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Gut Microbiota and Heart, Lung and Neurogenerative Diseases

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Abstract

More than 100 trillion symbiotic microorganisms live on and within human beings and play an important role in human health and disease. Gut microbiota or Human microbiota is considered as an "essential organ" which is bearing 150 times approximately more genes that are discovered in the whole human genome. Important advances have shown that the gut microbiota is involved in basic human biological processes, including modulating the metabolic phenotype, regulating epithelial development, and influencing innate immunity.

Keywords: Gut microbiota, Cholesterol absorption, Lung, heart, Covid-19

Microbiome and Heart

In body's cholesterol balance gut lumen plays crucial role controlling it and majority cholesterol absorption take place via exogenous route [1-7]. Different sources accounts for luminal cholesterol which mainly obtained from our oral diet, hepatobiliary pathway [8] and trans-intestinal cholesterol efflux (TICE) to constitute de novo cholesterol [9,10]. Disease manifestations like atherosclerosis, hyper-lipidaemia, hypertension and Congestive heart failure have associations with altered gut microbiome diversity and metabolic syndrome with nonmodifiable risk factors include gender, aged and human genetics. It has both direct (via metabolites) and indirect (via Immune system) linkages with this phenomenon [11]. To maintain a healthy host state gut microbiota has vital role that includes nutrition to host and energy production, haemostasis of intestinal epithelial cells, metabolism of drugs and its toxicity, shelter from pathogens and response from body immune system [11].These microorganisms can also generate microbial products such as uremic toxins, bile acids, trimethylamine-N-oxide (TMAO), short chain fatty acids (SCFA), lipopolysaccharides (LPS), nitric oxide, vitamin K, vitamin B complex, gut hormones, and neurotransmitters, which can alter host metabolism and affect bodily functions in health and disease states [11].

Infectious pathogens like *H Pylori*, *Cytomegalovirus* CMV, *C pneumonia* and *P Gingivalis* have been linked to atherosclerosis [12]. There were differences observed in host microbiota between asymptomatic and symptomatic atherosclerotic plaques formation. Pathogenic microbiome families like *Thiotrichacaea, Helicobacteracaea* and *Neisseriaceae* were found in symptomatic plaques while *Porphyromonadaceae, Bacteroidaceae, Micrococcacaea,* and *Streptococcacaea* families of Microbiome were seen in asymptomatic plaques [13]. Gut Microbial species like *E. Coli, K pneumoniae* and *Strept viridians* have also been linked with heart failure [14]. Also increase opportunistic pathogens including *Enterobactor, Oscillibacter, Megasphaera* and *Desulfovibrio* with altered gut microbiota have been seen in patients with transient ischemic attack TIA and stroke [15]. There is significant contribution from gut microbiota towards considerable change in lipid composition of blood which can alter coronary artery disease advancement e.g Higher HDL is associated with *Firmicutes* such as *Lactobacillus reuteri*, whereas low HDL cholesterol have been linked with the genus *Eggerthella* [16].

The Effects of gut microbiota on CAD postulated to be via Direct effect, Bile acid modulation, Coprostanol production, Short chain fatty acid production, Trimethylamine-N-oxide production and Indirect effect via the manipulation of our immune system [11]. Gut microbiome modulation with production of different metabolites such as short chain fatty acids, Trimethylamine N-oxide, coprostanol and bile acids are directly and indirectly linked to diet with its effects on blood cholesterol levels and development of coronary artery disease. By understating the linkage among different bodily factors that co-ordinate together to alter gut microbiome and development of disease highlights on gut pathogen-mediated mechanisms which can various preventive and therapeutic approaches towards high-precision microbiome-based coronary disease can be adopted that can lead towards more effective and more precise microbiome-based coronary artery disease therapeutic and preventive approaches [11].

