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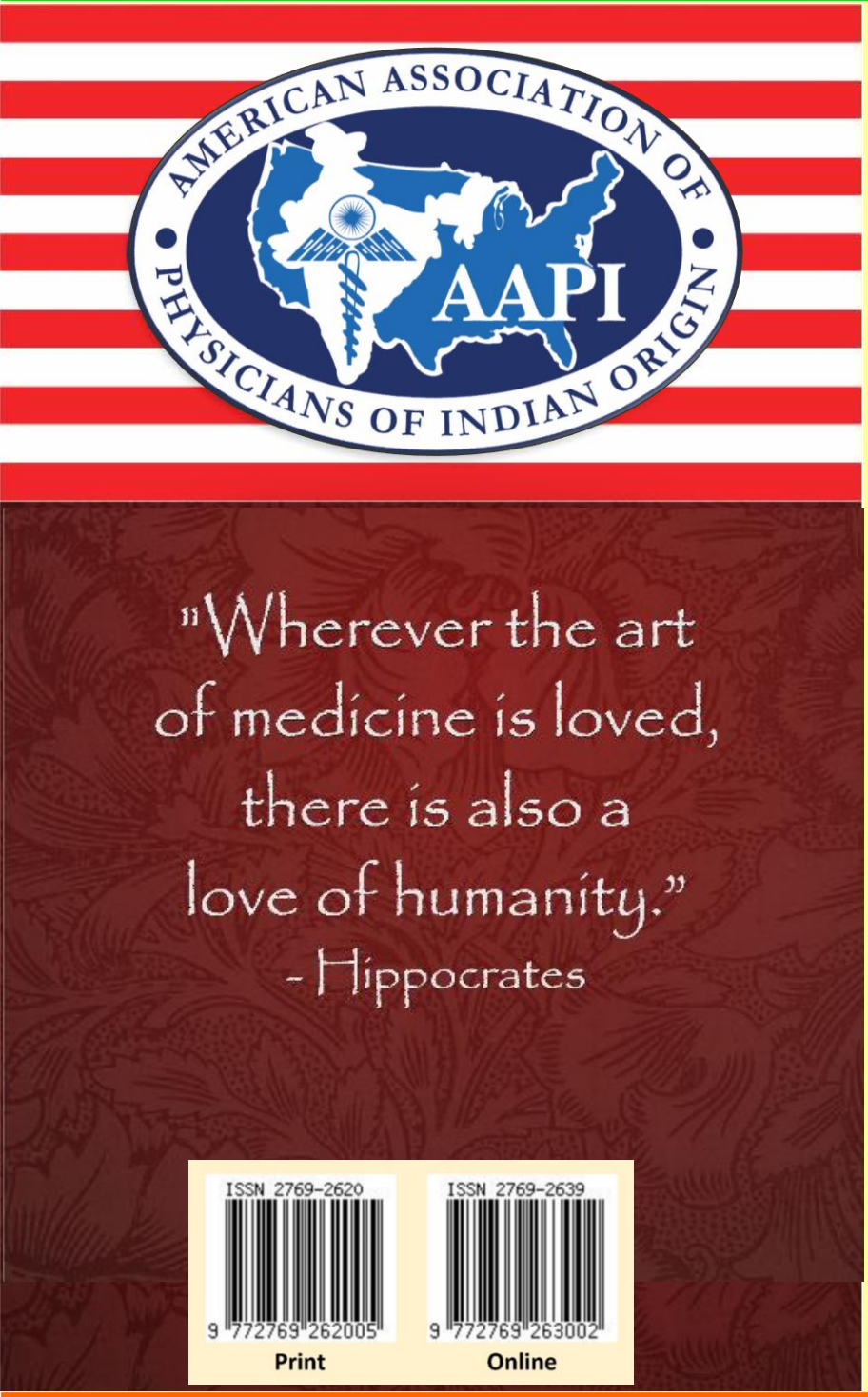

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In this Issue…

This Spring Issue of JAAPI is Dedicated to

Willem J. Kolff, M.D., Ph.D.

Father of Artificial Organs

(1911 -2009)

Photo: Courtesy of Kolff Collection, Univ. of Utah J. Willard Marriott Library (Altered)

Built the first artificial kidney, and first artificial heart.

Developed a membrane oxygenator, still in use during open heart surgery.

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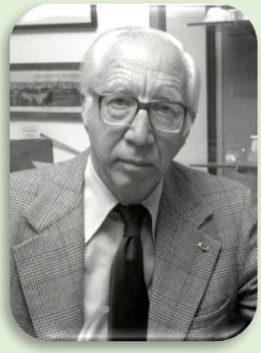


Pioneers in Medicine and Healthcare

Willem J. Kolff, M.D., Ph.D.

Father of Artificial Organs

Built the first artificial kidney, which became the modern hemodialysis machine.
Built the first artificial heart, which is still in use for patients awaiting transplants.
Developed a membrane oxygenator, still used to keep people alive during open heart surgery.

Photo: Courtesy of Kolff Collection, Univ. of Utah J. Willard Marriott Library (Altered)

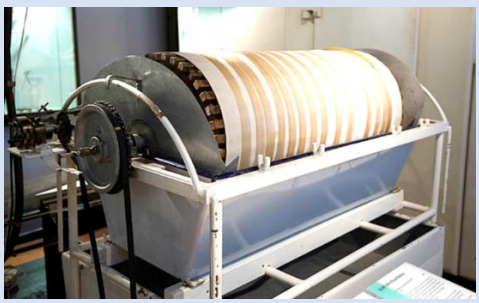
The exciting thing is to see somebody, who is doomed to die, lived and be happy – Willem J. Kolff

With a global prevalence rate of 11.7 to 15.1% chronic kidney disease, an estimated 4.901 to 7.083 million patients with end-stage renal disease (ESRD) need renal replacement therapy by dialysis. With about 500,000 ESRD patients on hemodialysis, the United States spends $90,000 per patient or $28 billion annually, which represents 7.2% of Medicare budget. But for the hemodialysis, these ESRD patients face a grim chance of survival. This is made possible due to the brilliant work of a Physician-cum-Engineer.

Dr. Willem Johan Kolff, also known as Pim Kolff, was a Dutch physician, and a pioneer of hemodialysis as well as in the field of artificial organs. He made his major discoveries in the field of dialysis for kidney failure during the World War II. In 1950 he immigrated to the United States, where he had a long and very productive and illustrious career. As a Resident in Medicine at the Groningen University, Dr. Kolff had to treat a 22-year-old man who was slowly dying due to chronic kidney failure. This prompted Dr. Kolff to start doing research on how to replace kidney function using an artificial organ. Using debris from downed war plans, an enamel bathtub, orange juice cans, used auto parts, and sausage casings, in 1943 Dr. Kolff built the first prototype dialyzer. Working with that and failing repeatedly, in 1945 Dr. Kolff successfully treated his first patient, a 67-year-old woman suffering from kidney failure, using his home-made crude hemodialysis machine (see below). That ushered the Age of Artificial Organs, which saved the lives of millions of patients with acute and chronic kidney failure over the decades. During the WW II, Dr. Kolff built several hemodialysis machines, and after the war he donated them to hospitals in Europe. One of them reached Mount Sinai Hospital in New York City, which was used to perform the first human dialysis in the United States on January 6, 1948, under the supervision of Drs. Alfred P. Fishman and Irving Kroop.

While in the United States, Dr. Kolff worked at the Cleveland Clinic, where he developed heart-lung machine. Later at the Brigham and Women's Hospital, Dr. Kolff produced prototypes of artificial kidney, which were manufactured commercially. In 1967, Dr. Kolff moved to the University of Utah as head of the Division of Artificial Organs and the Institute for Biomedical Engineering. There, he was involved in the development of the artificial heart, which was successfully implanted in 1982 in a patient Barney Clark. The patient survived for four months, with the heart still functioning at the time of her death. Later, Robert Jarvik, who worked with Dr. Kolff at the University of Utah developed the first permanent artificial heart. A brilliant physician and engineer, Dr. Kolff designed other artificial organs, including eyes, ears, and limbs, until his retirement in 1997. He was the founder of the American Society of Artificial Internal Organs. In 2003, Dr. Kolff was a co-nominee for Nobel Prize in Medicine or Physiology. Dr. Kolff left a rich legacy.

Replica of the drum-kidney plus blood pump first used successfully for acute dialysis treatment in 1945 by Willem Kolff



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Dr. Kolff and Dr. Scribner Share their ESRD Stories
https://www.youtube.com/watch?v=WjQCd7Hi5YQ

Gallery of Rich Collection of Dr. Kolff's Life and Contributions
https://achievement.org/achiever/willem-j-kolff/#gallery

Article Contributed by: **Bellamkonda K. Kishore, M.D.**

Invited Editorial

Science during the COVID-19 Pandemic

Soumya Swaminathan, M.D., FMedSci
Chief Scientist
World Health Organization, Geneva, Switzerland

COVID-19 has overwhelmed even the most advanced healthcare systems, no one government had the capacity or ability to operate at the scale required to address the COVID-19 pandemic. A new pathogen spreading rapidly among populations meant that decisions had to be made based on incomplete data, and policy shifts were needed in the light of new data.

World Health Organization's (WHO) unique role at the center of the global response network meant that from day one, it was able to access and harness technical and operational expertise at speed, promoting research, translating new knowledge into evidence-based guidelines, managing the infodemic and reducing its impact on health behaviors, playing the role of the first responder to countries in need and provider of last resort for essential commodities and services.

WHO also supports countries in need by strengthening healthcare systems capacities, infrastructure, and service delivery, empowering communities in the process and equipping them to tackle future healthcare crises. The varying and disparate pandemic landscape, with countries at vastly differing stages, with many countries not having adequate scientific expertise meant that many relied on WHO to drive coordinated action. WHO plays an instrumental role in providing the intelligence needed by all governments, including country-specific surveillance and capacity information, collaborating with partners leading on the supply, financing, and manufacturing of healthcare products and countermeasures. WHO works with a wide range of partners to ensure financing is used for the most critical elements of the COVID-19 response and plays a distinct convening role. These key features mean that if WHO had not existed at the start of the pandemic it would've been necessary to invent it.

In February 2020 the WHO organized the **Global Research and Innovation Forum on COVID-19**, to mobilize international action in response to the novel coronavirus emergency (1). This Forum brought together over 500 scientists from 60 countries to identify key research priorities. That meeting and research roadmap laid the foundation for developing tools that have helped prevent, detect, and treat COVID-19 as well as research in public health, ethics, and social science. The Solidarity trials for therapeutics conducted in over 30 countries (and 600 hospitals) generated high quality data on repurposed drugs and showed that globally coordinated clinical trial platforms can be useful for public health, even in emergencies.

The **Strategic Advisory Group of Experts on Immunization** (**SAGE**) advises on global policies and strategies on immunization and was constantly updating its recommendations on COVID-19 vaccines, as data emerged (2). The prioritization roadmap developed by SAGE also gave countries advice on which high risk population groups to immunize first, to reduce mortality. The COVAX initiative - a collaboration between WHO, Gavi the Vaccine Alliance, UNICEF, and CEPI – played an important role in addressing vaccine inequity by taking an end-to-end approach from supporting research and development, pooled procurement with advance market commitments to delivery of immunization and its linkages with other health interventions in countries (3). Today, the initiative has delivered over 1.5 billion doses and has been the only source of COVID-19 vaccines for about 40 countries worldwide.

The global scientific community can be proud of its many achievements in understanding the SARS- CoV-2 virus and the disease it causes and developing tests, treatments, and vaccines at record speed, including the use of novel mRNA technology for the first time at scale. However, there are **huge inequalities** across and within countries and societies in access to life saving technologies. Indeed, taking a broader view, there are four major gaps in biomedical R&D. First, lack of medicines in areas where market incentives are inadequate to attract private investment, such as for neglected diseases

of poverty, bacterial infections (Antimicrobial Resistance, AMR), and emerging infectious diseases. Second, there is a slow pace of progress in some areas, such as Alzheimer's disease, especially on its management in low-income countries. Third, risk of harm, such as adverse drug reactions need strong pharmacovigilance mechanisms. Fourth, many low- and middle-income countries (LMIC) have restricted access to technologies, caused by high prices, insufficient production, or inadequate supply. Therefore, we need to prioritize public-health needs through structured, inclusive, transparent, and informed processes at both national and global levels and conduct R&D in an ethical and scientifically sound manner. Only then, will the outcomes of R&D be beneficial to all populations.

COVID-19 has demonstrated the feasibility of more open research and data sharing with wide benefits. Among many examples, the **GISAID** (Global Initiative on Sharing Influenza Data) platform makes genomic data rapidly available with data protection rules in place for those who have contributed (4). AstraZeneca has committed to transfer technology and forgo profit from sales of the COVID-19 vaccine it jointly developed with the University of Oxford, United Kingdom, during the pandemic. Most scientific journals promised to publish research papers even after data were shared in preprints and made all COVID-19 papers open access to enable knowledge to have immediate impact on patient care and prevention.

The **WHO's COVID-19 Technology Access Pool** is a platform for technology holders to share intellectual property, knowledge, and data with potential product manufacturers (5). The **UN-backed Medicines Patent Pool** has negotiated licenses with the drug makers Pfizer and Merck for COVID-19 treatments to be sold as low-cost generic drugs in over 100 low-and-middle-income countries (LMICs) (6); however, several middle-income countries are excluded. The WHO has also set up an **mRNA Vaccine Technology Transfer Hub** to build and strengthen manufacturing capacity (using the new mRNA platform technology) in all regions, in order to strengthen regional health security and prepare for future needs (7). Such mechanisms involving the transfer of know-how and technology need to be more widely used not just for pandemics, but for all diseases of public health importance.

We need to strengthen mechanisms to fund global research priorities and sustain investments in existing research networks, platforms, and partnerships. At the same time, we need to build research capacities, capabilities, and infrastructure for research, including quality laboratories, especially in LMICs. The role and critical importance of science in solving local and global challenges is obvious and governments must strengthen mechanisms to use science advice in policy making, along with attention to other critical elements like economics, ethics, and impact on the public.

"Science knows no country because knowledge belongs to humanity and is the torch which illuminates the world."
- Louis Pasteur

URLs for Citations:

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Pioneers in Medicine and Healthcare

Soumya Swaminathan, M.D.

Chief Scientist

World Health Organization

Geneva, Switzerland

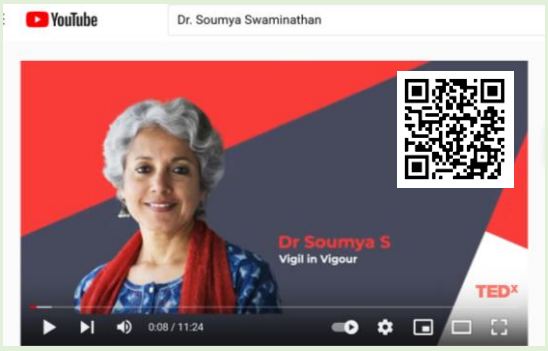
Photo: Ministry of Health and Family Welfare (GODL-India) via Wikimedia Commons

We must believe that we are gifted for something, and that this thing must be attained. – Marie Curie

In March 2019, Dr. Soumya Swaminathan was appointed the first Chief Scientist of the World Health Organization. A Pediatrician by profession from India, and a globally recognized Clinical Scientist for her research on tuberculosis and HIV, Dr. Swaminathan brings with her 30 years of experience in healthcare and research. Prior to being appointed as Chief Scientist, Dr. Swaminathan was Deputy Director General of Programmes (DDP) at the WHO since October 2017. Before that that Dr. Swaminathan was Secretary to the Government of India for Health Research, and then Director General of the Indian Council of Medical Research (ICMR). While working in India, Dr. Swaminathan focused on bringing science and evidence into health policy making, building research capacity in Indian medical schools, and forging South-South partnerships in health sciences. From 2009 to 2011, Dr. Swaminathan also served as Coordinator of the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases in Geneva. In 2021, Dr. Swaminathan was appointed to the International Pandemic Preparedness Partnership (PPP), a new global partnership launched to fight future pandemics, under the UK G7 presidency, currently held by Prime Minister Boris Johnson. Thus, throughout her career Dr. Swaminathan relentlessly worked to translate research into impactful healthcare programs.

Dr. Swaminathan has published more than 350 peer-reviewed publications and book chapters. She is an elected Foreign Fellow of the US National Academy of Medicine, and a Fellow of all three science academies in India. The Science division's role is to ensure that WHO stays ahead of the curve and leverages advances in science and technology for public health and clinical care, as well as ensuring that the norms, standards, and guidelines produced by WHO are scientifically excellent, relevant, and timely. Dr. Swaminathan's vision is to ensure that WHO is at the cutting edge of science and is able to translate new knowledge into meaningful impact on population health worldwide.

Dr. Soumya Swaminathan was born in Chennai, India to Dr. M. S. Swaminathan, the Father of Green Revolution in India, and Mrs. Mina Swaminathan, an educationist. Dr. Swaminathan is married to Dr. Ajit Yadav, an Orthopedic Surgeon. Dr. Swaminathan graduated with M.B.,B.S. from the Armed Forces Medical College, and M.D. in Pediatrics from the All-India Institute of Medical Sciences in New Delhi. Dr. Swaminathan is a Diplomate of the National Board. She did post-doctoral medical fellowship in Neonatology and Pediatric Pulmonology at the Children's Hospital of Los Angeles, and Keck School of Medicine, University of Southern California, Los Angeles, California. Dr. Swaminathan also did a Research Fellowship in Pediatric Respiratory Diseases at the University of Leicester, United Kingdom. Throughout her career, Dr. Swaminathan received several national and international awards.



How Governments Can Build Resilience | Soumya Swaminathan | TEDxHyderabad

Our reaction to stress is either to lose all our faith, strength and confidence or to stand against it, building our resilience. In the face of global crisis of COVID-19 pandemic, it is the responsibility of the governments to build that resilience and define the response of individuals and communities. The disease outbreak cannot be controlled without effective involvement of the community, and to ensure 'infodemic', the pandemic of misinformation doesn't do as much harm as the pandemic itself. The spirit of solidarity for our fellow global citizens is what the fate of humanity depends on, and we have to win the day for all of us, tells Dr Soumya Swaminathan, the Chief Scientist of WHO in this eye-opening talk.

(Scan the QR Code to watch the video on your cell phone).

Compiled by: Bellamkonda K. Kishore, M.D. (Sources: WHO, Govt. of India, and other sources on the web)

From the Editorial Desk – In This Issue

Can Evidence-based Medicine *per se* Address the Healthcare Needs?

Bellamkonda K. Kishore, M.D., Ph.D., MBA
Editor-in-Chief of JAAPI

In 1991 Gordon Guyatt and his associates introduced the term "Evidence-based Medicine" (EBM) to shift the emphasis in clinical decision-making from 'intuition, unsystematic clinical experience, and pathophysiologic rationale' to scientific, and clinically relevant research (1). For about three decades EBM helped to integrate the experience of clinicians with the best available scientific evidence and thus guided in decision-making in the best interest of the patients. Despite its superiority over the older approaches of intuition and unsystematic clinical experience, of late EBM has been the target of criticism for various reasons, such as, it denigrates clinical expertise and ignores patient's values and preferences; promotes a "cookbook" approach to medicine; and is simply a cost-cutting tool (2), although these are unfounded (1). To overcome these critiques and downsides, we are now turning to Personalized Medicine. Also known as Precision Medicine (3), this approach can predict whether a treatment regimen will work for the given patient, and if not, it is not prescribed. The precision drug is far more likely to be effective against diseases than a drug that treats everyone in the same way. But before we usher the precision medicine into practice, there are three issues we need to be aware of, which are affecting selected populations of patients. Some articles published in this edition of JAAPI emphasize or deal with those issues.

First, as expounded in the Invited Editorial by Dr. Soumya Swaminathan, Chief Scientist, World Health Organization (WHO), there is a "need to strengthen mechanisms to fund global research priorities and sustain investments in existing research networks, platforms, and participants." The current COVID-19 pandemic has exposed the shortcomings and how much we need to strengthen this sector of healthcare, especially in developing and poorer countries. But for the timely and concerted efforts of WHO and altruistic gestures of a few vaccine and drug manufacturers, this pandemic might have resulted in substantial mortality and morbidity. It is time to wake up and proactively prepare the global health community for any future epidemics, so they will not surprise us.

Second, the Commentary by Dr. Suni Jani on Mental Health Payment Parity brings to the light a major healthcare issue. Despite Congress enacted a law requiring equal reimbursement for mental and physical healthcare (4), and the United States has the highest score for bipolar spectrum in the world (5), as per the commentary, the lack of adherence of insurers to the law is an issue today. And it has become a major barrier for immigrant communities, such as South Asians, who are experiencing rapidly growing incidence and prevalence of mental illnesses, and who are hesitant to seek help for mental health issues.

Third, it has been well documented that Asian Americans, especially the South Asians, have higher prevalence of cardiovascular diseases and face higher cardiometabolic risk. This has often been attributed to genetic factors, as both the people living in India and the immigrants from Indian subcontinent in the United States face the same level of risks. But, as described in the review article on Lean Diabetes by me, the problem is not simple or straightforward to explain or manage. Recent studies have unraveled that both evolutionary and maternal factors during pregnancy play significant roles for the higher prevalence of cardiometabolic risk in South Asians. Similar issues are being faced by other Asians and African Americans. On May 10, 2022, the Newsroom of the American Heart Association pointed out that "one-size-fits all" is flawed for assessing cardiovascular diseases risk among Asian Americans (6).

In view of the above, starting from this Spring Edition, JAAPI will run a section dedicated to **Asian American Healthcare Issues.** We welcome articles on all aspects of Asian American healthcare.

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Vision and Mission: JAAPI is a peer-reviewed medical and healthcare journal published by the AAPI. In line with the vision and mission of AAPI, JAAPI is dedicated to facilitating physicians to excel in patient care, teaching, and research, and thus pursue their aspirations in professional and community affairs. JAAPI is open to contributions from physicians and scientists of all backgrounds and from all over the world. Membership in AAPI is not mandatory for prospective authors.

Scope of JAAPI: JAAPI publishes a variety of articles, such as original research articles, clinical studies, reviews, perspectives, commentaries, case studies etc., covering all aspects of medical sciences, clinical specialties, and healthcare, including epidemiology, and policy, regulatory and legislative issues. Articles submitted to the JAAPI must be original and should not have been published or under consideration for publication elsewhere, except in abstract form in proceedings of conferences or meetings. Only manuscripts that meet professional and scientific standards will be accepted for publication. Review process is single fold blinded on the authors' side. But after acceptance of papers, the names of the handling Editors and Reviewers will be published on the front page of the article. This new trend started by some European journals is gaining momentum as it gives due credit to the Editors and Reviewers and ensures fair review process.

Publication Model: JAAPI is published as completely Open Access in electronic form (PDF). These will be archived in AAPI website (https://www.aapiusa.org/jaapi/), and the link to URL for each issue will be emailed to AAPI Members when it is published. A few hard copies will be printed for promotional purposes and for displaying at AAPI Conventions and other professional meetings or for distributing to libraries or dignitaries. There will be no submission fee or publication charges to the authors. Although materials published are copyrighted by the AAPI, others can cite or reproduce figures, schemes and pictures published in JAAPI without paying fee, but by giving due credit to JAAPI. This does not apply for materials reproduced in JAAPI from other journals, which are copyrighted by the original publisher.

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Editorial Board: The Editorial Board of JAAPI consists of one Editor-in-Chief, two Associate Editors-in-Chief, two Editorial Advisors, several Deputy Editors and Guest Editors covering different areas of medicine and health care, Editorial Board Members (Internal Reviewers). They will be aided by External Reviewers. The Editor-in-Chief and Associate Editors-in-Chief oversee the overall peer-review process, assign articles to Deputy Editors or Guest Editors, and accept or reject articles after peer-review. They also preview articles prior to peer-review process and determine whether they can be subjected peer-review process. The Editorial Advisors to provide advice to ensure good performance and stability of JAAPI and to help in logistics, administrative and fiscal issues. The Deputy Editors and Guest Editors will handle review process of submitted papers assigned to them with the assistance of internal (Editorial Board Members) and external reviewers. AAPI membership is required for all Editorial Board Members, except Guest Editors, who are expected to promote the vision and mission of AAPI through JAAPI.

CME Credits for Peer-Review Process: After indexing by PubMed, working through AAPI, JAAPI will obtain CME Credit eligibility for its reviewers by the Accreditation Council for Continuing Medical Education of the American Medical Association.

Journal Periodicity: Initially, JAAPI will have three issues per year (Spring, Summer, and Winter). As the journal picks up momentum and article submissions increase, the periodicity will be quarterly.

