Review

The contribution of gastrointestinal microbiota in the existence of type 2 diabetes in Saudi Arabia: Current information and perspectives

Nesreen Aljahdali

Department of Biological Science, College of Science, King Abdulaziz University, 42742, University Avenue, Jeddah 21551, Saudi Arabia

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ABSTRACT

Diabetes mellitus (DM) is a genuine international health issue, with Saudi Arabia ranking among the top nations with the largest diabetes prevalence. Following the International Diabetes Federation (IDF), 3.8 million Saudi Arabian people had diabetes in 2014. The occurrence of diabetes in Saudi Arabia is likely to elevate due to the current trend in the general rise of socio-economic status, which positively correlates with diabetes prevalence. The incidence of Type 2 diabetes (T2D) is highest within the age group $\geq$ 45 years, especially in Riyadh and Jeddah, the metro cities of Saudi Arabia. Previous studies have shown that the incidence of T2D is larger in urban regions (25.5%) than in rural regions (19.5%). Both Riyadh and Jeddah are urban areas with different food habits and locations in Saudi Arabia. Recent studies have indicated the correlation between altered alimentary tract microbiota with type 2 diabetes. Gut microbiota plays a critical role in degrading undigested dietary compounds and releasing a vast array of metabolites that directly and indirectly affects host health. In the current review, we shed light on the state of information on the realization of the types and functions of the alimentary tract microbiome and how it plays a causative agent in the up growth of T2D.

Contents

1. Introduction

The alimentary tract is home to bacteria, which include many species (spp.,) (Turnbaugh et al., 2007). The metagenomic repertoire of the human microbiome is greater than mankind's genome and encodes a huge diversity of crucial physiological and metabolic functions (Turnbaugh et al., 2007; Iatcu et al., 2022). The microbiome diversity in the alimentary tract depends on metabolic ill-

nesses like T2D and obesity (Larsen et al., 2010; Abd Elkader et al., 2022). High blood sugar levels are a sign of diabetes caused by a decrease in pancreatic insulin synthesis or insulin sensitivity in tissues that usually respond to insulin signaling (DeFronzo et al., 2010), in which both microvascular and macrovascular problems might occur. Diabetic nephropathy, neuropathy, and retinopathy are three microvascular diseases of type 2 diabetes that involve small blood vessels.

Cerebrovascular disorders, coronary cardiac disease, and peripheral vascular disorder are examples of prevalent macrovascular problems involving big blood arteries (Baig and Panchal 2019; Iatcu et al., 2022). Microbiome disorder and metabolic diseases such as T2D are attributed to the large-scale gut microbiome sequencing. The majority of previous studies focus on studying the microbiome disorder in Western peoples, but little investigations on T2D microbiome correlations in Middle Eastern societies, where T2D incidence was risen>20% (Al-Muhanna et al. 2021). In the Eastern Province of Saudi Arabia, stool samples were collected from 461 T2D diabetic patients and 119 non-T2D participants to correlate the abundance of microbial communities and T2D (Al-Muhanna et al., 2021).

In diabetic individuals, the genus *Firmicutes* was upregulated in contrast with non-diabetic persons, and T2D was linked to an enhanced *Firmicutes/Bacteroidetes* rate, which was symmetrical with earlier results. Differential abundance and alpha diversity assessments generally revealed consistent differences in stool composition standards on Saudi subjects' diabetes state and glucose concentration (Al-Muhanna et al., 2021).

2. Diabetes mellitus (DM)

The DM is a metabolic disorder distinguished by chronic hyperglycemia with alteration of carbohydrate, protein, and fat metabolism revealing either the pancreas not producing adequate insulin or the body cells not responding to the secreted insulin (Iatcu et al., 2022). Microvascular and macrovascular complications accompany hyperglycemia. Diabetes Mellitus is classified into 2 types: Type 1 diabetes (T1D) and Type 2 diabetes (T2D) (Abd Elkader et al., 2022; Iatcu et al., 2022). Type 1 diabetes exists from the pancreas' failure to secrete adequate insulin from β cells of the islets of Langerhans because T-cell-mediated autoimmune attack results in the damage of β cells and results in low insulin levels. This type most commonly affects young ages and pubescents. Type 2 diabetes results when the body's cells are unable to use insulin properly, and this type affects mostly adults (Alberti et al., 1998). Following the International Diabetes Federation (IDF) in 2014, it was conducted that 387 million people had diabetes worldwide, and T2D made up about 90% of the cases, which describes as a worldwide epidemic.

