

# Dietary Glycaemic Index and Type 2 Diabetes Mellitus: Potential Modulation of Gut Microbiota

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**Abstract:** Diet therapy is often the first-line approach in prevention and management of type 2 diabetes mellitus (T2DM). Adoption of low glycaemic index (GI) diet one of the recent dietary strategies to modulate glycaemic response in individuals with T2DM. Generally, diet has strong influence on the gut microbiota, which recently have been found to be associated with insulin resistance and the inflammatory response in diabetes. The possible modulation of the gut microbiota with dietary intervention is a topic of emerging interest, with limited evidence among T2DM population. In this review, we have narrated the available evidence and discussed the current knowledge about diet manipulation associated with dietary GI in order to shape the gut microbiota. As a conclusion, we have pointed out several key research directions that may have helpful impact on diet interventions with modulation of gut microbiota on the pathogenesis and therapeutic implications in T2DM.

**Keywords:** microbiome; type 2 diabetes mellitus; carbohydrate-glycaemic index; nutrition

**Received:** 10<sup>th</sup> April 2020

**Accepted:** 12<sup>th</sup> May 2020

**Published Online:** 19<sup>th</sup> May 2020

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**Citation:** Durganau H, Kunasegaran T and Ramadas A. Dietary Glycaemic Index and Type 2 Diabetes Mellitus: Potential Modulation of Gut Microbiota. *Prog Microbes Mol Biol* 2020; 3(1): a0000082. <https://doi.org/10.3687/pmb.a0000082>

## INTRODUCTION

Diabetes mellitus is defined as a “metabolic disorder of multiple aetiology characterised by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both”<sup>[1]</sup>. Type 2 diabetes mellitus (T2DM) is the most common form of diabetes, accounting for about 80% of all diabetes cases mostly after the age of 30<sup>[2]</sup>. T2DM is characterised by three basic abnormalities — insulin resistance, impaired insulin secretion and increased hepatic glucose production, either of which may be the predominant feature<sup>[3,4]</sup>. This results in a disorder of carbohydrate metabolism, and fat, protein and mineral metabolism also can be affected.

The World Health Organization has defined the diagnostic criteria for diabetes through a single raised glucose reading with symptoms, otherwise raised values on two occasions, of either fasting plasma glucose  $\geq 7.0$  mmol/l (126 mg/dl) or with a glucose tolerance test, two hours after the oral dose a plasma glucose  $\geq 11.1$  mmol/l (200 mg/dl)<sup>[1]</sup>. In diabetes management, nearly all T2DM related research outcomes are looking at reduction in glycosylated haemoglobin (HbA1c) and report from the UK Prospective Diabetes Study (UKPDS) has recommended HbA1c to be maintained below 7.1% to minimise T2DM-related complications<sup>[5]</sup>.

It has been shown that individuals from primitive societies, where the incidence of diabetes is low who then move to societies where food is too readily available, often progress to develop diabetes<sup>[6]</sup>. Although many people with T2DM could be managed by dietary modification alone, eventually they may require insulin therapy due to its progressive nature.

Although T2DM could be inherited, modifiable factors such as body composition and nutrition play important roles in the etiology of T2DM<sup>[7]</sup>. The goals of Medical Nutrition Therapy (MNT) in people with diabetes are to achieve and maintain normal blood glucose, lipid and lipoprotein and blood pressure levels by addressing the nutritional needs and maintaining the pleasure of eating which eventually, prevent or slow the development of complication<sup>[8,9]</sup>.

One of such dietary modifications that many MNTs recommend will be adoption of low glycaemic index (GI) diet. GI ranks carbohydrate-containing foods according to their effect on postprandial glycaemia<sup>[10,11]</sup>. GI is a measure of the increase in blood glucose two hours after consumption of the food of interest, with reference to glucose or white bread. Glycaemic load (GL), a product of GI and amount of carbohydrate in the food, is another measure of glycaemic response to carbohydrate-containing foods and could improve the

evaluation of glycaemic response to a diet<sup>[12]</sup>. Foods with low GI such as parboiled rice, barley, oats and legumes lower the postprandial hyperglycaemia, while high GI foods such as white bread, potatoes, white rice and commercial breakfast cereals will show the opposite effect<sup>[8,13]</sup>.