Types of Articles JAAPI Accepts:

- **Original Research Articles:** These describe original scientific or clinical research conducted on in vitro or animal models or human subjects after obtaining approval by the concerned institutional animal care and use committees or human subjects research review boards. The research should comply with the guidelines and regulations of US Public Health Service. The original research articles can be 3,000 to 4,000 words in length, excluding title page, abstract, legends and references. Maximum 7 figures or tables are allowed. Additional figures or tables need to be justifiable for the article. Supplemental Information (SI) containing data and text, such as methods, are allowed for deposition.
- **Review Articles:** The review articles can address any contemporary issue in medical or clinical sciences, or healthcare, including epidemiology, and policy, regulatory and legislative issues. The reviews should provide in depth analysis of the topics but should not be just presenting catalog of information. The review articles should be balanced and should cite literature without bias. The review articles can be 3,000 to 5,000 words, excluding title page, abstract, references, and legends. Not over 7 figures and tables combined. There is no limit on the number of references, but they should be recent and relevant ones. Review articles exceeding these limits will be considered if they are justifiable and provide
- **Clinical Studies:** Clinical studies can be observational or retrospective analysis of data or prospective randomized studies. All clinical studies should be conducted under the regulations and guidelines, documenting informed consent, protection of research subjects, inclusion of minorities etc., as per the guidelines of the US Public Health Service. Rigorous statistical analysis should be followed. Raw data should be provided for analysis if required. These articles can be up to 5,000 words, excluding title page, abstract, tables, legends, and references. Maximum number of figures or tables are 7 combined. Additional figures or tables should be justifiable for the study. Supplemental Information (SI) is allowed for deposition.
- **Brief Reports:** Brief reports of contemporary issues of high significance are accepted to disseminate information. These reports are up to 1,500 words in length, excluding title page, abstract, legends and references. About 4 tables or figures combined are permitted. Maximum 15 references are allowed.
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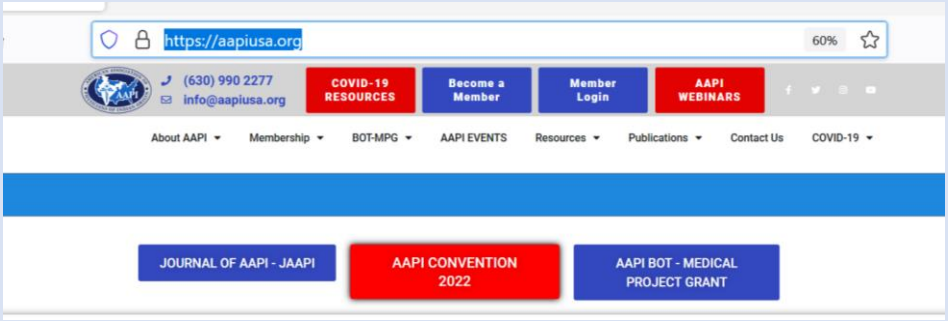

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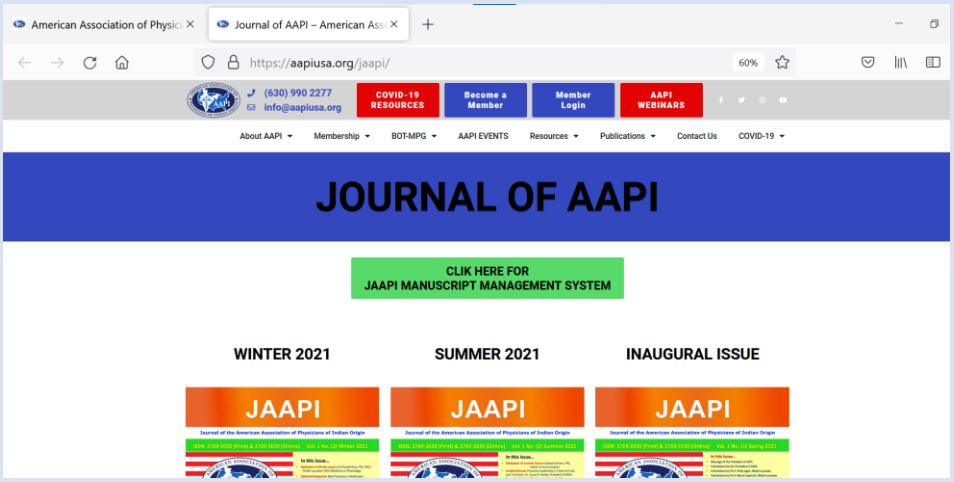

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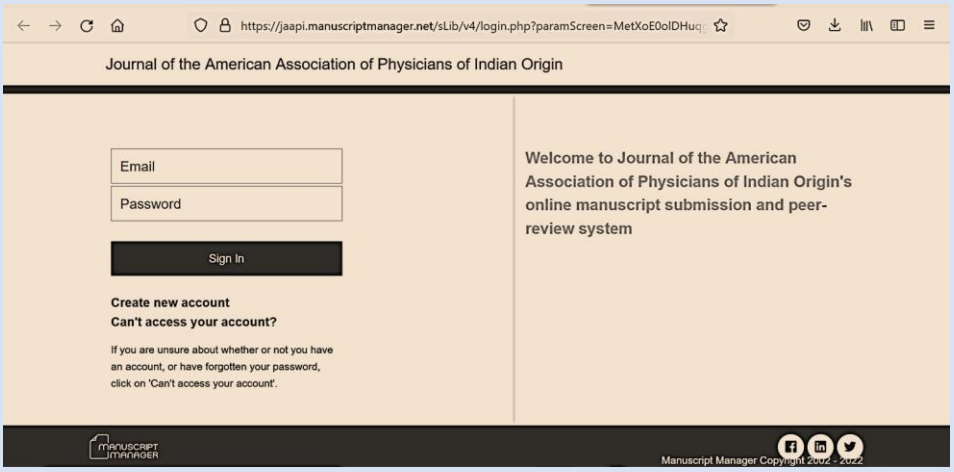

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Review Article

SARS-CoV-2 and the Liver:
Pathogenesis & Update on Prophylactic and Therapeutic Interventions

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Abstract: SARS-CoV-2 impacts the liver as part of the systemic inflammatory illness following viral infection of the aerodigestive tract and development of viral pneumonia. Patients with severe COVID-19 disease exhibit liver injury, cholangiohepatitis, vascular complications of associated thrombotic disease and may develop iatrogenic toxicity from necessary medications used to inhibit the viral replication, high levels of oxygen to support cellular processes and biological immunomodulators that dampen deleterious immune responses. Detection of SARS-CoV-2 RNA in liver tissues, bile and stool infers active viral spread and replication in hepatocytes and bile ductular cells following respiratory infection, presumably with infection mediated by viral protein interactions with the host angiotensin-converting enzyme 2 (ACE2) receptor. Severe disease resulting in death causes substantial hepatocellular and cholangiolar injury associated with microvascular thrombotic disease and futile attempts at hepatic regeneration. Individuals with pre-existing liver disease, including those with alcohol-related chronic liver disease, metabolic liver disease with diabetes, cirrhosis, and liver cancer, who develop COVID-19 have a greater risk of mortality, relative to people without hepatic disease. Moreover, liver transplant patients receive immunosuppressive drugs and are at elevated risk of having SARS-CoV-2 infection proceed to severe COVID-19 disease. This review addresses pathogenesis of COVID-19-mediated liver disease and provides current updates on prophylactic interventions with active/passive vaccination. We also note evolving therapeutic options to mitigate outcomes of the pandemic in these uniquely susceptible patients.

Key Words: SARS-CoV-2, COVID-19, Liver, Cirrhosis, Transplantation, Vaccines, Antibodies and Antiviral Drugs

Introduction: Clinical presentations following SARS-CoV-2 infection range from a short, self-limited illness with nonspecific symptoms, to more life-threatening acute respiratory syndrome characterized by multiorgan failure with all disease severities potentially followed by issues of chronic disease characterized by "long COVID". SARS-CoV-2 viremia, other viral (*e.g.*, Epstein-Barr virus,) reactivation, aberrant humoral or cellular responses and elements of the metabolic syndrome as in fatty liver and diabetes play a vital role in regulating immune homeostasis and may directly affect this "long COVID" disease course (1, 2).

Patients with preexisting liver disease, particularly those with toxic-metabolic illness, cirrhosis, and those who have received a liver transplant may have dysregulated immunity or immunosuppression and possess a greater risk of having COVID-19-related complications and mortality (Fig. 1).

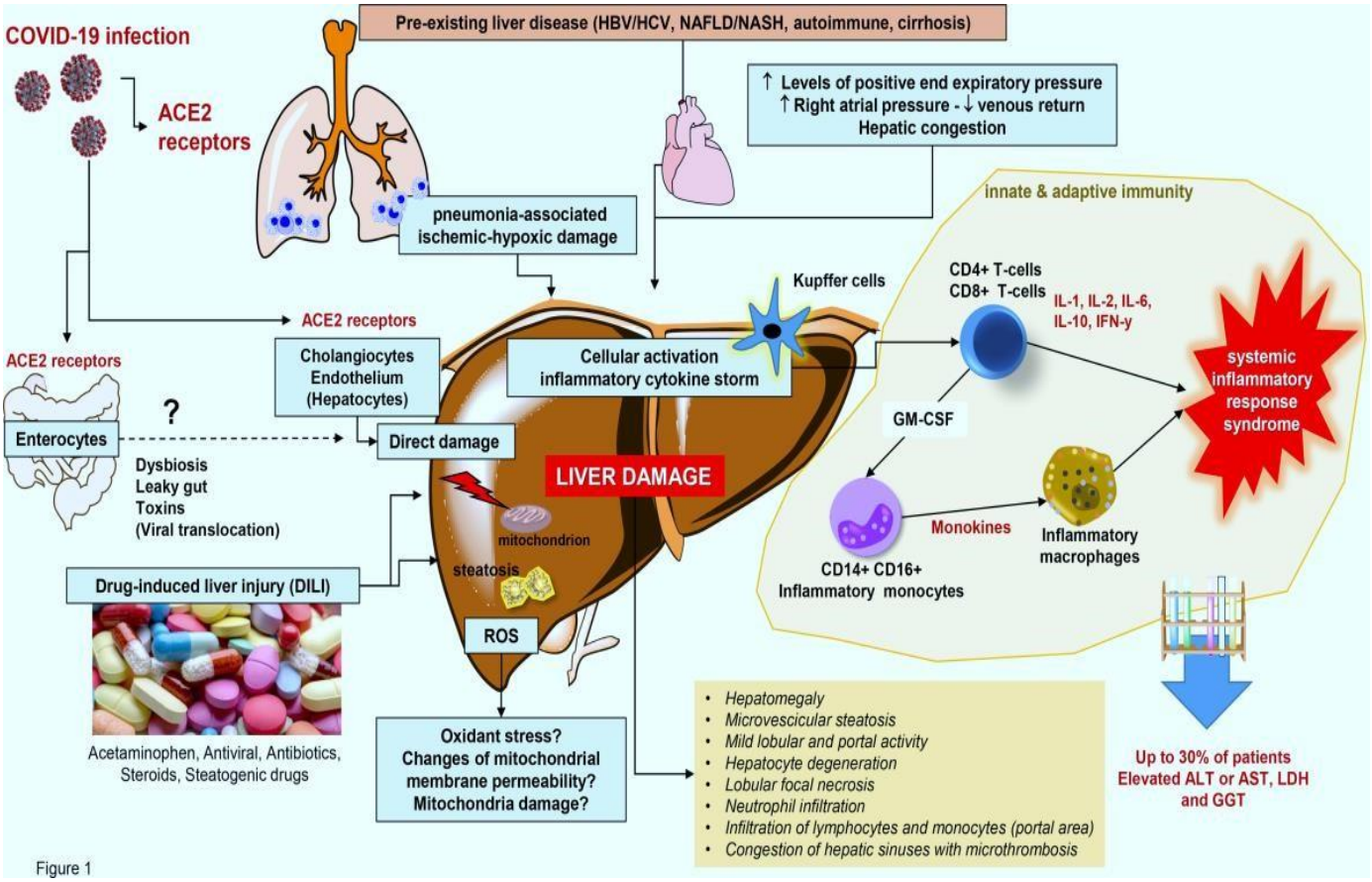

Figure 1: Major mechanisms involved in the pathogenesis of liver damage during COVID-19 infection. As shown, several factors contribute to liver damage, such as direct viral effect, drug-induced liver injury, pre-existing liver disease, hepatic congestion, ischemichypoxic damage. These factors activate inflammatory cytokine storm, where pathogenic T cells are activated, leading to production of granylocyte-macrophage colony-stimulating factor (GM-CSF), interleuinks (IL)-6, and other proinflammatory factors. Inflammatory monocytes CD14+ CD16+ respond to GM-CSF, producing larger amounts of IL-6 and other injurious cytokines. The resulting inflammatory storm evolves into immune damage in multiple organs, such as lungs and the liver as shown here. Figure and legend reproduced with permission from Portincasa P et al, *Eur J Int Med, 2020* (reference # 39).

Hepatic and Enteral Features of SARS-CoV-2: Hepatic involvement in COVID-19 disease could be related to the direct cytopathic effect of the virus, vascular injury, dysregulated regeneration, an uncontrolled immune reaction, sepsis or drug-induced liver injury. Moreover, in patients with underlying chronic liver disease, COVID-19 may lead to hepatic decompensation and acute-on chronic liver failure, with elevated mortality rates relative to the general population.

In the early stage of SARS-CoV-2 infection, 2-10% of patients were found to have viral RNA in fecal and blood samples (3). This finding was associated with gastrointestinal symptoms of diarrhea, nausea, vomiting, and abdominal pain, suggesting the virus is capable of infecting liver and biliary cells (4). Various biomarkers are associated with liver parenchymal inflammation and injury, such as elevated aspartate aminotransferase (AST) and alanine transaminase (ALT). Further, an increase in bilirubin can indicate liver dysfunction and increased alkaline phosphatase (ALP) indicates cholestatic disease or impaired of bile flow from the liver. In typical COVID-19 disease, mild to moderate elevation of amino-transferases are common, but signs of significant liver injury are less frequent. ALP elevation has been observed in severe cases, which suggests that SARS-CoV-2 can cause cholestatic injury associated with biliary tract inflammation. Other noted abnormalities have been hypoalbuminemia, elevated γ-glutamytransferase (γGT), and development of hyperbilirubinemia (5).

Pathological Features: There are many possible mechanisms in which COVID-19 infection affects the liver parenchyma, including hypoxia, severe inflammatory

response, direct cytotoxicity, reactivation of pre-existing metabolic liver disease, and viral and drug-induced liver injury (6). As noted in biopsy and post-mortem examinations, SARS-CoV-2 infection precipitates direct hepatocyte injury associated with cell apoptosis, ballooned hepatocytes, acidophilic bodies, and lobular inflammation (4, 6).

The virus uses its Spike protein to enter cells through the Angiotensin Converting Enzyme- 2 (ACE2) receptors, which are widely distributed in human tissues. The ACE2 receptors are a key entry points for SARS-CoV-2 in cholangiocytes, which corroborates a retrograde mode of liver injury following the infection of bile ducts (7). Viral entry requires modification of the Spike protein, which is achieved through host Transmembrane Serine Protease 2 (TMPRSS2) and paired basic amino acid cleaving enzyme (FURIN) activity; the expression of these proteins, along with ACE2 have been increased in patients with cirrhosis compared to healthy individuals (8).

This relates to ongoing discussion on how liver disease potentiates the severity of a SARS-CoV-2 pulmonary infection and the interactions between the gut/liver and lung axes (9). A subset of patients with COVID-19 have increased rates of thrombosis and adaptive immunity could be implicated in the pathogenesis. Besides infecting the bile duct cells, vascular and sinusoidal endothelial cells can also become infected with SARS-CoV-2. This disrupts barrier function, exposes subendothelial collagen, and releases prothrombotic plasma proteins, including von Willebrand Factor (vWF), from activated endothelial cells (10).

The presence of immune complexes containing the Spike protein and anti-Spike IgG is associated with enhanced thrombosis, but only when the complex is altered through glycosylation does it represent an aberrant response (11). It is speculated this aberrant formation of immune complexes causes a systemic immune response out of proportion to the physiologic insult known as a cytokine storm.

The maladaptive release of pro-inflammatory cytokines can lead to cardio-pulmonary manifestations and result in shock with tissue ischemia that can exacerbate underlying liver injury and increase markers of liver injury (12). Exposure to high levels of inspired oxygen in the setting of complex ventilation may exacerbate cytopathic effects, cause lung injury, provoke hepatic congestion and could impact pathogenesis of liver insults in COVID-19 (13). An informative graphic summary of these interactions is provided in Fig. 1.

Disordered Immunity in COVID-19: The SARS-CoV-2 virus infects a wide range of mammalian cells *e.g.*, myeloid lineages, bile ductular cells and others in the liver and lung, following close interaction between the viral Spike protein and the host ACE2 receptor (14). Besides functioning in cellular entry of the virus, the Spike protein is also expressed on the viral capsid surface and generates immune responses that might drive the heightened levels of mutation, as seen in variants of concern (VOC). Given the role of Spike in the viral life cycle and its accessibility, this protein is the major target for current COVID-19 vaccines and passive immunization approaches (15).

An adaptive immune response to SARS-CoV-2 infection includes T cell responses and humoral B cell activation resulting in the secretion of antibodies that bind to the virus, of which IgG is the most prevalent, [reviewed in (16)]. The generation of antisera against viral proteins is an important part of the immune response against the virus and yet, elevated antibody titers achieved during severe infection can be associated with uncontrolled inflammation rather than resolution of illness (17). This is an area of ongoing controversy with a key area of discovery being that post-translational modification of the Fc, (crystallizable fragment), portion of anti-SARS-CoV-2 antibodies impacts immunity. The Fc portion of the antibody, as opposed to the Fab or antibody binding fragment, influences antibody function through the binding affinity to Fc receptors on immune cells. This Fc region can be N-glycosylated or modified at asparagine residues, which in turn influences interactions with its cognate receptors. These are immunomodulatory and can be activating or inhibitory (18). Hence, differential modification of the Fc domain by varied sugar substitution may play a role in the finding of increased antibody titers being paradoxically associated with severe disease. Prior work has shown that such fucosyl modifications, mediated by the FUT8 gene product, impair the ability of the Fc fragment to interact with the FcγRIIIa receptor, a key receptor on macrophages that initiates an inflammatory response. In contrast, hypofucosylated antibodies, *cf.* those lacking this translational modification, bind up to 50x more strongly to FcγRIIIa receptor allowing for a more pro-inflammatory response (19); this response is advantageous in the clearance response to some pathogens, including HIV and tuberculosis (20). In addition, a clear understanding of the advantage of this response in the

immune clearance of cancer cells has been taken advantage of in the engineering of immunotherapeutic monoclonal antibodies (21).

Evolving data in the COVID-19 patients has suggested that the heightened pro-inflammatory response with activation of the inflammasome may be maladaptive in host clearance of SARS-CoV2 (22, 23). Such responses, drive hepatic acute phase responses and the associated lymphopenia and T cell exhaustion phenotype (Fig. 1), with heightened CD39 expression as described by Wang and colleagues (24).

Along this route, early clinical studies considered using an anti-CD73 antibody for COVID-19 immunotherapy to improve immune responses to SARS-CoV-2 (25). Further development of this potential therapeutic was stopped at the phase 3 trial stage due to the effectiveness demonstrated by concurrently developed COVID-19 vaccine strategies.

Prophylaxis for and Treatment of COVID-19 in Liver Disease: Small molecule antiviral therapies and immunotherapies, together with passive and active vaccination have been developed to prevent or limit the impact of COVID-19 disease (26). All patients with chronic liver disease, cirrhosis, hepatocellular cancer and those being evaluated for a liver transplant or have undergone transplantation should be immunized and boosted with COVID-19 vaccines. Besides active vaccination, using monoclonal antibodies as a passive form of immunoprophylaxis should be strongly considered for people who are moderately or severely immunocompromised. Passive immunization, however, is not a substitute for COVID-19 vaccination, as detailed below for the transplantation population.

The American Association for the Study of Liver Diseases (AASLD) recommends that patients with preexisting liver disease and/or elevated liver tests should be considered for anti-viral therapeutics, including remdesivir (27). Potential clinical benefits from remdesivir, even if administration can be associated with liver inflammation, should not preclude these patients' eligibility to receive it. Tocilizumab, similarly, is associated with mild serum elevations of aminotransferase and bilirubin levels. However, this drug may increase the risk of HBV reactivation; HBV screening is mandatory and when needed antiviral prophylaxis should be given. Recently developed antiviral therapies supplement early approaches with passive immunity to disease mitigation and include nirmatrelvirritonavir and molnupiravir. Nirmatrelvir targets the main protease (Mpro), a key viral enzyme involved in replication, with the ritonavir decreasing endogenous degradation of nirmatrelvir (28). Molnupiravir is a small molecule prodrug which, after being converted into its active form within the body, is incorporated into viral RNA and induces missense mutations during replication; treatment was found to reduce risk of hospitalization or death in at risk unvaccinated adults with COVID-19 disease (29).

Unlike vaccination, these small molecule viral inhibitors, while not uniquely tested in liver disease or liver transplant patients, are not anticipated to have a decreased ability to reduce effects of disease in these populations (30). Patients who have received a solid organ transplant require immunosuppressive agents. This necessary therapy prevents full function of the induced adaptive immune response and places this patient population, similar to patients with immunodeficiencies secondary to hematologic cancers, at greater risk of having COVID-19 disease progress to severe disease when compared to similarly vaccinated but immunocompetent persons (31, 32).

Hydroxychloroquine, used initially in the treatment of patients suffering from COVID-19 infection, is a rare cause of clinically apparent acute liver injury. Ivermectin can infrequently cause clinically apparent liver injury. These medications do not show efficacy for treatment or post-exposure prophylaxis for COVID-19 disease (33, 34) and do not have a role in treating SARS-CoV-2 infection.

Low level immunosuppressive therapy is typically maintained in patients with stable and quiescent autoimmune liver disease. Decreases in doses should be considered only if severe COVID-19 disease occurs similar to other special circumstances, for example, cytopenias or lymphopenia in the settings of bacterial or fungal superinfection.

The complexities surrounding the management of patients' needing liver transplantation are addressed next.

Management of Pre- and Post-Liver Transplant patients: Solid organ transplant recipients are at an increased risk of infection because of the immunosuppressive agents used to prevent graft rejection. All vaccinations including COVID-19 should be given before listing for liver transplant. Potential benefits of COVID-19 vaccination far outweigh any risk that may be involved.

Booster doses using mRNA vaccines are recommended in all patients with moderate or severe immunosuppression, ages 12 years and older, as these individuals are at increased risk for severe disease. As per CDC guidelines, the booster dose is recommended at least 3 months after the third dose in the primary series, for a total of four doses. People aged 12 years or older may receive a second booster dose with age-appropriate mRNA vaccine 4 months after the first booster dose, thus making 5 doses total in the immunosuppressed population. Vaccines in the early post-transplant period may have attenuated responses owing to high levels of immunosuppression.

Passive immunization using tixagevimab/cilgavimab has been supplementary to COVID-19 vaccination in this transplant population. In this area of clinical practice, the only thing that has remained constant in the COVID-19 guidelines has been change; this is due to rapid therapeutic developments and viral evolution, including the onset of Omicron strain BA.2. and BA.4 subvariants. Always refer to updates to the vaccine recommendations from the CDC (35).

Following a liver transplant, in our opinion, patients who have contracted COVID-19 infection should be managed at a center that specializes in the care of this patient population. In line with management of other infections in liver transplant recipients, lowering the overall level of immunosuppression has been proposed. Specifically, antimetabolite dosages should be reduced. If severe disease and inpatient hospitalization occurs, mycophenolate should be discontinued with a temporary conversion to calcineurin inhibitors or everolimus until disease resolution. Calcineurin inhibitors (CNIs) can be continued at their routine doses as calcineurin and mTOR inhibitors do not appear to be associated with worse outcomes in the setting of severe viral disease (36, 37).

Similar to the general patient population, further exogenous steroid administration with dexamethasone in patients with severe COVID-19 infection may help prevent the cytokine storm associated with COVID-19 infection. It may also provide adequate immunosuppression in the event of a reduction in dosage of antimetabolites. Antiviral therapies are increasingly available for COVID19 positive organ transplant patients. However, as noted, interactions between antiviral and immunosuppressant drugs, *e.g.*, the combination of nirmatrelvir (300 mg) and ritonavir (100 mg) with tacrolimus, sirolimus and everolimus, complicate their use (38, 39). Please refer to AASLD Guidelines for further updates in management in this regard (27).

Hepatocellular Carcinoma (HCC): Most patients suffering from COVID-19 infection recover within 3–4 weeks. It may be reasonable to delay treatment of HCC for this interval. Systemic treatment for HCC should be held temporarily in patients diagnosed with COVID-19 infection. Treatment can be resumed once the patient has been asymptomatic for three days. Procedures such as loco-regional therapies should also be postponed until the patient has been asymptomatic for at least three days. These decisions should be individualized to each patient based on their liver function, age, functional status, severity of COVID-19 infection and prognosis as determined by status of malignancy.

Conclusions: This review addresses the impact of COVID-19 disease on patients with healthy, normal livers and those with preexisting hepatic disease. We have provided a current update on disordered humoral immunity and inflammatory responses that exacerbate acute illness in COVID19. These pathogenetic pathways may predispose to high rates of mortality or severe morbidity with COVID-19 seen in patients with toxic-metabolic liver disease, cirrhosis or liver transplant. Updates on prophylaxis and treatment options are described in brief with consensus documents and guidelines provided in this rapidly changing area.

Disclosures: J.S., J.M.L. and T.S. declare no competing interests. S.C.R. is a scientific founder of Purinomia Biotech and ePurines. He consults for eGenesis, AbbVie and SynLogic Inc; his interests are reviewed and managed by HMFP at Beth Israel Deaconess Medical Center in accordance with the conflict-of-interest policies.

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Original Research

Perceived Parenting Style, Drug Abuse, Depression, and Suicidal Behavior among Late Adolescents: A Cross-sectional Study

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Abstract:

Context: Parenting style is a psychological construct that defines various strategies the parents use in child-rearing. Drug abuse, depression, and suicidal behavior among adolescents are increasing globally. Parenting style has an enormous role in shaping the personality characteristics and emotional development of adolescents. Research from the West has found mediating effect of parenting styles on drug-abuse behavior, depression and suicidal ideation among adolescents.

Aims: The study was aimed to assess the association of perceived parenting style with drug abuse, depression, and suicidal behavior among late adolescents in the Indian context.

Materials and Methods: The study had a cross-sectional design. A sample of 120 subjects was randomly selected from a group of college students pursuing engineering course. Semi-structured pro-forma to collect socio-demographic data, Parental Authority Questionnaire (PAQ) by Dr. John R. Buri, Drug Abuse Screening Test (DAST-20) by Skinner H.A., Brief Suicidal Scale Revised (SBQ-R) developed by Osman A et al., and The Centre for Epidemiological Studies-Depression (CES-D) scale by Radloff were used to study the variables. Descriptive and inferential statistical analyses were done using appropriate and valid methods.

