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Effects of Dietary Fiber in Patients with Type-2 Diabetes Mellitus: A Meta Analysis

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Abstract

Nine published studies were involved in this meta- analysis, sample size wide-ranging from 6 to 35 subjects, adding together 154 subjects for intervention group and from 6 to 23 subjects, totaling 129 for control group. Fiber consumption extended from 4 to 40g per day. Different types of fiber were involved in this study. All the studies included in this study involved measurement of fasting blood glucose in mmol/L and glycated hemoglobin as percentage of hemoglobin for both the intervention group and control groups. Methods of diet were different, the durations of treatment with different types of fiber were varied from 4-week period to 6-month period. The overall mean difference was a decrease of Fasting Blood Glucose (FBG) by fiber intake of 0.91 mmol /L (95% CI, 1.18 –0.64) more than the decrease from placebo in fixed effect model and -1.17 (95% CI:-1.97 ; -0.36) in random effect model ,high heterogeneity was witnessed (p less than 0.01, I^2 = 88.0%). The overall mean difference was a reduction of glycosylated hemoglobin by fiber intake of 1.03 mmol/L (95% CI, 1.31; –0.76) more than the reduction from placebo in fixed effect model and -1.08 (95% CI: -1.94;-0.21) in random effect model. High heterogeneity was witnessed (p less than0.01, I^2 = 89.0%).

Key words : Diabetes mellitus, Fiber, Meta-analysis, Type 2 Diabetes Mellitus

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Introduction

The collection of abnormalities caused by deficiency of insulin is called diabetes mellitus (1). It is one of the oldest diseases which humankind has information about it (2). This disease is caused by relative or complete absence of insulin which results in elevating in blood sugar levels (3). There are four important types of diabetes mellitus; *Type 1 diabetes:* Absolute insulin deficiency caused by immune mediated and idiopathic forms of cell disorder. This autoimmune-mediated disease process produces total insulin deficiency and thereby total dependency on insulin for surviving (4). *Type 2 diabetes*: Adult commencement disease, which originates from secretory defect of insulin, its resistance and relative insulin deficiency. This type of disease exhibits a strong genetic predisposition and results from a mixture of insulin insufficiency secretion and its insensitivity by tissues of the body. As a result, diabetics of this type show relative insulin insufficiency (3). *Type 3 diabetes*: It represents an extensive-ranging of particular types diabetes comprising of different genetic defects in insulin action, and pancreas disorders (5). It is a neuroendocrine disease which shows the progression of type 2 diabetes to the Alzheimer's disease (AD) (6). *Type 4 diabetes*: It is also known as gestational diabetes. This type of disease was discovered during pregnancy for the first time, as the pregnant cannot produce sufficient insulin to encounter the extra pregnancy needs. It vanishes after delivery and may point toward an increased possibility of type 2 diabetes (3).

Polyuria, polydipsia, weight loss, polyphagia (increased appetite), hyperglycemia, glycosuria, ketosis, acidosis, and coma are the characteristics of diabetes mellitus. Decreased glucose uptake into different peripheral tissues and increased glucose release from liver into circulation leading to increased glucogenesis are well-known biochemical abnormalities of diabetes mellitus (7).

Incidence and mortality of diabetes; Diabetes is one of the essential chronic disease worldwide. Nearly 415 million people who are between 20-79 age suffer from diabetes nowadays. Also, approximately 75% of them are living in poor and undeveloped countries. According to current investigations diabetes pandemic will increase in coming periods. It is predicted that the prevalence of the diabetes will reach 642 million by 2040 (8). Physical inactivity, uptake of carbohydrate, aging populations, and social factors like education, housing and food availability increase the prevalence of the diabetes (8). Also, family history, obesity, alcohol, smoking, stressful lifestyle and unhealthy diet have been defined as important risk factors for the diabetes (9,10). Approximately more than 20,000 young people yearly die because of diabetes related disease, basically due to macrovascular complications of diabetes including myocardial infarctions and cerebrovascular disorders. The number of people dying early in the diabetic population is double that of the non-diabetic population (11).

