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Role of Gut Microbiome on Metabolic Disorders

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Authors' contributions

This work was carried out in collaboration among all authors. Authors IOO and NRA designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors IOO and NRA managed the analyses of the study. Authors IOO, NRA, EUU, OO, NAO and GUJ managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Microbiome that reside in the human gut are key contributors to host metabolism and are considered potential sources of novel therapeutics in metabolic disorders. This review discusses the role of gut microbiome in the pathogenesis of obesity, type 2 diabetes mellitus (T2DM), chronic kidney disease and cardiovascular disease. Gut microbiome remains quite stable, although changes take place between birth and adulthood due to external influences, such as diet, disease and environment. Understanding these changes is important to predict diseases and develop therapies. In gut heamostasis, Gut microbiome converts high fibres intake into short-chain fatty acids like butyrate, propionate and acetate which normalize intestinal permeability and alter de novo lipogenesis and gluconeogenesis through reduction of free fatty acid production by visceral adipose tissue. This effect contributes to reduce food intake and to improve glucose metabolism.

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Propionate can also bind to G protein coupled receptors (GPR)-43 expressed on lymphocytes in order to maintain appropriate immune defence. Butyrate activates peroxisome proliferator-activated receptor-γ (PPAR-γ) leading to beta-oxidation and oxygen consumption, a phenomenon contributing to maintain anaerobic condition in the gut lumen. In contrast, diets most especially western diet consisting among others of high fat and high salt content has been reported to cause gut dysbiosis. This alteration of gut microbiome result to chronic bacterial translocation and increased intestinal permeability that can drive a systemic inflammation leading to macrophage influx into visceral adipose tissue, activation of hepatic kuffer cells and insulin resistance in type 2 diabetes. This effect contributes to lower mucus thickness, decrease butyrate and propionate producing bacteria, L-cells secrete less gut peptides, lack of PPAR-γ activation lead to higher oxygen available for the microbiome at the proximity of the mucosa and increases the proliferation of Enterobacteriaceae with commensurate increase in opportunistic pathogens. However, Gut microbiome are major biomarker for early prognosis of diabetes and other metabolic disorders.

Keywords: Gut microbiome; obesity; diabetes; chronic kidney diseases; cardiovascular diseases.

1. INTRODUCTION

Gut dysbiosis contributes to the development of various diseases including cardiovascular disease (CVD) [1], obesity [2], type 2 diabetes mellitus [3,4], non-alcoholic fatty liver disease [5,6] and even some types of cancer [7,8]. Both animal and human studies have demonstrated that diet can influence the composition and function of the gut microbiome [9]. However, other factors, including genetics; the mode of delivery at birth; the method of infant feeding; and the use of medications, especially antibiotics, also contribute to the composition and function of the gut microbiome [10].

Diet plays an important role in obesity, in addition to other factors [11,12]. Obesity is a predisposing element of the metabolic syndrome in the development of type 2 diabetes mellitus (T2 DM). Obesity is a major risk factor for type 2 diabetes which accounts for 90–95% of all diabetes cases [13]. Dysbiosis is a state in which the homeostasis of the gut microbiome is disrupted, often leading to health problems. One of the causes of dysbiosis is diet, and studies have shown that diet may change the gut microbiome and contribute to obesity and diabetes [14]. Obesity and T2D are characterized by an altered gut microbiome, inflammation, and gut barrier disruption [15,16]. Diabetes mellitus is a group of metabolic disorders of carbohydrate metabolism in which glucose is underutilized, producing hyperglycemia and has become a major public health concern [17]. It is caused either by inadequate production of insulin, or the body's improper response to insulin, or both [17].

