International Journal of Basic & Clinical Pharmacology
Ofor CC et al. Int J Basic Clin Pharmacol. 2024 Jul;13(4):536-542
http://www.ijbcp.com
pISSN 2319-2003 | eISSN 2279-0780

DOI: https://dx.doi.org/10.18203/2319-2003.ijbcp20241656

Review Article

Pharmacological effect of walnuts consumption on metabolic syndrome: a current view

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Received: 01 February 2024
Accepted: 06 March 2024

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ABSTRACT

Cardiovascular disease (CVD) is the leading cause of death worldwide (WHO, 2017). In addition to the global and national morbidity and mortality burdens of the disease, it imposes a substantial economic burden on society. The American heart association predicts that by 2035, 45% of Americans will suffer from CVD with costs expected to reach $1.1 trillion annually. Clinical trials have demonstrated that a nut-containing diet low in saturated fat and cholesterol, while high in poly and monounsaturated fatty acids has a beneficial effect on plasma lipids and lipoproteins when compared with either a low fat or average American diet. Other bioactive compounds present in walnuts, including micronutrients, fiber, and phytochemicals, may also contribute to their cardio protective effect by reducing inflammation, improving vascular reactivity, and lowering oxidative stress. It has been demonstrated that the consumption of walnuts resulted in significant reduction in body mass index (BMI), percentage of body fat, increased lean body mass and an increased amount of water in the body. A large population cohort study also demonstrated a marked reduction in body weight and other anthropometric parameters in people on regular consumption of walnuts.

Keywords: Metabolic syndrome, CVD, Walnuts, Oxidative stress

INTRODUCTION

Metabolic syndrome (Mets) is a medical condition that has a combination of a minimum of three of the following parameters-abdominal obesity (waist circumference (WC) larger than 102 cm for men and 88 cm for women), triglyceride levels of 150 mg/dl or higher, or taking fibrate medication, high density lipoprotein cholesterol (HDL-C) of less than 40 mg/dl for men and 50 mg/dl for women; blood pressure of 130/85 mmHg/ higher/ taking antihypertensive drugs and fasting blood sugar (FBS) of 100 mg/dl or higher/ taking anti-diabetic medications.[1-4]

CVD is the leading cause of death worldwide.[5] In addition to the global and national morbidity and mortality burdens of disease, it imposes a substantial economic burden on society. American heart association has made a prediction that by 2035, 45% of Americans will be afflicted with CVD with estimated cost implication of about $1.1 trillion every year.[1] High rate of consumption of extremely processed foods and markedly reduced intake of whole grains and nuts in population has been linked to elevated CVD. Improper diet has been shown to affect many CVD risk factors such as obesity, high BP, low density lipoprotein cholesterol (LDL-C), insulin resistance, oxidative stress, liver function and inflammatory conditions among many other significant clinical conditions.[6]

The worldwide prevalence of Mets ranges from 20 to 30% of the adult population.[7] The prevalence is higher in United

States of American where about 34.2% of the adult population is affected.[8] The proportion of people with abdominal obesity and high blood glucose levels has continued to be on the upward trajectory globally.[9] This is most likely going to result in an increase in the prevalence of chronic diseases, such as type 2 diabetes mellitus (T2DM) and CVD and a subsequent increase in health care costs with the attendant high mortality rate. Diet and exercise have been proposed as the major interventions in the prevention of Mets.[9] Some vegetarian and Mediterranean diets have also been associated with decreased risk of developing Mets. An essential component of this diet is tree nuts. The most commonly consumed nuts include walnuts, pistachios, cashews, almonds and hazelnuts.[10,11]

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.[10,11] Studies have shown that consumption of diet rich in nuts with low saturated fats and cholesterol and high monosaturated 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.[12] 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.[13]