Type 2 Diabetes Mellitus (T2DM); T2DM is the most common type of diabetes and more than 90% of people have been diagnosed. It has affected 246 million people globally. T2DM occurs due to insulin resistance, relative insulin deficiency, and beta cell dysfunction which hamper control of blood glucose (12). It is also known as non-insulin-dependent diabetes so the patients do not require insulin treatment for surviving (13). Although the exact etiology of T2DM is not

known, many different factors are associated with type 2 diabetes. Lifestyle, diet, Body Mass Index (BMI), hypo vitamins D and family history are genetic and environmental factors affecting the onset of T2DM. Also, there are more than 64 widespread genetic variants which affect T2DM (12). T2DM is generally observed in families and has hereditary pattern. According to genome-wide association studies (GWAS) there are prevalent genetic variants related with T2DM. A single-nucleotide polymorphism (SNP) in TCF7L2, SLC30A8, FTO, CDKAL1, CDKN2A, CDKN2B, HHEX, IGF2BP2, GCKR has strong connection with T2DM (14). Especially some dietary compounds are related with decreased risk of T2DM. These components are higher uptake of whole grains, green leafy vegetables, nuts and coffee; lower uptake of refined grains, red and processed meat and sugar-sweetened beverages and low uptake of alcohol. As a result, T2DM can be prevented up to 90% by applying healthy diet, protecting a BMI value under 25 kg/m2, doing exercise 30 minutes per day minimum, quit smoking and lower the alcohol consumption (14).

Type 2 Diabetes Mellitus (T2DM) is defined as a metabolic disfunction of carbohydrate, lipid and proteins. This defect causes problem in insulin secretion and insulin resistance. The fundamental cause of T2DM is progressive and impairment of insulin secretion. It is a chronic disease that needs continuous medical treatment, checking of anormal glucose levels by patient and multifactorial risk decreasing ways to make a normal blood glucose stages, lipid profiles and blood pressure for decreasing risk for macrovascular and microvascular complications (14). Individuals affected by T2DM is generally obese and obesity can contribute to the insulin resistance. Also, ketoacidosis is rarely seen in this kind of disease. The diagnosis of the T2DM cannot be defined for many years due to development of the hyperglycemia gradually and at the early stages of the disease, severity of the symptoms of the disease are not sufficient for patients to notice. Nonetheless, these patients have tendency to develop macrovascular (such as cardiovascular comorbidities) and microvascular (including retinopathy, nephropathy, and neuropathy) complications (13).

Type 2 diabetes mellitus and dietary fiber; Dietary fiber or roughage is a kind of plant-derived food. It cannot be digested totally by human digestive enzymes (15). These foods contain different chemical structure and may be classified by their solubility, viscosity, and fermentability which impact how fibers are utilized in the body. Soluble fiber (including pectin, gums, mucilages) and insoluble fiber (including cellulose, hemicellulose, lignin) are two important components of dietary fibers (16). These kinds of fibers are compounds of plant foods such as legumes, whole grains and cereals, vegetables, fruits, and nuts or seeds. Higher and regular diet by using fiber is considered to support health and decrease the risk of some diseases (17). It is generally proposed that healthy people should eat between 20 and 35 g dietary fiber each day (16). There is inverse association between intake of dietary fiber and risk of T2DM. Especially, it was shown that insoluble fiber (not soluble fiber) is inversely related with the risk of T2DM. Previous research has shown that increased total dietary fiber intake is inversely correlated with markers of insulin resistance, and subjects consuming diets high in insoluble fiber may reduce the risk of diabetes by increasing insulin resistance (18).

