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Nuts, hypertension and endothelial function

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Abstract *Background and aims:* High blood pressure (BP) is considered a major risk factor for cardiovascular disease. Among lifestyle factors, diet plays a key role in the prevention and control of high BP. Therefore, it is important to elucidate which dietary components can exert beneficial effects on BP through modulation of endothelial function (EF) or by other mechanisms. In this paper we review the role of nutrients, foods, particularly nuts, and dietary patterns on BP control.
Data synthesis: Because nuts are low in sodium and contain significant amounts of mono- and polyunsaturated fatty acids, fiber, minerals such as magnesium, potassium and calcium, and antioxidants, they have been suggested as potentially protective foods against hypertension. Limited evidence from prospective studies and clinical trials suggests that nut consumption has a beneficial effect on both BP and EF. However, BP changes were a secondary outcome in nut feeding trials and no study used ambulatory BP monitoring as the standard for BP measurements.
Conclusions: Further clinical trials, ideally using ambulatory BP monitoring, are needed to establish the potential protective effect of nut consumption on hypertension and vascular reactivity.

Introduction

High BP is a major risk factor for cardiovascular disease [1] and is responsible for most preventable deaths in the world [2]. It affects approximately 25% of the adult population worldwide, and its prevalence is predicted to increase by 29% in the year 2025, when a total of 1.56 billion people will be affected [3]. Both genetic and environmental factors, including age, diet, physical activity, psychosocial factors, and interaction between them have been

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associated with the development of hypertension. Among the environmental factors, diet has a predominant role in BP homeostasis [4]. Some dietary changes have the potential to decrease BP in nonhypertensive, prehypertensive and hypertensive subjects, with a subsequent reduction in the risk of complications from hypertension. The impact of BP reduction, even if its magnitude is small, could be remarkable at the population level. For example, it has been estimated that a decrease in 3 mm Hg in systolic BP (SBP) is associated with an 8% reduction in stroke mortality and a 5% reduction in coronary heart disease mortality [5]. Therefore, it is important to elucidate which dietary factors can modulate EF and have a beneficial effect on BP.

Dietary factors modulating blood pressure

Several specific nutrients and dietary patterns have been proposed to exert an effect on BP. They can be classified according to the response of BP and the level of scientific evidence into two groups: a) dietary factors that effectively lower BP, and b) dietary factors with limited or uncertain effect on BP (Fig. 1).

Dietary factors that effectively lower blood pressure

Lowering dietary salt intake is considered to be important for the prevention of hypertension [6]. In the INTERSALT epidemiologic study, a 5.8 g decrease in salt intake was associated with a 3.1 mm Hg decrease in SBP [7]. More recent epidemiological studies have also found that salt intake is an important determinant of BP at the population level [8—10]. Moreover, results from a meta-analysis of randomized trials showed that a median reduction in urinary sodium excretion of 1.8 g/day (78 mmol/day) was associated with reduced SBP and diastolic BP (DBP) by 2.0 and 1.0 mm Hg in nonhypertensive subjects and by 5.0 and 2.7 mm Hg in those with hypertension [11].

The intake of omega-3 fatty acids (from fish oil supplements or fish consumption) has also been related to improvements in BP [12—16]. Doses of 3—4 g/day of omega-3 fatty acids reduced SBP and DBP by approximately 2 mm Hg in normotensive subjects and an average of 4.0 and 2.5 mm Hg, respectively, in hypertensive patients [14,17]. As high doses of omega-3 fatty acids are required to reduce BP, the usual recommendation for subjects at risk is to eat fatty fish once or twice per week [4].

Considerable scientific evidence supports a positive association between excessive alcohol intake and an increased risk of hypertension [18—20]. A meta-analysis of randomized clinical trials among subjects initially consuming 3—6 drinks per day found that reductions in alcohol intake significantly decreased both SBP and DBP by 3.3 and 2.0 mm Hg, respectively [21]. In this study, the estimated decrease in BP was similar both in non-hypertensive and hypertensive individuals. Importantly, a dose—response relationship was observed between the decrease in the mean percentage of alcohol consumption and mean BP reduction [21]. However, moderation in alcohol consumption ($\leq$2 drinks per day in men and $\leq$1 drinks per day in women) among those who usually drink is felt to help lower BP [4,22,23].

Some dietary patterns such as the vegetarian diet or the DASH diet have been found to be effective in reducing BP. Vegetarians have markedly lower BP levels than do nonvegetarians [24,25]. Several components of the vegetarian diet (high vegetable and fiber intake, low or moderate consumption of alcohol, and avoiding meat and processed foods), and some non-dietary factors (increased physical activity and lower body mass index) present in vegetarians may be responsible for this observation. The DASH diet is also a dietary pattern that is characterized by a high intake of fruit, vegetables and low-fat dairy products, including whole grains, poultry, fish and nuts, and low intake of fats, red meat, sweets and sugar-containing beverages. Compared to a control diet, the DASH diet significantly lowered mean SBP by 5.5 mm Hg and DBP by 3.0 mm Hg [26].