Walnuts (*Juglans regia*) have been used for thousands of years as a healthy food and folk medicine. Many studies have confirmed that walnuts have strong antioxidant and anti-inflammatory functions. Walnut kernels contain large quantities of unsaturated fatty acids, peptides, proteins, and phenolic compounds, which have anti-inflammatory properties.[10,14] Among common plant foods consumed worldwide, walnuts (Juglans regia) were ranked second only to rose hip (Rosa canina) in their antioxidant activity, as determined by the ferric reducing antioxidant power (FRAP) assay. Polyphenols isolated from walnuts, including ellagic acid monomers, polymeric tannins, and other phenolic compounds, are potent inhibitors of plasma and LDL oxidation in vitro and have been found to reduce biomarkers of oxidative stress in diabetic mice.[14]

Melatonin, another antioxidant constituent present in walnut, has been positively correlated with increased plasma antioxidant capacity in rats.[15] Walnut (*Juglans regia L*) originated in central Asia and the Mediterranean region and are one of the oldest tree foods consumed by humans.[14,15] Walnut are rich in the polyunsaturated fatty acids linoleic acid and α- linolenic acid at 52.4 percentages and 12.5 percentages of Kcals respectively and thus potentially susceptible to oxidation.

There lipids are naturally protected by tocopherols in the seed and phenolic compounds in the pellicle or the seed coat.[16]

LITERATURE RESEARCH

Preferred reporting items for systematic reviews and meta-analysis (PRISMA) checklist was employed in the review of literature. Search terms used to identify relevant articles published in PubMed, Google scholar and EMBASE were: Mets, CVD, walnuts and oxidative stress. Review included articles published in the preceding ten years which came up to 8640 articles. 1426 articles were screened, including snowballing and others. A total of 40 articles were finally included in the review process. The literature search was done from November 2nd to November 25th, 2022.

EFFECT OF WALNUTS CONSUMPTION ON LIPID PROFILE

A lot of studies have been done to determine the effects of walnut consumption the biochemical parameters of the population, especially the effect on the lipid profiles. In an intervention study by Berryman et al in the United State of America, it was shown that consumption of walnuts led to significant reduction in the level of lipids in the body.[17] Total cholesterol (TC) also dropped from 4.3±03, the values obtained for triglycerides (TG), very low-density lipoproteins (VLDL) and low-density lipoproteins (LDL-C) all dropped significantly following the consumption of walnuts for a period of time. Supplementing 43 g of walnuts for eight weeks was also found to cause a drop in the levels of TC, low density lipoprotein cholesterol (LDL-C), non-high density lipoprotein cholesterol (non-HDL-C), TGs and ApoB (Bamberger et al, Haddad et al). Another study by Abbaspour revealed a contrasting finding in which there was no significant difference in the lipid profile parameters between groups that took walnuts and those that did not.[18]

In a recent study by Sala-Vila, it was observed that incorporation of 30 g/day of walnuts, almonds and hazelnuts into a Mediterranean diet significantly decreased insulin and glucose level in overweight and obese adults at high risk of CVD compared to low-fat diet after 3 months.[14] Another recent study on mixed nuts (30 g/day walnuts, peanuts and pine nuts) in Korean adults with Mets found significant improvement in TC and LDL-C.[19,20]

Supplementing 43 g of walnut daily for eight weeks significantly decreases fasting lipid parameters, including non-HDL-C, apo B, TC, LDL-C, VLDL-C, TG, and VLDL-TG in healthy individuals.[4,17] These results suggests that the increased n-3-PUFA evidence that a high n-3-PUFU intake provides cholesterol-lowering effects through several potential mechanisms non-HDL-C reduced by 5.8%, TC: by 3.9%, apo B by 6.2% VLDL-C by 13.2%, TG by 5.4%, VLDL-TG by 4.0%.[18,21] A study done in 2020 showed that consumption of walnut (*J. regia*) by ninety (90) hyperlipidaemic patients after 56 days resulted in significant decrease in the levels of TC, TG, LDL cholesterol (LDL-C), and increased HDL-C.[22] It has also been proposed that the favorable changes in lipid profile, which follow long-term consumption of nuts such as walnuts, could also account at least in part for the cardio-protective effect of walnut consumption. In a recent meta-analysis, three to six weeks of walnut consumption has been demonstrated to increase HDL cholesterol concentration and decrease total LDL cholesterol and triglyceride concentrations.[23,24]

