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Perspective

Gut Microbiome: A Hidden Clue to the Complications of COVID-19 - 8

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ABSTRACT

As the COVID-19 pandemic rages on, the race to solve the puzzle has taken huge strides in recent times. One of the areas that have remained in the shadows to date is the role gut microbiota in COVID-19 and its implications in the natural course of SARS-CoV-2 infection. Its probable underlying involvement is not only attributable to the pathogen per se, but also the revolutionary measures taken to control the spread of the disease across the world.

ABBREVIATIONS

COVID-19: Coronavirus Disease- 19; LPS: Lipopolysaccharide; SCFA: Short Chain Fatty Acids; TMAO: Trimethylamine N-Oxide; IPA: Indole-3-Propionic Acid (IPA); RA: Rheumatoid Arthritis; SLE: Systemic Lupus Erythematosus; DM: Diabetes Mellitus; AD: Alzheimer's Disease; PD: Parkinson's Disease; ALS: Amyotrophic Lateral Sclerosis; CKD: Chronic Kidney Disease; NAFLD: Non Alcoholic Fatty Liver Disease; NASH: Non Alcoholic Steatohepatitis; IBD: Irritable Bowel Disease; HTN: Hypertension; MIS-C: Multisystem Inflammatory Syndrome In Children With COVID-19; IFN Γ : Interferon Gamma

BACKGROUND

The direct and indirect impact of SARS-CoV-2 on the composition of gut microbiome