Type 2 Diabetes (T2D) is featured by insulin resistance and lowered insulin secretion. The specific etiology of T2D is unknown and is influenced by age, sex, obesity, physical inactivity, and unhealthy diets (Al Dawish et al., 2015). Additionally, people who are at risk of T2D, are more likely to have other metabolic syndromes (MS), such as hypertension $\geq$ 140/90 mmol/l, decreased high density lipoprotein cholesterol level (HDL) < 35 mg/dl (<1.03 mmol/l), increased low density lipoprotein cholesterol level (LDL) > 100 mg/dl (>2.6 mmol/l), increase triglyceride level > 150 mg/dL (>1.7 mmol/L), body mass index $\geq$ 25 kg/m^2, waist-hip ratio > 0.90 (male); > 0.85 (female), glycated hemoglobin (HbA1c) $\geq$ 6.5 DCCT %, and microalbuminuria $\geq$ 20 μg/min) (Alberti et al., 1998). Furthermore, higher circulation of endotoxin has been found in people with T2D. A study conducted for patients with T2D in Saudi Arabia showed a positive correlation between endotoxin and triglycerides, total cholesterol, fasting plasma glucose, and fasting insulin. Furthermore, they found an elevated level

of endotoxin in patientsan elevated level of endotoxin in patients treated with antidiabetic medication compared to non-diabetic people. Elevating prosperity, physical inactivity, socio-economic status, and lifestyle differences were the cause of metabolic syndrome in Saudi Arabia, which increased the diabetes prevalence (Aljabri, 2011).

3. Type 2 diabetes in Saudi Arabia

Physical inactivity and dietary patterns, such as consumption of Kabsa (rice with meat), dates, French fries, and bakery diets, are common and on the rise. These unhealthy practices are accountable for the increasing incidence of type 2 diabetes among Saudi people (Midhet et al., 2010). It has been recorded that 54% of 234 patients with T2D lack exercise. Moreover, 67.3% of 234 cases took>2 drugs, 23.9% took 2 types of drugs, and only 8.8% were not taking any medication (Alsenany and Al Saif, 2015). Also, in another study, on the dietary practices among 222 Saudi patients with T2D, the carbohydrates concentration in diet was 56.9%, which increased with 21% over the recommendations by American Diabetes Associations (ADAs) which is 48%. Also, they found that some people with diabetes had a negative attitude to fruits and vegetables near 12% of 222 did not involve the fruits and vegetables in their meals, accounting for the low fiber intake (Mohamed et al., 2013). Therefore, the intake high-fiber diet may be vital for overcoming the disease (Saad et al., 2015; Saad et al., 2021a). Al-Nozha et al. (2004) reported that 4004 out of 16,917 people were diagnosed with DM among the Saudi population. Saudi people who lived in urban areas had a DM prevalence rate of 25.5% compared to rural areas with a 19.5% rate. Additionally, diabetic male subjects were found to have a slightly higher prevalence (26.2%) than females (21.5%).

They concluded that DM increased with age, especially 60–70 years old. A study conducted on abnormal glucose metabolism among participants in 13 administrative areas of Saudi Arabia revealed that the prevalence of T2D with age extended its peak in the age group after 65 years at 40.6% of 53,370 people. Furthermore, the age range of patients with T2D was 45–65 (Al-Rubeaan et al., 2014).

In Jeddah, Alsenany and Al Saif (2015) reported that patients over age 50 years had diabetes with long-term complications and the mean age of these patients with T2D was 58 years. Additionally, Murad et al. (2014) found that male patients over 40 years old, low educated, married/divorced, jobless, and smokers, had more risk factors associated with T2D among adult Saudi patients. Likewise, in Riyadh, a center region of Saudi Arabia and on a desert plateau, male patients with T2D were found to have a higher prevalence of T2D than female patients. Also, they concluded that Riyadh had an increased incidence of T2D by 10% in a decade (Al-Daghri et al., 2011). The incidence of metabolic syndrome (MS) has been raised among Saudi adults, so the risk of developing type 2 diabetes has elevated in people diagnosed with MS (Bahijri and Al Raddadi, 2013). In Jeddah, Alzahrani et al. (2012) stated that MS incidence between 600 healthy Saudi adults aged 35–50 years increased with age. Also, they found that decreased high-density lipoprotein cholesterol level (HDL) showed the highest incidence, followed by high triglycerides among participants.