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Epigenetics and diabetes mellitus; Epigenetics is heritable changes in gene which do not alter the nucleotide sequence of DNA (20). DNA methylation, histone modifications, and RNA-mediated processes (MicroRNAs) are essential processes of epigenetic mechanisms. These epigenetics mechanisms are defined as epigenome and unbalance between them causes some pathological diseases such as obesity and type 2 diabetes (21). Since differences in DNA methylation are observed in diabetic and non-diabetic individuals, it is likely that epigenetic symptoms play a key role in the pathogenesis of type 2 diabetes. Moreover, Histone modifications also played a powerful role in diabetes. Apart from these, Histone Deactylases (HDAC) inhibitors have important roles in treatment of diabetes. Nutrient compounds that cause HDAC inhibition may have potential in the treatment of type 2 diabetes and the development of miRNA-based therapeutics. (22). Epigenetic mechanisms are also impacted by environmental factors and this makes them essential pathogenic factor for complex multifactorial diseases such as T2DM (20).

Alterations in environmental conditions such as dietary content, exercise, circadian rhythms, alteration of temperature by seasonal changes and age can affect the cellular epigenome. The epigenetic response to this unfavorable environmental condition causes transcriptional alterations through some tissues such as insulin-producing beta cells and insulin-sensitive organs containing liver, muscle, and adipose. This changes finally result in dysfunction of beta cells and disrupted insulin secretion and drive insulin resistance as well. Consequently, glucose homeostasis is disrupted to start pathogenesis of T2DM. Moreover, epigenetic changes in vascular cells, kidney, retina, neurons, and immune cells may cause microvascular and macrovascular complications of diabetes. Epigenetic alterations response to unfavorable environment may happen in germline and can pass to the offspring resulting in the inheritance of T2DM (23).

In this meta-analysis, the effect of dietary fiber on type 2 diabetes patients were investigated by using of statistical methods.

Materials and Methods

A hand searching of required published studies was performed randomly on internet network on April 2018, using “dietary fiber” and “type2 diabetes mellitus” as keywords. The studies reference that met our criteria were examined for more probable related studies.

Selection of the Studies

Inclusion measures of our meta-analysis comprised randomized trials that included a rise in intake of dietary fiber as an intervention. Evaluated of glycated hemoglobin (HbA1c) and FBG as a result, used human contributors with known type 2 diabetes mellitus. Exclusion criteria included are those on diets different other than fiber, lack of specific effect data, patients other than diabetics type 2 included or comparison of two types of fiber (absence of control group). Table 1 shows the details of the intervention of the nine studies.

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Extraction of Data

Data were taken out from all studies are pass in Excel spreadsheet (Microsoft, Corp., Redmond, WA). Population factors such as number of subjects, fasting blood glucose and glycated hemoglobin were used. Final means of HbA1c and FBG of the intervention groups and control groups were measured as outcomes. Mean standard deviation of studies were used. If studies described FBG in mg/dl, this is multiplied by 0.0555 in order to convert it to the standardized international unit of mmol/L. Table 1 and Table 2 summarize means and SD of FBG and HbA1c for the selected studies.

Statistical Analysis

R is a programming language and used to compute statistical analyses. It was created by John Chambers in 1976 (24). The R program is used by statisticians and data miners widely (25). Therefore, all statistical analyses were performed by using the R (software/programming-version 3.6.2 – CRAN) Statistical Package. According to our meta-analysis p value was considered as ≤ 0.05 statistically significant.

Analysis and Data Synthesis

Meta-analysis of the mean differences was officiated with Review Manager (version 5.0.23, The Nordic Cochrane Center, Copenhagen, Denmark). Distinct analysis was done for FBG and glycated hemoglobin. By using inverse variance method, final means in control and intervention groups were matched by calculating a mean difference. Studies possessing less variance in their effect assessment are given more weight. Fixed effect model and random effects model were introduced together in this analysis. Comparison of final means is deemed a proper analysis method in randomized trial since, baseline data of both intervention and control groups in a randomized effect model are statistically same, so final values for each trial should represent a change from common baseline. A heterogeneity test was done to decide if a fixed-effect model results can be considered lawful. When heterogeneity showed P equal or less than 0.05, the results of a random effect model would be deemed valid only. Forest plots for HbA1c and FBG were generated.

