A Possible Link of Gut Microbiota Alteration in Type 2 Diabetes and Alzheimer's Disease Pathogenicity: An Update

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Abstract: Imbalances in gut microbiota are associated with metabolic disorder, which are a group of obesity-related metabolic abnormalities that increase an individual's risk of developing type 2 diabetes (T2D) and Alzheimer's disease (AD). Although a number of risk factors have been postulated that may trigger the development of AD, the root cause of this disease is still a matter of debate. This review further investigates the etiology of AD by accumulating the current role played by gut microbiota in human, and trying to establish an inter-link between T2D and AD pathogenesis. There is a growing body of evidence which suggests that obesity is associated with alteration in the normal gut flora, reduced bacterial diversity, metabolic pathways and altered representation of bacterial genes. Obesity and T2D are considered to be induced as a result of changes within the composition of gut microbiota. The evidence gathered so far clearly advocates the involvement of gut microbes in causing obesity, a state of chronic and low-grade inflammation. Hence, understanding the microbiota of the gut is significant in relation to inflammation, as it is a key contributor for diabetes which has a direct relation to the AD pathogenesis. Comparative analysis of gut microbiota may enable further novel insight into the complex biology of AD, which is very important in order to take preventive measure such as early diagnosis, identification of new therapeutic targets and development of novel drugs.

Keywords: Alzheimer's disease, Inflammation, Insulin resistance, Macrobiotic, obesity, Tall–like receptor, type-2 diabetes.

INTRODUCTION

Humans usually coexist with their gut microbiota as mutualists and enable to carry out a lot of beneficial functions in our digestive tract. The humans would be unable to digest some of the carbohydrates it consumes in the absence of enzymes produced by bacteria in the gut such as certain starches, fiber, oligosaccharides and sugars. These gut microbes are also essential for production of short-chain fatty acids and synthesis of vitamins. However, when the normal composition of gut flora altered, the relationship of gut microbes with host may become pathogenic, and it leads to energy imbalances, obesity and diabetes. It has been observed that the abundance of Firmicutes was much lower, while the proportion of Bacteroidetes and Proteobacteria was higher in diabetic people compared with their non-diabetic counterparts [1].

The epidemic of type 2 diabetes (T2D) generated a wealth of literature regarding the intricate mechanisms of human metabolism in general and insulin resistance in particular. Many studies have focused on the biology of relationships between various human organs and cell systems. The geneticists have mainly focused on the human genome in their efforts to unravel the risk factors for T2D. However, recently, there has been an increasing body of literature that directs its mind to a possible third culprit: the gut microbiota [2, 3]. The gut microbiota has been linked to insulin resistance or T2D and obesity *via* metabolic disorder [4]. Therefore, the purpose of this review is to elaborate the contribution of gut microbiota in pathophysiology of T2D which is ultimately linked to AD [5, 6]. Recent studies based on large-scale 16S rRNA gene sequencing, quantitative real time PCR and fluorescent in situ hybridization (FISH), have shown a relationship between the composition of the intestinal microbiota and metabolic diseases like obesity and diabetes. For example, the improved glucose-tolerance and low-grade inflammation in prebiotic treated-mice have been associated significantly and positively with levels of *Bifidobacterium* [7]. It has been proposed that the gut microbiota instructs the host to increase hepatic production of triglycerides, which is linked with the development of insulin resistance [8]. In several studies on mice and humans, it has been found that increase in body weight was associated with a larger proportion of *Firmicutes* and relatively less *Bacteroidetes* [9, 10]. All these studies point towards a clear role of gut microbes in the development of obesity, a type of chronic and low grade inflammation, and diabetes. Several studies have already established the link between inflammation, diabetes and AD. Inflammation leads to β-cell dysfunction, insulin resistance, increased Advanced Glycation End-products (AGE) formation, micro and macro vascular diseases in diabetes. On the other hand, in AD it has been associated with neurofibrillary tangle (NFT), Aβ deposition, activated astrocytes and microglia formation. Pro-inflammatory cytokines such as IL-1β, IL-6, TNF-α as well as other mediators like c-reactive protein and α-1-antichymotrypsin have also been shown associated with both AD and T2D [11, 12]. In other words, better understanding of the relationship between gut microbiota and inflammatory agents may prove useful in limiting the menace of pathogenesis of T2D and AD.

