% reported by the MMM 2019 study for the Americas region.[6,10] Of those with hypertension, 18.0% were unaware they might have it, 21.0% were uncontrolled hypertensives and 61.0% had BP values <140/90 mmHg, therefore were considered to be well-controlled patients for this study. These numbers are far more optimistic than those reported by previous studies with only 45.6% and 37.1% of controlled subjects and 40.0% and 53.5% of unaware patients in national and global surveys, respectively.[10,12] This could be explained by the opportunistic nature of this study. Also, through this campaign, hypertension awareness was raised in only 113 individuals across Mexico.

According to Ríos-Blancas et al.,[13] low and very low SGI states have a higher probability of receiving a pharmacological treatment than states with a high and very high SGI, which accounts for three in four cases receiving treatment, but less than a third of these achieving BP control. This is consistent with the findings in this study, which showcased that states with a high marginalization were found to be the largest contributor to the pool of uncontrolled cases (33%). On the other hand, the largest proportion of hypertension unawareness was observed at very low SGI states (34%), almost doubling the national figure. In contrast, states with medium (67%), low, and very high SGI (66%) had the highest proportion of controlled hypertensives. Possible explanation for this could be that limited access to medications adds

to their perceived value among populations that are not accustomed to receiving medical treatment, which improves compliance in these groups.

More than half of the participants taking antihypertensive agents were on a single medication, achieving blood pressure control in almost 8 in 10 patients. This is the largest proportion compared with the use of additional medication in this study, which contrasts with the findings of the MMM 2019[6] where almost 4 in 10 patients on a single agent were uncontrolled. However, these findings do not dispute the recommendations to initiate pharmacological treatment with two agents[14,15] as a 67.6% controlled rate was observed with this regimen. The questionnaire used in this study did not allow to collect data about specific types of antihypertensive drugs used by participants, only the number of pharmacologic agents they used. On the other hand, aspirin was taken by a large proportion of participants, 33.5% of hypertensives and 12.8% of non-hypertensives, which goes against the latest recommendations about minimizing the routine usage of aspirin for the primary prevention of CVD because of lack of net benefit.[16]

A strong association consistent with previous publications was observed between BP and several known risk factors such as smoking and alcohol intake,[17,18] with the latter showing a dose-response effect with a greater increase in BP in heavy drinkers similar to what has been described by other authors.[19] A higher BMI was consistently related to a higher BP, although participants considered to have obesity in this study had a much higher increase in BP (SBP 13 mmHg and DBP 8 mmHg) compared to that reported by previous studies.[6,19,20] This is a serious concern because Mexico has one of the highest rates of obesity worldwide, and these are continuing to rise,[21] therefore a similar trend in hypertension could be expected if no further actions are taken.

On the other hand, subjects with a history of stroke and MI showcased a surplus in BP compared to the control group with an increase of 12 and 13 mmHg in SBP, respectively. A similar phenomenon was also observed in people with diabetes. These findings could suggest that patients with a history of stroke and MI in this population were not adequately controlled, even though hypertension is the most important factor for stroke recurrence.[22] However, a J-curve phenomenon has been described[23] in which a permissible BP target should be achieved to prevent the overly strict controlling of BP increasing the risk of adverse outcomes. On the contrary, evidence suggests that prompt, long-term BP control is imperative to improve secondary prevention of MI.[24] Thus, further studies are needed to explore this topic, specifically in the Mexican population.

Risk of ascertainment and selection bias were inherent to the design because participants presented voluntarily at screening sites; therefore, people worried about their BP were more likely to participate. Thus, prevalence should not be inferred. It is worth noting that standardized by age and sex mean BP was within the normal range in all states. Coahuila had the highest mean BP with 130/85 mmHg, whereas Aguascalientes had the lowest with 110/70 mmHg. As an opportunistic campaign and cross-sectional study using convenience sampling, it could be expected that a higher proportion of health-conscious individuals (either well-controlled hypertensive patients or otherwise healthy people) took part in the study, which could explain atypical results. Any generalization about these results should be made cautiously.

Despite efforts to provide training on standardized BP readings to volunteers, differences in screening locations, and the usage of different equipment account for some degree of error in measurements. Although data about the devices used to measure BP was collected, the heterogeneity in reporting and the vast array of brands and models did not facilitate further analysis. However, as reported by Varshney et al.,[25] there is no significant difference in BP readings using automated and auscultatory methods to determine SBP in the context of a community-based screening program, but DBP might differ between methods. Likewise, the main researchers did not have control over the number of students working at screening sites, which further limits the accuracy of measurements.

Most current guidelines recommend using ambulatory or home BP measurements,[14,15] this approach was not cost-effective for this study, and the diagnosis of hypertension was based on a single set of readings. While this might not be ideal, spaced serial measurements including three BP readings provided a means to mitigate the impact of atypical values, errors in measurement or factors related to the patient such as white coat syndrome. On the other hand, at least one BP reading was missing for 31.4% of participants, which could significantly affect the statistical analysis and lead to an over-diagnosis of hypertension. Using multiple imputation, it was possible to mitigate that error by estimating mean second and third BP readings from a single measurement with minimal error in data distribution models. Nevertheless, the interpretation of results from this imputed data should be taken carefully.

A questionnaire was used to obtain the medical history of participants. This limits our ability to explore other comorbidities not included in the original questionnaire, but it does not mean that other associations with hypertension (apart from diabetes, MI, and stroke) could not be found. Also, this questionnaire asked participants about the usage of pharmacological agents prescribed by a physician for BP control, thus, differences in the accuracy of recollection could have led to a recall bias involving the number of drugs taken by participants.

To our knowledge, this is currently the only medical student-led campaign to raise hypertension awareness at a national level in Mexico. It was observed that a significant proportion of the study population was unaware of having hypertension, especially in states with a lower level of marginalization and considered to be more developed. In contrast, a larger number of subjects within BP control targets were found in more marginalized, less developed regions.

Most uncontrolled hypertensive patients in Mexico belong to marginalized states. These results could inform state legislative policy to help bridge these healthcare gaps by improving hypertension detection, especially among those who do not partake in regular health checkups or have limited access to healthcare.

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Author Contributions

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ULS

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Supplementary Material

Supplementary Material:

Hypertension Awareness, Treatment and Control in Mexico: An Opportunistic Medical Student-led Blood Pressure Screening Campaign – A Cross-Sectional Study

The Mexican Association of Medical Students Blood Pressure Reading, 2019. Study Protocol

Executive Summary

In May 2017 and 2018, the International Society of Hypertension (ISH) performed a global BP awareness campaign including more than 2.7 million people from more than 100 countries to raise hypertension awareness.[1,2]

Hypertension is defined as the sustained elevation of the pressure within the blood vessels. In Mexico, the cutoff values to diagnose hypertension are 140/90 mmHg and above.[3]

The aim of this protocol is to conduct a national opportunistic blood pressure (BP) detection campaign in Mexico to raise awareness and estimate control of those screened who were detected as hypertensive.

Background

Hypertension is the modifiable risk factor to which more deaths are attributed around the world. In Mexico, the National Health and Nutrition Survey (ENSANUT) 2016 showcased that around 30% of the population above 20 years of age lives with hypertension, and roughly half of these people do not know about their condition. Another worrying figure is that 65% of people with hypertension do not adhere to anti-hypertensive treatment.[3]

Several strategies have been implemented globally and nationally to fight hypertension—one of the most recent and ambitious ones is the May Measurement Month (MMM), created by the ISH.[1,2] The MMM is a cross-sectional study which aims to raise awareness and determine prevalence, control and associations related to elevated BP.[1,2] In 2018, our national medical students' association (AMMEF) performed a longitudinal pilot study across Mexico about knowledge and control of hypertension. However, the methodological complexity of that project has deterred its analysis and publication.

Justification

Social and economic consequences derived from hypertension have been devastating to health systems around the world.[4] There is a gap in hypertension awareness and control in our country.[5] And more information is needed about the characteristics of people who live with uncontrolled hypertension in Mexico.

As previously mentioned, our association has tried to contribute in increasing the knowledge about this phenomenon. However, study designs previously selected for this purpose were too ambitious to be carried nationally by medical students and no background information was obtained prior its implementation to justify the need of such type of study.

This is the reason why a cross-sectional design is best suited to explore issues that could later be studied through a longitudinal methodology.

Study Aims

General Aim

To perform an opportunistic blood pressure reading campaign in the Mexican population to raise awareness and study control of hypertension.

Specific Aims

- To measure BP in a population obtained by convenience sampling around Mexico
- Apply the ISH MMM Questionnaire to determine associated factors
- Raise awareness of hypertension
- Raise awareness of the importance of knowing one's BP numbers through printed materials and talks at screening sites
- Estimate the prevalence of hypertension, the proportion of controlled and uncontrolled individuals within the study population
- Compare hypertension prevalence, awareness, and control of participants between states of Mexico

Methodology

Study design

A cross-sectional study based on an opportunistic screening campaign.

Sampling

Convenience sampling will be the method to include participants in the study, given the characteristics of an opportunistic screening campaign. We have not calculated a sample size to reach statistical power.

Temporality

All training about BP measurement and questionnaire application should be carried out before June 10, 2019. The first phase of screening at hospitals and clinics waiting rooms and entrance will be performed from June 10 to August 9, 2019. The second phase of screening in public spaces will be carried out from September 23 to October 21, 2019, in the same cities as the hospital/clinic screenings were performed.

Territory

This is protocol is applicable throughout Mexico.

Inclusion criteria

- People older than 18 years of age
- Informed consent by participants conforming to local dispositions (an informed consent form will be provided as a document and digital to local screening teams)

Study Steps

- Students should give ample information about the study to participants as well as obtain informed consent to participate. All information (including written material) should be given in a clear and easy to understand language.
- Data collection about the screening site and basic demographic information
    - All data must be collected and registered before BP readings.
    - If using the digital format (see Questionnare below), data will not be changed and therefore should be registered only one time
    - Indispensable information includes: City and state, address of screening site, date, participant's age, sex, at least 1 BP reading of systolic blood pressure and diastolic blood pressure, and heart rate.
- Other variables that should be registered when available:
    - Screening site identification and/or e-mail from the center at which is screening took place
    - Type of screening site: hospital/clinic, pharmacy, workplace, open public space, closed public space, home, other
- Students must apply the questionnaire to all screenees according to training, and after completion perform the BP reading.

Measurements by the International Society of Hypertension Questionnaire

- The Questionnaire should be filled into the digital format or using the official printed version
    - When was the last time you had your blood pressure read? Never / >12 months ago / <12 months ago
    - Have you been diagnosed with hypertension/high blood pressure by a health professional? Yes / No
    - Currently, are you taking any medication/prescription for hypertension/high blood pressure? Yes / No / Does not know, if YES:
        - How many drugs are you taking for your blood pressure? 1 / 2 / 3 / 4 / 5 or more
    - Are you taking a statin (give examples)? Yes / No
    - Are you taking aspirin (give alternative names)? Yes / No
    - If WOMAN: Are you pregnant? Yes / No
        - Has your blood pressure increased in this or a previous pregnancy? Yes / No
    - Self-declared ethnic origin
    - Right now, are you fasting? Yes / No
    - Do you have diabetes or have been diagnosed with diabetes by a doctor? Yes / No / Does not know
    - Do you smoke or use any tobacco product? Yes / No
    - Do you consume alcohol? Never or almost never / 1-3 times per month / at least 1 time per week
    - Have you had a heart attack? Yes / No / Does not know
    - Have you had a stroke? Yes / No / Does not know
    - Height (measured at screening site [preferably] or declared if not possible to measure, approximate if necessary)
    - Weight (measured at screening site [preferably] or declared if not possible to measure, approximate if necessary)
- Systolic blood pressure (1-3 readings)
- Diastolic blood pressure (1-3 readings)
- Heart rate (1-3 readings)
- Name of the brand and model of the device(s) used to perform BP reading

Blood pressure readings

- All students must use the method described in: https://youtu.be/9kesU_3_7As to perform BP readings.
- BP should preferably be measured by an automated electronic device or, if this is not available, a conventional sphygmomanometer using a stethoscope can be used.
    - If a sphygmomanometer is used, the first and fifth Korotkoff sounds (the appearance and disappearance of sounds) will be recorded as the systolic and diastolic BP.
- BP should be measured on the upper-arm
- Ensure that the correct size of arm cuff is used
    - For arms with circumference < 32 cm, use regular cuff
    - For arms with circumference 32-42 cm, use large cuff
    - For arms with circumference >42 cm, use extra-large cuff
    - For arms with circumference <20cm use pediatric cuff
    - The cuff should be placed at the heart level
- The screened subjects' arm, being used for the measurement, should rest comfortably on a table
- BP should be measured on one arm only, preferably left
- Prior to measurement:
    - The participant should be seated with their backs supported, legs uncrossed and feet flat on the ground for 5 min (during which time the Questionnaire should be applied)

- Participants should not have smoked immediately before or during the measurement and should not talk during and between BP measurements.
- Three (3) BP readings should be taken with 1 min between readings and recorded
- For each BP reading, the automated BP devices also provide data on heart rate, and this information should also be captured
- If the auscultatory method/sphygmomanometer is used, the heart rate should be established during the 1 minute after each BP reading, and also recorded

Definitions

- Hypertension
  - Hypertension was defined as a systolic blood pressure (SBP) .140 mmHg or a diastolic blood pressure (DBP) .90 mmHg in at least two of the readings, OR
  - Taking at least one anti-hypertensive agent.
- Unaware hypertensive
  - Those that satisfy the hypertension definition at screening but did not have a previous diagnosis or treatment.
- Controlled hypertensive
  - Those with normal BP values at screening but with a previous diagnosis or treatment for hypertension.
- Uncontrolled hypertensive
  - Those that complied hypertension criteria at screening and had a diagnosis and/or treatment for hypertension.

Materials to be used at screening site

- Mobile devices with Internet access to the digital Questionnaire or printed copies of the Questionnaire (MMM_Cuestionario.pdf)
- Stethoscope
- Sphygmomanometer (aneroid)
- Digital BP reading devices
- Calibrated body weight scales
- Calibrated stadiometer
- Printed copies of informed consent (InformedConsent_Example.docx)
- Tables, chairs and tents as necessary

Recommendations that could be made to screened participants

- Reducing salt consumption
- Moderate ingests of alcohol
- Stop smoking
- Reducing caffeine consumption
- Reducing sugar and fat consumption
- Regular physical activity at least 30 minutes a day, almost every day
- Consumption of fruits and vegetables every day
- Maintaining a normal body weight
- Avoiding stress as possible and having relaxation moments

Statistical analysis

- The sample size was not calculated, in aims to include the largest number of participants as attainable by the local screening teams.
- The analysis will include, but not be limited to:
  - Hypertension prevalence in study population
  - Proportion of unaware patients
  - Proportion of controlled patients
  - Proportion of uncontrolled patients
  - Relationship between associated factors and change in BP compared to non-hypertensive patients

Ethical issues

- Conforming to local dispositions. All participants should give their informed consent to be included, which will be recorded in the digital and/or printed forms.

All participants must receive a verbal and/or written explanation of the study.

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Review

Novel Combination Strategies to Enhance Immune Checkpoint Inhibition in Cancer Immunotherapy: A Narrative Review

Jonathan A. Hermel,[1] Cassi M. Bruni,[2] Darren S. Sigal.[3]

Abstract

Programmed cell death protein-1 (PD-1) is an immune checkpoint receptor that induces and maintains tolerance of T cells, invariant natural killer T (iNKT) cells, and natural killer (NK) cells, among other lymphocytes. Immune checkpoint inhibition by PD-1 blockade restores the lymphocytic immunostimulatory phenotype and has been successful in the treatment of various malignancies. However, while immune checkpoint blockade has been shown to provide robust antitumor treatment outcomes, its overall response rate remains low in a significant portion of cancer patients. An essential unmet need in cancer therapy is the development of novel pharmacologic strategies designed to lower rates of resistance associated with immune checkpoint blockade. Therefore, efforts that seek to enhance the efficacy of PD-1 inhibition possess profound immunotherapeutic potential. Here, three promising combination strategies that harness the antitumor effects of immune checkpoint inhibitors (ICIs) together with non-ICI antitumor therapeutic agents are reviewed. These agents include (1) ABX196, a potent inducer of iNKT cells, (2) chimeric antigen receptor (CAR)-T cell therapy, and (3) NK cell therapy. A comprehensive literature search was conducted using the PubMed and ClinicalTrials.gov databases for scientific articles and active trials, respectively, pertaining to immune checkpoint inhibition, iNKT cells, CAR-T cells, and NK cell immunotherapy. Preliminary clinical and preclinical data suggest that these combination treatment regimens greatly suppress tumor growth and may serve as innovative methods to enhance and optimize anticancer immunotherapy.

Key Words: Immunotherapy; Immune checkpoint molecules; Invariant Natural Killer T Cell; Chimeric Antigen Receptor; Natural Killer T-Cells (Source: MeSH-NLM).

Introduction

Immunotherapy represents the newest pillar in anticancer therapy. The first fifty years of anticancer therapy consisted solely of cytotoxic chemotherapy, but this began to change in the 1990s with the advent of monoclonal antibodies and again in the early 2000s with the development of small molecule tyrosine kinase inhibitors. Each successive new approach has increased therapeutic efficacy and resulted in improved patient outcomes. United States Food and Drug Administration (FDA)-approved immunotherapies, in the form of immune checkpoint inhibitors (ICIs) to the cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) and programmed cell death protein-1 (PD-1) checkpoint receptors, may represent the most profound advances in anticancer therapy in modern history. Cancers notoriously difficult to manage, including non-small cell lung cancer (NSCLC) and melanoma, have responded well to ICI immunotherapy, whether administered solely as monotherapy or in combination with chemotherapy in the neoadjuvant, adjuvant, and advanced late-stage settings.[1,2,3] However, despite their proven antitumor treatment outcomes, ICIs have modest overall response rates, not only between varying cancer types, but also among patients who share the same malignancy.[4] The identification of novel tumor biomarkers is an ongoing area of research aimed at predicting resistance to ICI immunotherapy and developing targeted approaches that seek to overcome this resistance.[5] It remains that a key unmet need in cancer therapy is improving the consistency and functional efficacy of ICIs in a majority of cancer patients. A variety of novel immune therapies and targeting approaches are in clinical development that may mark another important step forward towards this goal. This review will examine the preclinical and clinical data of ABX196, a non-checkpoint inducer of invariant natural killer T (iNKT) cells; chimeric antigen receptor (CAR)-T cell therapy; and natural killer (NK) cell therapy, each in combination with ICIs for improved anticancer immunotherapy.

Methods

An extensive scientific literature search was performed using the PubMed database for peer-reviewed articles published in academic journals related to immune checkpoint inhibition, iNKT cells, CAR-T cells, and NK cells. The literature search was conducted between the months of May and July 2020. Search parameters included combinations of the keywords "ABX196," "α-GalCer," "invariant natural killer T cell," "iNKT cell," "chimeric antigen receptor T cell," "CAR-T cell," "natural killer cell," or "NK cell," with the terms "PD-1," "immune checkpoint inhibitor," "immune checkpoint inhibition," or "immunotherapy." Only studies published in English with full available text were screened for use. Because of the intended comprehensive nature of this review, a small portion of the manuscript pertaining to the background and history of α-GalCer mechanistic studies includes original articles published from 1994 to 2018. For the remainder of the paper, only articles published within the past 10 years were considered for use. Article abstracts were closely reviewed for applicability to the research question and those without clear relevance were removed from consideration. For information regarding active clinical trials, a detailed search of ClinicalTrials.gov was conducted. Initial search parameters included the keyword phrases, "ABX196," "CAR-T cell," "NK cell" or "natural killer cell." Trials located in all countries were included for

[1] BA, Tulane University School of Medicine, Department of Graduate Medical Education, United States
[2] MS, University of California, San Diego, Department of Cellular and Molecular Medicine, United States
[3] MD, Scripps Clinical Medical Group, Division of Hematology/Oncology, United States

About the Author: *Jonathan A. Hermel is a third-year medical student at Tulane University School of Medicine in New Orleans, Louisiana. Darren S. Sigal is a hematologist/oncologist at Scripps Clinic in La Jolla, California, where he is head of the gastrointestinal cancer division. He is an active participant and developer of on-going clinical studies focused on the treatment of pancreatic cancer, colorectal cancer, and liver cancer. Cassi M. Bruni is a recent graduate with honors of the M.S. Biology program at the University of California, San Diego, Department of Cellular and Molecular Medicine.*

Correspondence:
Darren S. Sigal
Address: 10710 N Torrey Pines Rd, La Jolla, CA 92037, United States
Email: Sigal.Darren@scrippshealth.org

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review; however, trials that were not in the recruiting or pre-recruiting stages were filtered out. Listed trial titles and descriptions were then manually screened for protocols that included additional ICI immunotherapies. Trials that did not meet the aforementioned criteria were excluded.

Results and Discussion

ABX196 in Combination with PD-1 Blockade

Background and rationale: iNKT cell anergy is associated with PD-1 upregulation

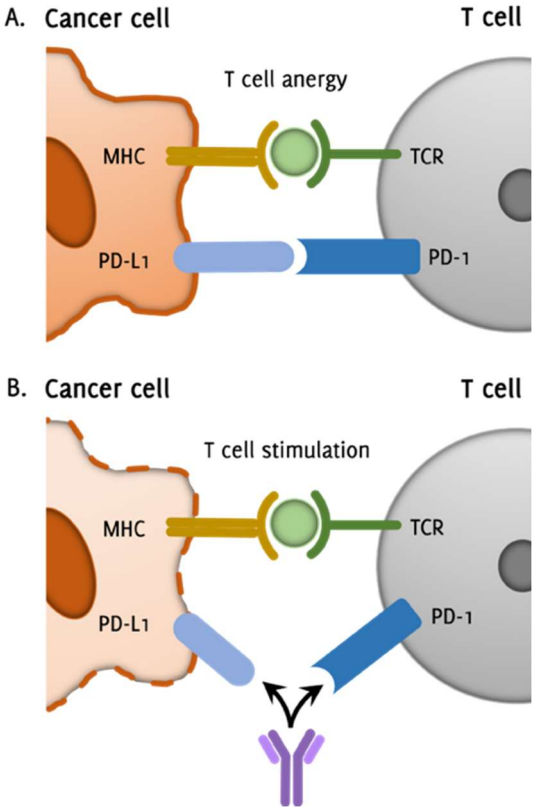
ABX196 is a synthetic glycolipid analogue of α-galactosylceramide (α-GalCer), a strong agonist of invariant natural killer T (iNKT) cells. In contrast to conventional T and NK lymphocytes, iNKT cells induce both innate and adaptive antitumor immune responses.[6] iNKT cells express an invariant T cell receptor (TCR) composed of Vα14-Jα18/Vβ8.2 gene chain rearrangements in mice and Vα24-Jα18/Vβ11 gene chain rearrangements in humans.[7] These invariant TCRs recognize endogenous and exogenous lipid moieties bound to and presented on non-classical, major histocompatibility complex (MHC) class I-like CD1d molecules.[8] CD1d is a membrane-bound cell surface glycoprotein expressed primarily by B lymphocytes, macrophages, and dendritic cells (DCs).[9] When lipid moieties are presented within the hydrophobic binding-groove of CD1d, they interact with the iNKT TCR; this association stimulates iNKT cells, which in turn modulate the immune system.[10] Specifically, *in vivo* administration of α-GalCer in mice triggers iNKT cells to i) rapidly proliferate, ii) release a variety of cytokines, including IFN-γ and IL-4, iii) cross-prime dendritic cells to release IL-12, and iv) slow tumor growth and prevent metastasis.[11,12] Although α-GalCer is a powerful iNKT cell-stimulating antigen, its antitumor efficacy is restricted by the fact that α-GalCer-stimulated iNKT cells release cytokines with opposing immune system actions, specifically IFN-γ, which initiates an immunostimulatory T helper 1 (TH1) response, and IL-4, which initiates an immunoregulatory T helper 2 (TH2) response.[13] The favorable effect of iNKT cells in antitumor immunity is due, in large part, to IFN-γ production.[14] ABX196 consists of an acetamide group linked to the galactosyl C6 of α-GalCer, and this structural modification has been shown to enhance the secretion of TH1 cytokines.[15] As compared to α-GalCer, ABX196 produces high levels of systemic IFN-γ but significantly lower levels of IL-4, confirming a pro-inflammatory TH1 skew in cytokine production.[15]

While ABX196 induces a more potent immunostimulatory response beneficial for antitumor immunity, iNKT cell activation quickly leads to a long term unresponsive, anergic state for two primary reasons: one, the iNKT TCR becomes downregulated;[16,17] and two, PD-1 receptors become upregulated at the surface of iNKT cells.[18,19] PD-1 is a T cell checkpoint receptor that, when bound to its ligand PD-L1, functions to induce and maintain T cell tolerance (***Figure 1***).[20] The FDA has approved a number of monoclonal antibodies that target and interfere with the PD-1/PD-L1 signaling pathway for use in cancer therapy.[21] These include anti-PD-1 antibodies nivolumab, pembrolizumab, and cemiplimab, as well as anti-PD-L1 antibodies atezolizumab, avelumab, and durvalumab.[21] The aforementioned ICIs have emerged in recent years as effective therapeutics for a variety of cancers due to their unique ability to block and reverse T cell anergy.[22] These findings have led to the pharmaceutical approach of simultaneously administering both an iNKT cell agonist and an anti-PD-1 antibody to limit iNKT cell anergy and thus enhance antitumor immunity.