Additionally, increasing evidence has highlighted that the role of gut microbiota in a multitude of human illnesses, both inside and outside of gut, including irritable bowel syndrome<sup>[14]</sup>, colorectal cancer<sup>[15,16]</sup>, skin diseases<sup>[17,18]</sup>, neurological-related diseases<sup>[19,20]</sup>. Similarly, there are also emerging findings on the strong association between development of diabetes and gut microbiota<sup>[21,22]</sup>. Gut microbiota is a dynamic identity that can result in various pathophysiological changes in human's internal environment, though the composition changes gradually over the lifetime<sup>[23,24]</sup>. Gut microbiota plays a critical role in several metabolic functions namely amino-acid synthesis, absorption of dietary fats and fat-soluble vitamins, production of short-chain fatty acids (SCFAs), activation of glucose homeostasis, lipid energy metabolism, calorie removal and regulating bile acid transformation among others<sup>[25]</sup>. This may predispose or protect an individual against diabetes.

As gut microbiota can be easily influenced by environmental factors especially one's dietary intake, there is a potential for gut microbiota to act as a modulator of dietary GI and T2DM relationship. In this review we will be summarizing the evidence associating dietary GI and T2DM, and subsequently discuss the potential role of gut microbiota in modulating this relationship.

## **DIETARY GLYCAEMIC INDEX AND DIABETES**

A cross-sectional study in South Italy found a dose-dependent relationship between dietary GI and GL with HbA1c, where patients with diabetes with highest GI and GL had the highest HbA1c levels<sup>[26]</sup>. GI-based dietary education has been suggested to be a useful tool in diabetes management<sup>[27,28]</sup>. Miller and Gutschall<sup>[29]</sup> reported a nine-week nutrition education regarding GI and GL which improved dietary intake, knowledge, outcome and efficacy expectations and empowerment for diabetes management. Although GI could lead to a better dietary intake in people with diabetes, only few organisations recommended the use of low GI diets<sup>[30-32]</sup>.

Retrospective study by Burani *et al.*<sup>[26]</sup> found a reduction in HbA1c of 19% and body mass index (BMI) of 8% following inclusion of low GI diet in lifestyle intervention, which was well accepted by the participants. Several trials have supported the role of GI in glycaemic control in patients with T2DM<sup>[34]</sup>. Significant improvements have been seen in HbA1c and/or FPG<sup>[34-37]</sup>, insulin sensitivity<sup>[34]</sup> and serum fructosamine<sup>[36]</sup> with low GI diets. The role of GI diets in glycaemic control has been confirmed by several meta-analyses and reviews<sup>[13,38,39]</sup>. However, there is a lack of studies on the technology assisted low GI interventions, and only one feasibility nutritionist-delivered, PDA-assisted low-GI dietary intervention by Ma *et al.*<sup>[40]</sup> has been discovered.

Low GI diets also have been shown to have favourable impact on lipid profile and reduction in cardiovascular risk of patients with T2DM<sup>[35,41-44]</sup>. Studies have reported significant decrease in total cholesterol and LDL-C with prescribed low GI diets<sup>[34]</sup>. Longer educational programmes to improve diet quality by emphasizing low GI diets also have shown to lower the LDL-C<sup>[45,46]</sup> and increase the HDL-C<sup>[37]</sup>. Besides the cholesterol levels, a low GI or GL diet may be preferred for the dietary management of T2DM because of sustained reductions in postprandial glucose and c-reactive protein<sup>[47]</sup> and the increase in the plasma adiponectin concentrations<sup>[48]</sup>.

There is also evidence showing the positive impact of low GI diet on other health outcomes in people with diabetes. Low GI diet accompanied with exercise programme was found to improve cardiovascular health<sup>[49]</sup> and protect against-induced hypoglycaemia in T2DM patients<sup>[50]</sup>. Low GI diet could assist with the weight management programme in patients with diabetes<sup>[43,46]</sup>. Yusoff and colleagues<sup>[36]</sup> reported a significant reduction in waist circumference in Asian patients after 4 months of following a low GI diet. Low GI diet has also generally results in better cognitive performance in the postprandial period in adults with T2DM and reduce their dependency on diabetes medication<sup>[45,51]</sup>.

Interestingly, there were studies which did not support the role of GI in diabetes management<sup>[52]</sup>. In one of such studies, low GI diet with calorie restriction in overweight patients with T2DM did not find any significant reduction in HbA1c<sup>[46]</sup>. Data derived from the Atherosclerosis Risk in Communities study suggest high GL intake to be a CHD risk factor only among Whites without diabetes and not in individuals with diabetes<sup>[53]</sup>. Cheong *et al.*<sup>[54]</sup> concluded addition of a low-GI component to a walking did not improve anthropometric or metabolic outcomes in diabetic patients. A review by Barojek and Morello<sup>[55]</sup> has identified short coming in terms of power of the study and confounders, which could have affected otherwise positive findings in these studies.

