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REVIEW ARTICLE

Regulation of Gut Microbiota a Potential Therapeutic Option for Insulin Resistance - A Review

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ABSTRACT: There has been an exponential rise in the incidence of metabolic diseases globally in recent years. In the metabolic disease spectrum, insulin resistance is considered to be a precursor of Type 2 Diabetes Mellitus. If insulin resistance is left untreated, it leads to hyperglycemia, hyperuricemia, dyslipidemia, and eventually, frank diabetes. While genetic susceptibility plays a role in disease development, non-genetic factors such as diet and lifestyle have been instrumental in disease progression. One such factor that has been increasingly linked to insulin resistance and type-2 diabetes is gut dysbiosis. A healthy gut microbiome regulates metabolism and endocrine signaling. An imbalance of the gut microbiome has been shown to increase gut permeability, cause low-grade inflammation and immune dysfunction, and lead to insulin resistance. This review focuses on the role of gut dysbiosis in metabolic disease and explores interventions like diet, prebiotics, probiotics, and fecal microbiota transplantation as potential strategies to regulate gut microbiota to ameliorate insulin resistance. By providing an up-to-date analysis of the therapeutic options, this review underscores the potential of targeting gut microbiota as a promising approach to prevent the progression of insulin resistance to type 2 diabetes mellitus, suggesting the need for personalized gut microbiota-based therapies in the future.

KEYWORDS: Translational Medical Sciences, Disease Treatment and Therapies, Gut Microbiota, Gut Dysbiosis, Insulin Resistance.

Introduction

Insulin resistance (IR) is an impaired biological response to insulin stimulation of target tissues like the liver, muscle, and adipose tissue, which eventually results in hyperglycemia, hyperuricemia, dyslipidemia, and ultimately full-blown type 2 diabetes mellitus (T2DM) if left untreated. Insulin resistance, therefore, is considered as a precursor to T2DM.[1]

In IR, there is inadequate disposal of glucose from the bloodstream into the skeletal muscle. The circulating glucose then requires more insulin to facilitate its uptake into the insulin-resistant tissues resulting in hyperinsulinemia. Hyperglycemia occurs over a period of time as the beta cells in the pancreas are unable to meet the insulin demand. This vicious cycle that continues between insulin demand and supply over the years leads to blood glucose levels consistent with T2DM. Excess circulating glucose enters the hepatocytes, creating excess fatty acid production in the liver, which is not only deposited in the liver but also throughout other organs. Similarly, when adipose tissue becomes insulin-resistant, there is insufficient lipolysis, causing an increase in the circulating free fatty acids (FFA). Higher levels of FFA lead to lipotoxicity-induced beta-cell dysfunction, contributing to the development of T2DM.[2]

A recent analysis of the National Health and Nutrition Examination Survey (NHANES) data from 2021 found that 40.3% of US adults aged 18-44 are resistant based on Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) measurements.[3] Although IR is known to affect all ethnicities and races, comparable data between them is limited. The global diabetes prevalence in 2019 is estimated to be 9.3% (463 million people), rising to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045.[4] Although genetic susceptibility plays a role in T2DM development, non-genetic factors such as diet and physical activity cause insulin resistance eventually leading to T2DM.

An association between gut dysbiosis (alteration of healthy microbiota), insulin resistance, low-grade inflammation, T2DM, and obesity has been reported over the past decade **(Figure 1)**.[5] Gut microbiota (GM) is the microbial population in the gut and is the largest microbial community in the human body. A healthy gut microbiome regulates metabolism, endocrine signaling, and brain function (brain-gut axis).[6] Diet and lifestyle modification are the mainstay of treating insulin resistance. The relationship between gut microbiota and IR suggests the role of regulating gut microbiota as a potential therapeutic target for the treatment of IR and prevention of its progression to T2DM. In this article, we summarise the role of GM in insulin resistance and provide an up-to-date review of diet, prebiotics, probiotics, and treatments like Fecal microbiota transplantation (FMT) as probable interventions for amelioration of IR and prevention of its development into DM.