In Riyadh, Al-Daghri et al. (2010) found that males had a critical large incidence of elevated blood pressure, impaired fasting glucose, and triglycerides while females had a significantly larger prevalence of belly obesity. The duration of diabetes is found with major risk factors for many complications seen in Saudi adult patients. This is confirmed by Alzahrani et al. (2015), who noticed that persons who had diabetes over 15 years had the highest diabetic foot disorders in Jeddah, including peripheral vascular dis-

eases, peripheral neuropathy, foot gangrene, ulcer, and amputation in diabetic cases. Like Riyadh, diabetic foot disease was associated with a long duration of males who were illiterate and older than 40 years (Abolfotou et al., 2011). Many studies have proven that the main factors affecting T2D are age, sex, and metabolic syndromes (Ealovega et al., 2004). These factors, along with dietary habits and physical inactivity, influence the gastrointestinal tract (GIT) microbiome, which has shown to play a causative role in the existence of T2D as environmental factors (Tai et al., 2015).

4. Human gut microbiota

The human body inhabits trillions of microbial cells. Most of the microbial diversity is in the man alimentary tract, which has become the best examined microbial ecosystem in recent years. The quantity and quality of bacteria that have been found in the GIT differ from one part to another. To illustrate, the bacterial quality found in the stomach are practically acid-tolerant, such as *Helicobacter pylori* with the quantity 10^2-10^3 cells/ ml. The bacterial multiplication found with the small intestine mucosa contains the phylum *Bacteroidetes* and members of the *Clostridiales* clusters XIV and IV and those of the lumen involve members of the *Enterobacteriaceae*. In contrast, bacterial biomass is low (10^4-10^5 cells/ ml) in GIT to limit competition for substrates and malabsorption of nutrients. Most bacteria in large mucosal intestine were phylum *Firmicutes* and Bacteroidetes, but *Actionobacteria, Verrucomicrobia,* and *Proteobacteria* were in less content.

Unlike the stomach and the small intestine, the large intestine has a high bacteria population (10^{11} cells/ml). These bacteria can release short-chain fatty acids (SCFAs) by fermenting and degrading of food ingredients. Besides bacteria, there are other kinds of gut microbiota found in the large intestine, such as *Archaea*, protozoans, viruses, and fungi, which were found in soil and plants rhizosphere, playing a precious role in mitigating the stress and diseases (Desoky et al., 2020a, 2020b). Still, the gut microbiota is dominated by anaerobic bacteria (Walter & Ley, 2011). Gut microbiota is extremely important as it helps the host with improved metabolism, protection against pathogenic microorganisms, maturation of immune organs, and development of the GIT (Noverr & Huffnagel, 2004; Abd El-Hack et al., 2020, 2021a; Swelum et al., 2021). The beneficial products provided to the host are SCFAs like butyrate, propionate, and acetate found in (El-Saadony et al., 2022). Butyrate is an excellent energy source of epithelium tissue, and all three SCFA have anti-inflammatory and anti-proliferative roles against malignant cells (Hamer et al., 2008). Interestingly, butyrate and propionate have been shown recently to activate alimentary tract gluconeogenesis gene expression (De Vadder et al., 2014).

Usually, GIT bacteria live within the host commensal, but changes in the gut microbial structure and its function can alter host health either beneficially or detrimentally (Saeed et al., 2017; Abd El-Hack et al., 2021b; El-Saadony et al., 2021a). Arguably dietary habits are the main cause of the diversity of man's GIT microbiome (Ashour et al., 2020; Reda et al., 2021).

The inclusion of prebiotics (Abd El-Hack et al., 2018,2021c; Alagawany et al., 2018; Yaqoob et al., 2021) such as bioactive plant compounds (El-Saadony et al., 2021b; Abd El-Hack et al., 2016, 2021d), bioactive peptides (Aladaileh et al., 2020; El-Saadony et al., 2020, 2021c,d; Saad et al., 2021b), phytogenic active compounds (Abdel-Moneim et al., 2022; Abdelnour et al., 2019, 2020; Abou-Kassem et al., 2021) may enhance the gut microbiome by increasing the beneficial bacteria and reducing the pathogenic ones.

