



Managing the F:B Ratio in DM; A Review of the Role of Firmicutes and Bacteroidetes in Diabetes Mellitus



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Submission: 📅: January 29, 2019; Published: 📅: February 04, 2019

Abstract

Globally, the incidence of diabetes continues to rise and significant resources are spent on its prevention and treatment. However, the pathogenesis of this disease has yet to be fully understood or explained. Current research indicates that diabetes, especially type 2 diabetes, is highly correlated to an abnormal intestinal microbiota. Bacteria in the gut are essential for numerous metabolic processes including the production of hormones and neurotransmitters and the biosynthesis of vitamins and amino acids. Several studies have shown that gut bacteria play a significant role in controlling type 2 diabetes. The following research aims to show how gut bacteria can be manipulated to improve outcomes in managing diabetes mellitus. This review of research was conducted to determine the role of the gut bacteria in modulating metabolic health and insulin resistance. Various articles, journals, and books were reviewed, and a meta-analysis of the results conducted. From this review of literature, it was noted that alteration of gut bacteria to a more natural balance might reduce oxidative stress on the pancreas and enhance cell permeability glucose uptake. However, an imical alteration in gut bacteria can spur the overgrowth of certain bacterial species that contribute to diabetes. Thus, it is advised to consume requisite dietary fibers to maintain or restore the gut microbiome in promoting healthy body weight and blood glucose level.

Preface

Diabetes mellitus (DM) affects approximately 150 million people worldwide according to the data from the World Health Organization (WHO) [1]. The number of people affected by DM is likely to double by 2025 due to population growth, an unhealthy diet, sedentary lifestyle, obesity, and aging. Currently, DM is primarily managed with pharmacological agents (such as insulin) or insulin secretagogues (such as metformin). Nonpharmacologic management is also used, eg, dietary regulation, exercise, and psychological counseling. It has been shown that only 40% of DM patients respond satisfactorily to glucose control using secretagogues or insulin injections [2]. According to the World Health Organization (WHO), countries allocate vast sums of money and dedicate massive amounts of resources to help manage DM resulting in an overwhelming burden to families and state governments [1]. As such, there is a desperate need to explore and develop less expensive alternative treatment options with fewer side effects (as compared to conventional and readily available medicines) particularly for countries with limited resources.

Keywords: Alternative treatment; Bacteroidetes; Diabetes mellitus; Firmicutes; Gut bacteria; Insulin; Microbiome; Oxidative stress; Pancreas

Abbreviations: DM: Diabetes Mellitus; IFN- γ : Interferon-Gamma; IL-1: Interleukin-1; IL-2: Interleukin-2; T2DM: Type 2 Diabetes Mellitus; WHO: World Health Organization

Introduction

Diabetes mellitus (DM) is a chronic disease condition that is characterized by the inability of the body to properly regulate blood sugar leading to fluctuations between hyperglycemia and hypoglycemia with no apparent point of balance [3]. The inability to regulate blood glucose level results from insufficient insulin production by the pancreas. DM is classified into type 1 (which results from the inability of the pancreas to produce insulin) and type 2 (which is a relative insulin deficiency) [4].

DM was initially a lifestyle health risk mainly associated with an affluent lifestyle in developed countries. However, current statistics indicate, diabetes is afflicting individuals regardless of social status or economic class. It is no longer the "executive disease" it once was [5]. According to Gruber & Haller (2014), diabetes mellitus is a genetic disease and its expression is controlled by such factors as diet, physical activities, and medication. Current studies have shown the occurrence of DM can be influenced by certain microbes that invade or inhabit the intestines. Thus, there is a call to probe