Discussion

Gut microbiota (GM) and Insulin resistance (IR):

Human GM is primarily anaerobic, belonging to phyla *Firmicutes* (~60%), *Bacteroides* (15%), *Actinobacteria* (~15%), *Verrucomicrobia* (2%), *Proteobacteria* (~1%), and *Methanobacteriales* (~1%).[7] These are distributed throughout the gastrointestinal tract, and balancing the composition of GM is critical to maintaining gut permeability, metabolism, immune function, and prevention of metabolic disease. Several studies have shown that gut dysbiosis (alteration in the GM) can lead to disease. Dysbiosis can be of three different kinds- over-

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microbiota, and loss of overall microorganism diversity.[8] These can occur in isolation or, more often, simultaneously. For example, dysbiosis in the form of low microbiota diversity has been shown to increase the risk of weight gain, insulin resistance, low-grade inflammation, and T2DM in human studies.[9] Similarly, patients with T2DM compared to healthy individuals have a decreased ratio of *Firmicutes* to *Bacteroidetes* in the majority of studies.[10] Specific bacterial species have a definite role in maintaining gut health and preventing disease.

A decrease in *Prevotella* species, a bacteria that helps in glucose homeostasis, was observed in 50 Japanese T2DM patients compared to healthy subjects,[19] but studies in 291 Nigerians and 171 Chinese with T2DM showed an increase in Prevotella.[20] This contrasting result may be due to inter-ethnic variation with genetics, diet, medication use, and sequencing technique, necessitating the use of new technologies to establish firm associations between GM in healthy and diseased individuals among different ethnicities. Similarly, data on *lactobacillus* is dependent on species. While *L. gasseri*, *acidophilus*, and *salivarius* are positively correlated with T2DM, *L. amylovorus* demonstrates a reverse correlation.[17]

Table 1: Role of various intestinal bacterial species in maintenance of gut health and gut dysbiosis in the form of increase in harmful bacteria or decrease in beneficial GM in IR/T2DM patients compared to healthy controls in human studies.

Gut bacteria	Changes in IR/T2DM	Role in glucose metabolism	Reference studies
Akkermansia muciniphila	↓	SCFA-producing bacteria strengthen the gut barrier against pathogenic bacteria	11
Roseburia intestinalis *Roseburia feces*	↓	SCFA producing bacteria	12
Faecalibacterium prausnitzii	↓	Inhibits pro-inflammatory cytokine secretion	13
Bacteroides caccae *Bacteroides vulgatus*	↑	Opportunistic bacteria	14
Bacteroides intestinalis	↓	Preserves intestinal wall integrity; reduces LPS production	15
Firmicutes	↓	Mucin-producing bacteria help with the gut barrier	15
Clostridium clostridioforme	↑ in DM ↓ in prediabetes	Opportunistic bacteria: increase in plasma glucose levels	16
Lactobacillus gasseri *Lactobacillus acidophilus* *Lactobacillus salivarius*	↑	Maintain mucosal barrier function by increasing the mucin levels in the gut	17
Streptococcus mutans	↑	Opportunistic bacteria	18
Prevotella capri	↓ in Japanese ↑ in Nigerians	Increases inflammation and risk of obesity	19,20
Clostridia sp.	↑	Opportunistic bacteria	21
Bifidobacterium	↓	Maintains glucose homeostasis	22
Ruminococcus gnavus	↑	Pro-inflammatory bacteria	23