There are two major types of diabetes: Types 1 and 2 diabetes. Diabetes mellitus type 2 (DM2) accounts for 90% of all diabetes cases worldwide [18]. It is closely related to unhealthy lifestyles, overweight and physical inactivity. Unhealthy diet, lack of exercise, and other unhealthy lifestyle habits are associated with the development of diabetes [18]. Type 2 diabetes (T2D) is a complex metabolic disorder in which islet beta cell failure occurs together with insulin resistance where the body becomes resistant to the insulin it produces and combination of genetic and environmental factors contributes to the development of both T1DM and T2DM [19,20]. T1D is caused by autoimmune destruction of the beta cells of the pancreas, representing approximately 10% of all cases of diabetes worldwide [19]. At present, lifelong insulin therapy is the only treatment for the disease [19]. Although the prevalence of T1D is <1% in most populations, the geographic variation in incidence is enormous, ranging from <1/100,000 per year in China to approximately 40/100,000 per year in Finland [21]. It has been estimated that approximately 20 million people worldwide, mostly children and young adults, have T1D [22]. Studies on type 2 diabetes in Finland reports that 46% of type 2 diabetes is attributed to heritary while environmental factors accounted for 53% [23]. The incidence of T1D is increasing worldwide at a rate of about 3% per year [24]. Epidemiologic studies have revealed no significant gender differences in incidence among individuals diagnosed before age 15 [25]. There is also a notable seasonal variation in the incidence of T1D in many countries, with lower rates in the warm summer months, and higher rates during the cold winter [26].

Diabetes can cause many complications if left untreated, including cardiovascular disease, stroke, and kidney failure [27]. The International

Diabetes Federation reports that the world has 415 million adults with diabetes and 318 million people at risk of developing diabetes [28]. According to the WHO standard, Nigeria has a comparative prevalence of 4.83% with over 88,681 Diabetes-related deaths [29]. In South Eastern Nigeria the prevalence of diabetes mellitus is about 6.7% [29]. This study aims to explore the effects of gut dysbiosis on metabolic disorders.

2. DEVELOPMENT OF THE MICROBIOME

There are different factors influencing the development of the microbiome in the early years of life, starting with the mode of birth [30], breastfeeding or formula-feeding infants, and possibly the introduction of solid food [31]. The intestinal microbiome stabilizes about 3 years after birth, when it resembles the adult microbiome and stays relatively stable over time [32]. In adulthood, the microbiome can be altered by changes in diet [33], as well as by the use of several types of medication such as antibiotics [34], metformin [35], and even proton pump inhibitors [36].

2.1 Method of Birth

The composition of the gut bacterial community is different in infants delivered by cesarean section from that of infants born by vaginal delivery [38,39]. Infants born by vaginal delivery are exposed to the mother's bacteria at birth, which influences the infant's gut bacteria and stimulates white blood cells and other components of the immune system [40]. In 2014, the Center for Disease Control (CDC) reported that 32.2% of all deliveries in the United States were performed by cesarean section [37]. Several studies have suggested that infants born by cesarean section are at greater risk of developing obesity and/or diabetes than those born vaginally [41,42,43]. Similarly, a cohort study in 672 preschool children who were born by cesarean section showed prevalence rates of 15.6% and 12.9% for overweight and obesity respectively [42]. However, opposite findings were also reported [44].

2.2 Infant Feeding

Infant feeding is another important factor for establishing the bacterial community in the gut because the mother's milk is not sterile [45]. Human breast milk has been recognized as a source of commensal and potential probiotic bacteria that influence the development of infant gut bacteria [46]. Human breast milk has been reported to contain>700 species of bacteria [47]. Although, human milk bacterial communities are generally complex and vary individually, the median bacterial load is $\sim 10^6$ bacterial cells/mL through time [48]. It appears that *Streptococci* and *Staphylococci* are predominant bacterial genera in human milk [45]; both of these are also predominant in the skin microbiome. Therefore, human milk may also contain some skin bacteria. However, *Weissella*, *Leuconostocus*, *Staphylococcus*, *Streptococcus* and *Lactococcus* are predominant in colostrum samples of infants, whereas in milk taken at 1 and 6 months, *Veillonella*, *Leptotrichia*, and *Prevotella* increased significantly [46] Evidence suggests that the transfer of microbiota from mothers to their infants affect infant growth and development [49,50]. Milk from obese mothers also showed more proinflammatory properties [50]. In addition, breast milk from mothers who underwent cesarean section contained bacteria that were different from milk samples from mothers who had vaginal deliveries [47]. The bacteria present in breast milk, as well as those on the mother's skin are among the first microbes to enter the infant's body, and they could play an important role in health [47]. Breast milk is also a rich source of IgA antibodies against different pathogens [51,52]. The Borsh-Johnsen et al. [53], also postulated that the lack of immunologic protection from insufficient breast-feeding may increase risk for T1D later during childhood. Breast milk contains growth factors, cytokines, and other substances necessary for the maturation of the intestinal mucosa [54].