Results: On the Chi-Square test perceived parenting style had shown statistically significant relationship with drug use (P=0.004), depression (P<0.001), and suicidal behavior (P=0.001) among the study subjects. Authoritative parenting style had shown a possible protective role against drug abuse and depression; and a definite protection against suicidality among the study subjects. There is a significant positive correlation between drug abuse and depression (r=0.389, P<0.001); drug abuse and suicidal behavior (r=0.516, P<0.001); and depression and suicidal behavior (r=0.512, P<0.001).

Conclusion: This study revealed the significant impact of parenting style on risky behaviors such as drug abuse and suicidal behavior among adolescents. Educating parents about sympathetic and rationale parenting attitudes, conducting regular screening camps in colleges for early diagnosis of depression and drug abuse prevention programs can help in preventing youth suicides.

Keywords: Parenting Style, Drug abuse, Adolescent depression, Adolescent suicide

Introduction: Parenting style is a psychological construct that defines various strategies the parents use in child-rearing (1). Darling and Steinberg defined Parenting style as "a constellation of attitudes and behaviors of the parents' toward their children and an emotional climate in which the parents' behaviors are expressed (2). This represents how the parents respond to and make demands on their children. Diana Baumarind in her

phenomenological work 'parenting typology' has classified parenting styles into three types: authoritarian, authoritative, and permissive type of parenting (3). Authoritative parents show high demandingness and highly responsive to the needs of their children. They set clear rules and expectations for their kids while practicing flexibility and understanding. Authoritarian parents are low in responsiveness but show high demandingness. They enforce strict rules with little consideration of their kids' feelings or social-emotional and behavioral needs. Permissive parents show low demandingness, but they are highly responsive. They typically go through great lengths to keep their kids happy, sometimes at their own expense. Previous studies have found that children's perception of parenting style has a great impact on their social relationships and emotional development. Parenting style is an indicator of parenting functioning that predicts child well-being across a wide spectrum of environments and across diverse communities of children. Good parenting comprises a balance between parental responsiveness and demandingness. Parenting styles have a great role in shaping the personality characteristics of adolescents. Research had shown that childhood experiences with adverse parenting styles are associated with several risky behaviors and personality abnormalities (4). Higher substance use, lower self-esteem, and lower social competence in adolescents are associated with authoritarian parenting in comparison to authoritative parenting, whereas adolescents with authoritative parents have significantly higher self-esteem, higher self-control, and stronger resistance to peer influence, thus reporting lower substance use and violence-related behaviors (5).

Substance abuse is a broader term that implies the use of harmful or hazardous psychoactive substances including alcohol, tobacco, and other illicit drugs like opioids, heroin, amphetamines, cannabis, and many more. According to World Health Organization (WHO), substance abuse is defined as "persistent or sporadic use of a drug inconsistent with or unrelated to acceptable medical practice" (6). Research indicates that the authoritative style is the most protective against substance use, whilst the neglectful style or uninvolved parenting would increase the risk of drug use; research on the authoritarian and permissive styles is yet inconclusive.

Globally, depression accounts for the most common mental health disorder among adolescents. Lifetime prevalence of depression among adolescents varies between 15% to 20 % due to different definitions, and study methods used (7). Depression is a major risk factor for suicide, substance use and serious social and educational impairments (8, 9). Suicide is defined as death caused by self-directed injurious behavior with the intent to die because of the behavior (10). Suicidality refers to the occurrence of suicidal thoughts or ideas or suicidal behavior. Suicide rates vary substantially between regions. About 80% of all suicides are reported from low and middle-income countries (11). Suicide mortality rates vary from 15.6 per 100,000 inhabitants in South-East Asia to 5.6 per 100,000 in the Eastern Mediterranean region (12). In India suicide rate was 11.3 per 100,000 population in 2020 (13). Suicide is the second leading cause of death among 15–29-year-olds globally. There are multiple reasons for suicides among college students. Self-esteem issues, role confusion, increase in responsibilities, changes in the environment, failed romantic relationships, academic demands, and conflicts with parents are some of the etiological factors for stress, depression, and suicidality in the late adolescence. There is a strong relationship between mental illnesses like depression, schizophrenia, substance use, personality disorders and suicide among adolescents (14, 15). Several studies have shown how parenting style affects adolescents' suicidal ideation. A study of Hong Kong teenagers revealed that negative parenting styles are associated with suicidal behaviors (16). One study reported that parenting style affects the formation of attachment for adolescents, and that attachment with parents affects suicidal ideation (17).

Adolescence refers to the period of human growth that occurs between childhood and adulthood. Adolescence begins at around age 10 and ends around 21. Adolescence can be divided into three stages: early adolescence (10 to 14 years of age), middle adolescence (15 to 17 years) and late adolescence (18 to 21 years). Late adolescence is characterized by more emotional and psychological independence. There is a marked increase in mental health issues among late adolescents worldwide.

According to The World Health Organization, in India, suicide is an emerging and serious public health issue. As prevention of suicide is a major health goal by global health policy makers, studying the association of various

factors associated with suicide in young people is of utmost importance. A plethora of research on this topic was done in Western countries. Studies done on the relationship between parenting styles, drug abuse and suicide are scarce in India; hence we have undertaken the present study.

Subjects and Methods: The present study was conducted at an engineering college in a suburban area of Vijayawada in the state of Andhra Pradesh in Southern India. After obtaining the permission of the college principal, approval of the Institutional Ethics Committee (IEC), and informed consent from students and their parents, the study was performed in the month of December 2021. Based on previous literature with a minimum correlation of 0.61 in the study domain, 99% statistical power, 5% level of type I error, and 1% type II error rate, minimum sample size was calculated as 40. To increase the power of study we have taken 120 as the study sample size after discussing with the statistician. We have called for volunteers to participate in the study through the college principal. Inclusion criteria for the study are those who are 18-21 years old, living with their parents, and attending college as day scholars. Students who were already diagnosed with a psychiatric illness or staying in the hostel for more than a year were excluded from the study. We have received a total of 354 responses. All these 354 subjects were telephonically interviewed to check whether they meet the study criteria or not. Out of these 354 subjects, 120 subjects were selected randomly by the lottery method. They were personally interviewed, and the scales were administered by the authors after taking informed consent. Participants were instructed to refer their current perceptions of their parents while answering the parental authority questionnaire. A semi-structured pro forma was used to collect socio-demographic data of the participants.

The Parental Authority Questionnaire (PAQ) by Dr. John R. Buri was used to measure the parenting styles. The PAQ is designed to measure parental authority or disciplinary practices, from the point of view of the child (of any age). It has 30 items and three subscales (10 items each): authoritarian, authoritative/flexible and permissive parenting. Participants are asked to answer the statements about their parents on a 5-point Likert scale (strongly disagree, disagree, neutral, agree, and strongly agree). Though the scales are available for father and mother separately, we instructed the subjects to identify one parent whom the participant perceives as most influencing parent and asked to rate that version of PAQ only. The PAQ score was calculated by adding the individual items which comprise the subscale scores. Each subscale score ranges from 10 to 50. Subscale with higher scores was taken as the dominant parenting style (18).

Drug Abuse Screening Test-20 item version (DAST-20) by Skinner H. A. was used to measure the risk of drug abuse. The DAST-20 yields a quantitative index of the degree of consequences related to drug abuse. This instrument takes approximately 5 minutes to administer and may be given in a questionnaire, interview, or computerized format. The various classes of drugs may include cannabis, solvents, tranquilizers, barbiturates, cocaine, stimulants, hallucinogens, or narcotics and exclude alcohol and nicotine. A score of 6 or more on the DAST-20 indicates the likelihood of drug dependence. DAST-20 was evaluated on different populations in different settings with a very good internal consistency (Chronbach alpha =0.86) (19).

The Centre for Epidemiological Studies-Depression (CES-D) scale was used to screen for the depression in the study subjects. It was originally published by Radloff in 1977. The CES-D is a 20- item Likert-type scale that measures for depressive symptoms frequency during the last week. Each answer is scored from zero to three points, and the total score ranges from 0 to 60. Usually, a score of 16 is taken as a cut-off point for clinically important depressive symptoms with good sensitivity, specificity, and high internal consistency (Cronbach's alpha of 0 .90) (20).

Brief Suicidal Scale Revised (SBQ-R) developed by Osman A et al., was used to screen for suicidal ideation and behaviors. The SBQ-R consists of 4 items: each measures a different element of suicidality. The total scores range from 3 to18. The cut-off score of 7 or above is significant with 93% sensitivity and 95% specificity. The scale was well validated in different age groups, normal population, and psychiatric inpatients (21). Permissions were obtained from all the original authors to use the questionnaires.

Statistical Analysis: Data entry and analysis were performed using Microsoft Excel (2019) and R environment version 3.4.4 (Vienna, Austria). Descriptive statistics

Continuous variables were described as mean with standard deviation (S.D.), and categorical variables were reported as a number with the percentage of the total. Inferential statistics: The Chi-square test was used to find the relationship between perceived parenting styles and other variables. The relationship between individual parenting styles and other three variables was done by Two-Proportions Z test. The Pearson correlation coefficient test was used to study the relationship between drug abuse, depression, and suicidal behavior. For all analyses, the probability level considered to indicate statistical significance was set at $P< 0.05$.

Results: In the current study 51.7% males (n = 62) and females 48.3% (n = 58) participated. More than half of the study participants (55%, n = 66) were between 18-19 years of age. The mean age of study subjects was 19.36 years (SD ± 0.96). Most of them were either in the 2nd year (30%, n = 36) or the 3rd year (33%, n = 40) of the engineering program. Majority of subjects belong to either middle (43%, n = 52), and upper (39%, n = 47) socio-economic status. Nearly half of the participants (n= 58) were following the Hindu religion. About forty percent (42.5 %; n =51) subjects perceived their parents parenting style as authoritarian, 26.7% (n = 32) reported as authoritative and the remaining 30.8% (n = 37) reported their parents parenting style as permissive.

Most of the subjects (55%, n = 66), denied active use of drugs in the past 12 months whereas 20% (n = 24) reported substantial to severe levels of drug use requiring further intervention. The mean score on DAST-20 scale was 3.49 (SD ± 5.03). About a third (31%, n = 37) of the participants reported moderate to severe depression on the CES-D scale. The mean CES-D score was 17.10 (SD ±12.48).

Less than one-fourths of study subjects (21.67%, n = 26) reported a statistically significant score of 7 or greater on the SBQ-R, whereas the remaining three-fourths scored less than 7. The mean score on SBQ-R was 4.42 (SD ± 2.76). (Table 1).

Relationship among Perceived Parenting Styles, Drug Use, Depression, and Suicidality: On Chi-Square test perceived parenting style had shown a statistically significant relationship with drug use (P = 0.004), depression (P <0.001), and suicidality (P = 0.001) among the study subjects (Table 2).

Table 1: Socio-demographic Data of Study Subjects

Gender	Numbers of Subjects n (%)
Males	62 (51.7)
Females	58 (48.3)
Age in Years (Mean ± SD: 19.36 ± 0.96)	
18	26 (21.7)
19	40 (33.3)
20	39 (32.5)
21	15 (12.5)
Year of Study	
First	29 (24.1)
Second	36 (30)
Third	40 (33.4)
Fourth	15 (12.5)
Socio-economic Status	
Upper	47 (39.2)
Middle	52 (43.3)
Lower	21 (17.5)
Religion	
Hindu	58 (48.4)
Muslim	24 (20)
Christian	36 (30)
Others	02 (0.16)
Perceived Parenting Style	
Authoritarian	51(42.5)
Authoritative	32(26.7)
Permissive	37(30.8)
DAST-20 Score (Mean ± SD: 3.49 ± 5.03)	
None	66 (55)
Low	22 (18.33)
Intermediate	08 (6.67)
Substantial	23 (19.17)
Severe	01 (0.83)
CES-D (Mean ± SD: 17.10 ± 12.48)	
No to Mild depression	83 (69.16)
Moderate depression	11 (9.17)
Severe depression	26 (21.67)
SBQ-R (Mean ± SD: 4.42 ± 2.76)	
<7	94 (78.33)
≥7	26 (21.67)

On the two proportion Z-Test there was a significant difference in the proportion of above normal DAST-20 scores between authoritarian and permissive parenting styles (P <0.001); authoritarian and permissive parenting styles (P = 0.004), but no significant difference in DAST-20

scores between authoritarian and authoritative parenting styles (P = 0.54).

Table 2: Relationship among Parenting Styles, Drug Use, Depression and Suicidal Behavior using Chi-Square Test

	DAST-20 Score			
Parenting Style	None to Low	Intermediate	Substantial to severe	P-Value
Authoritarian (n=51)	44	2	5	
Authoritative (n=32)	26	2	4	0.004*
Permissive (n=37)	18	4	15	
	CES-D			
Parenting Style	No to Mild Depression	Moderate Depression	Severe Depression	
Authoritarian (n=51)	40	1	10	<0.001*
Authoritative (n=32)	29	3	0	
Permissive (n=37)	14	7	16	
	SBQ-R			
Parenting Style	<7	≥7		
Authoritarian (n=51)	37	14		
Authoritative (n=32)	32	0		
Permissive (n=37)	25	12		0.001*

*P value < 0.05
DAST-20 Drug Abuse Screening Test
CES-D Centre for Epidemiological Studies-Depression
SBQ-R Brief Suicidal Scale Revised

Regarding depression and parenting styles, there was a significant difference in depression scores between authoritarian and permissive parenting styles (P < 0.001); authoritative and permissive parenting styles (P=0.001). No statistically significant relationship found between authoritative and permissive parenting styles on SBQ-R scores (P=0.610) (Table 3).

Table 3: Z Test of Proportions Comparing Individual Parenting Styles, Drug Use, Depression and Suicidal Behavior

DAST-20 Score >6		Z- Value	P value
Authoritarian (7/51)	Authoritative (6/32)	-0.613	0.54
Authoritarian (7/51)	Permissive (19/37)	-3.81	**<0.001***
Authoritative (6/32)	Permissive (19/37)	-2.81	0.004*
CES-D score >16		**Z- Value**	**P value**
Authoritarian (11/51)	Authoritative (3/32)	1.44	0.14
Authoritarian (11/51)	Permissive (23/37)	-3.86	**<0.001***
Permissive (3/32)	Permissive (23/37)	-4.51	**<0.001***
SBD ≥7		**Z- Value**	**P value**
Authoritarian (14/51)	Permissive (12/37)	-0.505	0.610

*P value < 0.05
DAST-20 Drug Abuse Screening Test
CES-D Centre for Epidemiological Studies-Depression
SBQ-R Brief Suicidal Scale Revised

There is a significant positive correlation between drug abuse and depression (r = 0.389, P <0.001); drug abuse and suicidal behavior (r = 0.516, P<0.001); and depression and suicidal behavior (r = 0.512, P <0.001) (Table 4).

Table 4: Relationships among Drug Abuse, Depression and Suicidal Behavior using Pearson Correlation Test

Variables	r value	*P* value
Drug abuse and Depression	0.389	<0.001*
Drug abuse and Suicidality	0.516	<0.001*
Depression and Suicidality	0.512	<0.001*

*P value < 0.05

Discussion: Previous reports studied the relationship between parenting styles, drug abuse, stress, and suicidal ideas separately whereas we tried to study all these parameters in a single study. Despite the cultural differences, differences in the study population and study settings, most of our research findings replicated the findings of earlier studies performed in the West. This clearly shows that drug abuse, depression, and suicidal behaviors are universal in nature and parenting style has a significant relationship in shaping the behavior of late adolescents across the population.

Parenting Styles and Drug Use: Calafat et al in their study on the protective role of parenting styles and substance use among 7718 adolescents in six Eurasian countries found that permissive parenting style is as protective as authoritative parenting against substance use among the study participants (22). In a study conducted in Sweden, the authoritative type of parenting was correlated with less drinking frequency and the neglectful style of parenting was associated with the worst substance use outcome. Other factors associated with substance use outcomes at follow up were deviant friends, delinquent behavior, parents providing alcohol, and a previous history of other substance abuse (23). We found a statistically significant relationship between parenting style and drug abuse, but we couldn't examine the relationship between different parenting styles and drug use patterns due to the methodological issues. On the Z-Test there was a significant difference in the proportion of above normal DAST-20 scores between authoritarian and permissive parenting styles and authoritarian and permissive parenting styles. Though this doesn't reveal the exact direction of the results it shows there is a clear difference between drug abuse patterns between different parenting styles. Authoritative parents are more responsive to the

needs of their children and adolescents with Authoritative parents have significantly higher self-esteem, higher self-control, and stronger resistance to peer influence. This would probably explain the lower substance use among them.

Parenting Styles Depression and Suicidal Behavior: McKinney et al did a study on 475 adolescents of 18–22-year age group. They have found that perceived parenting style was significantly associated with emotional adjustment among late adolescence (24). Lipps et al in their study on the relationship between parenting styles and depressive symptoms among adolescents in four Caribbean societies found that authoritative and permissive parenting styles were associated with lower levels of depressive symptoms in adolescents (25). In their study nearly half (52.1%) of all adolescents reported mild to severe symptoms of depression and about a third (29.1%) reported moderate to severe symptoms of depression. In our study, 31% reported moderate to severe depressive symptoms and there was a statistically significant relationship between parenting style and depressive symptoms**.** There was a significant difference in depression scores between authoritarian and permissive parenting styles; authoritative and permissive parenting styles.

When we examined the relationship between parenting styles and suicidal behaviors, we found a statistically significant relationship between these variables. In a study performed on 2708 undergraduate students, Bhat et al observed that 15.6% of the participants reported ending their lives whereas in our study 21.67% of study subjects reported suicidal behavior which is slightly higher (26). Shakir et al in their study on relationship between parenting styles and suicidal behavior among university students found positive correlation between suicidal behavior and authoritarian and permissive parenting styles. They couldn't find any statistical significance between authoritative parenting and suicidal behavior (27).

Donath et al concluded that authoritative parenting style had a protective role against suicide whereas rejective-neglecting parenting is a risk factor for suicide in adolescents (28)**.** Hong Kong adolescents who considered their parents' upbringing style to be authoritarian were reported to have more suicidal ideations and attempts compared with those who considered their parents' upbringing as authoritative (12). In our study, no subject from the authoritative parenting style group had reported suicidal behaviors and hence proving its possible protective role against suicidality in this age group. No statistical significance was found between SBQ-R scores between authoritarian and permissive parenting styles. Authoritative parents are less demanding in nature, provide more warmth, create a positive family climate and they are sensitive to the emotional needs of their children better than other parents, which could explain the protective role of authoritative parenting against depression and suicidal behavior among adolescents.

Relationship among Depression, Drug Use, and Suicidality: In our study, there is a significant positive correlation between drug abuse and depression ($r=0.389$, $P<0.001$); drug abuse and suicidal behavior ($r=0.516$, $P<0.001$); and depression and suicidal behavior ($r=0.512$, $P<0.001$). Magklara et al found that substance use had a significant association with depression in late adolescence (29). Drug abuse and depression have a bidirectional relationship. Drugs can alter the brain's chemical levels. Cannabis along with other illicit drugs leads to dysregulation between serotonin and other neurotransmitter triggering depressive symptoms. Depression can increase substance use. Substance use is considered as a way of self-medicating among adolescents.

Previous studies have shown that drug use is relatively common and concerning suicide risk factor among college students (30, 31). The San Diego Suicide Study was one of the earliest studies that reported an association between suicides and drug abuse (32). Fowler and colleagues opined that suicide might be regarded as a late manifestation of alcohol and drug use disorder (33). Lewinsohn et al in their study found that the use of much harder drugs is associated with more serious suicide attempts.[34] Foreman-Hoffman et al in their systematic review stated that depression is strongly related to suicidal ideation and attempts in adolescents (35). According to Wilcox H.C. genetic susceptibility along with family process could possibly explain the relationship between drug abuse, depression, and suicide (36).

Conclusions: This study revealed a significant impact of parenting styles on risky behaviors such as drug abuse and suicidal behavior among adolescents. Educating parents about sympathetic and rationale parenting attitudes, conducting regular screening camps in colleges for early diagnosis of depression, and drug abuse prevention programs can help in preventing youth suicides.

Limitations and Strengths: The sample size is small and done from a single study centre. Generalization of the

results needs to be done carefully. All the data analyzed in this study rely on self-stated information which would have resulted in information bias. Though we have studied the association between parenting styles and other variables, the study design is not enough to describe the mediating effect of parenting style. The information provided about drug use and suicidal attempts was not verified. Other variables like personality traits, alcohol use, and family history of psychiatric illness and suicide were not included in our study. A good study design with a large population sample using the regression analysis method will give a much better understanding of the relationship between the study variables. Despite the methodological limitations, this was the first study of its kind, which studied the relationship between parenting styles, drug abuse, and suicidality from the Indian perspective.

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Case Report

Dilemma in the Delivery Room:
Refractory Bradycardia Despite Adequate Neonatal Resuscitation

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Highlights:

- Bradycardia at birth may have multifactorial etiology, requiring investigations to tailor treatment.
- Fetal bradycardia may be caused by transplacental accumulation of maternal medications.
- Stable bradycardia with adequate oxygenation delivery may not warrant additional therapeutic intervention.

Abstract: Bradycardia in delivery room is frequently encountered by neonatologists. Bradycardia is defined as heart rate below the lowest normal for age and depends on the gestational age and physiologic maturity. Inadequate ventilation and oxygenation at birth is the most common cause of neonatal bradycardia. Other etiological factors such as placental insufficiency, maternal medication such as exposure to general anesthesia, magnesium and sedatives may play a role. Maternal medical conditions such as collagen vascular diseases and hypothyroidism may manifest as refractory bradycardia. In this case report, we describe a 30-week gestation infant admitted to the neonatal intensive care unit following bradycardia at birth that persisted despite following the neonatal resuscitation program (NRP) algorithm. His perfusion indices were adequate. This is the first known neonatal case involving profound bradycardia not responsive to resuscitation after trans-placental passage of losartan. We encourage readers to think of maternal medications such as Angiotensin II Receptor Blockers (ARB) in their differential diagnosis of an infant with bradycardia of unclear etiology. We provide a stepwise approach to investigate the cause(s) of neonatal bradycardia at birth.

Key Words: Neonatal resuscitation, Bradycardia, ACE inhibitor, Maternal medication, Transplacental drug transport, Congenital heart attack

Case Report: Informed written consent was obtained from the mother for this case report. A 1650-gram preterm Caucasian newborn male was noted to have bradycardia at birth. The infant was born to a 28-year-old G2P0111 mother via primary Cesarean delivery at 30 and 0/7-week gestation due to maternal preeclampsia and HELLP syndrome (hemolysis, elevated liver enzymes, low platelet count). Prenatal history was significant for lack of awareness of pregnancy and hence absent prenatal care. On presentation to the emergency room, a sonogram showed fetus with an estimated gestational age of 29 and 6/7 weeks. Her medical history was significant for reactive airway disease, bicuspid aortic valve, and chronic hypertension diagnosed at 21 years of age. Her medications included prescription losartan 50 mg orally twice a day. Upon admission, her urine toxicology screen was positive for methamphetamines. She was treated with magnesium 24 hours prior to delivery and a single dose of betamethasone immediately prior to delivery.

At delivery, amniotic fluid was noted to be clear. Neonate was delivered in cephalic position followed by delayed cord clamping for sixty seconds. Under the warmer, he had no spontaneous respiratory effort, had poor tone with heart rate of 60 beats per minute (bpm). Positive pressure ventilation (PPV) with a Neopuff and face mask was

initiated with a peak inspiratory pressure (PIP) of 20 cm H_2O, peak end expiratory pressure (PEEP) of 5 cm H_2O and 30% fraction inspired oxygen (FiO_2). As the heart rate remained less than a 100 bpm with oxygen saturations below goal ranges, the PIP was adjusted in stepwise fashion to 30 cm H_2O and FiO_2 was increased to 80%. At 3 min of life, the heart rate was noted to be 104 bpm and pulse oximetry reading was 92%. At this time, the infant had a vigorous spontaneous cry, was centrally pink, and had a capillary refill of 3 sec. PPV was discontinued and he was placed on continuous positive airway pressure (CPAP) of 6 cm H_2O at FiO_2 of 30%. EKG showed sinus rhythm with a heart rate of 103-109 bpm till fifteen minutes of life. He was admitted to the neonatal intensive care unit (NICU) due to his prematurity.

Subsequent care in the first 24 hours included caffeine therapy for apnea of prematurity, placement of umbilical venous and arterial lines for delivery of parenteral nutrition and blood pressure monitoring. A sepsis evaluation done at birth with antibiotic initiation was later reported to be negative. His heart rate continued to rise slowly and at 4 hours of life a 12-lead EKG demonstrated a sinus rhythm with a heart rate of 133 bpm. The infant's toxicology screens were significant for urine and meconium screens positive for amphetamine, marijuana, and opiates. In the NICU, he tolerated advancement of enteral feeds, remained hemodynamically stable, on CPAP for a week and nasal cannula and caffeine until 1 month of age. On discharge at 37 weeks post-menstrual age, he was completing his feeds orally. He was healthy and growing appropriately at his follow-up visit.

Discussion: Bradycardia at birth is a common presentation of neonates who need resuscitation. Approximately 5 to 10% of all newborns need some assistance to establish normal breathing at birth including positive pressure ventilation (PPV), 0.1% receive cardiac compressions, and 0.05% receive cardiac compressions with epinephrine (1, 2). The NRP recommends the following sequence of resuscitation: rapid assessment, initial stabilization, ensuring adequacy of ventilation, medications and chest compressions (3). Newborn resuscitation differs from adult and pediatric resuscitation whereby ventilation is the most important therapeutic intervention of resuscitation. A rise in heart rate is the best indicator of effective ventilation and response to resuscitative interventions (1). However, there are certain situations where the heart rate might not respond despite adequate resuscitation and improvement in oxygenation. In such instances, pausing in an effort to delineate possible etiologies is a prudent practice as it can help guide further therapeutic interventions (Table 1).