Preclinical Data: iNKT Agonist with PD-1 Blockade

Several preclinical studies have explored the immunotherapeutic potential of α-GalCer-mediated iNKT induction in combination with PD-1 blockade. Parekh et al.[19] demonstrated that antibody-mediated inhibition of PD-1/PD-L1 interactions at the time of α-GalCer treatment prevented the induction of iNKT cell anergy and enhanced the anti-metastatic activity of α-GalCer in wild-type mouse models. The same study showed that PD-1 deficient mice were resistant to α-GalCer-induced iNKT cell anergy. Durgan et al. [23] performed similar experiments with murine melanoma models. In their study, PD-L1 deficient mice were administered DCs loaded with antigen and α-GalCer; these mice subsequently had a significant reduction in tumor size associated with increased trafficking of antigen-presenting cells (APCs) and $CD8^+$ cytotoxic T cells to the sites of tumors.[23] The importance of α-GalCer and PD-1 blockade on $CD8^+$ T cell cytotoxic activity has been demonstrated by Bae et al.,[24] who found that administration of an iNKT agonist in an anti-PD-1-resistant tumor model re-stimulated exhausted $CD8^+$ T cells through the enhanced secretion of IL-2 and IL-12. They also observed a synergistic increase in the antitumor effect between α-GalCer-loaded APCs and PD-1 blockade. Moreover, *in vitro* assays with human peripheral blood mononuclear cells (PBMCs) showed that the simultaneous co-administration of an anti-PD-L1 antibody and α-GalCer-pulsed APCs enhanced both the direct cytotoxic and indirect TH1 cytokine release functions of iNKT cells, enhancing their antitumor immunostimulatory functions.[25] Lastly, preclinical studies in mice have confirmed the similarities between ABX196 and α-GalCer concerning *in vitro* and *in vivo* stimulation of iNKT cells.[15] Toxicity reports from these same experiments suggested no considerable adverse effects of ABX196 in mice and monkeys at the doses necessary for immune activation, although hepatic toxicity in the form of elevated transaminases was observed in mice at doses higher than that required for immune activation.[15]

Figure 1. Mechanism of Checkpoint Inhibition in Promoting Anti-Tumor Immune Stimulation



Legend: Simplified illustration demonstrating the mechanism of immune checkpoint inhibition in cancer immunotherapy. ***Figure 1.A.*** shows the T cell programmed cell death protein-1 (PD-1) receptor interacting with the corresponding tumor programmed cell death protein-1 ligand (PD-L1) receptor, leading to T cell anergy and inactivity. This occurs despite appropriate antigen presentation on the major histocompatibility complex (MHC) and proper recognition by the T cell receptor (TCR). ***Figure 1.B.*** demonstrates the targeted interruption of the PD-1/PD-L1 interaction by a monoclonal antibody immune checkpoint inhibitor (ICI). This inhibition of PD-1/PD-L1 signaling promotes continued stimulation of the T cell to induce tumor cell death.

Clinical Data: ABX196 and Nivolumab in the Treatment of Hepatocellular Carcinoma

Clinical studies assessing the immunotherapeutic rationale of administering iNKT agonists in combination with ICIs are sparse and have only recently been initiated for the treatment of hepatocellular carcinoma (HCC). HCC nearly always develops secondary to chronic liver inflammation, as this produces an immunosuppressive microenvironment that accommodates immune cell exhaustion.[26] Exhausted immune cells exist in an inactive anergic state, expressing high levels of inhibitory co-receptors, such as PD-1 and CTLA-4, and low levels of effector cytokines. As a result, anti-PD-1 antibodies have been studied in HCC and found to be an effective treatment.[27] Nivolumab received FDA approval in September 2017 for patients with advanced HCC previously treated with the multi-kinase inhibitor sorafenib during the phase I/II dose-escalation and dose-expansion CheckMate-040 study.[28] Nivolumab resulted in significant tumor diminution compared to first-line sorafenib therapy; however, its objective response rate (ORR) remained low at 15% (95% CI 6-28) in the dose-escalation phase and 20% (95% CI 15-26) in the dose-expansion phase. This has prompted additional efforts to improve nivolumab response rates in HCC treatment, and the first open label, uncontrolled phase I/II clinical trial to assess combination therapy of ABX196 with nivolumab is now underway at the Scripps M.D. Anderson Cancer Center [NCT03897543]. Importantly, the trial addresses the question of whether the immunostimulatory effects of ABX196 may help bolster the efficacy of nivolumab immunotherapy in HCC by specifically targeting and reversing iNKT cell anergy.

Since Hepatitis B infection is associated with increased risk of HCC, the adjuvant activity of ABX196 may play a critical role in HCC immunotherapeutic control. In a phase I first-in-human dose-escalation study, ABX196 induced a strong anti-HepB antibody response when used as an adjuvant for a prophylactic hepatitis B vaccine.[15] In all forty-four healthy male subjects treated, ABX196 elicited a stimulation of NKT cells *in vivo* as demonstrated by the downregulation of NKT TCR and pronounced antibody response. Adverse side effects were mild to moderate and associated with elevated IFN-γ levels, consistent with acute activation of hepatic iNKT cells by ABX196. Similarly, many clinical trials (***Table 1***) have tested the anticancer therapeutic potential of α-GalCer in humans, and it has been shown to be a safe and well-tolerated treatment plan, although its effectiveness in these trials was limited due to iNKT cell anergy and the development of immunosuppressive tumor microenvironments.[42]

CAR-T Cells in Combination with PD-1 Blockade

Background: The Therapeutic Evolution of CAR-T Cells

Chimeric antigen receptor (CAR)-T cells are genetically modified T cells designed to express a synthetic TCR for use in anticancer immunotherapy. T cells are isolated from human blood and engineered to express a unique CAR. CAR-T cells are then stimulated to expand *ex vivo* and are infused back into the patient to kill tumor cells expressing the corresponding CAR-T cell antigen.[43] CAR constructs are hybrid molecules consisting of three regions: i) the extracellular ectodomain, usually composed of a single chain variable fragment (scFv) obtained from a tumor antigen-reactive antibody, ii) the transmembrane domain to support CAR stability, and iii) the intracellular endodomain, composed of signaling peptides responsible for cell activation and co-stimulation following tumor antigen recognition (***Figure 2***).[44] CAR-T cells are separated into four generations based on the composition of their endodomains.[45] First generation CARs contain a scFv attached to a CD3ζ-derived intracellular signaling molecule, the primary transmitter of endogenous TCR stimulation. Second generation CARs contain an additional co-stimulatory molecule as part of the signal transduction region.[46] Third generation CARs combine multiple intracellular co-stimulatory domains to increase cytokine production. Fourth generation CARs, also referred to as T cell redirected for universal cytokine-mediated killing (TRUCKs), contain a transgenic load of immune modifiers, such as cytokines, co-stimulatory ligands and enzymes, that

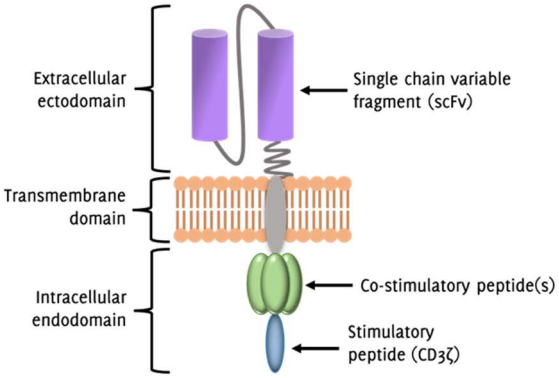
Table 1. Clinical Trials Evaluating α-GalCer-Mediated Stimulation of iNKT Cells

Clinical trial	No. of participants	Treatment	Result	Cancer type(s)
Giaccone et al.[29]	24	α-GalCer; intravenous	7 SD	Solid tumors
Nieda et al.[30]	12	α-GalCer-pulsed CD1d-expressing DCs; intravenous	3 reductions in tumor markers/mass	Solid tumors
Ishikawa et al.[31]	11 enrolled, 9 completed	α-GalCer-pulsed DCs; intravenous	5 SD	NSCLC
Chang et al.[32]	6 enrolled, 5 completed	α-GalCer loaded onto monocyte-derived mature DCs; intravenous	4 reductions in tumor markers or SD	MM, RCC, Anal SCC
Motohashi et al.[33]	6	α-GalCer-activated Vα24 iNKT cells; intravenous	4 SD	NSCLC
Uchida et al.[34]	9	α-GalCer-pulsed APCs; administered in nasal submucosa	1 PR, 5 SD	HNSCC
Motohashi et al.[35]	23 enrolled, 17 completed	α-GalCer-pulsed PBMC cultured with IL-2 and GM-CSF; intravenous	5 SD	NSCLC
Kunii et al.[36]	8	Intra-arterial infusions of α-GalCer- activated Vα24 iNKT cells + submucosal injections of α-GalCer-pulsed APCs	3 PR, 4 SD	HNSCC
Kurosaki et al.[37]	17	α-GalCer-pulsed APC injections into nasal or oral floor submucosa	Increased levels of iNKT cells/IFN-γ	HNSCC
Yamasaki et al.[38]	10	Nasal submucosal administration of α-GalCer-pulsed APCs + intra-arterial infusion of α-GalCer-activated iNKT cells via tumor-feeding arteries	5 PR, 5 SD	HNSCC
Nicol et al.[39]	12	α-GalCer-pulsed DCs; 2 treatments intravenous, 2 treatments intradermal	3 PR, 3 SD	Solid tumors
Nagato et al.[40]	4	α-GalCer-pulsed APCs; intravenous	Increased levels of iNKT cells in TILs, increased IFN-γ levels	NSCLC
Richter et al.[41]	6	α-GalCer-loaded monocyte-derived DCs + low-dose lenalidomide; intravenous	3 reductions in tumor-associated monoclonal immunoglobulin	Asymptomatic myeloma

Abbreviations: SD, stable disease; PR, partial remission; HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small cell lung cancer; MM, multiple myeloma; RCC, renal cell carcinoma; SCC, squamous cell carcinoma; DC, dendritic cell; APC, antigen presenting cell; TIL, tumor infiltrating lymphocyte.

upon release help activate and recruit innate immune cells to eliminate antigen-negative tumor cells.[47] TRUCKs enhance antitumoral activity through inducible IL-12, creating an immunostimulatory tumor microenvironment and favorably redirecting host lymphocytes toward the tumor site.[48]

Figure 2. Structure of the Chimeric Antigen Receptor (CAR)-T cell



Legend: Simplified diagram of the chimeric antigen receptor (CAR)-T cell structure. The extracellular ectodomain communicates with a specific tumor cell antigen via the single chain variable fragment (scFv), which is derived from an antibody that reacts with a given tumor antigen. The transmembrane domain provides stability to the CAR structure. The endodomain is responsible for communicating intracellular signals that promote T cell activation.

Rationale for CAR-T Cell Combination Therapy with ICIs

While conventional CAR-T cell therapy has demonstrated clinical success against B cell hematologic malignancies,[49,50] its efficacy is limited by several important obstacles, including high toxicity, immunosuppressive tumor milieu, and CAR-T cell dysfunction.[51] One of the primary reasons for poor treatment response and relapse after CAR-T cell therapy is inefficient T cell expansion and a lack of persistent T cell activation following infusion of CAR-T cells into patients.[44] It is thought that CAR-T cell dysfunction and non-persistence is driven by co-inhibitory pathways induced by checkpoint blockade that lead to T cell anergy.[52] CAR-T cells were shown to upregulate immune checkpoint receptors, such as PD-1, CTLA-4 and lymphocyte activating gene-3 (LAG-3), in patients with chronic lymphocytic leukemia (CLL) unresponsive to anti-CD19 CAR-T cell therapy.[53] CLL is a hematologic malignancy with particularly poor response rates to CAR-T cell therapy and is known to facilitate an immunosuppressive, pro-tumor microenvironment.[54] PD-L1 expression was found to be significantly higher in 112 CLL patients than in non-CLL controls.[55] Similarly, mesothelin-specific CAR TILs (tumor-infiltrating lymphocytes) administered to mice bearing human mesothelin-expressing flank tumors underwent rapid and spontaneous loss of functional activity associated with increased expression of the surface inhibitory receptors PD-1, LAG3, T cell immunoglobulin- and mucin-domain-containing molecule 3 (TIM3) and 2B4 (CD244).[56] The aberrant expression of inhibitory molecules has been demonstrated in CAR-T cell clinical trials as well.[57] Infusion of anti-CD19 CAR-T cells to patients with advanced B cell lymphomas resulted in at least three-fold increase in expression of PD-1 at the surfaces of $CD4^+$ CAR-positive cells in 8 out of 11 patients.[57] These studies suggest that checkpoint-based immunosuppression is an important mechanism mediating tumor resistance to CAR-T cell therapy. Therefore, strategies that block inhibitory immune checkpoint pathways in combination with CAR-T cell therapy possess powerful immunotherapeutic potential.

Preclinical Data: CAR-T Cells with PD-1 Blockade

CAR-T cell combination therapy with PD-1 blockade has demonstrated improved antitumor effects in multiple preclinical models. In adoptive transfer studies of mice bearing human epidermal growth factor receptor-2 $(HER\text{-}2)^+$ tumors, anti-PD-1 antibodies enhanced HER-2-specific CAR-T cell functionality, significantly increased markers of activation and proliferation, improved tumor growth inhibition, and reduced the percentage of myeloid-derived suppressor cells, which – when produced in excess – are known to aid in tumor metastasis and immune evasion.[58] Similarly, PD-L1 inhibition in mouse CLL models reactivated immune effector functions and restored cytotoxic $CD8^+$ T cell activity as well as immune synapse formation *ex vivo* and *in vivo* by preventing exhaustion-like T cell phenotypes.[59] Experiments conducted with an orthotopic mouse model of pleural mesothelioma showed that PD-1 pathway interference restored the effector function of exhausted CD28-specific CAR-T cells.[60] Gargett et al.[61] demonstrated that third generation GD2-specific CAR-T cells would undergo significant activation-induced cell death (AICD) after repeated antigen stimulation *in vitro*; however, PD-1 blockade enhanced both CAR-T cell survival and promoted killing of $PD\text{-}L1^+$ tumor cell lines. CRISPR-Cas9-mediated editing of CAR-T cells, which rendered them non-responsive to PD-1 signaling, improved antitumor CAR-T cell activity both *in vitro* and *in vivo*.[62] Finally, Hui et al. [63] showed that PD-1/PD-L1 interactions suppressed CAR-T cell activity by blocking CD28 signaling, suggesting that upregulation of costimulatory pathways is an important mechanistic response of CAR-T cells to anti-PD-1/PD-L1 therapy.

Clinical Data: CAR-T Cells with PD-1 Blockade

Clinical trials employing CAR-T cell combination therapy with PD-1 blockade have already shown promising results. In a single-institution study at the Children's Hospital of Philadelphia, fourteen pediatric patients with heavily treated, relapse B cell acute lymphoblastic leukemia (B-ALL) and poor responses to CAR-T cell therapy were treated with CD19-specific CAR-T cell therapy in combination with an anti-PD-1 monoclonal antibody.[64] Encouraging results were particularly observed in patients with early B-cell recovery and bulky extramedullary disease. Three of 6 patients treated with PD-1 inhibitor and CAR-T cells for early B cell recovery reestablished B cell aplasia, an indication of persistent CAR-T cell activation. In a cohort of four patients treated with pembrolizumab and CAR-T cells for extramedullary disease, 2 partial remissions (PRs) and 2 complete remissions (CRs) were seen. However, in the 4 remaining patients who were unsuccessful in achieving remission with initial CAR-T cell therapy, only PRs were observed with CAR-T cell and pembrolizumab combination therapy. Adverse effects of combination therapy included fever, acute pancreatitis, hypothyroidism, joint pains, as well as moderate to severe pancytopenia. The study supports the hypotheses that upregulation of the PD-1/PD-L1 signaling axis may be a driving force in the development of resistance to CAR-T cell immunotherapy. The study also suggests that ICI combination therapy at the time of CAR-T cell administration may be a safe and durable strategy for preventing subsequent AICD in the treatment of B-ALL.

A similar single-institution trial at the Abramson Cancer Center of the University of Pennsylvania attempted to evaluate the role of pembrolizumab as salvage therapy for patients who experienced worsening disease following initial CAR-T cell infusion.[65] The study enrolled 12 patients with progressive or relapse B cell non-Hodgkin lymphomas with partial or no response to CD19-specific CAR-T cell therapy. Pembrolizumab was administered to these patients every 3 weeks until disease progression or adverse toxic side effects were observed. The addition of PD-1 blockade after prior ineffective anti-CD19 CAR-T cell therapy produced an ORR of 27% (1 CR and 2 PRs), including 1 patient with stable disease and 7 patients with progressive disease. Nine of 12 patients demonstrated a re-expansion of peripheral blood CAR-T cells after the first pembrolizumab dose, although this cellular re-expansion did not correlate with clinical outcome. Nevertheless, this study highlights the key theory that ICIs may reinvigorate exhausted CAR-T cells in patients with poor or failed responses to initial CAR-T cell therapy, and further studies should be explored to translate this CAR-T cell re-expansion into clinically efficacious use. At the moment, several clinical trials (***Table 2***) are attempting to address the optimal timing of administration, dosing, efficacy, and safety of CAR-T cell combination therapy with ICIs, particularly in patients who have failed first-line therapies with relapsed or refractory progression of their cancers. These

Table 2. Clinical Trials Evaluating CAR-T Cell Combination Therapy With PD-1 Blockade

Clinical trial identifier	Sponsor/study name	Patients enrolled	CAR-T	ICI	Cancer type(s)
NCT03310619	Celgene/PLATFORM	100	JCAR017	Durvalumab	NHL, DLBCL, FL
NCT03287817	Autolus Limited/ALEXANDER	120	AUT03	Pembrolizumab	DLBCL
NCT02706405	Fred Hutchinson Cancer Research Center	42	JCAR014	Durvalumab	NHLs + gene rearrangement(s), DLBCL, PMBL
NCT03630159	Novartis Pharmaceuticals/ PORTIA	32	CTL019	Pembrolizumab	DLBCL
NCT02926833	Kite, A Gilead Company/ZUMA-6	37	KTE-C19	Atezolizumab	DLBCL
NCT03726515	University of Pennsylvania	7	CART-EGFRvIII	Pembrolizumab	Glioblastoma
NCT04003649	City of Hope Medical Center	60	IL13Ralpha2-CRT T cells	Ipilimumab, nivolumab	Glioblastoma
NCT03525782	The First Affiliated Hospital of Guangdong Pharmaceutical University	60	Anti-MUC1 CAR-T cells	Nivolumab	NSCLC
NCT02414269	Memorial Sloan Kettering Cancer Center	66	iCasp9M28z, T cells	Pembrolizumab	Lung/breast cancers, mesotheliom

Legend: NHL, non-Hodgkin lymphoma; DLBCL, diffuse large B cell lymphoma; FL, follicular lymphoma; PMBL, primary mediastinal B cell lymphoma; NSCLC, non-small cell lung cancer

trials address ICI and CAR-T cell combination therapy in two primary treatment scenarios: 1) when the agents are administered simultaneously, or 2) when the ICI is administered for a limited duration shortly after CAR-T cell infusion. Taken together, these studies attempt to assess both the potential of concurrent ICI and CAR-T cell therapy to prevent the development of future AICD as well as the salvage potential of ICIs to enhance prior ineffective CAR-T cell therapy. Investigating ICI and CAR-T cell combination therapy from both of these angles may provide a better understanding of the appropriate timeframe in which ICIs can most effectively enhance and prevent resistance to CAR-T cell therapy.

NK Cells in Combination with PD-1 Blockade

Applications, Advantages, and Challenges of NK Cell Therapy

Natural killer (NK) cells are cytotoxic innate lymphoid cells that play a vital role in antitumor immunity due to their unique ability to detect and eliminate malignant cells with downregulated surface expression of self-MHC-I molecules.[66] NK cell functions vary widely and include degranulation, cytokine secretion primarily in the form of IFN-γ, and direct cytotoxicity due to an elaborate interaction of inhibitory and activating signals.[67] Many antitumor therapeutic strategies have emerged in recent years that utilize the cytotoxic and immunoregulatory activities of NK cells. Adoptive transfer therapy, in which NK cells from a healthy donor are isolated, activated *ex vivo* in an IL-2 or IL-15 solution, then infused into cancer patients, has proven to be an effective and nontoxic antitumor treatment.[68] More recently, isolated NK cells have been genetically modified to express a unique tumor-antigen CAR prior to re-infusion. CD19- and CD20-specific CAR-NK cells have shown successful preclinical tumor growth inhibition in a variety of B cell malignancies.[69] CAR-NK cells targeting HER-2, epidermal growth factor receptor (EGFR), natural killer group 2D (NKG2D), and disialoganglioside GD2 receptors, all of which are overexpressed in tumor cells, have also shown preclinical antitumor efficacy against solid tumors.[69] CAR-NK cell therapy has advantages over CAR-T cell therapy in that it does not induce graft versus host disease (GVHD),[70,71] nor does the CAR modification prevent the NK cell from carrying out its non-specific innate functions, thus limiting the occurrence of antigen loss and tumor escape.[72] In addition, CAR-NK cell therapy eliminates the need for a personalized, autologous product typically required with CAR-T cell therapy. CAR-NK cell therapy, therefore, has the potential to be an affordable and readily available, "off-the-shelf" treatment option. The aforementioned therapeutic benefits are limited in part by the ability of injected NK cells to migrate to tumor sites, persist, and expand *in vivo*.[73] NK cells express a range of inhibitory receptors, including PD-1, PD-L1, CTLA-4, T cell immunoglobulin and mucin-containing protein 3 (TIM3), T cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain (TIGIT), LAG-3, interleukin-1 receptor 8 (IL-1R8), and CD96, in addition to more well-established inhibitory receptors, like killer-cell immunoglobulin-like receptor (KIR) and the C-type lectin inhibitory receptor CD94/natural killer group 2A (NKG2A).[74,75] Research into the blockade of these inhibitory NK cell immune checkpoint pathways is ongoing and early data reflect an encouraging possibility of immune checkpoint inhibition to overcome the immunosuppressive limitations currently associated with NK cell therapy.[76] For the purposes of this review, literature pertaining specifically to inhibition of the PD-1/PD-L1 axis was the focus.

Rationale for Combining NK Cell Therapy with PD-1 Blockade

PD-1 is highly expressed on a distinct subpopulation of NK cells with impaired immunostimulatory capabilities that are detectable in approximately 25% of healthy people.[77] NK cell populations with high PD-1 expression demonstrate significantly reduced function and are found in greater proportion in patients with ovarian carcinoma,[77] Kaposi sarcoma,[78] multiple myeloma,[79] and head and neck cancers.[80] *In vitro* studies have confirmed that PD-1 receptors become upregulated at the surface of healthy control NK cells upon extended contact with activating ligands,[78] suggesting that PD-1 helps induce, as it does for T lymphocytes, NK cell anergy. This increased expression of PD-1 at the surface of NK cells correlates with poorer survival prognosis in esophageal and liver cancers.[81] More recent studies have determined that upregulated PD-L1 expression at the surface of NK cells also mediates exhaustive NK phenotypes. Dong et al., [75] for instance, discovered that some tumors can induce PD-L1 expression on NK cells via protein kinase B (AKT) signaling. These discoveries support the idea that NK cells are a valuable target in immunotherapeutic approaches that inhibit PD-1/PD-L1 interactions, especially when these ICIs are used to treat tumors that are MHC-I deficient. Thus, utilizing PD-1 blockade may be an excellent additive strategy for immunotherapy regimens that harness the antitumor capabilities of NK cells.

Preclinical data: NK cells with PD-1 blockade

Preclinical studies have shown that inhibiting PD-1 and PD-L1 checkpoint receptors enhances the immunotherapeutic efficacy of NK cells. Benson et al.[79] demonstrated that a PD-1 blocking antibody improved human NK cell functionality against autologous, primary multiple myeloma cells *in vitro* through a mechanism involving NK cell trafficking, immune complex formation, and enhanced cytotoxicity directed toward PD-L1$^+$ tumor cells. Blocking PD-1/PD-L1 signaling notably enhanced cytokine secretion and inhibited NK cell apoptosis *in vitro*. Importantly, administration of an anti-PD-1 antibody significantly slowed tumor growth in HCC xenografts, and this beneficial antitumor response was diminished by NK cell depletion, indicating an NK-dependent antitumor mechanism in response to PD-1 blockade.[81] Hsu et al. [82] performed similar experiments on several mouse models of cancer, including lymphoma, melanoma, prostate adenocarcinoma, and colon carcinoma, and determined that the release of PD-1-imposed inhibition activated an NK response that was indispensable for the full

effect of ICI immunotherapy. Oyer et al. [83] observed a significant improvement in NK cell antitumor efficacy, persistence, and retention of cytotoxic activity in mouse ovarian cancer models when combined with anti-PD-L1 antibody. The group showed that expanded NK cells secreted large amounts of IFN-γ, which induced expression of PD-L1 on human ovarian cancer cells *in vivo*. These findings support NK cell combination therapy with anti-PD-L1 antibody, irrespective of initial tumor PD-L1 status. Lastly, Dong et al. [75] determined that various PD-L1$^-$ tumor cell lines still responded favorably to anti-PD-L1 monoclonal antibody therapy, because the anti-PD-L1 antibody directly targeted and activated PD-L1$^+$ NK cells in a PD-1 independent process.