EFFECTS OF WALNUTS CONSUMPTION ON ANTHROPOMETRY AND BLOOD PRESSURE OF PATIENTS WITH Mets

Anthropometric measurements were performed using standard procedures including body height, body weight, BMI, and WC.[5]

Study participants in previous studies had their blood pressure measured at baseline and post intervention with walnut consumption. Participants were considered to have hypertension if they (a) reported a previous diagnosis of hypertension or (b) reported to use of anti-hypertensive medication or (C) had a mean systolic BP ≥140 mmHg or mean diastolic pressure ≥ 90 mmHg.[3,25]

Petrovic-Oggiano et al have demonstrated that the consumption of walnuts resulted in significant reduction in BMI, percentage of body fat, increased lean body mass and an increased amount of water in the body.[26] The study revealed the following effects on the anthropometry and blood pressure (BP) of the participants: BMI (kg/m^2)=-0.59, (p=0.0064), WC=2.25 (p=0.1473), fat mass (kg)= +1.62 (p=-0.0006), lean body mass (kg) + 1.65 (p=0.003), systolic blood pressure SBP=-9.2 (p=0.0015), diastolic blood pressure DBP (mmHg)=-2 (p=0.793).

A large population cohort study by Freisling et al also demonstrated a marked reduction in body weight and other anthropometric parameters following the consumption of walnuts by the participants in the study.[27]

The blood pressure lowering effect could be due to the increased content of minerals in walnuts, that is magnesium and potassium. The impact of walnuts nutritional intervention on decreasing effect on blood pressure has also been demonstrated in previous study "health track study" which reported significant reductions in the systolic blood pressure (SBP) which was attributed to the intake of 30 g of walnuts.[28,29]

Most of the CVD risk factors (WC, serum glucose, TC, LDL cholesterol, ApoB, ApoE and blood pressure) decreased significantly with walnut consumption.[28,29] A cross-sectional study conducted on an elderly population at high-risk cardiovascular risk, showed that nut intake decreased both WC and BMI (p trend<0.005 in both).[19,28]

MACRO AND MICRONUTRIENTS COMPONENTS OF WALNUTS

Major nutrients that are present in walnuts in terms of quantity per dose are as follows: Total fat is 139 g in 2 kg walnuts an 278 g in 42 g of walnuts, fatty acids (g) 8.6 g in 21 g of walnuts and 17.1 g in 42 g of walnuts, α tocopherol (mg) 0.2 g in 21g of walnuts and 0.3 g in 42 g of walnuts, ϒ-tocopherol (mg) 4.4 mg in 21 g of walnuts and 8.9 mg in 42 g of walnuts, vitamin B6 (mg) 0.1 mg in 21 g of walnuts, 0.2 mg in 42 g of walnuts and folate (ug) 21 µg in 21 g of walnuts and 42 ug in 42 g of walnuts, magnesium (mg) 34 mg in 2 kg of walnuts and 67 mg in 42 g of walnuts.[29,30]

Table 1: Mean macronutrient content of Serbian walnuts according to the European food information resource (EUROFIR databases, 2013).

Macronutrient	Mean (SD)
Carbohydrate	8.10 (0.22)
Protein	16.21 (0.05)
Fat	68.38 (0.04)
Water	3.60 (0.02)
Ash	1.84 (0.01)
Fiber	1.86 (0.11)

Values are expressed as % by weight, (SD=standard deviation).

Table 2: Mineral composition of walnuts from Serbia.

