Effects of the Modulation Gut Microbiota by Oat Beta Glucan on Type 2 Diabetes Mellitus

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Abstract: In last decade research interest of microbiota in diabetes mellitus increased. Various research articles have demonstrated that human intestinal microbiota modulates numerous physiologic processes.

Oat beta glucan is a fermentable dietary fiber, which is digested by anaerobic intestinal microbiota into short chain fatty acids, significantly increased butyric and propionic acids, which have been shown to exert multiple beneficial effects on diabetes mellitus.

Research interest of communication between the microbiota and diabetes mellitus increased mostly in recent years. The data and mechanisms relating oat beta glucan, its fermentation by microbiota, prevention and treatment of type 2 diabetes mellitus is not clearly established. Oat beta glucan-microbiota mediated mechanism may be involved in some anti-diabetic processes. However, it is important to recognize underlying potential mechanisms how oat beta glucan effect microbiota and how it interact in diabetes.

The objective of the current review was to identify the microbial activities implicated in health by fermentation of oat beta glucan and its potential mechanisms implicated in T2DM that might contribute to the further understanding of the involved processes in prevention and treatment of type 2 diabetes mellitus (T2DM).

Keywords: Intestinal microbiota, diabetes mellitus, oat beta glucan, dietary fiber.

1. INTRODUCTION

Today, there are 382 million people living with diabetes. A further 316 million with impaired glucose tolerance are at high risk from the disease – an alarming number that is set to reach 471 million by 2035. Diabetes is on the rise all over the world and countries are struggling to keep pace [1].

As a field of study, human microbiome research has exploded in the last decade, which has led to a new awareness of the importance of these associated microbes to overall health [2].

A number of diverse diseases have been associated either causally or consequentially with dysregulation of the gut microbiome including diabetes, metabolic syndrome, cardiovascular disease [3].

Oat beta glucan, fermentable dietary fiber, is digested by anaerobic intestinal microbiota into short chain fatty acids (SCFA), which have been shown to exert multiple beneficial effects on mammalian health. Natural products containing beta glucans have been used for thousands of years for the benefits of human health, but beta glucans were identified as active components recently [4,5]. Since 1960 oat beta glucan has been studied extensively, mostly its effect on cholesterol level.
The Objective of this review was to evaluate concepts and potential mechanisms of oat beta glucan that might contribute to the further understanding of the involved processes in prevention and treatment of type 2 diabetes mellitus (T2DM).

Materials and Methods. The electronic databases Pubmed (http://www.ncbi.nlm.nih.gov) was searched using key words: oat beta glucan, microbiota, dietary fiber, SCFA, type 2 diabetes mellitus. Studies analyzing communications between oat beta glucan, dietary fiber, short chain fatty acids (SCFA), microbiota and its possible mechanisms in type 2 diabetes mellitus (T2DM) were reviewed.

2. LITERATURE REVIEW

The human body contains over 10 times more microbial cells than human cells, because bacteria are 10-100 times smaller than human cells, the entire microbiome weighs about 200 grams [6,7] with some weight-estimates ranging as high as 1,400 grams.

An important role of the gut microbiota is to catabolize particularly non digestible carbohydrates (dietary fibers) [8], which are fermented in the proximal colon by saccharolytic bacteria. This fermentation results in short chain fatty acids (SCFAs) together with the gases CO2 and H2 [8]. SCFA are absorbed from the colonic lumen and metabolized by body tissues.

Research interest of communications between the microbiota and diabetes mellitus increased mostly in recent years (fig. 1).

Fig 1. Number of publications studying communication between microbiota and diabetes mellitus over the last decade: PubMed Citations by year using search terms ‘microbiota, diabetes’.

Overweight or obesity was the single most important predictor of diabetes [10]. A new study suggests that all three SCFAs (acetate, propionate, butyrate) protected against diet-induced obesity, with butyrate and propionate being more effective than acetate [11]. Butyrate and propionate regulate body weight at least partially by inhibiting food intake, consistent with their stimulatory effects on anorexigenic gut hormones, such as peptide tyrosine tyrosine (PYY) and glucagon-like-peptide 1 (GLP-1). PYY and GLP-1 are secreted by enteroendocrine L cells located in the colon and rectum. Stimulation of gut hormones and food intake inhibition by butyrate and propionate may represent a novel mechanism by which gut microbiota regulates host metabolism [11].

Study in diet-induced obese mice has shown that oat beta glucan increases peptide YY secretion [12]. Another study in pigs found that dietary supplementation of 6% oat β-glucan concentrate decreased net glucose flux, increased net SCFA flux, and decreased peak apparent insulin production, changes that were associated with gastric inhibitory peptide (GIP) and GLP-1 mediation [13].

