REVIEW ARTICLE

ROLE OF GUT MICROBIOME ON METABOLIC DISORDERS

Abstract

Numerous reviews on gut microbiome and metabolic disorders have been published so far. 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 1diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), Chronic kidney disease and cardiovascular disease. The establishment of gut microbiome is dependent on the type of birth. With effect from this point, 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. 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. 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 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 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 and also, early exposure to personal hygiene and insufficient breast feeding during childhood result to decrease in propionate which contribute to the lower abundance of specific T cells (mucosal-associated invariant T cells (MAIT) and regulatory T-cell (Treg) in the lamina propria of the gut leading to immature gut microbiome and predispose to type 1 diabetes in childhood.

Key words:Gut microbiome, obesity, diabetes, Chronic kidney diseases, cardiovascular diseases

1. Introduction

Gut dysbiosis contributing 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]. 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]. Over 80% of patients with T2D in the Western world are overweight. 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 1 diabetes (T1D) is characterized by the autoimmune destruction of pancreatic beta cells. The rapid rise in T1D incidence during the past 50 years suggests environmental factors contribute to the disease [19]. 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 these diseases [20]. T1D is caused by the autoimmune destruction of the beta cells of the pancreas, and represents approximately 10% of all cases with diabetes. At present, lifelong insulin therapy is the only treatment for the disease [19]. Without exogenous insulin injections, individuals with T1D will not survive. 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]. Based on best fit models, heritability was 46%, and environmental effect accounted for 53% of the liability for type2 diabetes in Finland [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. In South Eastern Nigeria the prevalence of diabetes mellitus is about 6.7% [29]. This review will focus on the following fields: Microbiome composition and role of microbiome on diabetes, pathophysiology and evolving therapeutic strategies in the 3 disorders; Obesity as a prequel to type 2 diabetes (sometimes referred to as "diabesity"); type 2 diabetes and type 1 diabetes (T1 DM).

2. Factors influencing the 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

According to the Center Disease Control(CDC), as of 2014, 32.2% of all deliveries in the United States are performed by cesarean section [37]. 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]. 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]. A similar study in a small cohort also showed that the prevalence rates of overweight and obesity were 15.6% and 12.9%, respectively, in 672 preschool children who were born by cesarean section [42]. However, opposite findings are 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 contains >700 species of bacteria [47]. Although human milk bacterial communities are generally complex and vary individually, the median bacterial load is ~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 was 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]. Breast-feeding also protects against enteric infections during infancy, and promotes proper colonization of the gut. Interestingly, enteroviral infections can also interfere with gut immunoregulation, which may explain the epidemiologic associations between viral infections and T1D [54].

2.3. Infections

Enteroviruses especiallyCoxsackie virus B (CVB) infections are frequent during childhood and are known to have systemic effects on the pancreas [55]. Recent prospective studies are helping to elucidate the role of viruses to the etiology of T1D. For example, enteroviral infections occurring as early as *in utero* appear to increase a child's subsequent risk of developing type 1 diabetes mellitus [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 some bacteria that can be used by 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 to help with control of hyperglycemia in T2D. The drug increases the insulin sensitivity of body cells, especially fat cells, muscle cells, and hepatocytes. Metformin also prevents the overproduction of glucose by hepatocytes. Furthermore, metformin delays glucose absorption during digestion after a meal. Interestingly, recent studies have found that the administration of meformin alters the composition of the microbiome [71].

2.5. Diet

The role that food-ingested bacteria play in the gut microbiome had been underestimated in the past, possibly because of methodologic limitations that have been overcome in recent years [72]. Numerous studies, both in research mice and in humans, have shown that high-calorie diets contribute to obesity and T2D [73]. However, increasing evidence suggests that the link between diet and obesity lies in the gut microbiota [73]. Interventional studies show that dietary changes result in substantial and rapid changes in the make-up of the gut microbiome [74]. Studies in mice have demonstrated that a high-fat diet (60% fat) decreases the number of bacterial species (α diversity) in the gut microbiome, and the composition of the gut microbiome between mice given a high-fat diet (unpurified) and those given a regular unpurified diet is very different (β diversity). One study in mice found that the abundance of *A. muciniphila* decreased in obese

mice and those with type 2 diabetes and that prebiotic feeding of *A. muciniphila* normalized its abundance and improved metabolic profiles [16]. 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[74]. Studies in humans by 16S ribosomal RNA sequencing have characterized the human gut microbiota into different enterotypes distinguished by the types of bacteria present [75]. Enterotypes were strongly associated with long-term diets, particularly those with protein and animal fat. Wu *et al*. [14], showed that protein and animal fat were associated with *Bacteroides,* whereas carbohydrates were associated with *Prevotella*.

