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The influence of gut microbiome on the initiation and advancement of chronic non-communicable disorders.

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ABSTRACT:

Non-communicable diseases (NCDs) are responsible for causing a significant proportion, specifically, up to 72%, of worldwide mortality. NCDs exert their impact on individuals across all geographical regions. Out of the total global mortality count of 52.8 million in the year 2010, NCDs accounted for 34.5 million deaths. Chronic low-grade inflammation, characterized by increased pro-inflammatory cytokines, has been associated with a range of health conditions including obesity, cardiometabolic illnesses, various malignancies, respiratory and auto-immune disorders, arthritis, and depression. These NCD-related fatalities encompass a range of conditions, namely cardiovascular diseases (such as coronary heart disease, cerebrovascular diseases like strokes, and peripheral vascular diseases), diabetes, cancers, and chronic renal diseases, gastrointestinal diseases etc. The development of some conditions is associated with a combination of hereditary factors and lifestyle choices, such as physical inactivity, inadequate diet, and excessive alcohol use. The establishment of healthy gut microbiota baselines is advantageous for determining dysbiosis in several chronic non-communicable conditions. The genome of all gut microbes is essential to the body's nutritional, metabolic, physiological, and immunological activities. Altering the gut microbiota to lessen the risk of numerous NCDs by diet and lifestyle modifications is of significant interest. This review has shown a correlation between gut health and its impact on the susceptibility to non-communicable diseases. The gut microbiota has been identified as a significant contributor to the development of these diseases.

Keywords: Non-communicable diseases, Pro-inflammatory cytokines, dysbiosis, Cardiovascular

diseases, Gut microbiota.

1. Introduction

World is currently facing an epidemiological shift with its growing development both socially and economically. Emphasizing nationally, there is a visible shift in disease pattern with mortality due to non-communicable diseases reaching to 65% in India out of all the deaths that occurred in 2019 [(2)]. The overall disability adjusted life years due to non- communicable diseases rose from 30.5% in 1990 to 55.4% in 2016 [(1)]. On one hand where there is a notable decrease in deaths because of communicable, maternity, neonatal and nutritional diseases (CMMNDs), there is an increase in health loss due to non-communicable diseases like cardiovascular diseases (CVD), obesity, cancer, diabetes etc. [(1)]. The risk factors responsible for the increasing burden of NCDs points to behavioral and metabolic elements. The risk factors include use of tobacco and alcohol, insufficient consumption of fruits and vegetables, physical inactivity leading to overweight and obesity, high blood pressure and blood sugar values. These factors contribute in developing cardio vascular diseases, diabetes, cancer etc. [(2)]. Change of the dietary pattern from diets rich in fruits, vegetables, and whole grain cereals to diets high in fat, sugar and salt are leading to an increased incidences of high blood pressure and high blood sugar. According to the studies more than half of the Indian population is physically inactive [(3)]. It is predicted that prevalence of overweight population will increase by two folds and that of obesity will increase by three folds till 2040 [(4)]. According to the Great Indian Blood Pressure Survey, 30.7% of the population suffers from hypertension [(5)]. The gastrointestinal tract of a human contains more than 100,000 billion microorganisms that is 10 to 100 times greater than the number of human cells [(7)]. The human microbiota majorly contains 2 bacterial phyla- *Firmicutes and Bacteroidetes;* apart from this human gut has diverse microbial community that depends on variability in dietary patterns and lifestyle habits [(10)]. The gut composition depends on the
Difference in lifestyle, age transitions, use of any antibiotics, dietary habits as well as cultural habits. Recent studies have linked gut microbiota with various non communicable diseases such as cardiovascular diseases, diabetes, obesity, cancer, and various gastrointestinal disorders [(8)]. Gut being associated with CVD development, has emerged as a target for therapeutic approach towards NCDs [(87)]. Diet is said to be one of the main controllers of composition of the gut microbiota that plays a key role in processes such as homeostasis and other biological functions that takes place through metabolites from nutrient fermentation done by microbes- short chain fatty acids [(9)]. The human- microbial interaction can be modulated by altering dietary habits. Studies have shown that when physical exercise is combined with diet, the gut microbiome becomes more diverse and enhanced [(11)]. The interplay between dietary exposure, gut microbiome, host genetics and other environmental exposure influence our metabolism, physiology, and disease susceptibility. It is known that dysbiosis (abnormal changes in intestinal microbial composition) is responsible for pathogenesis of altered intestinal diseases which has now extended to various metabolic diseases. Studies have regarded gut microbiota as the largest endocrine organ of the human body that can produce several biologically active compounds that can be carried in circulation or distribution to various sites in the body of the host [(12)]. In this review we will highlight various non- communicable diseases and the role gut microbiota plays in their development.

2. Methodology

Searches were conducted in PubMed, Medline, and Google Scholar for articles published in English from 2000 to December 2021, as well as other bibliographic references and appropriate

sources using the keywords "gut microbiota," "microbiota," "pathogenesis," "colorectal cancer," "Chronic Kidney Disease," "Inflammatory bowel diseases," " Irritable bowel Syndrome," "Diabetes and Obesity," "Cardiovascular Diseases" and we divided them into five primary groups based on the study scopes, "Cardiovascular disorders", "Diabetes and Obesity", "Cancer", "Renal disorder", "Gastrointestinal disorders". This review involves 88 research paper including original researches, review researches and case studies. An average of 200 research papers were studied, out of which those which did not include factors associated with gut or risk of developing NCDs were excluded.