Results

Study Characteristics

Nine studies were involved in this meta-analysis. Table 1, 2 and 3 show intervention details of included studies and sample size wide-ranging from 6 to 35, adding together 145 subjects for intervention group and from 6 to 23, totaling 129 for control group. Fiber involvements extended from 4 to 40g/day of addition fiber. Three studies did not postulate the dietary fiber type (25, 26, 27). Fuessl et al., have reported on guar granules (27), James et al., have reported on insoluble oat fiber (28), David et al., have reported on wheat bran fiber (29),

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Dall'Alba et al., have reported on soluble fibers (30), Ziai et al. have reported on Psyllium husk fiber (31) and Simpson et al., have reported on cereal food & tuber vegetable dietary fiber (32). All the studies included measurement of fasting blood glucose in mmol/L and glycated hemoglobin as percentage of hemoglobin for both the intervention group and controls. Methods of diet were different, the durations of treatment with different types of fiber were varied from 4-week period (28) to 6-month period (27**,** 30).

Table 1: The Results of Fasting Blood Glucose (FBG) Studies Included in the Study.

Studies	Intervention group			Control group		
	N	Mean	SD	N	Mean	SD
Fuessl	18	8.290	0.470	18	8.700	0.510
James	8	12.00	1.400	8	12.22	1.330
Ikem	35	5.901	1.300	17	8.000	2.300
Tommy	7	7.001	1.400	6	7.501	1.400
Chandalia	6	7.101	2.100	7	7.550	2.000
David	23	7.500	0.310	23	7.900	0.410
Dall Alba	23	7.101	2.800	21	7.100	1.800
Ziai	27	9.410	0.391	22	12.09	0.585
Simpson	7	6.501	0.400	7	7.400	0.500

Table 2: The Results of HbA1c % Studies Included in the Study.

Studies	Intervention group			Control group		
	N	Mean	SD	N	Mean	SD
Fuessl	18	8.700	0.330	18	9.010	0.310
James	8	8.100	0.500	8	7.130	0.610
Ikem	35	7.230	0.500	17	8.230	0.211
Tommy	7	5.501	0.700	6	5.900	0.590
Chandlia	6	6.900	1.200	7	7.201	1.300
David	23	7.201	0.220	23	7.400	0.310
Dall Alba	23	6.600	0.800	21	6.901	0.900
Ziai	27	8.901	0.200	22	10.50	0.600

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Simpson	7	8.500	0.300	7	9.500	0.400

Table 3: Intervention Details of Included Studies

Study	Type Of fiber	Intervention
Simpson (1979)	Cereal food & Tubers vegetable	14 diabetic patients were treated with high CHO modified fat diet for 6 weeks. This diet resulted in a fall in FBG & HbA1c%.
Fuessl (1987)	Guar Granules	Eighteen patients with T2DM were given 5g granules sprinkled on each meal for 4 weeks, and 4 weeks placebo period (separated by 14 days),5g wheat bran was given. Mean FBG and HbA1c on completion of study were reduced than after period of placebo.
James (1991)	Insoluble oat fiber	8 type2 diabetics were given 30g of insoluble hull oat fibers for 2 weeks in hospital and further 10 weeks on discharge. The hospital oat fibers decreased FBG by 13% but the values returned to pretreatment values after discharge period.
Chandalia (2000)	Not specified	13 patients with T2DM were given 50g of dietary fibers for 6 weeks compared with 24g of dietary fibers for same period the two diets were isoenergetic. On completion the study, the mean FBG was lower by 8.9% with 50g fiber diet, HbA1c also was reduced from 7.2 to 6.9.
David (2002)	Wheat bran	23 patients with T2DM were given 19g/d cereal fibers for two 3-month phases. On the finish of the study, there were no significant differences in the means of FBG and HbA1c levels.
Ziai (2005)	Psyllium husk fiber	49 subjects with T2DM were given 5.1g twice a day for 8 weeks. On the end of the study, psyllium showed decrease in FBG &HbA1c.
Ikem (2007)	Not specified	35 type2 diabetics were given 40g/day for 8 weeks, on the completion of the study, mean FBG was reduced by 4.9±2.7 mmol/L.
Tommy (2009)	Not specified	13 type2 diabetics were given Paleolithic diet including fruits, root vegetable, lean meat, fish, , , and nuts in 2 successive 90-days periods. Results included decrease of means of FBG and HbA1c values.
Dall Alba (2013)	Soluble fibre	23 subjects with T2DM were compared with 21 controls were given 10g /d, the duration of treatment was 10 weeks. The means of HbA1c was decreased but FBG didn't change.

