Prevention and Management of Hypertension Without Drugs

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Abstract: Lifestyle modifications and non-drug therapies are a vast group of measures essential to the prevention and management of hypertension. International experts unanimously recommend some of them. However, not all measures are equally valuable or have the same evidence base. The first step in the management of patients at any age who have hypertension should be a reduction in salt intake, either alone or in combination with drug therapy, to which is often additive. A high potassium diet achieved with an increase in the consumption of fruit and vegetables is also recommended. Weight reduction, regular dynamic exercise and reduction of alcohol consumption should be included in management plans for the prevention and non-pharmacological treatment of hypertension. The qualitative composition of diet is also an important factor to consider for the prevention and management of hypertension. Beyond the benefits associated with specific nutrients, adherence to a dietary pattern based on the DASH (Dietary Approaches to Stop Hypertension) diet, as part of a comprehensive lifestyle intervention, is a suitable, cost-effective approach to prevent high blood pressure in normotensive individuals; moreover, if combined with reduced sodium intake, it may represent an alternative to drug therapy for individuals with mild hypertension willing to comply with long-term dietary changes.

Key Words: Hypertension, lifestyle modifications, weight loss, salt reduction, dynamic exercise, alcohol reduction.

INTRODUCTION

Cardiovascular diseases (CVD) are the leading cause of mortality, morbidity, and disability worldwide [1]. Although CVD are proportionally more relevant in developed countries, currently 70% of the total number of cardiovascular deaths occurs in developing countries. In fact, in the past several decades, the process of changes in patterns of diseases and their interaction with the socio-economic transformation, known as "epidemiological transition", has caused an increasing burden of CVD in many developing countries [2]. Thus, preventing CVD represents a formidable public health challenge not only in developed but also in developing countries. The strategy for the primary prevention of CVD resides in the detection and management of their main risk factors. Seventy-five percent of the global burden of CVD results from smoking, high blood cholesterol, and high blood pressure or their combination. Globally, cholesterol causes more than 4 million premature deaths a year, tobacco causes almost 5 million, and high blood pressure causes 7 millions [1]. In particular, hypertension affects approximately 1 billion individuals worldwide, thus representing the most common cardiovascular condition in both developed and developing countries as well as the number one attributable risk for death throughout the world [3]. Indeed, according to a recent World Health Organization report, about 62% of cerebrovascular disease and 49% of ischemic heart disease are attributable to sub-optimal blood pressure levels (systolic blood pressure > 115 mmHg) with little variation by gender [1]. The burden of hypertension-related diseases is likely to increase as the population ages, as suggested by data from the Framingham Hearth Study, whereby normotensive individuals at 55 years of age have a 90% lifetime risk to develop hypertension [4]. Overall, high blood pressure is the most important and independent risk factor for many CVD such as myocardial infarction, heart failure, stroke, and kidney disease. Accordingly, prevention and treatment of hypertension are increasingly regarded as a public health priority in both developed and developing countries.

Non-pharmacological interventions, also termed "lifestyle modifications", represent an essential approach to the primary prevention of high blood pressure and an important component of the treatment of hypertension. They represent as well cost-effective measures in the context of a multifaceted public health strategy to reducing blood pressure at a population level. The current lifestyle modifications that effectively lower blood pressure include: weight reduction if overweight or obese; reduction of dietary sodium intake; increased potassium intake; moderation of alcohol consumption; adoption of a dietary plan based on the DASH (Dietary Approaches to Stop Hypertension) diet, that is a diet rich in fruit, vegetables, and low-fat dairy products with a reduced content of saturated and total fat; and regular aerobic exercise [5]. These lifestyle modifications are effective in reducing blood pressure, increasing the efficacy of pharmacological therapies, and reducing the global risk of CVD.

In this review, we will examine the available literature and discuss the importance of these non-pharmacological measures, for which the current evidence consistently demonstrates their efficacy in lowering blood pressure. In particular, we will focus on findings from randomized clinical trials.

WEIGHT REDUCTION

Obesity is a worldwide public health priority [6]. For example, in the United States, the prevalence of obesity, defined as Body Mass Index (BMI) $\geq$ 30 kg/m^2, as well as of

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overweight (BMI ≥ 25 kg/m^2) has steadily increased since the second half of the last century as the population has aged. Data from the National Health and Nutrition Examination Survey (NHANES), obtained in 2003-2004, indicate that 32.2% of American adults (20 years or older) are obese whereas only one-third (33.7%) are in the range of normal weight (BMI < 25 kg/m^2) [7]. The obesity trends in the United Kingdom have been similar; recent prevalence data indicate that over half of women and about two thirds of men are either overweight or obese [8]. Obesity and overweight are becoming increasing public health issues in many developing regions as well (e.g., Latin America, Middle East) and re present major contributors to the global burden of disease [9].

Obesity is an independent risk factor for coronary heart disease, stroke, and total cardiovascular morbidity and mortality; in addition, it is strongly associated with several cardiovascular risk factors such as diabetes, high cholesterol, and high blood pressure [10]. In particular, the relationship between obesity and hypertension is very well documented. Blood pressure is strongly correlated with BMI. In the INTERSALT study, the relationship between BMI and blood pressure was examined in over 10,000 men and women, between 20 and 59 years of age, sampled from 52 centers around the world [11]. BMI was linearly associated with systolic and diastolic blood pressure, independent of age, alcohol intake, smoking habits, sodium and potassium excretion. The prevalence of obesity-related hypertension varies with age, ethnicity, and sex of the population studied [12]. Approximately one-third of cases of hypertension are attributable to obesity, although in young adults (under 45 years of age) the figures may be substantially higher. For example, in the sample of young adults of the Framingham Offspring Study, 78% of cases of hypertension in men and 64% in women were attributable to obesity [13]. Additionally, variations have been observed by ethnic group. For example, results from the Atherosclerosis Risk in Communities Study suggest the association to be stronger in whites than in African Americans [14].

Not only is obesity associated with high blood pressure, but weight gain, even of a modest magnitude, is itself an important risk factor for the development of hypertension in adulthood. This effect seems to be independent of baseline BMI and baseline blood pressure, present in both genders, stronger in young adults and weaker in people of black African ancestry; conversely, weight loss reduces the risk of hypertension [15-17].

While many of the earlier studies have examined the association between obesity and blood pressure relying on BMI as an indicator of relative weight, more recent investigations have emphasised the importance of body fat distribution in this association. Specifically, abdominal adiposity has been reported as a stronger determinant of hypertension risk compared to measures of relative weight [14, 18-20]. In epidemiological studies, several anthropometric measures have been used as proxy measures for body fat distribution, such as waist-to-hip circumference ratio, waist circumference, and abdominal sagittal diameter. Current clinical guidelines propose waist circumference as a reference measure of central adiposity in adults because its measurement is the least affected by observer bias [21].