A decrease in mucin-producing bacteria increases intestinal permeability, allowing pathogenic bacteria to enter the bloodstream and causing 'metabolic endotoxemia,' triggering low-grade inflammation involved in the pathogenesis of IR and the development of T2DM.[24] *Akkermansia*, *Roseburia*, *lactobacillus*, and Bacteroides can decrease pro-inflammatory cytokines (IL-6, IL-8, IL-7, and TNF-alpha) and are thought to be protective against IR and T2DM by restoring insulin sensitivity and improving glucose homeostasis, while *Fusobacterium nucleatum* and *Ruminococcus gnavus* can increase cytokine production.[25] Another study from Denmark with 123 non-obese and 169 obese individuals showed that individuals with high gene count microbiome had reduced susceptibility to metabolic disease and individuals with low gene count were more prone to harboring pro-inflammatory bacteria such as *Ruminococcus gnavus*.[26] Thus, depending on the GM composition, the microbiota can increase or decrease inflammation and metabolic dysregulation impacting IR **(Table 1)**.

Role of GM and Their Metabolites in Metabolic Pathways:

Metabolites are molecules derived from gut microbiota, and their role is to mediate a response between the host and the intestinal bacteria. Gut microbiota is responsible for the fermentation of dietary plant fibers in the intestine, producing short-chain fatty acids (SCFA) such as butyrate, propionate, and acetate. SCFA is instrumental in the regulation of appetite, insulin response, and inflammatory processes. Propionate and butyrate have anti-obesogenic action, while acetate promotes fat storage.[27] Propionate improves the function of beta-cells in the pancreas, promotes insulin secretion and glucose uptake in muscles, and decreases glucagon production in the pancreas. Butyrate is also responsible for maintaining the integrity of the intestinal barrier. Various bacterial components such as lipopolysaccharides (LPS), flagellin, and peptidoglycans can enter the bloodstream if the intestinal barrier is compromised, triggering a chronic inflammatory response that, over time, contributes to metabolic dysregulation and insulin resistance **(Table 2)**.[28] Bacteroidetes produce acetate and propionate, and Firmicutes produce butyrate by fermenting dietary fibers.[29] Reduction in butyrate-producing bacteria such as *Faecalibacterium* and *Roseburia* can, therefore, potentiate insulin resistance and T2DM, as evidenced in human studies.[16] Obese subjects treated with the antibiotic Vancomycin steadily developed insulin resistance due to inhibition of the growth of butyrate-producing bacteria in the gut.[30]

Table 2: Role of gut microbiota dysbiosis in the pathogenesis of insulin resistance. The table shows the cascade of events triggered by an imbalance in the gut microbiota leading to impaired glucose metabolism, setting the stage for insulin resistance and eventually diabetes mellitus over time.

1. Increased gut permeability
2. Lipopolysaccharide leakage into the bloodstream (metabolic endotoxemia)
3. Increase in pro-inflammatory cytokines
4. Increased oxidative stress
5. Increased chronic low-grade inflammation
6. Altered glucose homeostasis

While the association between gut microbiota, glucose metabolism, and insulin resistance in diabetic patients has been relatively well-established through human studies, similar data in patients with pre-diabetes (characterized by abnormal blood glucose levels below the T2DM threshold) is limited. In a recent study from Asia, 57 pre-diabetic patients were compared to 60 healthy individuals in the age group of 18-65, and the pre-diabetics showed a lower GM diversity with respect to the healthy cohorts.[31] More such studies are needed with larger cohorts and across different population groups to substantiate the GM variability in insulin resistance. **Figure 1**

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shows how gut dysbiosis leads to metabolic dysregulation and insulin resistance.