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Meta-Analysis on Fasting Blood Glucose

Meta-analysis results of FBG are shown in figure 1-A which shows the odd ratios for individual studies and combined studies for the intervention fiber against placebo intake. The overall mean difference was a decrease of FBG by fiber intake of 0.91 mmol /L (95% CI, 1.18 –0.64) more than the decrease from placebo in fixed effect model and -1.17 (95% CI:-1.97; -0.36) in random effect model ,high heterogeneity was witnessed (p < 0.01, I^2 = 88.0%). This result is line with high heterogeneity. Therefore, the results of Random effect model have to be considered.

Meta-Analysis on Glycated Hemoglobin

HbA1c meta-analysis results are shown in figure 1-B. The overall mean difference was a reduction of glycosylated hemoglobin by fiber intake of 1.03 mmol/L (95% CI, 1.31 –0.76) more than the reduction from placebo in fixed effect model and -1.08 (95% CI: -1.94;-0.21) in random effect model. High heterogeneity was witnessed (p < 0.01, I^2 = 89.0%). This result is line with high heterogeneity. Therefore, the results of Random effect model have to be considered.

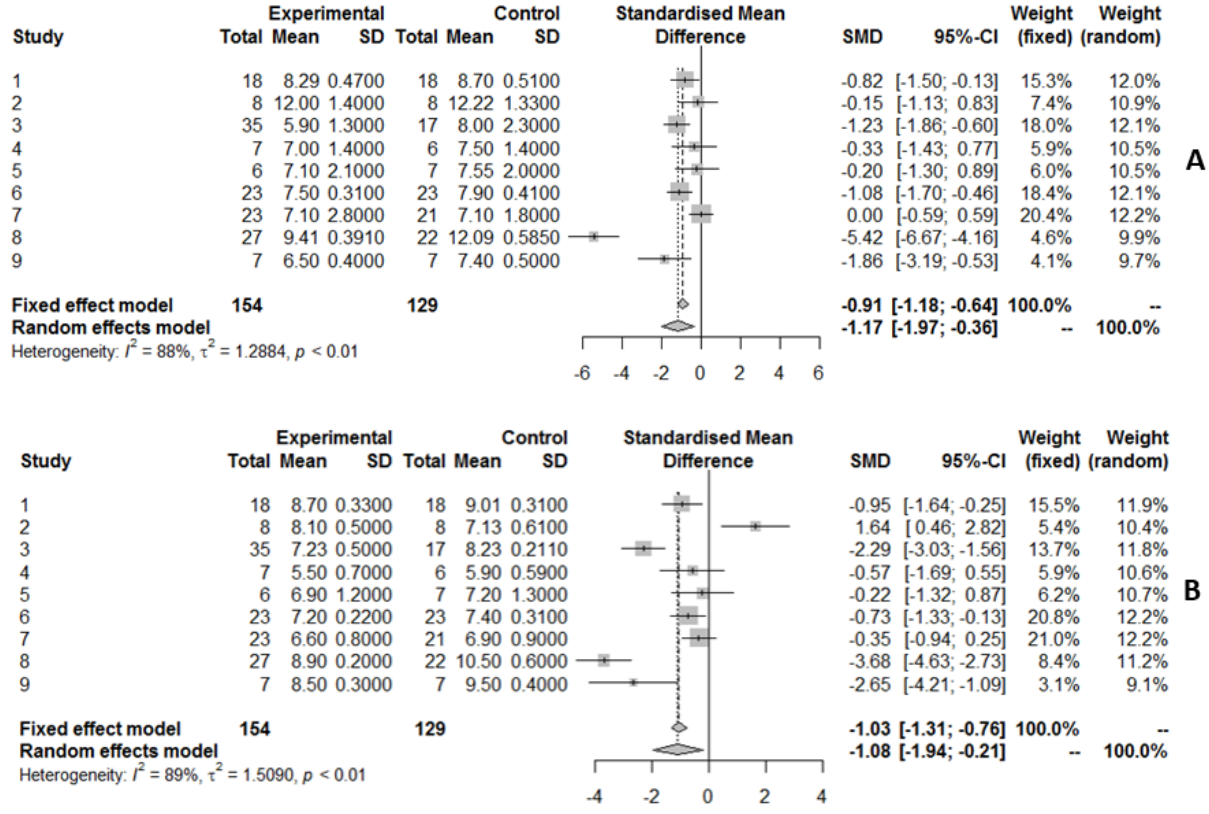

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Figure 1. Forest plot for Fasting Blood Glucose was shown in figure 1-A and forest plot for glycosylated hemoglobin was shown in figure 1-B. Mean, SD, and mean difference are in mmol/L unit. *SD*, standard deviation. *SMD*, standard mean difference.

Discussion

The term dietary fibers, was well-defined by American Association of Cereal Chemists International, are the eatable but indigestible and non-absorbable portions of vegetation or related carbohydrates (15). Growing in total dietary fiber consumption has showed a decrease in body fat (33), improve glycemic response and reduce blood pressure (25), triglycerides and low-density lipoprotein (34). Dietary fiber intake was proposed to encourage weight loss in obese people and avoid weight recover (35). Confirmation of consumption of dietary fiber and its weight regulating effect has been studied (36). The mechanisms by which dietary fiber affect diabetes are proposed to be associated to energy dilution (37), lessening in nutrients absorption rate (38), appetite clampdown (39), regulation of energy homeostasis (40) and change of gut microbial (41). Dietary fiber eating has showed decreased the risk of type 2 diabetes in observation studies (42). Insulin resistance and glucose tolerance in diabetics and subjects those having weakened glucose tolerance was improved and observed in intervention studies (43). The worthwhile dietary fiber effects on insulin resistance may attribute to increasing glycemic index of food, reducing the obesity (44), improving homeostasis of glucose (41), regulating hormonal responses (45), modulating inflammatory cytokines (46), and changing gut microbiota (41). The dietary fiber effect on GIT is via its physical and chemical properties through their size of particle, type and amount of fiber, viscosity, content of amylose and amylopectin, delaying time of emptying, reducing sugar concentration (47, 48).

Discussion on the Meta-Analysis

Meta-analysis technique was officiated to epitomize observational studies on the relation between dietary fibers consuming and its effects on diabetics type 2. Our meta-analysis grouped together FBG and HbA1c studies, and presented a converse relationship between consuming of dietary fiber and FBG and the same with HbA1c% mean values. On interpreting the meta-analysis results, many factors are worthy to be taken in consideration such as duration of treatment and the amount of fiber that is given to the subjects per day, subjects adherence with the diet etc. The criteria for management of T2DM can affect the results and must be considered fussily. A random and fixed effect models were applied to combine the effect of fiber intake on the FBG and HbA1c in diabetic patients type 2. Test of heterogeneity was officiated using the I^2 and Q statistic. The I^2 statistic prescribes variation % crossways studies due to heterogeneity instead of chance (49). I^2 less than 25% was deemed as few or no heterogeneity, 25 to 50% was deemed as moderate heterogeneity, and more than50% proposed as high heterogeneity, correspondingly. For the Q statistic, p less than 0.1 were deemed significant statistically (50). Fixed effect model, by referring to figure 1 the dietary fiber effect on FBG is proposed to be more apparent in study 8 and weakened in study 7. Although the amount of fiber intake in the two studies were 10.2 g/day versus 10 g/day respectively, the mean of FBG reduced by 28% in the former study while it remained unchanged