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GUT MICROBIOME: A FORGOTTEN ORGAN OF HOST

Gut flora consists of microorganisms that live in the digestive tracts of humans and animals. In this context, gut is identical with intestine, and flora with microbiota or microbiome. The human body, consisting of about 10 trillion cells, carries about ten times as many microorganisms in their intestines [4, 13, 14]. The metabolic activities performed by these bacteria resemble those of an organ. This has led O'Hara & Shanahan to coin gut bacteria as a "forgotten" organ [15]. It has been estimated that in the aggregate, these gut microbiota contain approximately hundred times as many genes as there are in the human genome. Bacteria make up most of the microbiota in the colon [16]. Up to 60% of the dry weight of feces is made up of the gut microbes [17]. Sears [18] estimated that between 300 and 1000 different species live in the gut. However, about 99% of the bacteria come from 30 to 40 species. Interestingly, in spite of bacterial dominance, fungi and protozoa also make part of the gut microbiota. Research findings suggest that the relationship between gut flora and humans is not merely commensal, rather a mutualistic though people can survive without gut microbiota. These gut microorganisms involve in accomplishing a number of useful functions within host, such as fermenting unused energy substrates, training the immune system, preventing growth of pathogenic bacteria, producing vitamins for the host such as biotin and vitamin K, and producing hormones to direct the host to store fats [18, 19].

Till recently, the species in the gut have not been identified since most of them cannot be cultured. However, sequencing based identification revealed that gut microbiota comprised of more than 1000 phylotypes [20]. In a given healthy human, the gut microbiota can be classified into six bacterial divisions or phyla: *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, *Actinobacteria*, *Fusobacteria* and *Verrucomicrobia* [21, 22]. In gut microbiota, more than 90% are comprised of *Bacteroidetes* and *Firmicutes*. Species from the genus *Bacteroides* alone constitute about 30% of all bacteria in the gut, signifying that this genus is especially important in the functioning of the host [18]. Other major genera of gut microbiota is obligate anaerobes like *Bacteroides*, *Eubacterium*, *Clostridium*, *Ruminococcus*, *Peptococcus*, *Peptostreptococcus*, *Bifidobacterium*, and *Fusobacterium*, as well as fewer predominant facultative anaerobes, such as *Escherichia*, *Enterobacter*, *Enterococcus*, *Klebsiella*, *Lactobacillus* and *Proteus* [23, 24]. Methanogenic archaea are restricted to one species, *Methanobrevibacter smithii* [25]. The bacteria in the gut are over 99% anaerobes, but in the ceacum, aerobic bacteria reach high densities.

MODULATION OF GUT MICROBIOTA AND DIETARY COMPOSITION

There are wide variations in populations of species among different individuals but stay quite constant within an individual over time, even though some alterations may occur with changes in lifestyle, diet and age [15]. There are three enterotypes in humans: *Prevotella, Bacteroides* and *Ruminococcus* [26]. An enterotype is a classification of living organisms based on its bacteriological ecosystem in the human gut microbiome. The bacteroides enterotype is linked with higher dietary consumption of protein and saturated fats, whereas the Prevotella enterotype is associated with low intake of protein and fats but high ingestion of carbohydrates and simple sugars in the diet [27]. Human health is affected by diet, to some extent by modulation of the gut microbiome composition. Humans coexist with their gut microbiota as mutualists, but sometimes this relationship may become opposite and can cause diseases such as obesity or diabetes due to changes in the gut composition often triggered by factors like an individual age, genetic make-up or components of diet intake habit. Larsen *et al*. [1] demonstrated that T2D is associated with compositional changes in the intestinal microbiota. The relative abundance of Firmicutes was significantly lower, while the proportion of *Bacteroidetes* and *Proteobacteria* was higher in diabetic persons compared to their non-diabetic counterparts. Accordingly, the ratios of *Bacteroidetes* to *Firmicutes* significantly and positively correlated with reduced glucose tolerance. They found significantly higher levels of *Bacilli* and the *Lactobacillus* group in diabetic subjects compared to controls in accordance with earlier reports in relation to T2D in mice models [28] and to obesity in human adults [29, 30]. There is an association between the concentration of each microbial community and dietary components. For example, *Prevotella* is related with carbohydrates and simple sugars, indicating an association with a carbohydrate-based diet more typical of agrarian societies, while *Bacteroides* enterotypes is associated with animal proteins, aminoacids and saturated fats, components typical of a Western diet. Such a pattern indicates that one enterotype will dominate over the other depending on the diet [27]. Human body would be unable to utilize some of the undigested carbohydrates such as certain polysaccharides, certain starches, fiber, oligosaccharides and sugars in the absence of the gut microbiota. As human cells lack such enzymes to break down these undigested products as compared to gut microbiota that helps to consume it by secreting these enzymes within host. Further, it has been shown in a study that rodents need to eat 30% more calories to maintain the same weight as their normal counterparts when they were raised in an environment lacking gut microbiota [18].