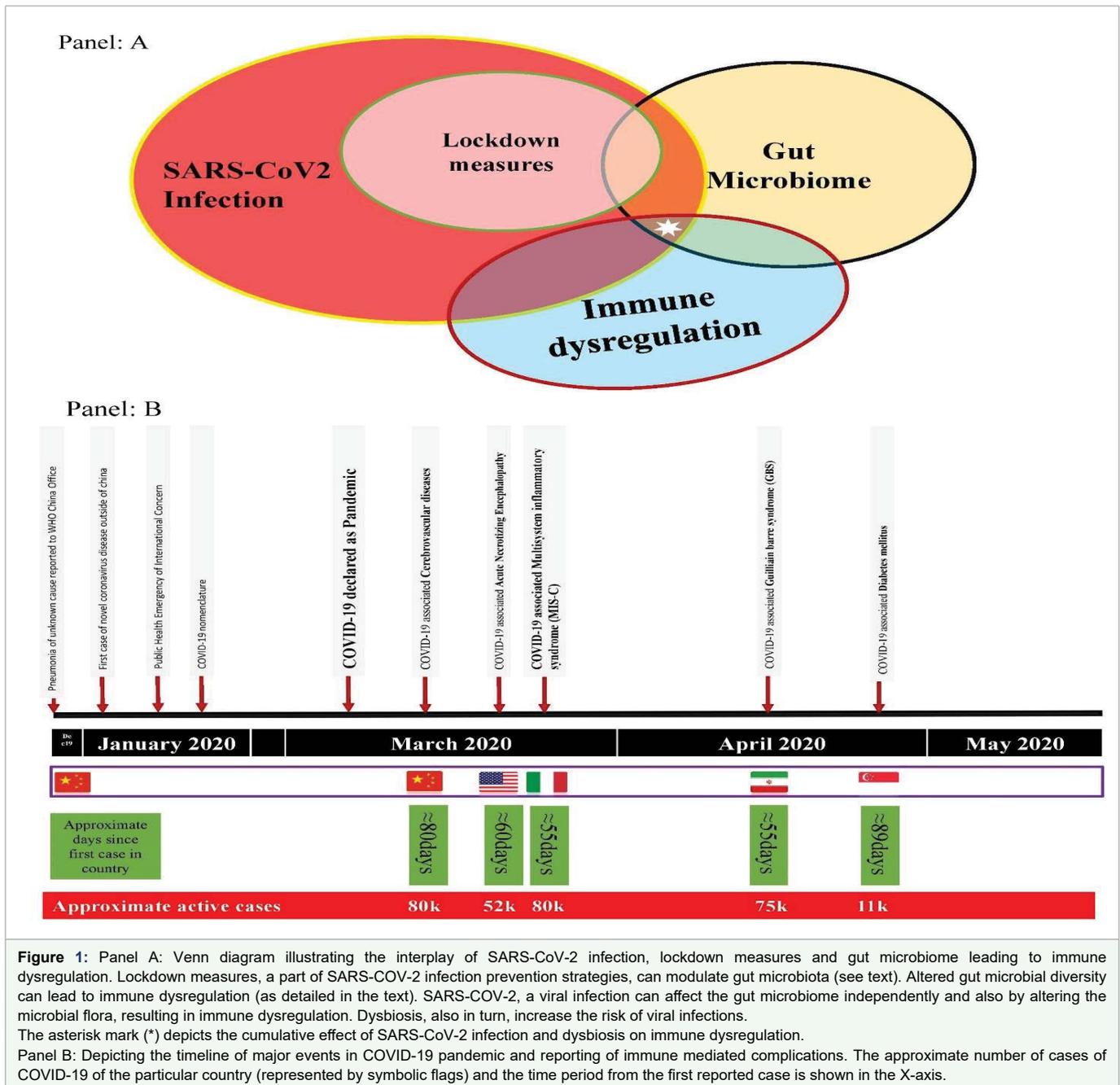
A multitude of researches has shed light on the bidirectional communication between the human commensal microbes and invading viruses, proving how dysbiosis can alter infectivity [1,2]. SARS-CoV-2, with its ability to bind to ACE-2 receptors (Angiotensinogen Converting Enzyme-2) which are also expressed by enterocytes [3], bears the Potential to modulate the composition of gut microbiota. As a matter of fact, gastro-intestinal symptoms have been reported as one of the common manifestations of SARS-CoV-2 infection [4]. Environment and diet are the two key pillars that have emerged in numerous studies as the main determinants of human gut microbial composition and maintaining a stable gut community [5,6]. Despite the massive importance of the various measures taken by the majority of the nations including lockdown, mandatory use of masks, hand hygiene measures, social distancing, and closure of all non-essential services, their silent impact on the gut microbial composition and their kinetics cannot be overlooked. (figure 1). The widespread lockdowns have forced a significant proportion of the world population into a state of major economic crises with drastic changes in their diet and day to day lifestyle. People, in millions, have been forced to resort to a ration based supply of food with minimal variety; while in developed nations, they have to rely on processed packaged foods. The severe restrictions have either led to the non availability or non affordability of consumables. With the stress from caring for the diseased exponentially increasing and the void of a definite cure haunting the people, the resultant aftermath has led to rampant use of irrational antibiotics and unproven indigenous compounds, all of which are known to potentially disrupt the delicate balance of human holobiont [7]. Confinement to the poorly infra structured temporary isolation units and lack of outdoor activities leading to reduced exposure to sunlight can also have detrimental effects on the delicate skin gut axis.

Gut microbiome and COVID-19 the link

The rationale behind the potential role of the gut microbiome

stems from the very dynamics of COVID-19 itself. Since the first reported cluster of cases, the spectrum of COVID-19 has expanded manifold. The world has witnessed the emergence of numerous manifestations of immune dysregulation in the form of several reports of cytokine storm, macrophage activation syndrome, secondary Hemophagocytic Lymphohistiocytic Syndrome, autoimmune cytopenia, Anti Phospholipid antibody syndrome and Guillain Barre syndrome. The pediatric and adolescent sector has witnessed the upsurge of Kawasaki like illness among children (Multisystem inflammatory syndrome in children or pediatric inflammatory multisystemic syndrome in children). A flurry of cases of ischemic cerebrovascular accidents in young with no apparent cardiovascular risk factors has flooded the emergency wards [8]. Among the metabolic diseases, many SARS-CoV-2 infected patients have been diagnosed with new onset Diabetes Mellitus. The striking racial and ethnic discrepancies among the patients have come to the forefront in this pandemic. There has been a disproportionately higher incidence of infection, hospitalizations, complications, and death among the Black and Native Americans [9]. It remains a matter of argument, whether the architectural difference in their gut microbiome [10], resulting from discrepancies in their dietary habits either due to non accessibility or as a part of their culture, is actually one of the attributable factors, responsible for this racial differences. Thus, are we missing the active yet silent role of gut microbiota underlying the late emergence of these entities? The answer may be right in front of us. Yeoh et al., in a two hospital cohort study performed serial stool analysis till 30 days post resolution of COVID-19 and concluded the presence of significantly lower representation of gut commensals with potential immunomodulatory effects compared to that of healthy controls [11]. An exploratory pilot study on 15 COVID-19 infected patients revealed similar results [12].