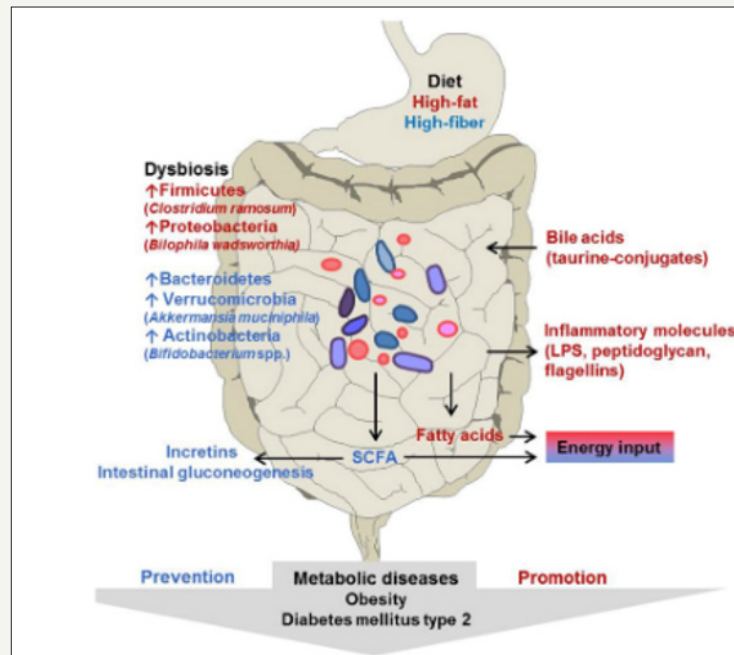
the diabetes-microbe connection. Understanding and manipulating this connection might be utilized in the management of DM [6].

Discussion

A survey by Gardner et al. (2012) established that human resident microbiota play vital roles in health maintenance; thus, the need to explore its role in managing metabolic syndromes, such

as DM. According to Meo (2012), [disadvantageous] alteration in the [normal and healthy] microbiota influences the development of type 2 diabetes and the comorbidities thereof, e.g., retinopathy, diabetic foot ulcers, and nephropathy. Conversely, the favorable manipulation of the microbiome can aid in the management and treatment of DM and its sequelae (Figure 1) [7].

Figure 1: The diet-gut microbiota connection in metabolic disease



Note: Reproduced from Woting and Blaut (2016). The Intestinal Microbiota in Metabolic Disease [9].

The composition of gut microbiota varies widely between healthy and sick individuals depending on the disease condition. Again, it is for this reason that the manipulation of intestinal microflora can be utilized in managing various diseases, namely DM [8]. Although the cause-effect relationship between the alterations in gut microbiota and disease is not always clear, targeting gut microflora might offer possibilities for managing certain disease conditions. There is a growing understanding of how the microflora is linked to obesity-related diabetes mellitus providing a new potential pathway for managing DM [9].

The gut microbiota participates in energy harvesting; hence, an aberration or alteration in the microbiota may account, at least in part, for the development of obesity. DM is one of the disorders associated with abnormal energy distribution and low-level chronic inflammation among obese individuals. According to Niafar (2012), gut bacteria play an essential role in the progression of prediabetic conditions, such as insulin resistance. Obese individuals show an altered composition of gut microbiota particularly elevation of the Firmicutes: Bacteroidetes (F:B) ratio [8]. The transplantation of gut bacteria from obese individuals to animals negatively affected energy harvesting processes in those animals. This finding from the transplantation of gut bacteria from obese humans to animals

strongly suggests there may be a method the gut bacteria can be manipulated to control DM [10].

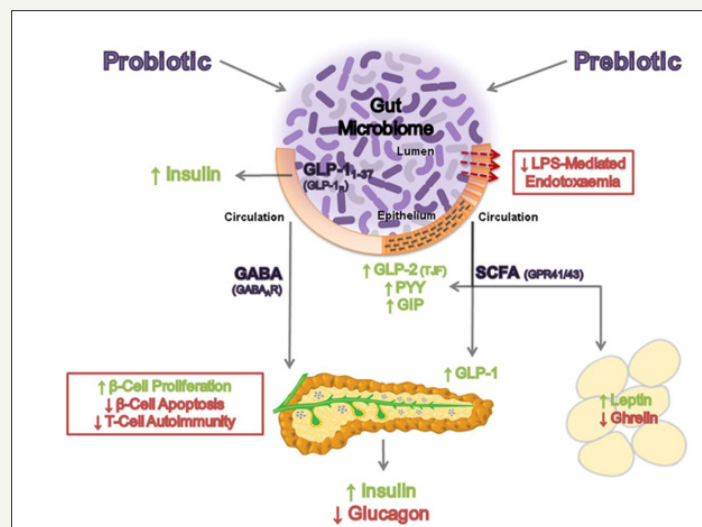
Shalem & Weiss (2015) illustrated that adverse alteration of microbiota in obese individuals affects intestinal permeability. This alteration increases metabolic endotoxin secretion resulting in chronic low-level inflammation and the pathogenesis of insulin resistance [11]. Commensal bacterial species (*Akkermansia muciniphila*, *Escherichia coli*, and *Bacteroides thetaiotaomicron*) have shown some influence on intestinal mucus and the glycocalyx layer altering intestinal permeability. This influence on permeability may also apply to glucose molecules [1].