MODIFICATION IN GUT MICROBIOTA AND HOST ENERGY IMBALANCE

There is clear evidence for the role of gut microbiota versus regulation of host energy balances. Bacteria convert carbohydrates into short chain fatty acids (SCFAs) by saccharolytic fermentation producing acetic acid, propionic acid and butyric acid [31]. These materials provide a major source of useful energy and nutrients for humans, as well as help the body to absorb minerals such as calcium, magnesium and iron. Acetic acid is used by muscle, propionic acid helps liver in producing ATP, and butyric acid provides energy to gut cells. Evidence also indicates that bacteria enhance the absorption and storage of lipids [32].

In an extensive investigation, it was observed that germ-free mice had 40% less total body fat than conventionally raised mice despite 29% higher caloric intake than that of

conventionally raised animals. In 2 weeks, conventionalization of their gut with a cecum-derived, distal microbial community of germ-free mice produced a 57% increase in total body fat, a pronounce increase in insulin resistance (IR) (insulin resistance is a condition in which cells cannot use insulin properly; the hormone needed to help glucose leave the blood and enter cells that need it), and more than 2 fold increase in hepatic triglycerides, without affecting chow consumption or energy expenditure [33]. Later, in another experiment, Beckhed and coworkers demonstrated that in contrast to conventional mice, Germ Free (GF) mice fed a high-fat and sugar-rich diet failed to develop obesity or IR supporting a role for gut microbiota in the development of diet-induced obesity [34]. GF mice who were conventionalized with microbiota from obese mice became significantly fatter than recipient GF mice who were conventionalized with microbiota from lean mice. These results suggest that the energy harvest phenotype could be transmitted by the gut microbiota [35]. Resistance to the obesigenic effects of a high sucrose, high palm oil 'western' diet to the GF mice was later confirmed in another study [36]. However, in these studies GF mice were not resistant to the obesigenic effects of a low sucrose, lard-based high-fat diet (HFD). These results indicate that diet composition and/or genetic make-up influences the protection from diet-induced obesity conferred by GF status.

Microbial fermentation of dietary polysaccharides generates SCFAs, which can be absorbed and used as energy by the host. Conventionally raised mice absorbed more monosaccharides from the gut than GF mice [33]. Microbiota generated SCFAs, predominantly acetate, butyrate and propionate are readily absorbed by colonocytes. A considerable amount of acetate enters systemic circulation and reaches peripheral tissues. Most of the butyrate and propionate are utilized by the colonic epithelium and liver, respectively [37]. Generation of SCFAs by gut microbial fermentation also involves in the metabolic actions of methanogenic archaea and chemoautotrophs that use hydrogen gas as a source of electrons for reducing carbon dioxide. Since hydrogen is the end product of fermentation, methanogens in the human gut are supposed to increase the efficiency of bacterial fermentation and SCFAs production, thereby promoting energy harvest and weight gain. Consistent with this concept, co-colonization of GF mice with *Methanobrevibacter smithii* (the principal methanogenic archaea species in the human gut) and *Bacteroides thetaiotaomicron* (ferments dietary polysaccharides) has been reported for greatly increasing the efficiency of bacterial fermentation and SCFAs production and promoting increased fat pad mass [38].

