A Study on the Relationship among Dietary Fiber Intake, Type 2 Diabetes, Microbiota and Immune System

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Abstract. With rapid socioeconomic development and demographic changes, the global diabetes mellitus pandemic becomes an alarming problem. It is necessary to extenuate the incidence of diabetes mellitus and discover potential effective treatments. Dietary fiber (DF) takes an important place in a healthy diet and they are mainly present in plant-based foods, such as vegetables, nuts, and beans. The global dietary fiber consumption trend is projected to continuously increase as the public became aware of its importance. Recent clinical trials indicated that the amount of dietary fiber was correlated with the Type 2 Diabetes Mellitus (T2DM) rate. In the current research, an underlying mechanism will be investigated. Several groups proved that dietary fiber intake could influence the diversity of intestinal microbiota and a decrease in microbiota composition could further affect the level of inflammation in the human immune system. Other studies also reflected that both the composition of gastrointestinal microflora and inflammation level was associated with the incidence of T2DM. The finding suggested a lower level of inflammation tended to have a lower rate of T2DM. Hence, the level of dietary fiber intake could eventually have an impact on T2DM incidence.

Keywords: Dietary Fiber, Diabetes, Microbiota, Immune System.

1. Introduction

Diabetes mellitus is considered nowadays as a worldwide epidemic. It is a chronic disease that has problems with patients' insulin, which is a hormone that regulates blood sugar [1]. Diabetes can result from insufficient insulin production by the pancreas or inadequate insulin usage by the body, and hyperglycemia is one of the primary symptoms. Currently, the most prevalent variety is type 2 diabetes mellitus (T2DM); however, there are still certain specialized variants that are rare. Since the incidence of T2DM continuously increases, scientists start to investigate the underlying causes and treatments of T2DM [1]. Dietary fiber (DF), an indigestible part of plant foods, is crucial in a healthy diet and in reducing the risk of chronic health conditions [2]. Human gut microbiota composed of bacteria and archaea has an impact on many vital functions in the human body, including maintaining immune and metabolic homeostasis [3]. Additionally, the immune system plays an essential role as well since it keeps preventing us from outside invaders. Findings have revealed that eating habits, the diversity of microbiota, and the immune system seem to be associated with T2DM respectively [2]. In the previous studies, there is a lack of articles researching the association between DF, T2DM, microflora composition, and inflammation. In short, this study is to point out the association between the intake of DF, T2DM, gut microbiome, and the immune system (Fig. 1).

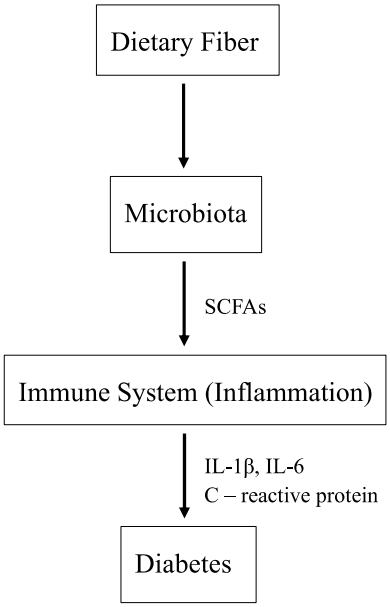


Fig. 1 The general mechanism of DF intake affects the prevalence of diabetes.

2. DF and T2DM

2.1. T2DM

In recent decades, diabetes mellitus become one of the largest epidemics in both developed and developing countries. By 2021, 537 million adults (20-79 years old) will be diabetic worldwide. It is anticipated that patients would expand to 700 million by 2045 [4]. Compared to 1990, when it was listed as the eighteenth major cause of mortality, diabetes mellitus has risen alarmingly to become the ninth top cause of morbidity. The majority of people with T2DM reside in low- and middle-income nations, with the prevalence showing a distribution pattern that is consistent with socioeconomic progress. Developed countries, notably Western Europe, have significantly higher incidence rates despite all actions taken on the public healthcare system and the rate of growth does not seem to be slowing. In addition, diabetes affects upwards of 37 million Americans, with 90-95 percent of them suffering from type 2 diabetes. Though it mostly influences people over the age of 45, it is starting to have an impact on adolescents. Current studies illustrated that healthy eating habits and exercise could synergistically minimize the occurrence of T2DM in both high-risk and general populations [1]. Diet interventions often contain primarily low calories and carbohydrates and high fiber. In terms of physical activity, aerobic or anaerobic exercises and resistance training are involved. Moreover, people can employ healthcare professionals to give the right instructions to achieve their goals. Finally, dietary education in public should be given priority as well, which could consistently improve the life quality of the public via ameliorating eating habits, adhering to the most recent dietary recommendations for the management of diabetes, and maintaining overall metabolic control [1].