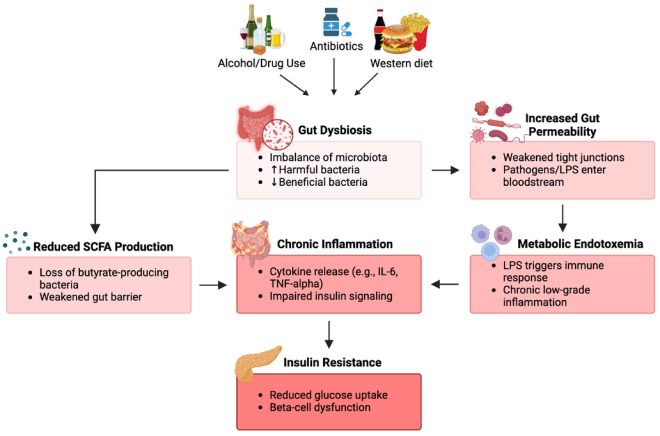

Figure 1: Impact of gut dysbiosis on the pathogenesis of insulin resistance and T2DM through various mechanisms eventually leading to altered glucose metabolism. Abbreviations: LPS: lipopolysaccharide, SCFA: short-chain fatty acids, IL-6: interleukin 6.

Modification of Gut Microbiota to ameliorate Insulin Resistance:

In recent years, there has been an increase in the incidence and prevalence of metabolic disorders like obesity, insulin resistance, type 2 diabetes mellitus, and non-alcoholic liver disease, underscoring the need for therapeutic options to prevent disease onset and progression. With increasing evidence supporting the link between gut dysbiosis and metabolic disorders in animal and human studies, the use of microbiome-based therapies through the manipulation of intestinal bacteria and their metabolites to restore metabolic health is promising.

Gut dysbiosis can be induced by certain medical treatments such as the administration of broad-spectrum antibiotics and chemotherapy, a diet characterized by intake of highly processed foods and foods with low-fibre content, sedentary lifestyle, poor sleep, excessive alcohol consumption, chronic stress, and exposure to environmental pollutants.[32] This section will review the current literature on the interventions aimed at regulating GM to prevent insulin resistance and its eventual progression into T2DM.

Diet and Gut Microbiota:

The major predictor of GM composition is diet.[33] Long-term consumption of the Western diet increases gut permeability, lipopolysaccharide leakage, oxidative stress, and the release of proinflammatory cytokines, leading to IR and T2DM over time.[34] Studies have reported that a Mediterranean diet can impact intestinal bacteria positively. It increases the *Firmicutes* to *Bacteroidetes* ratio and reduces the abundance of *Ruminococcus* and *Prevotella* while increasing the presence of *Faecalibacterium prausnitzii*, as shown in a randomized control trial with 20 obese men following a Mediterranean diet for 1 year.[35] Another study showed an improvement in HOMA-IR compared to the control group after 6 months.[36] However, changes in HOMA-IR were dependent on the baseline gut microbiota composition. Those with increased levels of Bacteroidetes and decreased levels of Prevotella showed a reduction in insulin resistance, providing protection from T2DM and metabolic syndrome.[36] Similarly, lower saturated fatty acid and high-fibre-containing plant-based diets have shown an increase in *Bacteroidetes* and a decrease in *Ruminococcus* compared to omnivorous diets,[37] though studies are limited. Patients with prediabetes who maintain a high-fiber and low carbohydrate intake have increased intestinal barrier integrity and reduced inflammation as the gut bacteria are able to utilize the dietary fiber to produce short-chain fatty acids (specifically butyrate) effectively.[38]

Natural bioactive compounds found in certain food sources can also positively influence gut microbiota (Table 3). Anthocyanidins contained in strawberries, blueberries, and cherries have been shown to increase lactobacillus and bifidobacterium, thereby improving glucose and lipid metabolism and, consequently, IR by improving gut barrier function.[39] The action of GM modulation by bioactive compounds is attributed to increases in the levels of *Bifidobacterium spp. Lactobacillus* spp. *Akkermansia spp*., as well as to the reduction in the *Firmicutes* to *Bacteroidetes* ratio.[47]

Table 3: Effect of foods containing bioactive compounds on the gut bacteria composition and their mechanism of action in reducing insulin resistance.