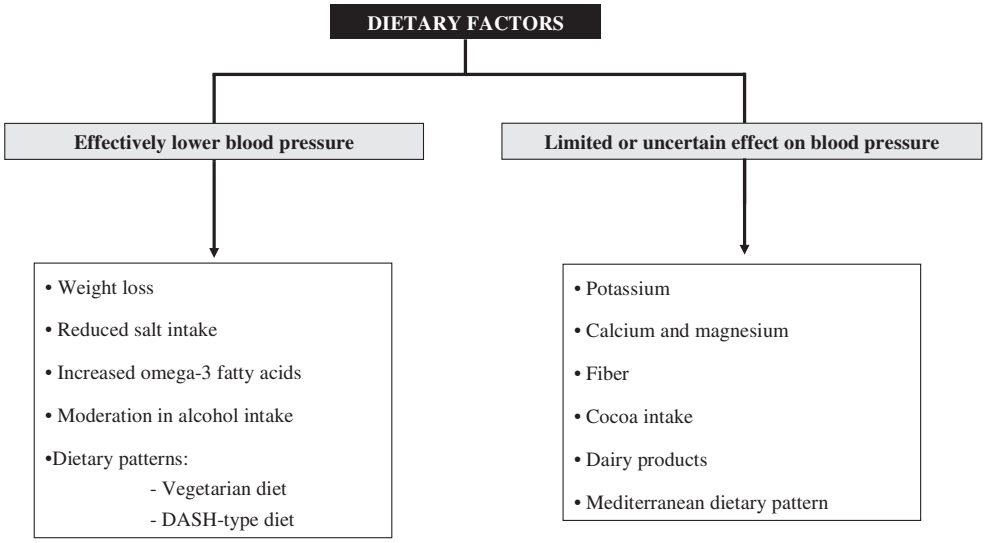

Figure 1 Dietary factors that can modulate blood pressure.

Finally, weight loss is one of the most important factors directly associated with a decrease in BP. Most of the clinical trials have documented that losing weight through dietary energy restriction and/or increased physical activity in obese or overweight subjects is an effective way to lower BP, even if the desirable body weight is not attained [4]. A meta-analysis of randomized controlled trials showed reductions in SBP and DBP of 1 mm Hg for each kilogram of weight lost [27], while a systematic review of long-term studies indicated that a 10 kg weight loss might decrease SBP and DBP by 6.0 and 4.6 mm Hg, respectively [28]. The estimated decrease in BP was similar in nonhypertensive and hypertensive subjects, but was greater in those who lost more weight. In summary, available evidence indicates that weight loss is an effective measure in the prevention and treatment of BP.

Dietary factors with limited or uncertain effect on blood pressure

Evidence derived from several observational epidemiological studies, more than 30 clinical trials as well as a meta-analysis of these trials suggest that high potassium intake is associated with a reduced BP in both hypertensive and nonhypertensive subjects [29–31]. Because a high potassium intake can be achieved through diet rather than pills and because potassium derived from foods is also accompanied by a variety of other nutrients, the preferred strategy to increase potassium intake is to consume foods that are rich in potassium, such as fruits and vegetables, rather than using supplements. According to a systematic review [17], there is no clear evidence demonstrating that potassium supplementation reduces BP. Therefore, in a healthy population with normal kidney function, it is recommended to consume foods rich in potassium rather than potassium from pills or supplements.

Observational studies have suggested weak inverse associations (mean reductions $<$1.5 mm Hg) between BP and calcium intake from milk and dairy products, meat, fish, eggs, cereals, legumes and nuts [4]. In relation to calcium supplementation in hypertensive patients, two meta-analyses showed contradictory results, as one showed no effect on BP [17] while another showed significant mean reductions of 2 mm Hg in SBP and 1 mm Hg in DBP, with a greater effect in subjects with habitual low calcium intake [32]. Likewise, the evidence implicating magnesium as a major determinant of BP is inconsistent from both observational studies evaluating its usual consumption [4] and clinical trials using supplements [17]. Therefore, the intake of non-fat dairy products or vegetables rich in these minerals can be recommended to hypertensive patients, but available data are insufficient to recommend supplemental calcium or magnesium in order to lower BP.

Two recent meta-analyses suggest a modest independent BP lowering effect of an increase in dietary fiber intake or the consumption of fiber supplements, especially in hypertensive subjects. Streppel et al. (2005) [33] reported that the effect of fiber intake averaging 11.5 g/day was modest, with mean decreases in SBP of 1.0 mm Hg and DBP of 1.3 mm Hg (reductions were greater in hypertensive and older subjects). Similarly, a meta-analysis of 25 clinical trials indicated that dietary fiber was associated with non-significant changes in SBP ($-$1.2 mm Hg) and significant reductions in DBP ($-$1.7 mm Hg), although significant reductions in SBP ($-$6.0 mm Hg) and DBP ($-$4.2 mm Hg) occurred in hypertensive subjects or in subjects treated for $\geq$8 weeks [34].