With the massive restrictions imposed on the usual daily outdoor activities and self measures to avoid contracting the virus, the overall exposure to the surrounding microbes has come down significantly. As per the "Hygiene hypothesis", lower level exposure to microbes is a predisposing factor implicated in immune dysregulation [13]. Several studies have highlighted the role of TMAO (Trimethylamine N-oxide), an extremely atherogenic metabolite generated by altered gut microbes, in the pathogenesis of cerebrovascular accidents and major cardiovascular adverse events [14]. Reduced levels of gut microbe derived Short Chain Fatty Acids (SCFA) have been implicated in the pathogenesis of metabolic syndrome, atherosclerotic disease, insulin resistance, dysregulation of hematopoietic stem cells and altered inflammatory response of respiratory tract to pathogens [15]. The Human Functional Genomics Project (HFGP) has shown the complex interplay of cytokines TNF- α and IFN- γ with microbial metabolic pathways, indicating the vivid interaction between immune regulation and commensal microbes [1]. The imbalance of gut microbiota has been reported as an indirect mediator of Kawasaki



disease among children in several studies. The probable role of commensal-immune axis in the pathogenesis of Antiphospholipid syndrome is under research. According to the Centre for Disease Control (CDC) reports, patients with diabetes, cardiovascular disease, and chronic lung disease had six times greater rates of hospitalizations and twelve times higher fatalities. While these facts may appear obvious to many of the readers, the wide availability of evidence of dysbiosis in all of these predisposing conditions, elucidate the need for further studies on these subgroup of COVID-19 affected individuals (figure 2).

CONCLUSION

A glimpse into the future

As the world continues its voyage in this uncharted sea, little is known what the future holds. If dysbiosis does turn out to be

the possible link, the coming future may witness new waves of non communicable diseases, the resurgence of communicable diseases from disruption of herd immunity, a massive escalation of Immune Mediated Inflammatory Disorders (IMID) [16], disproportionate rise of neurodegenerative conditions, demyelinating neurologic diseases, the emergence of a wide array of psychiatric ailments, frequent exacerbations of atopic diseases, altered immune response to vaccines, rise in the incidence of Autism spectrum disorders, Inflammatory bowel disease, Irritable bowel syndrome, Celiac disease, Non alcoholic fatty liver disease, fibromyalgia, altered metabolism of xenobiotics leading to increased incidence adverse events of known drugs and many others [17]. As bleak as the future may sound, the clinicians and policy makers must prepare themselves for the coming surge of not only the infection per se but its wide consortium of all other clinical associates. Only time will tell if the gut feeling was right.