Nabavi et al. (2015) showed the deleterious cycle between altered microbiota and low-level inflammation observed in obese patients is causative in developing type 2 diabetes mellitus (T2DM). T2DM patients exhibit altered intestinal microflora based on an altered F:B ratio [12]. Decreasing the level of Firmicutes in the gut will reduce insulin resistance and other factors that lead to the development of T2DM [2]. Firmicutes bacteria alter host energy metabolism by usurping polysaccharide loci mechanisms leading to increased levels of bacteria inflammatory molecules in the intestines, such as LPS, flagellin, and peptidoglycans. This increase

accelerates the inflammatory process in those suffering T2DM [2]. Gastric bypass surgery has been utilized in certain diabetic patients

resulting in a beneficial alteration of the gut microbiome and normalizing blood glucose levels especially in T2DM patients [13].

Figure 2: Probiotics can enhance immunity, increase β -cell proliferation, and decrease β -cell apoptosis.



Note: Reproduced from Patterson, Ryan, and Cryan (2016). Gut microbiota, obesity, and diabetes [16].

The gut microbiota can be manipulated by using probiotic strains; certain strains can influence blood glucose homeostasis (Figure 2). Probiotics act as immune system modulators against (altered) microbiota-induced chronic inflammation resulting in obesity-induced DM [14]. Also, some probiotics prevent the onset of DM by down-regulating inflammatory interferon-gamma (IFN- γ) and interleukin-1 (IL-1) or -2 (IL-2). In some cases, probiotics may stimulate a rise in interleukin-10 (IL-10) levels; low IL-10 levels are associated with metabolic syndrome and T2DM [5].

Scott, Antoine & Midtvedt (2015) reported *Lactobacillus reuteri* GMNL-263 suppressed serum glucose, leptin, GLP-1 level, TNF- α , insulin, glycated hemoglobin, interleukin IL-6, C-protein, GLUT-4 gene expression, and PPAR- γ [15,16]. Insulin, GLUT-4, and PPAR- γ demonstrated considerable influence on the development and progression of DM. Thus, regulating their production and actions by ingesting certain strains of *Lactobacillus* could contribute to the management of DM. *Lactobacillus* strains aid in lowering the ratio of Firmicutes to Bacteroidetes in the gut. This alteration in the F:B ratio inhibits the development and progression of DM. Certain probiotic strains demonstrate favorable antioxidant effects against chronic inflammation. This antioxidant characteristic makes it plausible and possible to alleviate pancreatic oxidative stress that leads to apoptosis of insulin-secreting pancreatic beta cells [16-18].

Conclusion

DM is a metabolic disease that results from the inability of the body to control and maintain proper blood glucose level. Manipulation of gut microflora may be a fundamental factor in reducing oxidative stress on the pancreas and enhancing cell

permeability for glucose uptake. Lowering the ratio of Firmicutes to Bacteroidetes is beneficial in managing obesity and obesity-related DM and its sequelae. Certain probiotic strains and combination of strains have a positive impact on gut bacteria which could help manage DM as well as ameliorate certain consequences [19,20]. The introduction of *Lactobacillus reuteri* GMNL-263 (contained in some probiotics) into the gut can enhance antioxidant effects against chronic inflammation and apoptosis of pancreatic beta cells; and lead to secretion of sufficient insulin thereby augmenting the established medical protocol in the management of DM. Also, complementary medicine alternatives may lessen dependency on certain drugs particularly those with notable adverse effects [21]. Including dietary fibers can aid in rebalancing the gut microbiome promoting healthy body weight and proper blood glucose levels.

Conflict of Interest Statement

The authors declare that this paper was written in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

Acknowledgment

T.L. Brown (Harvard University) is acknowledged for his early contribution to this project.

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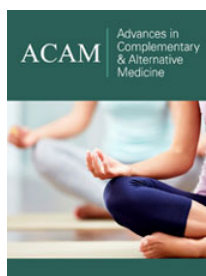
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