As low GI foods are generally rich in fiber and other nutrients, the consumption of this diet has been shown beneficial to diabetic patients<sup>[56]</sup>. Incorporation of such foods in every day diet may be an effective approach for weight management, glycaemic control and favourable lipid profile. However, the concept of GI should not be used in isolation, but to be used as an adjunct treatment to existing lifestyle management of T2DM in fine-tuning the glycaemic control<sup>[45,57]</sup>.

## **DIETARY GLYCAEMIC INDEX AND GUT MICROBIOTA**

Exploration of a potential association between dietary GI and changes in the proportion of certain gut microbiota is relatively a newer research area, with limited evidence among T2DM population.

An experimental study among individuals at risk of metabolic syndrome showed largest increase in the *Bifidobacterium* spp. (an established gut health biomarker) level in high carbohydrate/high glycaemic index (HC/HGI) group compared to control group<sup>[58]</sup>. This change was

associated with reduced fasting glucose, fasted insulin and cholesterol levels compared to baseline. Furthermore, HC/HGI group was also associated with increased *Bacteroides* numbers as well as reduction in body weight, BMI and waist circumference. Both *Bacteroides* and *Bifidobacterium* spp. have been independently associated with reduction in risk factors for metabolic syndrome and improved body energy regulation in the past<sup>[59]</sup>. Interestingly, the study found an increased abundance of *Faecalibacterium prausnitzii* with both high saturated fat (HS) diet and high carbohydrate/low glycaemic index (HC/LGI) diets. HS group also experienced an increase in faecal SCFA concentration. However, faecal acetate percentage may be inversely correlated with absorbed acetate percentage (after rectal infusion), as demonstrated by Vogt and Wolever<sup>[60]</sup>. In that case, higher SCFA noted in the HS group may be due to decreased absorption, instead of higher colonic fermentation.

A study exploring specific foods with lower GI responses *in vitro*, found minimally processed wholegrain cereals such as wholegrain oats and granola resulted in significant growth in the friendly bacteria namely *Bifidobacterium* genus and *Lactobacillus-Enterococcus* group<sup>[61]</sup>. Wholegrains with minimal processing also resulted in increase in *Atopobium* cluster and *Bacteroides-Prevotella* group after 10 hours. Increase in *Clostridium histolyticum* after instant porridge fermentation (highly processed wholegrains) is also noted to be significantly higher compared to the decrease observed in minimally processed wholegrains.

Another low GI grains that were investigated in the past were barley grains. An *in vivo* study found barley intake lead to increased abundance of *Prevotella* and *Lactobacillus*, as well as *Candidatus homeothermaceae* in obese and lean mice<sup>[62]</sup>. Barley intake was also linked with lower levels of plasma insulin and resistin, a cysteine-rich peptide secreted by adipocytes, immune cells, and epithelial cells which are found in higher levels in metabolic syndrome cases<sup>[63]</sup>.

Another study utilised models such as static *in vitro* digestion and dynamic gastric model to simulate the normal digestion process in investigating relationship between different types of barley grains and microbiota<sup>[64]</sup>. During early stage of digestion in the study, it noted that the digesta of wild-type barley *Hordeum vulgare* cv Golden Promise (Hv) and Amylose-only (AO) breads portrayed higher abundance of Firmicutes, whereas wheat and wild barley *Hordeum vulgare* subsp. Spontaneum (Hs) grain bread digesta contained lower levels of it. Hs grain bread digesta demonstrated increased abundance of actinobacteria (30-fold higher than control) to the detriment of Bacteroidetes and Firmicutes. However, samples representing later stages of digestion behaved differently as Bacteroidetes and Actinobacteria were found to be abundant in all digesta. Specifically, increased Actinobacteria was noted in AO fermentation (compared to early digestion stage samples) while Bacteroidetes was more abundant in fermentation of Hs grain digesta. Aside from that, Proteobacteria levels in wheat bread digesta fluctuated from early digestion to late digestion stage. Therefore, these results portray the potential of low GI

barley-based bread in regulating gut microbiota.

## ROLE OF GUT MICROBIOTA IN TYPE 2 DIABETES

Several studies have investigated and showed some forms of association between gut microbiota and development of T2DM. The role of gut microbiota may be evaluated in several aspects.