Gut microbiota promotes storage of circulating triglycerides into adipocytes by suppressing intestinal secretion of an inhibitor of adipose tissue lipoprotein lipase called fasting-induced adipose factor (FIAF), also known as angiopoietin like protein 4. FIAF inhibits the activity of Lipoprotein Lipase (LPL), a key enzyme in the hydrolysis of lipoprotein-associated triglycerides and the release of fatty acids for transport into the cells. In adipocytes, fatty acids released by LPL are re-esterified into triglyceride and stored as fat. The increase in body fat observed upon conventionalization of GF mice was associated with a decrease in FIAF expression in the ileum and a 122% increase in LPL activity in epididymal adipose tissue [33]. In 2007, Beckhed *et al*. [34] observed only a 10% increase in total body fat on conventionalization of FIAF-deficient knockout mice compared with 57% fat gain observed in wild-type littermates. Furthermore, germ-free FIAF knockout mice fed a high-fat, high-carbohydrate diet were not protected from diet-induced obesity. Therefore, they concluded that blunted FIAF expression might have involved in triglyceride accumulation in adipocytes and adipose tissue hypertrophy of conventionalized germ-free mice.

AMP-Activated Protein Kinase (AMPK) (which is an enzyme in liver, brain and skeletal muscles and functions as a cellular energy sensor and metabolic regulator) activation increases cellular energy levels by stimulating catabolic pathways (e.g., glucose transport, fat oxidation) and by inhibiting anabolic pathways (e.g., fatty acid, protein and glycogen synthesis). Backhed *et al*. [34] demonstrated that the resistance to HFD-induced obesity in GF mice was associated with 40% more phosphorylated AMPK and acetyl-CoA carboxylase (Acc) and 15% less carnitine: palmitoyl transferase-1 (CPT1) activity in skeletal muscle as compared with conventional mice. The livers of GF mice had twice the phospho-AMPK compared with phosphorylated-AMPK from livers of conventional mice, and this AMPK activation was reflected in substantially reduced levels of glycogen synthase and glycogen. Enhanced AMPK activation in GF mice was associated with significantly elevated levels of AMP and NAD^+ in skeletal muscles and liver, respectively. They concluded that the gut microbiota predisposes the host to obesity and insulin resistance in part by decreasing AMPK activity and fatty acid oxidation in peripheral tissues.

SHIFT IN GUT MICROBIOTA AND OBESITY

Obesity is a state of chronic, low-grade inflammation and is one of the great pandemics of our time. The obesity is influenced by host susceptibility, environmental and lifestyle factors, such as diet and sedentary behavior. Obesity was earlier considered as the outcome of relative imbalance in energy intake versus energy spending. However, recent studies have highlighted that an alteration in microbial population of gut as a potential contributor to the pathogenesis of obesity [35]. The microbes occupying the human gut are directly related to causing obesity. A shift in the ratio between bacterial divisions *Firmicutes* and *Bacteroidetes* can be observed in lean and obese individuals - in the latter, a shift towards *Firmicutes* can be observed. The ratio between *Firmicutes* and *Bacteroidetes* dynamically reflects the overall weight condition of an individual, shifting towards *Bacteroidetes* if an obese individual loses weight. The mutual influence of gut micro-biota and weight condition is connected to differences in the energy-reabsorbing potential of different ratios of *Firmicutes* and *Bacteroidetes*, especially in the digestion of fatty acids and dietary polysaccharides. An increase in weight was observed despite a decrease in food consumption when gut microbiota of obese mice were transplanted into germ-free recipient mice [34, 39]. Lay *et al*. 2005 observed that the gut microbiota of genetically obese ob/ob mice had a 50% lower relative abundance of *Bacteroidetes*, whereas the *Firmicutes* were correspondingly higher. Similarly, the provision of a