3. Discussion

Gut Microbiome and Cardiovascular Diseases

Evidence of Gut Microbiome Disruptions as a Cause of Cardiovascular Diseases

WHO defines CVD as "a group of disorders of the heart and blood vessels". CVD is emerging as an epidemic of the recent times with its increasing burden on low and middle income nations due to various transitions like " personal and collective wealth (economic), social structure (social), demographical and behavioural" [(86)]. Out of several metabolites that are identified in plasma associated with cardio- vascular disease (CVD) risk, three got the structural validation linked to phosphatidylcholine (PC) metabolism- choline, betaine and Trimethylamine N-oxide (TMAO) [(13)]. TMAO is known to develop from bacterial metabolization of choline through an intermediate trimethylamine (TMA) which subsequently goes through liver to form TMAO by the oxidative action of flavin monooxygenase (FMO3) [(14,15)]. PC is the main source of choline in omnivores and its ingestion is linked to increased levels of choline, betaine and TMAO levels. Further, TMAO levels in plasma have shown the strongest correlation with CVD risk [(13, 16)]. In a study, subjects underwent coronary angiography wherein increased TMAO levels predicted major cardiac incidences like myocardial infarction, death, and stroke over three years of time period. Patients lying in the upper quartile of increased TMAO levels had 2.5 times increase in risk experiencing major cardiac incidence [(17)].

Gut Dysbiosis And CVD: What Role Does Gut Dysbiosis Play?

The primary sources of TMAO production- phosphatidyl choline, choline and carnitine are linked to gut microbiota. Therefore, dietary intervention strategy to reduce the levels of choline and carnitine can be done by diet modulation. Composition of the gut microbiota varies depending if an individual is vegetarian/ vegan or carnivorous/ omnivorous. Vegetarians possess less ability to synthesize TMA and TMAO from L-carnitine resulting in low levels of plasma TMAO [(18)]. TMAO is the amine that is dependent on the microbiota for its production and hence, is variable factor for development of CVD. An

Increase in TMAO levels can lead to inflammation, atherosclerosis, dysfunction and remodelling of vascular and cardiac systems [(13)]. As shown in **Figure 1.** Food we consume provides the body with Choline, Betaine, L-carnitine, Phosphatidylcholine, Trimethylamine N-oxide which enters the gut. Enzymes TMAO reductase and Betaine reductase are produced by the microbes present in the gut that act on these amino acids and converts them into TMA. TMA on entering liver is acted upon by Flavin-containing monooxygenase 3 (FMO3) and gets converted into TMAO. Some of the converted TMAO clears through renal channels and passes in urine whereas some gets circulated in the body. The circulated TMAO can lead to accelerated atherosclerosis, heart failure and CKD.

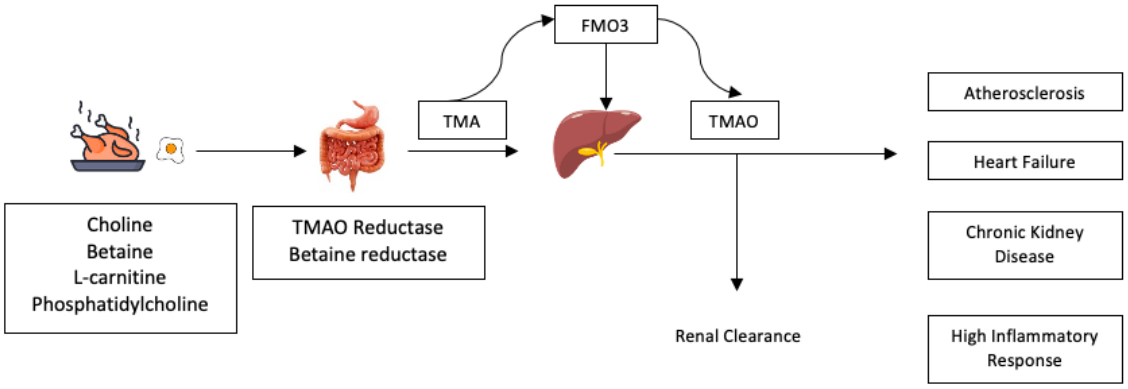

Fig.1 Metabolism of food containing choline, betaine, L-carnitine and phosphatedylch oline into trimethylamine-N-Oxide through hepatic pathway

It is necessary to reconcile the arbitrary role of elevated TMAO levels in CVD with the preventive benefits of its dietary precursors and the reduced CVD risk linked to red meat consumption. Future research should examine the utility of TMAO in CVD in more detail, to make the results of even miniscule changes in levels of TMAO clear, and test if elevated levels of TMAO leads to progressive increase in the risk of developing CVD. Further, strong reinforcement can help in double utilization of TMAO- as a target for treatment in high-risk people with numerous co-morbidities and as a biochemical indicator of CVD risk. The main challenge to address however, remains that of reducing the levels of TMAO without adverse effects [(19)]. In people with CVD, targeting of TMAO by dietary alterations may be beneficial. Consuming fewer foods contain TMA precursors and more foods that support the bacteria that don't produce TMA (for example, vegetables/ fruits) may offer the simplest approach to reducing TMAO. Recent research suggests that diets dominant in red meat and diets rich in white meat (or non-meat) differ by up to three times in terms of the amount of circulating TMAO. Omnivores or vegans are said to have 2-fold greater levels of circulating TMAO [(18)].