Another study has shown that in a dietary-induced obese C57Bl/6 mouse model, some mice developed a diabetic metabolic phenotype despite having the same genetic background and diet, while others were resistant and the diabetic metabolic phenotype was associated with gut permeability and a modified gut microbiota [14]. Study found that direct treatment of the gut microbiota using dietary fibers affects the metabolic adaptation of the mice independently from their genetic background or their diet [14].
Study results on streptozotocin-induced diabetic mice, which were fed with oat products for 6 weeks suggests, that oat beta glucan significantly decreased fasting blood glucose and glycosylated serum protein (p<0.05), but the hypoglycemic effect was not more than that of metformin (p>0.05). Oat products increased glycogen and nuclear receptor levels (p<0.05), decreased free fatty acid content and succinate dehydrogenase activity (p<0.05), and inhibited pancreatic apoptosis (p<0.05) [15].

Communications between dietary fiber, microbiota and diabetes mellitus have been described in several studies. Only few studies investigate the communication between oat beta glucan, SCFA and diabetes mellitus (fig. 2).

SCFAs are essential nutrients that act as signaling molecules. Recently, two orphan G-protein coupled receptors, GPR41 and GPR43, also known as free fatty acid receptors FFAR3 and FFAR2, were reported to be activated by SCFAs [16].

Different studies have shown that GPR41 plays an important role in regulating the environment and motility of the gut and the secretion of incretin such PYY via sensing SCFA produced by enteric bacterial fermentation [17]. It was noted, that propionate is the most potent activator of GPR41 [18].

However another study in wild-type and FFAR3 (GPR 41) knockout mice found that butyrate and propionate suppress food intake, protect against high-fat diet-induced weight gain and glucose intolerance, and stimulate gut hormone secretion predominantly via FFAR3 - independent mechanisms. FFAR3 is not required for normal body weight and glucose homeostasis [11].

Recent study shows, that GPR43-deficient mice are obese on a normal diet, whereas mice overexpressing GPR43 specifically in adipose tissue remain lean even when fed a high-fat diet [20]. Short-chain fatty acid-mediated activation of GPR43 suppresses insulin signaling in adipocytes, which inhibits fat accumulation in adipose tissue and promotes the metabolism of unincorporated lipids and glucose in other tissues. These findings establish GPR43 as a sensor for excessive dietary energy, thereby controlling body energy utilization while maintaining metabolic homeostasis [20].

Recent study on rats found that prolonged treatment with butyrate increased the rate of lipolysis in adipocytes approximately 2-3-fold [21]. It was noted, that concentrations of butyrate produced by oat beta glucan were greater than inulin [22]. Aminobutyric acid and acetate had little or no effect on lipolysis, however propionate stimulated lipolysis, suggesting that butyrate and propionate act through their shared activity as histone deacetylases (HDAC) inhibitors [21].

To improving insulin resistance and preventing β-cell inflammatory damage, there is evidence of genetic association between diabetes and HDAC, and HDAC inhibitors promote β-cell development, proliferation, differentiation and function and positively affect late diabetic microvascular complications. Christensen D.P. et.al. in their review propose that there is a strong rationale for preclinical studies and clinical trials with the aim of testing the utility of HDAC as a novel therapy for diabetes [23].

Studies in humans have shown differences in gut microbiota composition between obese and lean subjects. Altered gut microbiota composition have linked to the development of obesity, insulin
resistance and diabetes through several mechanisms, including increased energy harvest from the diet and altered fatty acid metabolism and composition in the adipose tissue and liver [24, 25].

Obesity in humans has already been associated with low intestinal concentrations of Bacteroides and high concentrations of Firmicutes [26, 27, 28]. The Firmicutes and Bacteroides are the two most predominant phyla in the human colon and together comprise >90% of the total gut microbiota [29]. Clinical studies also suggested that obese people with insulin resistance were characterized by an altered composition of gut microbiota, particularly an elevated Firmicutes/Bacteroidetes ratio compared with healthy people [30,31,32].

*In vitro* study results showed that the Bacteroides-Prevotella group increased with oat substrates, as well fermentation of oat beta glucan by gut microbiota increase mostly in propionate and butyrate production. [22, 34, 35].

Propionate has long been described as a hepatic gluconeogenic substrate [36]. However, recent study [37] has shown that propionate is converted into glucose by intestinal gluconeogenesis (IGN) (i.e., in the intestine before it reaches the liver). Propionate and butyrate activate IGN via complementary mechanisms. Butyrate activates IGN gene expression through a cAMP-dependent mechanism, while propionate, itself a substrate of IGN, activates IGN gene expression via a gut-brain neural circuit involving the free fatty acid receptor FFAR3. A major finding of this study is that propionate can directly initiate a gut-brain neural circuit that has beneficial effects on host physiology [37].