Given the overwhelming evidence on the relationship between body weight and blood pressure, weight reduction has been proposed as a measure to reduce blood pressure in both individual patients and the community at large. Over the past three decades, several randomized controlled clinical trials have reported on the beneficial effects of weight loss interventions on the prevention and treatment of hypertension. For example, the results of the multi-centre randomized clinical Trials of Hypertension Prevention (TOHP), Phase I and II, indicate that both short and long term weight loss is successful in reducing blood pressure. In TOHP I, an 18-month intervention was significantly associated with 77% reduction in the incidence of hypertension after a 7-year follow up [22]. Likewise, in TOHP II, a longer-term intervention of 36 months resulted in significant reductions in systolic and diastolic blood pressures and in a lower incidence of hypertension even in presence of modest weight loss [23]. In the latest published meta-analysis of 25 randomized controlled trials, which included only trials based on weight reduction through energy restriction, increased physical activity or both, average reductions of 4.4/3.6 mmHg for systolic and diastolic blood pressure, respectively, were reported for a 5 Kg weight loss [24]. A dose-response was observed, i.e. the greater the weight loss, the greater the blood pressure reduction. Furthermore, the lowering effect of weight reduction on blood pressure was independent of age, gender and initial BMI, although the effect appeared greater in patients on anti-hypertensive medication.

This meta-analysis also highlights the problem of lack of compliance during long-term interventions because the maximal effect was reached before the end of the trials. Additionally, the long-term effects of weight reduction on blood pressure are not fully understood; however, they seem to be in magnitude less than those reported in short-term trials. In fact, a recent systematic review, based on studies with follow-up of ≥ 2 years, demonstrated decreases of 6.0/4.6 mmHg for systolic and diastolic blood pressure, respectively, for 10 kg weight loss, about half of that predicted from the short-term trials [25]. Several factors such as initial blood pressure, length of follow-up, medication changes, and physiological restrictions may contribute to this reduced effect in the long-term studies. Nevertheless, weight loss programs represent an essential component of a multifaceted non-pharmacological intervention to manage hypertension; in addition, they are adjuvant measures to pharmacological therapies, as they decrease the dosage of anti-hypertensive medication needed to reach blood pressure control [26]. Indeed, clinical trials have reported on the efficacy of combined lifestyle interventions including weight loss, hypocaloric/low-salt diet, and regular exercise in reducing blood pressure levels to an extent comparable to that achieved with anti-hypertensive medication [27, 28].

Several biological mechanisms may explain the link between obesity, weight change, and blood pressure. In particular, an over-activity of the renin-angiotensin-aldosterone system has been regarded as a possible key mechanism of the hypertensive response in obese individuals, whose circulating levels of renin activity and aldosterone are higher than

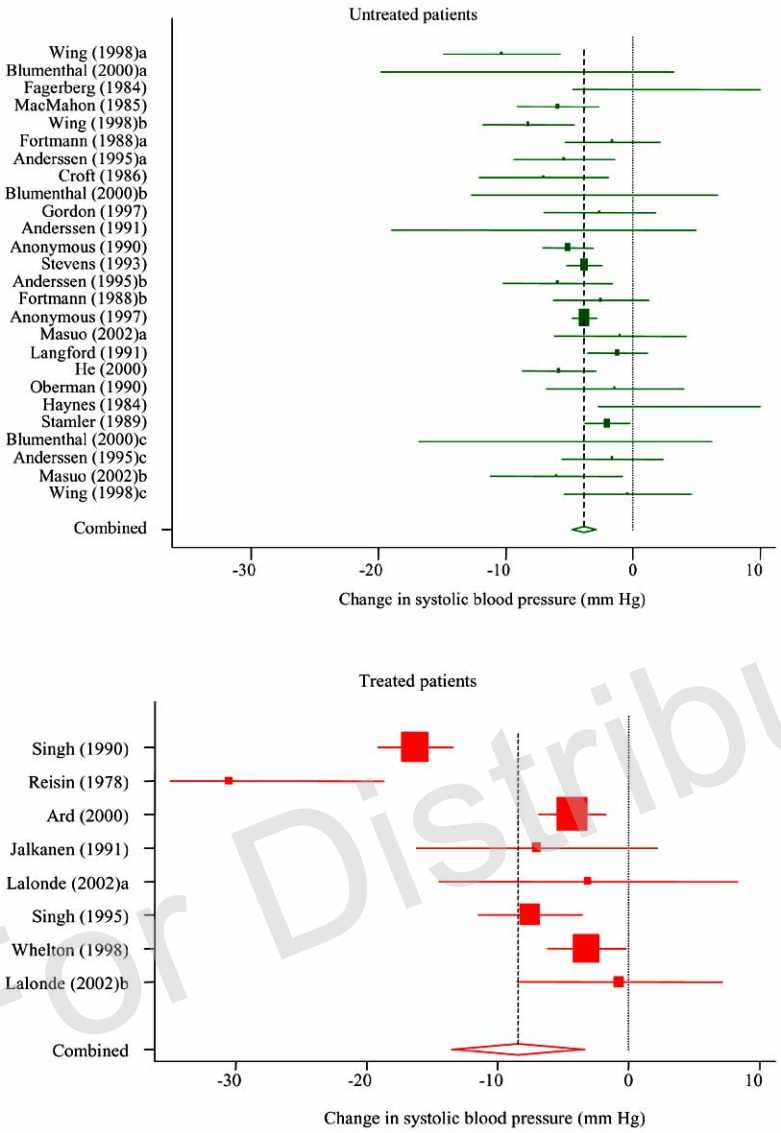

Fig. (1). Meta-analysis of randomized trials on short-term effects of weight reduction on systolic blood pressure in untreated and treated individuals with hypertension [24].

in nonobese subjects. Recent data support this mechanism suggesting that the over-activity of this system in obese individuals can be lowered by a reduction in body weight [29]. Further mechanisms may reside in: inhibition of the natriuretic peptides system, which is critical to prevent excess salt and water retention, promote vascular relaxation, and inhibit sympathetic outflow; increased activity of the sympathetic nervous system; reduced insulin sensitivity and hyperinsulinemia [30].