Variables	Copper	Manganese	Iron	Zinc
Mineral	(mg/100 g)	(mg/100 g)	(mg/100 g)	(mg/100 g)
Mean (SD)	1.29 (0.29)	3.45 (1.28)	2.20 (0.11)	4.52 (3.63)
	Nickel	**Chromium**	**Sodium**	**Potassium**
Mineral	Mg/100 g	Ug/100 g	Mg/100 g	Mg/100 g
Mean (SD)	0.29 (0.16	0.22 (0.02)	14.2 (1.90)	438.2 (60.90)
	Calcium	**Magnesium**		
Mineral	Mg/100 g	Mg/100 g		
Mean (SD)	113.5 (42.30)	147.2 (15.50)		

FATTY ACID COMPOSITION OF WALNUTS

Fatty acid/mean (SD), palmitic acid=7.03 (0.25), palmitoleic acid=0.11 (0.05), stearic acid=2.75 (0.26), oleic acid=14.47 (1.17), vaccenic acid=1.34 (0.39), linoleic acid=63.15 (0.93), alpha-linolenic acid=11.15 (0.71), values obtained were expressed as percentage of fatty acid.[26]

EFFECTS OF WALNUTS ON GLYCATED HAEMOGLOBIN AND BLOOD SUGAR IN TYPE 2 DIABETES PATIENTS

Consumption of an ad libitum diet supplement with 56 g of walnuts daily for a period of 8 weeks by T2DM patients significantly improved flow-mediated dilation (FMD), (p=0.019).[31] This a measure of the endothelial function. This was found to be significantly high when compared with patients that consumed nut-free diets ad libitum. Consumption of walnuts is therefore important in the clinical management of patients with diabetes mellitus with a view to reducing the level of glycated haemoglobin in the blood of the patients.

In a study performed by Tapsell et al the effects of polyunsaturated fatty acids in walnut were evaluated on metabolic parameters of diabetic methods patients.[32] They reported that dietary fat change in diabetic patients (increase in PUFA/saturated fatty acid ratio). This can effectively result in decreased levels of fasting blood glucose and glycated haemoglobin (HBAIc) and serum insulin levels after six months of the walnuts intervention.

Consumption of walnut has also been shown to have desirable effects on fasting blood glucose, HBA1c and adiponectin in adult patients with diabetes mellitus. The increased adiponectin levels among subjects with Mets might be an evidence of a potential antidiabetic effect of walnuts.[32,33] There is significant reduction in fasting blood glucose (p=0.000), HBA1C (p=0.021) and an increase in adiponectin (p=0.019) in another study by Hwang et al (Wang et al). The beneficial effect of walnut consumption on glycaemic control could be attributable partly to the substitution of carbohydrates with unsaturated fatty acids.[34]

After 12 weeks, levels of fasting blood glucose, 2-hour post prandial glucose (2PPG), and HbA1c decreased significantly compared to the control group.[23,34]

EFFECTS OF WALNUTS CONSUMPTION ON INFLAMMATION AND ENDOTHELIAL FUNCTIONS

Studies have shown that the integration of nuts into a healthy diet in diabetic Chinese patients as compared to the control diet can decrease the level of the inflammatory markers (Interlukein 6 (IL-6), Tumour necrosis factor α (TNF-α) and C-reactive protein (CRP). Both IL-6 and TNF- α are mediators of CRP synthesis in the lower and increased level of IL-6 was associated with insulin resistance, hyperglycemia and T2 diabetes mellitus (T2DM).[35,36]

A recent study done by Borkowski et al showed that walnuts can reduce the TNF- α-mediated production of pro-inflammatory cytokines.[37] Regular walnut intake among adults with Mets may have desirable effects, not only on fasting blood glucose and HbAic but also on circulating adiponectin. Adiponectin is an adipocyte-derived anti-atherogenic and anti-diabetic hormone and is abundant in human plasma.[34,38] Clinical studies implicated hypoadinopectinaemia in the pathogenesis of T2DM, coronary artery disease and hypertension.[38]