Microbiome and Lung

There is now data that indicate the existence of different microorganisms in the lung just like an association between the gut microbiome and heart [17]. Organism like *Proteobacteria, Firmicutes* and *Bacteroidetes* predominate in the lung while gut also has preponderance of *Firmicutes* and *Bacteroidetes* species [18]. The "gut-lung axis" has been defined as an important link between the lungs and gut microbiome as gut microbiota has been shown to influence the pulmonary environment of human body [19]. It is postulated to be bidirectional, like endotoxins, different metabolites can impact the lung parenchyma through hematogenous route and when there is inflammatory state of lungs it can also influence and alter the gut microbiota [20]. Migration of Microbial species, their eradication in healthy individuals and growth environment locally mostly in advance pulmonary diseases are three main determinants factors that constitute human respiratory microbiome [21]. So, modifications in microbiome can occur in different pathological circumstances secondary to changes in these mentioned major factors. Air Inhalation which constitutes 104-106 bacterial cells/mm3, aspiration of microparticles in healthy persons and direct spread through the mucosal tract of lung are possible causes of microbial immigration [21]. Various triggering elements like allergens, viruses and pollutants begins the airway inflammation with rapid stimulation of neutrophils, alveolar macrophages, eosinophils, lymphocytes, and dendritic cells, all of them affect the local growth environment of airway microbiota. All these conditions lead to

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disturbed microbiome that further promote airway inflammation via pattern recognition receptor interactions and pathogen-associated molecular patterns [21].

There is significant decline of probiotic species along with likely rise of pathogenic bacteria seems to be the key factor for vulnerability, chronization and advancement of pulmonary diseases that results from Lung microbiome transformation. Chronic obstructive airway disease COPD patients commonly had *Pseudomonas* species while in healthy population most commonly they found to have Bacteroidetes, mostly *Prevotella* species in there lower respiratory tract [22]. Also, there is less diversity of flora in COPD patients noted. More date showed that Haemophilus and Pseudomonas species were predominant in COPDs microbiome while Non-COPD group had more *Veillonella, Fusobacterium, Prevotella* and *Streptococcus* species [23]. Probiotics have postulated to effect by modulation of immune system there by alleviating different pulmonary disease severity, among few probiotics include galactosachharides (Gos), fructo-oligosachharides (Fos) and wheat bran. They raise butyrate levels leading to decline in inflammation and alleviation of aggravation in disorders like cystic fibrosis and asthma exacerbations [24,25].

Covid-19 or Coronavirus disease 2019 is a new pandemic calamity that is threatening the whole world with its additional socioeconomic affects. It is now named SARS-Cov-2 which is caused by the novel beta coronavirus. Its Silent features are highly transmissible and contagious, manifestation in elderly has high mortality with pulmonary infiltrated that require ventilatory support [24]. The gut microbiome role in affecting pulmonary diseases has been mentioned in literature. It is also evident that this virus infection causes alteration in the gut microbiome. Asa mentioned earlier oral diet, ecological factors and human genetics play a vital role in forming gut microbiota which can influence immunity. Gut microbiota diversity decline in older population with co morbidities and Covid-19 has been mostly deadly in elderly patients which again highlight the role of gut microbiota in this disease [25]. Enhancing gut microbiota diversity by personalized nutrition support and strengthening the microbiome environment known to enhanced immunity can be one of the potential ways by which the impact of this disease can be minimized prophylactically in old individuals and immune-compromised hosts. More studies are required to further elaborate the role of co-supplementation of individualised functional food supplements including prebiotics/ probiotics along with existing new treatment modalities [25].