Overall, the current evidence from clinical trials and observational studies strongly supports the notion that prevention of weight gain in normal weight individuals and weight loss in overweight and obese individuals, in combination with other lifestyle modifications (e.g., hypo-caloric diet, salt reduction, moderation in alcohol consumption and increased physical activity), are highly effective strategies for the prevention and management of hypertension both in individuals and population at large.

DIETARY SODIUM REDUCTION

Numerous animal studies, ecological analyses, observational epidemiological investigations, and clinical trials have supported a relationship between salt (sodium chloride) intake and blood pressure. The amount of dietary sodium is an important determinant of blood pressure levels and of hypertension risk both in individuals and populations. This relationship is direct and progressive without an apparent threshold. Thus, the reduction of dietary sodium intake is one of the most important and effective lifestyle modifications to reduce blood pressure and control hypertension [6, 31].

That habitual sodium intake could be associated with blood pressure levels was suggested several millennia ago, in

the history of human mankind, after the transition from food gathering to food producing with the addition of salt to preserve food and the consequent shift to a high salt diet [32]. Above and beyond earlier anecdotal observations, the relationship between dietary sodium and blood pressure has become the focus of intensive scientific scrutiny over the past decades. One of the earlier epidemiological studies to address this question was the INTERSALT study, a large, worldwide epidemiological investigation including 10,079 men and women, aged 20 to 59 years, in 52 centers from 32 different countries [33]. This study tested both the within- and cross-population association between 24/h urinary sodium excretion, reflecting the amount of sodium intake, and blood pressure levels. The within-center results showed a significant, positive, independent and linear association between 24/h urinary sodium excretion and blood pressure levels. Specifically, a 100 mmol per day higher sodium intake (about 2.3 g/day) would predict a 3-to-6 mmHg higher systolic and up to 3 mmHg higher diastolic blood pressure. Similar results were obtained in different subgroups analyses: men, women, young, elderly and for participants without hypertension. In the cross-population analysis, significant, independent relations were found between 24/h urinary sodium excretion and median systolic and diastolic blood pressure, prevalence rate of hypertension, and rise of systolic and diastolic blood pressure with age. These results were further supported by findings from the Multiple Risk Factor Intervention Trial. In this cohort of more than 11,000 participants followed up for 6 years, sodium intake, as assessed by questionnaire, was significantly, directly and independently related to systolic and diastolic blood pressure in both individuals receiving and not receiving anti-hypertensive medication [34].

Besides these observational investigations, over 50 randomized clinical trials have supported more persuasively a role of salt intake reduction in the prevention and management of high blood pressure. In the largest of these trials, the Dietary Approaches to Stop Hypertension (DASH) trial, 412 participants were randomly allocated to two dietary regimens: one following a control diet, which was representative of the average diet in the United States; one following the DASH diet – a diet rich in fruit and vegetables, low-fat or fat-free diary products and reduced in saturated and total fat content. Inside each arm of the trial, participants were randomly assigned to three groups with increasing amounts of sodium intake. As estimated from 24/h urinary collections, the 3 sodium levels (lower, intermediate, and higher) provided 65, 107, and 142 mmol per day, respectively, which correspond approximately to intakes of 1.5, 2.5, and 3.3 grams of sodium per day, respectively [35]. In this trial, a sodium reduction alone from a high to a low level was associated with a blood pressure reduction of 8.3/4.4 mmHg among hypertensive individuals and 5.6/2.8 mmHg among normotensive individuals. Moreover, the combination of this amount of sodium reduction and the DASH diet further reduced blood pressure by 11.5/5.7 mmHg and 7.1/3.7 mmHg, respectively, among those with and without hypertension. In subgroup analyses, significant effects of sodium reductions on blood pressure levels were present in both genders, all racial and age groups, though they were more marked among African Americans, women (for systolic blood pressure), and persons older than 45 years of age [36].

Pooled estimates from meta-analyses of clinical trials on the effects of salt reduction on blood pressure levels indicate a fall in systolic and diastolic blood pressure of 7.1/3.9 mmHg, respectively, in hypertensive individuals and 3.6/1.7 mmHg in normotensive individuals per 100 mmol reduction of 24/h urinary sodium excretion (about 6 g salt/day). For example, He *et al.* estimated blood pressure reductions of 5.0/2.7 mmHg in hypertensive individuals and 2.0/1.0 in normotensive individuals for a median reduction in urinary sodium of 78 mmol per day [37]. In the latest published meta-analysis of 40 randomized trials, an average reduction in urinary sodium excretion of 77 mmol per day was associated with a reduction in blood pressure levels of 2.5/2.0 mmHg [38]. Blood pressure response was significantly larger in hypertensive than normotensive individuals (systolic: -5.2 *vs*. -1.3 mmHg; diastolic: -3.7 *vs*. -1.1 mmHg).

Accordingly, findings from randomized clinical trials have supported a role of a reduction in dietary sodium in the primary prevention and management of hypertension. For example, in the Trials of Hypertension Prevention, phase II, a sodium reduction of 100 mmol per day, alone or combined with weight loss, prevented hypertension by 20% throughout 48 months of intervention in overweight adults [39]. Likewise, in the Trial of Nonpharmacologic Interventions in the Elderly (TONE), a sodium reduction of ~40 mmol per day was associated with a 30% decrease in the need for anti-hypertensive medication after 3 months of intervention in hypertensive individuals aged 60 to 80 years [27].

The response of blood pressure to dietary changes in sodium intake, as to other environmental stimuli, may vary between individuals. This phenomenon has been termed as "*salt sensitivity*" [40], and it is likely to be due to the degree of response of the renin-angiotensin system [41, 42]. The weaker the response of this system to a change in sodium intake, the larger the response of the blood pressure will be. This phenomenon explains why the blood pressure lowering effect of sodium reduction is larger in hypertensive individuals, elderly and "low-renin" black populations. These groups are all characterized by weaker responses of the renin-angiotensin system to changes in the amount of sodium ingested, showing a greater blood pressure fall as a result of a reduction of dietary sodium. Indeed, although a significant reduction of blood pressure induced by reduced sodium intake has been observed in children and adolescents as well [43], this response increases with age and is largest in the elderly [44].