2.6. Obesity

The major environmental risk factors for T2D are obesity ($\geq$ 120% ideal body weight or a body mass index $\geq$ 30 k/m^2) and a sedentary lifestyle [76]. Thus, the tremendous increase in the rates of T2D in recent years has been attributed, primarily, to the dramatic rise in obesity worldwide [76]. It has been estimated that approximately 80% of all new T2D cases are due to obesity [77]. This is true for adults and children. In the Pima Indians, 85% of the T2D children were either overweight or obese. Another study in the US reported that IGT was detected in 25% of obese children age 4-10 years, and in 21% of obese adolescents [78]. Undiagnosed T2D was detected in 4% of the adolescents. In addition to general obesity, the distribution of body fat, estimated by the ratio of waist-to-hip circumference (WHR), also has an impact on T2D risk. WHR is a reflection of abdominal (central) obesity, which is more strongly associated with T2D than the standard measures of obesity, such as those based on body mass index. The other major T2D risk factor is physical inactivity. In addition to controlling weight, exercise improves glucose and lipid metabolism, which decreases T2D risk. Physical activity, such as daily walking or cycling

for more than 30 minutes, has been shown to significantly reduce the risk of T2D [79]. Recently, intervention studies in China [80], Finland [81] and the US (Diabetes Prevention Program Study Group, 2002) have shown that lifestyle interventions targeting diet and exercise decreased the risk of progression from IGT to T2D by approximately 60% In contrast, oral hypoglycemic medication only reduced the risk of progression by about 30%. There is also considerable evidence suggesting that the intrauterine environment is an important predictor of T2D risk [82].

2.7. Behavior

The role of hygiene in the etiology of T1D is also currently being explored [83]. It also has been hypothesized that delayed exposure to microorganisms due to improvements in standard of living hinders the development of the immune system, such that it is more likely to respond inappropriately when introduced to such agents at older (compared to younger) ages [83]. This explanation is consistent with recent reports indicating that factors such as day care attendance [84], sharing a bedroom with a sibling, and contact with pets are protective against T1D [83].

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 [85]. 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 [86]. Gut microbiome act as critical stimuli, playing an important role for the maturation of the GALT and further induce IgA production by B cells [86]. Class switching to IgA-producing plasma