Expert View on CVD and Gut Microbiome

Existing studies have proposed direct and indirect pathways explaining the role of intestinal microbiome, enzymes and metabolic disorders. The role of biliary enzymes has been established in cardiovascular diseases, however, the understanding is poor. Future studies should emphasise on interpreting the mechanism responsible for bringing the alteration in gut and being the causal factor for cardiovascular diseases. Also, the treatments should focus on long term effects to establish the extent of therapeutic potential.

Gut Microbiome, Diabetes and Obesity

Evidence of Gut Microbiome Disruptions as a Cause of Diabetes and Obesity

The metabolic processes that takes place in gut microbiota helps in deriving calories from the food that is consumed which then helps store these calories for future use in terms of energy and nutrients [(20)]. Studies suggest that this calorie and nutrient extraction depends on the diversity of the microbiome from the diet. In an experiment, despite eating 29 percent more food each day, it was found that germ-free male mice ("mice that are raised in absence of any microorganism") had 42 percent less total body fat than conventionally reared mice with normal gut flora [(21)]. After colonization with cecal microorganisms from their normal counterparts, the mice that were formerly germ-free displayed a 57 percent rise in total body

fat, a 7% reduction in lean body mass, and a 27% reduction in daily food intake [21]. There was an increased uptake of monosaccharides from the stomach, as well as higher levels of lipogenic enzymes and increased occurrence of insulin resistance post colonization. Therefore, there is growing evidence that alterations in the gut microbiota cause changes in the host's metabolism and weight.

Gut Dysbiosis and Obesity: What Role Does Gut Dysbiosis Play?

Similar microbial clusters were found more in obese individuals as compared in healthy patients in recent research, showing that increasing body- mass index (BMI) is linked with decreased microbial diversity. *Firmicutes* and *Bacteroidetes* were the most common phylum across individuals of all weight groups, however large number of phylum *Proteobacteria* was found in obese people as compared to overweight or healthy people. Abundancy of *Bifidobacterium, Faecalibacterium* and bacteria producing butyrate were shown to be less in obese patients, but *Fusobacterium, Escherichia-Shigella*, and *Pseudomonas* were found to be more abundant [22]. There was a positive correlation between *Escherichia coli* and increased BMI and blood glucose, whereas *Fusobacterium* and *Bacillus* had a positive correlation with higher insulin levels [23]. In obese individuals, enzymes involved in glucose or insulin signaling pathways were also suppressed [22]. Changes in specific population of microbes may be of more importance rather than the overall "phylogenetic ratio" that leads to changes in short chain fatty acids (SCFA) and enzyme synthesis that directly impact glucose and insulin homeostasis in turn contributing to the growth of obesity.

Obesity has been linked to alterations in microbiome diversity in humans. Mixed evidence suggests higher *Firmicutes/Bacteroidetes* ratios is the reason. Loss of body weight was associated with a decrease in *Firmicutes* and a rise in *Bacteroidetes* in obese human individuals [24]. The result was independent of whether patients followed a fat-restrictive or carbohydrate-restrictive diet for a year. On the contrary, during a study when compared to thin participants, obese participants had higher levels of *Actinobacteria*, lower levels of *Bacteroidetes*, and low microbial diversity, but no significant change in *Firmicutes* abundance [25]. Some studies have indicated that obese patients had comparatively increased number of *Bacteroidetes* and lower *Firmicutes* than their lean peers, whereas some discovered no significant change in *Firmicutes/Bacteroidetes* ratio in obese vs lean subjects [26].

Gut Dysbiosis and Diabetes: What Role Does Gut Dysbiosis Play?

Changes in the gut microbiota have been linked to both prediabetes and type 2 diabetes. Researchers have found that prediabetic patients had much more abnormalities in their microbiomes than healthy controls, including reduced microbial diversity [27]. **Figure 2** shows the difference between gut of a normal person v/s gut of a person suffering from obesity and/or Type 2 Diabetes mellitus.