2.3 Infections

Interestingly, enteroviral infections can also interfere with gut immunoregulation, which may explain the epidemiologic associations between viral infections and T1D [54,55]. Although the gut microbiome affects viral and bacterial infections, the reverse is also true [56,57,58]. A human study of *Clostridium difficile* patients and asymptomatic carriers with the use of 16S ribosomal RNA gene pyrosequencing found that both had reduced microbial richness and diversity compared with healthy subjects [59,60]. *C. difficile* infection is a typical result of severe dysbiosis in the gut microbiome [61,62]. Interestingly, transplantation of the gut microbiome from healthy donors to infected patients increased microbial richness and

diversity and it is currently applied clinically [63,64].

2.4 Medications

Increasing evidence suggests that many non antibiotic drugs have an impact on the gut microbiome [65], including the drugs used to treat T2D. Likewise, the gut microbiome also affects the efficacy of drugs [66]. Broad-spectrum antibiotics reduce bacterial diversity while increasing the abundance of opportunistic pathogens and decreasing the number of beneficial bacteria [67]. The use of broad-spectrum antibiotics, such as clindamycin, in infants and young children has been found to have the longest-lasting effects on the composition of the gut microbiome [68]. Early antibiotic exposure in neonates can lead to microbial dysbiosis, which may be a predisposing factor to inflammatory bowel disease [69]. Studies in both mice and humans have found that the use of antibiotics early in life could promote obesity later in life, mediated by the alteration of the gut microbiome [70].

Meformin is routinely used in the control of hyperglycemia in T2D. The drug increases the insulin sensitivity of body cells, especially fat cells, muscle cells, and hepatocytes, while preventing the overproduction of glucose by hepatocytes [71]. Interestingly, recent studies have found that the administration of meformin alters the composition of the microbiome [71].

3. DIET

The role of gut microbiome on host metabolism has been under explored over the years, probably because of metagenomic sequencing limitations that have been overcomed in recent years [72]. There are reliable evidence to show that dietary changes result in substantial and rapid changes in the make-up of the gut microbiome [73,74]. Everard et al. [16] reported a decrease in the population of *A. muciniphila* in obesed mice and those with type 2 diabetes. On administration of probiotic feed, *A. muciniphila* normalized its abundance and improved the animal's metabolic profile. Treatment with *A. muciniphila* also reduced fat mass, inflammation, and insulin resistance induced by a high-fat diet [16]. A fiber-rich diet has been shown to be beneficial to health because it modulates the gut microbiome [73,74]. Enterotypes were strongly associated with long-term diets, particularly those with protein and animal fat [75]. Wu et al. [14], showed that protein and animal fat were associated with *Bacteroides,* whereas carbohydrates were associated with *Prevotella*.

3.1 The Role of Gut Microbiome in Immunity

B cells are involved in humoral and cell-mediated immunity. They secrete antibodies following differentiation into plasma cells, produce cytokines, and regulate T cell responses via antigen presentation and costimulation [76]. The humoral immune response in the gastrointestinal tract is mediated by IgA memory B cells and IgA-producing plasma cells in the gut-associated lymphoid tissue (GALT). The protective and nutrient-rich environment of the gastrointestinal tract accommodates an extremely dense and diverse bacterial community that in turn provides metabolic advantages and serves as a natural defense against colonization with pathogens [77]. Gut microbiome act as critical stimuli, playing an important role for the maturation of the GALT and further induce IgA production by B cells [78]. Class switching to IgA-producing plasma cells occurs in the Peyer's patches and lamina propria, following T cell-dependent or -independent mechanisms [78]. The secretory IgA (SIgA) in the gut provides a first-line defense against pathogens mainly by blocking toxins and pathogens from adhering to the intestinal epithelium at the earliest steps of the infection process [79]. The studies of Endesfelder et al. [80], suggest that an increased availability of butyrate and propionate in the intestinal tract have protective effects against the development of T1 DM related autoimmunity. According to studies carried out in Finland and Russia, *Bacteroidetes* are associated with higher susceptibility to autoimmune disease and produce a type of LPS with immunoinhibitory properties [81,82].