For example, in a double-blind randomised trial, a modest reduction in sodium intake in people over the age of 60 induced a significant reduction in blood pressure without untoward effect, irrespective of the initial blood pressure [45]. Furthermore, the blood pressure fall observed in the elderly as a result of a dietary sodium reduction may reduce the need for anti-hypertensive medication [27]. These observations are relevant to the prevention of hypertension-related diseases in developed countries, where the majority of strokes occur in the elderly and individuals with blood pres-

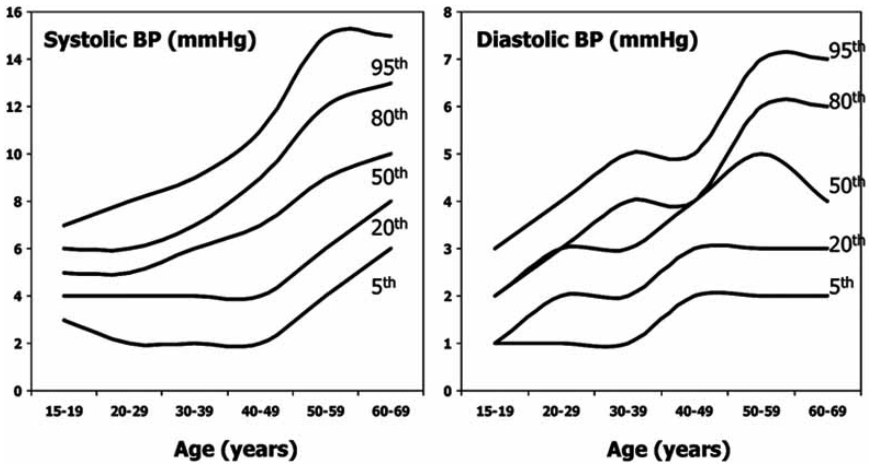

Fig. (2). Estimated changes in systolic and diastolic blood pressures for 100 mmol per day change in sodium intake by centiles of the blood pressure distribution [44].

sure levels below the treatment threshold for hypertension [44]. Nevertheless, several anti-hypertensive drugs blocking the renin-angiotensin system (e.g., angiotensin-converting enzyme inhibitors, beta-blockers, and angiotensin II receptors antagonists) have an additive effect on blood pressure reduction in those patients already on a reduced salt diet [46]. Furthermore, people of black African origin show a greater blood pressure response when dietary salt is reduced [35, 42, 47]. For example, the efficacy of a moderate reduction in salt intake has recently been tested in two short-term trials in both urban and rural areas of West Africa, namely Nigeria and Ghana, where the prevalence of hypertension is increasing [48, 49]. In both studies a moderate reduction in salt intake was associated with a significant reduction in blood pressure comparable to that seen in white populations. In areas such as sub-Saharan Africa, the prevalence of hypertension is increasing, the health care resources are scarce, and thus the identification of people with hypertension is still haphazard. The effectiveness of a reduction in salt intake at a population level might prove extremely important for policy makers.

Given the overwhelming evidence of the efficacy of dietary sodium reduction in the prevention and management of hypertension, the debate is currently based on issues regarding the long-term outcome benefits, and thereafter the appropriateness of a population wide strategy to reduce dietary salt intake. The major benefit of sodium reduction resides in lowering blood pressure. It has been argued that the blood pressure reduction realistically achievable at a population level (i.e., 1 to 3 mmHg in systolic blood pressure) is small, not clinically significant, and with long-term benefits remaining unclear [50]. However, in a recent meta-analysis of 61 prospective studies, it has been estimated that even a reduction of 2 mmHg in systolic blood pressure would determine a 10% reduction in stroke mortality and a 7% reduction in mortality from coronary heart disease or other cardiovascular causes, meaning a large number of premature deaths and disabilities avoided [51]. Other results corroborate these estimates, and suggest that the benefits of such a small reduction in blood pressure, induced by salt reduction, in the population would be almost immediate [37]. Moreover, although the principal benefit of salt reduction is the blood pressure reduction, it is not the only one. There is a large body of evidence that supports other benefits: regression of left ventricular hypertrophy, reduction in proteinuria and glomerular hyperfiltration, reduction in bone mineral loss with age and osteoporosis, protection against stomach cancer and stroke, protection against asthma attacks and possibly against cataracts [52]. Conversely, some potentially harmful effects have been reported following severe short-term sodium reductions, such as increased levels of renin, aldosterone, catecholamines, serum cholesterol and triglycerides [53]. However, these effects are caused by an acute volume concentration and are not detected after a moderate long-term sodium reduction.

In light of the current evidence, reduction of dietary salt intake appears a plausible population-wide recommendation for the prevention and treatment of hypertension. A decrease of dietary sodium to no more than 100 mmol per day (2.3 g sodium or 5.8 g sodium chloride) represents a reasonable goal at a population level given the current dietary patterns of high levels of salt intake worldwide. However, this reduction will be only feasible in Western societies if efforts are made by the food industry, manufacturers, and restaurants to decrease the amount of salt added to processed food. In fact, in these societies, a large proportion of sodium intake (75-80%) comes from processed food and bread [54]. On the contrary, in developing countries where the prevalence of hypertension continues to increase, more traditional health promotion strategies would be applicable and nutritional education might have an important effect in these settings [55-57].

DIETARY POTASSIUM INCREASE

There is an established inverse association between dietary potassium intake and blood pressure levels. The evidence is supported by findings of animal studies, observational epidemiological investigations, and clinical trials. In addition, meta-analyses of randomized controlled trials on the efficacy of potassium supplementation in reducing blood pressure levels in both normotensive and hypertensive individuals consistently demonstrate this inverse relationship.

Specifically, in an early meta-analysis including 19 clinical trials with both normotensive and hypertensive individuals, an overall effect of potassium supplementation of -5.9 mmHg (95% CI -6.6 to -5.2) and -3.4 mmHg (95% CI -4.0 to -2.8) was reported for systolic and diastolic blood pressure, respectively. The magnitude of the blood pressure lowering effect of potassium supplementation was greater in individuals with high blood pressure [-8.2 mmHg, (-9.1 to -7.3 mmHg), for systolic and -4.5 mmHg (-5.2 to -3.8 mmHg), for diastolic blood pressure] and appeared to be more pronounced the longer the duration of the supplementation [58]. Likewise, in a later meta-analysis including 33 randomized controlled trials, potassium supplementation was associated with a significant reduction in mean systolic and diastolic blood pressure of -3.1 mmHg (-1.9 to -4.3 mmHg) and -2.0 mmHg (-0.5 to -3.4 mmHg), respectively [59]. The average effect size was larger in trials conducted in hypertensive individuals (-4.4 and -2.5 mmHg for systolic and diastolic blood pressure, respectively). Furthermore, in this meta-analysis, the blood pressure lowering effect of potassium supplementation was greater in studies in which participants were simultaneously exposed to a high intake of sodium. Finally, a recent meta-analysis by Geleijnse *et al.* including 27 potassium trials showed a significant, inverse association between increased potassium intake (median: 44 mmol/24h) and blood pressure levels, although the effect size reported was slightly smaller than that previously published, that is a decrease in systolic and diastolic blood pressure of 2.4 mmHg (95% CI 1.1 to 3.7) and 1.6 mmHg (0.5 to 2.6), respectively [38]. Consistently with the two previously published meta-analyses, blood pressure response was larger in hypertensive than normotensive individuals (systolic: -3.5 *vs*. -1.0 mmHg, P=0.089; diastolic: -2.5 *vs*. -0.3 mmHg, P=0.074).