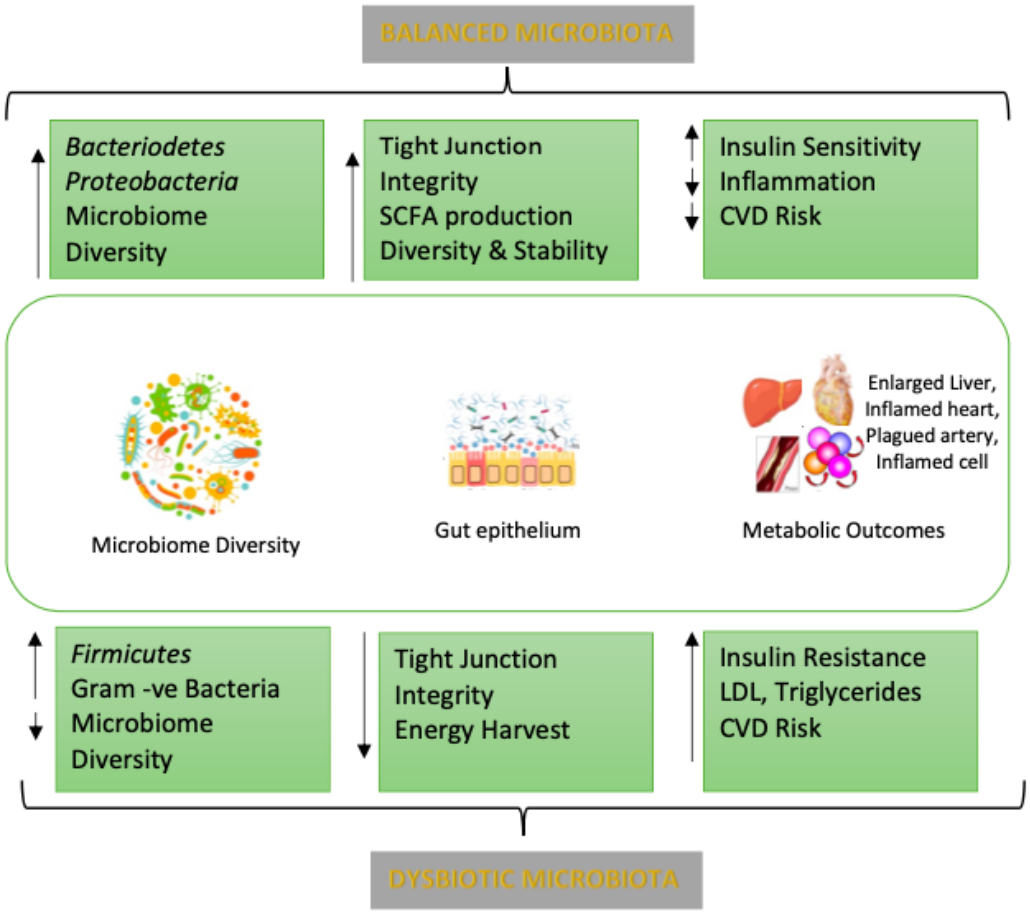

Fig 2 the difference between normal human gut and a dysbiotic gut. A dysbiotic gut leads to increase in gram negative bacteria increasing the lipopolysaccharide production, leading to CVD risk and insulin resistance.

This is consistent with research showing that a diverse microbiome is necessary for gut health in obese individuals and healthy controls. Increased amounts of *Ruminococcin* and *Streptococcu*s, as well as decreased levels of *Clostridium* were found in pre- diabetic patients [(27)]. This is in line with mouse studies that show a link between *Clostridium butyricum* (butyric producing gram-positive bacteria) and glucose and insulin tolerance, C-reactive protein and hemoglobin A1C levels, and body mass index (BMI) [(28)]. Diabetic mice treated with *C. butyricum* strains had lower blood sugar levels and less insulin resistance, as well as lower inflammatory markers, higher mitochondrial metabolism, and a reduction in gut dysbiosis [(27)]. As previously mentioned, butyrate, which is upregulated by *C. butyricum*, has positive effects on insulin resistance, brown adipose tissue thermogenesis, fat mass, and obesity [(29)]. A metagenome-wide analysis in which genes likely to be connected were classified into metagenomic linkage groups (MLG) and then aligned with bacteria based on sequencing revealed that MLGs from the diabetic cohort were primarily derived from pathogenic opportunists, whereas MLGs from healthy controls were primarily derived from butyrate-producing bacteria [(30)]. Furthermore, *Faecalibacterium prausnitzii* is a major butyrate generator, and faeces from slim people were shown to contain greater quantities of *F. prausnitzii* than obese people, with even lower levels in obese, diabetic people [(31)]. In fact, there was a substantial difference in *F. prausnitzii* abundance between obese people with and without diabetes [(31)], suggesting that butyrate levels differed between the two groups.

Expert View On Diabetes, Obesity And Gut Microbiome

The gut microbiome's function in the relationship between inflammation and insulin resistance has been well-documented in recent decades. Understanding host-microbiome interactions and precise mechanisms of modulation is merely the tip of the iceberg. Methodologies to determine gut microbial composition and function need to be standardised in order to make it easier to understand the role of mechanistic pathways involving short-chain fatty acids, propionate, butyrate, bile acids, and lipopolysaccharides in the pathogenesis of obesity, metabolic syndrome, and diabetes complications [(88)].