Data from experimental and clinical studies suggest that the consumption of flavanol-rich cocoa and chocolate products could reduce cardiovascular risk by improving EF and decreasing BP. A 2007 meta-analysis by Taubert et al. [35] including 5 trials concluded that flavonol-rich cocoa consumption significantly decreased SBP by 4.7 mm Hg and DBP by 2.8 mm Hg [35], while a 2010 meta-analysis by Desh et al. [36] including 10 trials reported significant decreases in SBP by 4.5 mm Hg and DBP by 2.5 mm Hg from intake of cocoa-rich products in hypertensive and normotensive subjects [36]. A more recent meta-analysis including 15 trial arms showed a small but significant BP-reducing effect of flavanol-rich cocoa products (SBP by 3.2 mm Hg and DBP by 2.0 mm Hg [37].

Several epidemiological studies have suggested that the intake of milk and dairy products, particularly non-fat dairy products, is inversely associated with the risk of hypertension. In some experimental and clinical studies, a decrease in BP has also been observed after the administration of fermented milk rich in bioactive peptides, which has been attributed to the inhibition of the angiotensin converting enzyme, although there may be other mechanisms implicated in this effect [38]. While further studies are needed to confirm the antihypertensive effect of milk proteins, identify the responsible compounds and elucidate its mechanism of action, low-fat dairy products are an integral part of the diet recommended for hypertensive subjects and for general health.

The traditional Mediterranean diet shares with the DASH diet a high intake of vegetables and a low intake of meat and processed foods, but differs significantly by its high content in vegetable fat (especially in the form of olive oil and nuts). In the EPIC cohort, the Mediterranean diet pattern and total olive oil intake were inversely associated with both SBP and DBP [39]. Recently, in the Seguimiento Universidad de Navarra (SUN) study cohort, adherence to the Mediterranean diet was not significantly associated with incident hypertension in young university graduates after a median follow-up of 4.2 years, but after 6 years it related to modest decreases in both SBP and DBP [40].

Components of nuts that may modulate blood pressure

Nuts are complex food matrices containing diverse macro and micronutrients and other chemical constituents that may modulate BP. Nuts, especially raw nuts, are potentially protective foods against high BP because they are low in sodium and contain significant amounts of mono- and polyunsaturated fatty acids, minerals such as magnesium, potassium and calcium, dietary fiber, and antioxidants, and all these components might interact to beneficially influence BP [41,42].

For example, unsaturated fatty acids, both PUFA and MUFA, are able to reduce serum levels of the vasoconstrictor

thromboxane 2, which might influence BP regulation [41]. Magnesium intake stimulates the production of nitrous oxide and vasodilator prostacyclins, and blocks calcium channels inducing vasodilatation [43]. Potassium intake may decrease BP by reducing extracellular fluid volume, modulating the activity of the renin-angiotensin system, reducing angiotensin effects, relaxing vascular smooth muscle, and reducing peripheral vascular resistance [44]. Calcium intake inhibits parathyroid hormone [45], which induces hypertension by increasing intracellular calcium levels. Finally, dietary fiber may decrease BP by inducing satiety, decreasing energy intake, contributing to a lower body weight, and ameliorating EF [46].

Because there are some nutritional composition differences among the various edible nuts, the effects of their consumption on BP and EF may differ. For example, nearly one half of the total fat content of nuts is made up of unsaturated fat, MUFA in most nuts; similar proportions of MUFA and PUFA, mostly linoleic acid, in Brazil nuts; a predominance of PUFA over MUFA in pine nuts; and mostly PUFA, both linoleic and α-linolenic acids, in walnuts [47]. Almonds, pistachios, hazelnuts and pecans are the nuts with highest fiber content (especially insoluble fiber) [48], whereas peanuts and hazelnuts are the richest in folic acid.

Nuts also contain different types of antioxidants. For instance, almonds contain flavonoids such as catechins, flavonols, and flavonones in their aglycone and glycoside forms [49], while pistachios contain flavonoids and have the highest concentrations of resveratrol of all nuts [50]. Walnuts contain a wide range of polyphenols and tocopherols, and cashews have alkyl phenols as the principal antioxidant. Almonds are a good source of α-tocopherol [51], while walnuts contain large amounts of its isomer γ-tocopherol, which is recognized for its anti-atherogenic properties [52]. On the other hand, Brazil nuts are an excellent source of selenium [51].