De Filippo et al. (2010) found a significant difference between the gut microbiome of European young people who delivered a diet high in animal protein and low in fiber and African young people with a fiber-enriched diet and reduced in animal protein. African children have revealed a serious enrichment in *Bacteroidetes* and lower Firmicutes with more short-chain fatty acids than European young people. Furthermore, *Enterobacteriaceae*, such as *Shigella and Escherichia* were significantly lower in African young people than in European young people. The report concluded that the elevated *Firmicutes* to *Bacteroidetes* rate in European young people, probably caused by their large-calorie diet, might predispose them to further obesity. Another study conducted between adult Native African (NA) people, who consumed a normal balanced food, mostly carbohydrate like fiber, and of African American (AA) people, who had food high in meat and reduced in fiber contents, showed an influence of their diet on colon cancer risk. The NA had a higher population of *Prevotella* (enterotype 2), which is involved in starch digestion, compared to AA, which had a high population *Bacteroides* (entrotype 1) and a larger abundance of serious pathogenic proteobacteria such as *Escherichia* and *Acinetobacter*.

Furthermore, the microbial gene encoding for butyrate-producing and the production of SCFAs were significantly larger in fecal samples of Native Africans, in contrast with African Americans. The authors concluded that African Americans might be at larger risk of colon cancer than Native Africans (Ou et al., 2013). Duncan et al., (2007) indicated that the structure of dietary carbohydrates that the large intestine microbiome can ferment to release SCFAs are polysaccharides and oligosaccharides of plant source. Also, they noticed that the release of SCFAs was higher in obese persons (114 mM), whose diets were rich in carbohydrates and low protein, than in obese people (56 mM), whose diets were rich in protein and low carbohydrates. Additionally, the widespread butyrate and butyrate-releasing bacteria correlated to *Roseburia* spp., and *E. rectale* were lower in obese people who consumed a diet with large protein and reduced carbohydrate, compared to obese people who were diet rich in carbohydrates.

Perturbation of the compositions and action of the GIT microbiome have been present with metabolic disorders such as insulin resistance, obesity, and T2D (Allin, Nielsen, & Pedersen, 2015).

5. Gut microbiota and type 2 Diabetes:

Previous studies based on both 16S ribosome RNA and shotgun metagenomics have provided evidence that the alteration of gut microbial communities and their functional repertoire are found with the increase of glucose intolerance. Larsen et al. (2010) reported that the structural change in the gut microbiome was found with T2D of Danish patients at both phylum and class levels. For instance, the proportion of phylum *Firmicutes* and class Clostridia and Erysipelotrichi were lower in people with T2D than in the controls. Still, class *Bacilli* and genus *Lactobacillus* were larger in people with type 2 diabetes than controls. Additionally, phylums *Bacteroidetes* and *Proteobacteria* and classes *Bacteroidetes* and *Betaproteobacteria* were slightly increased in T2 diabetics while phylum *Actinobacteria* and *Verrumicrobia* were not changed among diabetics and controls.

Moreover, this study found that the ratio of *Bacteroidetes* to *Firmicutes* related significantly to the value of plasma glucose. The authors concluded that intestinal microbiota composition in diabetics people with diabetes was different from non-diabetic people ranging from 30 to 70 years at both phylum and class levels of the V4 region of 16S r RNA gene. Larsen's studies were not consistent with Zhang et al. (2013), who characterized phylum *Firmicutes* and class *Clostridia* as being higher in Chinese with T2D, and the rate of *Bacteroidetes Firmicutes* did not relate with the value of plasma glucose. Also, phylum *Verrumicrobia* has been shown to decrease prediabetes and T2D; however, both studies had similar

results for class *Betaproteobacteria*, which was higher in prediabetes and T2D than in the controls.

Zhang et al. (2013) concluded that the relative abundance of genus *Bacteroides* was reduced in T2D than in the controls and prediabetes groups. However, *Dorea*, *Prevotella*, and *Collinsella* were larger in T2D than controls. Furthermore, this investigation found a negative correlation between fasting insulin concentration and diversity of gut microbiota. As for butyrate-releasing bacteria, *Akkermansia muciniphila* and *Faecalibacterium prausnitzii* had a higher abundance in control groups than in prediabetes and T2D. They concluded that there was a T2D-related dysbiosis and 28 taxa associated with T2D. Furet et al. (2010) found a negative correlation between *Faecalibacterium prausnitzii* and insulin resistance status.

A metagenome-wide association study (MGWAS) revealed the difference in taxonomic and functional changes between control and T2D samples. Qin et al. (2012) characterized T2D-associated gut bacteria in Chinese people at spp. level, and they found that the relative abundance of controls showed different butyrate-releasing bacteria, consisting of *Clostridiales* sp., *Eubacterium rectale*, *Faecalibacterium prausnitzii*, *Roseburia intestinalis* and *Roseburia inulinivorans*. However, most T2D samples had enriched opportunistic pathogenic bacteria such as Bacteroides caccae, *Clostridium hathewayi, Clostridium ramosum, Clostridium symbiosum Eggerthella lenta* and *E. coli*, which have been recorded to cause man diseases as bacteremia. This study described that patient with T2D had a mild degree of alimentary microbial dysbiosis and lowered butyrate-releasing bacteria.