The hypothesis of an inverse association between dietary potassium intake and blood pressure levels originated from findings of population studies showing that the prevalence of hypertension may be low in populations consuming high potassium diets. The INTERSALT co-operative study was one of the earlier epidemiological investigations to estimate the effect of potassium intake on blood pressure levels. This study tested both the within- and cross-population association between 24/h urinary sodium, potassium, and sodium/potassium ratio, reflecting the amount of dietary intake of these micronutrients, and blood pressure levels. Within the centers, a reduction in systolic and diastolic blood pressure of 3.4/1.9 mmHg was related to a higher potassium intake of 50 mmol per day. Furthermore, the sodium/potassium ratio was positively and significantly related to the blood pressure levels of individuals in both men and women. These relationships were more marked with increasing age [33]. Moreover, two large prospective studies on American cohorts of health professionals examined the association between dietary potassium intake and prevalence of hypertension. Specifically, Ascherio *et al.* analyzed a cohort of 30,681 US male professionals, aged 40-75 years, without diagnosed hypertension for a follow-up period of 4 years [60]. A significant, inverse association was found between potassium intake and risk of hypertension after adjustment for energy intake, age, relative weight, and alcohol consumption. When adjusted additionally for dietary fiber and magnesium intake the association was no longer significant. Similar results were observed in a large cohort of women, the Nurses' Health Study cohort [61]. These findings are not surprising considering the high correlation between potassium and other micronutrients (e.g., calcium and magnesium), because they are present simultaneously in foods such as fruit, nuts, vegetables, cereals, and dairy products. Indeed, these results underscore the difficulty to differentiate the importance of the potassium effect when adjusted for other micronutrients in epidemiological studies, and the need for randomized trials to determine whether there is a protective role of a specific dietary micronutrient in the regulation of blood pressure [62].

Numerous clinical trials have reported on the effect of potassium supplementation on blood pressure levels among both normotensive and hypertensive individuals. Although results have not been always consistent, pool estimates from meta-analyses consistently support a significant inverse association between potassium intake and blood pressure levels [38, 58, 59] among both normotensive and hypertensive individuals, as previously mentioned (Tab. 1). The lowering effect of potassium supplementation on blood pressure levels seems to be independent of the baseline potassium status, since it has been shown either among individuals with low dietary potassium intake [63] or in individuals consuming normal/high potassium diets (64). Moreover, this effect appears similar in women and men, whereas it is stronger among hypertensive individuals and individuals of black African origin, as also confirmed by pool estimates of a published meta-analysis [59]. For example, findings from two intervention trials in participants of black African origin

Table 1. Meta-analyses of Randomized Trials on the Effects of Potassium Supplementation on Systolic and Diastolic Blood Pressure

	Systolic Blood Pressure*		Diastolic Blood Pressure*	
	Net Change	**95% CI**	**Net Change**	**95% CI**
1991 – Cappuccio *et al.* (58)	-5.9	-5.2 to -6.6	-3.4	-2.8 to -4.0
1997 – Whelton *et al.* (59)	-3.1	-1.9 to -4.3	-2.0	-0.5 to -3.4
2003 – Geleijnse *et al.* (38)	-2.4	-1.1 to -3.7	-1.6	-0.5 to -2.6

* Results are reported as mean net blood pressure changes and 95% confidence intervals (CI)

show, on average, larger reductions in blood pressure levels after potassium supplementations than those reported in other ethnic groups [63, 65]. Furthermore, the lowering effect of potassium supplementation on blood pressure is dependent on the concurrent intake of dietary sodium and vice versa. This means that this effect is larger in individuals on a high-sodium diet and smaller in individuals on a low-sodium diet; conversely, the lowering effect of a reduction in dietary sodium intake on blood pressure is larger in individuals on a low-potassium diet and smaller in individuals on a high-potassium diet [31]. Accordingly, the ratio of urinary sodium-potassium excretion is more closely related to changes in blood pressure levels than either urinary sodium or potassium excretion individually [33, 59]. For example, in a 2x2 factorial trial examining the individual and simultaneous effects of reduced dietary sodium intake and increased potassium intake on blood pressure in 212 hypertensive individuals, the lowering effects on blood pressure levels were similar for either a reduced sodium intake or an increased potassium intake, individually. However, when both interventions were implemented together, there was no further lowering effect on blood pressure levels [66]. Thus, these data suggest sub-additive effects of reduced salt intake and increased potassium intake on blood pressure.

Fruit, vegetables, pulses and nuts are the main sources of dietary potassium in the form of inorganic or organic salts. These foods, especially fruit and vegetables, are rich in potassium as well as in other essential micronutrients; therefore, diet is a suitable strategy to increase the levels of potassium intake and prevents the need for supplements. Several randomized controlled trials have reported on the lowering effects on blood pressure of dietary interventions providing large intakes of potassium. For example, in the Dietary Approaches to Stop Hypertension (DASH) trial, the 2 groups that increased fruit and vegetable consumption, with consequently larger amounts of potassium, experienced significant reductions in blood pressure levels [35]. Likewise, in another trial examining the effects of fruit and vegetable consumption on plasma antioxidant concentrations and blood pressure, a significant reduction in blood pressure levels was detected [67]. Not only does the increase in dietary potassium help to reduce blood pressure, but it is a feasible and effective measure to reduce the need for anti-hypertensive medication. For example, Siani *et al.* found that after a dietary advice, which specifically aimed at increasing potassium intake, the intervention group increased their potassium intake compared to the control group. More importantly, as a result of the dietary intervention, blood pressure could be controlled using less than 50% of the initial pharmacological therapy in 81% of the patients in the intervention group compared with 29% of the patients in the control group [68]. Thus, an increase in potassium intake from natural dietary sources may be a feasible and effective measure to reduce antihypertensive medication.