Epidemiological studies on nuts and blood pressure

There is scarce information from epidemiological studies in relation to the ability of nut consumption to prevent hypertension. Only two prospective studies have evaluated the association between nut consumption and incident hypertension [53,54]. In a prospective cohort of 15 966 participants from the Physicians' Health Study I, Djoussé et al. (2009) [53] reported a lower incidence of hypertension in usual consumers of nuts compared to non consumers. However, this association was mainly observed among lean subjects (BMI < 25 kg/m^2) and not in overweight or obese individuals. These results must be taken with caution, however, because salt intake and changes in weight, two major factors that influence the risk of hypertension, were not accounted for this study. The second study, which involved 9919 Spanish university graduates followed-up for a median of 4.3 years in the SUN cohort [54], found no association between nut consumption and incidence of hypertension after adjusting for several confounders, including exposure to salt and weight changes during follow-up. The hazard ratio for the highest *versus* lowest nut consumption category was 0.77 (CI, 0.46—1.30) in this relatively young sample of well educated adults at little baseline risk for hypertension, thus a larger sample and longer duration of follow-up might have provided a better level of evidence. In summary, limited epidemiologic data provide only circumstantial evidence for a protective effect of nut consumption on the development of hypertension.

Clinical trials of nuts reporting changes in blood pressure

A total of 19 clinical trials, with different design, length and sample size, have reported the chronic [55—71] and acute effects [72,73] of nut consumption on BP, always as a secondary outcome (Tables 1 and 2).

Nuts were administered in different types, doses, and presentations. The nuts evaluated were walnuts [55,57,60,63,66,67,71,72], pistachios [56,65,68], almonds [58,59,73], cashews [63], or a mixture of walnuts, almonds and hazelnuts [62,64,69,74]. The total doses of nuts used varied between 30 and 108 g/day. In most studies, raw nuts were administered in the context of a meal or diet, but in some studies the nuts were dry roasted [56,61], raw or cooked [55], or in the form of oil or flour [73]. Comparisons were made with control diets or meals in which the subjects were asked to avoid nuts, nut butter, or nut oil of any kind. One study compared the effect of different doses of nuts [58].

The majority of the clinical trials showed that nut consumption was not associated with BP changes [55—58,60,61,65—68,70,72,73]. However, a reduction in SBP and/or DBP after the consumption of the diet enriched with nuts compared to the control diet was observed in four studies [59,62,64,69], whereas only in one, an increase in both SBP and DBP was reported [71].

The assignment for 24 weeks on a hypo-caloric diet enriched with 84 g/day of almonds (39% of energy from fat) was associated with an 11% reduction in SBP compared to a low calorie diet enriched with complex carbohydrates [59]. Moreover, results from the Prevención con Dieta Mediterránea (PREDIMED) pilot trial showed that, compared to a low-fat diet, individuals randomized to a Mediterranean diet supplemented with nuts or virgin olive oil had a 7.1 and 5.9 mm Hg reduction in SBP and a 2.6 and 1.6 mm Hg reduction in DBP, respectively, after 3 months of intervention in a total of 772 participants at high cardiovascular risk [62]. In a PREDIMED substudy conducted in 372 subjects, a decrease in SBP and DBP was observed in participants randomized to both Mediterranean diets compared to those randomized to the low-fat diet group. Because the Mediterranean diet supplemented with nuts was compared to either a Mediterranean diet supplemented with olive oil or a low-fat diet, it is difficult to estimate the individual contribution of nuts or olive oil to BP reduction in the PREDIMED trial.

As discussed, only one study reported an increase in both SBP and DBP after nut consumption. Ma et al. [71] showed in 21 subjects with type 2 diabetes that an *ad libitum* diet without walnuts significantly lowered BP compared with a walnut-enriched diet (SBP -4.9 ± 11.7 *versus* 4.0 ± 9.2 mm Hg and DBP -2.5 ± 6.4 *versus*

Table 1 Clinical trials evaluating the chronic effect of nut consumption on blood pressure.