high-calorie, high-fat/simple carbohydrate diet to wild-type mice brought about an overall decrease in the variety of the gut microbiota, a decrease in *Bacteroidetes* and increase in *Firmicutes* [35]. On the basis of these studies, it was suggested that the obese microbiome possess metabolic pathways that are highly competent in extracting energy from food. This has been supported by the observation that transplantation of the microbiota of chow-fed ob/ob or western diet-fed wild-type mice into germ-free wild type mouse resulted in mice receiving an 'obese' microbiota gaining more fat than recipients of a 'lean' microbiota [35]. Further, in another study, a progressive increase in *Firmicutes* was confirmed in both HF-fed and ob/ob mice reaching statistical significance in the former, but this phylum was unchanged over time in the lean controls. Moreover, reductions in *Bacteroidetes* were also observed in ob/ob mice [40]. Recently, utilizing systems genetics approach, Parks *et al.* [41] calculated the global gene expression, obesity traits and gut microbiota composition in response to a high-fat/high-sucrose (HF/HS) diet of more than 100 inbred strains of mice. Interestingly, their findings indicate that HF/HS feeding promotes robust, strain-specific changes in obesity that were not related to food intake alone rather it gives evidence that obesity is linked with genetically determined set point of an individual. Notably, human genome-wide association studies (GWAS) have determined several loci responsible for causing obesity and significantly many of these loci were also found in mice counterparts. Further, in this study, a strong relationship has been established between genotype and gut microbiota plasticity during HF/HS feeding. Moreover, this finding has also discovered new gut microbial phylotypes linked with obesity.

Obesity is associated with elevated plasma levels of bacterial lipopolysaccharide (LPS), the major component of the outer membrane of Gram-negative bacteria [42, 43]. It is well known that the lysis of gram-negative bacteria produces LPS in the gut. Intake of HFD increases gut permeability which in turn increases the plasma LPS levels 2 to 3 fold [44, 45]. LPS transits into the circulatory system reflect the passage of bacterial fragments across the gut into systemic circulation [46]. This phenomenon has been termed as ''metabolic endotoxaemia'' and is characteristically linked with the loss of gut *Bifidobacterium* spp., which are known to maintain mucosal barrier function against bacterial antigens [47-49]. Bacterial fragments such as LPS are recognized by Toll-like receptors (TLRs) which are a conserved family of integral membrane pattern-recognition receptors that have a vital role in the innate immune system and intestinal homeostasis [50]. Cani *et al*. [45] demonstrated that LPS is a factor that triggers secretion of pro-inflammatory cytokines such as TNF-α. They further reported that, continuous subcutaneous low-rate infusion of LPS led to too much weight gain and insulin resistance in mice. Moreover, mice deleted for the LPS receptor TLR4, or part of TLR4 machinery such as CD14, resisted the occurrence of obesity [51]. Earlier Song *et al*. [52] has reported that adipocytes when treated with LPS developed inflammation. Cani *et al*. [45] showed that a high-fat diet decreases the number of *Bifidobacteria* and increases plasma LPS. They further demonstrated that modulation of gut microbiota by antibiotic treatment or dietary intervention with oligofructoses has resulted in reduction of glucose intolerance, decrease in body weight gain and inhibition of inflammation in mice. These findings suggest that changes in the gut microbiota could be responsible for increased endotoxaemia in response to a high-fat diet, which in turn would trigger the development of obesity and diabetes. Vice *et al*. [53] suggested butyrate bioavailability as another link between microbiota and chronic inflammation as obese participants were characterized by decreased plasma butyrate levels. Butyrate also has anti-inflammatory properties besides an essential energy source for colon epithelial cells [54, 55]. The major butyrate producing bacterial groups are the *Roseburia*, *E. rectale* and *F. prausnitzii*. Many studies have observed that the dietary intake of fermentable carbohydrates can influence butyrate production. Diets containing high level of non-digestible carbohydrates stimulate the growth of butyrate producing bacteria leading to increase in plasma level of butyrate [56]. Interestingly, previous studies have also shown that increasing plasma level of butyrate improve insulin sensitivity. Further, increase in energy expenditure has been reported in animal models of diet-induced obesity [57]. Hence, all these accumulating evidence suggests that butyrate production from food glycans could be a contributing factor to obesity.

