Asian Journal of Research and Reports in Endocrinology

Volume 7, Issue 1, Page 26-33, 2024; Article no.AJRRE.114131

A Review of the Effect of Walnuts (*Juglans regia*) Supplementation on Type 2 Diabetes Mellitus

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Authors' contributions

This work was carried out in collaboration among all authors. Authors CCO and SIG conceptualized the study, Authors CCO, EOO, UO and BNN participated in the literature search and screening of the identified articles. Authors CCO and EOO drafted the manuscript while authors COO and SIG critically reviewed the manuscript for intellectual content. All the authors read and approved the final manuscript for submission.

Article Information

Open Peer Review History:
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Systematic Review Article

Received: 01/01/2024
Accepted: 05/03/2024
Published: 16/03/2024

ABSTRACT

A lot of significant studies carried out in the past demonstrated the beneficial effects of walnuts (*Juglans regia*) in clinical patients diagnosed with type 2 diabetes mellitus (T2DM). There are however some contradictions in the findings of the studies done. In this review, a search of some online databases (PubMed and Google scholar) was carried out to isolate some studies that

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examined the role of walnuts on glycaemic indices in type 2 diabetes mellitus. A randomized, cross over study recently found an increase in post-meal energy expenditure, but no difference in satiety between subjects fed walnuts versus fat-rich dairy products. This was based on reported appetite satisfaction after one meal in an outpatient setting. Other relevant studies showed that walnut extracts markedly lowered fasting blood glucose (FBS) and HBAIC and increased the insulin level in diabetic patients at the end of their study. The mechanism behind the hypoglycemic activity of walnuts could be due to increase in insulin release from remnants of β-cells in the pancreas, its antioxidant properties, the restoration of insulin sensitivity and interference with the absorption of dietary carbohydrates in the small intestine. The reported hypoglycemic effect of *juglans regia* may also be due to the presence of phenolic acids (gallic acid and caffeoylguinic acid) in walnuts. Various studies have shown that walnuts consumption could markedly reduce the incidence of type 2 diabetes mellitus in the population.

Keywords: Walnuts; juglans; glycemic control; diabetes mellitus; insulin resistance.

1. INTRODUCTION

The metabolic disorder known as type2 diabetes mellitus (T2DM) is reputed as one of the most prevalent disorders in the series of metabolic diseases worldwide. It is a chronic lifestyle disease. The incidence of type 2 diabetes mellitus has been predicted to scale up to three hundred million cases by the year 2030 [1,2,3]. The major features of this ailment are: high levels of insulin in the blood, resistance of the system to insulin, reduced β-cells reserves in the pancreas. These features are usually followed by dyslipidemia [4,5]. "*Juglans regia* is one of the most commonly used in traditional medicines for the treatment of diabetes" [6,7]. "Previous studies in Iran have even reached the stage of clinical trials by formulating 100 mg capsules of *Juglans regia* leaf extract in the treatment of diabetic patients" [8,9,10].

"The beneficial effects of nuts are attributed to their unique nutrient profile, which includes fiber, vegetable protein, monounsaturated fat (MUFA), polyunsaturated fat (PUFA), vitamin E, magnesium and other bioactive components" [11,12]. "Studies have shown that consumption of diet rich in nuts with low saturated fats and cholesterol and high monounsaturated and polyunsaturated fats have demonstrated to a significant beneficial effect on plasma lipids and lipoproteins when compared with either a low fat or average American diet" [13]. "Other bioactive compounds present in nuts, including micronutrients, fiber, and phytochemicals, may also contribute to their cardio protective effect by reducing inflammation, improving vascular reactivity, and lowering oxidative stress" [14,15].

"Recently, there are a few experimental studies on the hypoglycemic effect of *Juglans regia L.* leaf extract in diabetes mellitus" [9,16,17,18]. "These studies documented that administration of *Juglans regia L.* leaf extract significantly reduced fast blood sugar (FBS) and hemoglobin A1c (HbA1c) compared to control groups" [9,16,17,18]. "Moreover, results of two clinical trial studies have shown that fast blood glucose (FBG) and HbA1c significantly decreased after consumption of 100 mg *Juglans regia L.* leaf extract for 3 months and 200 mg *Juglans regia L.* leaf extract for 2 months compared to placebo groups [8]. An in vitro study also reported that walnut leaf extract inhibits protein tyrosine phosphatase 1B (PTP1B) and enhances glucose-uptake" [19]. This review is aimed at exploring alternative remedies in the treatment of type 2 diabetes mellitus with the use of walnuts supplementation. It is one of the options in ayurvedic medicines deployed in the treatment of diabetes because they contain polyphenols. Walnuts and other ayurvedic agents also have the advantage of minimal or no adverse effects when compared with the allopathic agents with the adverse effects of weight gain, metabolic acidosis, hypoglycemia and heart failure.