A low level of adiponectin which also have an anti-inflammatory property as well as antiatherogenic property is therefore perceived as a risk factor for cardiovascular events. Since the level of adiponectin is increased by intake of walnuts, by patients with Mets, it is therefore justifiable to propose that walnuts have a positive effect in relieving inflammation in the system.[39] Adiponectin is an adipocyte-secreted insulin sensitizer that improves insulin sensitivity and decreases inflammation.[39] Endothelial dysfunction, characterized by a decreased bioavailability of nitric oxide (NO), an endogenous vasodilator synthesized from the amino acid, L-arginine, is linked with a greater risk of cardiovascular events.[40]

Since tree nuts are a rich source of L-arginine, their intake might potentially improve endothelial dysfunction.[41] The trial of Ma et al on T2DM patients revealed that consumption of an ad libitum diet supplemented with 56 g of walnuts daily for a period of 8 weeks significantly improved FMD, a measure of endothelial function as compared to a nut-free ad libitum diet.[42] The team also found that in overweight adults with visceral adiposity, that daily ingestion of walnuts caused improvement in FMD significantly (p=0.019) as compared with the control diet, suggesting the potential for overall cardiac risk reduction. Walnuts and almond diets besides positively affecting FMD, can also decrease soluble vascular cell adhesion molecules.[30,42]

LABORATORY DETERMINATION OF NUTRIENTS IN WALNUTS AND OTHER PARAMETERS

Anthropometric and body composition measurements

Waist and hip circumference measurements were obtained by using a measuring tape (SECA-201; SECA Hamburg, Germany). Body weight was measured and rounded to the nearest 0.1kg and height was obtained by using a stadiometer BSM 330; Biospace Seoul, Korea) and rounded to the nearest 0.1cm blood pressure was measured on the right arm using an upload blood pressure monitor (BPB 103205; Biospace, Seoul Korea). BMI was calculated as weight (kg) divided by height in meters (m) squared.[24]

Blood sampling and determination of general serum biochemical variables

Blood samples were collected in the fasting state and samples were immediately centrifuged 3000r/min at 4ºC. Serum TC and TG levels were measured using an enzymatic-colorimetic method. HDL-C and LDL-C levels were determined via a homogenous enzymatic colorimetry method and the highly sensitive C-reactive protein (hs-CRP) level was measured by applying a particle-enhanced immuno-turbimetric method using a cobas 8000 c702 chemistry analyzer (Roche Diagnostics, Mannheim, Germany).

FBG was measured using a glucocard X-meter (Arkray, Kyoto, Japan). Serum insulin was measured with the commercially available ultrasensitive insulin ELISA Kit (80-INSHU-EO1.1, E 10.1; ALPCO, SALEM, NH, USA) using an Epoch microplate spectrophotometer (BIOTEK, Winooski, VT, USA). Serum leptin and adiponectin levels were measured using quantikine human leptin ELISA Kit (DL Poo, Ref D Systems Minneapolis, MN0 USA) and the quantikine human total adiponectin ELISA Kit (ARP 300; Rcf D systems, Minneapolis, MN, USA) respectively.

Haemoglobin AIc (HbA1c) separation and quantification were performed using a high-performance liquid chromatography analyzer (Tosho HLC-723 G8; sysmex, Kobe, Japan). Serum apoliproprotein B (apo B) were measured by Turbichmetric immunoassay using a HITACHI 7600 chemistry analyzer (HIFACHI, Tokyo, JAPAN). Endothelial activation markers sVCAM-1 and endothelin-1 were determined using commercially available ELISA kets (human sVCAM-1/CD106 quantikine ELISA kit ovcoo; endotholin-1 quantikine ELISA kit DETIOO; Rcf D Systems, Minneapolis, MN USA).