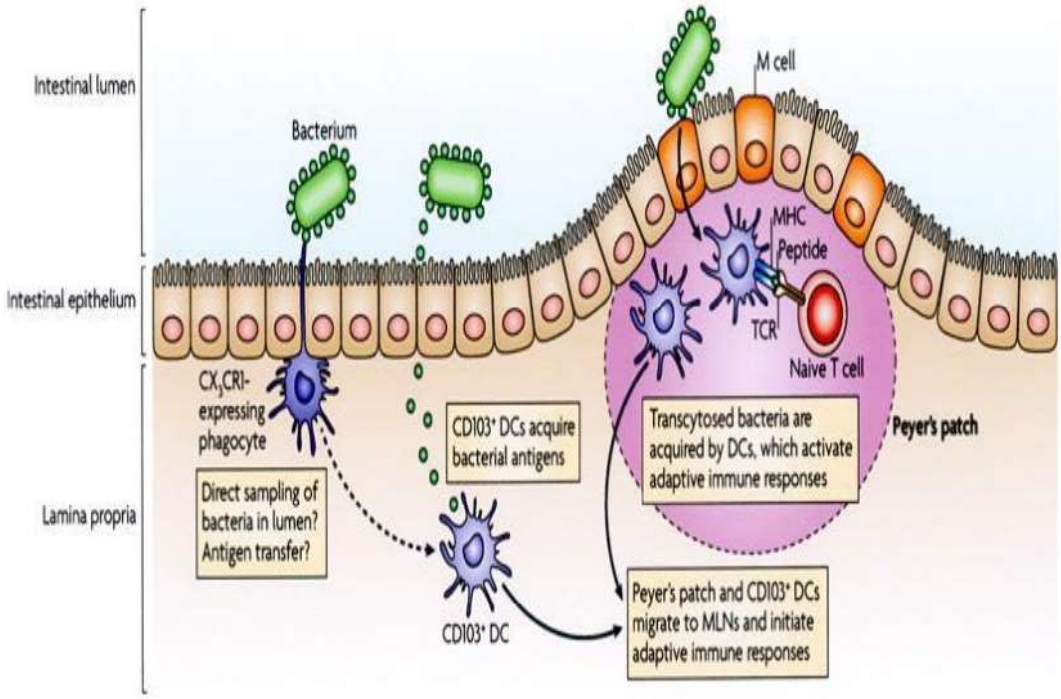
cells occurs in the Peyer's patches and lamina propria, following T cell-dependent or -independent mechanisms [87]. The secreted IgA (SIgA) into the gut provides a first-line defense against pathogens mainly by blocking toxins and pathogens from adhering to the intestinal epithelium at the earliest steps of the infection process [88]. The studies of Endesfelder *et al*., [89], suggest that an increased availability of butyrate and propionate in the intestinal tract (depending on breastfeeding and nutrition) have protective effects against a development of T1 DM related autoimmunity.

Several studies reported that the more prevalent *Bacteroidetes* species in the microbiome in countries like Finland and Russia have higher susceptibility to autoimmune disease produce a type of LPS with immunoinhibitory properties[90; 91].

This may somewhat antagonize the higher immunostimulatory properties of LPS and their Lipid A subunit produced by the *E. coli* strains. The phenomenon may preclude an early "immune education" and contribute to the development of autoimmune disease [92]. Mucin synthesis and Butyrate may play a major role in the prevention of autoimmune disease. Brown *et al*., [93], 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 [94].

3.2. The Role of Gut Microbiome in Diabetes Mellitus Type 1

Autoantibodies can originate from autoreactive B cells that escape immune tolerance mechanisms following molecular mimicry of infectious antigens with autoantigens, bystander activation, novel autoantigen presentation, or recognition of circulating autoantigens due to decrease of lactate and butylate producing bacteria that protect gut permeability and maturation of B-cells [95] (figure 1). They can clear target cells via antibody-dependent cell-mediated cytotoxicity or complement activation [95]. The authors speculate that the correlation of certain bacterial findings with the number of positive autoantibodies could indicate a role of gut dysbiosis as a regulator of β-cell autoimmunity in the progression of the autoimmune process towards clinical disease like diabetes mellitus type 1 [96].



Petta *et al*., [95]

Figure 1:Role of Gut microbiome in autoimmune and T1DM.

3.3. The Role of Gut Microbiome in Diabetes Mellitus Type 2 and obesity

SCFAs such as butyrate may protect against diet-induced insulin resistance. This can occur through 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 [97]. The main location of GLP-1-secreting cells is the distal ileum and colon and, interestingly, rectal but not intravenous infusions of SCFAs in humans stimulates an abrupt increase in GLP-1 secretion [97].

In contrast to the cases of gut dysbiosis, LPS are absorbed by enterocytes and they are conveyed into plasma coupled to chylomicrons [97]. 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 *Eubacterium rectale–C. coccoides* group, Gram-negative *Bacteroides* and in *Bifidobacterium* [97].

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 [98]. 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 [99; 100].

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 [101]. Moreover,

knockout CD14/TLR4 mice were even more sensitive to insulin than wild type controls [101]. 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 [102]. Karlsson *et al*., [103], reported that an increase in the abundance of four *Lactobacillus* species and decreases in the abundance of five *Clostridium* species in Diabetes mellitus type2.

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 [104]. 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 [105]. 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* [104;103], and an enrichment of opportunistic pathogens [104].