Fetal bradycardia is defined as a baseline FHR less than 110 beats per minute (bpm) that is present for 10 minutes or longer. In neonates soon after birth, a heart rate less than 100 bpm warrants resuscitation. Causes of fetal bradycardia are multiple and can be divided into maternal, uterine, cord, and intrinsic fetal factors (4). Some causes are self-limiting and resolve after the insult such as hypoxia or cord compression resolves. Major causes of neonatal bradycardia except for congenital heart block or maternal medications can be mitigated by following the NRP algorithm. About 50% of persistent fetal bradycardia is secondary to congenital heart block secondary to maternal autoimmune diseases (5). Fetal bradycardia can also be caused by exposure to maternal medications such as beta-blockers to control hypertension (6). Other medications such as magnesium sulfate can also cause fetal bradycardia (7). However, the heart rate responds to resuscitation in fetus exposed to magnesium sulfate (8). Herein, we describe a case of neonatal bradycardia associated with in-utero exposure to an uncommonly encountered medication, losartan.

Losartan, an ARB (angiotensin receptor blocker), is generally contraindicated in pregnancy in accordance with the American College of Obstetricians and Gynecologists, specifically during the second and third trimesters, due to its toxic effects leading to fetopathy. Women exposed to ARBs during pregnancy have a higher risk of adverse fetal outcomes, including malformations and oligohydramnios, pulmonary hypoplasia, hypoplastic skull bones, and subsequent fetal death (9-11). However, in this index case, mother was on losartan for chronic hypertension as she was unaware of her pregnancy. In adults, there is evidence of bradycardia caused by ARBs, notably in cases of toxicity secondary to ARB overdose (12, 13). In general, ARBs selectively block the vasoconstrictor and aldosterone-secreting effects of angiotensin II by inhibiting the binding of angiotensin II to the AT_1 receptor found on many tissues such as the vascular smooth muscle. These agents are metabolized via the cytochrome P450 system, specifically via CYP2C9 and CYP3A4 and are renally excreted. Though not as commonly seen with this class of antihypertensives, ARBs can potentially cause bradycardia due to parasympathetic (vagal) stimulation in adults.

Table 1: Suggested Stepwise Approach for Persistent Bradycardia at Birth

Intervention	Action Item	Next Step Considerations
Initial Examination		
Auscultation	Evaluate heart sounds (rate & rhythm) and quality (distinct or distant)	If abnormal, consider EKG, CXR
	Evaluate for murmurs and gallops	If abnormal, consider EKG, CXR, Echo
Monitor EKG	Confirm the rate and rhythm, voltage, relationship of P wave to QRS complex	If abnormal, consider EKG, CXR, Echo
Additional Investigations		
Blood Pressure & Perfusion	Assess hemodynamic stability	If abnormal, consider need for fluid resuscitation in Delivery room, and umbilical arterial monitoring in NICU
Arterial Blood Gas	Assess Adequacy of Oxygenation and Ventilation	Consider CXR, CPAP, Surfactant, need for positive-pressure ventilation
	Assess for presence of metabolic or lactic acidosis	Consider need for fluid resuscitation
12-lead EKG	Evaluate P-QRS-ST morphology	If abnormal, consider Echo
Echocardiogram	Evaluate cardiac structure and function	Vasoactive medication support as needed
Further Investigations		
Maternal history	Evaluate for medications such as beta blockers, recreational drugs	Monitor infant, continue supportive care
	Evaluate for auto-immune disorders, such as SLE, Sjögrens Syndrome, Hypothyroidism	Consider neonatal ramifications of disease
Placenta exam	Evaluate for placenta previa, abruptio placenta, retroplacental clots	Consider maternal Kleihauer-Betke test
	Evaluate for cord anomalies (velamentous insertion, Vasa previa, true knots)	Monitor infant, continue supportive care

We know ARBs readily cross the placenta leading to fetal toxicities. ARBs are metabolized by hepatic enzymes, typically not expressed in neonates until after the first week of life, and excreted via renal route (14). Given the foregoing, we hypothesize that, in our index case, accumulation of drug within the fetus may have caused a parasympathetic response that contributed to fetal bradycardia and bradycardia at birth. We acknowledge that a major limitation of this case report is the lack of literature in describing pharmacokinetic and pharmaco-dynamics parameters of losartan in the fetus. We theorize based on the patient's age and prematurity that his immature kidneys and liver enzymes may have led to fetal accumulation secondary to continued ingestion by mother, decreased metabolism/excretion of drug that was passed through the placenta resulting in fetal bradycardia.

Conclusion: This is a case of neonatal bradycardia unresponsive to routine NRP interventions and associated with in-utero exposure to an uncommonly encountered medication, losartan. It serves to remind us of the utility of a thorough medical history in the management of newborns who need resuscitation at birth. This is the first known neonatal case involving profound bradycardia not responsive to resuscitation after transplacental passage of losartan.

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Review Article

Gastrointestinal Involvement in COVID-19:
Mechanisms, Clinical Features, and Treatment Implications

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Abstract: Angiotensin converting enzyme-2 (ACE2) receptor expression in absorptive enterocytes facilitates the entry of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) into human gastrointestinal system via viral transmembrane S-glycoprotein. The most common digestive symptoms of COVID-19 infection are nausea and vomiting, diarrhea, and loss of appetite. Up to 10% patients present with isolated gastrointestinal (GI) symptoms leading to delayed diagnosis and poor outcomes. Defective intestinal barrier function has been implicated in microbial translocation explaining adverse outcomes in those with GI involvement. A gut-lung axis has been implicated in the pathogenesis of SARS-CoV-2. Probiotics and enteral/oral nutrition can be useful in maintaining mucosal barrier function. Proton pump inhibitor (PPI) use may increase the risk of COVID-19 infection as the usual acidic gastric pH help to inactivate the virus. Nearly half of the infected patients have detectable viral RNA in stool while one-third persistently shed the virus even after convalescence up to a month. Inflammatory bowel disease (IBD) in elderly, PPI use in gastroesophageal reflux disease/peptic ulcer disease, GI malignancy and chronic liver disease are GI comorbidities which increased risk of COVID-19 infection. Direct pancreatic injury via ACE2 receptor, virus induced lipotoxicity and ischemic injury may explain pancreatic involvement in COVID-19 which may range from idiopathic acute pancreatitis with complications, hyperglycemia, and new onset diabetes, pancreatic steatosis, and asymptomatic increase in pancreatic enzymes. COVID-19 infection and IBD have bidirectional relationship. COVID-19 infection increases risk of IBD flare whereas active IBD increased risk of COVID-19 related hospitalization. Age, sex, comorbidity, corticosteroid/ biologic use can reliably predict adverse outcomes of COVID-19 infection in IBD. IBD therapy needs to be modified in case of COVID-19 infection and more intensive immunization regimen is warranted for those on immunosuppressive therapy.

Key Words: COVID-19, Gastrointestinal tract, Inflammatory bowel disease, Angiotensin converting enzyme-2, Intestine, Gut microbiota, Pancreas

Introduction: Coronavirus disease-2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2); it was first reported in Wuhan, China, in December 2019 (1). The infection quickly escalated and evolved into a pandemic which has persisted for more than two years now. It typically presents with flu like symptoms of fever, fatigue, cough, and radiological evidence of pneumonia. However various organ systems involvement including gastrointestinal tract involvement leading to symptoms like diarrhea, nausea, and vomiting have been reported (2). Prolonged viral shedding in feces after convalescence have been reported based on isolation of viral RNA from rectal swab specimens of infected patients (3). This suggests a possibility of fecal-oral transmission of the virus. There is a close relationship between gastrointestinal (GI) involvement and SARS-CoV-2 infection. GI involvement can predict severity of COVID-19 infection (4). In this systemic review, we summarize the potential mechanisms and implications of GI involvement in COVID-19. Details of hepatobiliary injury have been discussed elsewhere.

Mechanism of SARS-CoV-2 Infection: Transmembrane spike (S) glycoprotein of SARS-CoV-2 unlocks the ACE2 (angiotensin converting enzyme-2) receptor on the host cell membrane like a key which is the prerequisite for SARS-CoV-2 infection. S protein has two subunits: S1 and S2 which are responsible for binding to host cell receptor and fusion of viral and host cell membrane respectively. S protein exists as trimer with each monomer consisting of 1300 amino acids and a receptor binding domain (RBD) with >300 amino acids which recognizes the cell surface receptors. S protein is cleaved at S1/S2 and S2 dominions by serine protease called TMPRSS which promotes SARS-CoV-2 enteric infection. TMPRSS2 is highly expressed in goblet cells and endocrine cells whereas TMPRSS4 is highly expressed in mature enterocytes (Figure 1). However, various cell surface receptors of SARS-CoV-2 other than ACE2 can explain its invasion of multiple organs (5). ACE2 receptor is expressed not only in esophageal stratified epithelial cells but also in ileal and colonic absorptive enterocytes. The expression of ACE2 is higher in cholangiocytes rather than hepatocytes. The expression pattern and level of ACE2 in GI tract determine the presence and severity of GI symptoms (6).

COVID-19 and Gastrointestinal Clinical Manifestations: Various studies have reported the GI manifestations of COVID-19 infection. In a systematic review of over 6500 patients, pre-existing GI comorbidity was present in 4% and pooled prevalence of GI symptoms was 15%. Nausea and vomiting, diarrhea and loss of appetite were the most common digestive symptoms seen in COVID-19 infection with patients with severe infection having higher incidence of abdominal pain. Pediatric patients have similar prevalence of GI symptoms as adults. About 10% patients with SARS-CoV-2 infection present with isolated GI symptoms making the diagnosis difficult. The prognosis in such patients is worse as compared to others (higher incidence of acute respiratory distress syndrome: ARDS and acute renal insufficiency) (4, 7). The markers of intestinal leakage (lipopolysaccharide binding protein-LBP), intestinal homing (C-C chemokine motif ligand 25: CCL25) and inflammasome (interleukin: IL-1, IL-18) activation are significantly increased in COVID-19 patients with GI involvement which may promote cardiac involvement in these patients plausibly explaining severe disease in this subgroup (8). Moreover, gut microbial products like butyrate can inhibit cytokine storm affecting the respiratory tract suggesting a possibility of gut-lung axis (Figure 2) (9). Pooled prevalence of abnormal liver functions was 19% with higher prevalence in those with severe COVID-19 infection (4). Other GI manifestations may include belching, abdominal distension and GI hemorrhage (6).

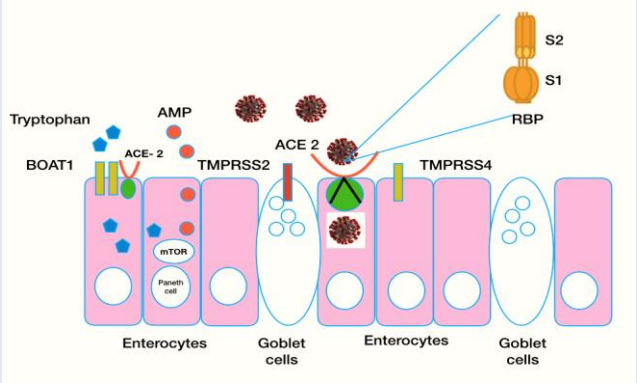

Figure 1: Proposed pathogenesis of GI manifestations in COVID-19. ACE- 2 is expressed in enterocytes which mediate SARS- CoV -2 entry into intestinal epithelium via S-glycoprotein. Tryptophan is absorbed in enterocytes through BOAT1/ACE-2 and is important for antimicrobial peptide (AMP) synthesis via m-TOR (mechanistic target of rapamycin) in Paneth cells. ACE-2: angiotensin converting enzyme-2, AMP- antimicrobial peptide, BOAT1- membrane bound amino acid transporter 1, S1 and S2- subunits of S glycoprotein in SARS-CoV-2, RBP- receptor binding protein.

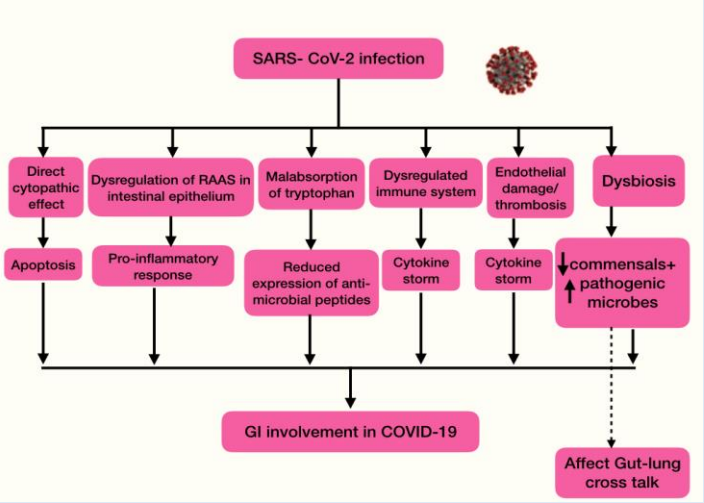

Figure 2: Proposed mechanisms of GI involvement in COVID-19. RAAS- renin-angiotensin-aldosterone system.

GI bleeding is the most common indication of endoscopy in COVID-19 infected patients. Up to three-fourth of these patients may have active lesions: esophagitis, gastritis, duodenal ulcer, malignancy and Mallory-Weiss tear in upper GI tract; diverticulum associated segmental colitis, ischemic colitis, hemorrhagic colitis and neoplasia in lower GI tract according to decreasing order of frequency (10). Steroid use, thromboprophylaxis with heparin, non-steroidal anti-inflammatory drugs (NSAIDs) use, stress related mucosal injury and ischemic injury are implicated in the pathogenesis of GI bleeding in these patients (11).

However, it is important to recognize that GI symptoms in SARS-CoV-2 infection like anorexia, diarrhea, nausea and vomiting may be caused by fever, fatigue or can be drug induced (e.g., lopinavir, ritonavir) (12). The higher incidence of GI symptoms in those with severe disease can be attributable to higher comorbidity (cardiac, renal) leading to various tissue injury (including GI) in these patients or a systemic cytokine storm and hypoxemia (6). GI bleeding is only seen in those with critically ill COVID-19 infection. This indicates stress induced mucosal injury as the underlying mechanism (6).

Management of Gastrointestinal Symptoms: Besides various anti-viral therapies for SARS- CoV-2, supportive management of GI symptoms include prokinetics for nausea/vomiting, glutathione for, liver dysfunction and loperamide and/or probiotics for diarrhea. Microbial dysbiosis with decreased Lactobacillus and Bifidobacterium is reported in COVID-19 infection (13). Probiotics (*Lactobacillus rhamnosus GG*, live *Bacillus subtilis*, and *Enterococcus faecalis*) can reduce the incidence of ventilator associated pneumonia (VAP) in critically ill patients as shown in a randomized controlled trial (14). Enteral nutrition should be considered rather than parenteral nutrition in critically ill patients with COVID-19 infection. Probiotics and enteral nutrition help in maintaining intestinal barrier function preventing bacterial translocation and infectious complications (e.g., gut lung axis is important to prevent ARDS or respiratory infections) (6).

Fecal-oral Transmission: Patients with SARS-CoV-2 infection can shed the virus persistently after the nasopharyngeal swab is negative in 32% patients for a period ranging from 5-35 days (15). In a systematic review of 26 articles positive fecal RNA was seen in 54% patients with COVID-19 infection (3). Median duration of virus shedding in stool is one week (16). These indicate possibility of fecal-oral transmission of the virus, although direct evidence is warranted. Disinfection of feces of infected patients could prevent such transmission.

COVID-19 and Proton Pump Inhibitors (PPI): It has been seen that SARS-CoV-2 is completely inhibited in extremes of pH (acidic: 1-3, alkaline: 11-12) (17). The pH of gastric and small intestinal secretions is 1-3.5 and 7.5-8 respectively. Hence, the gastric pH (1-3) in fasting state can inhibit of SARS-CoV-2. However, PPI use for various indications (e.g., gastroesophageal reflux disease: GERD or peptic ulcer disease: PUD) may increase the risk of COVID-19 infection (5). However, H2 receptor blockers were not associated with high risk of COVID-19 infection (18). PPI dose and current/past use also influence the risk of COVID-19 infection. Those using lower dose and once daily PPI are at lower risk of infection compared to those using higher dose and twice daily PPI (18). Current PPI use was associated with nearly 80% higher risk of severe COVID-19 infection (19). Hence PPI should be used judiciously in patients at high risk of COVID-19 infection and adverse outcomes.

Gastrointestinal Comorbidities Increasing Risk of COVID-19 Infection: IBD in the elderly, chronic liver disease (CLD), GERD/PUD, and GI malignancy can increase risk of COVID-19 infection and can predict adverse outcomes. The relation between IBD and COVID-19 infection have been detailed in a section below. Patients with CLD are at high risk of adverse outcomes with COVID-19 infection with increased mortality and possibility of acute decompensation (20, 21). Liver function abnormalities also correlate with COVID-19 severity. Detailed mechanisms and implications of hepatobiliary manifestations of COVID-19 are out of the scope of the current review. GERD and PUD increase the risk of COVID-19 due to PPI use in them. GI malignancy predicts two-fold increased risk of COVID-19 infection due to the immunosuppressed status caused by malignancy and systemic chemotherapy (11, 22).

COVID-19 and the Pancreas: ACE2 receptor involved in SARS-Cov-2 infection has been shown to be expressed in pancreas of normal individuals, even higher than lungs. Single cell RNA sequencing has shown ACE2 expression in both exocrine and endocrine (i.e., islets) (23). The later may partly explain SARS-CoV2 mediated hyperglycemia and new onset diabetes which is presumably mediated by neuropilin-1 leading to apoptotic beta cell death (24). However, the results of COVIDPAN study have shown that although pancreatic injury as evidenced by increase in

amylase and lipase was seen in 1-2% and 17% patients with mild and severe COVID-19 infection respectively, the relative contribution of drug induced pancreatitis (NSAIDs and steroids) can't be ruled out (23). Salivary amylase production, gut inflammation with increased permeability and impaired renal excretion can also explain increase in amylase levels besides pancreatic injury itself (25). The point prevalence of acute pancreatitis in hospitalized patients with COVID-19 is 0.27% (26). Complications of pancreatitis may include pancreatic necrosis, pancreatic fluid collections and venous thrombosis in spleno-portal axis which could potentially be higher in pediatric patients (27, 28). Pancreatic injury can have important clinical implications during COVID-19 infection by aggravating risk of ARDS and thus increasing hospital stay and the need for mechanical ventilation (23). Interestingly, pancreatic steatosis independently predicted severity and need for hospitalization in COVID-19 infection (29). Idiopathic pancreatitis is seen in 69% patients with COVID-19 infection compared to 21% in those without COVID-19 infection implying the possibility of direct pancreatic injury mediated via ACE2 receptors (26). Indirect pancreatic injury may be mediated by systemic inflammation, ischemic injury mediated by endothelitis and pro-thrombotic state or virus mediated lipotoxicity (11). The latter is mediated by toxic unsaturated fatty acids through mitochondrial injury produced as a result of lipolysis by interstitial leakage of pancreatic lipase and adipocyte triglyceride lipase (ACE2 expressed in adipose tissue) (30). Immediate post COVID-19 vaccination acute pancreatitis and pancreatic allograft rejection have been reported (31, 32).

The post-pancreatic transplant course has been similar in those with or without COVID-19 infection (33). Early monoclonal antibody treatment appears effective in SARS-CoV2 infected pancreatic transplant recipients (34). COVID-19 vaccination and seroconversion are important as serious infection is likely to occur in seronegative patients. Mycophenolate can impair seroconversion in a dose dependent manner and should be avoided (35). Pandemic induced delay in diagnosis can lead to stage-migration and worsen prognosis in pancreatic cancer (36).

COVID-19 and Inflammatory Bowel Disease: Patients with IBD are not at increased risk of COVID-19 infection in a meta-analysis of 17 studies showing pooled incidence rate of infection per 1000 population to be 4.02 in IBD compared to 6.59 in the general population (Relative risk: 0.47) (37). Advanced age is a risk factor of COVID-19 infection in IBD although a cut off has not been defined (38). The presenting symptoms of COVID-19 in IBD is not different from the general population except that GI symptoms are more prevalent. However, the latter could be due to active disease during COVID-19 infection. Diarrhea was seen in 27% and gastrointestinal symptoms like abdominal pain, nausea, and vomiting were seen in nearly 10% (39). Risk factors for COVID-19 related hospitalization were advanced age, active IBD and more than one non-IBD comorbidity (e.g. cardiovascular disease) (40, 41). The hospitalization rates can be as high as 47% in elderly (>80 years) compared to 5% in children and adolescents. With over 3 comorbidities, the rate of hospitalization increases to 60% compared to 9% in those without comorbidity. Disease subtype can influence hospitalization (UC>CD, RR-1.55) (37).

The rate of intensive care unit (ICU) admission (3%, RR-0.85), need for mechanical ventilation (2%, 9% in elderly, RR-1), risk of acute renal failure (RR-1) and renal replacement therapy (RRT) (RR-1) were similar between IBD and non-IBD patients (42-44). The mortality rate in COVID-19 and IBD according to meta-analysis and the SECURE-IBD registry are 4.3% and 2% respectively (37, 42). A validated model based on age, male sex, comorbidity, corticosteroid and biologic use can reliably predict hospitalization, ICU admission and death (area under the curve- AUC: 0.79, 0.88, 0.94 respectively) (45). Among drugs used for IBD treatment, corticosteroids were associated with higher risk of hospitalization (RR-2), ICU admission (RR-3.4), and mortality (RR-2.7) in patients with COVID-19 (46). COVID-19 infection predicted 1.3-fold higher risk of IBD flare as compared to non-COVID-19 infected patients due to enteric infection with SARS-CoV-2 and/or up-regulation of ileal/colonic ACE (angiotensin converting enzyme 2) (47). Among patients with IBD who tested positive for SARS-CoV-2, thiopurine, methotrexate, and tofacitinib should be stopped and 5-ASA, budesonide, rectal therapies and enteral nutrition maybe continued regardless of the severity and symptoms of COVID-19. Biologics should be delayed for at least 2 weeks for resolution of COVID-19 or development of convalescent titers (48). Response to SARS-CoV-2 vaccine may be attenuated in patients receiving systemic steroids, anti-TNF mono or combination therapy or Janus kinase inhibitors warranting more intensive immunization strategies although the evidence is still limited (44).

The risk of adverse events with COVID-19 vaccination in IBD patients is similar to general population. However, a slightly higher rate of GI adverse events has been observed

specially in younger patients with active IBD. Gi symptoms are reported in 15.6% after COVID-19 vaccination among 488 IBD patients which included increased stool frequency, abdominal pain, bleeding per rectum and vomiting. Most of the symptoms were mild and self-limited except a case of pouchitis which required hospitalization (49).

Gastrointestinal post-acute COVID-19 syndrome (PACS): In Individuals recovering from COVID-19, long term effects known as "long COVID" or "PACS" is increasingly being reported. The manifestations of PACS are systemic, cardio-respiratory, neurologic, and gastro-intestinal. Persistent inflammation driven by autoimmunity, persistence of viral antigens, reduced microbial diversity and aberrant neuro-immune crosstalk are the pathophysiological basis of GI PACS (50). In a prospective cohort of 1,783 COVID-19 survivors, nearly 30% reported GI symptoms at 6 months. These include diarrhea, constipation, pain in abdomen, nausea and/or vomiting and heartburn in 10%, 11%, 9%, 7% and 16% patients respectively. A very strong association was found between post COVID-19 GI symptoms and mental health symptoms (51).

Future Perspectives: Confirmation of fecal-oral transmission would warrant implementation of stool PCR (polymerase chain reaction) to confirm viral clearance which may help in minimizing spread of infection. Isolated GI symptoms should be considered by physicians in appropriate context to prevent delayed diagnosis and adverse outcomes. Validated predictive models for adverse outcomes like that in IBD can help in initiation of early therapy and improving outcomes (45). Understanding microbial dysbiosis in COVID-19 and its role in gut-lung crosstalk is important in development of future therapies targeting microbiome.

Conclusion: In this review, we summarized the mechanisms of GI symptoms in COVID-19 infection. Identification of GI symptoms as a sign of early COVID-19 infection can significantly reduce morbidity and mortality. Preventive measures are needed to halt fecal–oral transmission. Treating the primary disease (SARS-CoV-2 infection) is the key to prevent GI injury as specific gut directed therapies are scarce. Probiotics show some promise in maintaining intestinal ecological balance and preventing bacterial translocation although the particular strain that could be helpful is still not known. Given the multifaceted nature of COVID-19-associated gastro-intestinal injury, further translational research is needed to unravel the temporal sequence of events leading to multi-system involvement and adverse disease outcomes in COVID-19 infection.

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Commentary

Mental Health Payment Parity: A Fight for Health Equity

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Highlights:

- Both abroad and domestically, all generations of South Asians experience a rapidly growing incidence and prevalence of mental illnesses such as depression, anxiety, and substance use disorders.
- Societal and personal stigma is a reason many South Asians do not seek or receive mental healthcare but once they can overcome these self-imposed barriers, they face a tremendous mental healthcare provider shortage within the United States.
- A major reason for the mental healthcare provider shortage is that most psychiatrists and other types of mental healthcare providers are out-of-network from insurance companies due to lower reimbursement rates compared to primary care providers for the same services, no coverage, and extensive requirements for prior authorization compared to physical health services.
- Though the United States Congress passed a law requiring equal reimbursement for mental and physical healthcare, also known as parity, insurers do not adhere to these requirements which continues to create a major barrier for South Asians attempting to access mental healthcare.