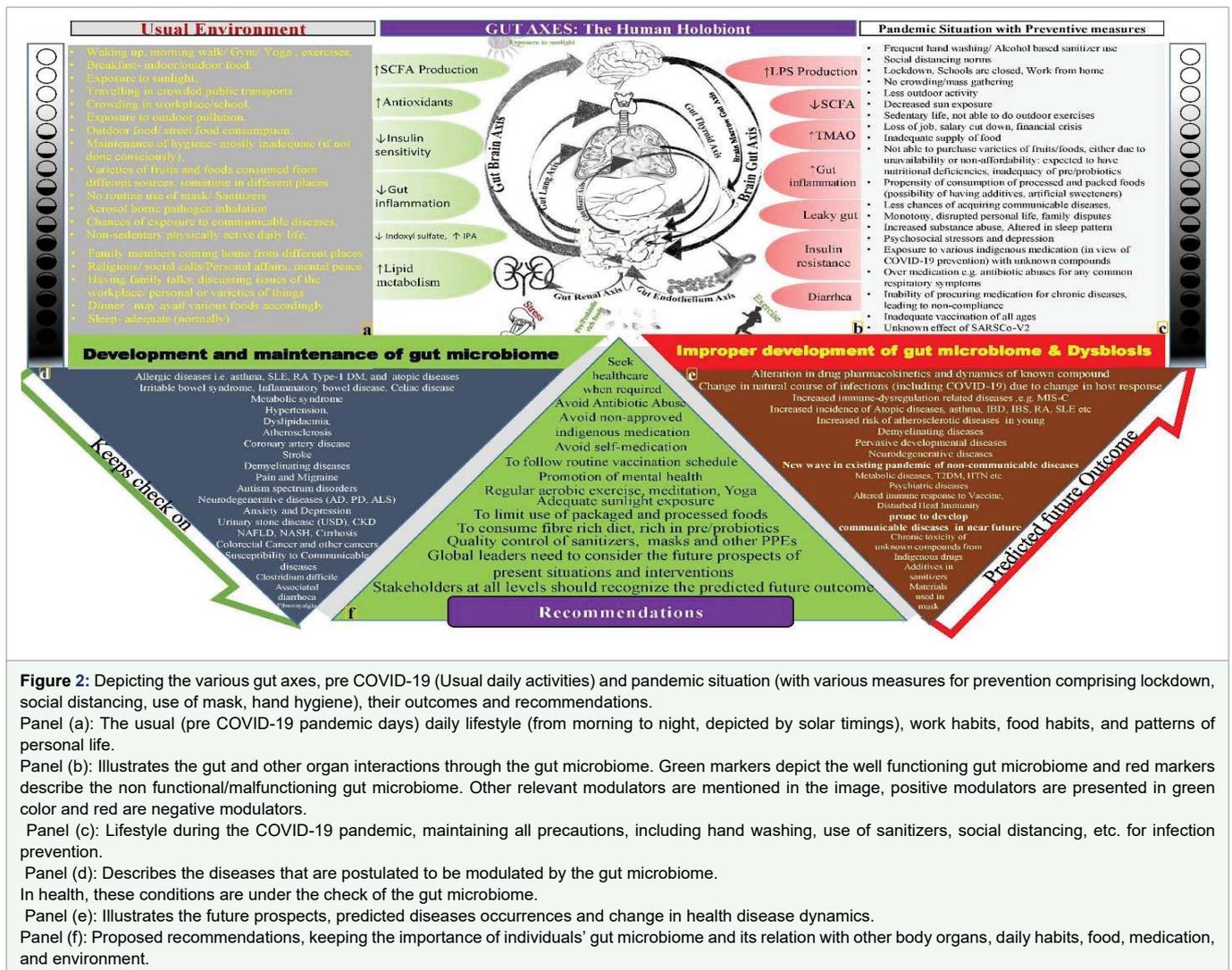


Figure 2: Depicting the various gut axes, pre COVID-19 (Usual daily activities) and pandemic situation (with various measures for prevention comprising lockdown, social distancing, use of mask, hand hygiene), their outcomes and recommendations. Panel (a): The usual (pre COVID-19 pandemic days) daily lifestyle (from morning to night, depicted by solar timings), work habits, food habits, and patterns of personal life. Panel (b): Illustrates the gut and other organ interactions through the gut microbiome. Green markers depict the well functioning gut microbiome and red markers describe the non functional/malfunctioning gut microbiome. Other relevant modulators are mentioned in the image, positive modulators are presented in green color and red are negative modulators. Panel (c): Lifestyle during the COVID-19 pandemic, maintaining all precautions, including hand washing, use of sanitizers, social distancing, etc. for infection prevention. Panel (d): Describes the diseases that are postulated to be modulated by the gut microbiome. In health, these conditions are under the check of the gut microbiome. Panel (e): Illustrates the future prospects, predicted diseases occurrences and change in health disease dynamics. Panel (f): Proposed recommendations, keeping the importance of individuals' gut microbiome and its relation with other body organs, daily habits, food, medication, and environment.

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