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Gut Microbiome Association with Chronic Inflammations in COVID-19 Patients

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Abstract

Objective: To investigate the role of Gut microbiome in correlation with corona virus disease 2019 (COVID-19) pandemic and variation in severity of symptoms induced by inappropriate immune responses.

Methodology: Analysis of different peer reviewed literature from prestigious journals on gut dysbiosis and the variation in disease progression of Covid-19 infection during the current pandemic has established a strong correlation. Our aim is to highlight the quantitative importance of metabolites (released by gut microbiome) for optimal cellular level functions against different disorders and diseases, especially secondary chronic infections and inflammations in post Covid-19 patients.

Results: Four themes emerged: (i) Intestinal dysbiosis can lead to prolonged hypoxic conditions during Covid-19 infection (ii) Diabetes (associated with intestinal dysbiosis) induces poor prognosis in patients with Covid-19 infection (iii) Co-morbidities associated with Covid-19 can be fatal (iv) For immune cells to acquire sufficient metabolites consumption and establish a more formulated and appropriate response, the diverse and abundant microbiome is a primary and prerequisite feature.

Conclusion: An existing Inflammation in the body is the leading cause of individual's poor prognosis in case of viral infections. Especially in the light of current pandemic, serious considerations should be taken into account for minimizing the risks associated between covid-19 and pre-existing inflammation in populations and therefore, probiotics might play a significant role in treatments of such conditions.

Introduction

In 1907 a Russian biologist named "Elie Metchnikoff" wrote a book named "The Prolongation of Life, Optimistic Studies" He mentioned in this book that "The dependence of intestinal microbes on food makes it possible to adopt measures to modify the normal flora in our bodies and can replace harmful microbes by useful microbes". [1]

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Humans have existed as omnivores. Humans are Able to eat variety of food compare to other species. So biological abundance of food provides a broad spectrum of shifting of humans between food during drought. Therefore, in the history of extinction of species, humans have successfully climbed up the evolutionary ladder of food chain .There are two reasons for it, The intestinal Resilience and The Intelligence.

Anthropological studies have shown that human ancestors were able to consume more diverse food compared to humans today. Humans microbiome has become more sensitive Over time, even minor changes such as travelling, stress and geographical changes, potentially affects the overall human health. Also Sensitivity to certain food can lead to medical conditions in some individuals. [2]

Scientifically there is a two way approach to build an intestinal resilience-Either to Minimize exposure to Herbicides and pesticides, Chlorine and fluoride in drinking water, Personal care products, Food preservatives and broad spectrum systemic antibiotics or maximize exposure to microbial world and also increase diversity of diet consumed in a daily routine. However if the intestinal microbiome is not resilient, it can lead to dysbiosis which eventually results in a condition called "leaky gut syndrome".[3]

NIH, American Diabetic Association and American Heart Association has published several research studies on Metabolic Endotoxemia (MET) in past few years, Which progressively indicates that majority of chronic illnesses are due to MET. So there is enough evidence available to demonstrate that leaky gut syndrome due to dysbiosis does exist and MET is a consequence of such condition. Leaky gut syndrome is related to a wide variety of conditions, including chronic kidney diseases, cardiovascular complications,type2 diabetes mellitus and Parkinson's disease, Alzheimer's disease and Anxiety consequently.[4]

Intestinal dysbiosis, Diabetes Type 2 and COVID-19 Infection

During the COVID-19 Pandemic it is clearly observed that high glucose environment favors viral replication in the body and leads to severity in symptoms. Therefore patients with diabetes mellitus when infected with covid-19 are presented with poor outcome comparatively to the non-diabetics.[5]

In addition to gram positive bacteria, a large proportion of intestinal microbiome is comprised of gram negative bacteria (*Bacteroidetes* and *Firmicutes).* Therefore, during any metabolic process, lipopolysaccharide (an endotoxin present in the outer membrane of gram negative bacteria), is released through leaky gut into the blood circulation, causing MET. However, an elevated LPS in blood can be considered as diagnostic marker to identify various types of chronic diseases. American diabetes association carried out a Study on 462 individuals for 60 months. With observation of all of the conventional markers such as obesity, family history of diabetes, consistently high cholesterol level and elevated LPS level in blood. The only marker with 100 percent Accuracy, being a predictor of risk factor for development of type2 diabetes was the elevated concentration of LPS in the blood, irrespective of age. The study suggested that the higher concentration of LPS in blood can be considered as a primary predictor of developing type 2 diabetes. Scientists believe that the biggest pandemic the world will ever face is type 2 diabetes mellitus in net decades.[6]