Clinical Data: NK Cells with PD-1 Blockade

While preclinical data has confirmed the immunostimulatory advantage of PD-1 blockade on NK cell functionality, clinical trials are new and in their early stages. A phase II study assessing the effects of pembrolizumab on NK cell exhaustion in patients with malignant melanoma was recently terminated due to enrollment difficulties [NCT03241927]. Nevertheless, several clinical trials (***Table 3***) evaluating the therapeutic benefit of PD-1 blockade on NK cell antitumor activity are currently underway.

Conclusion

Immunotherapy continues to revolutionize cancer treatment in the twenty-first century. ABX196, CAR-T cell and NK cell immunotherapies, in particular, have shown compelling preclinical data and are in early phase studies to determine if this activity can be translated into patient care. These therapeutics have mechanisms of action that are distinct from approved ICIs, which may overcome some of the limitations that have plagued ICI immunotherapy. Modulating multiple levers of the immune system simultaneously by co-administering ICIs with either ABX196, CAR-T cells or NK cells may further the essential, as-yet unmet, goal of overcoming tumor resistance to ICI immunotherapy. While awaiting the results of these agents' early clinical trials, additional studies should be pursued to both enhance and optimize these promising new immunotherapy approaches.

Table 3. Clinical Trials Evaluating NK Cell Combination Therapy With PD-1 Blockade.

Clinical trial identifier	Sponsor	Patients enrolled	ICI + NK	Cancer type(s)
NCT03958097	First Hospital of Jilin University	20	Sintilimab (anti-PD-1) + NK cells (autologous NK cells; collected by apheresis)	NSCLC
NCT03815084	Allife Medical Science and Technology Co., Ltd.	100	Pembrolizumab + DC-NK	Solid tumors
NCT03937895	SMT bio Co., Ltd.	40	Pembrolizumab + SMT-NK (allogeneic NK cells)	BTC

Legend: NSCLC, non-small cell lung cancer; BTC, biliary tract cancer

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Review

Glucose-6-phosphate Dehydrogenase Deficiency: A Review

Nidhruv Ravikumar,[1] Graeme Greenfield.[2]

Abstract

Deficiency of the glucose-6-phosphate dehydrogenase (G6PD) enzyme is a common X-linked disorder that affects people globally. It was first identified in the 1950s as a disorder that primarily affects the red blood cells, causing a myriad of symptoms including acute hemolytic anemia, neonatal jaundice and chronic nonspherocytic hemolytic anemia. This deficiency has been extensively studied and, especially within the last 5 years, there have been improvements in the diagnosis and management. Various methods of diagnosis exist; however, recent research focuses on the use of biosensors for a more accurate and less time-consuming diagnosis. Guidelines suggest controlling symptomology, as no specific treatment currently exists. A common complication of the disease is neonatal jaundice, and research on phototherapy has proved to show some effect in managing this condition. In the last year, protein-protein interactions have been used as targets to enhance enzyme stability and activity. AG1 is a small molecule activator that has demonstrated effectiveness in treating G6PD deficiency in models. This review summarizes existing literature and potential areas of research on glucose-6-phosphate dehydrogenase deficiency including clinical characteristics, diagnosis, and management.

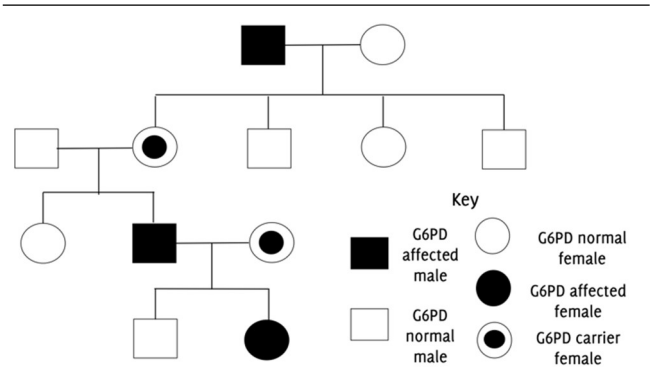
Key Words: Glucosephosphate Dehydrogenase deficiency, Hemolytic anemia, Neonatal jaundice, Erythrocytes (Source: MeSH-NLM).

Introduction

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is one of the commonest forms of enzymatic disorders affecting humans worldwide. Four-hundred million people across the globe are estimated to be affected, with the highest prevalence being in those of African, Asian and Mediterranean descent.[1,2] G6PD is an enzyme in the pentose phosphate pathway (PPP) that catalyzes the first step.[3] PPP plays a role in reductive biosynthesis, cell proliferation and processing of antioxidants. The products of this pathway are important in nucleotide synthesis, lipogenesis, cholesterol synthesis and glutathione reduction. Disruption of the PPP will lead to a generation of free radicals that cause oxidative damage to red blood cells (RBCs) and, in turn, hemolysis (breakdown of RBCs).[4]

G6PD deficiency was first identified in the 1950_s a small number of American soldiers who developed a hemolytic anemia upon exposure to anti-malarial drugs. In later years, the genetic cause of the disease was identified and was attributed to mutations in the *g6pdx* gene located on the X chromosome.[5] Since the gene is located on the X chromosome, it is inherited in a sex-linked manner (***Figure 1***). Males have only one copy of the X chromosome; hence, those who inherit the mutation are considered hemizygous and will develop the condition. However, females can be either homozygous (two pairs of mutant alleles) or heterozygous (only one mutant allele). Homozygous females will be G6PD deficient, while heterozygous females will be carriers. Carriers are not usually affected by the condition and rarely present with symptoms.[3] The majority of the population with the deficiency, mainly males, do not develop symptoms unless they are exposed to certain oxidative stressors (i.e., fava beans), oxidative medications (i.e, antimalarial agents) and infections.[3,5] The geographical distribution of the condition is similar to sickle cell anemia and thalassemia, and corresponds to the global distribution of malaria. This has led to the hypothesis that G6PD deficiency offers some protection against the parasite *Plasmodium falciparum*, a cause of malaria.[6] This review thus seeks to evaluate existing literature regarding the pathophysiology, diagnosis, and management of G6PD deficiency, and provide insight into potential areas for further research.

Figure 1. Pedigree chart indicating X-linked inheritance pattern of G6PD deficiency.



Methods

Search Strategy and Selection Criteria

A comprehensive literature search was performed through PubMed resources to identify the articles which discussed the prevalence, pathophysiology, diagnosis and management of G6PD deficiency. Keywords used includeed 'Glucose-6-phosphate dehydrogenase deficiency' or 'G6PD deficiency', 'Favism' and 'Congenital hemolytic anemia'. The search terms were used as keywords and in combination as MeSH terms to maximize the output from literature findings. In conjunction to this, a manual search of reviews and other relevant studies was conducted. A staged literature search was done, whereby

[1] Medical student, Queen's University Belfast, Northern Ireland, UK.
[2] BA, BM, BCh, MRCP. Wellcome Trust, Queen's University Belfast, Belfast City Hospital, Northern Ireland, UK.

About the Author: *Nidhruv Ravikumar is currently a 3rd year medical student at Queen's University Belfast of a 5-year program in MBBCh BAO. He is enthusiastically involved in research in various fields of medicine, and keeps himself well-informed with latest advancements in the field. He is also an active member of various medical societies and is the Vice-President of the Asian Medical Students Association Northern Ireland.*

Correspondence:
Nidhruv Ravikumar
Address: University Rd, Belfast BT7 1NN, United Kingdom
Email: nravikumar01@qub.ac.uk

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Student Editors: Yusuff Adebisi & Brandon Belbeck
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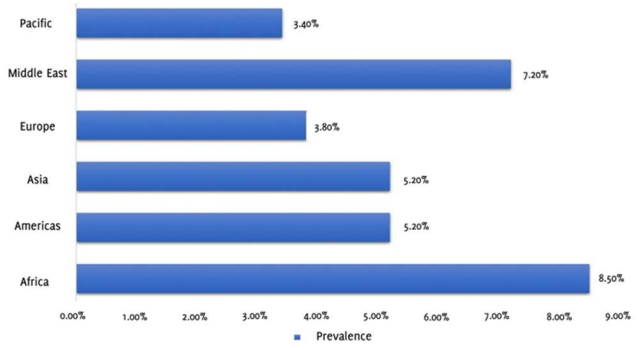
Figure 2. Regional prevalence estimates of G6PD deficiency (Data collected from: Nkhoma E, Poole C, Vannappagari V, Hall S, Beutler E. The global prevalence of glucose-6-phosphate dehydrogenase deficiency: A systematic review and meta-analysis. Blood Cells Mol Dis. May-Jun 2009;42(3):267-78).[8]



a separate literature search was performed for each section within this article and all the relevant studies were identified and summarized separately. The relevant articles are cited and referenced within each section separately. No limits were placed on publication time of the article.

Results

Epidemiology

It is estimated by The National Organization for Rare Disorders that there are four hundred million people who are living with G6PD deficiency. An estimate suggests that approximately 8% of the world's population carry the alleles responsible for the development of G6PD deficiency, ranging from a maximum of 35% in regions of Asia to 0.1% in Japan and certain parts of Europe, which makes it a significant public health problem.[7] It is observed to have higher prevalence in Asia, the Middle East, Latin America and the Mediterranean (***Figure 2***).[1] Since the mode of inheritance is X-linked, males seem to be more affected, compared to females; however, the most common genotype is a heterozygous female.[3] In the past it was noted that there was an increased prevalence of the disease in high-risk countries which often correlated to the demographics observed with malaria. However, in recent times due to significant globalization and the accompanying migration of individuals, there has been a considerable change in population demographics. Hence, in the majority of countries, there exists pockets of population groups that are affected by the disorder, causing an increase in prevalence of this disorder in countries where it would be considered rare in the past.[9] In the United States, for instance, people of African-American descent are observed to be predominantly affected by the disorder. In recent years, the frequency of the affected population is as high as about 10-14%.[1]

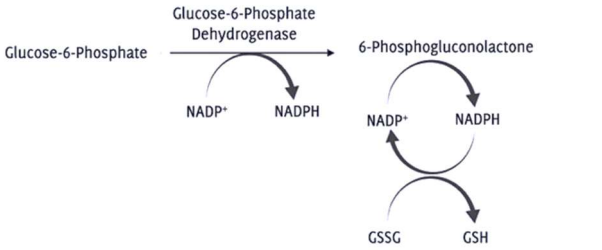
The high prevalence of the condition increases its probability of being associated with other pathological conditions, particularly those affecting RBCs (sickle cell hemoglobinopathy and thalassemia).[5]

Pathophysiology

Pharmacogenetics is the process in which the genetic determinants of an individual's response to drugs are measured. In fact, G6PD deficiency was discovered using this technique. In the 1950s, primaquine, an antimalarial drug, was produced in large-scale when the US military was deployed to areas endemic to malaria. The army physicians observed that, apart from the predicted side effects of gastrointestinal complaints, some soldiers developed jaundice and anemia. This toxic side effect was then termed as primaquine sensitivity syndrome. In the years following, Brewer *et al.*,[10] tested the effects of primaquine on human volunteers, which provided valuable insight into the mechanism of the condition, despite its lack of ethical compliance. The group conducted enzymatic analysis and concluded that there was a marked reduction in the levels of the G6PD enzyme in the RBCs of primaquine-sensitive patients, thus coining the term G6PD deficiency. Further genetic analysis of the condition revealed that the gene coding for the enzyme is located on the X chromosome, prompting an X-linked inheritance pattern.[11] Prior to this discovery, favism was a well-known condition that caused similar symptoms in certain populations upon consumption of fava beans. It was later concluded that the underlying biochemical effect was the same as that caused by primaquine.

In a G6PD-deficient person, no abnormalities are observed in the steady state. This comes down to the role of G6PD in the RBCs.[11] It is an enzyme present in the cytosol that is involved in the PPP by controlling the entry of glucose-6-phosphate (G6P) into the pathway. G6PD oxidizes G6P to 6-phosphogluconolactone and, in the process, reduces $NADP^+$ to NADPH (***Figure 3***).[12] Hence, its main role is to provide reductive potential by the production of NADPH.[11] This reaction is the rate determining step of the pathway, and therefore, decreased activity of G6PD causes reduced levels of NADPH.[12] NADPH is a key reductive agent that maintains glutathione in its reduced state (***Figure 3***). Glutathione in its reduced form is important in scavenging potentially harmful reactive oxygen species (ROS) and confers vital protection to RBCs.[13] Excess ROS have detrimental effects on the cell function –causing an increase in erythrocyte membrane fragility leading to hemolysis, release of hemoglobin into the plasma and systemic nitric oxide scavenging leading to vasoconstriction.[13] This is caused by its interference in reactions involving proteins, nucleotides and lipids.[12]

Figure 3. Oxidative stage of Pentose Phosphate Pathway (PPP) indicating deficiency of Glucose-6-phosphate dehydrogenase leads to decreased NADPH levels. In the glutathione reduction pathway, decreased NADPH causes accumulation of GSSG (oxidized glutathione), that prevents the conversion of H_2O_2 to H_2O leading to its accumulation (Reactive oxygen species).



Although G6PD deficiency affects every cell of the body, its primary effects are blood related, as RBCs do not have an alternate source of NADPH. Non-RBC cells, on the other hand, have other non-specific enzymes (hexose-6-phosphate dehydrogenase) that work in a similar way to G6PD to generate NADPH. In the steady state, the levels of NADPH in the RBCs are adequate. However, exposure to oxidative stressors poses a challenge to G6PD-deficient RBCs, due to the generation of excess ROS.[11] This leads to the lysis of RBCs, causing hemolytic anemia.[13] As with other RBC enzymes, the activity of G6PD reduces as the cell ages. This is not endangering in G6PD-normal red cells; however, in G6PD-deficient cells, the older RBCs have lower levels of the enzyme, as compared to the younger cells. This then correlates to the reduced RBCs life span and acute haemolysis.[7] A classification system can thus be formulated based on the variation in enzyme activity levels.

Classification of G6PD Deficiency

The level of disease severity varies depending on residual enzyme activity and substrate binding, which are influenced by the type of mutation.[13] The World Health Organization (WHO)[7] categorizes the disease into the following 5 classes:

- Class I (very severe deficiency): less than 1% G6PD activity and is commonly caused by the Mediterranean mutation
- Class II (severe deficiency): G6PD activity is between 1% and 10%

- Class III (moderate deficiency): 10% to 60% activity of G6PD
- Class IV (normal): G6PD activity is between 60% and 150%.
- Class V: G6PD activity is greater than 150%

A$^-$ and *Med* are common alleles that cause moderate to mild severe deficiency and they belong to class II and III. Patients affected by the *A*$^+$ and *B* variants fall under class IV and class V. Most people affected by the deficiency fall in Class II and III, i.e., moderate deficiency and have fewer problems.[7,10] The symptoms observed and prevalence of each class is summarized in ***Table 1***.

Table 1. Classification of G6PD Deficiency.

Class	Variant	Enzyme Activity	Symptoms	Prevalence
I	Mediterranean type	< 1%	Chronic non-spherocytic anemia	Uncommon across populations
II	A$^-$/Med	1% - 10%	Intermittent acute hemolysis	More common in Asian and Mediterranean populations
III	A$^-$/Med	10% - 60%	Intermittent acute hemolysis	US black males
IV	A$^+$/B	60% - 150%	No clinical symptoms	Rare
V	A$^+$/B	> 150%	No clinical symptoms	Rare

Genetics

The gene that codes for G6PD, *g6pdx*, is situated proximal to the telomeric end of the distal arm (q arm) at band 28 of the X chromosome in humans (Xq28) (***Figure 4***).[7,14-15] This gene has 13 exons and 12 introns, spans 18.5 Kilobases, and has a GC rich promoter region that encodes a product of 1545 bp.[2,16,17] It has a high rate of heterogeneity, and over 300 variants have been found. Only 217 precise mutations, however, are currently known.[1,11,14,18] Majority of the mutations observed are point mutations that occur in the coding DNA, introns and 5' and 3' untranslated regions.[14] *S188F* (Mediterranean mutation) in the Arab population, *C131G* and *G487A* in Bangladesh, and *A376G* in North America, Africa, Yemen and Saudi Arabia are the commonest mutations discovered in G6PD-deficient patients.[2,19-21] These variants can be either polymorphisms, with milder clinical signs, or sporadic variants. The frequency of variant polymorphs is higher than sporadic variants, 50% to 1% respectively. Nevertheless, the frequencies of sporadic variants have reached polymorphic frequencies, due to some protection offered against malaria caused by *Plasmodium falciparum*.

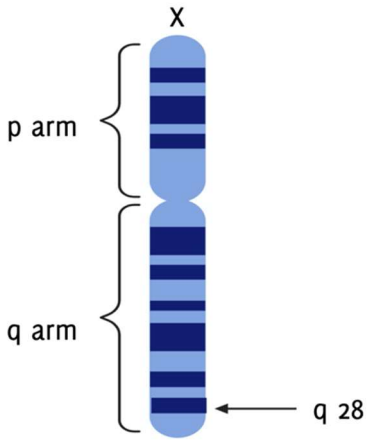
All mutations cause a decrease in enzyme stability.[14] Active G6PD enzyme occurs as a homodimer or homotetramer. The majority of the mutations in the gene cause a change in the amino acid sequence of the enzyme, thus decreasing stability. The postulated mechanism for this decrease in stability is disturbance in protein folding. This affects particularly the dimer interface, causing a disturbance in effective dimerization. Moreover, it was also observed that a structural NADP molecule is an essential moiety that maintains the structural integrity of the enzyme. Mutations that alter the binding of this structural NADP molecule also contribute to the decrease in stability of the enzyme.[5]

Males are predominantly affected, as the gene is present on the X chromosome. They can be either hemizygous normal or hemizygous deficient. In contrast, females can be homozygous normal, homozygous deficient or heterozygous. A mosaic pattern of the wild type and the deficient variant is observed in heterozygous females, caused by X chromosome inactivation (i.e., lyonization). This leads to the presence of differing levels of normal and deficient RBCs. Due to the random nature of this phenomenon, the proportions of deficient variant vary, resulting in a spectrum of symptomology.[16] If the proportion of deficient RBCs is greater than 50% in heterozygous females, they become more susceptible to hemolysis, but with less severity when compared to homozygous deficient females and hemizygous deficient males.

Clinical Manifestation

The majority of the population with a polymorphic G6PD gene does not manifest any clinical symptoms. In fact, with sporadic variants, the chance of developing acute hemolysis is 1 in 10^6, which is particularly infrequent.[5] For the greater part of their lifespan, people with the disease are asymptomatic; however, symptoms manifest when the body is subjected to oxidative stress. The most common stressors include medications and infection, while diabetic ketoacidosis (DKA) is also a precipitator in certain variants.[2] Although the mechanism of action of DKA is not known, the increased risk of infection that accompanies DKA is postulated to link DKA with specific variants of G6PD deficiency.[3]

Figure 4. *g6pdx* Gene Located on the Telomeric End of the q Arm at Band 28 of the X Chromosome (Xq28).



Typically, G6PD deficiency presents as acute hemolytic anemia, chronic nonspherocytic hemolytic anemia, neonatal jaundice and favism.[5] The most common presentation is acute hemolytic anemia, with symptoms of anemia, fatigue, back or abdominal pain, jaundice and hemoglobinuria occurring promptly after exposure to an oxidative stress. Hemolytic anemia is characterized by premature lysis of RBCs.[3] Due to the polymorphic character of G6PD deficiency, a number of clinical presentations are observed in different individuals. Different mutations in the gene lead to variable severity and the associated symptoms tend to vary in a similar fashion. For instance, people with the Mediterranean mutation often fall under Class I and develop very severe clinical signs such as chronic nonspherocytic hemolytic anemia (CNSHA).[5]

An important complication of G6PD-deficiency is neonatal jaundice, which can occur in neonates 2 to 3 days after birth with varying severity. Neonates with the G6PD mutation also inherit a variant allele for uridine-diphosphate-glucuronosyltransferase 1 (UGT1A1).[16] This mutation is responsible for Gilbert syndrome, where the conjugation of bile and glucuronic acid is impaired, leading to a condition where the levels of bile in the body are very high (i.e., hyperbilirubinemia).[5,16] This increases the risk of babies developing jaundice. If hyperbilirubinemia is not treated effectively, bilirubin encephalopathy (kernicterus) can result and potentially leave the neonate with permanent neurological damage or may lead to death.[16]

Favism is another precipitating disorder in individuals with G6PD deficiency. The compounds innately present in fava beans, divicine, and isouramil, are strong oxidizing agents, thereby placing the cells under oxidative stress. In addition, neonates exposed to fava beans, through breast milk or passively, can soon develop neonatal jaundice.[16]

In males with the rare G6PD sporadic variants with severe deficient function, chronic nonspherocytic hemolytic anemia (CNHSA) is a recognized complication. This occurs when there is a lack of NADPH in the steady state for maintaining the levels of oxidizing agents. The excess build-up of oxidizing agents in the cell damages the RBC membrane, resulting in reduced RBC lifespan and chronic haemolysis.[5]

Differential Diagnosis

A variety of different disease processes often clinically manifest in a similar fashion to that of G6PD deficiency, characterized primarily by hemolytic anemia. Therefore, it is important to consider the following diseases in the differential diagnosis:[1]

- Acquired autoimmune hemolytic anemia
- Pyruvate kinase deficiency
- Cold antibody hemolytic anemia
- Hereditary spherocytosis
- Sickle cell anemia
- Thalassemia
- Bilirubin conjugation disorders (i.e., Gilbert Syndrome)
- Hemolytic disease of the newborn (Erythroblastosis fetalis)
- Methemoglobinemia
- Acquired conditions (i.e., Black Water Fever, *Clostridium welchii* Septicemia, Parvovirus B19, hemolysis secondary to drugs).

Diagnosis

In order to prevent the occurrence of hemolytic episodes, the presence of G6PD-deficiency should always be considered in populations of high-risk background, including people of African, Asian or Mediterranean descent. It is important to note that screening for the deficiency needs to be performed in such individuals prior to commencement of any treatment that may induce an oxidative stress. Although people carrying the variant allele for the disorder are usually asymptomatic, the influence of a particular oxidative stressor may prove to be fatal. Hence the deficiency should be considered, especially in those with a family history of recurrent jaundice, splenomegaly, cholelithiasis, or anemia. Individuals who experience hemolytic anemia after exposure to a known oxidative stressor, those with characteristic blood film findings and neonates who have jaundice should also be considered for diagnostic testing of G6PD deficiency.[3]

Different methods of diagnosis can be used. Clinically, quantitative measurement of the enzyme function provides the required information to classify G6PD-deficiency.[22] The most widely used tests are the fluorescent spot test (FST) and the quantitative spectrophotometric assay, both of which rely on the principle of conversion of $NADP^+$ to NADPH.[5] Identification of the genetic mutations through molecular analysis can confirm the exact underlying genetic defect.[3]

The FST is the first line diagnostic tool that is used in patients suspected with G6PD deficiency.[14,22] It is a quick and inexpensive test that is often used in regions where the deficiency and malaria are more prevalent, ensuring that the patient will not experience hemolytic anemia upon exposure to antimalarial drugs.[5] Although inexpensive, FST requires the use of special equipment like UV light, a water bath or heat block, and a dark room.[3] To combat the difficulty of accessing special equipment, researchers recently developed new techniques that do not require such apparatus.[5] The formazan-based spot test is the most commonly used method, which can detect less than 50% of normal G6PD activity.[3] The formazan method uses a substrate of 3-(4,5-Dimethylazolyl-2)-2,5-diphenyltetrazolium bromide (MTT) and a hydrogen carrier, phenazine methosulphate (PMS). A formazan substrate is formed from these substrates under the influence of the NADPH that G6PD produces. New studies have demonstrated that the water-insoluble formazan is formed by MTT, therefore making the quantitative analysis of G6PD activity difficult. Tantular and Kawamoto[23] have now discovered a new formazan substrate, 2-(2-methoxy-4-nitrphenyl)-3-(4-nitrophenyl)-5-(2,4-disulphophenyl)-2H tetrazolium monosodium salt (WST-8), that does not react with hemoglobin and is water soluble. They have proved that the WST-8 formazan-based spot test is a less time consuming and more accurate method of detecting G6PD deficiency.[23]

At the laboratory level, the spectrophotometric assay is the gold standard in diagnosing the deficiency. It uses the hemolysate of blood (resulting product from the lysis of RBCs) to detect the total enzymatic activity. Enzyme activity is measured as a change in the absorbance at 340 nm at a given temperature, for a given hemoglobin concentration (unit of enzyme per grams of hemoglobin; IU/gHb) or, in rare cases, for a given number of RBCs (unit of enzyme per RBC; U/RBC).[24] Normal activity is considered to be 7 to 10 IU/gHb.[3] This technique is dependent on the concentration of hemoglobin in the blood. A disruption in the levels of hemoglobin can therefore lead to abnormal results. In individuals with anemia or iron deficiency, the G6PD activity will be falsely elevated.[24]

Due to the disparities in enzyme activity through spectrophotometric assay measurement, recent studies have focused on flow cytometry as an alternative option.[24] Earlier models of flow cytometry exploited the capacity of G6PD to reduce oxidized methaemoglobin (MetHb) to normal hemoglobin. Newer models are based on the capacity of G6PD to reduce MTT insoluble tetrazolium salts.[24] The principle behind flow cytometry corresponds to the light scattering ability of the moving particles and fluorescence emission. Fluorescence emission is the primary property that is measured in determining the levels of G6PD.[25] Tetrazolium salts are stained with a fluorescent dye.[24] The levels of the enzyme are directly proportional to the amount of fluorescent probe bound to the salt.[25] This is a laborious process and requires several hours for processing the sample and staining it. Nowadays, however, a simpler and quicker flow cytometric assay using the same principle has been developed.[24]

A study conducted by Bancone *et al.*,[26] has shown that the flow cytometric assay and spectrophotometric assay are equally reliable for the diagnosis of G6PD deficiency in patients with normal hemoglobin and without anemia. However, they proved that flow cytometric assay is the tool of choice in anemic patients and those with other haemoglobinopathies, as it is not influenced by hemoglobin concentration.