Key Words: Mental illness, Mental health parity laws, South Asian mental health

Background: In 2008, Congress passed the Paul Wellstone and Pete Domenici Mental Health Parity and Addiction Equity Act (MHPAEA) to ensure equal coverage of treatment for mental illness and addiction. It was not until November 2013 that the federal government released rules to implement equal coverage which resulted in some improved coverage of care. Regardless of passing law ensuring parity, adequate mental health care, consisting of psycho-pharmacological care and therapy as well as more intensive services, is not guaranteed particularly if the insurance company operates within a state with weaker parity laws. Insurance plans that follow federal parity requirements, which can ensure better coverage, are typically provided by employers with 51 or more employees, Medicaid Managed Care Plans (MCOs), State Children's Health Insurance Programs (S-CHIP), the Federal Employees Health Benefits Program, and most individual and group health plans purchased outside the Health Insurance Marketplace. Medicare (besides cost-sharing services for outpatient mental health care), Medicaid fee-for-service plans, and plans that received an exemption based on cost increase do not have to adhere to the federal parity laws. (1)

Mental Health Parity: Mental health parity refers to the equal treatment of mental health, substance use disorders, and non-psychiatric health conditions in public and private insurance plans. An insurance plan with parity ensures unlimited psychiatrist and other allied health professional visits for depression and schizophrenia, the way unlimited visits are guaranteed for other chronic conditions such as diabetes. In summary, low payments for psychiatric care by public insurers leads to poor access to care for individuals with mental health needs including minority and immigrant populations.

Mental Illness in South Asians: Prior to the onset of the coronavirus (COVID-19) pandemic, 20.8% of South Asians reported a lifetime prevalence of having ever met criteria for DSM-IV affective, anxiety, or substance abuse disorder (2). Much of the etiology of poor mental health in South Asians in America and their children originate from loss, separation, alienation, and anxiety about the new cultural

environment, challenges with English language communication, immigration status, financial limitations, family and intergenerational stress, and discrimination (3). Despite this epidemic within an immigrant community, South Asians within the United States often express greater personal stigma toward mental illness than other groups (4). Mental illness is also varied across the diaspora, with older South Asian women facing a disproportionate burden of psychosocial stress in the community thought to be due to abuse and neglect, social isolation, intergenerational conflict, and acculturative stress. This depression in older adults can also exacerbate risk for poor physical health and lead to slower recovery from physical illness (5).

This coinciding pattern of high incidence and high stigma regarding mental illness persists in younger generations of South Asians, including those born in the United States. South Asian youth in the United States are more likely to report suicidal thoughts and demonstrate behaviors of self-harm compared to other minority groups, often attributed to interpersonal problems with family members, domestic violence, gender role expectations, and cultural conflicts (6-8). These stressors and the cultural barriers to seeking care have resulted in high incidence of alcohol use. Alcohol use and episodic binge drinking is growing rapidly in South Asian populations due to cultural acceptance, and as a method to demonstrate 'acculturation'. Alcohol is also a common form of "self-medication" to treat existing psychiatric illness attributed to acculturation stressors in lieu of seeking mental health care related to an increase in severe alcohol use disorder, colloquially called alcoholism (9, 10).

It is crucial to maintain an ongoing dialogue regarding South Asian mental health care, particularly in the United States where mental health conditions have not received the same parity as non-mental health related illnesses (sometimes referred to as "physical health", though psychiatric conditions do have established neurobiological origins). While the coronavirus (COVID-19) pandemic has undeniably worsened social, physical, and psychological wellbeing worldwide, the existing unaddressed mental illness in the South Asian community will likely exacerbate with pandemic and parity related barriers. A literature review of the impact of COVID-19 in the Netherlands indicated people with pre-existing mental illness who continued treatment were not as severely impacted by the pandemic as those without depressive, anxiety, or obsessive-compulsive disorders, who showed a greater increase in mental illness related symptoms during the COVID-19 pandemic (11). While no research has occurred on the South Asian population, it is a safe assumption this community, with its severe levels of stigma related to seeking mental health care, is now at a much higher risk of succumbing to individual, family, and community-level morbidity and mortality than before the pandemic.

With the existing and now COVID-19 related worsening risks to the mental health of South Asians, it is critical to ensure equal access and payment for mental health in public (Medicare and Medicaid) and private insurance. There is no existing research on South Asian utilization of mental health resources by generation or how the community is affected by the lack of parity in the United States where access issues are unique to other countries due to the for-profit nature of its healthcare system. Even after overcoming the stigma of seeking mental health care, many individuals struggle to access psychiatric or other therapeutic support due to lack of providers, and due to the widespread lack of parity for mental healthcare.

Reimbursement for Mental Healthcare: A review of 2014 Medicaid claims data found that psychiatrists are often reimbursed by Medicaid less than primary care physicians are when coding for mental or substance use disorders. This disparity is linked to the reason psychiatrists are less likely than primary care physicians to accept patients covered by Medicaid (12, 13) leading to poor access to care and reimbursement. A 2015 analysis by healthcare consultants Milliman reviewed claims records from insurers that provide coverage for nearly 42 million people and found for every $1 primary care receives, mental health providers received 83 cents. As a result, Americans are four to six times more likely to use out-of-network mental health care compared to medical care. There is no updated research on reimbursement rates since 2015, but recent studies maintain that due to these low payment rates and excessive requirements for prior authorizations, all types of mental health providers historically are unwilling to accept any insurance coverage despite a shortage of providers and growing population of individuals with mental illness (14).

Advocating for South Asians: Navigating a mental health access treatment designed with barriers in place is a frustrating and overwhelming experience, even for seasoned physicians. Overcoming stigma towards mental illness is a difficult process for many South Asians with significant added frustration due to an addressable barrier in insurance reimbursement and coverage. Proper access to any psychiatric care, ideally care that demonstrates cultural humility, for South Asians can ensure a reduction and prevention of the growing incidence and prevalence of mental illness in the community. As a policy matter, the sub-optimal payment schedule is a major deterrent to delivery of psychiatric care to individuals struggling with mental health issues and cultural barriers. For psychiatrists, the low payments may deter the acceptance of Medicaid. Physicians of all specialties within the AAPI are invited to support their local mental health management board, National Alliance for Mental Illness (NAMI) chapters, and work with medical associations to fight for true parity and open the door to comprehensive psychiatric treatment with equal access for immigrant communities such as the South Asian community.

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In-Depth Review – Asian American Healthcare Issues Section

Lean Diabetes:
Epidemiology, Pathophysiology, and Clinical Management

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Abbreviations Used:

ADA – American Diabetes Association; **AMA** – American Medical Association; **BF** – Body Fat; **BMI** – Body Mass Index; **CDC** – Centers for Disease Control and Prevention; **HOMA-IR** - Homeostatic Model Assessment of Insulin Resistance; **hs-CRP** - *high-sensitivity C-reactive Protein;* **ICMR** – Indian Council of Medical Research; **LADA** – Latent Autoimmune Diabetes in Adults; **LD** – Lean Diabetes; **MHNW** – Metabolically Healthy Normal Weight; **MODY** – Maturity-onset Diabetes in Young; **MONW** – Metabolically Obese Normal Weight; **NCD** – Non-communicable Diseases; **NIH** – National Institutes of Health; **NIDDM** – Non-insulin Dependent Diabetes Mellitus; **NWNO** – Normal Weight Non-obese; **NWO** – Normal Weight Obese; **OWNO** – Overweight Non-Obese; **OWO** – Overweight Obese; **PCOS** – Polycystic Ovary Syndrome; **T1DM** – Type 1 Diabetes Mellitus; **T2DM** – Type 2 Diabetes Mellitus; **WHO** – World Health Organization

Abstract: Overweight and obesity are established risk factors for type 2 diabetes mellitus (T2DM). However, a significant proportion (11-25%) of diabetic patients are normal or underweight as determined by their BMI, leading to the term Lean Diabetes (LD). Also known as Atypical Diabetes, Malnutrition-related Diabetes, Tropical Diabetes, and other names, LD does not meet the classical ADA/WHO classification of T2DM and is more like a hybrid of T1DM and T2DM. Epidemiologically, LD is predominantly seen in men of Asian or African ancestry of lower or middle socioeconomic status, with history of childhood malnutrition. Within these susceptible populations, there are ethnic and gender differences in the characteristics and manifestation of LD, while sharing the same underlying pathophysiology of impaired insulin secretion and increased insulin resistance. Central to the susceptibility of Asian Indians to LD are evolutionary origin of smaller body structure with low lean mass, and the thin-fat Indian babies born with low lean body mass and relatively higher percentage of body fat. Maternal nutrition during pregnancy has significant role in the birth of thin-fat Indian babies, while certain postnatal conditions can sustain the growth of lean children leading to LD in adulthood. Recent studies brought out molecular evidence for maternal factors programming fetal cardiometabolic development. Clinically, LD has an early age of onset, severe hyperglycemia with absence of ketosis on withdrawal of insulin and has higher combined cardiovascular and non-cardiovascular mortality rate as compared to obese diabetics. The LD patients also have higher prevalence of microvascular complications of diabetes. Currently, there are no specific guidelines for the clinical management of LD. Therapeutic strategies should aim to increase insulin secretion and decrease insulin resistance. To achieve this goal, a combination of GLP-1 receptor agonist (to increase insulin secretion) and a glitazone (to decrease insulin resistance) appears to hold promise. However, randomized control trials in large number of susceptible populations must lead to formulation of specific guidelines using anti-diabetes medicines within the reach of the affected populations. Considering that Asia harbors over 300 million diabetes patients, a significant proportion of whom are lean, the problem of LD is huge and so it needs global response. This review provides a comprehensive and in-depth presentation of epidemiology, pathophysiology, and clinical management of LD.

Key Words: Lean Diabetes, Atypical Diabetes, Tropical Diabetes, Obesity, Body Mass Index, Non-communicable Diseases, Insulin Resistance, Thin-fat Indian Baby, Gestational Diabetes, Maternal Nutrition, Fetal Programming

Prologue: Experimental, clinical, and epidemiological evidence link overweight (BMI 25-30 kg/m^2) and/or obesity (BMI > 30 kg/m^2) to developing type 2 diabetes mellitus (T2DM) and metabolic syndrome. According to World Health Organization (WHO) Global Report 2016, obesity is a major burden in the development of T2DM (1). Obesity predisposes to development of T2DM by causing insulin resistance through increased inflammation in adipose tissue, increased release of free fatty acids, glycerol, hormones, pro-inflammatory cytokines, and other factors (2). In June 2013, the American Medical Association (AMA) officially recognized obesity as a disease (3). Obesity is the 5th leading cause of death, and is the second preventable cause of death, just trailing behind deaths due to nicotine use. About 30% of overweight people have diabetes, and 85% of diabetic patients are overweight or obese. According to the Centers for Disease Control and Prevention (CDC), in the United States about 37 million people (1 in 10) have diabetes, of which 90-95% suffer with T2DM (4). Thus, overweight and obesity are intricately related to T2DM, leading to coining of the term "diabesity" to describe the combined adverse health effects of obesity and diabetes mellitus (5). Public health officials are concerned that diabesity is becoming an epidemic worldwide. It is estimated that by the year 2040 there will be 6-fold increase in the number of obese adults in the world resulting in 642 million diabetic patients (5). At present there are about 77 million individuals with diabetes mellitus in India, the second largest after China (116 million). About 57% remain undiagnosed. By the year 2045, the number of diabetes patients in India will reach 134 million (6).

While the link between overweight/obesity and diabetes mellitus is well-established, it was found that significant number of Asians and African Americans exhibit a unique lean diabetic (LD) phenotype. More Asians are falling into this category, thus increasing the pool of LD. Similarly, significant number of African Americans are also exhibiting LD. Studies revealed that LD is a distinct class of diabetes, often a hybrid of T1DM and T2DM, with typical history, distinctive pathophysiology, and clinical features with complications, thus posing challenges in management. Hence, in this review we will present the epidemiology, pathophysiology, and clinical management of LD.

Epidemiology of Lean Diabetes: Lean diabetes is seen predominantly in men of Asian or African ancestry with low or middle socioeconomic status and with a history of childhood malnutrition. Geographically, LD is often seen in tropical countries, including India and sub-Saharan Africa.

Lean Diabetes in Asian Indians: As per the recommendation of the WHO, the cut-off limits for normal and underweight categories among Asians are BMI 18.5-22.9 kg/m^2, and <18 kg/m^2, respectively (7). Table 1 shows the cut points for overweight and obesity indicators used for South Asians and Westerners. A 1997 study performed on 9,873 non-insulin dependent diabetes mellitus (NIDDM) patients in Chennai, India, identified 374 (3.5%) as lean diabetics (BMI < 18.6 kg/m^2), 6,274 patients (63.5%) with ideal body weight, and 3,252 patients (32.9%) with obesity (7).

Table 1: Cut Points for Overweight and Obesity Indicators Used for South Asians vs. Westerns

Indicators	South Asians	Westerners
Body Mass Index (BMI) kg/m^2		
Underweight	< 18.5	< 18.5
Normal Weight	18.8 to 22.9	18.5 to 24.9
Overweight	23.0 to 24.9	25.0 to 29.9
Obese I	25.0 to 29.9	30.0 to 34.9
Obese II	30.0 to 34.9	35.0 to 39.9
Obese III	35.0 to 39.9	> 40.0
Waist Circumference (cm)		
Men	≥ 90	≥ 102
Women	≥ 80	≥ 88
Waist Hip Ratio		
Men	≥ 0.9	≥ 0.9
Women	≥ 0.8	≥ 0.8
Body Fat Percentage		
Men	≥ 20%	≥ 25%
Women	≥ 33%	≥ 35%

Adopted from Kapoor N, Endotext [Internet] 2021 (12)
https://www.ncbi.nlm.nih.gov/books/NBK568563/ Creative Commons License. Attribution-NonCommercial-NoDerivs 2.0 Generic (CC BY-NC-ND 2.0)

However, data from other parts of India, reported much higher prevalence of LD among T2DM patients. In a prospective study sponsored by the Indian Council of Medical Research (ICMR), involving 9 centers in India, the prevalence of LD varied from 11 to 25% (9, 10). The leanness in patients of this ICMR study persisted even after five years of follow up period, suggesting that leanness was the inherent characteristic of these individuals (9, 10). Interestingly, studies conducted in India also suggested that LD was not strictly associated with lower socioeconomic status as over 80% LD patients were from middle socio-economic class, with no evidence of dietary protein deprivation (11). Thus, basically, up to 80% of

T2DM patients in India are not obese, whereas in the Western countries 60-80% of T2DM patients are obese (10).

Lean Diabetes in East Asians: A prospective analysis of 37,091 men and women aged 45-74 years in the Singapore Chinese Health Study revealed that starting with BMI 18.5-23.0 kg/m^2, the risk of T2DM significantly increased, and continued in a monotonic fashion across the spectrum of BMI. Thus, BMIs considered as lean or normal in Singapore Chinese are strongly associated with increased risk of T2DM (13). In a 9-year population-based cohort study in China (China National Diabetes and Metabolic Disorders Survey), the risk of developing diabetes in normal weight obesity (NWO) was investigated (14). NWO was defined as normal BMI (<24 kg/m^2) but with an excess body fat (BF) (≥ 24% in men; ≥ 33% in women). Of the 1128 individuals participated in this study, 528 (47%) were normal weight non-obese (NWNO), 118 (10.5%) normal weight obese (NWO), and 63 (5.5%) were overweight non-obese (OWNO), and 419 (37%) were overweight obese (OWO). During the study period, 113 individuals (10%) developed diabetes. Cox multivariate regression analyses revealed that Chinese people with NWO are at increased risk of developing diabetes, suggesting the need to incorporate body fat percent measurement into the regular physical examination in medical practice in China (14).

Lean Diabetes in African Americans and Latinos: African Americans have a higher risk for T2DM, due to genetic traits, higher prevalence of obesity, and insulin resistance (15). Studies revealed that both African Americans and Latinos were prevalent ethnicities with LD apparently due to rapid pancreatic β-cell failure (16). However, further analyses showed that LD in the United States minority population is more prevalent in men than women (62% vs. 48%) and is associated with alcohol use (5.7% vs. 2.4%) as compared to obese diabetic subjects. The etiology of higher prevalence of LD among minority populations in the United States is not clear, but may be related to acquired factors, genetics, and autoimmune disorders. Caucasians and African Americans have greater insulin sensitivity as compared to other races/ethnic groups, such as East Asians and South Asians as assessed by direct measurement of insulin-mediated glucose utilization (17). Lean African Americans have higher fasting insulin levels when compared to Caucasians or Mexican Americans. However, overweight Mexican Americans have higher fasting insulin levels when compared to Caucasians or African Americans. These differences are more pronounced in women than in men (18). The factors responsible for these observed differences are yet to be investigated, but they do caution us about designing screening programs.

Lean Diabetes in Europeans: In a cohort of 37,870 T2DM patients in German DIVE (Diabetes Versorgungs-Evaluation) and DPV (Diabetes-Patienten-Verlaufsdo-kumentation) database, LD was associated more with use of nicotine and alcohol (19). However, in a Danish Diet, Cancer, and Health cohort of 37,053 men and women, aged 50-64 years at baseline (1993-1997) lean body mass was not associated with incident T2DM (20).

Insulin Resistance in Lean Women: In recent years much attention has been drawn to insulin resistance in women vis-à-vis their ethnicity, BMI, and health status revealing new findings. Compared to Caucasian females, the prevalence of obesity and insulin resistance is higher in African American females, apparently due to metabolic inflexibility to switch between carbohydrates and lipids in peripheral tissues, such as muscles based on the availability of the substrates (21). Premenopausal African American women, with greater skeletal muscle volume as compared to Caucasian women have significantly higher insulin resistance, although Caucasian women tend to have greater intra-abdominal adipose tissue with higher levels of inflammation (22). Insulin sensitivity is lower among African American women independent of obesity, fat distribution, inflammation, and lipotoxicity (23, 24). A study from China conducted on postmenopausal women found that individuals with normal weight central obesity also had a significantly higher prevalence of metabolic syndrome when compared to normal weight individuals without central obesity (25).

Insulin Resistance in Lean Polycystic Ovary Syndrome: Polycystic ovary syndrome (PCOS), which affects about 4-12% of women during their reproductive age, is a complex endocrine and metabolic disorder, characterized by hyperinsulinemia and hyperandrogenism. PCOS is associated with increased risk of T2DM, metabolic syndrome, cardiovascular diseases, and endometrial cancer. PCOS has two phenotypes, one lean and another obese with different biochemical, hormonal, and metabolic profiles (26). Lean PCOS patients have higher insulin levels in their blood than those without PCOS (27), The reported prevalence of insulin resistance among lean PCOS patients is 6-22% (28, 29). Lean women with PCOS have a 3-10% incidence of undiagnosed diabetes (26). An observational study reported two clear phenotypic variations among

Indian women with PCOS, obese hyperinsulinemic dysglycemic women from Delhi and lean hyperandrogenic women from Srinagar (28). A retrospective study from Turkey reported that 47% of lean PCOS patients have insulin resistance (29). These reports underscore the need for testing all lean women with PCOS for glucose intolerance and the presence of metabolic syndrome (30).

Gestational Diabetes in Lean Women: Gestational diabetes, which occurs in about 2-10% of pregnancies in the United States, is often due to insulin resistance and/or diminished hepatic insulin extraction or inability to utilize insulin because of hormonal changes that happen in pregnancy. It can be also due to increased need for insulin during pregnancy, or because of hormonal activity of placenta, which can potentially increase glucose pools of the body. A recent study from Japan reported that leaner women with impaired insulin secretion account for about 40% of gestational diabetes mellitus (31). It has been reported that lean Japanese pregnant women with gestational diabetes mellitus have impaired pancreatic β-cell function, which may be associated with hereditary traits (32). About 20% of lean gestational diabetics in Japan required intensive insulin therapy during pregnancy, suggesting that it may be associated with insulin resistance (33). In a study from Austria, it was found that pronounced insulin resistance and inadequate β-cell secretion are characteristic features of lean gestational diabetes during and after pregnancy (34). Thus, the defective insulin secretion in lean gestational diabetes sets it apart from prediabetic condition or other forms of gestational diabetes.

LADA and MODY: Uncommon Diabetes Types: Latent Autoimmune Diabetes in Adults (LADA) and Maturity-onset Diabetes of the Young (MODY) are two uncommon types of diabetes mellitus, that do not fit neatly into T1DM or T2DM. They share some features of both these classical types of diabetes. Knowledge of these two uncommon types of diabetes helps in differential diagnosis with mixed feature of T1DM and T2DM. LADA, caused by antibodies attacking insulin-making cells in the pancreas, usually starts after 35 years in non-obese subjects, and it shares genetic, immunologic, and metabolic features with both T1DM and T2DM. Hence, it is also known as type 1.5 DM. LADA is insulin-dependent for the first 6 months after diagnosis, and the American Diabetes Association lists it as T1DM. Checking for antibodies against insulin-making cells of pancreas in the blood clinches the diagnosis (35, 36). On the other hand, MODY has an adolescent or young adult onset (before 25 years) in non-obese subjects, progresses slowly, and is often associated with a family history of diabetes. MODY diabetes is caused by autosomal dominant inheritance (37, 38).

Origin of Low Lean Mass in Asian Indians:

Compared to the Westerners, Asian Indians have low lean mass tissue relative to height, which makes them susceptible to T2DM, especially when accompanied by overweight or obesity. Asian Indians have higher proportion of fat mass in their body as compared Westerners. Figure 1 shows the diabetic risk in Asian Indians as a function of three dimension of body size. The length (A), and cross-sectional area (B) of an internal cylinder of lean mass (C) is considered as a marker for metabolic capacity, whereas the volume of the external cylinder of fat mass is considered a marker for metabolic load. As illustrated in Figure 2, Asian Indians have relatively greater adipose tissue vs. lean mass, which increases metabolic load at the given BMI, thus the risk for insulin resistance at a lower BMI as compared to Europeans or Caucasians (39).

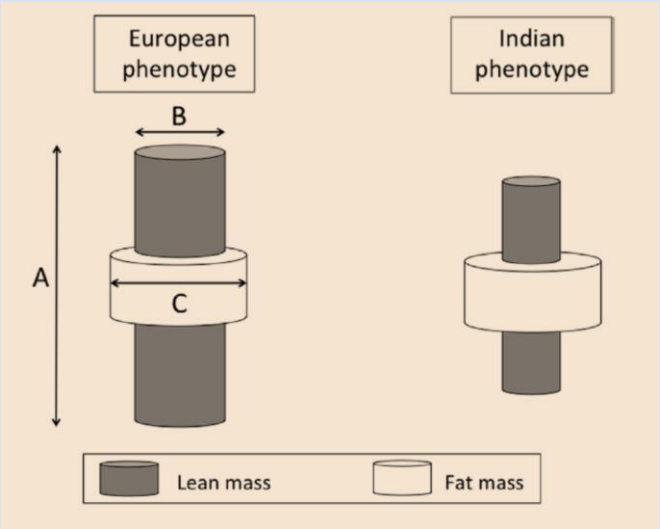

Figure 1: Schematic diagram illustrating diabetic risk as function of three dimensions of body size. The length (A) and cross-sectional area (B) of an internal cylinder of lean mass is considered a marker for metabolic capacity, whereas the volume of the external cylinder of fat mass (C) is considered a marker of metabolic load. (From: *Wells et al, Font Pub Health, 2016 (39)*; Creative Commons Attribution 4.0 International CC BY 4.0)

Furthermore, due to their low lean mass, Asian Indians have reduced ability to clear glucose load as compared to Europeans or Caucasians. The resulting reduced metabolic resilience predisposes Asian Indians to develop T2DM at a relatively younger age as compared to Europeans or

Caucasians (39). An Indian National Family Health Survey 2005-2006 revealed that 10% of both fathers and mothers exceeded BMI of 23.5 kg/m^2, the cut-off for overweight in the Indian population (40).

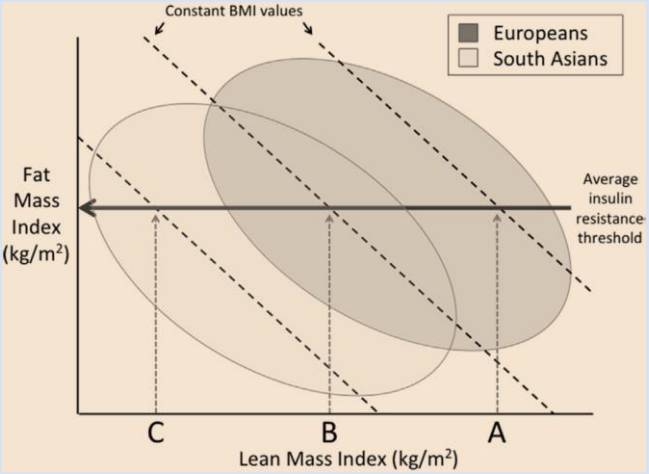

Figure 2: Schematic diagram illustrating differences between Europeans and South Asians on a plot of fat mass index (fat mass divided by height squared) and lean mass index (lean mass divided by height squared), in which the sum of these two traits is equal to body mass index (BMI). Above a certain threshold of fat mass index, insulin resistance develops. However, due to their lower lean mass index, Asian Indians develop insulin resistance at lower levels of BMI compared to Europeans. (From: *Wells et al, Font Pub Health, 2016 (39)*; Creative Commons Attribution 4.0 International CC BY 4.0)

While an increase in maternal BMI even by 1 unit is associated with a lower relative risk for childhood undernutrition, within the context of Asian Indians, that considerably increases the metabolic load, especially when it is not matched with increased metabolic capacity. Due to this imbalance between metabolic capacity and metabolic load, even a moderate increase in metabolic load results in substantial metabolic penalties in Asian Indians, such as diabetes mellitus, metabolic syndrome, and cardiovascular diseases (39).

Evolutionary Basis for Low Lean Mass in Asian Indians: Anthropometric evaluation of skeletons of Asian Indians spanning over the past 11,000 years for lean mass and stature in comparison with a worldwide sample revealed that stature-adjusted lean mass increase in Asian Indians over that period was very minor as compared to other ethnic populations. As compared to other worldwide populations the stature of Asian Indians decreased sharply when agriculture was adopted in early Holocene (about 9,000 years ago) (41). So, it seems the early adoption of agriculture and settling down in plains in Indian subcontinent leaving their hunter-gatherer lifestyle, might be responsible for the decreased stature and lack of significant increase in lean mass, which effectively decreased the metabolic capacity of modern Asian Indians. These phenotypic changes that occurred over 9,000 years might have resulted from a combination of genetic mutations and epigenetic effects, which were carried over generations of Asian Indians. Thus, the modern Indians are genotypically and phenotypically conditioned so much, that they are susceptible to T2DM whether they are living in India or abroad (39). This phenotypic profile cannot be changed within a short period of time or over years, especially because modern lifestyle of increased metabolic load works against any attempts to change. This phenomenon has been well documented in the two published studies on Asian Americans, namely the MASALA (Mediators of Atherosclerosis in South Asians Living in America) and Multi-Ethnic Study of Atherosclerosis (MESA), which have been recently reviewed (42-45).