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]. In accordance with these findings, an increasing number of observational studies have reported changes in the gut microbiome associated with type2 diabetes, but the outcomes are not always concordant. Although, diets most especially western diet consisting among others of high fat and high salt content has been reported to cause gut dysbiosis [106]. 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 [106] (figure 2).

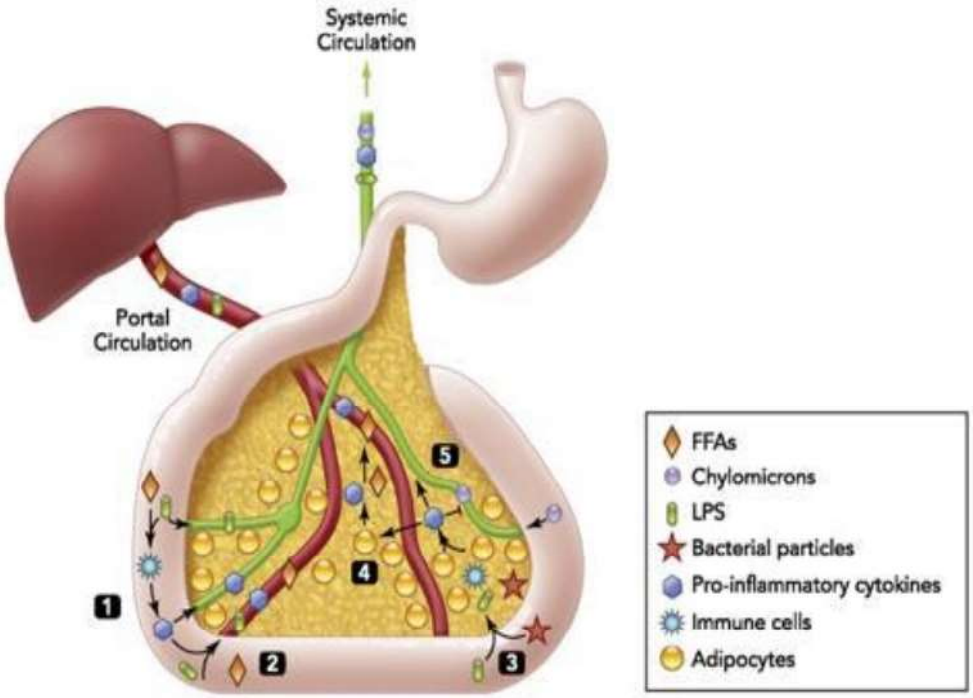


Figure2: Bacterial products, changes in adipose tissue lead to insulin resistance and decrease insulin release [106]

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

4.The Gut Microbiome in Cardiometabolism

Inflammation is commonly involved in a number of diseases [105], including atherosclerosis, which is a classical chronic inflammatory disease [106]. Gut epithelium is the first barrier of the host, which protects against the invasion of pathogens [107]. 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 [108; 109]. 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. 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. The association between LPS and CVD was first proposed in 1999 by measuring plasma endotoxin levels in the clinic. Subsequently, the relationship was gradually confirmed by multiple experiments by different research groups [110]. For example, in one study, it was concluded that the level of circulating endotoxemia was most notable in patients with the highest CVD burden [98], 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 [111]. Gut dysbiosis-derived LPS may play important roles by modulation of Toll-like receptors (TLRs) and their downstream targets [112]. As part of the pattern-recognition receptors

family, TLRs can recognize bacterial products and modulate the host immune system [113]. Circulating LPS can bind to cell-surface-receptor complexes composed of TLR4 and its co-receptors cluster of differentiation 14 (CD14) [114]. Consistently, clinical investigations have revealed that upregulation of TLRs was associated with inflammatory activation in human atherosclerosis, and promoted the development of atherosclerosis [115]. Moreover, the binding of LPS to TLR4 activated its downstream pathways including MYD88 and nuclear factor kappa B (NF-κB), contributing to the increased production of pro-inflammatory cytokines such as IL-6, IL-1, IL-27, and tumor necrosis factor-alpha (TNF-α), leading to an increased risk of developing CVD, showed that a deficiency of MyD88 reduced atherosclerosis by decreasing macrophage recruitment. First, the microbiome alters rapidly when exposed to great and fast changes in diet. Short-term dietary changes such as switching between plant- and meat-based diets, or adding more than 30 grams of fiber per day to the diet, or following a diet with a different fat/fiber content can change the human gut microbiome in function and composition significantly in 48 hours. Fiber-enriched diets have been shown to improve insulin resistance in lean and in obese subjects with diabetes [116]. However, only long-term dietary habits are most important in actually shaping the composition of the gut microbiome. Short-term dietary interventions failed to change the major features and classification of the microbiome [14]. Another aspect to consider is the high interpersonal variance in the effect of changed diets on the gut flora, thus mirroring the individualized nature of our gut microbiome.