Bioactive compounds and foods containing them	Gut microbes impacted	Effect on insulin resistance	Reference papers
Anthocyanidin (Berries)	↑ *Bifidobacterium* ↑ *Lactobacillus*	Improved gut barrier function and IR	39
Hesperidin, Naringin (citrus fruits)	↑ *Bifidobacterium* ↑ *Lactobacillus*	Increased production of SCFA and improved insulin sensitivity	40
Berberine	↑ *Bifidobacterium*	Reduced endotoxemia and inflammation	41
Alkaloids and polyphenols (oat bran)	↑ *Lactobacillus* ↓ *Ruminococcus* ↓ *Prevotella*	Reduced inflammation through SCFA production	42
Polyphenols (Green tea, black tea, oolong tea)	↑ *Akkermansia* ↑ *Bifidobacterium* ↑ *Lactobacillus*	Increased production of SCFA Improved insulin secretion	43
Resveratol (Red wine)	↑ *Bifidobacterium* ↑ *Lactobacillus*	Improved glucose tolerance	44
Lycopene (tomato, moringa)	↑ *Bifidobacterium* ↓ *Proteobacteria*	Better gut barrier function Reduced LPS-induced insulin dysfunction	45
Beta-glucans (mushrooms, yeast)		Reduces blood glucose levels by retarding sugar absorption	46

Prebiotics:

Prebiotics are non-digestible food ingredients (fibers) that affect the host positively by stimulating the growth or activity of one or more species of gut microbiota. There is growing evidence to suggest that prebiotics can improve glucose homeostasis in insulin resistance.[48]

One such prebiotic is Inulin, a fructose polymer that cannot be digested by humans, but the gut microbes break it down into short-chain fatty acids. Inulin increases *Bifidobacterium* and *Faecalibacterium*, resulting in increased butyrate levels.[49] A systematic review summarised clinical trials evaluating the effect of inulin on *Akkermansia muciniphila* in control versus T2DM patients and found increased abundance in the treated group compared to the control.[50] A meta-analysis of randomized controlled trials to assess the impact of prebiotics in general on IR reported a decrease in serum insulin and blood glucose levels.[51] Keeping the high-fiber content as a basis, a

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study using 5 raw materials acorn, quinoa, sago, sunflower, and pumpkin seeds, assessed the effect of these prebiotics in healthy and diseased individuals. The study established that prebiotics not only produce beneficial metabolites like SCFAs but also improve gut dysbiosis by promoting the growth of favorable gut bacterial species.[52] *Lactobacillus* and *Bifidobacterium* are the usual targets for prebiotics and diet, as shown in **Table 3**.

The ability of prebiotics to produce a positive impact on glucose metabolism makes it a good adjunct to traditional anti-diabetic drugs. However, their benefit, if started early in the process of metabolic dysregulation, still needs to be established to truly evaluate their role in disease prevention.

Probiotics:

Probiotics are live bacteria that are beneficial to human health in ways such as improving gut health, inhibiting the growth of pathogenic bacteria in the gut, producing SCFAs, and stimulating the immune system.[53] There is enough data to support that alteration of the GM through administration of probiotics improves T2DM by reducing intestinal permeability and pro-inflammatory cytokines.[54]

A randomized, double-blind, placebo-controlled trial of administration of *Akkermansia muciniphila* in IR volunteers improved insulin sensitivity, decreased plasma insulin levels, and reduced body fat mass due to its anti-inflammatory effects.[55] Recent meta-analysis of studies showed that probiotic supplementation improved fasting blood sugar, HbA1C, and HOMA-IR in T2DM.[56]

Probiotics influence GM composition at multiple levels, like strengthening the intestinal barrier, production of SCFAs, and immune modulation, especially specific strains of *Lactobacillus* and *Bifidobacterium*. Numerous studies have shown the beneficial effects of individual bacterial strains, but there are more than enough studies to also show that when a combination of probiotics using more than one bacterial strain is used, it is more effective in improving glucose metabolism.[57] Supplementation with a mix of probiotics containing *Lactobacillus acidophilus*, *Lactobacillus casei*, and *Bifidobacterium bifidum* in DM patients showed a decrease in insulin levels, HOMA-IR, and improvement in insulin sensitivity compared to controls after 6 months in a study.[58]