The mechanisms responsible for the lowering effect of increased potassium intake on blood pressure are not fully understood. Several hypotheses have been put forward [69]. High potassium intake might exert a vascular protective effect and reduce the development of atherosclerosis. It may also reduce arteriolar thickening in the kidney. Moreover, potassium infusion increases acetylcholine-induced vasodilatation, and this effect is inhibited by the consequent infusion of the nitric oxide synthase inhibitor l-NMMA (l-nitromonomethylarginine). This suggests that potassium could lower blood pressure by a nitric oxide-dependent vasodilatation. Conversely, potassium depletion in humans is accompanied by sodium retention and calcium depletion and also by an altered response to vasoactive hormones. These metabolic effects together with the direct vasoconstrictive effects of hypokalemia might be the cause of the augmentation in blood pressure during a decrease of potassium intake

Given the existing evidence, the adoption of a high-potassium diet is a reasonable, effective non-pharmacological measure to improve blood pressure control in hypertensive individuals and to reduce the risk of hypertension in the general population. The level of intake that should be recommended is still a controversial issue depending upon the levels of potassium status in a specific population, and the presence of conditions or drug therapies that can impair potassium excretion. A recent statement from the American Hearth Association sets the recommended level of potassium intake, among healthy individuals, as 4.7 g/d (120 mmol/d) [31]. This level of intake is based primarily on findings from clinical trials as well as on the potassium content of the DASH diet. Indeed, in the Western populations the current levels of potassium intake are generally lower than this recommended level. Moreover, in individuals affected by disease conditions impairing potassium excretion (e.g., diabetes, chronic renal insufficiency, end-stage renal disease, severe heart failure, and adrenal insufficiency) or on drug therapies that may interfere with potassium excretion (e.g., ACE inhibitors, angiotensin receptor blockers, non-steroidal anti-inflammatory agents, and potassium-sparing diuretics), a lower level of intake [i.e., < 4.7 g/d (120 mmol/d)] is recommended to prevent the risk of hyperkalemia [70]. In conclusion, an increase in potassium intake from natural dietary sources is a feasible and effective measure of preventing and treating hypertension.

MODERATION OF ALCOHOL CONSUMPTION

Extensive epidemiologic evidence suggests that heavy alcohol consumption is associated with elevated blood pressure and increased risk of hypertension, independent of age, gender, ethnic group and other potential confounders [71-73]. For example, findings from the multinational INTERSALT study showed that heavier drinkers of both sexes had higher mean systolic and diastolic blood pressures than non-drinkers [72]. The increased risk of hypertension occurs at levels of consumption above ~ 2 drinks per day in men and ~ 1 drink per day in women and lighter-weight individuals [5, 31]. The observational data have been corroborated by findings of randomised controlled trials showing a blood pressure-raising effect of alcohol, which is reversible in both normotensive and hypertensive individuals [74, 75] Pool estimates from a meta-analysis of 15 randomized controlled trials show a reduction in systolic and diastolic blood pressure of 3.3/2.0 mmHg, respectively, for a median 76% reduction in alcohol consumption from a baseline of 3 to 6 drinks per day [76]. Blood pressure reductions were similar in hypertensive and normotensive individuals. Importantly, the relationship between reduction in mean percentage of

alcohol and decline in blood pressure was dose dependent. Findings from this meta-analysis also suggest that the reduction in blood pressure following a reduction in alcohol intake can be sustained over time. Therefore, altogether these results reinforce recommendations for moderation of alcohol consumption to prevent and treat hypertension.

There are still open questions, however, about this relationship. For example, it remains unclear whether, in the range of low-to-moderate alcohol consumption, the association is linear, J-shaped or whether there is a threshold effect. In the Kaiser-Permanente Study [71], there was no difference in the hypertension-related hospitalization between non-drinkers and light drinkers (i.e., < 2 drinks/day), which suggests a threshold effect. Conversely, findings from the INTERSALT study suggest a continuous relationship between alcohol consumption and blood pressure in men and, if anything, a weaker relation at levels below 300 mL per week [72]. However, recent findings from the Nurses' Health Study II showed a J-shaped association between alcohol consumption and risk of developing hypertension, with light drinkers demonstrating a modest decrease in risk and more regular heavy drinkers demonstrating an increase in risk [73]. Other open questions concern the possible effect of different patterns of alcohol consumption on blood pressure elevation. Indeed, increasing, though not conclusive, evidence suggests that the association between alcohol consumption and blood pressure levels is function not only of the average quantity consumed but also of the pattern in which alcohol is consumed. These patterns include beverage preference, frequency and intensity of consumption, and drinking in relation to food consumption. For beverage preference, findings from observational studies are inconsistent [73, 77]; moreover, a recent randomised controlled trial did not detect a beverage specific effect on the association between alcohol consumption and blood pressure [78]. For frequency and intensity of consumption, some studies suggest that episodic-heavy drinking may be associated with elevated blood pressure levels compared to regular drinking [72, 79, 80]. For example, in a crossover study of hospitalized hypertensive patients, heavy alcohol intake (4 pints of beer per day) significantly raised blood pressure, whereas alcohol withdrawal was associated with a significant fall in blood pressure [79]. More recently, findings from a study on the health consequences of binge drinking in 1,154 men and women, aged 18 to 54 years, showed that consumption of 8 or more drinks on one occasion was associated with a significant increased risk of coronary heart disease and hypertension compared to a regular pattern of drinking [80]. However, no effect on the risk of other cardiovascular disease was observed. Episodic drinking produces greater differences in blood pressure compared to regular drinking. This result is corroborated by the conclusions of the INTERSALT study [72]. Additionally, the effects on blood pressure of daily heavy drinking are more prominent than those of weekend heavy drinking [81]. However, other studies have reported inconsistent findings [73, 82]. Furthermore, two population-based cross-sectional studies have examined the association between drinking pattern in relation to food consumption and hypertension risk [77, 83]. Trevisan and colleagues, in a large sample of adult men and women from the Italian Nine Communities Study, found that drinkers of wine with and without meals experienced significantly higher systolic blood pressure levels and a higher prevalence of hypertension than wine drinkers mostly with food, even after adjustment for differences in volume of alcohol consumption among the various drinking pattern categories. This associa-