The phenomenon may preclude an early "immune education" and contribute to the development of autoimmune disease [83]. Mucin synthesis and Butyrate may play a major role in the prevention of autoimmune disease. Brown et al. [84], hypothesized that a consortium of lactate- and butyrate-producing bacteria in a healthy gut may induce sufficient mucin synthesis to maintain gut integrity. In contrast, non-butyrate-producing lactate-utilizing bacteria prevent optimal mucin synthesis, as identified in autoimmune subjects [85].

3.2 Gut Microbiome in Diabetes Mellitus Type 2 and Obesity

Short-chain fatty acids (SCFAs) such as butyrate may protect against diet-induced insulin resistance, through the engagement of Gpr43 and 41 and the release of glucagon-like peptide 1 (GLP-1), an incretin hormone that can improve insulin secretion and resistance as well as preserve beta-cell function [86].

In contrast to the cases of gut dysbiosis, LPS are absorbed by enterocytes and they are conveyed into plasma coupled to chylomicrons [86]. In this way, dietary fats can be associated with increased absorption of LPS which in turn can be related with changes in the gut microbiome distinguished by a decrease in the *Eubacteriumrectale–C. coccoides* group, Gram-negative *Bacteroides* and in *Bifidobacterium* [86].

This causal role of LPS was demonstrated by infusing LPS in mice with a normal diet inducing hepatic insulin resistance, glucose intolerance, and an increase in the weight of adipose tissue [87]. It has been recently shown that the LPS-induced signaling cascade via Toll-like receptor 4 (TLR4) impairs pancreatic β-cell function via suppressed glucose-induced insulin secretion and decreased mRNA expression of pancreas-duodenum homebox-1 (PDX-1). LPS binds to the CD14/TLR4 receptor present on macrophages and produces an increase in the production of proinflammatory molecules. A rise in LPS levels has been observed in subjects who increased their fat intake [88,89].

When LPS injections were administrated to mice with a genetic absence of the CD14/TLR4 receptor they did not develop these metabolic characteristics and there was no start of TDM2 or obesity, showing the important role of LPS in the mechanism of CD14/TLR4 [90]. Moreover, knockout CD14/TLR4 mice were even more sensitive to insulin than wild type controls [90]. LPS can also promote the expression of NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) and activation of the MAPK (mitogen-activated protein kinase) pathway in adipocytes with several target genes [91]. Karlsson et al. [92], reported that an increase in the abundance of four *Lactobacillus* species and decreases in the abundance of five *Clostridium* species in Diabetes mellitus type 2 diabetes signified that either increase or decrease in this gut microbiome might predispose to diabetes mellitus. Metagenomic data have revealed that patients with type 2 diabetes exhibit a moderate degree of gut microbial dysbiosis compared with patients with inflammatory bowel disease [93]. The proportions of the phylum *Firmicutes* and the class *Clostridia* are significantly reduced, whereas the class of the gram-negative *Betaproteobacteria* is highly enriched in the faeces of type 2 diabetic patients compared with non-diabetic individuals, and the proportion of *Betaproteobacteria* is positively correlated with plasma glucose levels [94]. Interestingly, the microbiome of type 2 diabetic patients are characterised by the depletion of several butyrate-producing bacteria, including *Clostridium* species, *Eubacterium rectale*, *Faecalibacterium prausnitzii*, *Roseburia intestinalis* and *Roseburia inulinivorans* [92,93], and an enrichment of opportunistic pathogens [93].