Moreover, there are two mechanisms through which LPS Causes the insulin deregulation in blood, either by targeting islets cells in pancreas directly, causing inflammation in Pancreas or through crossing blood brain barrier and causing inflammation in hypothalamus, leading to a disorder in

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terms of blood sugar levels measurements of brain. The latter is known as "central insulin resistance". [7,8]

Recent studies have shown that younger individuals ranging from age groups of 15 years and older are diagnosed with type2 diabetes mellitus and C-section mode of birth is found to be the reason behind it. A major inoculation of microbiome usually takes place through the birth canal of mother into the child during natural birth process. While babies born through C section remains deprived of such inoculations, which is part of the reason, these babies develops diabetes mellitus type2 at very young age. In addition to diabetes mellitus type2, dysbiosis or inappropriate composition of microbial species (leading to insufficient or excessive metabolites synthesis required by human cells) comprising the gut microbiome, results in conditions such as hormonal deficiency, immune discrepancies, neurological dysfunctions ,systemic and cardiac disorders. Probiotics are therefore an advance approach to develop and reestablish the gut micobiome.[9,10] Conventional probiotics, made up of *Bifidobacterium* and *lactobacillus* species of bacteria are used in people with irritable bowel syndrome and ulcerative colitis. According to a 2014 analysis of several studies, probiotics that seem to be effective for fat loss include *Lactobacillus gasseri*, *Lactobacillus rhamnosus* and the combination of *Lactobacillus rhamnosus* and *Bifidobacterium lactis*. Which can be considered as prophylactic treatments while taking cardiac complications into account, as a consequence due to excessive fats accumulation in the body.[11,12]

Discussion

There is a clear evidence of emerging chronic illnesses among the majority of human population since last decade. These chronic illnesses sometimes are represented with mild symptoms, most of the times neglected by the human population. It is observed during the current covid-19 pandemic that the severity of symptoms of SARS-COV2 varies between individuals. Such differences in symptoms might be the result of the specificity of type of chronic illnesses in each individual, in addition to the status of immune system.13 There are reported cases throughout the world, where apparently healthy individuals are presented with severe symptoms of SARS-COV2 and have suffered cardiac arrest, kidney failure, liver dysfunction and neurological disorders between infection and recovery phase. Such conditions are also reported weeks and months after these patients have completely recovered from COVID-19 infection. While on the other hand Individuals with undergoing treatment for an existing medical conditions are when infected with SARS-COV2 are sometimes reported with better outcome comparatively. [14]

IMPACT OF LOCKDOWNS ON INTESTINAL MICROBIOME AND COVID-19

There is evidence that one of the leading cause of intestinal dysbiosis is due to less exposure of individuals to the environmental microbiota. Finnish allergy studies have proved the importance of environmental microbiota and its association (of low exposure) with chronic inflammations in human.[15,16] In cities like Abbottabad, Islamabad, Karachi, Lahore and Peshawar, where the infrastructure of houses differs widely.one race of people lives in close and isolated apartments while others have houses widely opened. During the lockdown as a counter health measurement by the government, people in small houses are likely to have achieved inadequate inoculation of microbiome from environment, which might have resulted in intestinal dysbiosis in these populations. However, periodically these populations are vulnerable to different kinds of chronic inflammations,

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especially women which expose less to the outside environment than men in countries like Pakistan. In such circumstances when these individuals are infected with SARS-COV2, the underlying chronic inflammations might lead to poor prognosis for COVID-19 (depending on the type of chronic inflammation).

PREDISPOSITION OF GUT MICROBIOME AND EMERGENCE OF CYTOKINES STORM DURING COVID-19 INFECTION

Dysbiosis also occurs due to regular use of oral antibiotics.[17] So, the severity of Covid-19 symptoms might be correlated to the extent of predisposition of gut microbiome in individuals by inappropriate administration of systemic antibiotics.[18]Also Chronic inflammations derived from dysbiosis of Gut microbiome and the acute phase inflammation caused by COVID-19 infection together leads to hyper-inflammation.[19] Therefore, individuals with intestinal dysbiosis most likely establishes a "cytokine storm" more rapidly. Majority of cytokines (IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-17, TNF-alpha, TNF-beta, INF-gamma, Eotaxin, TGF-beta, and GM-CSF) involved in this cytokines storm are generated due to chronic inflammation and a small number of cytokines(IL-1, IL-6, IL-8, IL-11, IL-16, IL-17, G-CSF, TNF-alpha, Eotaxin, GM-CSF) are required for up regulation of cytokines storm, in order to restrict the viral replication. The common cytokines shared by chronic and acute inflammation include IL-1, IL-6, IL-11, IL-17, TNF-alpha, Eotaxin and GM-CSF. Thus, in principle, it is conceivable that against a background of chronic inflammation, a viral infection could potentially serve as a trigger to establish a phase of acute inflammation, through the addition of only 3 further cytokines (IL-8, IL-16 and GCSF) to the condition which already contains the remaining seven cytokines (IL-1, IL-6, IL-11, IL-17, TNF-alpha, Eotaxin and GM-CSF) due to a pre-existing chronic inflammation (illustrated in Figure 1). In effect, therefore, the pre-existence of a chronic inflammation could act as a platform from which an acute inflammation could be launched much more easily than otherwise, through the addition of only three cytokines (IL-8, IL-16 and G-CSF) to the pre-existing inflammation. [20, 21 ,22]