LINKING GUT MICROBIOTA WITH INFLAMMATION, T2D AND AD

The microbiota of the gut is significant in relation to inflammation. Interaction of TLRs and macrophages with bacterial molecular patterns such as LPS results in activation of a complex intracellular signalling cascade, up-regulation of inflammatory genes, production of pro-inflammatory cytokines and interferons such as TNF-alpha, IL-6, and IL-1 [58]. Cani *et al*. [28] demonstrated that a high-fat diet increased the LPS concentration in the blood by increasing the permeability of the gut, causing endotoxemia, which induce systemic inflammation in the mouse leading to obesity and diabetes. Therefore, the better the barrier effect of the mucosa the smaller the risk of translocation of pro-inflammatory components originating from the gut microbiota. Chronic low grade inflammation is a common phenomenon associated with the pathogenesis of T2DM and AD. In diabetes, inflammation is associated with β -cell dysfunction, insulin resistance, increased AGE formation, micro and macro vascular diseases; while in AD inflammation is implicated in NFT, Aβ deposition, activated astrocytes and microglia formation. Increased expression of pro-inflammatory cytokines such as IL-1β, IL-6, TNF-α and other mediators such as c-reactive protein and α-1-antichymotrypsin were also identified associated both with AD and T2D [59-61]. As such, the anti-inflammatory agents may prove useful in limiting the pathogenesis in T2D and AD (Fig. **1**).

The beta cells from T2D subjects contain elevated levels of IL-1β, a potent pro-inflammatory cytokine, and reduced levels of IL-1 receptor antagonist (IL-1ra) [62]. High glucose concentration induces IL-1β expression, but reduces expression of IL-1ra, resulting in the imbalance between IL-1β and IL-1ra, which impaired insulin secretion and cell proliferation and increased apoptosis [63]. A study in T2D Goto-Kakizaki (GK) rats has shown that IL-1ra treatment at