Bacteria increased in the gut of type 2 diabetic patients also include the sulphate-reducing bacteria *Desulfovibrio*, as well as *Lactobacillus gasseri*, *Lactobacillus reuteri* and *Lactobacillus plantarum* [103]. Although, diets most especially western diet consisting among others of high fat and high salt content has been reported to cause gut dysbiosis [95]. This alteration of gut microbiome producing obesity and insulin resistance through chronic bacterial translocation due to increased intestinal permeability that can drive a systemic inflammation leading to macrophage influx into visceral adipose tissue, activation of hepatic kuffer cells and insulin resistance [95] (Fig. 1).

4. THE GUT MICROBIOME IN DIFFERENT METABOLIC ORGANS

Inflammation is commonly involved in a number of diseases [94], including atherosclerosis, which is a classical chronic inflammatory disease [95]. Gut epithelium is the first barrier of the host, which protects against the invasion of pathogens [96]. Given its critical role in preventing the translocation of intestinal content, mainly bacterial components, the integrity of the gut barrier is essential for maintaining the health of the host. Intestinal permeability is associated with reduced expression of tight junction proteins, including zonula occludens-1 (ZO-1), claudin-1, and occludin, and an imbalance between intestinal epithelial cell death and regeneration [97]. If the intestinal epithelial barrier is impaired, the invasion of pathogen associated molecular patterns (PAMPs) drives an immune response and results in systemic and

tissue-specific inflammation. Accordingly, impairments to the gut barrier integrity induced by gut dysbiosis have been suggested as risk factor for chronic inflammation in various diseases (ref). It is noteworthy that lipopolysaccharide (LPS) and peptidoglycan are microbial components that are recognized as risk factors for CVD. Lipopolysaccharide is a cell wall component of Gram-negative [G (–)] bacteria, which has been extensively studied as it is one of the PAMPs involved in CVD risk [98]. Subsequently, the relationship was gradually confirmed by multiple experiments by Mitra et al. [99]. In a different study, it was reported that the level of circulating endotoxemia was most notable in patients with the highest CVD burden [87]. Also, Harris et al. [100] found that gut dysbiosis suppressed the expression of tight junction proteins, leading to an increase in intestinal permeability and subsequently the translocation of LPS into the blood. Gut dysbiosis-derived LPS may play important roles by modulation of Toll-like receptors (TLRs) and their downstream targets [101]. As part of the pattern-recognition receptors family, TLRs can recognize bacterial products and modulate the host immune system [102]. Circulating LPS can bind to cell-surface-receptor complexes composed of TLR4 and its co-receptors cluster of differentiation 14 (CD14) [103]. Consistently, clinical investigations have revealed that upregulation of TLRs was associated with inflammatory activation in human atherosclerosis, and promoted the development of atherosclerosis [104]. Fiber-enriched diets have been shown to improve insulin resistance in lean and in obese subjects with diabetes [105]. However, only long-term dietary habits are most important in actually shaping the composition of the gut microbiome.