In multiple human studies, elevated trimethylamine-N-oxide (TMAO) has been independently associated with prevalent CVD and incident risks for Myocardial Infarction, stroke, death, and revascularization. Choline is an essential dietary nutrient. While it can synthesize much of its requirements, there is still 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 pathways, and neurologic disorder [117].

An obligatory role for gut microbiome in both trimethylamine (TMA) and TMAO formation from ingested PC was confirmed in animal model studies, which included germ-free mice [118], as well as human clinical investigations involving ingestion of egg yolk, isotope-labeled PC, and a cocktail of oral antibiotics [103]. 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 flavin monooxygenases (FMOs) [119; 120; 121]. Gut microbe–produced TMA reaches the liver rapidly via the portal circulation, where a cluster of hepatic FMO enzymes efficiently oxidizes TMA into TMAO (figure3). 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]) [122].

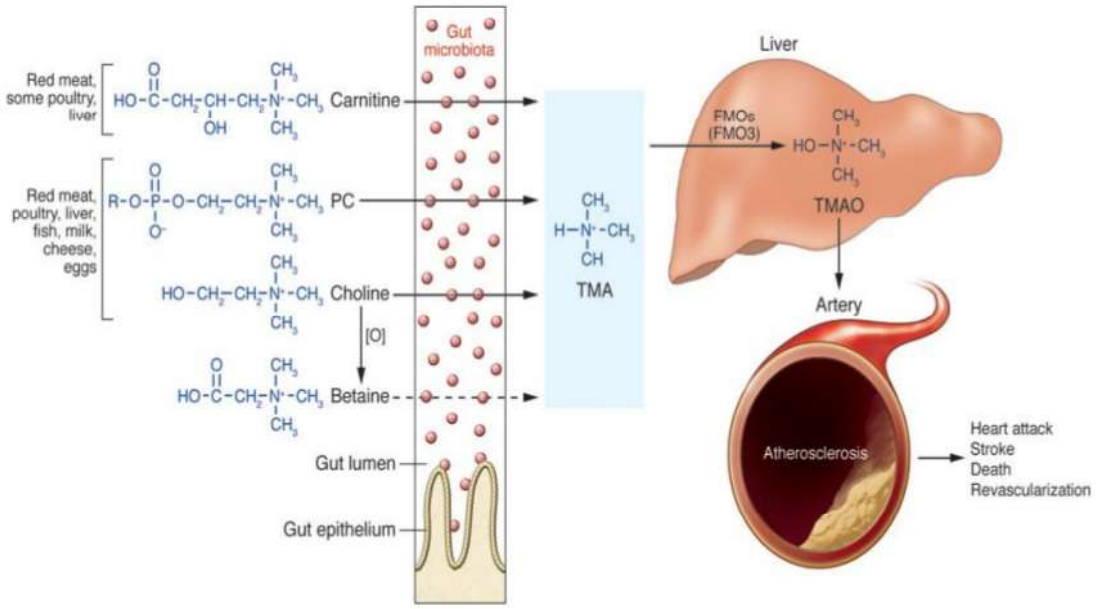


Figure 3: Nutrient/meta-organismal pathway associated with atherosclerosis and major adverse cardiovascular events [123].

