

A Novel Approach for the Management of Diabetes Mellitus

Chandra Kanti Chakraborti*

Kanak Manjari Institute of Pharmaceutical Sciences, Rourkela- 769015, Orissa, India

Abstract

Recent research has shown that there is a link between metabolic diseases (like diabetes, obesity and cardiovascular diseases) and bacterial population in the gut. The results of such studies indicate that Type 2 Diabetes Mellitus (T2DM) in humans is associated with compositional changes (dysbiosis) in intestinal microbiota. It has been observed that populations of certain bacteria are increased (harmful) while some of others are reduced (beneficial) in T2DM. Hence, an entirely different approach for management of T2DM may be made by administering the beneficial bacterial species as a probiotic.

Keywords: Diabetes; Microbiota; Endotoxaemia

***Corresponding Author:** C K Chakraborti, Professor, Kanak Manjari Institute of Pharmaceutical Sciences, Rourkela- 769015, Orissa, India; E-mail: chandrakanti_12@rediffmail.com

Introduction

Recommended management of blood sugar control and Insulin Resistance (IR) in diabetics consists of exercise, diet and drugs. Antidiabetic drugs produce their beneficial effect by several ways: like increasing insulin secretion from islet beta-cells, decreasing insulin resistance, reducing intestinal absorption of carbohydrates, interfering with the secretion and function of counter-regulatory hormone glucagon and lastly substituting insulin by administration of the exogenous hormone

(insulin). In spite of such multifaceted approaches, control of blood sugar and IR in diabetics is still not up to full satisfaction. Hence, research in this field is going on, not only through conventional approaches, but also through some seemingly unrelated body components, like intestinal microflora. Recently, many workers have shown a positive as well as a negative correlation between the metabolic activities of this microflora with diabetes mellitus and IR. Hence, some of these microfloras are diabetogenic while others possess an antidiabetic property.

Association of both obesity and diabetes with a chronic low-grade inflammation along with increased production of pro-inflammatory cytokines like TNF-alpha and IL-6 is well-established [1]. These two cytokines have been shown to suppress insulin transduction [2]. Recently, Cucak et al. (2014) have shown that during initial stages of Type 2 Diabetes Mellitus (T2DM), pro-inflammatory macrophages invade pancreatic tissues and release large quantities of cytokines which, in turn, cause destruction of islet beta-cells [3]. Moreover, such activated macrophages also invade adipose tissue, liver and skeletal muscles, where they release cytokines who are responsible for the development of IR in these tissues [4].

Recently, studies based on latest modern techniques (like quantitative real time PCR and fluorescent in situ hybridization) have demonstrated a correlation between the composition of intestinal microflora and metabolic diseases like obesity and diabetes [1]. It has been observed that in such metabolic diseases these microfloras are altered. Such an alteration may lead to altered production of microbial metabolites which may initiate a local inflammatory reaction or a systemic one by

leaking through impaired mucosal barriers. Such impaired mucosal barrier may be due to gut-microflora-induced alteration in intestinal mucus, glycocalyx layer, gut tight-junction proteins, endocannabinoid system and intestinal alkaline phosphatase [5]. Such an assumption has been supported by the fact that patients with metabolic syndrome and T2DM show a remarkable endotoxaemia. Such demonstrations appear to be in line with the recent concept of 'metabolic infection', where parts of the intestinal microflora are thought to be involved in systemic inflammation including the adipose tissue [6]. Gastrointestinal microfloras are thought to contribute towards the development of diabetes, because they take part in the process of energy harvest. As T2DM is associated with abnormal energy metabolism and obesity (usually), it may be inferred that gut microflora play some role in the genesis of diabetes [5].

Researches relating gut microbiota with progression of prediabetics having IR to frank diabetes are gradually increasing. In such studies, more stress is attached to the alteration in the ratio of two groups of microbiota rather than an increase or decrease in either of the two. One such study on obese persons with IR has demonstrated an elevated ratio of Firmicutes/Bacteroidetes compared with healthy people. In another study on T2DM patients, it has been observed that not only there is a decrease in the Bacteroidetes/ Firmicutes ratio along with a decrease in Bifidobacteria (a functional bacteria), but also an increase in several opportunistic pathogens including endotoxin-producing Gram negative bacteria [5]. Moreover, it has been observed that there is a significant reduction in the relative abundance of Firmicutes associated with a somewhat higher proportion of Bacteroidetes and Proteobacteria in persons having diabetes than those of the non-diabetics. The above observations suggest a positive role of the ratio between Bacteroidetes and Firmicutes in improving glucose tolerance [1].