The spectrophotometric assay for G6PD-deficiency testing is fairly expensive and requires skilled operators, an equipped laboratory and a reliable source of material. Ironically, these are available in hospitals only and are inaccessible in tropical countries, where the disease is highly prevalent.[26] Point-of-care rapid diagnostic tests (POC RDT) is now considered a relatively inexpensive diagnostic tool. It is a quantitative test, and the most commonly used ones are BinaxNOW and CareStart.[3] These devices are biosensors and have been developed in recent years to provide a more accurate diagnosis.[26] The activity of G6PD can be obtained quantitatively in 4 minutes by these handheld devices to devise a suitable treatment plan.[27] In a study comparing the diagnostic power of CareStart and spectrophotometric assay, it was demonstrated that CareStart has a higher diagnostic power, with appreciable sensitivity and specificity.[26] Even though technicians easily operated CareStart, certain changes in the model were required to make it more user-friendly.[26] With improvements, POC RDTs shall be used more often in detecting G6PD deficiency.

The timing of quantitative assay is crucial, as this can influence the results of the test drastically. During active periods of hemolysis, the

bone marrow response falsely elevates the levels of the enzyme, due to consequent reticulocytosis. Therefore, measurement at the steady state is important.

The aforementioned techniques are useful and accurate in the detection of homozygous males and females, yet they fail to diagnose accurately in heterozygous females with intermediate enzyme activity (due to lyonization).[5] In these cases, an accurate diagnosis can be made by molecular analysis methods. Molecular analysis involves sequencing the *g6pdx* gene to detect known mutations that cause the disease.[3] Different methods have been employed for the simple detection of the common mutations. Classical molecular techniques include restriction enzyme analysis (PCR-RFLP), amplification refractory mutation system (ARMS), gradient gel electrophoresis (DGGE), denaturing high-performance liquid chromatography (DHPLC), probe melting curve and reverse dot blot assay.[28]

Management and Prevention

Once the diagnosis of G6PD deficiency is made, the most important next step is to discontinue the use of the offending oxidative stressor, most commonly a medication. Most patients recover spontaneously but should undergo careful monitoring. Bone marrow function in these patients tends to be normal; hence, they respond by increasing the production of RBCs. This causes a reduction in age of the circulating RBCs, making them less susceptible to hemolysis. This process plays a role in the self-limiting nature of the deficiency, thus limiting the need for management.

However, there are circumstances that require management. Firstly, if the anemia caused by the stressor is very severe, then a blood transfusion can be lifesaving. Anemia can be severe if the patient had pre-existing anemia, or if the stressor caused a rapid decline in the level of hemoglobin. There are no consensus guidelines on the use of transfusion in acute hemolytic anemia caused by G6PD. One proposal put forth by Luzzatto *et al.*,[11] suggests that if the level of hemoglobin is less than 70 g/L, consideration should be given to a blood transfusion. If hemoglobin is less than 90 g/L, and there are signs of significant hemolysis (hemoglobinuria), then immediate blood transfusion should again be considered. If there are no signs of hemoglobinuria, blood transfusion is not necessary, rather the patient should be monitored closely for 48 hours.[11] Consideration of co-morbidities, hemodynamic stability and the patients previous hemolytic experience may help guide the decision to initiate transfusion.

Acute kidney injury is a possible complication that occurs with severe acute hemolytic anemia. This is due to a situation, such as in the case of hypovolemic shock, and not because of damage caused by hemoglobinuria. Renal function usually recovers with time; however, the patient needs to be put on hemodialysis in some cases.[11]

Moreover, in children with severe anemia, administration of oxygen and fluids is critical. They might also need to have healthy blood cells transfused.[29] There are no specific treatments for the management of G6PD deficiency, rather avoiding the oxidative stressor is the recommended management plan.

Patient education about avoiding the triggers and recognition of signs and symptoms is critical in the management of the deficiency and to prevent further exacerbations. This is particularly important in patients with severe deficiency and lower enzymatic activity. Advice regarding diet and lifestyle modifications are usually given to the patient to prevent complications.[9]

Phototherapy

Neonatal jaundice is a common condition that occurs in children that are affected with G6PD deficiency. In order to manage this condition, phototherapy is a technique that is often used.[30] The probability pf developing severe hyperbilirubinemia is a deciding factor for the initiation of phototherapy. An increased risk of brain damage due to hyperbilirubinemia is present in G6PD deficiency, thus potentiating the need for phototherapy in the management of neonatal jaundice.[31] Phototherapy is a technique that uses visible light in the treatment of hyperbilirubinemia in neonates. This intervention involves reducing serum bilirubin by transforming it into water soluble isomers.[32] It is traditionally provided by fluorescent lamps, with radiance of 296 $\mu w/cm^2$ in the 400-480 nm range and 250 $\mu w/cm^2$ in the 425-475 nm range, directly on the infant's skin. Phototherapy has been proved to be effective in prophylaxis along with management of neonatal jaundice.[30] It may be used often, however, in certain cases where the adverse reactions caused are detrimental. It can cause acute side effects, including interference in the mother-child relationship, thermal and hydro-electrolytic imbalance, skin lesions and bronze baby syndrome, in addition to late side effects.[31,33]

Side Effects

Interference in the Mother-Child Relationship

The nature of the treatment is such that the neonate has to be separated from the mother for a period of time, thus limiting skin-skin contact and breastfeeding.[31] Moreover, there exists an increased risk of vulnerable child syndrome, wherein parental reactions to a life-threatening illness can cause long-term psychological effects on the children.

Thermal and Hydro-Electric Imbalance

A change in the thermal environment occurs within the neonate upon initiation of phototherapy. Subsequently, insensible water loss, hypothermia or hyperthermia and dehydration are potential side effects that may occur. It has also been noted that there exists reduced absorption of water, sodium and potassium. However, this is often transient, and resolves upon discontinuation of the treatment. Dehydration is seen as a serious complication, and thus in order to prevent dehydration during the course of the treatment, it is recommended to increase water supply by 10 to 15 ml/kg/day.[31]

Calcium levels are also closely monitored in neonates on phototherapy, due to an increase in urinary calcium excretion. Moreover, light affects calcium homeostasis by inhibiting melatonin secretion from the pineal gland leading to hypocalcaemia. The levels of calcium tend to return to normal within 24 hours after ending the treatment.[34]

Skin lesions

Macules, papules and a maculopapular rash may often be caused as a consequence of phototherapy. In cases of haemolytic disease, such as G6PD-deficiency, an increased risk of purpuric eruption exists, due to simultaneous transfusion of blood and intravenous immunoglobulins.[31] Phototherapy also poses an increased occurrence of common and atypical nevi as was demonstrated by Csoma *et al.*[35]

Neoplasms

There were multiple in vitro studies that were conducted on the risk of phototherapy causing subclinical carcinogenic risk hypothesising that a wavelength of 400-450 nm would pose a problem in phototherapy.[36-39] This was thought as it induces photosensitization of riboflavin which is an endogenous substance. However, this was proved wrong by a group of researchers who demonstrated the shielding effect of the Soret band of haemoglobin at wavelengths of 400-500 nm.[33] There were 2 studies conducted by the same group of researchers to demonstrate the risk of developing cancer with phototherapy. Both studies demonstrated that relative risk of developing cancer with phototherapy is statistically insignificant.[40,41] With the control of confounding variables, the association of cancer and phototherapy can be eliminated, but due to the possibility of partial causality, the use of phototherapy should be controlled.[41]

Bronzed Baby Syndrome

Phototherapy is also known to cause bronze baby syndrome (BBS) in certain neonates. This is an uncommon alteration in the colour of the

skin (dyschromia) that occurs as a consequence of phototherapy.[42] Kopelman *et al.,* reported the first case of BBS in 1972.[43] Increased accumulation of photoisomers of bilirubin, metabolic precursors or degradation products, or copper-porphyrin conjugates is the proposed cause of BBS. However, the true mechanism remains unknown. Despite the occurrence of BBS, it is still indicated to continue phototherapy in neonatal jaundice due to the innately toxic effects of excess conjugated bilirubin.[42]

Small Molecule Activators

A group of researchers, in 2019, looked at devising therapeutic measures for G6PD deficiency.[44] They postulate that the use of small molecule activators of the enzyme can promote the activity of the enzyme in deficient patients. The primary principle behind this is protein-protein interactions (PPIs). PPIs are the reason for the immense signalling networks that are present for normal cellular functions. These molecular interactions together are termed as the interactome, and intervening in these is prime for modifying disease pathogenesis. Apart from signalling events, the interactome comprises of interactions between the quaternary structure of proteins to modulate enzyme stability, activity and function.[44] Hence the use of small molecules that target this aspect of the interactome is essential in enhancing enzymatic activity of G6PD.

The primary cause of pathogenicity in G6PD deficient individuals are mutations that affect the homodimer interface of the enzyme. This is because only the homodimer and homtetrameric forms of the enzyme are active and stable. Raub *et al.*,[44] identified AG1, a small molecule activator, from a common pathogenic mutation of *g6pdx*. In order to develop a suitable therapeutic agent, the mechanism of the molecule, AG1, was studied by the group. They postulated that AG1 promoted G6PD dimerization. This was achieved by the bridging of two $NADP^+$ binding sites. The C_2-symmetric region of the G6PD homodimer is important for activation which is targeted by AG1.[44] Due to the observed increase in activity of enzyme by AG1, it can be considered in the treatment of G6PD deficiency. This drug can also be used in the prevention of complications that arise as a consequence of the deficiency.[45] However, it was observed that AG1 was not able to activate the enzyme in certain kinds of mutations. AG1 still is a novel class molecule that promotes activation in multiple pathogenic mutants.[44]

Conclusion

G6PD deficiency is a common enzymatic disorder that is inherited in an X-linked manner. Unlike other enzymatic disorders, G6PD is not rare; however, the majority of the population affected by the disease are asymptomatic, unless they inherit a severe mutant copy of the enzyme. Clinical features appear only after exposure to certain oxidative stressors which primarily include antimalarial drugs and fava beans. Diagnostic measures to detect the presence of G6PD deficiency include enzymatic activity detection and molecular analysis. Newer techniques have been formulated in the past few years that have demonstrated better efficacy in diagnosing the condition compared to existing techniques. Currently, there is no effective treatment for the deficiency, removal of the trigger is frequently all that is required. In certain cases, blood transfusion and haemodialysis may be necessary.

Neonatal jaundice is a common early clinical manifestation of the disease. In the recent past, phototherapy has been used as a prophylactic measure for the management of the condition, along with avoidance of offending oxidative stressors. Various studies have been conducted to prove the effectiveness of the therapy and, although there are serious adverse reactions that have been reported due to phototherapy, its therapeutic effect outweighs the risk. Pharmacological modulation of the interactome is the future in drug discovery in this area. It is known that PPIs are important in enzyme stability and activation along with cell signalling. Hence, interventions acting on this target will likely prove immensely valuable in drug discovery, particularly for G6PD deficiency. Treatment strategies for the deficiency have seen significant advances in recent years, with small molecule activators demonstrating effective increases in enzymatic activity, albeit in *in vitro* studies. Further research needs to be conducted in this area to develop these small molecule activators for the treatment of G6PD deficiency.

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ULS

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Case Report

Case Report: General Anesthetic Management for Laparoscopic Cholecystectomy in Paramyotonia Congenita

Analise McGreal,[1] Daniel Slagle,[1] Andrew Dickens.[2]

Abstract

Background: Paramyotonia congenita (PC) is a rare disorder affecting skeletal muscle. Patients with this non-progressive condition experience intermittent episodes of sustained myotonia. Due to the predisposition for prolonged muscle contraction, special attention must be given to anesthetic management during operative procedures to prevent complications similar to those experienced in patients with malignant hyperthermia. To date, however, limited reports of anesthetic management in paramyotonia congenita are available. **The Case:** The present report describes successful general anesthetic management given to a patient with paramyotonia congenita using propofol and ketamine for induction, non-depolarizing rocuronium for muscle paralysis, and continuous nitrous oxide and IV propofol infusion for sedation. The patient remained stable throughout the case without myotonic episodes or other complications. **Conclusion:** Our report describes successful anesthetic management in a patient with paramyotonia congenita. This provides a potential management plan that may be applied to PC patients undergoing a variety of surgical procedures and eliminates risk associated with succinylcholine and possibly volatile anesthetics. Further research is needed to determine whether this approach is superior to previously reported techniques and should also identify which agents may be effectively utilized to reverse an intra-operative myotonic episode in PC.

Key Words: Anesthesia; Paramyotonia congenita; Laparoscopic cholecystectomy; Sodium channel; General anesthesia; Malignant hyperthermia (Source: MeSH-NLM).

Introduction

Paramyotonia congenita (PC) is a rare muscular disorder with an estimated prevalence between 1/100,000 to 1/200,000.[1] The disorder is characterized by periodic muscle contraction, or myotonia, followed by flaccid paralysis.[1] It is caused by an autosomal-dominant mutation in the SCN4A gene, which is normally responsible for regulating the amount of sodium and potassium ions present across the skeletal muscle cell membrane. Therefore, the mutation in this gene is thought to interfere directly with normal muscle contraction and relaxation.[1] Most patients with PC experience periodic myotonic contraction and paralysis by adolescence. However, in contrast to some other muscular disorders, PC is non-progressive and patients are expected to have a normal life expectancy.[1] Many patients with PC do not require pharmacologic intervention and treatment is primarily symptomatic. For example, symptomatic treatment may include reduction of cold exposure, which may act as a trigger for myotonic episodes.[1] Patients who do receive pharmacologic treatment may be treated with mexiletine for muscle relaxation.[1]

Patients with PC experience a broad range of symptom severity. They are at increased risk when undergoing general anesthetic management, especially with succinylcholine (***Figure 1***).[1-2] While this is similar to the better-known presentation of malignant hyperthermia (MH), it is important to note that patients with PC are not at an increased risk for malignant hyperthermia.[3]

MH is usually triggered by succinylcholine and/or halogenated volatile anesthetics and presents with hypercarbia, muscle rigidity, hyperthermia, and rhabdomyolysis following anesthetic induction.[3] In patients with PC, the only symptom is myotonia, typically in the hands, face, or neck.[4] Nevertheless, there is clear risk for patients with PC who undergo anesthesia.[1-2] Despite the known risk associated with the use of common agents such as succinylcholine and some volatile anesthetics for general anesthesia in patients with PC, there are few reports of anesthetic management for this condition. Previously reported techniques included intubation without neuromuscular relaxant for pyloromyotomy and continuous IV anesthesia with intercostal nerve block for repair of congenital nasal dysplasia using autologous costal cartilage.[5-6]

Successful anesthetic induction has been reported in patients with myotonic dystrophy (a similar disorder), using rocuronium, a non-depolarizing muscle relaxant. To the authors knowledge, there are no reports of anesthetic management using rocuronium for paralysis in patients with PC.[7] Thus, the present report describes successful management of anesthesia in a patient undergoing laparoscopic cholecystectomy, a common surgical procedure, using non-depolarizing rocuronium for muscle paralysis, propofol and ketamine for induction, and propofol infusion/nitrous oxide for general anesthesia

Highlights:

- In this case report, we describe general anesthetic induction and management for a patient with paramyotonia congenita, a rare disorder affecting skeletal muscle.
- Special attention must be paid to anesthetic management during operative procedures to prevent complications similar to those seen in patients with malignant hyperthermia.
- Our report provides a potential management plan that may be applied to PC patients undergoing a variety of surgical procedures and eliminates risk associated with succinylcholine and volatile anesthetics.

[1] BS, Medical Student. Mercer University School of Medicine, Georgia, United States.
[2] MD. Anesthesiologist. Anesthesia Associates of Columbus. Emory-St. Francis Hospital in Columbus, Georgia, United States.

About the Author: *Analise McGreal is currently a fourth year medical student at Mercer University School of Medicine in Columbus, GA, USA. She is a member of the Alpha Omega Alpha Honor Medical Society.*

Correspondence:
Analise McGreal
Address: 1550 College St, Macon, GA 31207, United States
Email: analise.elizabeth.mcgreal@live.mercer.edu

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maintenance. Written consent and Health Insurance Portability and Accountability Act (HIPAA) authorization were obtained from the patient.

The Case

A 36-year-old Caucasian female presented to the outpatient general surgery office with complaints of several months of recurrent postprandial nausea. Upper endoscopy did not reveal an obvious etiology for nausea. Subsequent diagnostic testing, including cholescintigraphy scan, was pursued and revealed a reduced gallbladder ejection fraction, diagnostic for biliary dyskinesia. Thus, it was recommended that the patient undergo elective laparoscopic cholecystectomy for symptomatic relief. The patient underwent pre- and peri-operative anesthesia exam, which revealed a past medical history of PC, chronic cholecystitis, gastroesophageal reflux disease (GERD), hypertension, asthma, hypothyroidism, and anxiety. The patient had not previously undergone general anesthesia, though she was aware of the risk associated with anesthesia due to her PC.

Current medications at the time of surgery included mexiletine (150 mg every 12 hours), omeprazole (40 mg each day [qd]), montelukast (10 mg every night at bed time [qhs]), azelastine hydrochloride-fluticasone propionate (137 mcg-50 mcg nasal spray twice a day [bid]), levothyroxine (50 mcg once a day [qd]), clonazepam (0.5 mg qhs), eszopiclone (3 mg as needed [prn]), and propranolol (10 mg prn). Cardiovascular and respiratory review of systems revealed no significant findings, aside from history of asthma as stated (mexiletine used for chronic pain and muscle relaxation) and the patient took nothing by mouth for over 8 hours. She had not used propranolol (for anxiety) prior to surgery.

Airway exam revealed Mallampati score of 1, thyromental distance > 3 fingerbreadths, and mouth opening > 3 fingerbreadths. Cardio-respiratory exam revealed a regular rate and rhythm, no murmurs, rubs, or gallops, and non-labored respirations. Pre-operative labs including complete blood count (CBC) and electrolytes were within the normal limits and pregnancy test was negative. Vital signs prior to anesthetic induction included temperature of 37°C, heart rate of 96 beats per minute, respiratory rate of 18 breaths per minute, blood pressure of 112/65 mmHg, and oxygen saturation of 100% on a 2L nasal cannula. To maintain normothermia, the patient was covered with heated blankets in the preoperative area and in the operating room. A Bair Hugger system was also utilized throughout the duration of the case.

Core temperature monitoring was established via the esophagus and recorded periodically. Normal sinus rhythm was confirmed with electrocardiogram (EKG). Anesthetic management began with 100 mcg of fentanyl, 4 mg of odansetron, and 2 mg of midazolam for pain, nausea, and anxiety. Antibiotic prophylaxis with 900 mg of clindamycin was given. Next, 200 mg of propofol and 20 mg of ketamine were used for induction. Rocuronium (35 mg) was given for non-depolarizing muscle paralysis. The trachea was smoothly intubated by video laryngoscope. This was performed by a registered nurse anesthetist under the supervision of an attending anesthesiologist. Nitrous oxide and continuous propofol infusion (10 mg/mL IV emulsion 100 mL at 7.59 mg/hr) were used for maintenance of general anesthesia for the remainder of the case.

Pre-operative and post-operative electrolytes were within normal limits. Intraoperative EKG monitoring was performed throughout the entire procedure and the patient maintained normal sinus rhythm. No indication of hyperkalemia (such as peaked T waves, flattening of P waves, or prolongation of the PR interval) was apparent for the entirety of EKG monitoring. Thirty minutes after anesthetic initiation, an additional 50-mcg fentanyl and 20 mg ketamine was given for pain management and sedation. Dexamethasone 4 mg and glycopyrrolate 0.6 mg were given just prior to the completion of anesthesia (***Table 1***). The patient's vitals remained stable throughout the case, with an increase in systolic blood pressure prompting further pain management at 30 minutes. Total anesthetic time was 85 minutes. The patient awoke from anesthesia without complications and was discharged home on the same day, approximately 2 hours after the case concluded. She was seen for follow up in the general surgery office one week later. She reported some mental fatigue following surgery and did experience a delayed return to work as a result. She otherwise recovered well without complications.

Table 1. Medications Used for Anesthetic Management.

Procedure	Drug and dose/Procedure
Antibiotic Prophylaxis	900 mg clindamycin
Induction	200 mg propofol, 20 mg ketamine
Paralytic (Non-Depolarizing)	35 mg rocuronium
Anesthetic Maintenance	Nitrous oxide via nasal cannula, continuous propofol 10 mg/mL IV emulsion 100 mL @ 7.5 mg/hr
Intraoperative Monitoring	Potassium checks; electrocardiogram monitoring; temperature via esophagus
End of Sedation	4 mg dexamethasone, 0.6 mg glycopyrrolate

Discussion

The present case describes successful general anesthetic management in a patient with PC using propofol and ketamine for induction andnon-depolarizing rocuronium for muscle paralysis, with continuous nitrous oxide and IV propofol infusion for anesthesia maintenance. The patient remained stable throughout the case without myotonic episodes, evidence of hyperkalemia, or other complications. Given the clear contraindication to succinylcholine, this suggests that the use of non-depolarizing agents during intubation is a viable alternative strategy in patients with PC when general anesthesia is required. Moreover, it is known that use of volatile anesthetics for maintenance anesthesia poses a risk for volatile anesthetics for maintenance anesthesia poses a risk for patients with malignant hyperthermia. There are minimal reports regarding the use of volatile anesthetics in patients with PC, so, we opted to not use sevoflurane for maintenance in our patient to avoid unnecessary risk.

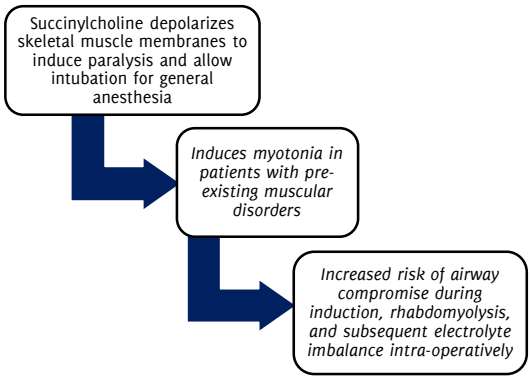
Regardless of anesthetic strategy used, hypothermia and hyperkalemia are the two biggest perioperative risks for a myotonic episode and should be monitored accordingly with a temperature probe, EKG, and electrolyte panels. Unfortunately, there is little evidence available to date regarding agents that could potentially reverse an acute myotonic episode, should one occur. There is only one reported case study in the literature that describes an acute reversal of a myotonic episode in PC during surgery.[8] The patient was a 40-year-old female who did not know that she had PC and was given succinylcholine during induction. Immediately, she was noted to have rigidity of her upper extremities, neck, and masseter muscles to the extent that her mouth could not be opened for intubation. Mask ventilation was performed and a 100 mg IV propofol bolus was given and within 4-5 minutes her myotonia receded allowing for intubation. The surgery was then performed without complications.