Thin-Obese Paradox Babies of India: Compared to babies of Caucasians, Asian Indian babies are born with a 'thin-fat phenotype', comprising thin muscles and relatively more adipose tissue (46).

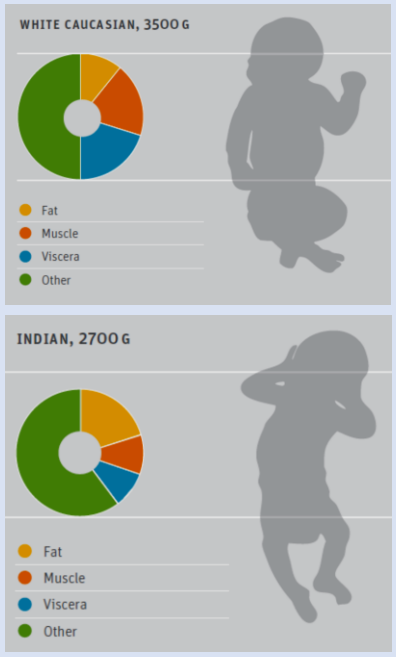

Figure 3: Thin-Fat Indian Baby: A schematic diagram to compare the body composition of Indian and white Caucasian babies. Indian babies were ~800 g lighter; muscle thin but more adipose tissue compared to the white babies. Reproduced from: Deshmukh et al, *Sight Life Mag* 2011 (46) under Creative Commons Attribution 4.0 International License https://creativecommons.org/licenses/?lang=en

The thin-obese paradox babies in India perpetuate the susceptibility of Asian Indians to T2DM as well as LD. A study that compared the body size, and fat mass of babies born in rural India with Caucasians born in Southampton, United Kingdom revealed these findings (47).

The Indian mothers were younger, lighter, shorter and had lower mean BMI (18.2 $kg.m^2$) as compared to Southampton mothers (23.4 kg/m^2). Compared to Southampton babies, the Indian babies were small and thin (mean birthweight: 2.7 kg vs. 3.5 kg). However, the Indian babies preserved subscapular skinfold thickness thus showing preserved body fat. This thin-obese paradox babies in India with its origin *in utero*, potentially fosters early onset diabetes in adulthood, including LD. The 'thin-fat phenotype' found in Indian newborns remains throughout infancy and childhood (48). Furthermore, it has been documented that truncal adiposity is present at birth and in early childhood in South Indian children, and its significant predictors being maternal BMI and socio-economic status (49). The same study also reported that at four years subscapular skinfold thickness in South Indian children is significantly larger than those in UK children (49). Figure 3 schematically compares the body composition of Indian newborn with Caucasian newborn (46). The Indian newborns have low muscle mass and small abdominal viscera but preserved subscapular skinfold. This composition may persist postnatally thus predisposing to insulin resistant state (47, 50).

Role of Maternal Nutrition During Pregnancy on the Birth of Thin-Fat Indian Babies: Evidence is emerging that maternal nutrition, especially regarding micronutrients such as folate and vitamin B_{12}, play a significant role in the birth of thin-fat Indian babies, who are prone to develop insulin resistant and diabetes at later stage in life (46, 51). Besides central obesity, infections in childhood may amplify insulin resistance due to cytokine production (52). The role of fetal programming in obesity-adiposity and non-communicable diseases (NCD) in the adulthood is increasingly recognized. The risk of obesity-adiposity-related NCDs is profoundly influenced by intrauterine and postnatal environmental modifications of the epigenome. It is becoming increasingly clear that a substantial proportion of adult health is programmed *in utero*. In this context, both maternal undernutrition and overnutrition contribute to NCDs (Figure 4). And in rapidly emerging economies such as India, these two can co-exist in parallel thus making it a major and tougher public health problem to tackle (53).

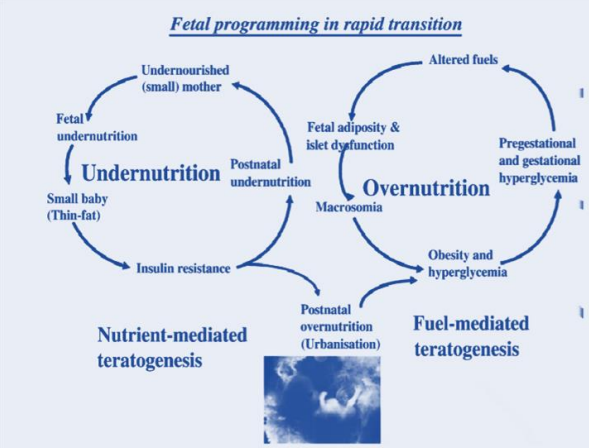

Figure 4: Consequences of maternal undernutrition and overnutrition on fetal programming and their interrelationship. Undernourished mothers produce small (thin-fat) insulin resistant babies. If these thin-fat babies remain undernourished in postnatal life, the cycle is propagated. Conversely, if these thin-fat babies are over nourished, they become obese and hyperglycemic. An obese and hyperglycemic mother produces a "macrocosmic" baby at higher risk for obesity and hyperglycemia. Thus, an intergenerational insulin resistance-diabetic cycle is propagated through a female child. Rapid transition shifts the balance from undernutrition to overnutrition and contributes to escalation of the diabetic epidemic. Improving health of a female child is of paramount importance in controlling the diabetic epidemic. Image and caption are reproduced with permission from: *Yajnikik CS, Ing J Gynecol Obstet 104:S27-S31, 2009* (54).

For example, although in theory the thin-obese paradox of Indian newborns can be reversed by improving maternal nutrition during pregnancy, in the absence of a counterbalancing metabolic capacity, such an increased metabolic load may precipitate gestational diabetes in mothers. Carefully planned nutritional programs to ensure proper intake of micronutrients, with balanced macronutrients and increasing the metabolic capacity of expectant mothers through walking and such other physical activities are needed. This emphasizes the need to educate pregnant mothers or women of reproductive age as a national program of high importance if India has to manage burden of rapidly evolving NCDs. It is not only T2DM, but also other NCDs are disproportionately higher among Asian Indians as compared to Westerners, as revealed in a recent study (12). As shown in Figure 5, the prevalence of diabetes, hypertension, and dyslipidemia in normal weight Asian Indians constitute bulk of the disease population as compared to obese individuals. In 2011, NCDs accounted for 60% of all deaths and 44% of disability-adjusted life-years (DALYs) lost in India (12).

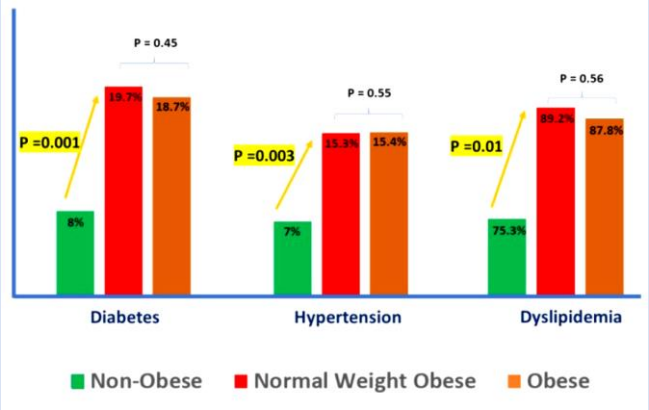

Figure 5: Prevalence of diabetes, hypertension, and dyslipidemia in individuals with normal weight obesity as compared to non-obese and overtly obese individuals. The prevalence of cardiometabolic risk factors were similar to individuals with obesity. After adjusting for other risk factors the odds of normal weight obese individuals having T2DM was 2.72 (95% CI:1.46 – 5.08) as compared to non-obese individuals. Reproduced From: *Kapoor N. Endotext 2021 (12)* Under Creative Commons License Attribution-NonCommercial-NoDerivs 2.0 Generic (CC BY-ND 2.0).

Maternal Factors Programming Fetal Cardiometabolic Development: Besides the above-described maternal nutritional issues, recently a novel possibility that an adiposity-related maternal factor crossing the placenta to reprogram fetal cardiometabolic development pathways has been discovered by Robert J. Freishtat and his team at the Children's Research Institute, Washington DC. They identified adipocyte-derived exosomes (nanoparticle sized subcellular vesicles) that can cross the placenta and their microRNA contents are predicted to alter developmental pathways of gene expression. The US National Institutes of Health has funded a project for further investigation as a collaboration between the Children's Research Institute, Washington DC and King Edward Memorial Hospital, Pune, India (55). If established in further studies, this novel concept that maternal factors are capable of programming adiposity at birth and cardiometabolic development, may prompt a paradigm shift in the global war against obesity from nutritional and lifestyle changes in adulthood to prenatal, perinatal, and postnatal maternal nutrition and fetal/infant care. Although most cases of T2DM could be prevented or controlled by adoption of healthier lifestyle, however, improvement in prenatal and postnatal nutrition and care will have a much stronger impact in preventing or reducing the obesity pandemic, especially in the rapidly developing countries, which are also the most populous ones (56). This may also hold good for other NCDs, such as hypertension, dyslipidemias etc.

Limitation of BMI as a Measure of Adiposity Across Populations: BMI is not reliable measure of adiposity, especially when considering different ethnic population. So, as shown in Table 1, different cutoff points were given for South Asians vs. Westerners. Chittaranjan S. Yajnik, M.D. of King Edward Memorial Hospital Research Center, Pune, India, and John S. Yudkin, FRCP of International Health and Medical Education Center, University College of London, United Kingdom, who did extensive research on low birth weight and insulin resistance and diabetes in later life illustrated the limitations of BMI as a measure of adiposity by comparing the BMI and adiposity of their own bodies in Figure 6.

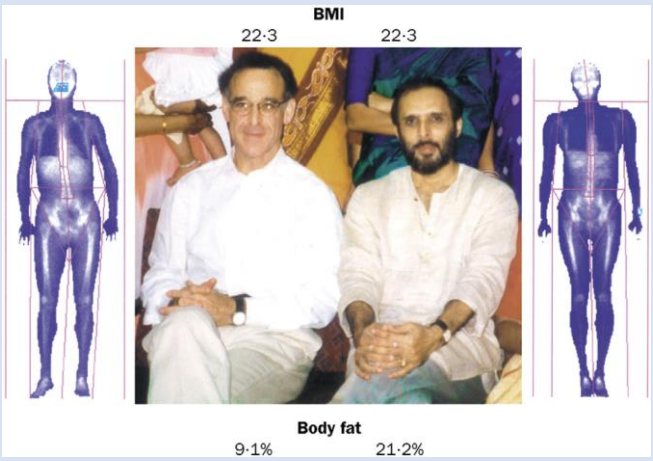

Figure 6: Two physician-scientists, Dr. John S. Yudkin (left) and Dr. Chittaranjan S. Yajnik (right) share a near identical BMI (22.3), but as dual X-ray absorptiometry imagery shows where the similarity ends. Dr. Yajnik has a substantially more body fat (21.2%) than Dr. Yudkin (9.1%). Lifestyle may also be relevant. Dr. Yudkin runs marathons whereas Dr. Yajnik's main exercise is running to beat the closing doors of the elevator in the hospital every morning. The contribution of genes to such adiposity is yet to be determined, although the possible relevance of intrauterine under-nutrition is supported by Dr. Yajnik's low birthweight. Thus, this image illustrates the role of both birthweight and lifestyle practices in body composition. *Image and caption are reproduced with permission from: Yajnik CS, Yudkin JS, Lancet 363: P163, 2004 (57).*

Thin-fat Phenotype in South Asian Population: As shown in Figure 7, several factors have been implicated in the pathogenesis of thin-fat phenotype in South Asian population. Although the overall prevalence rates of overweight and obesity are increasing in South Asia, which harbors numerically large number of overweight and obese subjects, however, disproportionately large percentage (up to 80%) of T2DM patients in South Asia are low to normal weight, whereas 60 to 80% of T2DM patients in the West are overweight or obese.

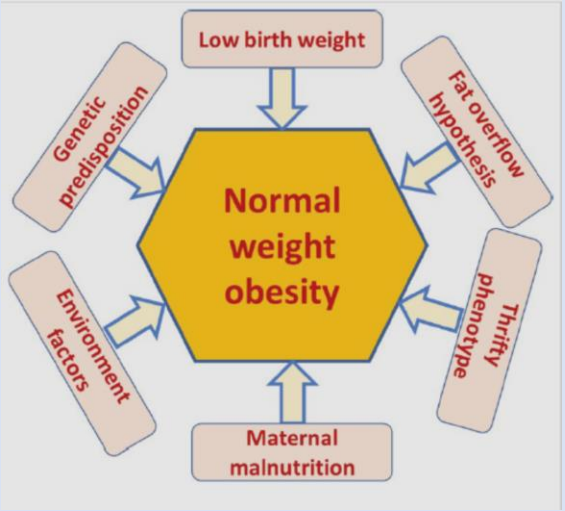

Figure 7: Key factors implicated in the pathogenesis for developing thin-fat phenotype in South Asian population. Reproduced From: *Kapoor N. Endotext 2021 (12)* Under Creative Commons License Attribution-NonCommercial-NoDerivs 2.0 Generic (CC BY-ND 2.0).

So, LD is a real problem in South Asia. Factors such as increased urbanization, increased consumption of calories (metabolic load), decreased physical activity (metabolic capacity) are the obvious factors, which can be remedied to certain extent, Yet, we still have to understand more about genetic predisposition, low birth weight, maternal nutrition, and environmental factors to comprehensively address the problem of thin-fat phenotype in South Asian populations.

Pathophysiology of Lean Diabetes: The pathophysiology of LD is not yet fully understood. There are many aspects of LD which we do not know. However, LD patients have certain characteristics, complications, and have a higher mortality rate compared to obese individuals. Central to the pathophysiology of LD is the dysfunctional balance between insulin secretion and insulin resistance, resulting in a phenotype that is hybrid of T1DM and T2DM. The pathophysiology of insulin resistance seen in LD patients is comparable to the one in obese patients. But the defect in insulin secretion in LD patients is often more severe compared to obese phenotype (58). Until we understand the pathophysiology of LD, management of this condition is challenging. In these sections we will describe some of the known pathophysiological features of LD.

Metabolically Obese, Normal Weight (MONW) Phenotype: The prevalence of MONW, which forms the basis for LD, varies from 5% to 45% depending on social and demographic factors as well as in defining the parameters (59).

Table 2: Metabolic Characteristics of MONW and MHNW Individuals

Parameter	MONW	MHNW
Body Mass Index	Low	Low
Visceral Fat	High	Low
Fat Mass (as % of Body Mass)	High	Low
Lean Body Mass	Low	High
Insulin Sensitivity	Low	High
Liver Fat	High	Low
Serum Triglycerides	High	Low

Adopted from *Karelis et al, 2004 (61)*

MONW phenotype is associated with high prevalence of cardiometabolic dysregulation, metabolic syndrome, and cardiovascular risk factors. In women, MONW is independently associated with increased risk of cardiometabolic mortality (60). Table 2 shows differences in metabolic characteristics between metabolically obese, normal weight (MONW) and metabolically healthy, normal weight (MHNW) individuals (61). These characteristics can be evaluated easily in a clinical setting, except insulin sensitivity. Table 3 lists the cardiometabolic abnormalities to be considered in the patients. To be considered as MONW, the subject should have BMI <25 kg/m^2 and two or more cardiometabolic abnormalities (62).

Table 3: Cardiometabolic Abnormalities to be Considered in Patients

	Cardiometabolic Abnormalities to be Considered in Patients
1	High Blood Pressure ≥ 130/85 mm Hg or use of antihypertensive medications
2	High fasting serum triglyceride levels ≥ 150 mg/dL
3	Low HDL cholesterol level <40 mg/dl (men) or <50 mg/dL (women) or use of statins
4	High blood glucose levels ≥100 mg/dl (fasting) or use of anti-diabetic medications
5	Insulin resistance: HOMA-IR >5.13 (90th percentile)
6	Systemic inflammation: hsCRP level >0.1 mg/L (90th percentile)

Adopted from *Wildman et al, 2008 (62)*

Abnormalities in Adipose Tissue of Lean Diabetics: In addition to significantly higher body fat percentage as compared to lean body mass, the LD individuals exhibit specific qualitative and quantitative abnormalities in their adipose tissue. Studies conducted on LD patients in North India revealed the following abnormalities in adipose tissue. Compared to control subjects, LD patients have higher waist circumference, subscapular skinfolds and total truncal fat, and lower calf, total peripheral skinfolds, and total leg fat. The volumes of the following were higher as compared to controls: total abdominal fat (19.4%), total intra-abdominal fat (49.7%), intra-peritoneal fat (47.7%), retroperitoneal fat (70.7%), pancreatic volume (26.6%),

pancreatic volume index (21.3%), and liver span (10.8%). Significant positive correlations were observed between pancreatic volume and BMI, waist, and hip circumferences and other parameters (63). Another study from Chennai, India evaluated adipocyte size, telomere length, and serum adiponectin levels in control subjects, T2DM patients, obese subjects without diabetes and obese subjects with diabetes. The study reported that compared to control subjects, adipocyte size (both subcutaneous and visceral) from diabetic, obese, and obese-diabetic subjects was significantly larger. This was associated with shortened telomere length and hypoadiponectemia. The study concluded that these alterations seen in lean diabetics reflect a state of "metabolic obesity" (64). We knew that adipocyte hypertrophy causes hypoxia, apoptosis, adipose tissue stress, immune cells infiltration, necrosis and fibrosis leading to metabolically unhealthy obesity (65). Under such conditions, adipocytes spill fat metabolites and cytokines into the circulation, instead of storing fat. In the 57th Annual Meeting of the European Association for the Study of Diabetes (EASD), September 2021, it was discussed that outwardly lean diabetics have increased intra-organ fat and by losing weight they can achieve diabetes remission. Based on this and other findings, the concept of "personal fat threshold" has been introduced, whereby people who develop T2DM have stored more fat in their body than their body can manage. These fat depots include fat in the liver and pancreas, apart from subcutaneous and visceral fat, as demonstrated by Misra et al (63) in non-obese T2DM Asian Indians.

Insulin Secretion and Insulin Resistance: Perhaps simultaneous presence of impaired insulin secretion and insulin resistance may be the characteristic feature of LD that sets it apart from T1DM and T2DM and makes it more like a hybrid of these two. Several studies have documented these two abnormalities in LD subjects. While the pathogenesis of insulin resistance in LD subjects is the same as seen in obese individuals, the insulin secretory defects in LD subjects is more severe than in obese individuals (58). A prospective study from Tamil Nadu state in India reported that lean diabetics have severe hyperglycemia (fasting and postprandial) with poor metabolic control. They are more prone to infections. However, their lipid profiles were normal (66). A study from New Delhi, India reported that higher fasting and post-prandial levels of C-peptide, and surrogate measures of insulin resistance (HOMA-IR, Fasting Insulin Resistance Index, and Bennett's Index) in non-obese Asian Indian patients with T2DM are independently associated with intra-abdominal adipose tissue (IAAT) volume and liver span (67). A preliminary report presented at the American Diabetes Association in 2011 that lean, metabolically obese (LMO) subjects have significantly higher liver fat content and higher serum levels of Fetuin-A as compared to normal weight insulin sensitive healthy subjects (68). Fetuin-A is a 65-kDa glycoprotein secreted from both liver and adipose tissue. Fetuin-A levels are associated with impaired insulin sensitivity, and glucose tolerance, and pathogenesis of cardiovascular disorders. Fetuin-A has also been implicated in the impairment of insulin receptor signaling, toll-like receptor 4 activation, macrophage migration and polarization, adipocyte dysfunction, hepatic triacylglycerol accumulation, and liver inflammation and fibrosis (69, 70). Blood Fetuin-A levels can be reduced by weight loss, exercise, metformin, and pioglitazone (70).

Microvascular Complications in Lean Diabetes: In a hospital-based study from Assam, India it has been reported that among diabetes induced microvascular complications, neuropathy was significantly higher (75%) in lean diabetics than normal or overweight or obese diabetics. In contrast, the LD subjects had lower prevalence of retinopathy (40%) and nephropathy (5%), although they had more severe hyperglycemia (71). Similar findings were made by Barma and associates from Imphal, India (72). In both studies, the lipid profile was not significantly deranged in LD patients. Another study from Chennai, India reported that of all NIDDM patients seen the lean diabetic cohort had more severe diabetes with increased prevalence of retinopathy (both background and proliferative), nephropathy, and neuropathy (8). More controlled studies are needed to understand the extent and magnitude of microvascular complications in LD subjects.

Genetic Components in Lean Diabetes: There are reports that specific genetic abnormalities may play role in the LD, especially regarding β-cell function or failure. For example, inheritance of β-cell failure is known in patients diagnosed with the MODY (Maturity-onset Diabetes of the Young), and in permanent neonatal diabetes mellitus. A role for genes affecting glucose-stimulated insulin secretion has been proposed for some polygenic forms of diabetes mellitus (73). Latent autoimmune diabetes of adults (LADA) has been associated with TCF7L2, a gene involved in reduced insulin secretion, and one of the most significant loci for T2DM (73). KCNJ15, belonging to potassium inwardly rectifying channel, subfamily J, member 15 gene have been identified as a risk gene for

T2DM in lean Japanese subjects (74). About half of the diabetic patients in Japan are lean subjects with BMI <25 kg/m^2. The expression of KCNJ15 gene was higher in pancreatic islets of patients with T2DM and knocking down of it in pancreatic cells or in diabetic mice in the lab resulted in two-fold increase in glucose-stimulated insulin secretion (74). Genome-wide association studies from China identified 7 genes associated with the risk for lean diabetes and two with the risk for obese T2DM (75). A genetically engineered human pancreatic β-cell line exhibiting glucose-inducible insulin secretion has also been reported (76). This and other studies offer a hope for correction of genetic abnormalities in β-cell function in lean diabetic patients (77).

Clinical Management of Lean Diabetes: Unlike T1DM or T2DM, there are no specific guidelines for the clinical management of LD. Ironically, despite the rising prevalence of LD, a search of literature does not provide insights into the clinical management of LD. The American Diabetes Association Standards of Medical Care in Diabetes – 2017 publication did not deal with LD (78), thus leaving the burden on the discretionary power and clinical skills of the physicians. It is a challenge to physicians, especially in small urban or rural settings where access to non-routine investigations or laboratory tests are not available to arrive at the best approach and to follow up with prognosis. In the following section, we will provide insights based on the scanty literature available on this subject and the ongoing clinical trials on LD patients.

Determination of BMI, and anthropometric measurements such as waist circumference, ethnicity etc. in the clinic besides fasting and postprandial blood glucose may indicate LD in an individual. Precise assessment of lean body mass vs. fat percentage might not be readily available or expensive in certain communities. When available, they should provide precise information of visceral fat distribution, including fat in the liver and pancreas. Besides pathophysiological heterogeneity, LD patients may also have an immune component, which needs to be investigated. Attention should be paid to find presence of multiple metabolic defects in potential LD patients (79).

Once the diagnosis of LD is established based on various clinical criteria and metrics discussed above, it is better to ascertain the insulin secreting capacity of the patients. Biochemical assay for C-peptide levels in plasma will give a measure of endogenous insulin secretion in patients with diabetes (80). And if facilities are available, insulin sensitivity and/or insulin resistance can be determined using one or more technologies available for clinical use (81). Based on the information obtained thus, the goal is to induce insulin secretion and reduce insulin resistance. In addition, therapeutic strategies to reduce visceral fat, especially in the liver, need to be instituted. Although loss of 5 to 10% of total body weight is associated in significant reduction in hepatic steatosis, this approach is not advisable in LD patients, who are already lean. Instead, strategies involving changes in dietary regimen, physical activity, and exercise, which have potential therapeutic benefits in non-alcoholic fatty liver disease (NAFLD) should be considered (82). Obviously, the LD patients need the assistance of lifestyle management experts also.

Regarding pharmacological interventions, although metformin may lower fasting plasma glucose levels with improvement in oral glucose tolerance, and improve plasma lipid profile, metformin has no or very little stimulatory effect on insulin secretion (83). Adding SGLT2 inhibitors (gliflozins) to the treatment protocol of LD patients may induce euglycemic diabetic ketoacidosis (84).

Recently, there is substantial interest in using GLP-1 receptor antagonists in the management of Asian T2DM patients, including LD patients, apparently propelled by the marketing strategies of big pharma to position the GLP-1 RA in the huge Asian markets, where over 300 million diabetic patients are living. A meta-analysis of 20 randomized controlled trials on GLP-1 mimetics in the management of Asian T2DM with or without overweight/obesity, revealed that the glucose lowering effects of GLP-1 RAs were equivalent among Asian T2DM patients with their added advantages for weight-loss or weight maintenance. So, the study concluded that GLP-1 RAs are optimal medicines for Asian T2DM patients with and without overweight/obesity (85).

A South Asian Task Force comprising endocrinologists from India, Pakistan, Bangladesh, Nepal, Sri Lanka, Afghanistan, and the Maldives evaluated the use of GLP-1 RA in the management of T2DM in South Asia. The consensus report of the task force comprehensively evaluated use of GLP-1 RAs in Asian T2DM, where LD is very prevalent, and published in a peer-reviewed journal (86).

In December 2020, a clinical study was registered by researchers at the University of Leeds, United Kingdom to evaluate the combination therapy with Liraglutide (injectable GLP-1 RA) and Pioglitazone (orally administered

glitazone) (87). The basis for this clinical trial is Liraglutide increases the insulin secreting power of the pancreas, while Plioglitazone reduces resistance to insulin action.