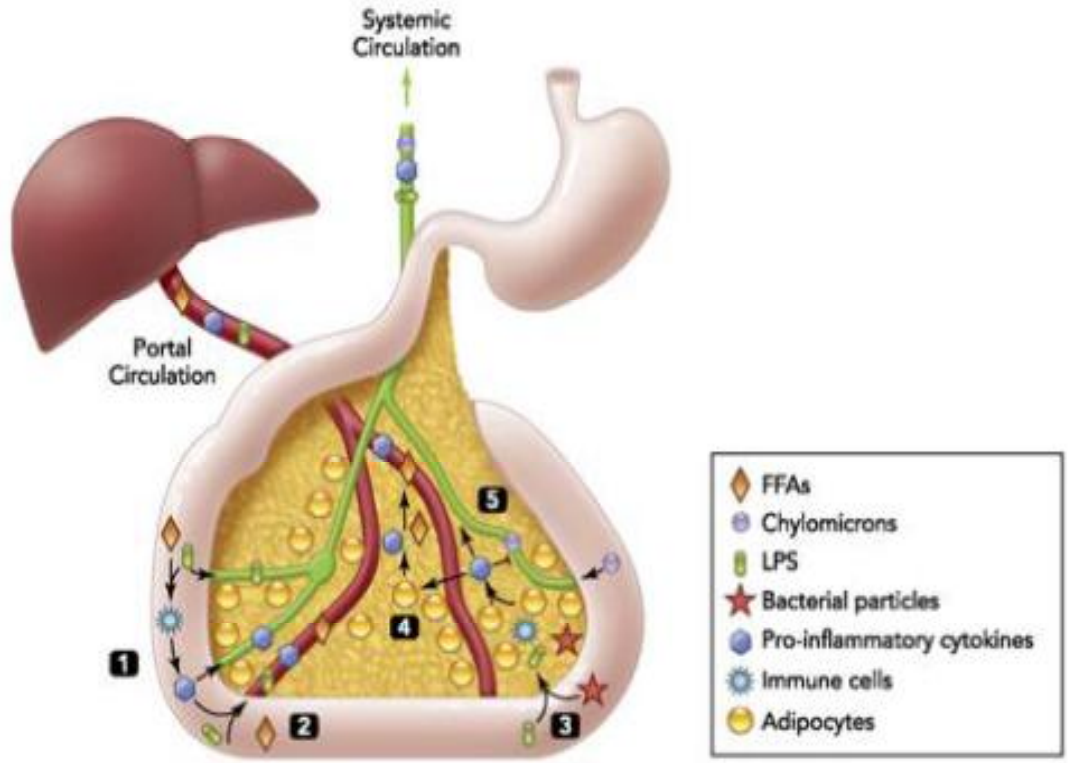

Fig. 1. Bacterial products, changes in adipose tissue lead to insulin resistance and decrease insulin release [95]

Keys: (1)↑ fat and sugar (Western) diet → ↑ bacterial release of lipopolysaccharide (LPS), (2)LPS → inflammatory cytokines into portal system, (3)↑ translocation of bacteria and LPS into visceral adipose tissue, ↑ inflammatory cytokines, (4)Adipocytes release free fatty acids (FFA), (5)Reduced clearance of inflammatory mediators from visceral adipose tissue, (6)↑ LPS, FFA, and cytokines into portal circulation ↓ liver metabolism and insulin sensitivity, (7)↑ delivery of LPS, FFA, cytokines into systemic circulation negatively affect B-cell and systemic insulin sensitivity

In human studies, elevated trimethylamine-N-oxide (TMAO) has been independently associated with prevalent CVD and incident risks for Myocardial Infarction, stroke, death, and revascularization [104]. Choline is an essential dietary nutrient and there is need to consume some choline in the diet or else develop a deficiency state, which is characterized by fatty liver,altered one-carbon methyl donor metabolic pathway, and neurologic disorder [106]. An obligatory role for gut microbiome in both trimethylamine (TMA) and trimethylamine-N-oxide (TMAO) formation from ingested phosphatidylcholine (PC) was confirmed in animal model studies, which included germ-free mice [107], as well as human clinical investigations involving ingestion of egg yolk, isotope-labeled PC, and a cocktail of oral antibiotics [92]. Recently, the association between acute egg yolk ingestion and increased plasma and urine TMAO concentrations was independently confirmed in humans [56]. The conversion from TMA to TMAO requires an oxidation step that is mediated by host enzyme machinery in the form of flavinmonooxygenases (FMOs) [108,109,110]. Gut microbe–produced TMA reaches the liver rapidly via the portal circulation, where a cluster of hepatic FMO enzymes efficiently oxidizes TMA into TMAO (Fig. 2). Previous studies have shown that subjects with a genetic defect in FMO3 can have markedly elevated TMA levels, leading to a noxious body odor that characterizes the condition (fish odor syndrome or trimethylaminuria [TMAU]) [111].