2. SEARCH STRATEGY FOR LITERATURE

The PubMed and Google Scholar databases were used for searching for both original and review articles that bothered on the impact of walnuts supplementation on Type 2 diabetes mellitus (Type2 DM). Search terms used included: walnuts [MeSH] AND "blood glucose" OR "plasma glucose" OR "blood sugar" OR "glycated haemoglobin" OR "Diabetes mellitus"

OR “type 2 diabetes”. Identified articles were critically assessed for this review.

3. EFFECT OF WALNUTS CONSUMPTION ON INSULIN DYNAMICS AND GLYCEMIC CONTROL

In a study by Arab et al. [20], it was discovered that walnuts consumption markedly reduced the incidence of type 2 diabetes mellitus in the population. Women were also found to demonstrate greater association between walnut consumption and fasting blood sugar levels. A similar finding was made in a randomized trial conducted in Spain which also revealed that a mediterranean diet supplemented with 30g/day of walnuts reduced the risk of diabetes mellitus [21] On the contrary, some other clinical trials recently conducted did not show any enhancement in the diabetes mellitus profiles in the study population [22]. Similarly, an eight-week cross over clinical trial which was performed on healthy caucasians revealed no significant difference in fasting blood sugar level, insulin, HBAIC or HOMA-IR in a diet enriched with 43g of walnuts per day [23].

An intriguing study by Konstantinos et al [24] demonstrated that a short-term consumption of walnuts resulted in a statistically significant increase in the concentration of circulating total adiponectin-A by about 15%. Adiponectin is an insulin sensitizer that enhances insulin sensitivity and also causes a reduction in inflammatory processes that occur in the body of humans [23]. Walnuts consumption in another study did not show a significant increase in adiponectin, and therefore no long-term effect on glycemic control in patients [25].

Another study showed that a diet rich in walnuts taken ad libitum did not show any change in the levels of fasting blood sugar, fasting insulin, and HOMA-IR when compared with the control diet in the control group of the experiment. In effect, there are contrasting findings in the overall impact of walnuts consumption on the blood levels of glucose and insulin [1,2,22,26]. This is difficult to explain, but it can however, be blamed on the different health status of the participants in the study, the specie of nuts used in the study and the duration of walnut consumption in the various studies reviewed.

It is believed that the positive effect of walnut consumption may be due to the substitution of carbohydrates with unsaturated fatty acids. It has also been shown that the alpha-linolenic acid (ALA) found in walnuts reduces fasting blood glucose (FBG) and also causes a reduction in insulin resistance in adult population [27,28]. The improved insulin sensitivity occasioned by the consumption of walnuts is due to the stimulation of glucagon-like peptide-1 (GLP-1) and insulin-like growth factor (IGF-1) [27]. The resultant reduction in blood sugar level from walnuts consumption may also be blamed on the high protein and fiber contents of walnuts [29].

A study by Hwang et al [30], there is an increased level of adiponectin especially in patients with metabolic syndrome (Mets). Adiponectin is an anti-atherogenic and anti-diabetic hormone derived from the adipose tissues and is abundant in the plasma of humans [29,31]. Low blood level of adiponectin has been implicated in the pathogenesis of type 2 diabetes mellitus according to some clinical trial studies [31,32].

Adiponectin has also been found to play a significant role in the reduction of glycated haemoglobin (HBAIC) in the blood. Studies done in the past looked at the overall impact of alpha Linoleric acid (ALA) on adiponectin in patients with type 2 diabetes mellitus. The studies revealed that ALA caused a marked increase in adiponectin with a consequent reduction and stability in the blood glucose levels in the individuals [32,33]. Walnuts consumption was also found to increase the level of Omega-3 Poly unsaturated fatty acid (PUFA) which in turn, increases the level of adiponectin in the blood. This ultimately results in decreased level of blood glucose in the participants [34,35].

“Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) values were generated from fasting blood glucose (FBG) and fasting serum insulin levels (HOMA calculator version 2.2.1) to gauge the degree of insulin resistance”. [36] However, a study by Katz et al. [35] showed that the ad libitum consumption of walnut-rich diet did not cause any significant change in the levels of fasting blood sugar, fasting insulin and also the level of HOMA-IR. It is therefore, difficult to establish a standard position on the role of walnut consumption on the dynamism of blood glucose and insulin. [21,22,26].