First author (year)	N (M/F) Study subjects	Study design	Duration of intervention (weeks)	Control groups	Intervention groups	Dose of nuts (g/day)	Type of nut	Blood pressure change
Sabaté 1993 [55]	18 (18/0) Healthy	Crossover	4 (each period)	Low-fat isocaloric step I diet	Low-fat isocaloric step I diet + walnut supplement	84	Raw or cooked	(NS)
Edwards 1999 [56]	10 (4/6) HC	Crossover	3 (each period)	Regular isocaloric diet	Regular isocaloric diet + pistachio supplement	66.7	Roasted, unsalted	(NS)
Iwamoto 2002 [57]	40 (20/20) Healthy	Crossover	4 (each period)	Japanese diet	Japanese diet + walnuts	44–58	Raw	(NS)
Jenkins 2002 [58]	27 (15/12) HC	Crossover	4 (each period)	Low-fat step II diet	a) Low-fat diet step II + high almonds b) Low-fat diet step II + low almonds	a) 73 b) 37	Raw	(NS) in high almond vs control group (NS) in low almond vs control group
Wien 2003 [59]	65 (28/37) Overweight and obese	Parallel	24	Hypo-caloric isocaloric diet + complex CHO-enriched formula	Hypo-caloric isocaloric diet + almond supplement	84	Raw	Decreased SBP ($P < 0.02$) in almond vs control group
Ros 2004 [60]	20 (8/12) HC	Crossover	4 (each period)	Isocaloric MedDiet	Isocaloric MedDiet + walnut supplement	40–65	Raw	(NS)
Chisholm 2005 [61]	28 (5/23) Healthy	Crossover	6 (each period)	Low-fat diet + canola oil cereal-enriched supplement	Low-fat diet + nut supplement	30	Raw or roasted	(NS)
Estruch 2006 [62]	772 (339/433) At high CHD risk	Parallel	12	*Ad libitum* low-fat diet	a) *Ad libitum* MedDiet + mixed nut supplement (walnuts + almonds + hazelnuts) b) *Ad libitum* MedDiet + VOO supplement	30	Raw	Decreased SBP ($P \leq 0.0001$) and DBP ($P = 0.001$) in MedDiet + nuts vs control group
Schutte 2006 [63]	62 (28/34) MetS	Parallel	8	South-African isocaloric diet	South-African isocaloric diet + a) walnut supplement b) cashew supplement	63–108	Unsalted	(NS) in walnut vs control group (NS) in cashew vs control group
Fitó 2007 [64]	372 (210/162) At high CHD risk	Parallel	12	*Ad libitum* low-fat diet	*a) Ad libitum* MedDiet + mixed nut supplement (walnuts + almonds + hazelnuts) b) *Ad libitum* MedDiet + VOO supplement	30	Raw	Decreased SBP ($P = 0.008$) and DBP ($P = 0.03$) in MedDiet + nuts or VOO vs control group
Sheridan 2007 [65]	15 (11/4) HC	Crossover	4 (each period)	Regular diet	Regular diet + pistachio supplement	57–85	Raw	(NS)

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Table 1 (*continued*)

First author (year)	N (M/F) Study subjects	Study design	Duration of intervention (weeks)	Control groups	Intervention groups	Dose of nuts (g/day)	Type of nut	Blood pressure change
Olmedilla-Alonso 2008 [66]	22 (12/10) At high CHD risk	Crossover	5 (each period)	Regular diet	Regular diet + walnut paste enriched meat and frankfurter sausages	19.4	Raw in form of powder	(NS)
Spaccarotella 2008 [67]	21 (21/0) Healthy	Crossover	8 (each period)	American isocaloric diet	American isocaloric diet + walnut supplement	75	Raw	(NS)
Sari 2009 [68]	32 (32/0) Healthy	Crossover	4 (each period)	Isocaloric MedDiet	Isocaloric MedDiet + pistachio supplement	60—100	Roasted, unsalted	(NS)
Llorente-Cortes 2010 [69]	49 (23/26) At high CHD risk	Parallel	12	*Ad libitum* low-fat diet	a) *Ad libitum* MedDiet + mixed nut supplement (walnut + almond + hazelnut) b) *Ad libitum* MedDiet + VOO supplement	30	Raw	Decreased SBP ($P \leq 0.01$) and DBP (NS) in MedDiet + nuts vs control group
López-Uriarte 2010 [70]	50 (28/22) MetS	Parallel	12	*Ad libitum* low-fat diet	*Ad libitum* low-fat diet + mixed nut supplement (walnuts + almonds + hazelnuts)	30	Raw	(NS)
Ma 2010 [71]	21 (9/12) Type 2 diabetes	Crossover	8 (each period)	*Ad libitum* regular diet	*Ad libitum* regular diet + walnut supplement	56	Raw	Increased SBP ($P = 0.01$) and DBP ($P = 0.02$) in walnut vs control group

Abbreviations: N, number; M, male; F, female; NS, non-significant; HC, hypercholesterolemic; CHO, carbohydrates; SBP, systolic blood pressure; MedDiet, Mediterranean diet; CHD, coronary heart diseases; VOO, virgin olive oil; DBP, diastolic blood pressure; MetS, metabolic syndrome.

Table 2 Clinical trials evaluating the acute effect of nut consumption on blood pressure.

First author (year)	N (M/F) Type of individuals	Design of study	Control group	Intervention groups	Dose of nuts (g/day)	Type of nut	Blood pressure
Cortés 2006 [72]	24(20/4) Healthy and HC	Crossover	High-fat olive oil-enriched meal	High-fat walnut-enriched meal	40	Raw	(NS)
Berry 2008 [73]	20 (20/0) Healthy	Crossover	Muffins with 50 g of sunflower oil blend	a) Muffins with almond macroparticles	a) 96.5	Baked	(NS) in almond vs control group
				b) Muffins with almond oil + defatted almond flour	b) 50 + 47		(NS) in almond oil + almond flour vs control group

Abbreviations: N, number; M, male; F, female; HC, hypercholesterolemic; NS, non-significant.