Determination of anti-oxidant activity of walnuts.[24,42] Sample for measurement of antioxidant activity while include: ORAC, ORAC with perchloric acid (Pea) precipitation, FRAP, and total antioxidant performance (TAP), lipid peroxidation (MDA), biomarkers of antioxidant status (total thiolsphenols, carotenoids and gluthathione peroxidase (GPX).[6,24]

ANTIOXIDANT ACTIVITY MARKERS

The ORAC values of whole plasma and perchloric acid treated protein free plasma were determined according to the method of Hwang et al.[24] The FRAP value of whole plasma was determined with the spectrophotometric method of Benzie with data expressed as µmol TE/L serum TAP determined by method developed by Aldini et al.[43]

THE ANTIOXIDANT CAPACITY OF WALNUTS

Result of studies on the antioxidant effects of nut-enriched diet have been mixed. A number of short-term randomized clinical trials showed reductions in lipid peroxidation by measuring. MDA production associated with nut-containing diets.[10,44] Some other studies showed no change in any of the measures of antioxidant status on lipid peroxidation.[10] However, studies that tested the postprandial effect of nuts consumed in the context of a meal usually showed antioxidant effects.[17] In addition, walnut meals were shown to acutely improve endothelia function and reduce the postprandial inflammatory response in mononuclear cells in human.[44] A study by Haddad et al showed a modest increase in hydrophilic and lipophilic ORAc (7.5% and 8.5%) respectively following walnut consumption reflecting antioxidant activity in both aqueous and lipid plasma fractions.[44]

When tested *in vitro*, walnut extracts show relatively high FRAP activity (highest among other nuts). However, Haddad et al did not observe a consistent effect of walnut meal on post prandial plasma FRAP concentration. On the contrary, a recent study reported increased postprandial FRAP following test meals of walnut oil and walnut skins in healthy over weight and obese adults.[17,45] Other studies did not find any chronic effects of walnut consumption (21 and 42 g/day) on antioxidant activity (e,g Malondialdehyde (MDA), ferric reducing antioxidant power (FRAP) and total thiols). Ros et al found that oxidized LDL and MDA remained unchanged for both the Mediterranean diet with or without walnuts. Similarly, Cortes et al reported an in vitro resistance of LDL against oxidation was unaffected by acute walnut consumption. Although walnuts contain numerous phenolic and other antioxidant constituents, the null effects on antioxidant measures in the study by Haddad et al may be attributable to a relatively small increase in their plasma concentration against an already sufficient antioxidant defense status in the moderately healthy although over weight/obese cohorts.[3,44,45]

In another study by Mckay et al following 6 weeks of daily walnut consumption, the changes in plasma total thiols and other antioxidant biomarkers, including total phenols and glutathione peroxidase (GPX) were not significant.[46] In addition, there was no improvements in other measures assessed within one hour of consumption of walnuts (total phenols, Oxygen radical absorbance capacity (ORAC), or Ferric reducing antioxidant power (FRAP)) except for a 3.1% increase in total phenols within 1 hours of walnut consumption during the baseline visit for the 42 g of dose of walnuts (p=0.063 compared with fasting plasma levels).

CONCLUSION

It has been demonstrated that consumption of walnuts causes significant reduction in the levels of body lipids (TC, LDL, VLDL and TG). Other established benefits of walnuts consumption include, marked improvement in anthropometry and blood pressure measurements, reduction in blood sugar and HbA1c levels in patients with T2DM, reduction in inflammatory conditions and improvement in endothelial functions. Walnuts have also been shown to possess some degree of antioxidant properties. Bioactive compounds present in walnuts, including micronutrients, fibers, and phytochemicals may also contribute to the cardioprotective effect of walnuts by reducing inflammation, improving vascular reactivity and lowering oxidative stress. All told, walnuts have an overall positive effect in management of Mets and should be integrated into the routine diets of patients with condition.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Ofor CC, Ohanme EO, Nwakelu BN, Ofonakara U, Aja DO, Shu EN, et al. Pharmacological effect of walnuts consumption on metabolic syndrome: a current view. Int J Basic Clin Pharmacol 2024;13:536-42.