The anti-obesogenic and anti-diabetic effects of short chain fatty acids may be also due partially to the up regulation of mitochondrial function, more specifically up regulation of skeletal muscle mitochondrial fatty acid oxidation and energy expenditure [38].

Human studies have shown that products rich in beta glucan reduce glucose and insulin responses more than low dietary fiber products [39, 40].

Study in overweight and obese adults has shown that the consumption of whole-grain ready-to-eat oat cereal as part of a dietary program for weight loss had favorable effects on waist circumference. Subjects consumed two servings of oat cereal per day (3g of beta glucan per day) or energy-matched low-fiber foods (control) as part of a reduced-energy dietary program that encouraged portion control, physical activity, and limited consumption of high-calorie, high-fat foods. After 12 weeks of intervention, weight loss was not significantly different between the oat and control groups, but waist circumference had decreased significantly more ( △ 1.5 cm) in the oat group [41]. Another study in overweight subjects found that 3.8 g beta glucan per meal from oat bran and 5.7 g beta glucan concentrate have been observed to reduce insulin responses in the first 2h postprandially compared with a control meal [42].

Studies have shown that effectiveness of beta glucan in modulating glucose and insulin parameters is related to dose and viscosity [43, 44].

It was observed that doses of beta glucan around 6.0g/person/day, for at least 4 weeks were sufficient to provoke improvements in the blood glucose levels and also lipid parameters of individuals with diabetes mellitus [45]. In fact, 85% of the variation in blood glucose concentrations is explained by the amount of beta glucan solubilized and not the total amount originally added to food [19].

Intervention studies in adults provide inconsistent results. Compared to a 5-week control diet, 5 weeks of oat beta glucan (5 g) significantly reduced postprandial glucose and insulin responses, while 5 weeks of barley beta glucan (5 g or 10 g) did not [33].

It was found that bread containing 9g/day of soluble fiber from oat bran concentrate (22.8% beta glucan) significantly improved the postprandial glucose and insulin response of eight men with non-insulin-dependent diabetes mellitus compared to their response after consuming white bread [46]. Type 2 diabetic men who consumed a low-glycemic breakfast containing 3g of beta glucan from oat cereal versus a high-glycemic (wheat cereal) breakfast for four weeks each had lower insulin concentrations and areas under the curve [9].

Thus, fermentable dietary fibers, such as oat beta glucan can promote metabolic benefits on glucose control and body weight. Further studies will be also needed to elucidate how concentrated oat beta glucan effect microbiota and how it interact in diabetes.
3. DISCUSSION

We briefly summarize novel findings from studies relating dietary fiber, oat beta glucan, SCFA and gut microbiota communications with diabetes mellitus. Some researches support the view that the human intestinal microbiota modulates numerous physiological processes. Studies show that oat beta glucan increases butyrate and propionate and this properties may have great potential for the prevention and treatment of diabetes and associated cardiovascular diseases. The foods containing beta glucan have been used for clinical trial in the treatment of diabetes, however the potential mechanisms linking the concentrated oat beta glucan-microbiota-2TDM have not been fully elucidated. Animal studies and in vitro studies provide important clues for mechanisms for a relationship between dietary fiber, microbiota and diabetes mellitus. These data help compare oat beta glucan, but need to be tested in human clinical trials to support its use in nutrition. Very few human studies examined the function of concentrated oat beta glucan in diabetes mellitus.

4. CONCLUSION

This review presents an overview of the health promoting by fermentable dietary fiber, especially oat beta glucan, in microbiota and its potential mechanisms, which may be involved in prevention and treatment of 2 type diabetes mellitus. Studies have shown that short chain fatty acids, especially propionic and butyric acids, produced by bacterial fermentation of dietary fiber (such as oat beta glucan), may prevent diet-induced obesity and be involved in some antidiabetic processes. Although gut microbiota manipulation can beneficially affect adiposity and glucose metabolism, a relationship between gut microbiota, oat beta glucan and diabetes mellitus still needs to be proven in humans.

Science have not unlocked all of oat beta glucans potential health benefits, but this review shows that it may help to prevent obesity and diabetes. Thus, oat beta glucan-microbiota mediated mechanism may be involved in some anti T2DM mechanisms. Continuing research with concentrated oat beta glucan and its effects on diabetes mellitus are needed.

REFERENCES


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