Also, patients with T2D showed enriched sugar transportation in the membrane, methane metabolism, and other metabolic functions. Interestingly, sulfate-reducing spp. *Desulfovibrio* and butyrate-producing bacteria *Akkermansia muciniphila* were high in T2D samples, which did not agree with the Zhang et al. (2013) findings that *Akkermansia* decreased in people with T2D. Qin's studies did not point out medication use information in cases with T2D. Although Karlsson et al. (2013) found similarities between the European and Chinese populations regarding decreased butyrate-producing bacteria, they also found that the two studies differ in the taxa of bacteria present in the gut. The metagenomics analysis of 70-year-old European women (Swedish) revealed an increase in the prevalence of four *Lactobacillus* spp. and decreased five *Clostridium* spp. in T2D, compared to controls. Moreover, *Lactobacillus* spp., correlated positively with clinical biomarkers of T2D, such as fasting glucose and HbA1c.

However, *Clostridium* spp. related negatively with fasting glucose, HbA1c, insulin, C-peptide, and plasma triglycerides but positively with adiponectin and low HDL. This spp. is neither correlated with body mass index (BMI) nor waist circumstances. In addition to spp., model, they described gut bacteria as metagenomics clusters model at order and spp., levels. They identified a positive correlation between *Clostridium clostridioforme* and clinical biomarkers such as triglyceride and C-peptide levels, whereas *Lactobacillus gasseri* related positively with fasting glucose and HbA1c. Besides identifying the gut bacteria as an spp., and cluster model, the microbial function for glucose, starch, fructose, and mannose metabolism and ABC transporters had the highest score in T2D metagenome.

They reported that glucose control and metformin did not have major confounding effects on fecal microbiota structure of T2D as only 2 spp., were affected by using metformin, which are opposed to the results of the investigation by Napolitano et al. (2014) that indicated relative abundances of four genera, which had a significant difference between intake and no intake metformin. Recent research using rat models indicated that metformin decreased gut microbiota diversity (Zhang et al., 2015).
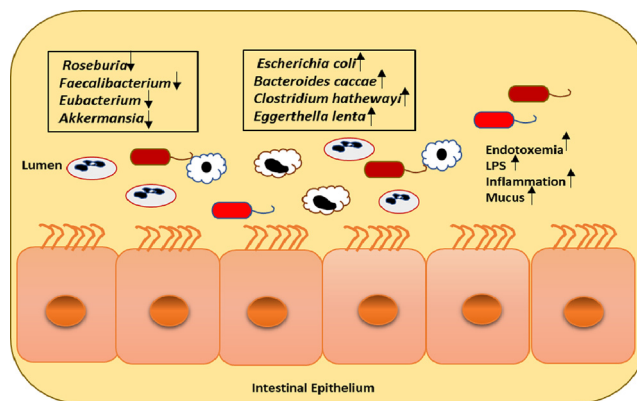

Fig. 1. Cross-talk between the gut microbiota and the host, obesity and type 2 diabetes (T2D) are linked to changes in gut microbiota composition, resulting in increases in some bacteria genera and decreases in others. Some bacteria are positively or negatively linked to obesity and T2D. Mucus breakdown is linked to increased intestinal permeability and metabolic endotoxemia, which causes inflammation and macrophage infiltration.

The important mechanisms by which alterations in alimentary tract microbiota might be linked to the existence of T2D have been mentioned by Amar et al. (2011) and Cani et al., (2007) using mice models that were fed a large fat food. Amar et al. (2011) demonstrated that the early onset of diabetes was characterized by increased translocation of Gram-ve bacteria, such as *E. coli*, through small intestinal mucosa to blood and adipose tissue, where they can induce cytokine production and inflammation. Cani et al. (2007) reported that lipopolysaccharides (LPS), are called endotoxin released from Gram-negative bacteria, would be a primary factor in triggering the high-fat diet-induced metabolic disease. In short, large-fat food revealed a change in the alimentary tract microbiota content and increased intestinal permeability by reducing epithelial tight junction protein expression, such as ZO-1 and Occluding (Cani et al., 2008; Swelum et al., 2020). LPS binds the receptor TLR4 at the surface of innate immune cells induce cytokine and low-grade inflammation (Cani et al., 2007) (Fig. 1).