1.6 ± 4.6 mm Hg) but they could not provide a logical explanation for this response.

In summary, few clinical trials have evaluated the effect of nut consumption on BP. Most of them have found either a beneficial effect or no effect, but it must be noted that ambulatory BP monitoring, the best standard for BP measurements, was used in none of these studies. Further clinical trials are warranted to clarify the effect of nut consumption on BP, preferentially using ambulatory BP monitoring data to firmly support or discount a beneficial effect of nuts on BP.

Dietary factors modulating endothelial function

Endothelial dysfunction is one of the mechanisms implicated in the etiology and development of atherosclerosis. The endothelium maintains the circulation and blood flow, regulates vascular tone, and modulates leukocyte and platelet adhesion and the transmigration of leukocytes [75]. It is well known that endothelial dysfunction is present in patients with cardiovascular risk factors, such as smoking, dyslipidemia, diabetes or hypertension [76]. If EF usually has been considered an etiologic factor of hypertension, it is unknown whether endothelial dysfunction is a cause or consequence of hypertension. Nonetheless, it is clear that endothelial dysfunction, which is reversible upon BP lowering, predicts future cardiovascular events in hypertensive patients [77].

Scientific evidence supports the hypothesis that dietary factors are important in modulating oxidation, inflammation and, consequently, EF [78]. Consumption of foods containing omega-3 fatty acids, folic acid, antioxidant vitamins C and E, polyphenolic compounds, and L-arginine could exert beneficial effects on vascular reactivity, either by decreasing endothelial activation or by improving flow mediated vasodilatation (FMD) in either healthy individuals or patients at cardiovascular risk [79]. In the last years, particular attention has been focused on the effects of dietary patterns on EF. There is evidence that the Mediterranean diet, characterized by high consumption of vegetables, fish, olive oil and moderate wine consumption, may have a beneficial effect on EF [80]. Conversely, diets rich in saturated and *trans* fatty acids or with a high glycemic load are associated with impaired EF [81]. Thus, as expected, healthy or unhealthy diets have similar positive or negative effects on cardiovascular risk and EF.

Effect of nuts on endothelial function

As discussed, bioactive compounds contained in nuts (alpha-linolenic acid in walnuts and L-arginine, selenium, antioxidant vitamins, folic acid, polyphenolic compounds, and phytosterols in all nuts) could contribute to the demonstrated beneficial effects of nut consumption on cardiovascular health, including improved EF.

Endothelial dysfunction has been assessed most frequently by the ultrasound technique, which consists in the measurement of the vasodilator response of conduit vessels like the brachial artery to the increased flow

Table 3 Clinical trials evaluating the chronic effect of nut consumption on endothelial function biomarkers.

First author (year)	N (M/F) Type of individuals	Study design	Length of intervention (weeks)	Control group	Intervention groups	Dose of nuts (g/day)	Type of nut	Endothelial function	
								FMD in brachial artery or EndoPAT index	Plasma VCAM-1 and ICAM-1
Ros 2004 [60]	20 (8/12) HC	Crossover	4 (each period)	Isocaloric MedDiet	Isocaloric MedDiet + walnut supplement	40–65	Raw	Increased ($P = 0.043$) in walnuts vs control group	Decreased VCAM-1 ($P = 0.045$) and ICAM-1 (NS) in walnuts vs control group
Kurlandsky 2006 [84]	47 (0/47) Healthy	Parallel	6	Low-fat diet	a) Low-fat diet + dark chocolate b) Low-fat diet + almonds c) Low-fat diet + dark chocolate and almonds	60	Raw	Not determined	In serum VCAM-1 and ICAM-1 (NS) in any treatment vs control group
Estruch 2006 [62]	772 (339/433) At high CHD risk	Parallel	12	*Ad libitum* low-fat diet	*a) Ad libitum* MedDiet + mixed nuts (walnuts + almonds + hazelnuts) b) *Ad libitum* MedDiet + VOO	30	Raw, unsalted	Not determined	Decreased VCAM-1 and ICAM-1 ($P < 0.05$) in MedDiet + nuts vs control group VCAM-1 and ICAM-1, (NS) in MedDiet + VOO vs MedDiet + nuts
Mercanligil 2007 [83]	15 (15/0) HC	Crossover	4 (each period)	Low fat, high-CHO diet	Low-fat, high-CHO diet + hazelnuts	40	Raw	(NS)	Not determined
Perez-Martinez 2007 [85]	16 (16/0) Healthy	Crossover	4 (each period)	Western diet	a) MedDiet, olive oil enriched b) High-CHO diet, walnuts-enriched	<30% Fatty acids which 12% PUFA from walnuts	Non reported	Not determined	Decreased VCAM-1 ($P < 0.05$) and ICAM-1 (NS) in walnut vs control group VCAM-1 and ICAM-1, (NS) in walnut vs olive oil group
Mena 2009 [86]	106 (64/46) At high CHD risk	Parallel	12	*Ad libitum* low-fat diet	*a) Ad libitum* MedDiet + mixed nuts (walnuts + almonds + hazelnuts) b) *Ad libitum* MedDiet + VOO	30	Raw, unsalted	Not determined	Decreased ICAM-1 ($P < 0.05$) and VCAM-1 (NS) in MedDiet + nuts vs control group VCAM-1 and ICAM-1, (NS) in MedDiet + VOO vs MedDiet + nuts