2.2. Fiber

Dietary fiber is generally beneficial for human health. The previous definition of fiber suggests that it contains complex, nonstarch carbohydrates, and lignin, which the small intestine cannot digest insofar as mammals lack the enzymes necessary to hydrolyze them into their constituent monomers [2]. These substances could reach the colon and are accessible for fermentation by the flora there. Recently, oligosaccharides, such as inulin and resistant starches, have been added to the concept. Moreover, we can even classify them into two categories – soluble and insoluble fibers [2]. Soluble

fiber, such as inulin oligofructose, psyllium, pectin, and resistant starch, can be fermented by the gut bacteria in the colon and can slow glucose absorption and reduce cholesterol levels in the blood. Barley, fruit pulp, and dried beans are enriched resources of them. Insoluble fiber, such as cellulose, hemicellulose, and lignin, can decrease constipation via increasing stool bulk but may only be fermented to a limited extent in the colon. They can be found primarily in oat and wheat bran and the skins of fruit [2].

2.3. Dietary Fiber Intake and T2DM

There was a meta-analysis studying whether the consumption of whole grains or cereal and the chance of gaining T2DM was related to each other (Fig. 2). The authors searched 36 studies through PubMed and finally, 8 studies were selected [5]. There was a total of 434903 subjects. In terms of whole grains, two studies pointed out that more intake of whole grains can prevent type 2 diabetes, so there was an inverse relationship between them. Although one study found no statistically significant relationship between them, the authors still deemed that increasing the intake of whole grains could help to diminish T2DM cases. Concerning cereal intake, while one study suggested the inverse association was not statistically significant, two studies illustrated more consumption of cereal could benefit type 2 diabetes. Additionally, one study indicated that it is time to confirm the correlation between cereals and the prevalence of T2DM by randomized controlled trials. Furthermore, 2 studies, researching the effects of the number of grain products and cereal on T2DM, examined that the level intake of DF was correlated with a small chance of getting the disorder. Therefore, as per the studies mentioned above, increasing the consumption of fiber is linked to a noticeable reduction in the occurrence of T2DM, and the influence is similar for both males and females. The publication bias test showed the results were statistically significant, which means the data were reliable [5].