Gut Microbiome and Cancer

Evidence of Gut Microbiome Disruptions as a Cause of Colorectal Cancer

Several investigations have indicated that there is an evidence that certain bacterial species contribute to the aetiology of colorectal cancer (CRC), and newer researches have suggested a mechanism on how the gut microbiome contributes to the development of CRC [(32)]. "*Clostridium septicum, Enterococcus faecalis, Streptococcus bovis, Bacteroides fragilis, Helicobacter pylori, Escherichia coli, and Fusobacterium spp."* have been discovered and are believed to have a part in the aetiology of colorectal cancer [(33)]. *Streptococcus gallolyticus* (formerly *Streptococcus bovis*) has been found in about 20–50 percent of colon cancers and 5% of normal colons, respectively. *"Ruminococcus bromii, Clostridium clostridioforme*, and *Bifidobacterium longum",* compared to the overall population, had a low prevalence among CRC patients. Additionally, numerous studies have noted a considerable increase in the numbers of "*Bacteroides, Prevotella* and *Fusobacterium"* nucleate in the CRC population [(33)].

Gut Dysbiosis and CRC: What Role Does Gut Dysbiosis Play?

Studies have discovered a strong connection between the microbiota in the gut and the development of colorectal cancer [(33-36)]. *Verrucomicrobia, Actinobacteria and Proteobacteria* are the next most prevalent species present in intestinal gut flora of a healthy individual after *Bacteroidetes and Firmicutes,* according to global research. Intestinal microbiota may produce genotoxin or other secondary metabolites that directly or indirectly alter cell transformation, such as precursor's reactive oxygen species that damage DNA. *Bacteroides fragilis, Helicobacter pylori (H. pylori), Clostridium septicum, Streptococcus bovis, Enterococcus faecalis, Fusobacterium spp*., and *Escherichia coli* are all thought to have a role in colorectal carcinogenesis. However, the processes of some of these bacteria are still partially understood.

The incidence of *S. bovis* and *C. septicum* in CRC patient's shifts between 33% and 100%, sometimes reaching up to 40%, according to several studies. [(37)]. Boleij, and colleagues in their meta-analysis investigation, confirmed the connection between CRC, *S. bovis* and infections caused by *C. septicum* [(38)]. Although *C. septicum* is typically found in soil and does not belong to the healthy gut flora, there is no clear processes explaining why *C. septicum* infection is so commonly associated to colon cancer ([(39)]. The present microbiota causes a strong inflammatory response in the colorectum tissues by creating inflammatory and angiogenic cytokines, which promotes the growth or development of colorectal cancer..

In a research with 179 people with colorectal cancer and 119 healthy people had colonoscopies, with the results showing greater number of Bacteroides/ *Prevotella* in patients with colorectal cancer [(40)]. *Bacteroides fragilis*, an enterotoxigenic bacteria (bacteria that produce intestinal toxins that may cause diseases like cholera), was found in higher numbers in CRC patients' faeces.

However, a study stated that there was no discernible difference between the microbiota present in the proximal colon and distal colon of 30 healthy individuals and 31 patients suffering from cancer; although, in tissue samples from colorectal cancer patients *Firmicutes, Fusobacterium, Lactococcus* and *Fusobacteria* were more common than *Escherichia-Shigella*, Pseudomonas and *Proteobacteria* [41].

Enterococcus faecalis, a naturally occurring bacteria in the digestive system, was discovered in patients with colorectal cancer. *E. faecalis* has recently been recognised to be pathogenic in human [42] as patients with CRC had much more *E. faecalis* in their stools than individuals without the illness [43]. The presence of these bacteria can lead to production of "reactive oxygen and nitrogen species (RONS)" that can result in breakage of DNA, point mutations, and unstable chromosomal structures. These skills show the evolution of a common commensal into an entity that can contribute to "colon oncogenic transformation" [44].

E. coli is a common commensal bacterium in the human gut, however numerous investigations have discovered a strong connection between mucosa-adherent E. coli and CRC [45] as a study reported in 2004 that *E.coli* was found in more than 70% of mucosa samples from CRC patients [46].

Expert Review on Microbiota and Cancer

According to the investigations, *Fusobacterium, Porphyromonas, Bacteroidetes*, and *Prevotella* were the most prevalent modifications to the gut microbiota in faeces and biopsy samples from CRC patients. In affluent and developing nations, however, there appears to be little difference in bacterial variety. As a result, while there is a clear link between the gut microbiota and CRC, some questions remain unsolved. As previously mentioned, the gut microbiota significantly contributes to the development of CRC through a number of pathways, including genotoxin, metabolism, and inflammation. As a result, research has demonstrated that alterations in the makeup of the gut microbiota can cause an immune reaction in the host and have a significant impact on the intestinal epigenetic pathways of the host. The researches reviewed in this review did not emphasise tumour categorization based on molecular characteristics, and why few adenomas develop into malignancies while others are stable or even regress, however, is unknown. *Fusobacterium* was found in greater quantity in cancerous tissues as compared to normal tissues. As a result, increasing *Fusobacterium* abundance might be connected to a higher risk of CRC.

Therefore, we strongly recommend that future studies focus on microbiota imbalances in relation to colorectal carcinogenesis molecular mechanisms in order to better understand the diversity of CRC tumours. Such research could also reveal any connections between the detrimental bacterial species present and the pathogenic features of adenomas. On the other hand, improvements in research techniques are probably going to produce useful data on the composition of both healthy and dysbiotic microbiota. To summarise, the gut microbiota has a definite role in the aetiology of CRC and may provide novel strategies for improved therapeutic management of CRC patients.