in the latter, this may attribute to the difference in duration of treatment between the two studies. This does not affect the common effect as the study 8 has small wt%, the same effect also affects the common effect by study 9. Studies 2, 4 and 5 showed small effect of fiber intake on FBG, their weights and their confidence intervals were convergent, there is no significant variances between the three studies. Studies 1, 3 and 6 exhibit convergent confidence intervals and close wt% overlap each other in their CI, so the studies shift the common effect toward its value -0.91 with CI (-1.18; -0.64) reflecting the inverse relationship between fiber intake and FBG of diabetics. Two studies (study 8 and 9) have close confidence intervals but high variances between the study (not overlap each other) causing the mean effect to shift toward the left as the sum of their weights in random effect is 19.6%. Study 1, 3 and 6 showed significant negative effect of fiber intake on FBG with close wt% and CI overlap each other and with studies 2, 4, 5 and 7 with smaller effect and smaller wt% . All these above studies give rise the mean effect of -1.17 with CI (-1.97;-0.36). In the current study, random and fixed model were found significant and also high heterogeneity was found significant ($p < 0.05$). Various types of fiber act in the treatment of T2DM in different mechanisms [50], the study proposes a decreased FBG with increasing intake of dietary fiber. This is in line with our results about the effect of fiber intake on FBG of type 2 diabetic mellitus patients. Fixed effect model in figure 1-B shows higher wt% for studies 1,6 and 7 with variable confidence intervals overlap each other with study 4 and 5 of smaller wt% around common effect and balance the remaining studies with smaller wt% that is (2, 3, 8 and 9 studies) with variable confidence intervals not overlap each other except for (8,9 studies) which are overlapping. The common effect is -1.03 with CI (-1.31;0.76) which means inverse relationship between fiber intake and HbA1c% study 2 showed positive relationship between fiber intake and HbA1c%, and this does not affect the final result greatly unless other studies have same relationship are present. In random effect model figure 1, study 9 exhibit 9.1% by wt however its wt% is 3.1% in fixed effect model, but here its effect is more profound as it has largest CI among the studies and this affect the mean effect of the final result especially when it overlaps with two studies 8 and 3 and to some extent with studies 1 and 4. All these factors make the mean effect to shift toward study 9. In addition, the overlapping of the studies 1,4,5,6 and 7 potentiate the mean effect value around its magnitude, that is -1.08 with CI (-1.94;-0.21). Again study 2 didn't affect the mean effect, although it exhibits good wt% and CI because there are no such studies potentiate its effect. Heterogeneity of 89.2% in term of I^2 can be considered high enough because the presence of sufficient variances between the nine studies as well as within the studies themselves. This result is consistent with the result of Robert A. Muenchen who stated that presence of inverse relationship between fiber intake and HbA1c%. Overall P- values was 0.0001 in fixed effect model and 0.0144 in random effect model making the two models are valid as the two values are less 0.1.

Conclusion

Evidence that based on nutrition principles and recommendations to treat diabetes mellitus and its problems has been established in many countries. It is obvious that there is a vital role of particular food products with a desirable chemical structure used for diabetes

mellitus treatment and its related consequences. The specialized nutritional foods should encounter the physiological body nutrition and energy, and exhibit preventive and therapeutic bioactivities to return to normal and reduce abnormalities of body metabolism. In general, an intervention with supplementation of dietary fiber for type 2 diabetes can reduce FBG by 0.91 mmol/L according to the fixed effect model and by 1.17 mmol/L according to the random effect model and HbA1c by 1.03% according to the fixed effect model and 1.08% according to the random effect model.

Author Disclosures

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