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 and diet [124; 125]. 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 [124]. Fermentation of the amino acids tyrosine (obtained usually from consuming turkey, chicken, beef, brown rice, nuts, fish, milk, eggs, cheese, fruit, and vegetables) and tryptophan (e.g., from beef, poultry, pork, fish, milk, yogurt, eggs, cheese, and soy products) by intestinal microbiome generates p-cresol and indole respectively. After absorption, these compounds are further metabolized in the liver to generate p-cresyl sulfate and p-indoxyl sulfate. Indoxyl sulfate and p-cresyl sulfate circulate in equilibrium between a free solute fraction and a fraction bound to serum proteins. The best characterized binding site is albumin, for which indoxyl sulfate and p-cresyl sulfate are competitive binding inhibitors [126]. 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 [127] (figure 4).

Dysbiosis in CKD patients may contribute to increased uremic toxin levels that in turn contribute to CKD progression. In a prospective, observational study of 268 patients with CKD, Wu and colleagues found the baseline concentration of indoxyl sulfate to be predictive of CKD progression [14]. Meijers and colleagues 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) [128]. Likewise, an elevated p-cresol concentration was associated with increased risk of death in end-stage renal disease (ESRD) patients treated with maintenance hemodialysis [129]. Trimethylamine N-oxide (TMAO) is another uremic toxin produced by the gut microbiome, and its role in CKD has also been examined [130].

CKD also affects the structure of the gut microbiome and contributes to dysbiosis due to decreased consumption of dietary fibers [131], frequent use of antibiotics [132], slow colonic transit, metabolic acidosis, volume overload with intestinal wall congestion, intestinal wall edema, and oral iron intake. 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 [133].

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.

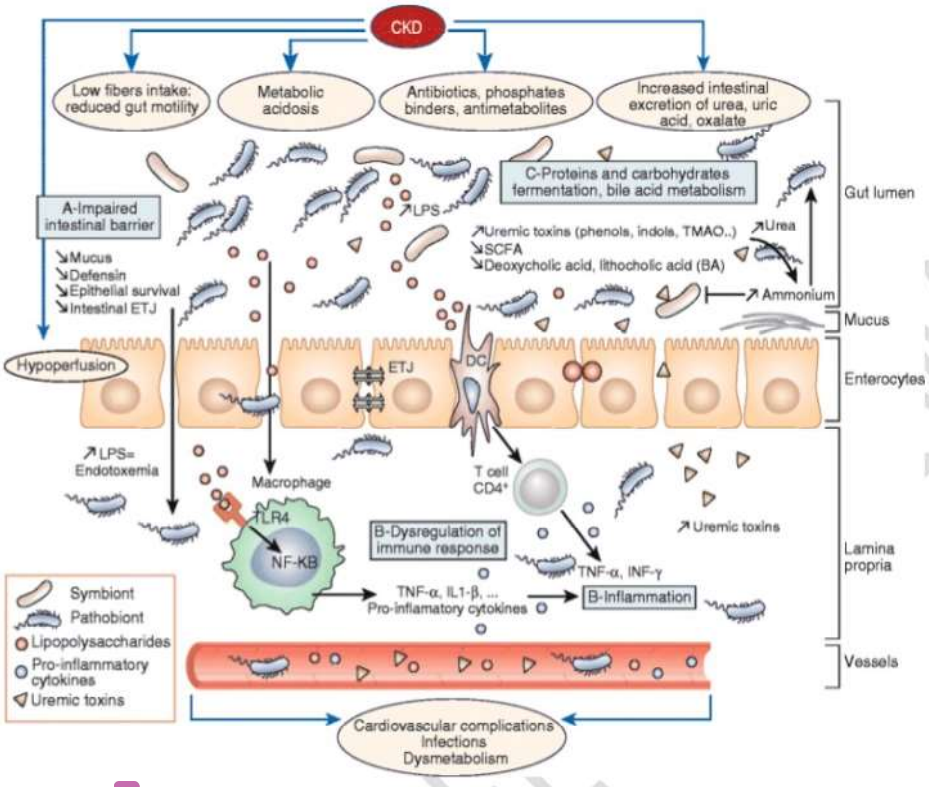


Figure 4: summarizes mechanisms and pathways of dysbiosis in diabetic patients with CKD (Koppe *et al*., 2015).

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 microbiome 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.

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