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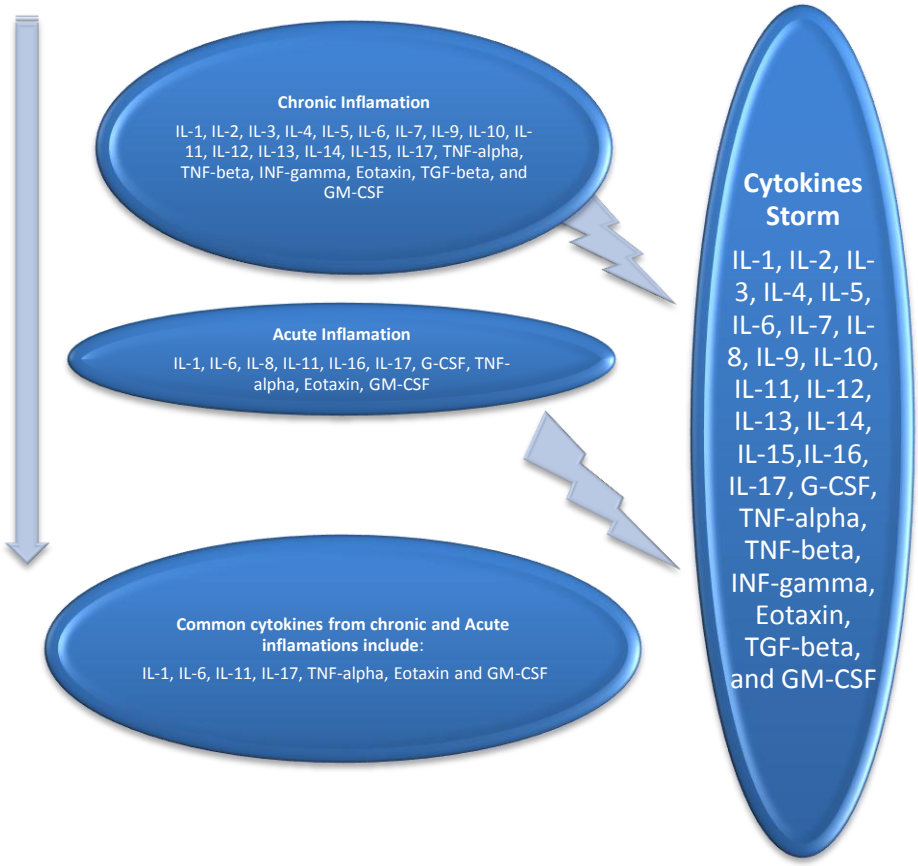

Figure 1: Chronic inflammation caused by intestinal dysbiosis and Acute phase Inflammation in COVID-19 Infection, Together Generates a more Rapid Cytokines Storm Which Damages Local tissues.

Intestinal Dysbiosis and Acute Cardiovascular complications in COVID-19

A broad range of clinical outcome studies have suggested links between Intestinal dysbiosis and Cardiac complications. An extensive scale of examinations has proved a strong correlations between intestinal dysbiosis induced inflammations and strokes as well as myocardial damages among humans. [23] Globally, there are several deaths reported due to heart failure in SARS-COV2 positive patients. Whereas, Studies have suggested that pro inflammatory cytokines such as TNF-α, IL-1, IL-2, IL-6 and C-reactive protein , are all elevated in patients with congestive heart failures. [24] However, serum endotoxin concentration can be controlled through an immediate diuretic treatments but the cytokines concentration can remain elevated for a longer duration of time, which is the main cause of heart failure. [25] Therefore, such individuals are when exposed to Covid-19 infection, the existing pro inflammatory cytokines (TNF-α, IL-1, IL-2, IL-6 and C-reactive protein) from chronic heart diseases are added to the cytokines released as a result of COVID-19 infection and severe cardiac complications are established as a consequence in a very short duration of time, which might ultimately be the cause of deaths due to heart failure in COVID-19 patients.