5. GUT MICROBIOME IN CHRONIC KIDNEY DISEASE (CKD)

Gut microbiome produce compounds that are normally excreted by the kidneys but can be considered as potential uremic retention molecules (URM) such as mammalian metabolism, microbial products and diet [113,114]. The principal role of the colon is to absorb salt and water and to provide a mechanism for orderly disposal of waste products of digestion. Moreover, the colon is responsible for salvage of energy and possibly nitrogen from carbohydrates and proteins that are not digested in the upper gastrointestinal tract. This is achieved through the metabolism of anaerobic bacteria, a process known as fermentation [113]. Fermentation of the amino acids tyrosine (obtained usually from consuming chicken, beef, brown rice, nuts, fruit, and vegetables) and tryptophan (e.g., from beef, fish, milk, yogurt, and soy products) by intestinal microbiome generates p-cresol and indole respectively [115]. After absorption, these compounds are further metabolized in the liver to generate p-cresylsulfate and p-indoxylsulfate. Indoxylsulfate and p-cresylsulfate circulate in equilibrium between a free solute fraction and a fraction bound to serum proteins. The best characterized binding site is albumin, for which indoxylsulfate and p-cresylsulfate are competitive binding inhibitors [115]. These toxins are eliminated mainly by tubular secretion in the kidneys and, therefore, are considered to be uremic toxins, with increased levels indicative of renal impairment and advancing CKD [116] (Fig. 3).

Dysbiosis in CKD patients may contribute to increased uremic toxin levels that in turn contribute to CKD progression. In a study of 268 patients with CKD, Wu et al. [14] found the baseline concentration of indoxylsulfate to be predictive of CKD progression. Meijers et al. measured p-cresol levels in 499 patients with mild-to-moderate CKD and showed that p-cresol sulfate levels increased with decreasing estimated glomerular filtration rate (GFR) [117]. Similarly, an elevated p-cresol concentration was associated with increased risk of death in end-stage renal disease (ESRD) patients treated with maintenance hemodialysis [118]. Trimethylamine N-oxide (TMAO) is another uremic toxin produced by the gut microbiome and its role in CKD has also been reported [119].

CKD also affects the structure of the gut microbiome and contributes to dysbiosis due to decreased consumption of dietary fibers [120], frequent use of antibiotics, slow colonic transit, metabolic acidosis, volume overload with intestinal wall congestion, intestinal wall edema, and oral iron intake [121]. Urea is hydrolyzed by gut microbes, resulting in the formation of large quantities of ammonia, which affects the growth of commensal bacteria and causes imbalance in the gut microbiome [122].

In healthy individuals, gut microbiome are classified into different enterotypes based on the abundance of specific bacterial groups, which are dominated by *Bacteroides*, *Prevotella*, or *Ruminococcus* [75]; these enterotypes are strongly associated with long-term diets, particularly the levels of proteins and animal fat (*Bacteroides*) versus carbohydrates (*Prevotella*) [14]. However, the intestinal microbiome in patients with CKD is altered, with lower numbers of *Lactobacillaceae* and *Prevotellaceae* families

(both are considered normal colonic microbiome) and 100 times higher *Enterobacteria* and *Enterococci* species (which are normally present in lower proportions [122].