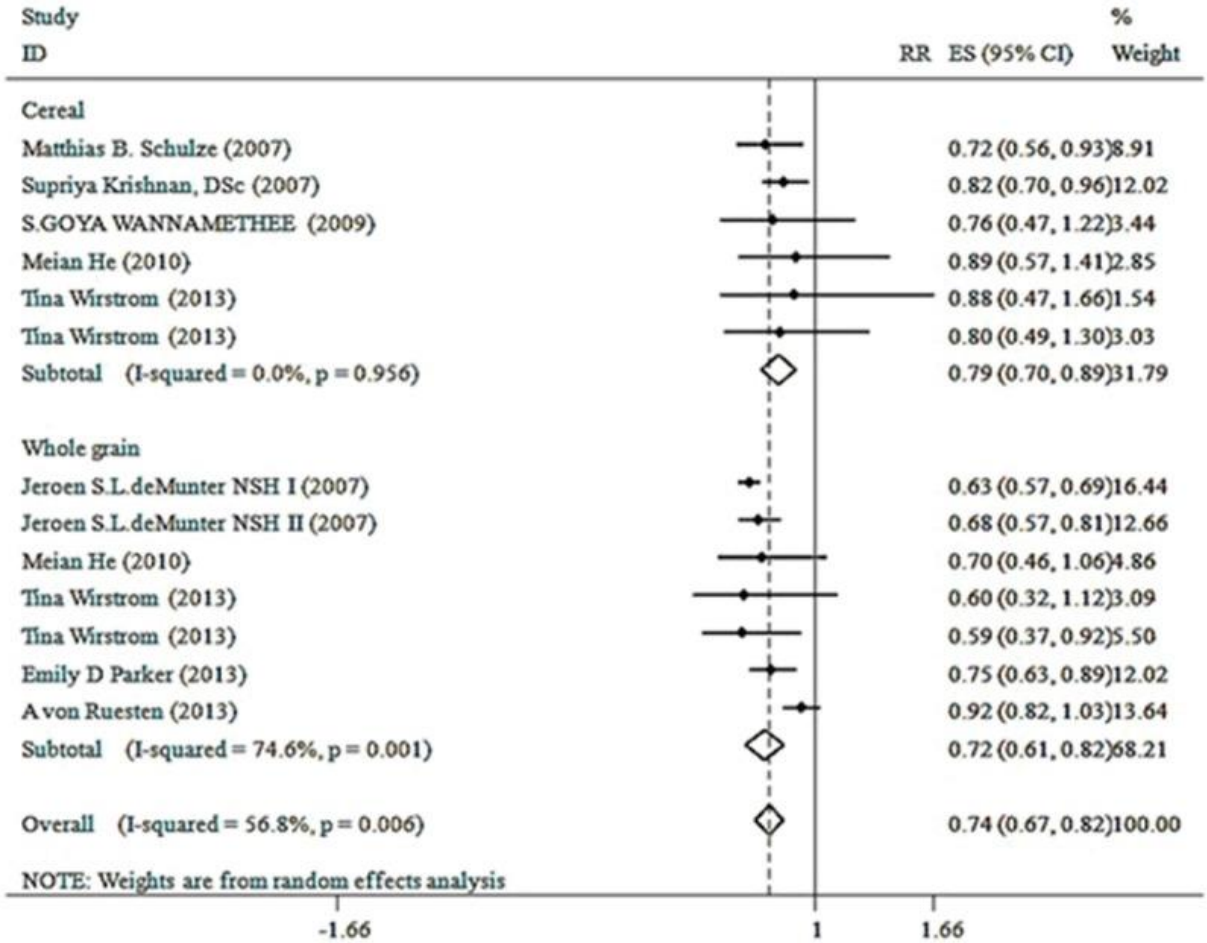


Fig. 2 The meta-analysis on fiber intake and the development of T2DM [5]

3. Fiber and Microbiota

3.1. Microbiota

There are several main phyla of bacteria existing in the gut: *Actinobacteria*, *Bacteroidetes*, *Firmicutes*, *Proteobacteria*, and *Verrucomicrobia*. Ninety percent of the gut microbiota are made up of Firmicutes and Bacteroidetes [3]. Different microbial ecologies are determined by these phyla, which are variably distributed throughout the gut. Compared to the human genome, intestinal bacteria are 150 times greater, and even their mass could reach 1.5 kg, roughly two percent of a person with 75 kilograms [3]. Gut microbiota performs structural, histological, and metabolic roles for the preservation of health, including the synthesis of amino-acid and the absorption of dietary fats and some fat-soluble vitamins. There were some studies conducted on germ-free animals illustrating that alterations in the diversity of the intestinal microbiome may control disease development [3]. Furthermore, evidence also demonstrated that the variety of microbiota could affect energy balance, intestinal permeability, and immune system, which were all associated with several disorders, including T2DM [3].

3.2. Dietary Fiber and Microbiota

The composition, variety, and abundance of gastrointestinal microorganisms could be influenced by DF intake [2]. In a study conducted in Europe, authors contrasted the gut microbiome of teenagers eating modern western diets with those having rural diets rich in dietary fiber [6]. They found that the level of *Prevotella*, *Bacteroidetes*, and *Actinobacteria* were higher in rural children and the level of Firmicutes and Proteobacteria were higher in urban children. Moreover, rural children had higher microbial richness and biodiversity than urban children. Another research found that fecal microbiota composition of the Yanomami tribe with high fiber eating habits in rural Venezuela had a higher abundance of *Precotella* than Americans, and the abundance of *Bacteroidetes* family, including *Verrucomicrobia*, *Bacteroidales*, and *Mollicutes* were lower [7]. Moreover, L Schnorr et al illustrated that Hadza (hunter-gatherers in Tanzania with high fiber intake) had better richness and biodiversity of microbiome than urban Italian. Bacteroidetes were more abundant in Hadza residents, while Firmicutes were less prevalent [8]. A study on Papa New Guineans who consumed plenty of dietary fiber also displayed that the abundance of Prevotella was high but the *Faecalibacterium*, *Ruminococcus*, and *Bifidobacterium* were low. In addition, this population also had a different *Prevotella*:*Bacteroides* ratio than Americans [9]. Therefore, these studies all affirmed that dietary fiber intake is associated with microbial population levels.

Additionally, microbiota-accessible carbohydrates (MACs) are known as indigestible and the food source for intestinal microbes [10]. There was a study demonstrated that giving mice a low MACs diet could decrease the gut microbiota diversity during a short period. This revealed a low-fiber diet was a primary contributor leading to the depletion of the microflora because intestinal microbes cannot obtain sufficient nutrients. If they lose the substrates they relied on, they cannot function properly, leading to the depletion of diversity [10].