While above initiatives are welcoming developments in the management of LD in South Asians, however, the costs involved in promoting GLP-1 RAs as the main line of treatment of LD in South Asian countries will be prohibitive, besides the fact that most of these drugs are injectables that need refrigeration with relatively shorter shelf life. Orally effective small molecules, with longer shelf-life and moderately priced are more useful in South Asian countries.

Conclusion: LD is emerging as a distinct category of diabetes mellitus affecting a significant proportion of diabetes patients in Asia and people in tropical countries. The epidemiology of LD is well documented. Thanks to numerous studies conducted in Asian countries, such as India, China, and Japan, we are able to understand more about the pathophysiology and clinical manifestations of LD. Even though a substantial proportion of over 300 million diabetes patients in Asia are LD, until now there are no specific guidelines in place for the clinical management of LD. Therapeutic options are also not clearly laid out. Hopefully, the South Asian Task Force of endocrinologists which reached a consensus on LD in South Asia will take a lead in formulating guidelines with recommendations for therapeutic options within the reach of the affected populations in South Asia. The WHO, ADA, NIH, and ICMR should form a joint task force to address the rapidly growing problem of LD in Asia and tropical regions, which are home for the largest numbers of diabetes patients, both obese and lean.

Disclosure: Author is lead inventor on patents for the prevention and/or treatment of diet-induced obesity, and kidney diseases. He is a Co-Founder, President, Chief Executive Officer, and Chief Scientific Officer of ePurines, Inc., a drug development startup focused on purinergic signaling based therapies for obesity, metabolic syndrome, and kidney and liver diseases. Author declares this review article has no relation to drug development program of ePurines, and it has been prepared with no industry or commercial support, and in the capacity of Adjunct Faculty at the University of Utah Health.

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The Young Physicians Section (YPS), and Medical Students, Residents and Fellows (MSRF) section of AAPI conduct joint Winter Medical Conference (WMC) on a yearly basis to promote research activities and social networking amongst the young physicians. This year's WMC was held on March 17-20, 2022, in Tampa Bay, Florida.

This section contains abstracts of the posters presented at the WMC as they are submitted by the YPS/MSRF without editing or peer-reviewing by JAAPI.

Soumya Reddy Neravetla, M.D.
President, AAPI YPS

Ayesha Singh, M.S.
President, AAPI MSRF

WMC-22-001: Survival of Patients with Gastric Cancer amongst PDL1 Expression

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Background: Patients with advanced gastric cancer have poor prognosis despite getting multidisciplinary treatment. Tumor expression of Programmed Death-Ligand 1 (PD-L1) has been associated with unfavorable outcomes in gastrointestinal malignancies. The relationship between prognosis and PD-L1 expression in gastric cancer patients has been studied before with conflicting results. We intended to evaluate the prognostic significance of PDL1 in gastric cancer in terms of overall survivability based on previously published meta-analysis. Methods: We performed an umbrella meta-analysis on previously published meta-analysis data over PubMed (January 01, 2016 to August 1, 2021), utilizing PRISMA guidelines, to investigate the association between PD-L1 expression and prognosis in gastric cancer patients. Review Manager (RevMan) 5.3 was used to estimate the effect size and 95% confidence interval using random-effects models and inverse variance method. We also assessed the between-study heterogeneity (I2). We considered overall survival as the primary outcome. We calculated Hazard Ratio (HR) and obtained a forest plot, considering p-value <0.05 as statistically significant. Results: Of total 567 articles screened; 14 studies were assessed for eligibility. Out of which, three meta-analyses were included for umbrella review with a total of 8,419 sample size. All the 3 studies included in the umbrella review showed that PD-L1 positive expression was associated with low overall survivability in gastric cancer with increased mortality (HR =1.44, 95% CI: 1.24 –1.68, P<0.00001). Interstudy variability (I2) was 0%. (Figure) Conclusion: Our findings reveal that the expression level of PD-L1 in gastric cancer has an inverse correlation with overall survivability and prognosis. Early identification of gene expression may help to tailor the treatment amongst patients with gastric cancer.

WMC-22-002: Under Recognition and Documentation of Hemodialysis Patient Symptoms

Neepa Gupta[1,2], Huei Hsun Wen[2] , Sai Akhila Reddy[2], Kinsuk Chauhan[2], Steve Coca[2], Lili Chan[2], University of Pennsylvania, Philadelphia, PA, USA[1]; Division of Nephrology, Icahn School of Medicine at Mount Sinai, New York, NY, USA [2]

Patients on maintenance hemodialysis (HD) experience a high symptom burden, yet it is unclear whether symptoms are recognized and included into provider documentation. We surveyed patients over the age of 18 from an outpatient HD unit who received thrice weekly maintenance HD treatments. At the end of every treatment for four weeks, we surveyed to assess the presence of 21 symptoms. Surveys were also administered after every treatment to nurses and once during the study period to physicians. Two researchers developed a dictionary of terms and synonyms for the six most frequent symptoms. We used spaCy libraries and pipelining in Python to parse provider notes documented during the four-week study period for these terms. There were 97 patients who participated in the study. The top 6 symptoms experienced by patients were fatigue (60.8%), cramping (58.8%), dry skin (52.6%), muscle soreness (43.3%), itching (41.2%), and intradialytic hypotension (35.1%). Of the 6 symptoms with the highest patient-reported prevalence, nurses under-recognized 5/6 by a mean relative difference of 69.5 ± 25.5%, and physicians under-recognized 6/6 by a mean relative difference of 51.5 ±17.0%. Medical documentation of these symptoms proved even more scarce, with all 6 symptoms being under-reported as identified by natural language processing (NLP) by a mean relative difference of 83.5 ±14.6%. Symptoms that patients report as most bothersome are under-recognized and under-reported, affecting future interventions and symptomatic

management. Routine recognition and evaluation of these symptoms can be highly beneficial for HD patients.

WMC-22-003: Female Infertility in the United States and India: An Analysis of Treatment Barriers and Coping Strategies

Devneet Singh, BS, MBA, Albany Medical College

This research studies barriers to accessing fertility treatment in the United States (U.S.) and India, as well as the coping strategies infertile women use. Barriers include reproductive health knowledge, cost, and politics, while coping is affected by cultural stigma, family, and religion. These two countries were chosen for their different cultural contexts, healthcare systems, and political infrastructure. Ten fertility specialists across both countries were interviewed as expert informants. Reproductive health knowledge was the most important barrier to accessing care in both countries, with similar gaps in understanding when and what type of care to utilize, though social media can educate and empower patients. Cost and politics played a greater role in the U.S. because of access and coverage inequalities by state. For coping, cultural stigma was cited as the most important factor in each country despite the difference in sources of stigma, namely the historical racial differences in who has been able to utilize fertility treatment in the U.S. and the closely intertwined nature of culture and family in India. In both countries, the link between coping and family remains unclear because support is highly individualized. Religion can be a great source of support for many patients, especially in India. Recommendations include providers, patients, and governmental organizations continuing to raise awareness for infertility using media, particularly around infertility diagnosis and treatment and better, age-appropriate reproductive health education. Further medicalization of infertility can ease the burden on individuals and ultimately achieve universal health coverage.

WMC-22-004: Depressive Symptoms and Associated Risk Factors in Hemodialysis Patients: Perspective from a Caribbean Island

Franz Erich Lopez Gonzalez, Medical student, Universidad Autonoma de Santo Domingo; Arsh Chowdhary, MBBS, Smt. Kashibai Navale Medical College and General Hospital, Pune; Prachi Bapat, MBBS, Smt. Kashibai Navale Medical College and General Hospital, Pune

Introduction: End stage kidney disease (ESKD) causes clinical manifestations that may alter the quality of life of patients. Depression is a frequent psychological problem in these patients. Objectives: We assessed the influence of various demographic factors in the severity of depressive symptoms in hemodialysis patients. Methods: An observational, cross-sectional study in the nephrology unit of the main internal medicine reference hospital in the Dominican Republic. Data was collected using a structured, paper-based questionnaire that included various sociodemographic variables and the Center for Epidemiological Studies Depression Screening Index (CES-D) scale, a validated scale in hemodialysis patients that assesses the severity of depressive symptoms. Data was then transferred to the Epi Info 7.2 software, where it was analyzed using means, frequencies, pooled T-test, ANOVA and Pearson correlation coefficient. Results: 81 hemodialysis patients were recruited, with a mean age of 51 (SD=14.35), of whom 56 (69.14%) were male. 41.77% of the population have a high risk for clinical depression (CESD ≥ 16). We found no association with the variables of age, hemodialysis vintage, partnership and physical activity. We found an association of the severity of depressive symptoms and the female sex (Females: 18.67 +/- 11.85, Males: 13.18 +/- 9.68, p=0.03). Also there is a mild negative correlation (r=-0.34, p=0.0018) with the monthly household income. Conclusion: Characterizing the factors associated with depression in hemodialysis patients is important as they may vary across countries. Knowledge of these factors may help improve earlier detection and management of depression, improving patient's outcomes. Key Words: Hemodialysis, Depression, Chronic kidney disease, Nephrology Source: MeSH

WMC-22-005: A Rare Case of Recurrent Myxofibrosarcoma and the Role of Immunotherapy: A New Treatment Strategy

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INTRODUCTION Myxofibrosarcoma (MFS) is a rare malignant soft-tissue sarcoma characteristically presenting as a painless slowly growing mass in the extremities of elderly males. It is a malignant tumour with a high risk of local recurrence and a low risk of distant

metastasis. It tends to become a progressively higher grade in recurrences. Local occurrences of MFS are treated surgically but metastatic presentations do not have effective treatment modalities. The recent development in genomic studies has provided us with an advanced treatment modality in the form of immunotherapy. Programmed Death Ligand 1 (PDL1) is a therapeutic target found in sarcomas. Pembrolizumab, a monoclonal antibody targeting PDL1, is highly effective against tumours with this marker. CASE PRESENTATION A 41-year-old female was diagnosed with MFS of her left leg which was surgically resected. The tumour relapsed 14 months later, in her right shoulder. The size and location of the tumour made her an unsuitable candidate for surgery. The genetic analysis gave an 80% positivity rate for PDL1. 10 cycles of immunotherapy with pembrolizumab a PDL1 inhibitor, was planned. She has undergone 2 out of 10 cycles of immunotherapy, 3 weeks apart. Significant improvement in pain levels was reported after just the first cycle of immunotherapy. DISCUSSION/CONCLUSION Treatment options for metastatic sarcomas are very minimal, consisting of toxic chemotherapeutic drugs. Genomic studies provide a targeted approach for the treatment of metastatic MFS using immunotherapy. With an 80% PDL1 positivity rate, treatment with the first cycle of Pembrolizumab showed a significant improvement in pain levels. Immunotherapeutic medications have a milder side effect profile while being more efficacious.

WMC-22-006: Lifestyle factors and their association with Nonalcoholic fatty liver disease - National Estimate

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Background: Nonalcoholic fatty liver disease (NAFLD) is metabolic dysfunction characterized by excessive lipids build-up which are triglycerides in the liver cells in absence of secondary cause such as alcohol or liver disorders. About 100 million individuals in the United States are estimated to have NAFLD. Data from "The Economic Tsunami of Liver Disease'' revealed that NAFLD, which affects approximately 100 million Americans, costs the U.S. healthcare system $32 billion annually compared with the $34 billion annual costs of strokes. Aim & objective: Primary outcome of the study was to identify the prevalence and epidemiological characteristics of NAFLD amongst participants. Secondary outcome was to evaluate association between the lifestyle factors and NAFLD. Methods: A population-based retrospective cross-sectional analysis performed using NHANES (National Health and Nutrition Examination Survey) database from 2015 to 2018. Lifestyle factors such as dietary fibers, sedentary lifestyle, annual household income, were identified by survey questionnaires. We used SAS 9.4 to perform univariate and multivariable logistic regression analysis to find out prevalence and epidemiology of NAFLD and association of lifestyle factors with NAFLD. Results: Of total 275968, the total number of people 717 (0.26%) was identified with NAFLD. NAFLD was more prevalent in older (median: 62 years), male, Mexican American and other Hispanic, and median household income >$100,000. We also performed multivariate analysis, when we considered lifestyle factors, we found that dietary fiber intake (OR:1.18; 95%CI:1.18-1.19; p<0.0001), sedentary lifestyle (OR:5.11; 95%CI:5,08-5.12; p<0.0001), and absence of exercise/vigorous-intensity activity (OR: 1.47, 95%CI:1,46-1.47 p<0.0001) had higher prevalence and odds of NAFLD Conclusion: In this study, we have identified several lifestyle factors such as dietary fiber, sedentary lifestyle, and non-vigorous exercise were modifiable factors and associated with higher NAFLD prevalence. More in-depth studies are required to develop preventive strategies to reduce these modifiable factors resulting in NAFLD.

WMC-22-007: Fibrocavitory Tuberculosis in Children –A Clinical Profile

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Summary: 1) Background: Epidemiologic data on the clinical profile of fibrocavitory tuberculosis (TB) in children is limited. We evaluated the epidemiologic, clinical, and laboratory features of patients who visited our clinic and were diagnosed with fibrocavitory TB. 2) Methods: Fibrocavitory TB was detected on chest radiography. Clinical symptoms, drug resistance status, and clinical course were extracted from patient charts.

Association between clinical symptoms, radiological scans, clinical course, and treatment were compared. 3) Results: Out of 1761 patients with TB, 88 (4.9%) patients had fibrocavitory TB. Three patients were lost to follow-up and were excluded from this study (N=85). The mean age of patients was 12.1+3 years. Male: Female ratio was 1:4. Malnutrition was seen in 30 (83.3%) of children with bilateral disease and in 28 (57.1%) with unilateral disease (p = 0.01). DR-TB was seen in 42 (64.6%) females and 8 (40%) males (p= 0.05). Treatment completion rates with cavitation involving 1 zone were 26 (53.1%) and 11 (30.6%) involving more than 1 zone (p=0.038). 4) Conclusion: Adolescent girls tend to be more susceptible to fibrocavitory TB and have a higher incidence of DR-TB. Unilateral lung involvement with cavitation is more common as opposed to bilateral lung involvement in children. Malnutrition is seen more in patients with bilateral disease. Treatment outcome is better in patients with 1 zone of lung involved in cavitation.

WMC-22-008: Multisystem Inflammatory Syndrome in Children (MIS-C) following SARS CoV-2 Infection in 5 Children with Tuberculosis.

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Abstract: 1) Background: Pediatric multisystem inflammatory syndrome temporarily associated with SARS COV-2 (PIMS-TS) is a novel syndrome affecting children all over the world. Research regarding the development of PIMS-TS in children with Drug-resistant tuberculosis (DR-TB) is scarce. We aim to describe a case series of 5 patients diagnosed with DR-TB who developed PIMS-TS and their subsequent clinical management, treatment, and outcome. 2) Methods: Patients were diagnosed as cases of DR-TB on sputum GeneXpert and sputum culture-drug susceptibility testing. Patients' diagnosis of PIMS-TS was made as per guidelines issued by the world health organization (WHO). 3) Results: All patients presented with fever, dyspnea, coughing, lethargy, and giddiness. Two patients also showed signs of acute kidney injury. None of the patients required intensive care support. Four patients were treated with human intravenous immunoglobulin (IVIG) and 1 patient with steroids. All patients showed improvement in clinical condition and down trending inflammatory markers post-treatment. 4) Conclusion: The clinical features of PIMS-TS can mimic acute exacerbation of tuberculosis. In this pandemic, clinicians should maintain a high level of suspicion of PIMS-TS in children with DR-TB who present with acute worsening in clinical condition. It is imperative to be able to distinguish between the two and provide timely and appropriate therapy.

WMC-22-009: Scar Endometriosis after Bilateral Tubal Ligation: A Rare Case Report

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Endometriosis is defined as the presence of functioning endometrial tissue outside the uterus. Incidence of scar endometriosis is about 0.03% to 0.15% of all cases of endometriosis. Surgical management is the definitive treatment. The diagnosis is usually confirmed on histopathological examination of the excised tissue. A 30-year-old female presented with a painful abdominal swelling at the incision site after bilateral tubal ligation; the procedure had been performed a year prior to the presentation. The pain was cyclical in nature: starting 7 days prior to menstruation, peaking in intensity during the menstrual cycle, and subsiding 7-8 days after menstruation. Per abdominal examination 7 days post menstruation revealed a nodular swelling at the scar site which was exquisitely tender on palpation. Pain did not respond to medical treatment taken for over 3 months. Definitive treatment with surgical excision was performed. The fibrous tissue had infiltrated the rectus sheath which was dissected to remove it. The diagnosis was confirmed on histopathological examination which showed fibrous tissue and endometrial glands. Bilateral tubal ligation has been associated with a 0.2% risk of scar endometriosis. In this case, the source of endometrial tissue was likely the tubal origin rather than the uterine. Tubal endometriosis occurs in 20-50% cases 1-4 years after tubal ligation. However, complete resolution of symptoms after surgery makes primary endometriosis less likely. The recurrence rate of scar endometriosis after surgery is 4.3%. To prevent such occurrence, careful surgical technique while manipulating endometrial tissue is required. Medical management with estrogen following surgery may be considered to prevent recurrence. Laparoscopic tubal ligation should be favored to reduce the chances of causing iatrogenic scar endometriosis.

WMC-22-010: The Utility of Radiographic and Serum Markers for Diagnosing Sarcoidosis with Ankle Arthritis as the Presenting Symptom: A Case Series in a Recourse Limited Setting

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Sarcoidosis is a granulomatous multisystem disease with an estimated incidence of 14.5 per 100,000 people per year. It has a male to female ratio of 1:2. Ankle arthritis is a significant check point in diagnosis Sarcoidosis. A study revealed that 82% of the patients with sarcoidosis was involved of one or both ankle joints. Thoracic radiologic abnormalities is seen in 90% of the patients. We present the case series of 11 patients with ankle arthritis who were diagnosed with Sarcoidosis in a recourse limited, third world setting. In this study, male to female ratio was 5:6. Mean age for the group was 34.09 years (SD=8.5). Apart from the ankle joint, polyarticular joint involvement was seen in 36% of the cases (n=4). The mean duration of symptoms for the group was 13.6 weeks (SD = 14.13). 18% of the cases had ophthalmic involvement (n=2). The average value of Serum ESR for the group was 60.8 (SD=22.89). The average Serum C-reactive protein was 12.043 (SD=11.82). 90% of the cases had radiographic findings of bilateral hilar lymphadenopathy (n=10). Mediastinal lymphadenopathy was present in 27% of the cases (n=3). Pulmonary parenchymal involvement was seen in 18% of the cases (n=2). After being started on Prednisone (0.5mg/kg OD) and Methotrexate (15mg subcutaneous, weekly), all the patients showed symptomatic improvement at 8 weeks of follow-up. The average cost of diagnostic workup for the group was 42.27$ (SD=8.88). The average income of a resident of Bihar is 436.5$/month. The cost of Transbronchial biopsy and EBUS-TBNA are 330$ and 250$ respectively. The availability of serum ACE tests is also limited. Considering that only 6% of the people in Bihar are covered under health insurance, there is a need for affordable surrogate markers. Increased affordability would enhance healthcare equity in the management of Sarcoidosis.

WMC-22-011: Acute Pancreatitis with Portal Hypertension and Ascites as the Presenting Manifestation of Sarcoidosis: A Rare Case Report

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Sarcoidosis is a multisystem granulomatous disorder with the involvement of two or more organs. Liver involvement is seen in around 10-30 % of patients which is similar to the frequency of eye and extrathoracic lymph node involvement. Most cases of hepatic sarcoidosis are not clinically apparent, only 5% of patients with abnormal liver function tests can progress to liver cirrhosis, portal hypertension, and ultimately liver failure. Sarcoidosis, on occasion, may indirectly involve the pancreas by causing pancreatitis secondary to hypercalcemia. Here, we describe an atypical case of a 34-year-old gentleman who presented with acute abdominal pain radiating to the back for the preceding 3 days along with elevated amylase and lipase levels suggestive of Acute Pancreatitis. Interestingly, he had been complaining of abdominal distension over the last 2 months. Ascites was noted on clinical examination which was found to be high SAAG after diagnostic paracentesis. Liver echotexture was coarsened as noted on abdominal ultrasonography along with a dilated portal vein. Calcium levels were persistently high (11.6 mg/dl). ACE levels were 62 IU/L (raised). HRCT Chest revealed with enlarged calcified bilateral mediastinal nodes. Liver biopsy showed evidence of non-caseating granulomas with presence of Schaumann bodies. After initial stabilization with Nasogastric decompression and guarded IV fluid therapy, our patient was initiated on Prednisone following which there was an improvement in his calcium levels, ascites and overall condition. Although there have been a handful of case reports describing either cirrhosis with portal hypertension or acute pancreatitis as the presenting feature of sarcoidosis, ours is an even rarer case as it describes both Acute Pancreatitis with portal hypertension and cirrhosis as the presenting manifestations of this disease.

WMC-22-012: A Qualitative Analysis of the Impact of a Cultural Affiliation Organization on Medical Student Wellness

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It is well-documented that many medical students battle with feelings of inadequacy, and the reduction of in-person interactions due to the COVID-19 pandemic has exacerbated these sentiments by negatively impacting student mental health. Many people, students included, find a sense of belonging within a cultural group they feel affiliated with, consequently improving wellness and academic success. One of the goals of the student chapter of AAPI (American Association of Physicians of Indian Origin) at Albany Medical College (AMC) is to bring students together and nurture a sense of belonging. Events provide students with opportunities to meet new people, build personal connections, and engage with a sub-community within the larger medical school community. We hypothesize that active cultural affiliation groups, such as our student chapter of AAPI, lead to an improved sense of belonging and well-being amongst medical students. A qualitative study was conducted among medical students at AMC in Albany, New York to study the impact of AAPI on medical student wellness. A questionnaire was distributed via Qualtrics to all medical students on the AAPI e-mail listserv. The survey consisted of 13 open-ended and Likert scale questions assessing student experience with stress, loneliness, and feelings of connection resulting from involvement with AAPI. Survey respondents were first- and second-year medical students (n=13). 81% of respondents identify as South Asian and first-generation immigrants. 88% of respondents reported feeling more connected to their peers and the AMC community at large by being a part of AAPI. 73% of respondents felt somewhat happy or extremely happy after attending an AAPI event. The survey is still active and collecting results. Based on the preliminary results, the AMC chapter of AAPI has an overall positive effect on medical student feelings of belonging and well-being.

WMC-22-013: A case of Bilateral Middle Ear Myoclonus

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Case report - Literature review A case of Bilateral Middle Ear Myoclonus Abstract OBJECTIVE We present a case of 81-year-old man of South Asian origin with Middle Ear Myoclonus. We discuss the heterogeneity of the diagnosis along with the acoustogenic mechanism and pathophysiological process involved. BACKGROUND Middle Ear Myoclonus (MEM) is a rare type of rhythmic tinnitus caused by repetitive contraction of the middle ear muscles. Patients present with symptoms of ear ringing, hissing and bubbling which may be persistent or intermittent. Specific forms of tinnitus such as pulsatile and muscular tinnitus are quite uncommon. Correct identification and differentiation will improve the patient management. METHODS This is a case report and review of literature. The literature search includes middle ear myoclonus, objective tinnitus, myoclonic tinnitus. RESULTS The patient presented with a one-year history of recurrent popping ear sounds. The degree of loudness was constant and rhythmic. On examination, the volume and pitch of tinnitus were more on the right side and feeble towards the left. The symptoms were subjective, on and off, often noted during daytime and absent during sleep. Audiometry revealed mild sensory neural deafness on right. High Resolution Computed Tomography and Magnetic Resonance Angiography were negative. Patient was treated with anxiolytics and ginkgo biloba, had minimal improvement. Hearing aid was prescribed to mask the tinnitus, however the tinnitus persisted upon removal of device. No surgical interventions were attempted. CONCLUSION Middle Ear Myoclonus is a heterogeneous syndrome as the underlying etiology may not necessarily be myoclonus. The possible mechanisms are spasms of the stapedial muscle, patulous Eustachian tubes, underlying tumour , infarction and other vascular etiologies (e.g.sigmoid sinus diverticulum). Management of patient should be done stepwise starting from medical to surgical interventions. Lack of literature and failure to diagnose limit its outcome in patients.

WMC-22-014: Dieulafoy's Lesion: A Case Report of Hemorrhoids and Rectal Hemorrhage.

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Dieulafoy's lesion is a rare vascular malformation of the gastrointestinal tract first described by Paul George Dieulafoy in 1898, it is also called aneurysm of the gastric vessels "Exulceratio Simplex Dieu Lafoy's". It is a rare gastric developmental malformation with 2% incidence of all gastrointestinal bleed and 6.5% causes of Upper GI non variceal bleeding. It accounts for 1.5 percent of all hemorrhage of the lower gastrointestinal tract and though exceptionally rare it has been reported to occur in different organs of the abdomen like the stomach, duodenum, colon, rectum, and the gallbladder.

WMC-22-015: Intramedullary Lipoma of Spinal Cord in a 2-year-old Child - Case Report and Literature Review

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Introduction Non dysraphic Intramedullary lipoma in children is a very rare entity. (1) An unusual case of extensive intramedullary lipoma of the cervicothoracic spinal cord causing spinal compression is described. We made a revision of literature and reported the clinical presentation as well as treatment options for this disease. Case description We present a case of a 2-year-old male child with intramedullary lipoma in the cervico - thoracic region and lack of limb movement since birth, the cause of which remained obscure. In the course of time, he developed abnormal posturing, feeding difficulties and episodes of severe respiratory difficulty, with brief periods of apnea. Craniospinal computed tomography and magnetic resonance imaging (MRI) were diagnostic for intramedullary lipoma. Urgent decompression and partial laminectomy (surgical debulking of lipoma) resulted in intraoperative complication and on-table death. Conclusion High cervical lipomas can present with alarming spinal cord/medullary compression and respiratory symptoms. Diagnosis is confirmed with the characteristic MRI findings of lipomatous tissue and relatively high signals on T1W images and relatively low signals on T2W images. (2) Total removal is not feasible, or necessary. The surgical indication and strategy for treatment are controversial as they depend on the clinical situations of patients. Treatment for this condition can be challenging as guidelines for management are still not well established. (3) References Aydemir F, Yilmaz C. Thoracic intramedullary lipoma in a 3-year-old child: Spontaneous decrease in the size following incomplete resection. Asian Journal of Neurosurgery. 2018;13(1):188. Abuzayed B. Nondysraphic spinal intramedullary lipoma: A rare case and management. Türk Pediatri Arşivi. 2020; Vila Mengual M, Miranda Lloret P, López González A, Simal J, Alvarez Garijo J. Spinal cord lipoma without dysraphism in the infancy that extends intracranially. Case report and review of the literature. Surgical Neurology. 2009;71(5):613-615.