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Table 3 (*continued*)

First author (year)	N (M/F) Type of individuals	Study design	Length of intervention (weeks)	Control group	Intervention groups	Dose of nuts (g/day)	Type of nut	Endothelial function	
								FMD in brachial artery or EndoPAT index	Plasma VCAM-1 and ICAM-1
Sari 2009 [68]	32 (32/0) Healthy	Crossover	4 (each period)	Isocaloric MedDiet	Isocaloric MedDiet + pistachios	60—100	Roasted, unsalted	Increased ($P = 0.002$) in pistachios vs control group	Not determined
López-Uriarte 2010 [70]	50 (28/22) MetS	Parallel	12	*Ad libitum* low-fat diet	*Ad libitum* low-fat diet + mixed nuts (walnuts + almonds + hazelnuts)	30	Raw, unsalted	(NS)	VCAM-1 and ICAM-1 (NS)
Ma 2010 [71]	21 (9/12) Type 2 diabetes	Crossover	8 (each period)	*Ad libitum* regular diet	*Ad libitum* regular diet + walnut supplement	56	Raw	Increased ($P = 0.04$) in walnut vs control group	Not determined

Abbreviations: N, number; M, male; F, female; FMD, flow mediated dilatation; VCAM-1, vascular cell adhesion molecule-1; ICAM-1, inter-cellular adhesion molecule-1; HC, hypercholesterolemic; MedDiet, Mediterranean diet; NS, non-significant; CHD, coronary heart disease; VOO, virgin olive oil; CHO, carbohydrate; PUFA, polyunsaturated fatty acid; MetS, metabolic syndrome.

induced by reactive hyperemia (FMD) after ischemic occlusion of the forearm, and by measuring changes in circulating levels of soluble cellular adhesion molecules, such as inter-cellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and E-selectin, which are released from the activated endothelium and macrophages [75,79]. There is evidence that the expression of these biomarkers is increased in patients with cardiovascular disease [82].

Epidemiological studies

To our knowledge, only two epidemiological studies have investigated the association between nut consumption and circulating markers of endothelial dysfunction. In a cross-sectional study conducted by our group [83] in 772 subjects at high risk of coronary heart disease, we observed that levels of ICAM-1, but not those of VCAM-1, decreased across tertiles of nut consumption after adjustment for various confounders (P for trend: 0.003). Recently, Li and colleagues [84] reported no association of nut consumption with the same plasma biomarkers ICAM-1 and VCAM-1 in a cohort of 6309 diabetic women from the Nurses' Health Study.

Clinical studies of the effect of nut consumption on endothelium-dependent vasodilation

We have identified five clinical trials analyzing the effect of nut consumption on endothelium-dependent vasodilation by measuring the FMD in the brachial artery following ischemic occlusion of the forearm (Tables 3 and 4). Three studies were performed with walnuts [60,71,72], one with pistachios [68], and one with hazelnuts [85].

Three studies using walnut-enriched diets observed improved FMD in comparison with control diets without walnuts [60,71,72]. Using a crossover design, Ros et al. [60] studied the effect of walnut consumption for 4 weeks on vascular reactivity in hypercholesterolemic patients. The authors showed a significant improvement in FMD after the consumption of 40—65 g/day of a walnut supplement replacing other sources of MUFA in the context of a Mediterranean diet compared to the same isocaloric diet without walnuts. In a recent crossover study conducted in type 2 diabetic patients, a walnut-enriched *ad libitum* diet for 4 weeks also improved FMD compared to the same diet without walnuts [71]. Finally, using a crossover design in an acute study, the effect of walnut consumption on postprandial FMD was studied after 2 high-fat meal sequences (separated by 1 week) to which 25 g of olive oil or 40 g of walnuts were added. In this study, the authors showed that, in comparison to olive oil, walnuts reversed the impairment of FMD associated to a fatty meal [72].

A similar beneficial effect on vascular reactivity was demonstrated in a recent brachial artery FMD study using pistachios [68]. In a crossover design, Sari et al. (2009) compared the effect of two Mediterranean diets enriched or not with pistachios (60—100 g/day). After 4 weeks of intervention, FMD was significantly increased during the pistachio-enriched diet in comparison to the intervention period without pistachio supplementation. Finally,

Table 4 Clinical trials evaluating the acute effect of nut consumption on endothelial function biomarkers.