3.3. Microbiota and T2DM

In terms of the association between microbiota and T2DM, clinical studies suggested that the incidence of T2DM was inversely associated with short-chain fatty acids (SCFAs) [11]. DF facilitated bacterial fermentation in the intestines and could lead to elevated levels of SCFAs, containing acetic acid, formic acid, and propionic acid. They are essential in manipulating glucose homeostasis in the human body. Butyrate could influence the way tight junction proteins were expressed and affect the intestinal mucosal efficacy. Besides, acetate could control mucosal permeability and gut barrier functions [11]. These can be done through a mechanism: the SCFAs activated G-coupled protein on the L-cells, then, GLP-1 and peptide YY (PYY) will be released in order to regulate glucose homeostasis. Meanwhile, SCFAs also participated in inflammation by regulating 5'AMP of the intestinal barrier. Hence, the deficiency in SCFAs could result in a higher incidence of T2DM [11].

4. Fiber and Immune System

4.1. Immune System

A complex network of organs, cells, and proteins constitutes the human immune system, which protects us from bacterial or viral infection [12]. The gastrointestinal tract is the largest and major immunological organ. Commensal bacteria, particularly those in the intestines, instruct and develop host immunity. Therefore, maintaining the balance of the microflora is key to modulating the operations of the immune system and controlling inflammation. Inflammation is a common symptom when people are infected [12]. The onset could trigger various immunological cells, including neutrophils, dendritic cells, and macrophages, to come to the infection region, trying to clean up the bacteria or virus infection. Nevertheless, sometimes the infection cannot be eradicated, then it might entail the body in a chronic inflammation status that the infection can stay in the patient's body either remain quiescence or reoccur unpredictably [12]. With this chronic inflammation, patients could encounter some severe situations in the future.

4.2. Dietary Fiber and Inflammation

Many studies suggested that the amount of DF was adversely correlated with the level of inflammation in the body. If people have a low fiber diet, one of the classical pathways leading to inflammation is via a potent pro-inflammatory cytokine IL-1β. It is essential for host-defense responses to infection and injury, and once released, it stimulates the cell surface interleukin receptor type I [13]. This could recruit receptor adaptor proteins, and then signal via different kinases. IkB kinases (IKKs) are one of them, as IKKs phosphorylated the IkB proteins, they could promote the destruction of IkB and secretion of NF-kB, translocating them from the cytoplasm to the nucleus. When disparate NF-kB subunits are in the nucleus, they can dimerize either heterogeneously or homogeneously, capable of transactivating a wide range of genes (including iNOS), which are implicated in inflammation that results in tissue malfunction or cell apoptosis [13].

The SCFAs mentioned above can recruit macrophages and dendritic cells to determine the expression of human monocytes genes and diminish the generation of proinflammatory cytokines produced by monocytes (e.g., IL-6). Moreover, they can facilitate the maturation of regulatory T cells, which would suppress the activity of inflammatory T cells [14]. The SCFAs also signal through G-protein-coupled receptors on intestinal epithelial cells IECs, such as GPR41, GPR43, and GPR109a, to downregulate host inflammatory responses via reducing the activity of histone deacetylases (HDACs) [14].

4.3. Inflammation and T2DM

Several groups researched the relationship between inflammatory markers and T2DM occurrence. A group carried out a case-control study in European men and women aged 35-65 years old illustrated that a rising in the combination of IL-1β and IL-6 increased the incidence of T2DM more than an isolated elevation of IL-6 [15]. Another prospective study in the US proved that an elevated number of C-reactive protein (CRP) and IL-6 indicated the onset of the disorder in healthy middle-aged women. Since CRP and IL-6 were critical biomarkers of inflammation, the finding supported the potential role of inflammation in diabetogenesis (Fig. 3) [16]. Thorand et al also conducted a study on women and demonstrated that IL-6 was considered to be highly related to T2DM [16]. In addition, a study displayed that rising CRP levels were a robust independent predictor of T2DM [16]. Hence, these studies all demonstrated inflammation was statistically significantly related to the incidence of T2DM. The inflammation occurred in the pancreatic beta cells. A high glucose level could result in a release of IL-1β, and IL-1β can inhibit the activity of beta cells and induce Fas-triggered apoptosis by partially initiating the transcription factor NF-kB [17]. Another common factor macrophage along with other immune factors containing IL-8, granulocyte colony-stimulating factor, chemokine KC, and IL-6 could also be released leading to a decrease in the beta cell and its function. Since IL-8 was

produced, it will block the pathway of recruiting monocytes and neutrophils, so the inflammation could not be undermined [17].