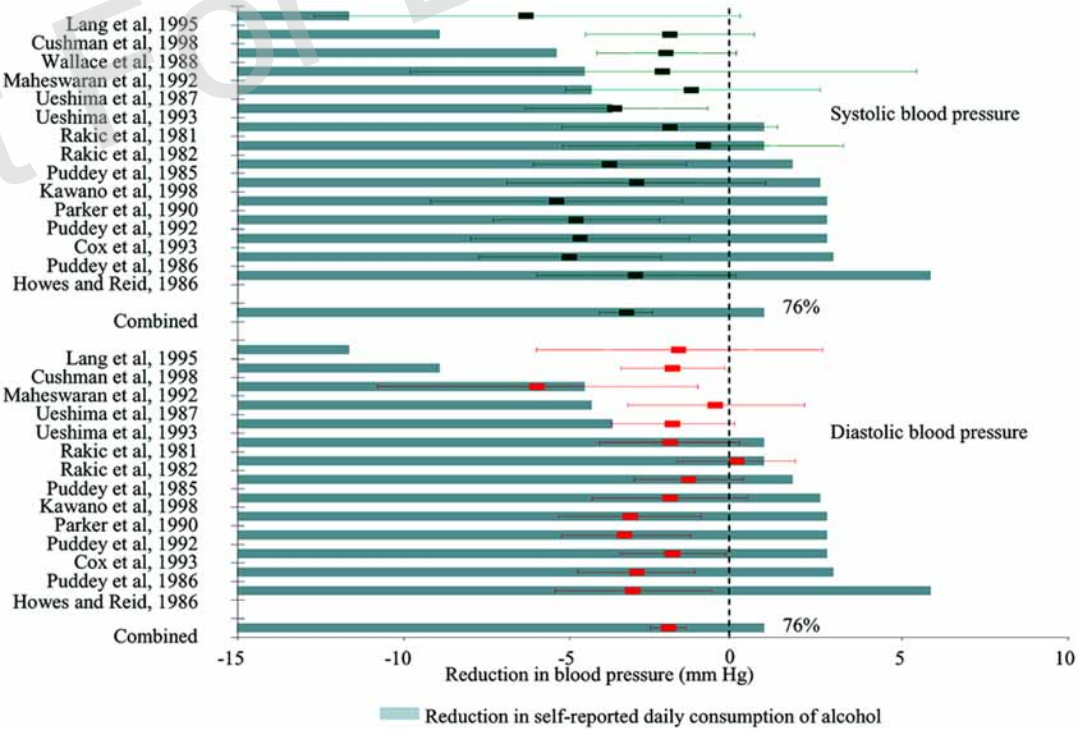

Fig. (3). Meta-analysis of randomized trials on the effects of alcohol reduction on systolic and diastolic blood pressure [76].

tion was similar in the two sexes [83]. These findings were recently replicated in an analysis of 2,609 white male and female healthy individuals from the Western New York Health Study [77]. Specifically, individuals drinking mostly without food experienced significantly higher risk of hypertension than those drinking mostly with food, after adjustment for several confounders including total volume of alcohol consumed in the past 30 days. More interestingly, in this study drinking without food was associated with a significantly 45% increased risk of hypertension even in individuals with light to moderate alcohol intake (i.e., < 2 drinks/day). This finding suggests that drinking without food may counteract the benefits associated with moderate alcohol use on the cardiovascular system. However, longitudinal studies are needed to support these findings and clarify the role of drinking pattern in the relationship between alcohol consumption and blood pressure.

In conclusion, moderation of alcohol consumption is a well-documented and effective recommendation to lower blood pressure among habitual drinkers. Currently, the recommended threshold is ≤ 2 alcoholic drinks per day in men and ≤ 1 alcoholic drink per day in women and lighter-weight persons (one unit = half a pint of beer, one glass of wine or one measure of spirits) [5, 31]. Extended recommendations should pertain to the way in which alcohol is consumed among habitual drinkers. Specifically, a regular consumption *vs*. a heavy-episodic drinking pattern, preferably in relation to mealtime, appears a reasonable, additional lifestyle behavior that should be adopted by habitual drinkers.

IMPORTANCE OF DIETARY PATTERNS

Diet plays a major role in the regulation of blood pressure and is one of the most important determinants of blood pressure levels in both individuals and populations. There are large variations in dietary patterns across populations that are likely to account for a considerable part of the observed differences in mean blood pressure levels, with populations consuming mostly plant-based diets having lower blood pressure than populations consuming hypercaloric high-fat diets, as those in industrialized countries. Additionally, even within industrialized countries, individuals consuming diets with increased intakes of fruit and vegetables and decreased intake of saturated fats tend to have, on average, lower blood pressure than individuals following more typical Western diets [84]. Differences from cross-cultural analyses have been corroborated by findings from numerous observational epidemiological investigations and randomized controlled trials, which have supported the crucial role of dietary patterns in the development of hypertension. In this section, we will focus on two dietary patterns, for which the current evidence is consistent with regard to their efficacy in lowering blood pressure: the vegetarian diet and the DASH diet.

Vegetarian Diet

Observational data clearly support the benefits on blood pressure levels derived from the adherence to a vegetarian dietary regimen with no or very little amount of animal-based products [84]. Many epidemiological investigations have been conducted in selective population subgroups, in which a vegetarian diet is part of a multifaceted lifestyle that may encompass proscription of alcohol, of tobacco use and other "unhealthy" behaviours. The Seventh Day Adventists represent one of the most studied population subgroups. Their members are expected, by religious belief, to abstain from alcohol and tobacco, and to follow a vegetarian diet supplemented with eggs and milk. Overall, they tend to have lower mortality from cancer, heart disease, and diabetes than non-Adventists living in the same communities. However, within this group, dietary patterns are not completely homogeneous and may resemble more typical Western habits. For example, in a cross-sectional analysis on a large cohort of 34,192 California Seventh-day Adventists, the prevalence of hypertension was nearly double among Adventists who followed a diet similar to a typical American diet than in vegetarian Adventists [85]. These findings emphasize the independent role of dietary patterns in the risk of hypertension within this group of individuals characterized otherwise by common lifestyle behaviours. Furthermore, the age-dependent rise in blood pressure levels, typically experienced by individuals living in industrialized countries, may be largely attenuated by a long-term adherence to a vegetarian dietary regimen [86]. Altogether, available data from observational studies indicate that vegetarians have lower systolic (3 to 14 mmHg) and diastolic (5 to 6 mmHg) blood pressure, and lower prevalence of hypertension than non-vegetarians (2-40% *vs*. 8-60%, respectively) [84].

Additionally, randomized controlled trials have reported on the blood pressure lowering effects of vegetarian diets in both normotensive and hypertensive individuals, independently of common non-dietary and dietary determinants of blood pressure. Indeed, a recent meta-analysis of 24 randomized placebo-controlled trials to estimate the effect of fiber supplementation on blood pressure overall and in population subgroups showed a moderate but significant reduction in blood pressure levels [87]. Specifically, fiber supplementation (average dose: 11.5 g/d) changed systolic blood pressure by –1.1 mmHg (95% confidence interval: –2.5 to 0.2) and diastolic blood pressure by –1.3 mmHg (–2.0 to –0.5), with larger reductions in older individuals (>40 years) and in hypertensive subgroups. The main characteristics of a vegetarian diet include a higher intake of fiber, potassium, polyunsaturated, and monounsaturated fatty acids and a lower intake of alcohol, animal proteins and saturated fats, which are all plausible contributors to the lower mean blood pressure levels in vegetarians, as compared to the general population. However, the lowering effects on blood pressure derived from a vegetarian diet are likely due as well to other non-dietary factors (e.g., increased physical activity) that tend to cluster with dietary components as part of a comprehensive "vegetarian" lifestyle.