4. WALNUTS CONSUMPTION AND SATIETY

Walnuts have been found to be rich in poly unsaturated fats (PUFA) and have also been found to increase satiety after three days of being on the diet of walnuts. The increased satiety generally results in reduced calorie intake which ultimately leads to reduced blood glucose levels in humans (25,26,36). "A 24 week of mixed tree nut consumption as part of a hypocaloric diet in overweight persons of about thirty to sixty eight years showed an increase in post meal satiety that was associated with weight loss" [37,38]. "Another study showed that walnut consumption increases satiation in the subjects but has no effect on insulin resistance or the metabolic profile over a four-day period" [25,37,38].

"A randomized, cross over study recently found an increase in post-meal energy expenditure, but no difference in satiety between subjects fed walnuts versus fat-rich dairy products. This was based on reported appetite satisfaction after one meal in an outpatient setting" [26,26,37]. Thus, although it has been proposed that whole foods, such as nuts, may provide superior satiation and lead to reduced calorie consumption [37,38], there have been no blinded and controlled feeding studies to evaluate the effects of walnuts on satiety.

5. MECHANISMS UNDERLYING THE CARDIOMETABOLIC PROTECTIVE EFFECTS OF WALNUT CONSUMPTION

The study by Tuccinardi et al. [39] observed huge changes in insulin and glucose area under the curve (AUC) after walnut consumption. Walnut consumption also reduced the levels of lethal lipid fractions such as ceramides and sphingomyelins [40,41]. Study by Hosseini et al. [8] showed that walnut extracts markedly lowered fasting blood glucose (FBS) and HBAIC and increased the insulin level in diabetic patients at the end of their study (2-month consumption of walnut extracts).

The mechanism behind the hypoglycaemic activity of walnuts could be due to increase in insulin release from remnants of β-cells in the pancreas and restoration of insulin sensitivity and interference with the absorption of dietary carbohydrates in the small intestine [17,42]. The hypoglycaemic effect of walnuts may also be due to the presence of phenolic acids (gallic acid and caffeoylguinic acid) in walnuts [6,43].

6. ANTIOXIDANT CAPACITY OF WALNUTS AND THE ROLE IN BLOOD SUGAR REGULATION

Walnuts are rated very high in terms of their ferric reducing antioxidant power (FRAP), total parameter (TRAP) the presence of polypherols and ellagitannins in walnuts accounts for the high antioxidant capacity [44,45]. However, some studies have shown that chronic walnut consumption has little effect on antioxidant capacity in humans when measured in ORAC, FRAP and TAP [46,47]. In in vitro studies, an assay of extracts showed that walnuts have markedly increased antioxidant activity with the presence of ferric reducing antioxidant power (FRAP), and oxygen radical antioxidant activity (ORAC) [45,48,49].

Alpha α and Gama γ-tocopherol are in abundance in walnuts and they are strong antioxidants and inhibitors of superoxide generation. They also inhibit lipid peroxidation and low density lipoprotein (LDL) oxidation [47,49,50]. Alpha and Gama-tocopherol also minimize the oxidant and postprandial Lipaemia [51] In another study by Berryman et al [52] in which participants were placed on a six- week walnut-rich diets, there was no chronic effect of walnut antioxidant activity as indicated in the levels of malondialdehyde (MDA), a lipid peroxidation marker, Ferric reducing activity power (FRAP) and Thiols. Similar report was made by other authors in their various studies [11,46,53,54,55]. The underlying principle in the glycaemic mechanism of walnuts in type 2diabetes mellitus is likely due to its antioxidant properties, bearing in mind that the pathogenesis of type 2 diabetes mellitus is largely influenced by inflammation and activated innate immunity factors [6,43,54,55].

7. CONCLUSION

This review has demonstrated to a large extent that the use of walnuts as supplements may favourably enhance the reduction of plasma levels of glucose and glycated haemoglobin. The mechanism behind the hypoglycemic activity of walnuts could be due to its increase in insulin release from remnants of β-cells in the pancreas, the antioxidant properties, the restoration of insulin sensitivity and interference with the

absorption of dietary carbohydrates in the small intestine. It can therefore, be recommended that walnuts (*Juglans regia*) should be adopted as supplements in the treatment of Type 2 diabetes mellitus to ensure an optimal glycaemic control in the affected patients.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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