In conclusion, a low intake level of dietary fiber could modify the composition of human microbiota via reducing the production of fermentation end products. Then, the change in the variety of intestinal microflora could further result in inflammation. Since findings showed that inflammation could impair the function of pancreatic beta cells, other studies suggested that inflammation is a plausible marker for T2DM, which is positively associated with the incidence of T2DM. Hence, dietary fiber can have an impact on T2DM, and people with a low fiber diet could have a higher chance of inflammation, leading to type 2 diabetes.

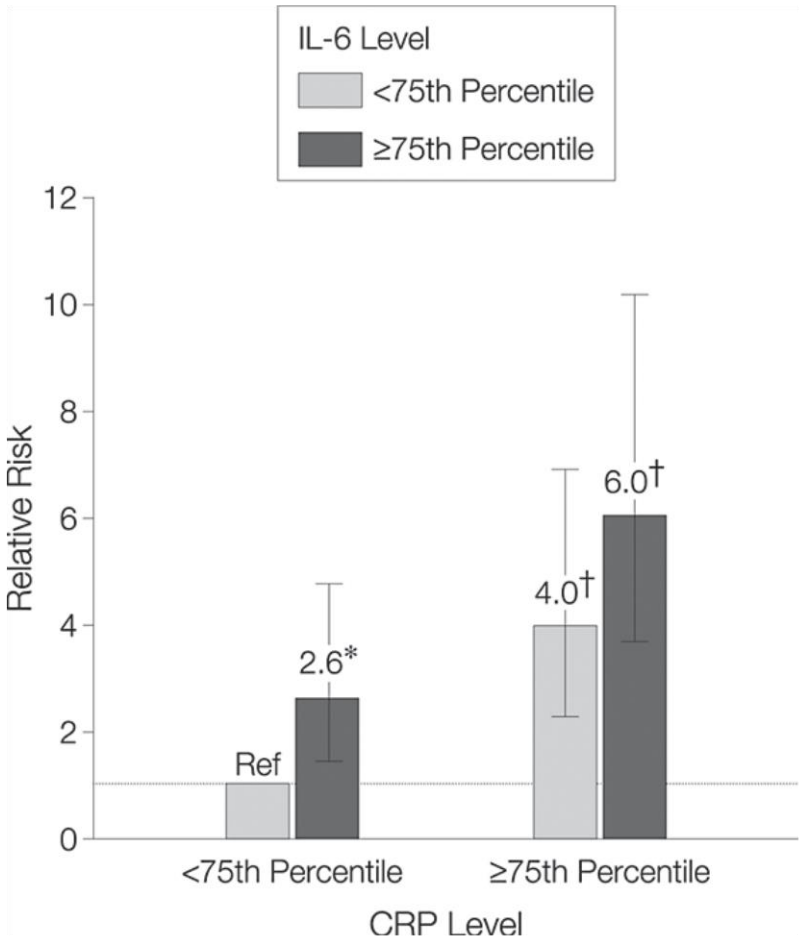


Fig. 3 Evidence shows that women with a greater relative risk of T2DM have an increase in IL-6 and CRP levels [16]

5. Conclusion

A potential relationship between DF intake, microbiota, immune system, and T2DM prevalence has been identified in this article. De Filippo et al studied the intestinal composition in central Europe and rural places of Europe which consumed a higher level of fiber and found that the level of *Actinobacteria*, *Bacteroidetes*, and *Prevotella* were higher in rural children, and *Proteobacteria* and *Firmicutes* were more common in youngsters from metropolitan areas. Another group studied the gut diversity of Papa New Guineans, since they consumed plenty of dietary fiber daily, the abundance of *Prevotella* was quite high among them. Furthermore, several studies demonstrated lower consumption of dietary fiber could limit flora composition in the gut. Due to the decrease in microbiota diversity, the decline of fermentation products by micro-organisms (e.g., SCFAs) could

lead to an increase in the level of inflammation via releasing pro-inflammatory cytokine IL-1β. If the amounts of SCFAs were sufficient, they could inhibit this process through recruiting macrophages and dendritic cells or downregulating the function of inflammatory T cells. Apart from these, a study conducted by Spranger et al suggested that IL-1β and IL-6, major pro-inflammatory markers could increase the chance of getting T2DM. Thorand et al also demonstrated that IL-6 was positively associated with T2DM in females. Moreover, the remaining studies mentioned above all showed that increased inflammation level is correlated with a greater incidence of T2DM. To sum up, DF intake could have an impact on the incidence of T2DM through decreasing the diversity of microbiota and increasing the level of inflammation.

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