Additional research has suggested that the successful reversal may be secondary to the ability of propofol to block not only wild-type sodium channels, but also mutant sodium channels in a patient with PC.[9] Moreover, Matsumoto et al., reported a case that suggested the class 1B anti-arrhythmic drug mexiletine could potentially be used as a reversal agent due to its sodium channel inhibition.[7] If considered from a purely mechanistic view, this is logical since PC is caused by a derangement in sodium deactivation and mexiletine blocks sodium channels. However, the cited randomized control trial is somewhat limited because it reports that mexiletine is superior to placebo in reducing stiffness symptoms over a four-week period, not reversing an acute myotonic episode immediately.[10] Interestingly, our patient was

taking mexiletine at the time of surgery for chronic pain and muscle rigidity. Although it is unclear if this lowered her risk of myotonia intra-operatively, this could represent an important limitation of the present report. There were no indications for holding this medication pre-operatively, and, given the beneficial effect of mexiletine in PC, doing so may not have been in the patient's best interest. It is therefore unknown, however, whether paralysis with the non- depolarizing agent rocuronium, as described in this report, would have been successful without the patient's prior prescription of mexiletine. Therefore, additional research is needed to examine anesthetic management with rocuronium in patients with PC who are not taking mexiletine. Additional areas of focus may also include whether starting mexiletine in the pre-operative period (i.e., one month prior to surgery) in patients with PC shows benefit in reducing intra-operative complications for patients undergoing elective procedures.

In conclusion, our report describes successful anesthetic management using non-depolarizing muscle relaxant, rocuronium, bolus propofol, ketamine, and continuous IV propofol with nitrous oxide in a patient with PC. This provides a potential management plan that may be applied to PC patients undergoing a variety of surgical procedures and eliminates risk associated with succinylcholine and possibly volatile anesthetics. Additionally, the use of rocuronium as a muscle relaxant may allow easier and more efficient intubations in these patients, reducing the risk associated with prolonged hypoxia that is occasionally observed in difficult intubations. Further research is needed to determine whether this approach is superior to previously reported techniques and should also aim to identify which agents may be effectively utilized to reverse a myotonic episode in PC patients if it occurs intra-operatively.

Figure 1. Risk of Succinylcholine Utilization for Anesthetic Induction in Paramyotonia Congenita.



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ULS

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Case Report

Fixed Drug Eruption: A Rare Case of Polysensitivity between Two Unrelated Fixed Dose Combination Preparations - A Case Report

Jessica Kaushal,[1] Abhimanyu Rakesh.[2]

Abstract

Background: A fixed drug eruption is a type IV hypersensitivity reaction to a medication that characteristically re-emerges on the same site each time the specific drug is taken. Antimicrobials (including fixed dose combinations) are frequently implicated in fixed drug eruption while gliptins (as separate drugs or as combined preparations) on the other hand are infrequent triggers. Drugs belonging to similar classifications and having similar chemical structures can show cross reactivity, but here we describe a case of cross reactivity between unrelated drug classes, also known as polysensitivity. **The Case:** A 58-year-old man presented with painful, burning, and pruritic blisters with ulcerations on the oral mucosa of his lips, hard palate, and tip of the tongue. The patient had been on vildagliptin - metformin fixed dose combination tablets for one year. He was asked to stop the drug and lesions started improving thereafter. A week later he suffered from gastroenteritis for which he took a combined preparation of ofloxacin - ornidazole and lesions re-appeared at the same site as before with severe itching and burning. **Conclusion:** This case highlights polysensitivity amongst chemically unrelated drugs, especially available in fixed dose combination. It is an extremely rare occurrence (less than 0.2%). Moreover, there have only been a few cases of such delayed reactions occurring to gliptins, especially vildagliptin. A clinician must keep a high index of suspicion to identify this phenomenon.

Key Words: Drug Eruptions; Delayed Hypersensitivity; Gliptins; Antimicrobial agents; Titanium dioxide (Source: MeSH-NLM)

Introduction

Fixed drug eruption (FDE) is a cell mediated type IV hypersensitivity reaction frequently seen with antimicrobials, anticonvulsants and non-steroidal anti-inflammatory drugs (NSAIDs).[1] FDE is characterized by well-defined macular eruptions associated with blistering, burning or pruritis.[1] Cross reactivity is frequently seen between drugs belonging to the same class. The lesions recur every time an offending agent is taken. Resolution of lesions is accompanied by a dusky pigmentation due to post-inflammatory disordered melanin distribution between keratinocytes. This hyperpigmentation is permanent in character.[1] The condition becomes lifelong and avoidance of the offending agent is the key to management.[1]

Type-2 diabetes mellitus is a prevalent chronic disease and the most common cause of significant morbidity around the world. Metformin, a biguanide, is the first line agent to which sulfonylureas (SUs) and dipeptidyl peptidase-4 inhibitors (DPP-4i) can be added as second line agents as the disease progresses.[2] In the last decade, prescribing gliptins with metformin as an initial combination therapy is becoming a popular practice in India due to comparatively rapid achievement of target blood glucose levels with a negligible risk of hypoglycemia as the incretin effect of gliptins is glucose dependent.[3] The additive effect of these two drugs also enhances insulin sensitivity.[3] DPP-4i are more promising than SUs due to a better side effect profile along with better control on weight when added to metformin.[4] Vildagliptin is a potent DPP-4i and is frequently prescribed in type-2 diabetics as an add on second line agent when the metformin monotherapy fails.[5] Several adverse reactions have been attributed to this drug; however, reports regarding FDEs with gliptins have been very few to date.[6]

Highlights:

- Fixed drug eruption is a delayed type of hypersensitivity reaction.
- Very few cases with vildagliptin have been reported; none has been reported with vildagliptin-metformin combination.
- Cross reactivity seen between chemically different drugs exists (with emphasis of fixed dose combination drugs).
- It may be plausible to hypothesize that the excipient titanium dioxide found in combined preparations could be the culprit.

In this case, the patient had already been on vildagliptin-metformin (V-MF) 50mg/1000mg twice daily for almost one year when he started experiencing perioral itching with oral mucosal blistering and ulcerations. After identifying the potential of V-MF as a trigger for these reactions, the patient was asked to stop the drug, after which he achieved remission of his oral lesions. One week later, the patient was prescribed ofloxacin-ornidazole (OFL-ONZ) 200mg/500mg for an episode of gastroenteritis, and the re-emergence of similar oral lesions occurred at the same previously involved site but this time with exaggerated symptoms of itching, burning and blistering. This case is unique for not only reporting an infrequent adverse event associated with DPP-4 inhibitors (gliptins) but also for focusing on polysensitivity of FDEs in chemically unrelated classes of medications, particularly those prescribed in fixed dose combination (FDC) tablets. The main aim of this article is to address an adverse event of polysensitivity which may be attributed to the common excipient used in the coating of these FDC tablets.

[1] MBBS, Intern, Government Medical College, Amritsar; Baba Farid University of Health Sciences, Faridkot, Punjab, India
[2] MBBS, Sri Guru Ram Das Institute of Medical Sciences and Research, Amritsar; Baba Farid University of Health Sciences, Faridkot, Punjab, India

About the Author: *Jessica Kaushal is an intern rotating at Guru Nanak Dev Hospital, Amritsar, Punjab, India. She has presented a paper at a national conference organized by Junior World Congress. She rotated at Cardiology department, Unicardio, Florida International University, Miami this year and has expressed her keen interest in Internal Medicine. She aspires to pursue her residency in the United States. Dr. Abhimanyu Rakesh is currently working as a resident medical officer at Magnus Hospital, Panchkula, Haryana, India. He recently graduated from Sri Guru Ram Das Institute of Medical Sciences and Research, Amritsar. He has rotated in the United States for 3 months to gain hands on clinical experience and has expressed his appreciation for the US clinical set up.*

Correspondence:
Jessica Kaushal
Address: Majitha Rd, Medical Enclave, Amritsar, Punjab 143001, India
Email: jessicakaushal1995@gmail.com

Editor: Ammar Ismail
Student Editors: Nikoleta Tellios, Adam Dinoff & Mohamed Fahmy Doheim
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Figure 1. Fixed Drug Eruption due to Vildagliptin-Metformin Fixed Dose Combination Tablet.

Figure 2. Residual Hyperpigmentation 10-Weeks After Cessation of the Offending Drugs

The Case

A 58-year-old man presented in the clinic with chief complaints of itching, burning, and appearance of blisters and ulcerations with erythema on the oral mucosa of his lips, hard palate, and tip of the tongue for the past 2 days. The lesions appeared within 2-3 hours after consuming breakfast in the morning 2 days ago. The patient assumed the episode to be an allergic response to fruits he had consumed in his breakfast and decided to omit fruits in his following meals. He took fexofenadine hydrochloride, an over-the-counter antihistamine, for the lesions but there was no relief. The patient presented 2 days later due to persistence of these lesions despite the steps taken (***Figure 1***).

He had no previous history of allergic reactions. Medical history was positive for diabetes mellitus type 2. He used to drink alcohol occasionally. Drug history included V-MF FDC oral preparation (50mg/1000mg, twice daily after meals) for the past year. He reported consuming the tablet from a new blister pack immediately after his breakfast a couple of days before presenting to the clinic. He continued to take the drug for the next 2 days as well. He was asked to discontinue the drug and follow up after 2 days. The patient claimed that he experienced relief in the following 48 hours after discontinuing the drug.

An oral drug provocation test (DPT) was performed with V-MF full dose (1 tablet) which led to itching, burning and ulceration around the previous lesions. The positive test therefore supported the diagnosis of FDE due to this FDC drug. He switched to metformin and vildagliptin (as separate tablets) thereafter and did not have any problem. One week later, the patient experienced an episode of gastroenteritis with acute onset diarrhea for which he was administered OFL-ONZ, a FDC oral preparation containing ofloxacin (200mg) and ornidazole (500mg). Soon after this, there was recurrence of itching, erythema and burning around the lips. On discontinuation of OFL-ONZ, lesions started healing. Two days later, a DPT with half the dose of OFL-ONZ, the itching re-emerged around the lips. The patient claimed no such reaction occurring with OFL-ONZ in the past. He was then advised to abstain from these as well as any FDC preparations in future.

Two months after cessation of V-MF and refraining from FDC medications, the skin eruptions had subsided but there was a residual dark pigmentation on both the upper and lower lips where the original lesions had existed (***Figure 2***).

Discussion

Vildagliptin is a potent DPP-4i that prevents breakdown of endogenous incretins by DPP-4 enzyme thereby enhancing insulin secretion. Extensive monotherapy trials have shown improved glycemic regulation and substantial glycated hemoglobin (HbA1c) reductions in type-2 diabetics along with a favorable adverse effect profile.[7] These features make vildagliptin a propitious agent for combination therapies (especially with metformin) which has been evidenced through clinical trials.[7] Metformin, a biguanide, has a different target of action. Both drugs are highly effective first line agents. Over time, regimens in diabetics require adjustments and new drug combinations to target different metabolic problems emerging within the body. FDCs help to simplify the already complex medication regimen in diabetics and helps improve patient compliance.

The rationale behind combining fixed doses of two different drugs with different mechanisms of action is the benefit of an additive effect and a smaller number of individual doses required to achieve that effect.[8] As a result, vildagliptin (V) and metformin (MF) are frequently prescribed in FDCs (e.g. V-MF, an FDC drug combing these two salts in the ratio of 50mg:1000mg, respectively). V-MF is often prescribed twice daily along with non-pharmacological interventions such as lifestyle modifications (exercise, diet control) to keep blood sugar adequately controlled. Ofloxacin, a potent fluroquinolone is effective against gram-negative and gram-positive bacteria covering both *Staphylococcus Aureus* and *Pseudomonas Aeruginosa* while ornidazole, a nitro imidazole derivative, is both an antibacterial and antiprotozoal. With a similar rationale, antimicrobials are also often prescribed in FDCs to hit several targets with a single dose and provide an additive effect. In addition, FDCs help to overcome antibiotic resistance and increase the antimicrobial spectrum.[9]

Drug allergies can occur at any time. Here the patient developed a delayed-type hypersensitivity reaction after 1 year of taking V-MF FDC. An FDE is a type-IV hypersensitivity reaction to a medication, that characteristically re-emerges on the same site each time the drug is taken.[10] Cross-reactivity between structurally or chemically similar drugs may occur. The lesions often involve the skin (trunk, limbs, etc.) and mucosal surfaces (lips, genitalia, perianal region) and may be localized or generalized. Healing begins once the offending agent is stopped, which is often followed by persistent dusky brown or purple post-inflammatory hyperpigmentation at the site of the reaction. This is called post-inflammatory hyperpigmentation that occurs once the inflammation subsides and is due to increased melanin production along with disordered distribution of melanin to the surrounding keratinocytes via melanosomes.[11] There have been very few reports regarding FDEs secondary to gliptins and metformin.[12] There has been no reported case of V-MF FDC drug-induced FDE to our knowledge. On the other hand, OFL-ONZ FDC induced FDE have been quite frequently

reported in the literature; however, polysensitivity (i.e. two structurally and chemically unrelated drugs inducing the same allergic reaction at the same site) has almost never been reported. Shiohara *et al.* once commented on an unusual case where polysensitivity was seen amongst three anticonvulsants.[13] He proposed that such phenomenon exists frequently in reality but is under-reported due to lack of awareness and suspicion, and it is possible that polysensitivity is due to a non-antigen specific phenomenon.[13]

In this case, the patient exhibited a polysensitivity phenomenon where two different FDC drugs induced hypersensitivity reactions at the same site. This was supported by the DPTs as well. DPT is the supervised administration of a suspected allergen to accurately diagnose hypersensitivity reactions. The patient did not experience any such reaction when individual drugs as separate salt-formulations were given. On reviewing the composition of all these drugs i.e., vildagliptin, metformin, their FDC preparation, ofloxacin, ornidazole and their FDC preparation, our attention was drawn towards the inactive inorganic ingredients. FDC drugs are usually coated with titanium dioxide nanoparticles (TiO_2NPs) while the uncombined drugs come in an uncoated form. This has also been confirmed by spectroscopic studies.[14] Titanium dioxide (TiO_2) is a Food and Drug Administration approved food and pharmaceutical additive, mainly to confer white opaque coating to confectionaries, dairy products, and medicine tablets. TiO_2NPs toxicity has not yet been established due to lack of sufficient research and reporting. TiO_2, as a macroparticle or microparticle, is generally not harmful; however, toxicity due to TiO_2 nanoparticles is a novel concern in biomedical research. In a recent study it was said that nanoparticles (defined as particles with diameter <100 nm) become a health concern, especially if their size is 30 nm or less as they are not phagocytosed effectively by phagocytes, and can potentially trigger a pro-inflammatory cascade causing free radical injury.[15] Also, a relatively small size of nanoparticles means higher surface area to volume ratio which potentially promotes nanoparticle deposition in tissues.[15] As an opacifying pigment, TiO_2 particle size spans over a range of 25 nm – 300 nm.[16] Since TiO_2 powders contain a variety of sizes, a fraction of nanoparticles does exist (which includes particles <30 nm in size) and it is roughly up to 36%.[16] A review study by Skocaj et al. mentions that although TiO_2NPs are considered safe, data on their toxic effects upon oral exposure has been very scarce. They propose that TiO_2, when exposed to the acidic pH of the stomach, gets solubilized and disseminated via the blood and lymph into the different tissues especially the liver, spleen, kidneys and lungs.[17] Although the amount of TiO_2 consumed via foods and medicines is far below the levels used for experimental studies that were reviewed to study the impact of TiO_2NPs on the intestinal microenvironment and systemic immunoregulation,[18] there still stands a possibility of the cumulative effect of TiO_2 being consumed in small doses and therefore being accumulated constantly over long periods of time and triggering adverse reactions.[18] However, there is a paucity of research in this domain.

Conclusion

FDEs are infrequently associated with antidiabetic agents as very few cases have been reported and none have been reported with FDC preparation of vildagliptin and metformin to our knowledge. Healthcare providers should be aware of such rare adverse events with these drugs. Polysensitivity, especially amongst FDC preparations is possible. This case also discusses the possibility of TiO_2 being a trigger antigen for type-IV hypersensitivity drug reactions as this patient experienced FDE with drugs containing TiO_2 as an excipient (inactive ingredient), but did not experience a reaction when he consumed the same drugs in uncombined preparations that lacked TiO_2.

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Case Report

Aberrant Lymphatic Drainage of Primary Invasive Lobular Carcinoma with Concurrent Primary Lung Adenocarcinoma: A Case Report

Rina Won Lee,[1] Emily Denney.[1]

Abstract

Background: Lymphatic spread of breast cancer is currently well understood and can be assessed in breast cancer patients through the use of lymphatic mapping with sentinel node biopsy, computed tomography or positron emission tomography. However, this case highlights a unique pattern of lymphatic spread of unknown etiology. **The Case:** A 73-year-old female with two distinct primary carcinomas, right-sided invasive lobular carcinoma of the breast and left-sided adenocarcinoma of the lung. We discuss the predictable and unpredictable lymphatic drainage of the lobular carcinoma, including ipsilateral drainage to the axillary chain and suspected contralateral hilar and mediastinal lymph node metastasis. **Conclusion:** The unique lymphatic spread of the breast cancer in this case emphasizes the use of lymphatic mapping for staging of disease and staining biopsied tissue samples for tumor markers to guide treatment. Additional anatomic research in this patient or supporting reported cases are needed to determine the frequency and cause of aberrant lymphatic drainage of primary invasive lobular carcinoma of the breast.

Key Words: Lobular carcinoma; Breast cancer; Adenocarcinoma of lung (Source: MeSH-NLM).

Introduction

Invasive lobular carcinoma (ILC) comprises approximately 10% of all breast cancers.[1] The malignant cells line up in a single file in the stroma and usually do not form a distinct, palpable mass. Overall, the prognosis tends to be good, due to the low grade of the tumor and its nature of being estrogen receptor positive (ER +).[2] However, ILC tends to be multifocal and multicentric and can involve both breasts.[3] Such characteristics have led to cases of distant metastases involving the peritoneum, ovaries, and uterus.[4] The vast majority of breast malignancies tend to spread via axillary lymph nodes, but there can also be nodal metastases outside of the axillary lymph nodes, involving the internal mammary, infraclavicular, and supraclavicular lymph nodes.[5] Furthermore, breast malignancies, using lymphatic and hematogenous routes, can have pulmonary involvement, called pulmonary lymphangitic carcinomatosis.[6]

Adenocarcinoma of the lung is the most common type of lung cancer and can quickly spread to distant sites via lymphatic and hematogenous routes, which often results in stage IV disease by the time of patient presentation.[7]

Here, we present an interesting case of a primary, right-sided invasive lobular carcinoma with ipsilateral axillary nodal involvement and primary, left-sided adenocarcinoma of the lung with suspected ipsilateral hilar and mediastinal lymph node metastasis, which actually turned out to be invasive lobular carcinoma. Informed consent of publication was obtained from the patient prior to submission/publication.

Highlights:

- This is a case report of a patient, with no known genetic abnormalities, who was found to have two primary carcinomas, invasive lobular carcinoma and adenocarcinoma of the lung, after workup of a breast mass found during self-examination.
- The lymphatic drainage of the invasive lobular carcinoma was found to be atypical, spreading to the contralateral lymphatic beds without involvement of the ipsilateral lymphatic beds.
- Furthermore, the case points to the use of imaging techniques in the diagnosis and treatment of cancers.

The Case

The patient is a 73-year-old African American female with no family history of breast or ovarian cancer who initially presented due to a right breast mass palpated upon routine self-breast examination. She had a screening mammogram completed, which showed a 2.5cm spiculated mass in the right breast at the 6 o'clock position, 16cm from the nipple along with a 1.1cm asymmetry anterior to the mass and a 0.8cm asymmetry in the right retroareolar region (***Figure 1***). The radiologist assessment was BI-RADS 0 (Breast Imaging Reporting and Database System), and additional imaging was recommended.

Two weeks later, the following diagnostic mammogram showed a 2.3cm irregular, spiculated mass in the right breast at the 9 o'clock position, 17cm from the nipple along with a 0.7cm mass, 2cm from the nipple. Whole breast ultrasound showed a solid mass in the right 8 to 9 o'clock position, highly suspicious for malignancy along with an abnormal lymph node in the right axilla. The radiologist assessment this time was BI-RADS 5: highly suggestive of malignancy, so biopsies of the lesion and lymph node were recommended.

The patient was seen by a breast surgeon, who examined the patient and noted the patient's breasts to be enormous and very pendulous with palpation of some nodularity in the extreme outer right breast,

[1] BS, Mercer University School of Medicine, Macon, Georgia, United States.

About the Author: *Rina Lee is a current third year medical student of Mercer University School of Medicine, Columbus, Georgia, USA of a four-year program. She is a member of the Alpha Omega Alpha Honor Medical Society. Emily Denney is also a current third year medical student at Mercer University School of Medicine, Columbus, Georgia, USA of a four-year program. She is a member of the Gold Humanism Honor Society.*

Correspondence:
Rina Won Lee
Address: 1550 College St, Macon, GA 31207, United States
Email: rinalee25@gmail.com

Editor: Paul MacDaragh Ryan
Student Editors: Samreen Fathima & Nikoleta Tellios
Copyeditor: Adnan Mujanovic
Proofreader: Sohaib Haseeb
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Figure 1. Screening Mammogram Showing Spiculated Mass in Right Breast.

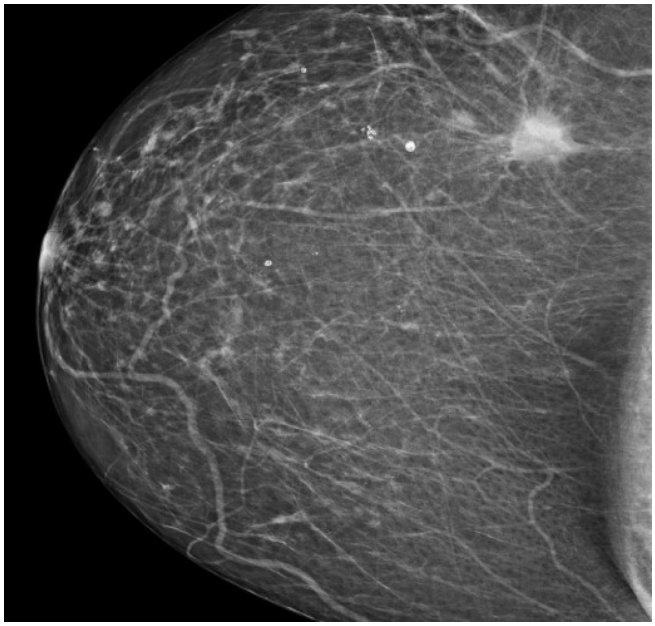


Figure 2: Ultrasound Image Showing Right Breast Mass Prior to Biopsy.

but no lymph nodes were palpated in the axillary and supraclavicular regions.

The following day, patient underwent an ultrasound-guided core biopsy with multiple cores taken from the primary lesion in the right breast at the 8 o'clock position, 13cm from the nipple (***Figure 2***). The 5-6mm satellite lesion was seen 3-4mm away from the primary lesion, but no biopsy samples were taken. Multiple cores were taken from an enlarged right axillary lymph node, which showed cortical thickening with compromise of the hilum that measured 1cm. The pathology report that followed showed invasive lobular carcinoma with positive axillary metastasis.

Figure 3. PET Image Showing Right Lateral Breast Mass with Fluorodeoxyglucose Uptake.

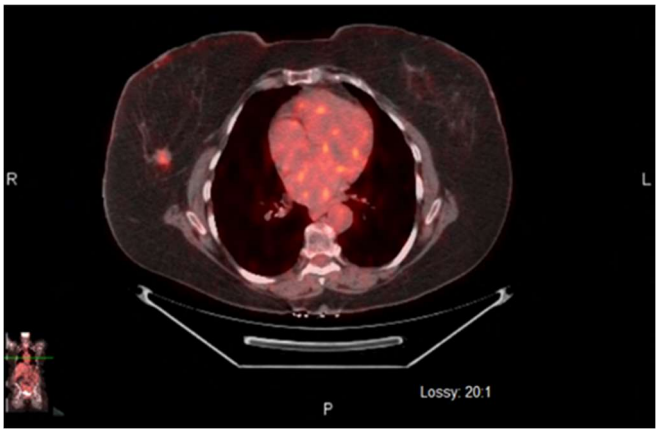
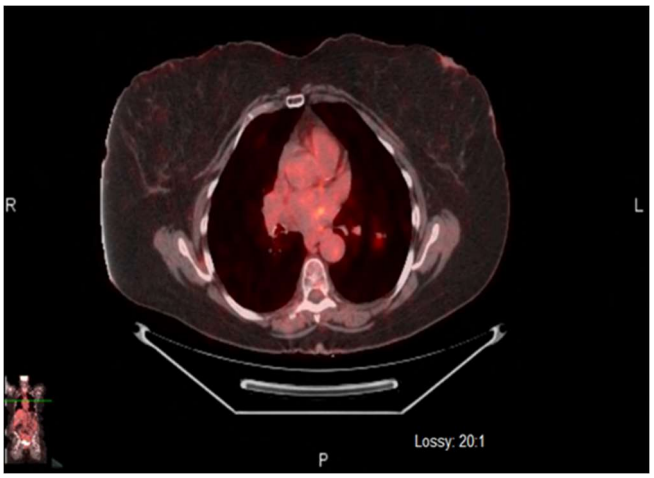


Figure 4. PET Image Showing Fluorodeoxyglucose Uptake in Superior Segment of Left Lower Lobe.