WMC-22-016: Perceptions and Attitude of Parents towards COVID-19 Vaccination for Children in Kashmir Valley

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Background: Since the launch of COVID-19 vaccination, nations across the globe are trying to bring in herd immunity by ensuring their population gets fully vaccinated. Vaccines for children less than five years is under trial. Since parents are the primary decision makers for their children, our study was conducted to assess parents' likelihood of getting their children vaccinated in Kashmir valley, India. Aim: The objective of this study was to investigate the perception and attitude of parents in Kashmir, towards getting their children vaccinated against COVID-19. Method: An online cross-sectional study was conducted between 5th November 2021 to 19th November 2021. Data was collected using self-administered and semi-structured questionnaire, that was shared online on various social media platforms. Our target group were parents of children below the age group of 5 years. Data collected in questionnaire included demographics details, questions about COVID 19 knowledge and willingness to vaccinate their children.

We used binary logistic regression analysis to identify independent variables associated with willingness towards vaccination. Result: Out of a total of 225 participants, 64% showed a willingness towards getting their children vaccinated against COVID-19. 21% parents were hesitant, and their concerns were mainly about long-term side effects (96%) and expedited trials (71%). Acceptability of COVID-19 vaccines for children was strongly associated with parents who themselves got vaccinated against COVID-19. Conclusion: This study shows that parents in Kashmir region, have a high level of willingness to get their children vaccinated against COVID-19. Our findings may help management authorities to take steps to continue raising awareness and curtaining disinformation in order to gain trust of those who are still hesitant about the vaccine.

WMC-22-017: An Unusual Presentation of Dengue and Chikungunya Virus Co-infection Manifesting as Vesiculobullous Lesions

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Background: Dengue and Chikungunya co-infection is characterized by fever and severe arthralgia. The Aedes mosquitoes are the common vectors for both. Its manifestation as vesiculobullous lesions is both rare and interesting, as the bullous rash can be easily mistaken as an autoimmune disease. Case Presentation: A 6-month-old female infant from India was admitted to the hospital with a 3-day history of high fever and a vesiculobullous rash of 1-day duration. The rash was initially erythematous and later associated with blistering. Vesicles and bullae filled with clear fluid and a few erythematous papules were noted over the extremities. On day 2 of admission, the child had an episode of febrile seizures, but was otherwise unremarkable with no history of joint swelling, vomiting, or loose stools. There was no history of any medication intake before the onset of blistering. Based on the clinical presentation a differential diagnosis of viral infection and autoimmune mucocutaneous disease with superadded viral infection was made with a high index of suspicion for dengue and chikungunya. Hemogram showed thrombocytopenia, blood, and blister fluid cultures were sterile. Tzanck smear of the lesions showed scattered neutrophils and lymphocytes. Skin biopsy showed no acantholytic cells. Serum samples sent on day 6 of fever were positive for chikungunya and dengue by IgM antibody capture enzyme-linked immunosorbent assays. Management was with Acetaminophen and intravenous fluids. The rash started exfoliating by day 6 and subsided with hyperpigmentary changes by day 14. Conclusion: This article aims to point out the possibility of co-infection with viruses sharing the same vectors. Because of the higher incidence of Dengue,and the similarities between the two, Chikungunya can be mistaken as Dengue. We suggest that Chikungunya and Dengue infections should be included in the differential diagnosis of febrile vesiculobullous eruptions in infants to avoid incorrect diagnosis and unnecessary investigations.

WMC-22-018: Understanding the Challenges, Behavioral Patterns, and Preferences towards Participation in Clinical Trials in Minority Patient Populations

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Introduction: For randomized clinical trials (RCTs), effective participant recruitment is crucial for both internal and external validity. Most cancer patients do not participate in clinical trials (CTs), and enrollment of patients from racial and ethnic minority groups is dismal. Our objective is to describe patients' understanding, beliefs, and attitudes regarding CT, and to determine whether these perceptions vary by race/ethnicity. Methods: A comprehensive questionnaire was created in English and Spanish consisting of 54 questions. Our target accrual is a minimum of 500 patients with at least 200 belonging to racial and ethnic minority groups. Accrual was performed in-person and remotely from across Mayo Clinic, with 404 patients accrued. Results: As of March 2021, preliminary data were available for 320 of the 404 accrued patients. 173 (54.2%) were female, 225 (72.1%) are Non-Hispanic White (NHW), 39 (12%) were Hispanics, 41% (13.1%) were Non-Hispanic African American (NHAA), 4 (2.2%) were Asian. Most patients (87%) have some college degree or higher. 68% had solid malignancies and 31% hematological malignancies.

Majority (82%) have never been in a CT. Most patients (60%) were seeking care as an initial visit for a new cancer diagnosis, and nearly all (96%) declared they knew what a CT was. 92% patients trust their physicians but only 65% would participate in a CT if their doctor recommends it, and 38% feel that the treatment may not work. Only 30% disagree with the statement that pharmaceuticals influence the results of the trials. Although 79% of patients have heard about CTs in the media, only 6% of patients trust what they hear. 22% believe that research subjects are treated like "guinea pigs". Mean domain scores for CT knowledge suggest that NHAA may have less understanding of CTs compared to NHW and Hispanics (p=0.007). Other domain scores are not significantly different thus far. Further recruitment of minorities is ongoing. Conclusion: This study will yield better understanding of how knowledge and attitudes of RCT participation vary by race/ethnicity. This information can be used tailor recruitment and outreach to improve RCT participation.

WMC-22-019: Myelomatous Ascites and Pleural Effusion in Relapsed Multiple Myeloma

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Background: Background: Multiple myeloma (MM) is a B-cell neoplasm characterized by clonal proliferation of neoplastic plasma cells in the bone marrow. Extramedullary involvement in the form of malignant myelomatous pleural effusion or ascites is seen in less than 1 % of myeloma cases. Infectious ascites can be differentiated from malignant plasmacytic ascites based on ascitic fluid cytology and other testing methods such as flow cytometry, immunofluorescence, or electron microscopy. Case presentation: A 70-year-old male with an initial presentation of back pain and difficulty walking was diagnosed with IgD lambda subtype of ISS (International Staging System) Stage II MM eight years ago. Lately, he developed new lytic bone lesions without renal disease which was managed by a laminectomy and radiation therapy. He was able to achieve a very good partial response with 6 cycles of lenalidomide, bortezomib, and dexamethasone (RVD). The patient developed multiple relapses with systemic complications and underwent multiple lines of therapy. He was most recently hospitalized with acute kidney injury and oliguria in the setting of progressive MM which improved significantly following treatment. But the patient had severe abdominal pain and ascites. After ruling out SBP and other causes, a peritoneal fluid cytology was performed which revealed atypical plasma cells positive for CD138 and lambda immunoglobulin light chains and confirmed our suspicion of plasmacytic ascites. Soon, his condition rapidly worsened and he was hospitalized repeatedly for pleural effusions with worsening dyspnea. A pleural fluid cytology and immunohistochemistry confirmed malignant effusion. Ultimately, he developed uncontrolled atrial fibrillation after which he was transferred to hospice care and died. Conclusions: Based on many similar cases with myelomatous involvement of body cavities, it can be stressed that ascitic or pleural fluid cytology is an invaluable diagnostic method in the presence of atypical MM symptoms. It is also helpful in identifying extra-medullary progression in some cases with aggressive disease requiring prompt evaluation and treatment.

WMC-11-020: Clinical Spectrum of Patients with Perianal Diseases in a Tertiary Care Centre in Northern India

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INTRODUCTION There is scarce data on the overall incidences of perianal diseases from India. Most research become specific disease-centric and don't do justice to the magnitude at which it affects the whole population. My project strives to add to that epidemiological pool through an observational, cross-sectional study with simple random sampling from the patients who presented to the Surgery OPD of Dayanand Medical College, Ludhiana. AIMS AND OBJECTIVES To study the clinical spectrum of Perianal diseases with respect to • Demographic variables • Disease classification (find most common presentation). • Etiological factors • Presenting symptoms • Co-morbidities and associated diseases (like inflammatory bowel disease) METHODOLOGY Sample size- 82 patients with perianal symptoms Site- Surgery

OPD, Dayanand Medical College and Hospital, Ludhiana Study characteristics- • Random selection • Over two months period • Informed consent taken • Observational, cross-sectional study RESULT AND CONCLUSIONS · Perianal disease presented chiefly as hemorrhoids (50%), fissures (33%), and fistula/abscesses (27%). · Majority of patients were from the age group 30-50 years (53.66%) with male predominance (69.51%). · The common presenting symptoms were pain (72%), bleeding (53%), perianal swelling, discharge, pruritis, mass from/in the anus, and fever, in that order. · Most of the cases required proctoscopy (74%) as an investigation. Fistulogram was needed in 11% of cases out of overall. Few patients required additional investigations. · Grade 2 internal hemorrhoids were present in 44%, followed by internal grade 1 (31%), internal grade 3 and external both having (12% patients each), and internal grade 4 hemorrhoids (2%). · 88% had acute and 12% had chronic fissures. · 30% had intersphincteric, 21% had subcutaneous and 9% had transsphincteric fistula/abscess but maximum cases were unclassified (39%).

WMC-22-021: Prevalence of Vitamin D deficiency in patients with Chronic Liver Disease

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INTRODUCTION There is now increasing researched data on the enhanced treatment response of chronic liver disease (CLD) with vitamin D. CLD also results in impairment of the liver dependant activation of dietary vitamin D into its functional form, hence it is imperative to know the prevalence of vitamin D deficiency in the patients with CLD, along with its relation to the severity of the liver disease. AIMS AND OBJECTIVES Study the relationship between vitamin D deficiency and CLD in terms of • Prevalence • Independence of risk factor w.r.t other variables • Effect of severity of CLD METHODOLOGY Sample size- 100 CLD Site- Department of Gastroenterology, Dayanand Medical College and Hospital, Ludhiana Study characteristics- • Random selection • Over two months period • Informed consent taken • Correlational analysis- between serum vitamin D levels and both Child-Turcotte-Pugh Score and MELD score RESULT AND CONCLUSIONS • Total prevalence of vitamin D deficiency was 76% of CLD patients • Prevalence of vitamin D deficiencies in the CLD patients under Child class A is 63.64%, Child class B is 71.43% and Child class C is 82. 98%. • Prevalence of vitamin D deficiencies in the CLD patients under MELD class 0-10 is 57.14%, MELD class 10-20 is 69.45%, MELD class 20-30 is 75.68% and MELD class >30 is 85%. • Chances of a patient having vitamin D deficiency are directly proportional to the severity of their liver disease. This result is significant with p=0.002 for Child-Turcotte-Pugh score and p=0.008 for MELD score assessment of the severity of the liver disease. • Gender was not a significant factor • Prevalence of vitamin D deficiency in all aetiologies is high (62%-86%). Alcoholic CLD- 74.42%, HBV- 66.67%, HCV- 62.50%, NASH- 85.71%, cryptogenic- 83.33%. • Combination of any two etiological factors leads to a higher prevalence, 85.71% in HBV + Alcoholic and 75.00% in HCV + Alcoholic.

WMC-22-022: Fibrocavitory Tuberculosis in children – A Clinical Profile

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Summary: 1) Background: Epidemiologic data on the clinical profile of fibrocavitory tuberculosis (TB) in children is limited. We evaluated the epidemiologic, clinical, and laboratory features of patients who visited our clinic and were diagnosed with fibrocavitory TB. 2) Methods: Fibrocavitory TB was detected on chest radiography. Clinical symptoms, drug resistance status, and clinical course were extracted from patient charts. Association between clinical symptoms, radiological scans, clinical course, and treatment were compared. 3) Results: Out of 1761 patients with TB, 88 (4.9%) patients had fibrocavitory TB. Three patients were lost to follow-up and were excluded from this study (N=85). The mean age of patients was 12.1+3 years. Male: Female ratio was 1:4. Malnutrition was seen in 30 (83.3%) of children with bilateral disease and in 28 (57.1%) with unilateral disease (p = 0.01). DR-TB was seen in 42 (64.6%) females and 8 (40%) males (p= 0.05). Treatment completion rates with cavitation involving 1 zone were 26 (53.1%) and 11 (30.6%) involving more than 1 zone (p=0.038). 4) Conclusion: Adolescent girls tend to be more susceptible to fibrocavitory TB and have a higher incidence of DR-TB. Unilateral lung involvement with cavitation is more common as opposed to bilateral lung involvement in children. Malnutrition is seen more in patients with

bilateral disease. Treatment outcome is better in patients with 1 zone of lung involved in cavitation.

WMC-22-023: An Unusual Presentation of Dengue and Chikungunya Virus Co-infection Manifesting as Vesiculobullous Lesions

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Background: Dengue and Chikungunya co-infection is characterized by fever and severe arthralgia. The Aedes mosquitoes are the common vectors for both. Its manifestation as vesiculobullous lesions is both rare and interesting, as the bullous rash can be easily mistaken as an autoimmune disease. Case Presentation: A 6-month-old female infant from India was admitted to the hospital with a 3-day history of high fever and a vesiculobullous rash of 1-day duration. The rash was initially erythematous and later associated with blistering. Vesicles and bullae filled with clear fluid and a few erythematous papules were noted over the extremities. On day 2 of admission, the child had an episode of febrile seizures, but was otherwise unremarkable with no history of joint swelling, vomiting, or loose stools. There was no history of any medication intake before the onset of blistering. Based on the clinical presentation a differential diagnosis of viral infection and autoimmune mucocutaneous disease with superadded viral infection was made with a high index of suspicion for dengue and chikungunya. Hemogram showed thrombocytopenia, blood, and blister fluid cultures were sterile. Tzanck smear of the lesions showed scattered neutrophils and lymphocytes. Skin biopsy showed no acantholytic cells. Serum samples sent on day 6 of fever were positive for chikungunya and dengue by IgM antibody capture enzyme-linked immunosorbent assays. Management was with Acetaminophen and intravenous fluids. The rash started exfoliating by day 6 and subsided with hyperpigmentary changes by day 14. Conclusion: This article aims to point out the possibility of co-infection with viruses sharing the same vectors. Because of the higher incidence of Dengue,and the similarities between the two, Chikungunya can be mistaken as Dengue. We suggest that Chikungunya and Dengue infections should be included in the differential diagnosis of febrile vesiculobullous eruptions in infants to avoid incorrect diagnosis and unnecessary investigations.

WMC-22-024: Stress, Anxiety and Associated Factors within the Transgender Population of India: A Cross Sectional Study

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Background: Transgenders are people who have a gender identity different from their biological sex. The transgender community may face discrimination due to their gender identity across the world. This study is aimed at assessing the frequency of stress and anxiety in the transgender population of Delhiin order to understand the various factors. Methods A cross sectional survey of self-consenting transgender individuals above the age of 18, residing in Delhi was done to assess their socio-economic status and experiential ecology. Recruitment of participants was done with the help of multiple NGOs. GAD-7 and PSS-10 were used to assess the stress and anxiety levels. The results of the survey were analyzed to understand the key factors associated with the mental health status of transgender people. Results The survey showed that the frequency of stress and anxiety is high in the transgender population. 44% of the participants reported facing discrimination on a daily basis, frequency of discrimination is higher in transwomen than in transmen. Only 34.5% participants said they had receptive family or friends. Majority of participants (72.7%) reported a positive or neutral experience with healthcare workers. Prevalence of discrimination is significantly lower in the higher educated groups. Analysis of data showed a positive impact of acceptance and reception on the mental health while discrimination is correlated with higher levels of stress and anxiety. Conclusion Prevalence of widespread transphobia and discrimination faced by the transgender community has culminated in high levels of stress and anxiety in the transgender population and show variance in conjunction to multiple socio-demographic factors. Educating people about LGBT community, formation of support groups, policies and laws is required to establish trust and promote integration. Keywords: Transgender, gender, stress, anxiety, mental health

WMC-22-025: Hypnic Headache: The Bizarre Annoying Alarm Clock

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We intend to summarize existing knowledge on hypnic headache (HH) scrutinizing clinical presentation, pathophysiology, polysomnography, and therapeutic options. We also aim to analyze published cases to look out for potential research options to boost understanding of the uncommon disorder. BACKGROUND: Hypnic headache (HH) is a rare nocturnal headache characterized by recurrent episodes that periodically awaken the sleeping patient, hence referred to as alarm headache, and typically occurs among the elderly. METHODOLOGY: HH cases published within the literature from 1988 to 2022 using major medical databases including PubMed. RESULTS: There are gaps within the understanding of the interrelationships of sleep physiology and hypnic headache pathophysiology. The new International Classification of Headache Disorders [ICHD]-3 criteria is additionally more accurate than the ICHD-2 criteria. CONCLUSIONS: The possible research topics include clinical trials for treatment methods, studies for a deeper understanding of the pathophysiology, and diagnostic methods for hypnic headaches.

WMC-22-026: A Case of Eravacycline Induced Hepatic Steatosis

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Background: Eravacycline (ERV) is a novel tetracycline antibiotic, used in the treatment of complicated intraabdominal infections. It is generally well-tolerated, with nausea, vomiting, and infusion site reactions being the most reported adverse events. However, it could be associated with sinister adverse effects, including life-threatening liver toxicity in the form of hepatic steatosis. Tetracycline-induced hepatotoxicity can progress to cirrhosis, resulting in decompensated hepatic failure commonly among pregnant women. Doxycycline and minocycline are frequently implicated agents. However, ERV-induced hepatic steatosis has not been well documented in scientific literature and is exceedingly rare. We present the clinical and histopathological progression of hepatic steatosis induced by ERV, in a patient with a transplanted liver. Case report: A 57-year-old female with a past medical history significant for HCV infection, hepatocellular carcinoma, and liver transplant was relisted due to biliary cast syndrome with MELD 40. She underwent re-orthotopic liver transplantation and washout due to increased pain, leukocytosis, and an intra-abdominal collection in CT scan. The culture grew vancomycin-resistant enterococcus, aspergillus, and mycobacterium avium complex. Eravacycline was added to manage the polymicrobial bacteremia following which she developed transaminitis. Magnetic resonance cholangiopan-creatography ruled out biliary pathology. Liver biopsy was notable for 80% microadenoma. Due to possible liver injury by ERV, it was replaced by Linezolid. Transaminases lowered and a repeat liver biopsy demonstrated resolution of hepatic steatosis. Conclusion: ERV use has been associated with a low rate of serum aminotransferase enzyme elevations during therapy, but the mechanism of liver injury is unknown. Intravenous tetracycline was withdrawn from use due to its ability to cause severe hepatic steatosis with lactic acidosis and severe hepatic dysfunction. We intend to highlight the importance of close monitoring of liver enzymes along with a liver biopsy and imaging during treatment with Eravacycline.

WMC-22-027: A Case of Asymptomatic Prolonged Sinus Bradycardia in Traumatic Chylo-Hemothorax

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INTRODUCTION There are rarely any recorded cases in the available literature of Chylo-Hemothorax manifesting as prolonged asymptomatic bradycardia in a post-traumatic patient. My case report strives to add to that scarce epidemiological pool, to alert any future

physicians in the emergency department who might encounter a similar situation, so they could provide prompt and optimized patient care. CASE REPORT A 20-years-old female presented to the emergency department of a tertiary care center in northern India with a history of fall from a height of 12 feet. She complained of severe lower back pain, left-sided chest pain, bilateral and symmetrical lower limb numbness, and weakness. Her findings on first day were as follows: - • Chest X-ray- left-sided 6th, 7th and 8th rib fracture with mild left-sided hemothorax • MRI of the lumbosacral spine- fractures of 12th thoracic vertebra and 1st to 4th lumber vertebral bodies along with disk protrusion at L3/4, L4/5, and L5-S1 On day 5, her hemothorax worsened on chest X-ray and she developed asymptomatic bradycardia on ECG. She was treated with analgesics, atropine for bradycardia, chest tube insertion for hemothorax, and immobilization. CONCLUSION While acute symptomatic/ asymptomatic bradycardia is a common symptom among patients with various aetiologies, it is rare to encounter one secondary to a haemothorax or chylo-hemothorax caused by trauma. The bradycardia was seen to resolve parallel to the resolution of chylohemothorax, which reinforces it being the root cause. It's imperative to keep it as a differential diagnosis, to aid physicians in a trauma setting to rule out the various causes of bradycardia.

WMC-22-028: Isolated Right Hepatic Duct Injury Discovered Three Days Post-Trauma in a Geriatric Patient

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INTRODUCTION An extrahepatic ductal injury has rarely been located anatomically in the right hepatic duct in the recorded cases throughout the epidemiological pool. Given scarce literature on post-traumatic right hepatic duct injuries, we all feel that this case can be a beacon in the discussion of the same issue among the surgical community who are the readers of your publication. CASE REPORT A 73-year-old female presented to the emergency department with multiple actively bleeding stab wounds and history of assault and fall from a chair. Being hemodynamically stable and with no findings on abdominal ultrasound (FAST protocol), she was given first aid and operated on for stab wounds. The patient improved till post-op day 3, and then developed severe abdominal pain and greenish discharge. Biochemistry identified bilious fluid and ERCP identified right bile duct laceration. She underwent exploratory laparotomy and duct repair. CONCLUSION The location of injury at the right hepatic duct is rare as it is protected below the liver. We think that the most probable mechanism for the injury was the non-uniform shearing forces in our patient. The patients who are hemodynamically unstable generally get diagnosed early unlike hemodynamically stable ones like ours. The absence of any significant features on the CT abdomen on the day next to the initial trauma did not rule out biliary tract injuries in our case. So, despite adequate imaging, one should always keep a differential diagnosis of biliary tract injury in the back of their mind as the failure to do the same might result in the development of various complications such as biliary leakage, biliary strictures, or recurrent cholangitis.

WMC-22-029: Telehealth Access to Geriatric Patients During COVID-19: A Cross-Sectional Provider Survey

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The COVID-19 pandemic has prompted a rise in the use of virtual healthcare through Telehealth. The importance of telehealth is multifold, from communicating with patients virtually to providing care when in-person services are unavailable. Although this virtual platform has significant benefits, the geriatric population is underutilizing this resource. Thus, our initial objective was to understand the perceptions of health care providers, and their assessment of the comfort level and utility of telehealth software for geriatric patients. We surveyed participants across the Greater Akron and Canton area in Northeast Ohio, specifically from Summa Health Akron City Hospital and the Direction Home Akron Canton Area Agency on Aging and Disabilities, on their perception regarding the rise and utility of telehealth before and after the pandemic. Sixteen out of 22 (72.7%) notified participants completed the survey. Out of the participants, five (33.3%) were physicians. Less than 25% of their patients resided in nursing homes per eleven participants (73.3%). Additionally, we surveyed the participants regarding patient capability and understanding of telehealth software. Nine (60.0%) of

the participants used TeleHealth, of whom five (55.6%) started utilizing it during the rise of the pandemic. A large subset of participants (69.2%) stated that their patients fell between somewhat uncomfortable to completely uncomfortable in utilizing telehealth. A greater majority (76.9%) stated their patients felt a medium level of comfort utilizing devices such as blood pressure monitors and glucose machines at home. Finally, 12 participants (92.3%) stated that a volunteer service to help patients and/or caregivers learn how to use telehealth and medical devices is something they would find extremely helpful. The data shows that practitioners perceive that geriatric patient find it difficult to utilize telehealth, and our future goal is to develop a student-led virtual program to better assist patients.

WMC-22-030: Physician Training and Credentialing in Endoscopic Submucosal Dissection in the United States: A Survey-Based Study

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Endoscopic Submucosal Dissection (ESD) is challenging and has a greater complication rate than most new endoscopic procedures. Formal credentialing guidelines for ESD are lacking in the United States (US). We surveyed ESD experts across the US to obtain their opinion on how training processes and credentialing for ESD should develop. The survey questions were developed by administering the survey to three investigators who have been performing ESD for > 5 years. The survey contained 45 questions addressing current practice, ESD training, and ESD credentialing. US gastroenterologists performing ESD were identified from those attending ESD expert conferences. Thirty five (58.3%) of 60 practicing US ESD experts responded to the survey. A majority (90%) of ESD experts were in university-based or tertiary care hospitals practicing for more than 5 years (92%). All practitioners practiced on porcine explants and observed live ESD procedures as part of training. Two-thirds also attended ESD training courses and received formal supervised hands-on training on porcine explants and/or humans before starting to perform ESD independently. Twenty-three (66%) ESD experts reported en-bloc resection in at least 85% of procedures. Only half indicated that their facility had written guidelines specifically for ESD credentialing. Four out of 5 felt that credentialing requirements should include attending weekend ESD courses, observing live procedures, practicing on explants, and advanced endoscopic training in interventional endoscopy such as an additional year of fellowship. Finally, 65% of the participants agreed that there should be a minimal number of ESD procedures performed annually as a requirement for continued credentialing. Standardized training and credentialing guidelines for ESD should be developed in the United States that incorporate expert opinion. ESD training should include practicing on explants, observation of live procedures, training in interventional endoscopy, and attending educational courses.

Portrait of Hippocrates (1787), by the Majorat of Setúbal.
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Science is the father of knowledge, but opinion breeds ignorance.
- Hippocrates