First author (year)	N (M/F) Type of individuals	Study design	Control group	Intervention groups	Dose of nuts (g/day)	Type of nut	Endothelial function	
							EDV in brachial artery or EdoPAT index	Plasma VCAM-1 and ICAM-1
Cortés 2006 [72]	24 (20/4) Healthy and HC	Crossover	High-fat olive oil enriched meal	High-fat walnut-enriched meal	40	Raw	Increased ($P = 0.006$) for HC in walnut vs control meal (NS) for healthy in walnuts vs control meal	(NS)
Berry 2008 [73]	20 (20/0) Healthy	Crossover	Muffins with 50 g of sunflower oil blend	a) Almonds with macroparticle size between 1.7 and 3.4 mm b) Crude filtered oil + almond flour	a) 96.5 b) 50 + 47	Raw	NS	Not determined

Abbreviations: N, number; M, male; F, female; EDV, endothelium-dependent vasodilatation; VCAM-1, vascular cell adhesion molecule-1; ICAM-1, inter-cellular adhesion molecule-1; HC, hypercholesterolemic; NS, non-significant.

a crossover study also evaluated the effect of hazelnuts on EF by the brachial artery ultrasound technique in hypercholesterolemic individuals. While the high-fat, MUFA-rich hazelnut diet was superior to a low-fat control diet in improving the plasma lipid profile, no effect of hazelnut consumption on FMD was apparent [85].

A chronic walnut study and a postprandial acute study after consuming a meal containing almonds did not show significant effects on EF measured by digital pulse amplitude tonometry [70,73]. However, it must be noted that this is a non-standard technique to measure EF with much less clinical trial experience than FMD of the brachial artery [75].

Interventional clinical studies assessing endothelial activation markers (adhesion molecules levels)

Seven clinical trials have assessed the effect of nut consumption on EF by determining peripheral changes in ICAM-1 and VCAM-1 concentrations [60,62,70,72,86–88]. All of these studies have found either a beneficial effect [60,62,87,88] or no effect [70,72,86] after nut consumption. A beneficial effect on VCAM-1 but not ICAM-1 levels was reported when fat in the form of olive oil was replaced by walnuts in the context of a Mediterranean diet [60]. Perez-Martínez et al. (2007), using a crossover design, showed an increase in plasma VCAM-1 concentrations after a Western diet compared to a Mediterranean diet enriched with virgin olive oil or a high-carbohydrate diet enriched with walnuts. However, no significant differences were found between the diet periods of olive oil or walnut enrichment [87]. Interestingly, the first results of the PREDIMED trial showed a significant decrease of plasma ICAM-1 and VCAM-1 concentrations in participants assigned to the two Mediterranean diet groups (supplemented with mixed nuts or virgin olive oil) compared to those assigned to the control, low-fat diet group [62].

Finally, two chronic studies using almonds [86] or walnuts [70] showed no effects of nut consumption on VCAM-1 and ICAM-1 levels compared to control diets. Moreover, no significant differences between groups were observed in a postprandial crossover study that assessed the effects of two high-fat meals, one enriched with olive oil and the other enriched with walnuts, on VCAM-1 and ICAM-1 plasma concentrations [72].

These data suggest that nut consumption may be associated with beneficial effect on vascular reactivity that are likely ascribable to the abundance of bioactive components in nuts, such as PUFA, L-arginine, and polyphenols, but further clinical trials are needed to confirm these effects and elucidate the responsible mechanisms. Furthermore, most studies assessing the effect of nut consumption on vascular reactivity and circulating markers of EF were performed in subjects with metabolic disorders (hypercholesterolemia, type 2 diabetes, metabolic syndrome, etc.), not in hypertensive subjects. The effect of nut consumption on the modulation of glucose and lipid response and systemic markers of oxidative stress have been extensively studied [41], but further studies are needed to examine the effects of nut consumption on BP and EF in hypertensive populations.

Conclusions

Nuts are low in sodium and contain significant amounts of mono- and polyunsaturated fatty acids, minerals such as magnesium, potassium, calcium, fiber, antioxidants and vitamins, and these compositional properties confer nuts as the potential to beneficially influence BP and vascular reactivity. The evidence summarized in this review indicates that nut consumption has no deleterious effect on these risk factors. Nevertheless, further clinical trials evaluating the effect of nut consumption on BP and EF as main outcomes measured with sound methodology are warranted.

Conflict of interest statement

J. Salas-Salvadó has received research funding from the International Nut and Dried Fruit Foundation, Reus, Spain. He is a nonpaid member of the Scientific Advisory Board of the International Nut and Dried Fruit Foundation. Emilio Ros has received research funding from the California Walnut Commission, Sacramento, CA and is a nonpaid member of its Scientific Advisory Committee. All other authors have no other conflicts of interest to declare.

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