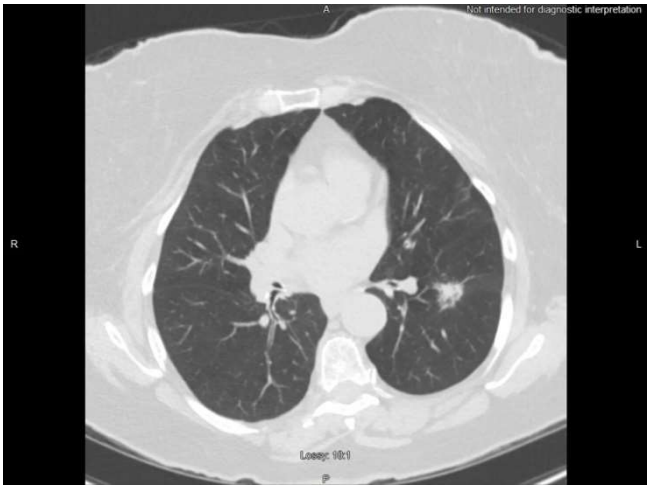


Breast-specific gamma imaging (BSGI) and Positron emission tomography-computed tomography (PET-CT) were ordered one week later. The BSGI showed a 2cm diameter area of intense focal uptake in the right breast at 9 o'clock, 15cm from the nipple with no evidence of multifocal, multicentric disease. The PET-CT findings included: an irregular right lateral breast mass, consistent with known right breast carcinoma, mildly enlarged right axillary lymph nodes consistent with nodal metastases (***Figure 3***), and an irregular nodule within the superior segment of the left lower lobe, which was concerning for metastasis or concurrent primary bronchogenic carcinoma (***Figure 4***).

Based on such findings, the breast surgeon and interventional radiologist agreed upon a CT-guided biopsy of the left pulmonary lesion (***Figure 5***) 2 weeks after the imaging studies were completed. Two 20-gauge core biopsy specimens were obtained with no complications, and the pathologist reported well differentiated pulmonary adenocarcinoma with predominant lepidic growth pattern. The specimens stained positively for cytokeratin 7, napsin-A, and TTF-1 (thyroid transcription factor-1). The major risk factor for the patient was a history of tobacco use, which started at 17 years of age.

At this point, the patient's diagnoses were stage II carcinoma of the breast and a primary tumor of the left lung. Three weeks later, the patient subsequently underwent a right needle-localized lumpectomy

Figure 5. CT showing left lung lesion prior to biopsy



and axillary dissection. The pathology report confirmed invasive lobular carcinoma, and 2/2 lymph nodes tested positive for metastatic lobular carcinoma. The tumor was ER (estrogen receptor) positive, PR (progesterone receptor) negative, and HER2 (human epidermal growth factor receptor 2) negative. The staging of the breast cancer was T1c N1 Mo stage IIa invasive lobular carcinoma.

The patient was referred to an oncologist and cardiothoracic surgeon. One month later, she had a left lower lobectomy and mediastinal lymph node dissection performed. An 18.5 x 12.0 x 4.0cm lobe of the left lung that weighed 173.4g was removed. The pathology report showed moderately differentiated adenocarcinoma with lepidic predominance; all the vascular and bronchial margins were free of tumor. However, the pathology report showed the left mediastinal lymph nodes to actually be invasive lobular carcinoma: 1 of 1 peribronchial, 5 of 6 interbronchial, 1 of 1 subcarinal, 1 of 1 aortopulmonary window, 1 of 1 left inferior pulmonary ligament, and 1 of 1 hilar. The hilar lymph nodes stained positive for pankeratin and GATA3 (transcription factor and breast cancer marker) (Takaku) and negative for TTF-1 (Schilsky) and CD68. They were strongly positive for ER 100%, positive for PR 2%, and HER2 negative. Based on such histological characteristics, the left hilar lymph nodes were most consistent with metastatic invasive lobular carcinoma and not lung adenocarcinoma. The patient's diagnoses were changed to stage IV carcinoma of the breast and stage IA2 (T1b, No, Mo) carcinoma of the lung. She is currently undergoing chemotherapy with letrozole and Ibrance (palbociclib).

Discussion

Here we presented a unique case of primary lobular carcinoma of the right breast, primary invasive adenocarcinoma of the left lower lung lobe with pankeratin positive, GATA3 positive, ER positive left peribronchial lymph node involvement. Lymphatic spread of breast cancer is thought to be well understood. This case highlights a unique pattern of lymphatic spread of unknown etiology. Review of other case reports indicates the pattern of lymph node involvement in this patient with invasive lobular carcinoma of the breast is quite unique. While other cases were found on spread of invasive lobular carcinoma to the contralateral breast and aberrant lymphatic drainage patterns in recurrent breast cancer after treatment, no additional cases were found in the literature of spread of invasive lobular carcinoma to contralateral hilar and mediastinal lymph nodes in a patient with no previous history or treatment of breast cancer.

Lymphatic drainage of the breast drains ipsilaterally through the axillary, transpectoral and internal mammary pathways.[8] Further drainage occurs into "lymphatics that course along the axillary and contiguous subclavian vein. From here, the lymphatics may drain directly into the jugulosubclavian confluence or initially pass through the jugular and bronchomediastinal lymphatics."[8] The variance of lymphatic drainage seen in various tumors may be attributed to the quality of the lesions, whether it is palpable or nonpalpable, and the location of the lesion within the breast, either in the right outer, right inner, left outer, or left inner quadrant or in the center. According to Estourgie et al, both palpable and nonpalpable lesions can drain toward the internal mammary chain, but this pattern is more commonly seen with nonpalpable lesions.[9] Furthermore, Estourgie et al. reveal 97.1% of palpable lesions in the left outer quadrant should be expected to drain to the axillary lymphatic bed while 26.1% of palpable lesions in the same location drained to the internal mammary chain of lymphatics.[9] Because of the location of the primary breast tumor in the left outer quadrant (9 o'clock position of the right breast), the most predictable pattern of lymphatic drainage in this patient would be to the axillary nodes. While this patient had involved lymph nodes in the axillary chain, including sentinel nodes, stain positive for the invasive lobular carcinoma, additional lymphatic drainage to the contralateral hilar and mediastinal lymph nodes without ipsilateral hilar and mediastinal lymph node involvement was unique and not currently explained by the literature.

The question raised by the physicians caring for this patient was, how did the breast cancer spread to a single, contralateral region of lymph nodes without involvement of other ipsilateral or contralateral lymph node beds? Could this be an anatomic variant in this patient? Were there additional factors that allowed the spread of the tumor to a contralateral lymphatic bed, or was the cancer undiagnosed for a length of time adequate enough for the lobular carcinoma to contralaterally spread? According to Sharma et al.,[8] obstruction of normal lymphatic flow allows for development of collateral lymphatic drainage pathways, including internal mammary and mediastinal lymphatics. Lymphatic mapping with sentinel node identification in this patient identified drainage of the primary tumor to the axillary nodes. An anatomical variant or development of collateral pathways not assessed during the lymphatic mapping could explain the unique spread of the invasive lobular carcinoma in this patient. This case may support the expansion of lymphatic mapping into further lymphatic regions to identify spread of the tumor and may prompt further developments and advancements in lymphatic mapping as it pertains to breast cancer. The unpredictable lymphatic spread in this case prompts the discussion of the appropriateness of routine PET scans prior to treatment in breast cancer patients with no evidence of additional lymphatic spread on CT. CT is commonly used in cancer imaging to determine lymph node involvement. Because involved lymph nodes appear normal on CT, fluorine-18 fluorodeoxyglucose (FDG) PET can be used for more accurate detection of lymphatic spread of the primary tumor and relevant lymph node involvement.[8] Additional reports and studies are needed to determine the incidence of contralateral spread of lobular carcinoma of the breast to unusual lymphatic beds to determine the benefit of FDG-PET in conjunction with current CT scanning on patients with suspected additional extra-axial or contralateral lymph node involvement.

During the initial assessment of the patient, the involved hilar and mediastinal lymph node was suspected to be secondary to the primary adenocarcinoma of the left lung by the treatment team. Only through further staining and discussion was the origin of the carcinoma in the hilar and mediastinal lymph nodes discovered.

The complexity of this case illustrates the importance of staining biopsied tissue samples for tumor markers to accurately stage the disease and to ensure a chemotherapy regimen and further treatment is appropriate. Further research is needed to determine the impact of the aberrant lymphatic drainage of primary invasive lobular carcinoma as seen in this patient.

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Author Contributions

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IJMS INTERNATIONAL JOURNAL of MEDICAL STUDENTS

Experience

A First Year Medical Student's Perspective on Working in ICU during the COVID-19 Pandemic

Erin McCabe.[1]

The Experience

The COVID-19 pandemic has brought forth unprecedented lockdown policies, affecting every individual within the United Kingdom (UK), and millions of people in other affected countries. On the 23rd March 2020, the UK Prime Minister announced a nationwide lockdown – for those in the UK this meant all non-essential businesses were closed, and individuals were only allowed to leave the house for essential shopping and one form of exercise per day.1 Medical students from across the world have had to make the transition to online teaching – this reduction in clinical contact leading individuals to question the value of this teaching.2 Like most medical students, I knew that this had to be done to protect those most vulnerable to the disease. Despite this, the transition process and significant changes of the support system felt incredibly difficult, particularly for those with existing mental health problems.3 I wanted to help, yet in a way I felt helpless.

I am a first-year medical student. At most medical schools, I would be in 'pre-clinical' years, meaning there would be limited opportunities to encounter patients until later in the course. The medical school I attend, thankfully, has frequent clinical exposure from the third course week, so I had met patients in both primary and secondary care. Although this was a helpful experience, it did not prepare me for my new role in a COVID-19 Intensive Care Unit (ICU). I managed to successfully get a job in one of the largest healthcare trusts in England and made the difficult decision to move and live in a hotel for two months, far from my home in the north. I expected a sharp learning curve and had heard of the difficulties faced by healthcare professionals. My family did not quite understand why I was going and they were worried for my safety. I was quite nervous, but I had decided that it was the right thing for me to do. My job was 'Bedside Buddy', a new role created to help support the ICU staff during the pandemic. It involved working one to one with patients, helping with both personal and medical care. This included tasks such as washing and helping to roll patients, stocking the bed spaces, and running arterial blood gases.

My first shift inside the COVID-19 ICU was a twelve-hour night, in full level 3 personal protective equipment (PPE) shown in **Figure 1**. I was assigned to a side room with a level three patient (meaning they had the highest level of dependency). But this was not just another patient, she worked in the NHS at the start of the pandemic and listened to Robbie Williams. It was a shocking experience as I had never seen someone so sick – she was sedated, on hemofiltration and had a tracheostomy connected to a ventilator. On the nurse's break, I had over an hour with the patient. I did what felt right – I chatted with her as I got her ready for bed, just how I would if I were at home. I brushed her teeth, washed and brushed her hair, and put her moisturizer on. These small aspects of care are relatively tiny compared to the massive care requirements of a critically ill COVID-19 patient, but they maintained normality for the patient. Before this experience, like most medical students, I did not consider the importance of a simple task like brushing hair in the long-term treatment of a patient. Numerous studies have shown the importance of communicating with unconscious patients, indicating that speaking with the patient helps to meet their psychological needs and prevents unnecessary stress.4 The small aspects of care also prevent matting of hair, oral infections and drying of the skin. A study has shown that practicing oral care and hygiene can reduce the incidence of pneumonia in ICU patients, with 3.9 cases when oral care is practiced as opposed to 10.4 cases in the control group (per 1000 ventilator days).5 These are the aspects of care which are neglected during the care for the critically ill patients.

Figure 1. Myself in Level 3 PPE at the Start of a Night Shift

[1] MBBS. Hull York Medical School, United Kingdom.

About the Author: *Erin McCabe is currently a second-year medical student at Hull York Medical School in England.*

Correspondence:
Erin McCabe
Address: John Hughlings Jackson Building, University Rd, Heslington, York, United Kingdom
Email: hyem17@hyms.ac.uk

Editor: Francisco J. Bonilla-Escobar
Student Editors: Nikoleta Tellios, Nguyen Tran Minh Duc
Copyeditor: Adnan Mujaovic
Proofreader: Leah Komer
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By nature, I feel both medicine and being a doctor leads to an overarching view of the clinical care of a patient. From this experience, I have seen that every part of a patient must be considered, in the example of this patient: being a fan of Robbie Williams. As she began to recover, we played his music for her, helping her through the delirium she was experiencing. Playing familiar music has been shown to aid delirium, and it was here used alongside constant communication and reorientation, as recommended by NICE.6,7 The importance of holding a hand and playing a favorite song is underestimated by so many as our education focusses on the administration of specific medications.

One of the most poignant lessons I have taken and want to share about this is the importance of every member of the healthcare team. We always discuss this in medical school, but it is a very different experience being part of the team as a Healthcare Assistant/Bedside Buddy. Some healthcare professionals who are not regularly on the ward are confused as to why I was there. It is hard to demonstrate and explain how a first-year medical student has a role in complex management. However, every time I brush patients' teeth, disinfect a surface, or take on other responsibilities, I know that we are needed.

Everyone is vital in a healthcare, pandemic or not.

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Experience

National Health Service Bury and Rochdale Doctors on Call (NHS BARDOC): Medical Students Working on the Frontline at the Greater Manchester COVID-19 Death Service

Imania Yaqub,[1] Bilaal Ghafoor.[1]

The Experience

This is an extraordinary time, one that we never thought we would have to experience in our lifetime. On the 11th of March, 2020, the World Health Organization (WHO) announced the COVID-19 outbreak caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), a pandemic.[1] A recent report by WHO states as of 29th June 2020, globally there has been 10 million cases of COVID-19 reported, of whom 500,000 have sadly passed.[2]

The COVID-19 pandemic had a significant impact on healthcare student's medical education across the globe. On the 13th of March, all universities and medical students' placements in the UK were disrupted and teaching was thereon provided remotely.[3] Therefore, resulting in students missing out on clinical exposure which is key in the development of our clinical skills.[4] Many third-year medical students like us were in the process of preparing for our examinations. We were automatically progressed to the fourth year, and our clinical placements came to an end. Recognizing the huge burden on the National Health Service (NHS), with the lack of healthcare resources and high demand for staff, we sought an opportunity to work in a clinical environment.

We have been working on the frontline as call handlers at the Emergency Community Death Service (ECDS) for an Out of Hours service provider named Bury and Rochdale Doctors on Call (BARDOC) for the NHS providing care across Greater Manchester (GM) in the North West of the United Kingdom (UK). The ECDS service was set up rapidly due to a large number of deaths in the community occurring daily that led to an increased workload on General Practitioners (GPs). We initially supported staff in setting up the service, which involved training other medical students and non-clinical staff about the role. Although we were unfamiliar with how deaths are dealt with in the community, we had to quickly learn the legislation around the verification of deaths, the completion of Medical Certificate of Cause of Death (MCCD), and how cremation papers are completed to complete our role effectively. The Coronavirus Act 2020 was introduced to increase the number of healthcare staff available to assist during the pandemic. It allowed both retired healthcare professionals to return to work and fifth-year medical graduates to begin their foundation training early. The main aim was to lessen the burden on the frontline staff. Due to the inadequate levels of personal protective equipment available to healthcare staff, it resulted in an increased mortality rate amongst them during the early stages of the pandemic.[5,6] The new legislation surrounding deaths in the community was also relaxed to allow timely and efficient verification of deaths, which is extremely important in the current crisis.[7]

Our role as a call handler meant we took calls from the deceased family members, or from care homes where residents had passed away. It was emotionally challenging being the first port of call for people after they found out their loved one had passed away. It also involved liaising with GPs and nurses and allocating them deaths to verify. Documenting death certificates and sending them to the registrars was a key part of the role. New legislation is in place regarding MCCDs and cremation papers made it a challenging and difficult ordeal for the family, as they were already dealing with the loss of a loved one, thus making it our priority to explain the new process whilst being aware of their unstable emotional state.

Reflecting on our experience, working as a medical student during the pandemic taught us a vast amount. There was one particular encounter with a deceased patients' family member which had a lasting impact on us. It was 6 am and we received a handover from the team on the night rotation about the tasks pending to complete. Just like every morning, there were many MCCDs to be written up; cremation forms needed to be filled in by the doctors and GPs needed to be allocated deaths to go verify in the community. We logged into the phones after handover and answered a call. We were greeted by a lady, sorrowing over the death of her dad. She was extremely fearful about how her dad's corpse had been laying in bed for over 16 hours and no doctor had been to verify the death. This meant that the funeral director couldn't move the body to the funeral home. The daughter was sobbing, and I remember her telling me the smell of her dad's body decomposing was extremely distressing for her. We had never in our time on placement or working here experienced a situation like this before. The way that we dealt with it was by apologizing and reassuring her that a doctor will be sent as a matter of urgency within the hour. Comforting her over the phone was extremely difficult as she was mourning the loss of her father, but it was a skill we had the opportunity to develop and it was important for us to be there for her as it is something she will remember for the rest of her life. It felt like we had failed on our end to send a doctor out on time; however, the lack of staff as a result of the pandemic delayed death verification. We saw firsthand how COVID impacted the healthcare system and the death verification process, resulting in not only delayed funeral times but more traumatic experiences for the families. Despite this, we gained invaluable skills such as emotional intelligence which allowed us to understand and deal with our emotions better as well as show empathy to those who needed it. This was a major learning curve for us in our medical career, knowing that we can provide better care for the next patient.

[1] Medical student, University of Manchester, United Kingdom.

About the Author: *Imania Yaqub is a 4th year medical student studying the 5-year MBCHB course at the University of Manchester. Bilaal Ghafoor is a 4th year medical student studying the 5-year MBCHB course at the University of Manchester.*

Correspondence:
Imania Yaqub
Address: Oxford Rd, Manchester M13 9PL, United Kingdom
Email: imania.yaqub@student.manchester.ac.uk

Editor: Francisco J. Bonilla-Escobar
Student Editors: Nguyen Tran Minh Duc, Colleen Campbell
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With the 6 am starts, night shifts, working over 50-hour weeks and the fear of contracting the virus, it was a psychologically challenging journey. However, the benefit to people and the NHS with the potential to save lives is a massive reward, which is exactly why we went into medicine. I am writing this a week before my fourth-year studies begin, in the hope that I won't be needed at the death service again. We now appreciate good health and how much we took it for granted previously. COVID-19 has truly changed our perspective in the way we see the world and personally how to deal with death in the community.

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Experience

Students Leading a Free Clinic: Lessons Learned About Digital Health in the Age of COVID-19

Marina E. Shatskikh,[1] Anna Kirillova,[2] Lucy Z. Shi.[3]

The Experience

Listening through the voicemail over the weekend, there is a missed call from our clinic patient, "Galina." She needs a hypertension medication but cannot obtain it without a paper prescription. We call our student secretary, in charge of maintaining paper-based charts. The secretary needs to bring the chart to the treating physician's office across town for a signature and then meet the patient to give her the prescription. Two weeks later, this method of issuing prescriptions becomes impossible. In response to the state-wide shelter-in-place order in California[1] due to the coronavirus disease 2019 (COVID-19), we are forced to close the doors of our student-led free clinic, disabling provision of essential care to our community.

Throughout the United States, free clinics play a unique role of providing care to underserved, often uninsured, populations who need preventative healthcare the most. Such student-led initiatives foster solidarity and equality within the community,[2-3] driving towards more accessible healthcare. In our clinic, 50% of patients are uninsured, 68% do not speak English, and many rely heavily on their community for social support. Many of our patients are ineligible for government-funded health insurance, which may be detrimental to their financial and physical well-being,[4] emphasizing the need for free, culturally-sensitive clinics to address gaps in access and drive towards health equity. To address these challenges, our clinic relies on volunteers to not only provide essential healthcare, but also offer medical interpretation services, prescription vouchers, and health insurance enrollment guidance to help patients navigate the medical system. Like many other clinics, we are focused on building a community center for free care and preventative medicine, striving to establish a rapport with our community by taking extra time to educate and help patients manage their health.[5] In light of the disproportionate impacts of COVID-19 on racial and ethnic minority groups,[6] there is now greater emphasis on establishing consistent healthcare within vulnerable communities.

A month into quarantine, Galina calls again requesting another medication. Our hands are tied. Without the ability to fulfill her requests in-person, we realize the need to innovate our system of care. Seeing the power of digital health within larger health systems, we aggressively pursue the implementation of telemedicine to enable virtual visits with our patients. Like most free clinics, dependence on private donations, grants, and university support to finance operating costs[5] has historically limited our ability to implement an electronic system. However, the spread of COVID-19 has emphasized the importance of implementing telemedicine to enable the continuation of essential care to vulnerable patient populations. Moreover, multiple organizations, such as the National Association of Free and Charitable Clinics, have established new funding opportunities. With the expansion of grants available, our clinic has been able to quickly obtain an electronic medical record system, teleconferencing equipment, and software to continue caring for our patients during this unprecedented time.[7] Re-opening our clinic virtually, we can continue treating chronic medical conditions while also distributing vital information to our local community regarding public health measures to reduce the spread of the disease. Many patients with pre-existing conditions, like Galina, can now be seen in the safety of their homes and we can reconnect with our community, decreasing the social isolation of sheltering-in-place.
The cost reduction and accessibility to resources associated with establishing a digital system have been instrumental in bridging the gap in care between low-funded clinics and established healthcare systems.[8] The diffusion of innovation inspired by the pandemic has the potential of bringing care to more places as limitations fade away. Our clinic, which operates from a repurposed community office, serves as an example that providers do not need sophisticated infrastructures or financial backing to be successful in this new age of digital health.

As we try to implement virtual visits clinic-wide, however, most of our patients are not keen on the idea. After announcing the new system of care to our patients, we learned that few are interested in being cared for virtually. Even our loyal patient "Oleg", who needs urgent help with a swollen elbow, still prefers an in-person visit with an herbalist instead of a tele-visit, due to concerns about the accuracy of diagnosis over video. Already disconnected from the Western medical system, many of our patients, like Oleg, value the human connection to build trust with a physician and ensure their concerns are heard and addressed. Oleg's reluctance showcases a limitation of telemedicine that may leave pockets of the population underserved. While telemedicine is becoming the standard of care in traditional hospital settings, such advancements may not be reached by small, disadvantaged communities, like ours, already struggling to find a bridge between traditional and Western medicine.

Although it is impossible to deny that the implementation of digital health technologies has made certain aspects of our clinic functions more streamlined, it is vital to address the arising challenges of transitioning to digital health. We are now able to quickly provide urgent assistance, such as medication refills, without a need for an in-person visit. However, more innovation may not be met with the same enthusiasm in patient populations. The lack of human connection that comes with digitized care may take away the human touch that is conducive to patient comfort and trust. Although our clinic now has an established telemedicine system, its real success will be demonstrated by how many patients are able to utilize it longitudinally. While technology is necessary for progress, disparities in its use will continue

1 Bachelor of Science, Bachelor of Arts, University of California-Davis, United States.
2 Bachelor of Science, University of Pittsburgh Medical Scientist Training Program, University of California-Davis, United States.
3 Doctor of Medicine, University of California-Davis Health, United States.

About the Author: *Anna Kirillova and Marina Shatskikh are graduates of the University of California-Davis and are co-founders of the Nadezhda Clinic, a free, student-run clinic affiliated with the University of California-Davis School of Medicine. Anna Kirillova is currently a first-year medical student at the University of Pittsburgh, and Marina Shatskikh is a full-time medicinal chemistry research associate at Gilead Sciences, Inc.*

Correspondence:
Marina Shatskikh
Address: 1 Shields Ave, Davis, CA 95616, United States
Email: mshatskikh@ucdavis.edu

Editor: Francisco J. Bonilla-Escobar
Student Editors: Madeleine Jemima Cox, Leah Komer
Copyeditor: Adam Dinoff
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to exist, widening the gaps in proper care delivery. Advocating for its use and communicating its true purposes is as important when striving for health equity. The COVID-19 pandemic has only illuminated these gaps in the context of underserved populations and emphasized patients' desire to maintain face-to-face interactions when seeking medical care. More education and advocacy about the safety and effectiveness of telemedicine is needed to implement this technology in patient care nationwide.