Gut Microbiome and Chronic Kidney Disease

Evidence of Gut Microbiome Disruptions as a cause of chronic kidney disease (CKD)

In one of the review research of CKD, it was found that the microbiome and the intestinal environment had a shift from a symbiotic to a dysbiotic state. According to the study, colonic protein fermentation spiked leading to an increase in uremic toxins produced by the microbiota, whereas carbohydrate fermentation decreased, leading to a reduction in the production of host-

beneficial metabolites (e.g., SCFAs) [47]. A study in 2017 has reported an increased population of aerobic (about 106 bacteria/mL) and anaerobic (roughly 107 bacteria/mL) organisms colonising the duodenum and jejunum in uremic patients than healthy people [48]. A study also discovered a considerable rise in the number of 190 bacterial "operational taxonomic units" (OTUs) from the *Brachybacterium, Enterobacteriaceae, Catenibacterium, Moraxellaceae, Polyangiaceae, Halomonadaceae, Thiothrix, Nesterenkonia,* and *Pseudomonadaceae* families in end-stage renal disease compared to healthy individuals [49].

Gut Dysbiosis and CKD: What Role Does Gut Dysbiosis Play?

A study has reported a significant rise in number of bacteria producing enzymes "urease, uricase, p-cresol and indole" and decrease in bacteria that produces enzymes that convert dietary fibre into short chain fatty acids in end stage renal disorder (ESRD) patients [50]. Renal failure alters the biochemical environment of the gastro intestinal tract which leads to gut microbiome dysbiosis and the ultimate disruption of mucosal layer in ESRD. There is a link between a dysbiotic gut microbiota, an uptick in the production of harmful metabolites and uremic toxins as well as a reduction in the production of metabolites that are beneficial (e.g., SCFA). The families yielding SCFA producing enzyme (butyrate) namely- *Prevotellaceae* and *Lactobacillaceae* were the microbial families among those four which were decreased in ESRD patients. Gut microbiome can be a potential target to minimise or end the uremic toxicity of the renal patients. The most prevalent species in ESRD patients were *Fusobacterium nucleatum*, which is involved in the manufacturing of indole and phenol, and *Eggerthella lenta*, which converts polyphenols into benzoic acid or 4-hydroxybenzoic acid, the precursors of hippuric acid ([51]. In the CKD rat model, these uremic toxins accelerated the onset of renal failure. On the contrary, no uniformity was discovered in the gut microbiota of ESRD patients, and a lack of distinctive microbial profile it possessed ([52]. As a result, it appears that CKD-related changes upregulate microbiota that produces particular uremic toxins and downregulates the microbiota that produces beneficial chemicals [53]. Poesen found increased creation of indoles, p-cresol, benzenes, aldehydes, furans, and branched-chain, medium-chain, and short-chain fatty acids in faecal metabolite profiles of patients on hemodialysis and lower formation of ketones [54]. He did, however, imply that the altered colonic microbial metabolism seen in CKD was linked to nutrition and, to a lesser extent, renal function loss. It was concluded that the increased accumulation of uremic toxins in CKD patients' plasma was not due to bacterial production of indole, p-cresol, or Indole acetic acid (IAA) [55]. It was also claimed that certain individuals, regardless of renal function, produce more particular protein-bound uremic toxins precursors than others. It's intriguing to consider how changes in hunger associated with renal failure can influence the consumption of foods that impact the microbiome [56]. Chronic renal disease may develop more quickly if there is a decrease in resistant starch content and a change in appetite. In cases of severe renal failure, the colon becomes the main route for the synthesis of oxalate and uric acid. *Actinobacteria, Firmicutes,* and *Proteobacteria* were shown to have the greatest increases in individuals with ESRD as compared to healthy controls in one research [57]. Patients undergoing peritoneal dialysis showed a distinct microbial community from healthy controls. *Bifidobacterium catenulatum, Bifidobacterium longum, Bifidobacterium bifidum, Lactobacillus plantarum, Lactobacillus paracasei*, and *Klebsiella pneumoniae* were shown to be less common in peritoneal dialysis patients [58]. There may be additional causes for the variation in microbiota composition between patients with uremia and healthy controls, including phosphate binders, comorbidities like diabetes, decreased fibre consumption in patients with CKD and ESRD, and a shorter intestinal transit time in patients with uremia. Dialysis patients frequently have constipation, with hemodialysis patients suffering it in 63% of cases and peritoneal dialysis patients in 29% of cases [59].

Expert View on Gut Microbiota and CKD

Understanding the gut microbiome's potential for metabolism and its crucial role in the cause of disease of various chronic inflammatory illnesses has significantly expanded in recent years. The gut represents as a promising future target for reducing uremia-related consequences. However, more researches are needed to establish the gut microbiome pattern in renal disorders and to investigate the relationships between different types of kidney diseases and the gut microbiota. It has already been shown that chronic kidney disease is associated with intestinal inflammation and epithelial barrier impairment, resulting in accelerated systemic translocation of bacterial-derived uremic toxins (e.g., p-cresyl sulphate, indoxyl sulphate, TMAO, and others) and oxidative stress injury to the kidney. These results have opened up new therapeutic avenues for the treatment of uremia, inflammation, and renal disease development in CKD patients, as well as the avoidance of negative consequences. Numerous therapies aimed at restoring appropriate gut microbiota composition and slowing renal disease development have been investigated. Dietary therapies containing prebiotics, probiotics, and symbiotic appear to be a promising technique for managing uremic toxins in CKD patients.