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Hypoxia, cardiac remodeling, Intestinal Dysbiosis and COVID-19 Infection

Individuals with chronic conditions or pre-existing medical conditions are more susceptible to SARS-COV2 infection. Whereas, a resilient microbiome, determines the prognosis of such conditions, as discussed previously. Furthermore, Individuals with chronic illnesses have up regulated expression of ace2 receptors, increasing the adsorption sites for viruses to successfully target high number of cells.26 Especially ,when the "Cardiac remodeling"(CRM) is a key risk factor for the development of heart failure due chronic inflammations, following thrombus formation or embolism in myocardial tissues. Studies have shown an anti-remodeling role of ACE2 (angiotensin-converting enzyme 2) in vivo during hypertensive conditions like hypoxia.27 eventually during the phase of cardiac remodeling, there are more ACE2 receptors available for SARS-COV2 virus to target. However, SARS COV-2 mediated cytokines formation, intestinal dysbiosis (due to hypoxia) mediated cytokines production and an existing chronic inflammation induced cytokines production, could collectively generate a "cytokines storm" during CRM, which can potentially manipulate the process of CRM and inappropriate pressure, volume and distribution of blood to various organs.28,29 This may lead to multiple organ failure or even the immediate death of an individual. Therefore, the Populations living at high altitude are at high risk of developing severe, acute cardiac complications, when infected with SARS-COV2 infection in addition to intestinal dysbiosis under hypoxemic conditions. Recent studies published in *New England Journal of Medicines* have suggested that high phosphatidylcholine foods such as egg yolks and red meat, may lead to a buildup of plague in arteries. Gut bacteria breaks down phosphatidylcholine into Trimethylamine N-oxide(TMAO).Which has been shown to cause a plague production in arteries. Gut bacteria plays a role in the development of metabolites in humans, the concentration of which is linked to heart diseases. An elevated TMAO levels in blood has recently been introduced as diagnostic predictor of future risks of heart attack, stroke and death. Especially during the current Pandemic of COVID-19, when Individuals are at risk of heart failure, due to chronic and acute inflammations. Measurement of TMAO levels in blood may provide high degree of value to identify individuals at risk of heart attack, which might not be possible through conventional blood tests or traditional risks factors measurement.[30,31]

Therapeutic interventions

Short chain fatty acids are postbiotics. For example, Butyrate is a short chain fatty acid produced by intestinal bacteria (bifidibacteria). Butyrate has a role in metabolism. It increases the body's sensitivity to insulin and body is able to detect insulin at a much higher degree of accuracy and it also helps in digestion of fats and storage of sugars as glycogen.[32] However Metformin is a prebiotics(nutrient) which helps in increasing the butyrate formation in the gut. Combination of these prebiotics and probiotics produces a significant benefit to overall health in terms of insulin regulation and general metabolism of the body.

Emerging evidence has shown that"short chain fatty acids" play a vital role in elevating immunity level as well. The innate immune cells Such as macrophages and dendrite cells achieve their energy for proliferation from postbiotics released by gut microbiome. However dysbiosis can lead to ineffective response from these immune cells. So, the prebiotics, probiotics or their combination might be helpful if specifically administered, in order to synthesize the desired postbiotics for the innate immune cells. Olive leaf extracts, complex mushrooms, zinc, magnesium, boron based

prebiotics improve the antiviral components of immune system and prebiotics based on these extracts have provided evidence of more formulated response against Viruses by cytotoxic T cells and Natural killer cells.[33,34]

The two main inflammation pathways includes, "The immune pathway", which involves the coordinated communication of different immune cells and blood vessels through an intricate cascade of molecular signals and "Arachidonic acid Pathway" whenever there is a tissue damage inside or outside Of the body, the inflammatory response is driven by this pathway. It includes the release of the prostaglandins and the leukotriene. Both of these pathways are equally prevalent in inflammatory response. A constant damage to the intestinal lining is due to the latter pathway.[35,36] However, a combination of short chain fatty acids such as, Docosapentaenoic acid (DPA), Eicosapentaenoic Acid (EPA) and Pre-resolving mediators (PRM'S) ,have proved a significant success in treatment of chronic conditions associated with damaged intestinal tissue linings.[37,38] Therefore Prebiotics and Probiotics might help in establishment of a healthy and more specific immune response in case of COVID-19 infection. Also the establishment of a cytokines storm during immunological phase of COVID-19 infection might not take place in a short duration of time, when the intestinal microbiome is in optimal composition and diversity.

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