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IJMS INTERNATIONAL JOURNAL of MEDICAL STUDENTS

Experience

COVID-19: Using Social Media to Promote Mental Health in Medical School During the Pandemic

Han G. Ngo,[1] Brianna L. Gibney,[1] Paul Patel,[1] Jennifer L. Nguyen.[1]

The Experience

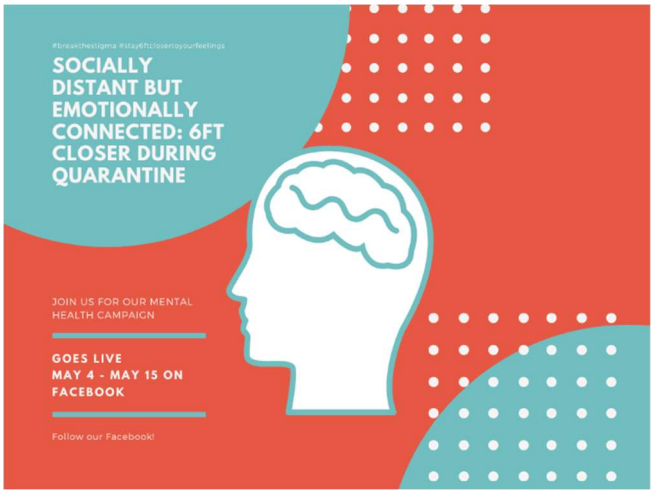
The Asian Pacific American Medical Student Association (APAMSA) is a national student organization that advocates for the health of the Asian American Pacific Islanders. One of APAMSA's long-standing traditions has been the mental health initiative, where local chapters are encouraged to take action to promote mental health and wellness for their members and communities.[1]

In May 2020, our APAMSA chapter at Oakland University William Beaumont (OUWB) School of Medicine hosted a mental health campaign titled, "Socially Distant but Emotionally Connected: 6ft Closer During Quarantine" (***Figure 1***). Given the coronavirus pandemic and social isolation, we selected our existing APAMSA Facebook page as the platform to host our campaign. The campaign lasted two weeks and featured both written responses and video responses from medical students and faculty who wanted to share how they were coping with the pandemic. The goal was to create a space for everyone at OUWB to engage in meaningful conversations about mental health and support each other during this difficult time.

From the mental health campaign, we soon discovered medical students and faculty members had a wide variety of thoughts and tips to share with their fellow peers. One student said, "nothing can quite replace the connection that is felt by the proximity of another person" when remarking on the — at the time — novel quarantine rules. Medical students had gotten accustomed to being around each other at school that we were flustered when isolation initially began. It was especially daunting for some students who were far away from their friends and family. However, the student also suggested that this was a perfect opportunity to reconnect with people one may have not heard from for a long time, saying, "I have enjoyed reviving old conversations and initiating new ones" and "it makes for great storytelling when months and years worth of accrued experiences are showcased in a spontaneous call."

One of the faculty members provided a visceral account of his experience during the pandemic saying, "I would describe myself as often agitated, worried, depressed…numerous adjectives melded into a single troubled state." He shared familial and work circumstances that had made the pandemic quite troubling for him. This was a tangible and genuine way to understand just how widespread the effects of the pandemic were even as an esteemed faculty member struggled in the same ways us students did. Nevertheless, he had warm words to support the students by saying, "While I have always said 'my door is always open to you,' that means little nowadays. Perhaps it's better to say 'I'm only an email or a phone call away.' I have always been and will always be, here for you."

Figure 1. OUWB APAMSA's Mental Health Initiative Campaign Poster in May, 2020.



Legend: Poster made by Jennifer L. Nguyen.

Figure 2. Photo Submissions from OUWB Students During the Daily Wellness Challenge.

Legend: One of the daily wellness challenges was to try a new recipe.

[1] BS, Oakland University William Beaumont (OUWB) School of Medicine, United States.

About the Author: *Han G. Ngo, Brianna L. Gibney, Paul Patel, and Jennifer L. Nguyen are second-year medical students at Oakland University William Beaumont School of Medicine, Rochester Hills, Michigan, USA of a 4-year M.D. program. We are part of the Asian Pacific American Medical Student Association (APAMSA).*

Correspondence:
Han G. Ngo
Address: 586 Pioneer Dr, Rochester, MI 48309, United States
Email: hngo@oakland.edu

Editor: Francisco J. Bonilla-Escobar
Student Editors: Lakshmimathy Subramanian, Nikoleta Tellios
Copyeditor: Nicole Katherine Conners
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Numerous other medical students and faculty members shared their feelings about xenophobia, loneliness, and lack of motivation during the pandemic. However, they also added helpful tips on how to adapt to a new normal. Though the pandemic came with its share of difficulties and problems, we were reminded again how close our community is as a family and that we will always be there to support each other during these difficult times.

Over the course of our two-week campaign, each post was able to reach an average of 220 followers and had an average of 84 engagements according to Facebook analytics. Although our campaign could have reached out to more people through broadening our social media platforms to Instagram and Twitter, we considered it a success in the following ways. Firstly, by including the voices of faculty and students, our campaign was the first of its kind at our medical school to bring members of the community together to discuss mental health. This was evident when several medical students voluntarily reached out and asked to share their stories on our platform. Secondly, we included a daily mental health challenge component as a way to motivate students and faculty to engage with each other in a way that otherwise would not have been possible during social isolation. For example, some of the challenges included trying a new recipe and reconnecting with a faculty member (***Figure 2***). Many students sent in photos from our daily challenges and we featured them on our Facebook page. Through our initiative, the emotional support within our OUWB community was able to penetrate the barriers of social distancing.

Overall, the meaningful connection created by our campaign made it a worthwhile endeavor. Social networking sites such as Facebook make information more accessible, help reduce stigma about certain health conditions, and provide social support for the general public.[2] In addition to the aforementioned benefits, an online health campaign can be held at no extra financial cost to the organization. We urge that other medical schools implement their own mental health awareness campaigns to destigmatize the topic in their communities. The following steps can be used to start the process:

1. Identify an interest group that advocates for mental health to start planning the campaign. Collaborate with other interest groups by asking them to promote posts on social media.
2. Narrow down the focus of the campaign by deciding who will be the participants and the subject matter. Will it be limited to medical students? Will it be topics related to preclinical education or clinical rotations?
3. Make a list of questions that you would like the participants to address.
4. Collect responses and decide which social media platform(s) to post on. Lastly, share with your community (***Figure 3***).

Mental health is a pertinent topic that is often overlooked in the medical school community. The theme of our campaign was #stay6ftclosertoyourfeelings during the pandemic, but we hope that regardless of the times, a long-lasting tradition of mental health promotion for medical students will be established.

Figure 3. Social Media Campaign Template for Each Participant's Post.

Legend: Sample template for a virtual campaign including the participant's name, photo, quote, and campaign's hashtag.

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Experience

COVID-19: Turning a Pandemic into a Learning Opportunity for Senior Medical Students

John C Garman.[1]

The Experience

The COVID-19 pandemic has been unexpected and tragic; nevertheless, it has also given some medical students the opportunity to step-up, use what they have learned throughout their training, and assume an important role in providing care for patients and assistance to their healthcare institution.[1-3] In the United States, during the first three years of medical school students are trained to assist in patient care, work in various clinics and learn from providers. By the time medical students are in their 4th year, they have developed a fair base of knowledge and clinical skills. Normally, the 4th year of medical school is the year when students narrow down their clinical experiences to reflect their interests, and prepare for the application cycle for residency programs. The COVID-19 pandemic has made this time difficult, forcing many senior students from the frontlines to the sidelines. Policy changes have forbidden students from attending some rotations in person and scrubbing in during operational procedures. The impact COVID-19 has had on medical curricula varies between institutions, with many being hindered significantly by the event. Some institutions, however, are using novel approaches to patient care, allowing senior students to help. In this way, these academic medical institutions are making the pandemic a time of valuable experience and learning for their students.

During this pandemic, our academic institution worked with senior medical students to implement a novel curriculum to allow them to serve our community. At my academic institution, COVID-19 has provided senior medical students the opportunity to be an asset for their affiliated healthcare system, and to earn school credit while doing so. Senior students are using telecommunication to connect with patients and assist them with their medical questions and needs. They are acting as Transitional Care Providers (TCP) and Patient Navigation Assistants (PNA), allowing them to use their knowledge and skills to help both the patients and the stressed healthcare system. As TCPs, students are making weekly contact with patients recently discharged from the hospital with COVID-unrelated ailments, to assure they have not become infected or in the case they have questions or concerns about their recent hospital admission or current recovery. Such transitional care interventions have been shown to reduce hospital readmissions and mortality.[4] PNAs are serving a similar role, helping patients navigate the convoluted health care system during this complicated time, a role that has been shown effective in improving patient satisfaction and outcomes.[5-7] In these roles, students are further learning to work with medical teams and local community resources to meet the needs of patients - many times acting as the patient's primary point-of-contact within the medical center. These roles are providing students a level of responsibility that fosters professional development in a unique time.

At our institution, other students are acting as "COVID-19 case-trackers," investigating and attempting to mitigate the spread of infections. Case tracking of infection transmission chains is a standard aspect of public health response to infectious outbreaks. Case tracking assists in breaking these transmission chains, hopefully disrupting viral spread and reducing the scale of outbreaks.[8] In taking this role, medical students are becoming better versed in the pathophysiological aspects of COVID-19 and remaining up-to-date on current guidelines, all while gaining a unique experience in pandemic response. No matter their designated role, senior students are working together with other healthcare staff to address issues during this unforeseen crisis, and they are seen as members of the team when discussing novel approaches to novel problems. As we students continue to provide our services to our institution, our institution recognizes and appreciates the motivated and trained asset they can call on for assistance. Likewise, we as students appreciate their respect and consideration in facing this pandemic.

Personally, I volunteered and worked as a TCP. As a TCP, I was in weekly contact with patients and their primary care providers, assisting them in their transition home from the hospital, and with any additional needs I could appropriately address. Without exception, I was asked by each patient about COVID-19 and their risk of infection. Due to their questions, I was motivated to better understand the pathophysiology of the virus and the clinical symptoms of those infected. Moreover, I remained current on the recommendations put out by the Center for Disease Control and Prevention. In so doing, I was able to help patients with their immediate health needs and address their concerns related to COVID-19. While these experiences were not what we expected going into our 4th year of medical school, I believe that they have given us something unique. They showed us the adaptability of medicine in a time of uncertainty, and they provided us an opportunity to work within our medical institution in a time of need. Despite missing normal 4th year rotations during this time, I feel no less prepared for my residency training on the horizon. In no way do I see this experience as a hinderance to my education and training; quite the opposite, I feel that it was uniquely valuable, allowing us to be actively involved in addressing the COVID-19 pandemic instead of watching from the sidelines.

This pandemic has been an unprecedented time, and along with its devastating impact on the health of many Americans, it has also caused major alterations in the training of future physicians. While many medical schools put a full halt in clinical experiences due to COVID-19, some schools like my institution did not, by creating and fostering student initiatives. This pandemic has led our medical center to recognize senior students as trained and motivated resources, utilizable during times of need. For some senior medical students, the COVID-19 pandemic, with all of its hardships, has become an invaluable

[1] BS, Penn State College of Medicine, Hershey, Pennslyvania, United States.

About the Author: *John Garman is currently a 4th year medical student of Penn State College of Medicine, in Hershey, Pennsylvania. He is a contributing member of the Hershey Medical Center Medical Ethics Committee.*

Correspondence:

John C. Garman

Address: 700 HMC Cres Rd, Hershey, PA 17033, United States

Email: jgarman2@pennstatehealth.psu.edu

Editor: Francisco J. Bonilla-Escobar
Student Editors: Najdat Bazarbashi, Ciara Egan
Proofreader: Adnan Mujanovic
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learning opportunity and chance to serve our community – it is an experience we will carry with us throughout our future careers.

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Experience

Eyes Wide Open – To Cornea, to Medical School, to Life

Aviad Sapir.[1]

The Experience

I was having a great time with Darya, my two-year-old baby girl, when my cellphone rang. It was Sarah, the hospital's transplant coordinator. "Hurry Up! we got family consent." The meaning of these six words for me was to kiss my daughter and proceed as soon as possible to the pathology department for corneal harvesting.

In parallel to medical studies, since my fourth year, I have been working as a corneal harvester for transplantation. Unlike general organ donation which requires brain death, corneal donation, due to its avascular properties, is more common.[1] In Israel, the law states that one cannot harvest an organ unless the relatives of the deceased have agreed to donate.[2] Many times, this may not be easy to achieve. In Israel some of the Jewish religious population who believe in resurrection, fear that if any organs are taken even from the deceased, the soul will be resurrected without the requisite organ. In like fashion, a tribal Muslim society is concerned about harming the dignity of the deceased if organs are taken from her or him after death.[3]

The procedure is performed by a resident or medical student, after ruling out clinical contraindications such as sepsis or the human immunodeficiency virus (HIV) and the hepatitis B virus (HBV) carriers and after contacting the family for consent.[2] Naturally, this position as corneal harvester has exposed me to countless medical experiences and both ethical and personal dilemmas. Today, as I stand before my final examinations and towards the end of this role, I chose to recall some particular events.

The first time I completed a solo harvest I was both excited and nervous, memorizing the order of actions required for the task. I organized all the necessary equipment and went quickly to the morgue. In paraphrasing Forrest Gump's words, "life is like a body bag, you never know what you're going to get." The first time it was a 72-year-old lady, who passed away as a result of severe heart failure. I immediately recognized her. A day earlier, I had presented her to my tutor in the Internal Medicine Department as part of my clinical clerkships. She was somewhat calm, despite her complicated situation, surrounded by her loved ones. Just a few hours after sitting in front of her obtaining the history with a notebook and pen, I stood over her with a blepharostat, scalpel and surgical tweezers. That time, I learned how the transition between life and death is a conjecture. How inventory invites role-playing games without any preparation.

A few months later, when I was a little more experienced, during a family holiday dinner, I was urgently called again to the hospital. This time it was a seventeen-year-old young man who had committed suicide by gun shot. When the damaged, pale face appeared in front of me, I wanted to cry. Cry for the loss of such a short life, for unfulfilled dreams, for unfulfilled loves. I'll never know what caused that young boy to hurt himself that way, what he thought in the seconds before he pulled the trigger. But from this difficult situation, I learned another of life's lessons, the way an unnecessary event can have meaning. The fact that the corneal recipient may see his grandchildren again, read the book he loves or look at a sunset thanks to these corneas, filled me with comfort and satisfaction.

The last story concerns a unique population living around the Soroka University Medical Center where I study and work is in Be'er Sheva, southern Israel. It is the only tertiary hospital in the region and serves more than a million citizens. This catchment area, the Negev, has a large Bedouin population. Due to various religious, historical and social reasons, the issue of organ donation has not been in the public awareness for many years.[4] In this case, I was already an experienced harvester after several dozen operations. A 5-year-old boy, the son of one of the community's dignitaries, was injured in a car accident. He suffered from multi systemic failure and was defined as being in a state of brain death. Surprisingly, it was none other than the father who requested to donate his son's organs, "I want other people's lives to be saved" he said sadly and confidently. As a father, my heart went out to him. Honestly, I didn't even think about trying to talk to the family about requesting a donation. Unfortunately, prejudice and social stigma are a global human disease, crossing countries and cultures. In one clear sentence by a bereaved father, I learned perhaps the most important lesson --We are all human, no matter what the color of our skin, what our beliefs are or what language we speak--.

I think of all these I have told about and of dozens more if not hundreds I've met over the years and want to thank them. First, on behalf of those who got the corneas and were able to see again. And secondly in my name – you, the dead donors, have made me a better father, a better future doctor and hopefully a better person.

[1] BSc, Joyce & Irving Goldman Medical School, Faculty of Health Science, Ben-Gurion University of the Negev, Beer-Sheva, Israel.

About the Author: *Aviad Sapir is currently a sixth-year medical student of (Joyce & Irving Goldman medical school, Beer-Sheva, Israel) of a six-year program.*

Correspondence:
Aviad Sapir
Address: Soroka University Medical Center, Beer-Sheva 84101, Israel
Email: aviadsap@gmail.com

Editor: Ryan T. Sless
Student Editors: Lakshmimathy Subramanian, Shawn Albers
Copyeditor: Shawn Albers
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Letter to the Editor

Recurrence of COVID-19: Treading the Fine Line Between Relapse and Re-infection

Ritwick Mondal,[1] Shramana Deb,[2] Durjoy Lahiri,[3] Gourav Shome.[4]

The etiological agent for the ongoing pandemic of COVID-19 is a novel coronavirus, known as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The most common symptoms of COVID-19 include fever, dry cough, sore throat, and headache.[1] Severe disease can progress to the highly morbid outcome of Acute Respiratory Distress Syndrome (ARDS).[2] The number of infected individuals during this pandemic is high while the worldwide mortality rate remain slow.[3] According to World Health Organization (WHO) guidelines, the infected patient should be discharged from hospital after containment period of 14 days along with two consecutive negative Quantitative Reverse Transcription Polymerase Chain Reaction (RT-qPCR) results of respiratory specimens at least 24 hours apart.[4] During January 28 to March 13, COVID-19 relapse cases have been documented in Shangqui, Henan province and later in Korea.[5,6] Pathogenesis of these relapse cases needs further exploration as they hold important links towards the development of a second wave of the pandemic. Here in this article, we propose the following hypotheses on how COVID-19 relapse can play a significant role in disease burden and further horizontal transmission based on available evidence.

Relapse vs. Reinfection: Immunological Perspective

The second wave of infection among COVID-19 patients has dazed the scientific world, but it has to be decided whether the second wave of infection is due to reinfection or relapse. According to recent documentation from China[5] and Korea,[6]there have been recovered patients testing positive after one or two consecutive negative results. Various methods for the diagnosis of the infection are used. These include RT-qPCR, high-throughput sequencing, CT scan, and immunological detection kits.[7] Furthermore, improper sampling procedure, different source of swab samples, and variable specificity/sensitivity of nucleic acid tests can lead to the false negative RT-qPCR results implying the persistence of infection rather than recurrence or relapse.[7,8] This particular limitation of antibody testing method should be carefully considered before declaration of reinfection or relapse. The durability of the infected patient's immune response plays a significant role to determine the reinfection. The presence of CD4+ T cells and memory CD8+ T cells are found to be protective in case of Coronavirus mediated infection by producing effector cytokines and IFN-gamma.[9]It is also noted that immunoglobulins alone are not sufficient to provide long-term immunity.[10] Accumulating evidence have shown that virus specific CD8+ T cells were persistent up to 6 years after Severe Acute Respiratory Syndrome Coronavirus 1 (SARS-CoV-1) infection, but memory B cells and accompanying antibodies were undetectable at that time.[11] A similar scenario may result from SARS-CoV-2 infection as it shows phylogenetic similarity with SARS-CoV-1.[12] A recent study performed by Zhang and colleagues investigated monocyte expression of Angiotensin Converting Enzyme 2 (ACE2), the endogenous entry receptor of SARS-CoV-2. They came to the conclusion that monocytes of COVID-19 patients express a lower concentration of ACE2 in comparison to healthy individuals.[13] Therefore, it can be interpreted that SARS-CoV-2 might exist in human Peripheral Blood Mononuclear Cells (PBMCs) (monocytes mainly) and cause relapse after negative PCR on samples from the respiratory tract.[14] Considering the aforementioned facts, further research work is required for fine delineation between relapse and reinfection.

Probable Association of Phylogenetic Perspective with Relapse

Distinct viral clades of SARS-CoV-2 (e.g., A2a, B1) appears to result in variation of virulence.[15]Considering this fact, there is a possibility that duration between primary infection and relapse may vary across different clades. Furthermore, there is a possibility that the nature and affinity of protective neutralizing antibodies (NAbs) may vary for different strains as well. Hence, it can be hypothesized that NAbs of primary infection may be unable to protect re-infection by other strains. It also remains to be seen whether, in the case of relapse, there is an insufficient increase in NAbs during the second course of infection.

Viral Reactivation in SARS-CoV-2 Relapse

Viral latency period might be considered as a potential factor in order to determine relapse or reactivation. Reports have suggested disparity amongst proposed viral latency period with a maximum duration of 24 days.[16] According to an article by Ye *et al*, the reported reactivation among 5 patients was a maximum time period of 17 days, but proper clinical characteristics to distinguish reactivation with relapse was not properly demarcated.[17] It might be suggested that the virus causes latent infection of cells, while later on the genome gets transcribed and translated into viral proteins. Hence, it could be inferred that the virus gets reactivated from a latent stage to a lytic stage where manifestation of symptoms might be observed as similar phenomenon were already observed for many other viruses.[18] Additionally, SARS-CoV-2 can survive and replicate in neuronal cell lines.[19] Therefore, another indication towards viral latency through neuro-invasion of virus and reactivation at a later stage is suggested. Considering the abovementioned fact, an important question can be raised: Can an asymptomatic individual with a latent infection spread the virus without being detected? Proper clinical investigation into the potential reactivation of this virus requires immediate further study.

[1] MBBS. Department of Internal Medicine, Institute of Postgraduate Medical Education and Research, SSKM Hospital, Kolkata, India.
[2] MSc, S.N. Pradhan Centre for Neurosciences, University of Calcutta, India.
[3] MD, DM. Bangur Institute of Neurosciences, Institute of Postgraduate Medical Education and Research, SSKM Hospital, Kolkata, India.
[4] MSc. Department of Microbiology, College of Science, Technology & Agriculture. University of Calcutta, India.

About the Author: *Dr. Ritwick Mondal is a first class MBBS graduate from Institute of Postgraduate and Medical Education and SSKM Hospital, Kolkata, India. He is currently engaged as a Junior Resident Department of Internal Medicine at the above institution. He has received various notable awards like ICMR-STS, international ambassador for the UMCG, Groningen etc. He is currently exposed to laboratory research at Bangur institute of Neurosciences.*

Correspondence:
Gourav Shome
Address: 35 Ballygunge Circular Road. Kolkata – 700019, India
Email: gshome007@gmail.com

Editor: Francisco J. Bonilla-Escobar
Reviewers: Mihnea-Alexandru Gaman, Paul MacDaragh Ryan
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Consideration of Viral Shedding to Determine Relapse or Reinfection

Another undermined and potentially influential factor might be the viral shedding which may cause transmission from an apparently recovered individual or asymptomatic individual to a healthy individual.[20] The viral shedding may begin 2-3 days before the appearance of symptoms with viral loads decreasing monotonically after onset of symptoms.[21] The virus has been detected in patients at a median of 20 days and up to 37 days post-infection.[22] The viral transmission not only comes through droplet or aerosol route but also through the fecal-oral route.[23,24] The participation of tears and conjunctival secretions in viral shedding has also been speculated.[25] All of these non-classical or non-respiratory tract routes of virus shedding might go unrecognized during discharge of patients who are tested negative through nasopharynageal swab RT-qPCR alone. It is possible that viral titers are still relatively high in various non-classical transmission sites of recovered patients, indicating that they are not only able to spread the infection but also may relapse themselves.

Conclusion

In conclusion, the ongoing public health emergency should look after protocols regarding both molecular testing and antibody testing to contain the pandemic. The infected individuals should strictly be discharged only after two proper consecutive RT-PCR negative results of swab samples from various sources so that it can reduce clinically recovered individuals with apparently hidden viral source. Even after that, the convalescent patients should be monitored by the health system during the post-discharge domiciliary quarantine period of 14 days, and on completion of this period they should be tested again. This should thereby avoid increment in numbers of asymptomatic individuals with reactivation or relapse. Moreover, antibody testing should not be authorized at the time of discharge as its variation of sensitivity/specificity has potential to provide unfounded confidence. That said, there remain a few unanswered questions at this point in time - Does the virus really clear out from the system after the primary infection?; Is it safe to assume that the fragments of virus residing inside the body cannot infect someone after the first course of infection ?;Have patients acquired immunity against the diseases for rest of their life?

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Author Contributions

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Letter to the Editor

Letter to the Editor Regarding "Survey among Medical Students during COVID-19 Lockdown: The Online Class Dilemma"

Akshara Mavunkal Thampan,[1] Davis Thomas Pulimoottil,[2] Angel Cham Philip.[3]

It was a pleasure for us to read the article titled "Survey among medical students during COVID-19 lockdown-The Online Class Dilemma" by Thomas et al. in your esteemed journal.[1] It is a succinctly written article and we would like to commend the authors on their excellent effort. It is significant in the present scenario and we would like to mention a few points that we feel would further enrich the article.

The major disruption brought on students and teachers in tertiary education by the pandemic in low- and middle-income countries was primarily by the sudden shift from the traditional classroom learning to e-learning without any extensive planning and faculty training.[2] In a low middle income country like India, a vast majority of students are underprivileged to access the e-learning facilities, as it will cost them extra in the form of data, gadgets and other paid e-learning platforms and therefore, the equitable distribution of knowledge to all is affected. To overcome this prejudice, special schemes for students which provide a certain amount of free daily data to attend online classes and technical training on online education may be considered by the government. It was also reported that teachers, especially female faculty, were facing difficulties in finding a work-life balance as a result of the abrupt onset and extent of impact that the pandemic has brought on our lives. Having a frank open discussion with all stakeholders would greatly assist in designing a more practical and organized work schedule with flexible hours and appropriate breaks, which would be beneficial to all.

Medical students, in general, will also be concerned about acquiring practical clinical skills which cannot be provided through e-learning. The drastic reduction in their patient contact time, time spent in wards learning clinical skills and bedside teaching may have a negative impact on the confidence of medical students in regard to their future career skills. They are also worried about the indefinite extension of their courses, as universities have failed to provide any meaningful clarity in their official statements. Immediate measures, such as the use of standardized patients, conducting mock clinics, timely conduct of exams and phased reopening of medical schools, need to be instituted effectively to address the fears of these groups so that the efforts of online education may bear fruit.[3]

Medical students are a natural reservoir of volunteers and they offer a vast wealth of potential which can be put to use in these times of crisis.[4] However, to harness this potential, the medical students should be prepared adequately to face the crisis. Inclusion of "pandemic/crisis specific" content in the medical curriculum and restructuring it accordingly may prove to be helpful in tackling these situations in future.[5] These proactive measures will also help the students to complete their transition from a 'student' to a 'doctor' less challenging.