Gut Microbiome and Gastrointestinal Disorders

Evidence of Gut Microbiome Disruptions as a Cause of Gastrointestinal Disorders

"Irritable bowel disease (IBD), irritable bowel syndrome (IBS), gastric cancer (GC), colorectal polyps, colorectal cancer (CRC), liver cirrhosis, non- alcoholic fatty liver disease (NAFLD)", have been associated with abnormalities in composition of gut microbiome and its function [(60)]. This section focuses on microbiome-gastrointestinal illness connections that have recently been discovered in the literature.

Gut Dysbiosis and IBD: What Role Does Gut Dysbiosis Play?

The two primary types of IBD- Crohn's disease (CD) and ulcerative colitis (UC), affect the digestive tract and is a persistent, recurring and remitting inflammatory illness. Despite numerous research, no definitive cause has been found, although it is most likely brought on by a confluence of both genetic factors as well as environmental factors that could impair the response of host's immune system to the gut bacteria. Intestinal dysbiosis is now recognised as a potentially significant factor underpinning IBD development [(61)]. It's important to remember that CD and UC are more common in regions with high bacterial loads, especially in the terminal ileum and colon. IBS frequently exhibits decreased microbiome diversity and stability due to an increase in *Firmicutes* and a deficiency in taxa related to *Bacteridetes* [(62)]. It is shown in two investigations that in genetically susceptible mice, dysbiosis can arise before the start of intestinal inflammation [(63)]. The loss of specific bacteria's defensive capabilities as a result of their depletion has a significant impact on illness. A reduced prevalence of *F. prausnitzii* in patients with IBD has been found in several recent investigations [(64)]. This commensal belongs to the *Firmicutes* phylum and is a major generator of SCFA, which has anti-inflammatory and cellular protective properties. The microbial function was regularly changed more frequently (12%) than composition (2%) as a result of developments in DNA sequencing, which led to the conclusion that studies on the composition of the microbiota may underestimate its impact on the aetiology of IBD [(65).]

Gut Dysbiosis and NAFLD: What Role Does Gut Dysbiosis Play?

NAFLD refers to a group of liver illnesses characterised by fat accumulation in the liver, ranging from steatosis to non- alcoholic steatohepatitis, fibrosis, cirrhosis, and finally hepatocellular cancer. NAFLD requires a daily fat intake of more than 20 g for women and more than 30 g for men. In recent years, NAFLD has emerged as one of the world's most

significant causes of liver disease [66]. The influence of lifestyle changes such as food and physical exercise on metabolic control and liver histology is significant [67], emphasising the relevance of environmental variables in this illness. However, there is a lot of variation in NAFLD development that neither genetics nor environment can explain. The liver is the first organ to be exposed to gut-derived metabolites, such as dietary nutrients and microbiota-related products, via the portal tract. Microbiota dysbiosis has been identified as a critical role in the pathogenesis of all phases of NAFLD [68] due to this direct contact between gut and liver. Dysbiosis can cause increased intestinal permeability, allowing commensal metabolites to pass through the vascular system and into the liver (endotoxemia), causing lipid metabolism disturbance and inflammatory processes in the liver [69]. Numerous researchers have looked into the microbiome makeup in NAFLD patients. When the gut microbiota of non-obese NAFLD patients and healthy controls were compared, the first group had more *Bacteroidetes* and less *Firmicutes*. Reduced numbers of 7-dehydroxylating and SCFA-producing bacteria were seen in *Firmicutes* [69]. Some researchers have attempted to link a particular bacteria to NAFLD-related liver fibrosis. Duarte [70] discovered a link between increased *Lactobacillus* and *Ruminococcus*, whereas Boursier [71] discovered a link between *Ruminococcus* and increased *Lactobacillus*. *Firmicutes* and *Bacteroidetes* dominated the NAFLD gut microbiota, according to a recent research, with *Proteobacteria* and *Actinobacteria* in smaller quantities. However, as fibrosis progresses, the quantity of the *Proteobacteria* phylum increases, while the amount of *Firmicutes* declines. Dysbiosis appears early in the course of liver illness and is mostly determined by the etiological causes [72]. It is clear that NAFLD causes microbiome modifications, which may account for the variations in microbiota composition seen. But given the terminology used in these studies, the research design, and the clinical objectives, it is inappropriate to draw broad conclusions.

Gut Dysbiosis and IBS: What Role Does Gut Dysbiosis Play?

Irritable bowel syndrome (IBS) is one of the most frequent gastrointestinal diseases in clinical practise, with a high rate of morbidity and a global incidence of roughly 11% [73].