Other microbiota ratios which distinguish diabetics from those of the non-diabetics include Bacteroidetes-Prevotella group versus class Clostridia and Clostridium coccoides-Eubacterium

rectale group. These ratios have been found to be significantly higher in diabetics. This finding is further supported by the observation that reduction in Bacteroidetes-Prevotella spp. is associated with a decrease in metabolic endotoxemia and inflammation in T2DM [1]. In addition to such ratios, in T2DM, the number of certain bacterial populations has been found to be increased. These include the opportunistic pathogens like *Bacteroides caccae*, various clostridiales, *Escherichia coli*, *Desulfovibrio* and various strains of *Lactobacillus* [1, 6]. Besides these opportunistic pathogens, there are certain commensal species like *Bacteroides thetaiotaomicron* and *Escherichia coli*, which increase intestinal permeability by altering intestinal mucus and glycocalyx layer [5].

Besides such seemingly diabetogenic gut microflora, there are certain other gut microbiota populations, which have been found to possess a protective role in diabetes. Out of them, *Bifidobacterium animalis* subsp. *lactis* 420 has been found to suppress the process of tissue translocation of bacteria, thought to mediate the metabolic bacteremia in the early phase of T2DM [5]. Mention has already been made about *Bifidobacterium*. This bacterial population is thought to be beneficial in diabetes as its role is positively correlated with improved glucose tolerance and low-grade inflammation in probiotic-treated mice. This observation is supported by the fact that this bacterial population is decreased in T2DM [7]. Another bacterial family, whose population is significantly decreased in T2DM, is Verrucomicrobiaceae [6]. Several experimental results have confirmed that some probiotic strains have the capability of modulating not only glucose homeostasis but also the immune system and its resultant inflammation, thereby improving T2DM. In this respect, recently demonstrated activities of *Lactobacillus reuteri* GMNL-263 may be cited. In fructose-fed mice, this probiotic species has been demonstrated to decrease the concentration of serum glucose, insulin, C-peptide, leptin, glycated haemoglobin and GLP-1; IL-6 and TNF-alpha in adipose tissues; and PPAR-gamma and GLUT4 gene expression. In murine models of obesity and T2DM, another probiotic strain *Lactobacillus casei* Shirota has been found to

reduce endotoxemia by increasing the plasma concentration of Lipopolysaccharide-Binding Protein (LBP) [5]. Besides the above mentioned protective bacterial population, it is important to discuss the role of *Akkermansia muciniphila* in rendering protection to T2DM. Several studies have shown that this microorganism possesses a key role in the integrity of the intestinal mucus layer. Moreover, it has been found to control fat storage and adipose tissue inflammation along with an overall improvement in various metabolic functions including glucose tolerance. It is important to note that the antidiabetic drug metformin increases the concentration of these organisms in the gut [6].

An intestinal dysbiosis in T2DM has been demonstrated which is characterized by a decrease in butyrate-producing bacteria like *Roseburia intestinalis* and *Faecali bacterium prausnitzii* (in contrast to healthy controls) with an increase in opportunistic pathogens like *Bacteroides caccae*, various *clostridiales*, *Escherichia coli* and others [6,7]. In addition, there is also an increase in sulphate-reducing species *Desulfovibrio*. Such dysbiosis may result in increased membrane transport of sugars, branched-chain amino-acids and sulfate reduction along with decreased butyrate biosynthesis. These enhanced/reduced functions may lead to an increase in oxidative stress which has a clear linkage with pro-inflammatory state of T2DM [6].

Conclusion

From the above discussion, it appears that intestinal microflora, in addition to their local protective role against various infections, are also involved in metabolic homeostasis of the body, specifically affecting carbohydrate and to a lesser extent lipid and protein metabolism. A gut microfloral species dysbiosis seems to be responsible for the distortion of metabolic homeostasis resulting in T2DM. Of all the gut microfloral species, some have a favourable role while some others exert an opposite effect.

Because of the above observations, a new approach for the management of IR and T2DM may be made through correction of the diabetogenic dysbiosis of gut microflora by administering the antidiabetic microflora as probiotics. Such probiotics may be tried as an adjunct to the primary therapeutic regimen which may further increase the overall beneficial response.

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