Several butyrate-producing bacterial species have shown improvement in insulin sensitivity in both animal and human studies. One such study showed that supplementation with a capsule containing a butyrate-producing species, *Anaerobutyricum soehngenii*, improved glycemic controls in patients with metabolic syndrome.[59]

The positive effects of probiotic supplementation have also been studied in pre-diabetics. A double-blind, randomized controlled trial in which patients were randomly supplemented with a probiotic (*L. acidophilus, B.lactis, B.bifidum*, and *B.longum*) or synbiotic (inulin and probiotic) over 24 weeks showed a significant decrease in fasting insulin, HOMA-IR, and HbA1c levels.[60] This suggested that probiotics and synbiotics can potentially reduce the risk of developing metabolic disease in patients with IR. Similar results were shown in a study by Kassian *et al.*, which found a higher concentration of bacteria in the probiotic supplement.[61]

Studies in patients with T2DM have shown less impactful results on glycemic control when probiotics have been compared with antidiabetic drugs, emphasizing their role more as an adjunctive treatment and not a replacement to mainstay therapy. However, the same may not apply to patients of IR or pre-diabetics who are not on any pharmacological anti-diabetic drugs and rely primarily on diet and lifestyle changes to improve their metabolic dysregulation. As previously elucidated, patients with IR differ in the composition of their GM compared to healthy controls. In such cases, the administration of prebiotics, probiotics, or a combination of these can be efficacious supplements to ameliorate the disease or prevent its further progression by improving glucose metabolism. Though most of these studies have been randomized, double-blinded, and placebo-controlled, sample size, inconsistency in measurement, and short duration of the study period warrant the need for more well-designed, longitudinal studies to establish a clear impact of probiotic supplementation as an adjunctive treatment to diet and lifestyle modification for insulin resistance reversal.

Synbiotics:

Synbiotics are dietary supplements that use a combination of both pre and probiotics. Studies have reported a decrease in HbA1c levels when diabetic patients on hemodialysis were administered a probiotic containing different bacteria species together with inulin. Meta-analysis of randomized controlled trials in T2DM patients treated with synbiotics has shown similar results with a reduction in fasting blood sugar levels in addition to HbA1c.[62] A double-blind, randomized control trial from China showed that berberine with probiotics improved HbA1c levels better than berberine alone.[63] These results highlight the synergistic effects of pre and probiotic co-administration. There have been some studies, however, comparing synbiotics with control supplements, which did not report any changes in insulin or glucose response and no alteration of glucose metabolism.[64] Inconsistency in the results of studies has prevented widespread use of synbiotics currently, necessitating larger studies across varied population groups.

The available evidence suggesting the use of probiotics, prebiotics, or synbiotics is not strong enough and, therefore, the therapeutic use of these supplements for metabolic disorders has not been recommended yet. Also, there are only a small number of studies designed to analyze the effects of probiotic and/or synbiotic administration in the prediabetes population who are at risk of developing diabetes and cardiovascular diseases.[61] Inconsistent use of microbial strains and formulas, heterogeneity of target population, and variation in the bioavailability of synbiotics may limit their use in patients with metabolic dysfunction.[63] Additionally, uncertainty in the duration of supplementation of synbiotics or pre- and probiotics may also pose a challenge when used in the clinical scenario. Furthermore, synbiotics are almost always used in conjunction with lifestyle modifications as part of the treatment plan making it difficult to quantify their impact in reducing insulin resistance.