IBS is classified as a bowel function impairment that can be identified by persistent stomach pain and discomfort combined with changed stool habits [74]. Functional disorders of the brain-gut axis that include gut dysmotility, sensory-motor dysfunction, and psychological stress have long been linked to IBS. Recent research suggests that gut dysbiosis, which results in persistent gut inflammation and abnormal intestinal immune activity, may be a risk factor for IBS [75]. The idea that dysbiosis might play a role in IBS pathogenesis stems from the fact that a bacterial gastroenteritis incident is the strongest predictor of IBS development [76].

FODMAPs (fermentable oligo-, di-, mono-, and polysaccharides and polyols) have been linked to IBS because they cause visceral hypersensitivity, increase gastrointestinal motility, and promote dysbiotic imbalance by inhibiting bacteria that consume gas. Despite the positive benefits of a low FODMAP ("fermentable oligosaccharides, disaccharides, monosaccharides and polyols") diet on IBS symptoms, it lowers luminal *Bifidobacterium* and *F. prausnitzii* concentrations [77, 78]. The long-term effects of a low-FODMAP diet are unknown.

Several studies have indicated that IBS patients have a distinct gut microbiota, and that intestinal symptoms are linked to certain bacteria. Microbial diversity is reduced in IBS patients in general [79]. *Firmicutes* were found to be more abundant while *Bacteroidetes* were found to be less abundant [80].

The authors verify these microbiome alterations in a 2019 comprehensive study encompassing 777 individuals [79]. IBS has been linked to an increase in potential harmful bacteria such *Ruminococcus*, *Clostridium*, and *E. coli* [81]. Despite the fact that Lactobacillus and Bifidobacterium have been utilised as probiotics, both have been found to increase in IBS patients in multiple studies [82, 83], raising questions regarding their function in IBS.

Faecal bacterium, more especially Faecal bacterium *prausnitzii*, was proven to be lowered in multiple investigations of dysbiosis in IBS, CD (Crohn's disease), and UC (ulcerative colitis), making this bacteria a "good gut signature." In vitro and in vivo, F. prausnitzii has a powerful anti-inflammatory action, which helps to preserve intestinal health [84, 85].

Expert View On Gut Microbiota and Gastrointestinal Disorders

Recent advances in microbiome genome sequencing have shown a slew of links between dysbiotic imbalances and gastrointestinal disorders. However, this is still early in the study process, and just a few causal correlations have been identified. According to studies in animal models, dysbiosis plays a role in the pathogenesis of inflammation-induced carcinogenesis and can occur prior to illness onset.

Most Proteobacteria are thought to be harmful, as evidenced by their increased prevalence in IBD and CD patients, as opposed to Firmicutes, which are seen in lower numbers in IBD, CRC, NAFLD, and CD patients. Diet, PPIs (proton pump inhibitors), and antibiotics all affect gut microbiota, even in healthy people. Long-term use of broad-spectrum antibiotics, a Western diet, and the use of PPIs to reduce stomach acidity are all well-known risk factors for dysbiosis-related disorders.

4. Conclusion

Over the recent years, researchers have shown an immense interest into the various aspects of gut microbiome, so much so, that it has now been regarded as a "second brain" of the human body. Gut microbiome is known to impact various biological functions in a body namely metabolic, immune and digestive functions. Microbiome diversity has been discovered using the famous gene sequencing technique which has helped in identifying various microbial genes present. Available researches- trials and experiments have very well documented the role of gut microbiota in the pathophysiology of a number of non- communicable diseases. Experiments started from mice and rodents to determine the shift in gut diversity have now been moved to explore the diversity shift in humans. Studies involving the effect of various diets, prebiotics and probiotics, physical activity on human body are being carried out. Although, establishing the long term effect of these interventions are still a gap that needs to be filled. Additional longitudinal cohort studies and controlled trials are required to collect more evidence in order to establish gut microbiota as one of the "pathogenic factor" in the risk of developing NCDs.

Abbreviations

NCDs- Non-Communicable Diseases
CMMND- Communicable, maternity, neonatal and nutritional diseases
CVD- Cardio vascular diseases
TMAO- Trimethylamine N-oxide
TMA- Trimethylamine
PC- Phosphatidylcholine
FMO3- flavin containing monooxygenase enzyme

BMI- Body- mass index
MLGs- Metagenomic linkage groups
CRC- Colorectal cancer
E. coli- Escherichia coli
C. butyricum- Clostridium butyricum
F. prausnitzii- Faecalibacterium prausnitzii
H. pylori- Helicobacter pylori
S. bovis- Streptococcus bovis
C. septicum- Clostridium septicum
E. faecalis- Enterococcus faecalis
RONS- Reactive oxygen and nitrogen species
CKD- Chronic kidney diseases
SCFA- Short chain fatty acids
ESRD- End stage renal disorder
IAA- Indole acetic acid
IBD- Irritable bowel disease
IBS- Irritable bowel syndrome
GC- Gastric Cancer
NAFLD- non-alcoholic fatty liver disease
CD- Crohn's disease
UC- ulcerative colitis
FODMAP- fermentable oligosaccharides, disaccharides, monosaccharides and polyols
PPI- proton pump inhibitors

Declarations

Ethics approval and consent to participate- Not applicable
Consent for publication- Not applicable
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