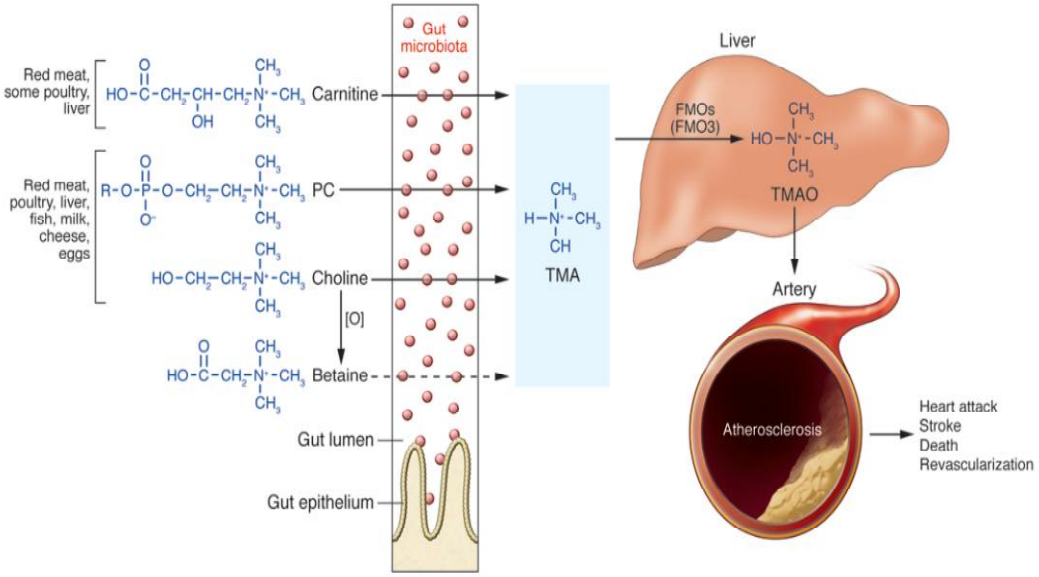

Fig. 2. Nutrient/meta-organismal pathway associated with atherosclerosis and major adverse cardiovascular events [112]

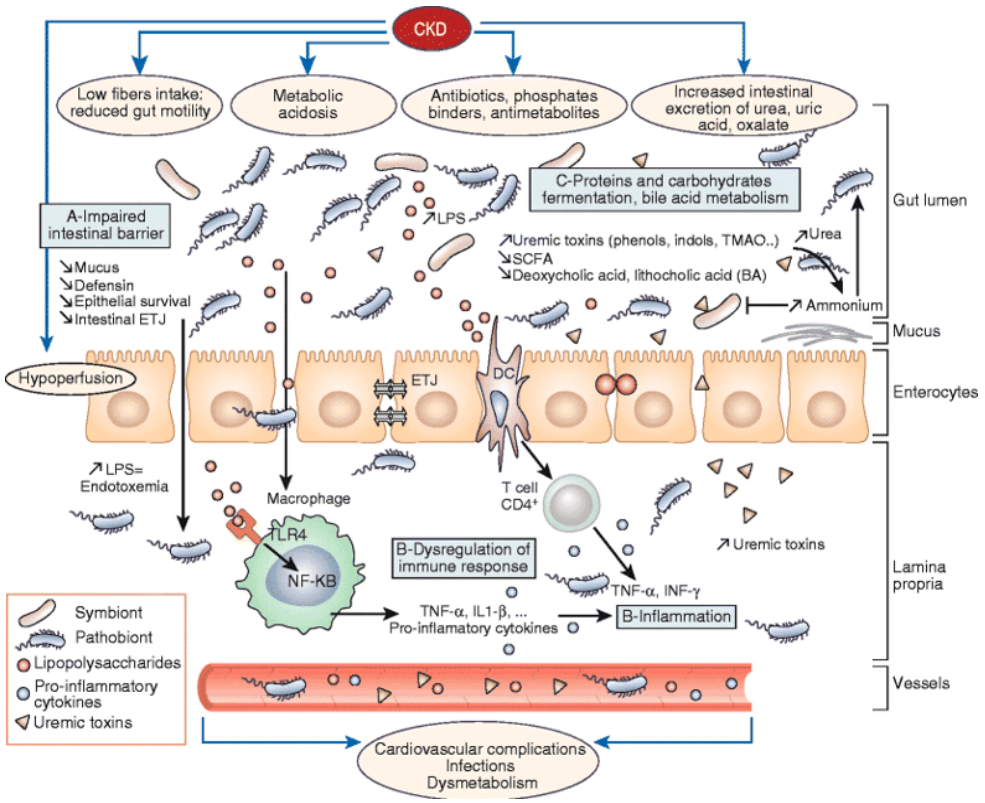

Fig. 3. Mechanisms and pathways of dysbiosis in diabetic patients with CKD [122]

6. CONCLUSION

Gut microbiome has recently been proposed as an environmental factor involved in the control of body weight and energy homeostasis. Numerous studies suggest that a high-fat diet can lead to gut dysbiosis, which contributes to increase in Gram negative (*Bacteroidetes*) and Gram positive ratio (*Firmicutes*). This in turn result to low-grade inflammation and insulin resistance and, ultimately, obesity, diabetes and other metabolic disorders. This evidence supporting Brillat-Savarins' statement that says, "Tell me what you eat, and I will tell you what you are.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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