Insulin resistance in T2DM patients may have resulted from increased production of hepatic triglyceride facilitated by Firmicutes and Bacteroidetes, as they enhance the monosaccharide uptake from the host gut<sup>[65]</sup>. Aside from the impact on carbohydrate metabolism, high ratios of Firmicutes to Bacteroidetes is also found to alter the production of SCFAs with an increase in acetate production and decrease in butyrate production<sup>[66]</sup>. The increased levels of acetate in the blood is found to result in insulin resistance and heightened production of ghrelin (an-appetite stimulating hormone) in the stomach, as illustrated by a recent study among individuals with metabolic syndrome<sup>[67]</sup>. On the other hand, decrease in butyrate levels also encourage insulin resistance through promotion of low-level inflammation<sup>[68]</sup>.

Aside from the diversity of gut microbiota, another aspect that could be looked into is its role in facilitating immune response which lead towards development of T2DM. Abundance of *Prevotella* bacterial species was found particularly in obese T2DM individuals, and known to increase the levels of pro-inflammatory cytokines, besides encouraging low-grade inflammation and insulin resistance<sup>[69]</sup>. *Verrucomicrobia*, on the other hand, which are known to contribute towards the maintenance of anti-inflammatory state of gut and improve insulin sensitivity were found less in T2DM individuals in a study conducted in Pakistan<sup>[70]</sup>. The same study also found an increase in the levels of gram-negative bacteria such as *Dialister* and *Allisonella*, which may have contributed to the rise in levels of lipopolysaccharide (LPS), which eventually binds with CD14 and mediates inflammatory response. Another class of bacteria which is found to be abundant among people with diabetes is *Fusobacteria*, which plays critical role in inflammatory responses, mounting adhesiveness to host epithelial cells and energy generation<sup>[71,72]</sup>.

Furthermore, the link between gut microbiota and T2DM can also be explored by looking into their association with bile acids. It is well-known that one of the important symbiotic roles played by gut microbiota is in terms of bile acid transformation, as their composition has been found to affect the concentration and composition of circulating bile acids<sup>[73]</sup>. This in turn affects the individual's risk in developing obesity and related disorders. Most of the bile acid biotransformation occurs in the large intestine which is extremely rich in microbiota, through a complex process<sup>[74]</sup>. This is one process in which the role of gut bacteria can be directly observed, as it is catalysed by bile salt hydrolase (BSH), an enzyme which is present in several gut bacteria such as *Clostridium*, *Bacteroides*, *Lactobacillus*, *Bifidobacterium* and *Enterococcus*<sup>[75]</sup>. Bile acids in the blood circulation play a role in homeostasis of carbohydrates and lipids, further reinforcing their importance as regulatory molecules in that aspect<sup>[73]</sup>. Bile acids also pose some direct

antimicrobial action which subsequently impacts the survival and colonisation of certain gut microbiota<sup>[76]</sup>.

As an individual's food consumptions affect both gut microbiota and development of diabetes, further exploration can be made to investigate the changes in gut microbiota according to the type of prescribed dietary pattern, and its impact on diabetes development and/or severity.

## CONCLUSION

The search for the optimal nutritional strategy in T2DM patients remains an unresolved issue. It is important that the potential benefits of suitable GI diet and the T2DM patient's microbiota, which in turn will impact on the progression of disease complication, are taken into consideration. In this review, we have provided evidence that different dietary patterns have different impacts on gut microbial composition. These findings suggest that the gut microbiota contribute to the pathophysiological regulation of glucose tolerance, insulin secretion and in inflammation.

Hence, future studies should define the features of the gut microbiome in diet consumption that contribute to the T2DM in defined populations. Furthermore, with the emerging advances in technology, the relationship between important biomarkers to changes in gut microbiota and microbiota metabolites modulated by recommended diets are worth investigating in future studies to aid prevent or treat diabetes-related disorders in a strategic manner. In addition, it is also important to focus on bile stress and its effects on the gut microbiota in future direction in finding therapeutic strategies to reduce the aggregate metabolic burden in human populations. Some bacteria can use bile as their host to regulate virulence determinants and produce secondary bile acids that regulate the normal homeostasis of tissues in human body which leads to unwanted complications. Thus, further studies should investigate how bacteria sense bile and regulate its response it induces and reveal the effect of different bile acid profiles in host tissues by virulence factor production. Lastly, approaches to modulate the microbiome-bile acid formation through diet may likely reduce the risk and/or treat metabolic diseases and this need further investigation.

## Author Contributions

The review and manuscript writing were performed by HD, TK and AR.

## Conflict of Interest

The authors declare that there is no conflict of interest in this work.

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