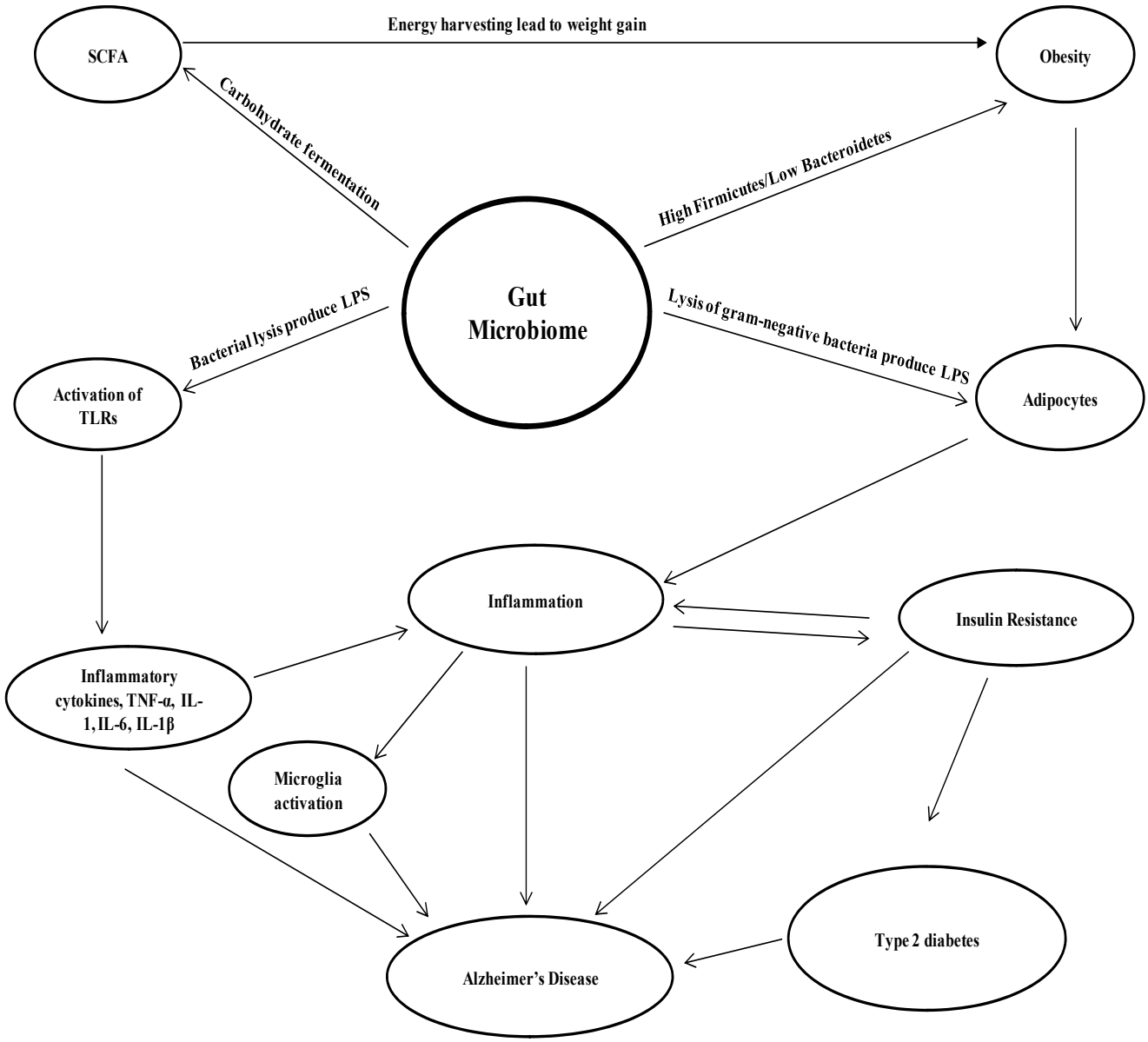

Fig. (1). Pictorial representation linking gut microbiota with obesity, inflammation, Type 2 diabetes and Alzheimer's disease (Abbreviations are given in the text).

a high dose improved glucose sensitivity, insulin processing, and suppressed inflammation and infiltration of immune cells. The GK rats developed T2D at a young age and the pancreatic tissues expressed elevated levels of IL-1β, and IL-1β-driven inflammatory cytokines and chemokines such as tumor necrosis factor-alpha (TNF-α), monocyte chemotactic protein-1 (MCP-1), and macrophage inflammatory protein-1alpha (MIP-1α), along with abnormal infiltration of macrophages and granulocytes. This study supported that the imbalance between IL-1β and IL-1ra leads to pancreatic islet inflammation and thus contribute IR [64].

The receptor for advanced glycation end-products (RAGE), which is a pattern-recognition receptor, interacts with its ligands resulting in persistent inflammatory responses at sites where the ligands concentrate. Advanced glycation endproducts (AGEs), which are derivatives of lipids, proteins, and ribonucleic acids are the major RAGE ligands in diabetes. These are modified by nonenzymatic glycosylation, followed by rearrangement, dehydration, and eventually becoming irreversible cross-linked macromolecules [65]. As the age progress, the amount of these heterogeneous products increases. There is evidence, which further suggests that these pro-inflamatory glycation end products are enhanced by diabetes or hyperglycemic conditions [66]. It has been demonstrated that diabetes associated RAGE-AGE interactions induce reactive oxygen species-mediated inflammatory responses in mononuclear phagocytes and vascular cells such as endothelial cells, smooth muscle cells, and pericytes. All these cells are critically involved in diabetes-associated atherosclerosis, nephropathy, and retinopathy [67]. Recent evidence also demonstrated that RAGE is involved in inflammation-based mechanisms of islet cell death [68]. Zhu *et al.* [68] observed

that the interaction of AGE with RAGE induced apoptosis of islet beta cell and impaired the function of insulin secretion.

TLRs are pattern-recognition receptors consisting of 12 family members in humans. They are crucial for innate immune functions. There is evidence that some of the TLR members are involved in mediating inflammatory responses in metabolic disorders like high glucose level in blood. TLR2 and TLR4 expressions were found elevated in the cell surface of monocytes from patients affected with metabolic syndrome which consequently released higher level of IL-1β, IL-6, and IL-8 when stimulated with lipopolysaccharide [69, 70]. The inflammatory responses induced by TLR2 and TLR4 are mediated through the activation of NF-*κ*B [71]. Interferon-inducible protein (IP)-10 which is a chemokine ligand has been identified to activate TLR4 leading to pancreatic islet cell death [72]. Cluster of differentiation 36 (CD36) is another pattern recognition receptor, which serves as a co-receptor for TLR2 and TLR6 heterodimers, as well as TLR4 and TLR6 heterodimers [73]. High glucose, oxidized LDL, free fatty acids, and low high-density lipoprotein receptors (HDLs) cholesterol concentrations were shown to increase the expression of CD36 in monocytes/macrophages, resulting in vascular oxidative injury, increased leukocyte adhesion, and promoting atherogenesis [74]. Kennedy and Kashyap [75] found that the deficiency of CD36 in transgenic mice improves insulin signaling, inflammation, and atherogenesis.