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5. O'Byrne L, Gavin B, McNicholas F. Medical students and COVID-19: the need for pandemic preparedness. J Med Ethics 2020 Sep;46(9):623-6.

[1] Medical student, Al Azhar Medical College and Super Speciality Hospital, India.
[2] MS, ENT. Al Azhar Medical College and Super Speciality Hospital, India.
[3] MD, Pediatrics. Al Azhar Medical College and Super Speciality Hospital, India.

About the Author: *Akshara Mavunkal Thampan is currently a third-year medical student of Al Azhar Medical College and Super Speciality Hospital, Ezhalloor, Thodupuzha, Idukki district, Kerala, India, of a total 5.5-year program.*

Correspondence:
Angel Cham Philip
Address: Thodupuzha - Ezhalloor Rd, Kumaramangalam, Kerala 685605, India
Email: angel.ffe@gmail.com

Editor: Francisco J. Bonilla-Escobar
Student Editors: Colleen Campbell, Vinson Chan
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Letter to the Editor

Response to the Letter to the Editor Regarding "Survey among Medical Students during COVID-19 Lockdown: The Online Class Dilemma"

Andrew Thomas,[1] Mohan T. Shenoy,[2] Kottacherry T Shenoy.[3]

Dear Editor:

We would like to thank Akshara et al, for their interest in our survey regarding online classes among medical students and for taking time to commend our work. We agree with the authors on unpreparedness. A well-designed course and availability of online training materials are some of the important pre-requisites for conducting an effective online class.[1] No one anticipated this pandemic; therefore, teachers were not prepared for any alternative teaching modalities.

The authors have also pointed out a lack of sufficient internet data for participation in online classes and recommended the provision of free data to students. While providing free data definitely would help, there are other things to be considered. Most private medical institutions are now struggling to keep up with the economic consequences of the pandemic and so, providing free data is simply not possible in many institutions. Also, the majority of students in our survey used only mobile phones which are not optimal for participating in online classes. The internet coverage rate is 50% in India.[2] Thus, accessibility to internet itself is lacking among students, especially those in remote places.[2] So, providing free data to all students is likely not going to cause any significant difference in the outcome.

Even before the coronavirus disease 2019 (COVID-19) pandemic, doctors were over-worked. They work in high stress environments and are expected to be available 24-7.[3] On the other hand, these same doctors are also teachers in clinical subjects who teach medical students on top of their clinical work. The authors have rightly highlighted that females are facing more difficulty. They are even more so overworked and underpaid.

The author highlights about students' concern on acquiring practical skills. While they are right in saying this can have a negative impact on the confidence of medical students, clinical skills can be taught through online learning.[4-8] This might not be as effective as regular hospital postings, as Sir William Osler once said "he who studies medicine without books sails an uncharted sea, but he who studies medicine without patients does not go to sea at all".[9] However, when a pandemic is in progress it would be unwise for an institution to advise their medical students to approach patients and learn basic clinical skills.

Students can learn methods of examining different organ systems using video demonstration.[8,10] They can practice these skills on fellow colleagues. During 8 years of war in a Syrian US based online platform, Osmosis helped medical students with videos, clinical cases diagnosis and flash cards.[4] The COVID-19 pandemic has given us an opportunity to explore newer modalities in education.[5] We should never hesitate to incorporate better modalities into our curriculum.

We do not concur with the author´s statement that "*universities have failed to provide any meaningful clarity in their communiqués*". Government and universities are providing regular updates and guidelines on the implementation of examinations and classes, both during and after the pandemic. We believe universities and the government are working on ways to avoid unnecessary extension of the courses. Lastly, the author talks about inclusion of "pandemic/crisis specific" content in the medical curriculum. While these contents are already taught throughout the undergraduate education,[11] we believe more emphasis should be put on public health and research, in order to make future doctors more capable in times such as during the COVID-19 pandemic.

[1] Medical student, Sree Gokulam Medical College and Research Foundation, Trivandrum, India.
[2] MBBS; MD; DM (Endocrinology), Sree Gokulam Medical College and Research Foundation, Trivandrum, India.
[3] MBBS; MD; DM (Gastroenterology), Sree Gokulam Medical College and Research Foundation, Trivandrum, India.

About the Author: *Andrew Thomas is currently a final year medical student of Sree Gokulam Medical College and Research Foundation, Trivandrum, India. He is also a recipient of Short-Term Studentship 2019 by ICMR (Indian Council of Medical Research), Best paper award at NATCON 2019, Government medical college, Trivandrum.*

Correspondence:
Andrew Thomas
Address: Aalamthara - Bhoothamadakki Rd, Venjarammoodu, Kerala 695607, India
Email: drandrewthomasj@gmail.com

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1. Sun, Anna, Chen, Xiufang. Online Education and Its Effective Practice: A Research Review. Journal of Information Technology Education: Research. 2016;15:157-90.
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Letter to the Editor

Benefits and Drawbacks of Online Open-Book Examinations for Medical Students in the COVID-19 Pandemic

Shuja Yaqub,[1] Hannah Suh,[1] Hozafa Ali.[1]

The COVID-19 pandemic has disrupted the flow of events, particularly concerning examinations for medical students. One of the adaptations to the disruption caused by the pandemic has been the adoption of online open book examinations (OBEs).[1] As third-year medical students at King's College London, we have encountered similar circumstances with our examinations and hope to highlight the benefits and drawbacks of this format.

It is important to recognize the potential benefits of online open book examinations. For instance, some studies imply that student self-confidence and efficacy improves with this style of examination.[2] Given the current predicament we are in, medical students are under considerable pressure and are still expected to both provide and attain the necessary skill sets that are required for the respective stage. Thus, online OBEs would reduce the psychological burden on students and better prepare them for the challenges associated with the pandemic.

The pandemic has led to deficiencies in the core knowledge base of students. This has manifested in the form of cancellations of OSCEs and electives, which correlated with a national survey published in BMC Medical Education where 59.3% of final year medical students felt less prepared for Foundation Year 1.[3] As a consequence of this fast-tracked graduation, students are being pushed early into positions of responsibility, despite the notable lack of training they have received this year. During this unprecedented crisis, it is imperative that we aim to provide a formal assessment of the curriculum. Online OBE is an appropriate format given the circumstances and acts as a satisfactory conduit for medical schools to meet educational standards set by the General Medical Council (GMC).

On the other hand, cheating is an evident drawback of online OBE.[1] This not only defeats the purpose of the exam to test the competency of students but can add further stress to individuals who are competing against each other. Normally, in-person exams are good deterrents against cheating. However, online based examinations are difficult to monitor, therefore cheating can go unchecked. From the perspective of medical ethics, cheating can be viewed as contradictory to the mantra of honesty and integrity. Despite this, we understand that ethics may not deter cheating online where invigilators are not privy to students' actions. Possible solutions to this issue could include a more robust system for online testing such as student authentication, tracking user inputs, or an indication of the consequences to cheating.

While *Jervis et al.* did not explicitly state their style of examination, another aspect to consider is the style of exam questions utilized in medical school. The multiple-choice question (MCQ) format has been widely adopted by medical schools, and in some cases also applied in an online setting. For instance, the United States Medical Licensing Examination (USMLE) and the Medical Colleges Admissions Test (MCAT) both utilize a type of multiple-choice format known as single best answer questions (SBAQs). However, a study published in the BMJ has suggested that SBAQs can actually give a false impression of students' competency as compared to very short answer questions.[4] An important question to raise is whether these SBAQs truly prepare students for their role in a clinical setting where multiple options are not always available to them.[5] For this reason, it is worth investigating further whether SBAQs are the best method of examining medical students, especially in an online open book environment.

An alternative format to MCQs are short answer questions (SAQs). When correctly used, this style of questioning has proven to be popular amongst students and has been a beneficial assessment tool. It eliminates the cueing effect, therefore encouraging students to gain a deeper understanding of their learning material, as well as requiring the use of key skills such as critical thinking.[5,6] Both students and examiners are able to grasp areas of weaknesses better with this method and can also provide a useful opportunity for giving and receiving feedback.[5] However, though this format may initially seem ideal, like the MCQ structure, it too does not come without its own issues. Limitations such as the complicated production of questions and marking schemes, subjective marking and restriction of materials being tested via this method, have been highlighted.[5,7] Regardless of whichever format is used in an examination, implementing robust guidelines related to the construction of questions that effectively assess one's ability can further engage higher cognitive skills among medical students, thereby improving competency.[8]

As with the style of question, it is important to assess the format of examination. The efficacy of open book examinations in comparison to closed book examinations (CBEs) has been investigated. Studies indicate that open book exams require higher cognition.[9] Furthermore, open book examinations provide better reinforcement and recall for students, thus bolstering their learning schemas and memory recall.[10] OBEs have also displayed potential as formative assessments, acting as sufficient predictors of exam performance in summative exams.[9] In spite of these benefits, OBEs can potentially mask weaknesses in memory retrieval for students when feedback is concerned [10]; it is suggested that using OBEs in conjunction with CBEs can improve memory recall and knowledge retention in students.[9]

In summary, one can acknowledge that there are multiple factors to consider in relation to online OBEs for medical students. We recognize that there are caveats to providing an online open book exam but realize that providing an examination as opposed to fast tracking

[1] MBBS, King's College London, GKT School of Medical Education, London, United Kingdom.

About the Author: *Shuja Yaqub is currently a 4th year medical student of King's College London, London, United Kingdom of a 6-year program. Hannah Suh is currently a 4th-year medical student of King's College London, London, United Kingdom of a 6-year program. Hozafa Ali is currently a 4th year medical student of King's College London, London, United Kingdom of a 6-year program.*

Correspondence:
Hannah Suh
Address: King's College London, Strand, London, WC2R 2LS, United Kingdom
Email: hannahsuh97@gmail.com

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students may prove more beneficial in preparing them for frontline work in this crisis. We believe that investigation into the efficacy and practicalities of online OBEs will be needed for universities in the coming year.

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Letter to the Editor

Putting Our First Responders First: A Call for Health Insurance in Retirement for Palm Beach Gardens Fire Rescue

Joseph Varney,[1] Kimberly Murry,[2] Natalie Humphrey.[1]

Firefighter and paramedic services have high rates of occupational exposure to not only physically harmful substances and situations, but also potential psychologically traumatic situations. As imagined, medical and mental health conditions occur at a high rate among these professions. A large-scale study determined that the average prevalence of depression among firefighters is 18.7%, which suggests a degree of distress higher than the general population.[1] Emergency responders have also been reported to be among the highest risk for burnout and death by suicide,[2-4] further supporting the physical and mental exhaustion this group faces. Alarmingly, paramedics are suggested to be less empathetic towards the struggles they face themselves,[5] which could potentially explain the increased depression and suicide rates. Medically, firefighters and paramedics are at an increased risk for various forms of cancer, such as bladder, thyroid, pleura,[6] malignant melanoma,[6,7] brain, stomach, multiple myeloma, non-Hodgkin lymphoma,[8] colon, rectum, prostate, and testis.[6,8]

From 1950 to 2009, in the cities of San Francisco, Chicago, and Philadelphia the incidence of occurrence of cancer in career firefighters was reported to be nearly 30,000.[7] Of the cancer incidences noted, increased mortality has been reported in lung cancer, leukemia,[9] rectal cancer, and Non-Hodgkin's lymphoma.[5] Despite these statistics, it wasn't until 2019 when the CS/CS/SB 426 — Firefighters bill was passed. This bill grants firefighters who are diagnosed with certain cancers the eligibility to receive certain disability or death benefits. Before this bill, sick days had to be used for the treatment of the very cancers that were linked to their occupation.

The brave men and women who are ready and willing to save us every day, without a doubt require saving themselves. My (Joseph Varney) time getting to know the five red (fire) and blue (rescue) teams of the Palm Beach Gardens Fire Rescue (PBGFR) has truly opened my eyes to not only the meaning of family but also the huge healthcare disparities that this department faces once retired. Upon meeting the firefighter paramedics, I was not met with the standard handshake. Rather, I was embraced tightly and told “Welcome to the family”, which for someone with almost no family to speak of, these words meant more than they could ever know. Yet after serving to protect their community from inclement weather (i.e., hurricanes) to deadly pandemics (i.e., COVID-19), our firefighters and paramedics at PBGFR are left to retire without health insurance, forcing many to find second careers to ensure that the medical needs of themselves and their families are met. This led to the creation of organizations such as Firefighters to the Rescue to help offset the cost of fellow first responders and their medical bills. I ask you, with the increased risk of medical and mental health problems faced by first responders, how could we possibly abandon this group upon retirement?

The incredibly selfless moving stories of the PBGFR crew changed my understanding of what it meant to truly give back to the community. A soon-to-be retired firefighter paramedic at one of the stations expressed his fear of health insurance costs and the burden it would put on his family. In fact, he was so worried about it that he was planning to move to Sweden to ensure that he and his family would have the proper insurance. Upon hearing this I felt a sickness in my stomach. I had no idea that some firefighter paramedics did not receive health insurance pro-bono, for all they have done to protect us day in and day out. I was lucky enough to have been able to speak with one of the female firefighter paramedics at the station to better understand what the job entailed. Some of the quotes from a Lieutenant and a Firefighter at Palm Beach Gardens Fire Rescue were:

> "For over a decade now, on every third day I put on my uniform and report to shift after juggling who will be caring for my child for the ensuing entire 24-hour shift. My 'Game Face' is always washed, dried, and pressed without a crease, ready to hide all the stresses in my own life while I ensure that everyone else is okay. For those 24 hours, people rely on this collection of brothers and sisters to put them first through their emergencies, no matter the risk of self-harm. Sometimes it is as simple as being a hand to hold or giving a hug to let someone know that they are not alone. That 'It will all be okay because I'm here for you, to see this through.' No matter what the call type, I love my job, I really do. Despite being over 40 and living in a dorm setting every third day away from my family, I couldn’t imagine myself doing anything other than serving the good people of Palm Beach Gardens. My people"-
>
> *Lieutenant*

> "My gut said 'don't go in that house' but being the new guy, I kept my mouth shut, which to this day is my biggest regret to this day. It got really hot out of nowhere and visibility went to pitch black instantly. Once this happened the two guys I was with disappeared and I found myself upstairs in an open area with no idea where the stairs or my 'partners' were. After accepting my fate, the pain went away, and I felt numb. I thought of everything possible from as early as I could remember as a kid up until the minute I walked into that house. In hindsight, I'd have rather gotten fired from the department, than having burned over 50 percent of my body. On my bad days, I remember

[1] BS. American University of the Caribbean School of Medicine, Sint Maarten.
[2] BS. Barry University, Florida, United States.
[3] PhD. American University of the Caribbean School of Medicine, Sint Maarten.

About the Author: *Joseph Varney is a second-year medical student at The American University of the Caribbean School of Medicine (AUC), who holds a dual Bachelor’s Degree in Biology and Psychology. During his time at AUC, he received multiple awards including being selected for the Tarek Award, which is given out once a semester to the top tutor who goes above and beyond for their fellow student body, and an award for Teaching Excellence in a Pandemic for his dedication to the Harvey Lab, teaching murmurs and EKG to fellow students.*

Correspondence:
Joseph Varney
Address: 1 University Drive at, Jordan Dr, Cupecoy, Sint Maarten
Email: themedicalmuscle@gmail.com

Editor: Francisco J. Bonilla-Escobar
Student Editors: Lakshmimathy Subramanian, Madeleine J. Cox, Anup Chalise, & Bahadar Srichawla
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how bad it was to have been left in those flames and it reminds me of what it's all for. Doing my part to make sure that doesn't happen to anybody else. Not on my watch."-
Firefighter

A final heart-wrenching story was that of a young male firefighter who suffered tremendous burns at 22 years of age, only to return to the job six years later. This firefighter paramedic then went on to talk about falling in love with being a firefighter again through meeting the staff at PBGFR. "After the incident, I hated firefighters and considered them all the same. But once I met the staff here, I knew they were different. I knew they had my back. I knew the flames would engulf all of us or none of us at all." This story is only one of many that show the dangers of this job, yet someone must do it. So, let us reward those who do this job, as we do our military, with healthcare benefits upon retirement.

Legislative reforms like the Firefighters bill are a good start, but more needs to be done. Our veterans receive coverage for their service and so should our firefighters and paramedics. Tricare and VA healthcare services[10] could be utilized to provide coverage to the first responders to bridge the gap until they are Medicare eligible. Though not considered active duty, they are uniformed personnel that serve and protect our community. Furthermore, lowering the age of eligibility for Medicare benefits for firefighters and paramedics is another option to explore. The people of PBGFR deserve better and we can do better. As a future physician, I feel obligated to ensure that they receive better care in their retirement, even if that means seeing each one of them and their families free of healthcare charges once I am a licensed physician.

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Letter to the Editor

Carotid Intima-Media Thickness and Cardiovascular Risk Factors

Vitorino Modesto dos Santos,[1] Laura Campos Modesto.[2]

We read the review by Albers SS et al. emphasizing the relationship between carotid artery morphology and the evolution of atherosclerotic carotid artery disease (CAD).[1] The authors commented on the anatomic changes developing since birth and increasing with aging, which play a significant role in the development of atherosclerotic CAD. Mainly, due to the interactions with well-known risk factors of atherosclerotic plaques including hypertension, dyslipidemia, diabetes mellitus, and smoking; they also focused on intra-individual differences in the extension of carotid involvement.[1] Their findings are useful in daily practice by indicating anatomical and demographic factors related to the CAD pathogenesis, and showing that people may have unilateral carotid changes when both arteries underwent actions of the same systemic risk factors.[1] Increases in internal carotid kinking, carotid bulb diameter, internal and common carotid tortuosity, and bifurcation angle are more frequent with aging. Even in absence of disease, these alterations can contribute in disturbances of the intramural elastin, but the threshold at which the changes cause or protect from atherosclerotic CAD is not clear.[1]

In this setting, evaluations of carotid intima-media thickness (CIMT) in people with obesity, chronic kidney disease (CKD), and hyperparathyroidism seem be appropriate.[2-4] For example, the comparison of CIMT in two groups (G1 and G2) of hemodialysis people with levels of parathormone (PTH), 200 pg/ml (G1), mean age: 46 ± 5 years and above 500 pg/ml (G2), mean age: 48 ± 5 years. Patients were between the ages of 18 to 65 years and an ultrasonography study in the middle third of the right common carotids which showed no significant enhanced thickness and calcified plaques (G1: 42.86%, G2: 71.43%). CIMT was correlated with PTH levels. Worthy of note, the time on dialysis made no difference between CIMT of the groups.[2] CIMT was studied in three groups of patients aged between 30 and 60 years: G1 obese with CKD; G2 non-obese with CKD; and G3 obese without CKD.[3] All groups had measurements of CIMT higher than normal, mainly in patients of G3 (control group of study), showing that arterial changes are more related with obesity.[3]

There is a general accordance about the adoption of the earliest as possible procedures to reach and maintain a low cardiovascular risk during the entire life course. The role of vascular remodeling and risk factors for cardiovascular disorders since conception to 2 years of life also merit attention to allow for effective prevention.[4] Recent review with meta-analyses of 6,221 studies including 7,977 individuals assess for CIMT in ages from 0 to 18 years revealed risk factors in the first 1,000 days of life. Small size for gestational age was the most significant association with increased CIMT in childhood, which is related to disturbed blood flow and pressure and atherosclerosis. Although further research is needed to confirm the findings, preventive measures are justified, as eradicating gestational smoking and providing adequate maternal nutrition.[4]

Additional concern is on the relation of increased CIMT with stroke risk and vascular dementia development; with the growing population of older individuals, preventive procedures should initiate as early as possible.[5] Guidelines for control cardiovascular risks highlight the cost-effectiveness of primary and secondary prevention of stroke and high blood pressure, associated conditions with atherosclerosis that play a role in the evolution of vascular and Alzheimer's dementia. The weight control since the earliest infancy would reduce future cerebrovascular disorders and the development of dementia, increasing the quality of life of the elderly.[5]

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5. Santos VM, Sá DAR. [The growth of centenarians: when to start dementia prevention?] Gac Méd Caracas. 2009 Sept;117(3):250-1. Esp.

[1] MD, PhD, Adjunct-Professor of Internal Medicine, Armed Forces Hospital and Catholic University of Brasília-DF, Brazil.
[2] Medical student, University Center of Brasília-DF, Brazil.

About the Author: *Laura Campos Modesto is currently finishing the first-year as medical student in a six-year program of the Medical Course at the University Center of Brasília (Uniceub), Brasília-DF, Brazil.*

Correspondence:
Vitorino Modesto dos Santos
Address: 707/907- Campus Universitario, SEPN – Asa Norte, Brasilia, Brazil
Email: vitorinomodestos@gmail.com

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Thinley Dorji - Jigme Dorji Wangchuck National Referral Hospital, Thimphu, Bhutan.

Saran Tenzin Tamang - University of Peradeniya: Peradeniya, Central, LK, Srilanka.

Farrugia Bonnici Georgiana - BSc (Hons) Diagnostic Radiography, M.D. Department of Family Medicine, University of Malta, Msida, Malta.

Fátima Rodriguez Acosta - Instituto de Investigaciones en Ciencias de la Salud, San Lorenzo, Paraguay.

Gabriel Motoa - Internal Medicine Resident at University of Miami / Jackson Memorial Hospital

Hossam Elfeki - Mansoura Univ Hosp, Mansoura Fac Med, Dep Gen Surg, Colorectal Surg Unit, Egypt & Aarhus Univ Hosp, Dept Surg, Denmark.

Hugo Mendieta Zerón - Universidad Autónoma del Estado de México, Toluca, Mexico.

Ipseeta Ray - MGM Medical College, Kamothe, Navi Mumbai, India.

Janhavi Patel - Michael G. DeGroote School of Medicine, McMaster University, Hamilton, Canada.

Jimmy Tam Huy Pham - University of California, Los Angeles (UCLA), California.

Jonathan Yabes - University of Pittsburgh, Pittsburgh, Pennsylvania.

Kuenzang Wangdi - Orthopaedic and Spine Surgeon, Head, Department of Orthopaedic Surgery, Jigme Dorji Wangchuck National Referral Hospital, Thimphu, Bhutan.

Luis Gabriel Parra-Lara - Facultad de Ciencias de la Salud, Universidad Icesi, Cali, Colombia.

Lukas Käsmann - Department of Radiation Oncology, university clinic München, München, Germany.

Lukas Rasulic - School of Medicine, University of Belgrade, Belgrade, Serbia & Department of Peripheral Nerve Surgery, Functional Neurosurgery and Pain Management Surgery, Clinic for Neurosurgery, Clinical Center of Serbia, Belgrade, Serbia.

Mahjabin Mamun - Sir Salimullah Medical College, Dhaka, Bangladesh.

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Mariagiovanna Cantone - Consultant Neurologist - Department of Neurology, St'Elia Hospital, Caltanissetta, Italy.

Mina A. Botros - Meharry Medical College, Nashville, Tennessee.

Correspondence:

Executive Committee of the International Journal of Medical Students

Address: 1400 Locust Street, Suite 3103, Pittsburgh, PA 15219. USA. Tel.: 413-232-7884, Fax: 412-232-8966

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PavanKumar Tandra - University of Nebraska Medical Centre, Department of Internal Medicine, Division of Hematology and Oncology, Omaha, NE 68198, USA.

Piotr Rzymski - Department of Environmental Medicine, Poznan University of Medical Sciences, Poznań, Poland.

Prateek Kumar Dinkar - King George's Medical University, Lucknow.

Rameeza Bee Z Hussain - Sapthagiri institute of medical sciences and research centre, Bengaluru, India.

Saeed Alshahrani - College of Medicine, King Saud bin Abdulaziz University for Health Sciences, King Abdullah International Medical Research Center, National Guard Health Affairs, Saudi Arabia.

Saran Tenzin Tamang - University of Peradeniya: Peradeniya, Central, LK, Srilanka.

Thiago Henrique Roza - Federal University of Rio Grande do Sul, Porto Alegre, Brazil.

Thinley Dorji - Jigme Dorji Wangchuck National Referral Hospital, Thimphu, Bhutan.

Varahabhatla Vamsi

Vardhmaan Jain - Cleveland Clinic, USA.

Vitor Laerte Pinto Junior - Fundação Oswaldo Cruz: Brasília, DF, BR

Wael Abuzeid - Queen's University Kingston, Ontario, Canada.

Yimeng Zhang Zhang

Yosuke Kakisaka - Tohoku Univeristy, Sendai, Japan.

Zaheen Iqbal - College of Applied Medical Sciences, Department of Rehabilitation Sciences, Rehabilitation Research Chair, King Saud University, Riyadh, Saudi Arabia.

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