Fecal Microbiota Transplantation (FMT):

Fecal Microbiota Transplantation (FMT) is an intervention wherein fecal material from a healthy donor is transferred to a recipient to improve their gut microbiota composition. The process involves meticulous screening of the healthy donor and processing the microbiota from their fecal material. This is then administered to the recipient through the upper gastrointestinal route (nasogastric tube), lower gastrointestinal route (colonoscopy), or oral route (capsule form). Fecal Microbiota Transplantation has been successfully used for recurrent Clostridium difficile infection secondary to antibiotic-induced gut dysbiosis and is currently being evaluated for GM modulation in IR/T2DM patients.[65]

A study published by Mocanu CV *et al*. suggested that FMT, especially with low fermentable fiber supplementation, can improve insulin sensitivity by increasing the microbial diversity within the gut microbiota, proposing it as a potential therapy for metabolic syndrome.[66] In one study, obese patients with IR given frozen FMT capsules had significantly improved HbA1c levels after 12 weeks with an abundance of *Prevotella* in the recipient.[67] Other studies have also shown improvement in gut barrier function, an increase in GM diversity, and an increase in butyrate-producing bacteria such as *Roseburia intestinalis* and *Bifidobacterium pseudopodium*.[68] Allegreti JR *et al*. studied the effect of FMT in obese but metabolically healthy individuals and found improvement in both glucose and insulin levels after 6 and 12 weeks of treatment compared to a placebo.[69] Administration of FMT capsules led to improvements in total cholesterol, fasting glucose, and HbA1C levels compared to placebo in subjects who had low microbiome diversity to start with. The authors, however, state that the changes in microbial composition were not specifically correlated to the metabolic outcomes suggesting FMT as an adjunct to dietary intervention and exercise to achieve statistically significant changes in insulin sensitivity.[69]

All these studies provide promising evidence; however, other studies showed no significant change in insulin sensitivity in patients with mild to moderate insulin resistance.[70] The difference in the outcome of the studies could be due to multiple factors like the degree of GM dysbiosis in recipients, FMT preparation, and route of administration. This warrants the need for standardization of the procedure to tap the true potential of this innovative therapy to stop the progression of early IR into frank T2DM. Additionally, while FMT is considered relatively safe, transmission of infectious agents does pose a potential risk preventing FMT from becoming a widely accepted form of treatment.[71] One way to offset this risk would be to manufacture synthetic bacterial communities resembling eubiotic gut microbiota for administration to patients with metabolic dysregulation.[72]

Drugs and GM:

Studies assessing interactions of anti-diabetic drugs and GM composition are emerging. GLP-1 receptor agonists, a class of anti-diabetic drugs can change the *Firmicutes* to *Bacteroides* ratio modifying the GM composition. However, most studies are animal-based.[73] Metformin, on the other hand, has a well-established therapeutic effect mediated through GM. It increases bacteria such as *Enterobacteriales* and *Akkermansia muciniphila*.[76] Additionally, metformin use has been associated with a higher production of SCFA's and is known to strengthen the intestinal barrier. Through the modulation of GM, increasing the SCFA levels and enhancing the intestinal barrier integrity, metformin prevents metabolic endotoxemia and thereby reduces insulin resistance.[75]

Conclusion and Future Direction

Insulin resistance is considered a precursor of T2DM in the spectrum of metabolic disorders. Recent data has shown the role of gut microbiota dysbiosis in both IR and T2DM. An increase in pro-inflammatory microbes and a decrease in anti-inflammatory GM causes low-grade chronic inflammation and metabolic dysregulation through an increase in gut permeability and immune dysfunction, leading to IR and, eventually, T2DM. This gut dysbiosis is further exacerbated by a Western diet and poor lifestyle, accelerating the progression of the disease. Modulation of GM through bioactive compounds in diet, prebiotics, probiotics, synbiotics, and FMT to restore gut eubiosis can improve insulin sensitivity and slow the progression of IR along the metabolic disease spectrum, as demonstrated by various animal and human studies. There is a definite and increasing need for large-scale, longitudinal studies across population groups to establish a role for gut-modulating therapies for the prevention of metabolic dysregulation, which may need to be tailored to each patient considering inter-individual variations in GM and different responses to nutritional strategies, further emphasizing the need for individualized treatment strategies.

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