Too much insulin may lead to inflammation, which can contribute to damage in the brain. Growing evidence demonstrate pivotal roles for brain insulin resistance and insulin deficiency as mediators of neuro-degeneration, particularly AD. The endogenous brain-specific impairments in insulin and insulin-like growth factors (IGFs) signaling accounts for the majority of AD-associated abnormalities characterized pathologically by the occurrence of intracellular neurofibrillary tangles rich in tau protein and extracellular plaques containing amyloid peptide [76]. It has been documented that too much insulin in the brain can contribute to β -amyloid (Aβ) production and subsequent accumulation of amyloid plaques [77]. Hence Type 2 diabetes leads to destructive deposition of Aβ build up, which causes AD. IR and hyperinsulinemia trigger inflammation and are associated with the elevated level of inflammatory markers that enhance the risk for AD [11, 78]. Patients with AD have elevated cerebrospinal fluid (CSF) concentrations of the inflammatory cytokine IL6 and the lipid peroxidation marker F2- isoprostane [79]. Insulin may also contribute to inflammation in the central nervous system (CNS), partially through effects on Aβ. Insulin promotes the release of Aβ from intracellular neuronal compartments and inhibits its degradation by the metalloprotease insulin-degrading enzyme [12]. Human and experimental animal studies revealed that neuro-degeneration associated with peripheral insulin resistance is likely accomplished *via* a liver brain axis whereby toxic lipids, including ceramides, cross the blood brain barrier and cause brain insulin resistance, oxidative stress, neuro-inflammation, and cell death. In essence, there are dual mechanisms of brain insulin resistance leading to AD-type neuro-degeneration: one mediated by endogenous, CNS factors; and the other, peripheral insulin resistance with excess cytotoxic ceramide production [80].

CONCLUSION

In this article, we have focused on the current knowledge available in the literature regarding significant role being played by the gut microbiota in human health and disease. In this review, we have made an attempt to establish possible links between the pathogenesis of T2D and AD by systematically summarizing the associated risk factors often caused due to changes in the gut flora. Obesity and T2D, the two most prevalent metabolic disorders worldwide, are considered to be induced by the impact of the microbiota imbalances. The growing bodies of evidence suggest that the obesity is associated with phylum-level changes in the microbiota, reduced bacterial diversity, and altered representation of bacterial genes and metabolic pathways. The evidence gathered so far clearly advocate the involvement of gut microbes in causing obesity, a state of chronic, low-grade inflammation. Hence, understanding the microbiota of the gut is significant in relation to inflammation as it plays an important role in diabetes, which has a direct relation to the AD pathogenesis. It has been found that in diabetes, inflammation is associated with β-cell dysfunction, insulin resistance, increased AGE formation, micro and macro vascular diseases; while in AD inflammation is implicated in NFT, Aβ deposition, activated astrocytes and microglia formation. It has been shown that TLRs expression dictates the levels of IL-1β, IL-6, and IL-8 upon stimuling with LPS. Moreover, (IP)-10 activates TLR4, which lead to pancreatic islet cell death, thus causing insulin resistance as often observed in T2D. Thus, gut microbiota seems to exert its effect on the host nearly at all aspects of daily lives. The requirement to maintain the overall balance in the composition of the microbiome, as well as the presence or absence of key species capable of affecting specific responses are central in ensuring homeostasis of the host health. Therefore, there is a need to answer some key questions such as investigating specific aspects of host-microbe relations in healthy and disease individuals, as well as understanding the mechanisms through which gut microbiota exerts its beneficial or detrimental impacts on health status. Moreover, understanding of signaling molecules leads to perturbation of cellular immunity as well as responsible for metabolic disorder will further our knowledge of their role in health and disease, allowing customization of existing and future therapeutic and prophylactic modalities. Further, enhancing the improvements in the exiting tools available for microbiota research along with discovery of new tools for diagnostics will be a great leap towards unraveling the deep impact of microflora on human health and will pave the way forward in order to take the preventive measures against associated diseases in metabolic disorders.

LIST OF ABBREVIATIONS

AD = Alzheimer's disease

T2D = Type-2 diabetes

IR = Insulin resistance

TLR = Toll like receptor

GF = Germ free mice

RAGE = Receptor for Advanced glycation end products

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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