Cytokines, such as interleukin-6, interleukin-1B, tumor necrosis factor (TNF-α), and other cytokines, are produced by a variety of cell types, such as macrophages and monocytes in response to inflammatory processes (Gabay and Kushner, 1999), and they develop the risk of T2D (Spranger et al., 2003). TNF-α was elevated in skeletal muscle, serum, and adipose tissue in T2D cases (Plomgaard et al., 2005; Creely et al., 2007). TNF-α was found to elevate the phosphorylation of insulin receptor substrate (IRS-1) on Serine residue, leading to insulin resistance (Tanti et al., 2004). Moreover, Spranger et al. (2003) reported that an individual with a combined rise of IL-6 and TNF-α or a collective rise of IL-6 and IL-1B had an elevated risk of T2D than an individual with raised IL-6 alone. To illustrate, the impacts of IL-6 on C-reactive protein (CRP) synthesis depends on interaction with IL-1B or with TNF-α in the liver (Pickup and Crook, 1998). C-reactive protein (CRP) was found with the existence of T2D and the levels of the former raised in response to inflammation because it binds to the phosphocholine expressed on the surface of some bacteria (Thompson et al., 1999; Spranger et al., 2003).

Additionally, IL-6, TNF-α, and IL-1B were reported to act on the hepatic tissue to secrete the dyslipidemia of the metabolic disorder resulting in elevated LDL and lower HDL, which are common in T2D (Pickup and Crook, 1998). Fagiolo et al. (1993) recorded that cytokine production elevated with age. Moreover, the administration of LPS in rodents has been reported to elevate triglyceride levels by de novo fatty acids synthesis, which have been shown to increase the sein phosphorylation of IRS-1) (Feingold et al.,
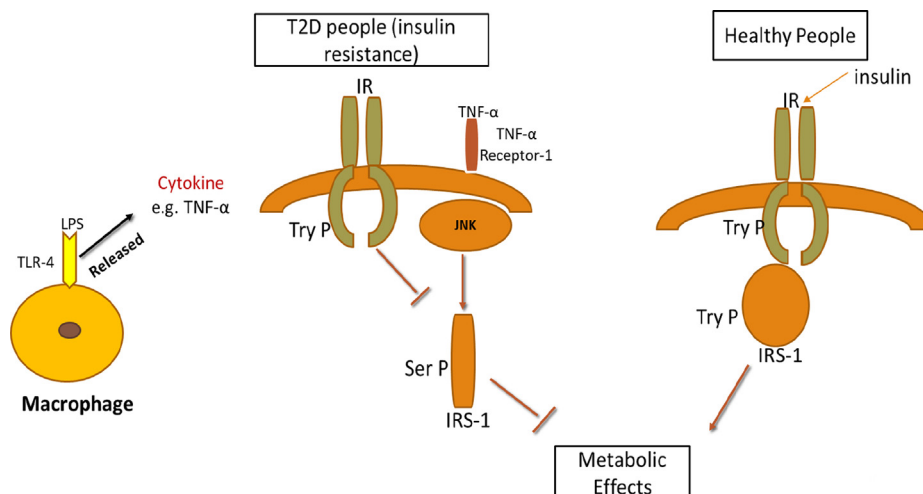
Fig. 2. The bacteria in your gut play a role in the development of T2D. LPS is secreted by bacteria and binds to TLR-4 on macrophages, which respond to inflammatory processes by producing cytokines such as tumour necrosis factor (TNF-). TNF- causes insulin resistance by phosphorylating the insulin receptor substrate (IRS-1) on Serine residues, preventing insulin from binding to the cell's receptor (IR).

1992; Tanti et al., 2004) (Fig. 2). Therefore, the gut microbiota appeared to link LPS of plasma, cytokine, inflammation, fatty acids, and insulin resistance.

6. Conclusions and perspectives

Gut microbiota dysbiosis has been associated with diabetic patients. As a result, modulating the gut microbiota with prebiotics, probiotics, synbiotics, or fecal microbiota transfer may be advantageous in the handling of diabetes and its bad consequences; nevertheless, more research involving human trials should be a priority. Efforts should be made to identify microbial profiles and metabolites that allow for early detection of disease risks and the mechanisms involved, allowing for personalized therapeutic action based on an individual's needs, stage, and illness specificities.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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