Microbiome and Neurodegenerative Disorders

There is increasing understanding about the gut-brain axis and its alteration by gut microbiota which potentially may play a significant role in the genetic and physiological basis of age-related disorders and neurodegenerative diseases. Awareness about the impact of intestinal microbiome towards the performance and mediation of the nervous system can intervene using unique microbial-based approaches to treat neurological disorders [26]. Classification of neurodegenerative disease includes Parkinson Disease (PD), Alzheimer's Disease (AD), Amyloid Lateral Sclerosis (ALS) and Multiple Sclerosis (MS). Although physiological symptoms of each of these diseases are different, they have common cause associated with disease pathology following during normal aging process. Two major systemic events Oxidative damage and tissue inflammation exacerbate further neurodegeneration, which are additional insult towards normal aging process. Decline in intestinal stability and diversity in microbiota in the elderly is associated with reduce in brain volume and decline in cognitive functions. With advancing age alteration in brain morphology is linked with diminished immune system, enhanced oxidative stress, and amyloid plaque deposition in the brain tissue. All these factors lead to impaired cognitive and behavioral functions and manifest various age-related memory diseases.

Gut microbiome is an vital environmental factor related to the risk of PD, a substantial decrease in *Prevotellaceae* levels is observed in patients with PD compared to healthy controls, a positive association between *Enterobacteriaceae* levels and the severity of postural instability and gait difficulty was discovered, suggesting potential role of gut microbiota in the PD phenotype, the *Ralstonia* genus *Proteobacteria*, which are hypothetically "pro-inflammatory" were significantly increased in the mucosa of PD patients than in healthy controls [26]. Probiotics supplementation can be a useful means to modify the PD-associated microbiome environment and enhance further GI function and therefore decrease intestinal leakage, bacterial translocation, and associated inflammation in the enteric nervous system. Through the Gut-brain-axis, gut microbiota may alter CNS function by production of various neurotransmitters and neuromodulators such as dopamine, serotonin, or short chain fatty acids. Gut microbiome may change the function of intestinal enterochromaffin cells that generate different hormones and neurotransmitters. Alterations or dysregulations along the brain-gut-microbiota axis can substantially impact towards the pathogenesis of Alzheimer's disease (AD) like neurodegenerative disorders. Various studies revealed that probiotics have a positive effect by enhancing intestinal epithelial integrity, protective affect to prevent barrier disruptions, modulate proinflammatory response in host, and preventing the initial damage or may prevent further progress of neuroinflammatory and neurodegenerative phenomena. Furthermore, literature supports the supplemental probiotics including Lactobacilli and *Bifidobacteria* which considerably improved the Mini-Mental State Examination scores in patients with AD [27].

Multiple sclerosis (MS) is a common neurological disorder of young individuals in western world, in which both combination of genetic and environmental factors is involved in pathogenesis of this disease. There is increasing evidence that supports important role by changes in the gut microbiota. In MS patients; Species of *Eubacterium rectale, Faecalibacterium, Fusobacteria and Corynebacterium* were lower in their gut flora while large fraction of species of *Escherichia, Shigella, Clostridium, Firmicutes were found, when* compared to healthy population [28,29]. Introduction of probiotics that includes *Lactobacillus casei, Lactobacillus acidophilus, Lactobacillus reuteni, Bifidobacterium bifidum,* and *Streptococcus thermophilus*) before the initiation of treatment in experimental autoimmune encephalomyelitis EAE resulted in its delayed onset and milder course [30,31].

There is sufficient evidence in literature for the presence of association between CNS, gut and intestinal microbiota and studying its linkages between gut microbiota diversity and CNS diseases has become a innovative approach in disease understanding pathophysiology and new areas are explores in the field of research, explore new and effective treatment modalities [32].

Conclusion

It is crucial that we should explore and elaborate further the interlinked bodily factors that work simultaneously to affect intestinal microbiome and various heart, lung and CNS disorders in order to fully recognise role of gut microbiota in human host and to explore new therapeutic options. New research in microbiota to discover more diversities, has driven our understanding to new horizons in infectious and chronic disorders. Covid-19 has severely affected the whole world in various aspects including health, psychological, social, and economic

in our daily lives. We need more research trials to explore further therapeutic options about Covid-19 so that we will be more organised in future if similar pandemic hit us again. Other organism like fungi and phages that also constitute a major portion of ecosystem in human gut might have a role for treatment options in Covid-19?

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