Dietary Approach to Stop Hypertension (DASH) Diet

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [5] and a recent Scientific Statement from the American Heart Association [31] emphasize the importance of adopting a dietary regimen resembling the so called "DASH" diet as one major lifestyle modification to prevent and treat hypertension. The DASH dietary plan provides large intakes of fruit, vegetables, and low-fat dairy products; comprises whole grains, poultry, fish and nuts; and has limited amounts of red meat, sweets, and sugar-containing bev-

erages. Thus, in comparison with habitual diets of Western societies, the DASH dietary pattern provides higher intakes in potassium, magnesium, calcium, fiber, and proteins and lower intakes in total fat, saturated fat, and cholesterol [88]. The blood pressure lowering effect of this diet is the result of the combined effects of these nutrients when consumed together in food, rather than of the specific effect of a single nutrient. Indeed, the Dietary Approaches to Stop Hypertension (DASH) trial was designed to test the effects on blood pressure of a change in dietary patterns, rather than the effects of a change in a single nutrient, as generally tested in previous trials [89]. This trial was an 11-week feeding program including 459 adults with (n=133) and without hypertension (n=326). For three weeks, participants followed a control diet that was low in fruit, vegetables, and dairy products. The fat content was representative of the average consumption in the United States. Then, for the next eight weeks, participants were randomly allocated in three groups and each group was fed three different diets. One group was fed the same control diet, the second group a diet richer in fruit and vegetables but similar to the control diet for other nutrients, and the third group was fed the DASH diet, that is a diet rich in fruit and vegetables, low-fat or fat-free dairy products and reduced saturated and total fat content, in other words a high potassium, magnesium, calcium, fiber, and protein diet. The sodium intake was held constant in the three groups. Alcohol intake and body weight did not change during the trial or among the groups. Overall, findings indicated a gradient in the reduction in blood pressure among the diets. The DASH diet significantly reduced systolic and diastolic blood pressure by 5.5/3.0 mmHg, respectively, compared to the control diet, whereas the "fruit and vegetables" diet significantly reduced systolic and diastolic blood pressure by 2.8/1.1 mmHg, respectively, compared to the control diet. Among subjects with hypertension, the blood pressure reductions in the DASH group were more marked, that is 11.4/5.5 mmHg for systolic and diastolic blood pressure, respectively, compared to the control diet. Interestingly, the blood pressure lowering effects of the DASH diet occurred within the first two weeks of the trial. Further subgroup analyses showed significant effects of the DASH diet in all major subgroups (e.g., sex, race, age, body mass index, etc.), although the effects were more marked among African Americans (6.9 and 3.7 mmHg) than in whites (3.3/2.4 mmHg) [90].

Moreover, a further trial on the same population tested the effects of the DASH diet in combination with a reduction in sodium intake (35). 412 participants were randomly allocated to two dietary regimens, one following a control diet representative of the average diet in the United States and one following the DASH diet. Within these two dietary regimens, participants were randomly assigned to 3 decreasing levels of salt consumption, defined as high (150 mmol per day, 3.5 g of sodium/day, reflecting typical consumption in the United States), intermediate (100 mmol per day, 2.3 g of sodium/day, reflecting the upper limit of the current recommendations), and low (50 mmol per day, 1.6 g of sodium/day). Each feeding period lasted 30 consecutive days. Overall, findings indicate that: 1) the DASH diet may lower blood pressure independent of the level of sodium intake; 2) the blood pressure lowering effect of a reduction in sodium intake may occur by reducing the sodium intake even to levels below the currently recommended limit (i.e., 100 mmol per day); 3) the effects of sodium reductions are observed in all major subgroups; 4) greater lowering effects on blood pressure may derive from the combination of the two interventions than from adopting either the DASH diet or low sodium diet individually. In fact, the difference of systolic blood pressure between the DASH-low sodium group and the control-high sodium group was a substantial reduction of 7.1 mmHg in participants without hypertension and 11.5 mmHg in participants with hypertension. The last finding resembles the effect of a single-drug therapy in hypertensive individuals. Thus, the combination of the DASH diet and reduced sodium intake represents an alternative to drug therapy for individuals with mild hypertension and willing to comply with long-term dietary changes.

More recently, findings from the Optimal Macronutrient Intake Trial to Prevent Heart Disease (OmniHeart) have extended the observations derived from the DASH trials [91]. This trial examined the effects of three dietary patterns with documented lowering effects on blood pressure and serum lipids, among 164 adults with pre-hypertension or stage 1 hypertension. One diet, resembling the DASH diet, was rich in carbohydrates (58% of total calories); the other two dietary regimens partially replaced carbohydrates with either a higher content of proteins (about half from plant sources) or a higher content of unsaturated fats (predominantly monounsaturated fats). The feeding periods lasted 6 weeks and body weight was held constant. Systolic blood pressures were lowered in each of the three intervention groups compared with baseline. However, blood pressures were further lowered in the two dietary regimens providing a partial substitution of carbohydrates (10% of total kcal) with either proteins or unsaturated fats (1.4 and 1.3 mmHg, respectively). Thus, these findings indicate that, along with known determinants of blood pressure [i.e., micronutrients (sodium and potassium), body weight, alcohol consumption, and the DASH diet], macronutrients and the qualitative composition of diet are also important factors to consider for the prevention and management of hypertension.

REGULAR AEROBIC EXERCISE

Engaging in regular aerobic exercise represents an essential component of lifestyle modification to reduce cardiovascular risk and is an important part of current recommendations for the prevention and treatment of high blood pressure [5] It has been estimated that the risk of hypertension is 30-50% higher in individuals who are physically inactive [105]. At least 30 minutes per day of aerobic activity of moderate intensity (for example, quick walking) on five or more occasions per week is the recommended level set by current guidelines for the prevention and management of high blood pressure. Aerobic exercise comprises activities like walking, running, cycling or swimming. Although all forms of dynamic exercise seem to be effective in reducing blood pressure, adherence to the intervention program is crucial to be successful in achieving and maintaining the benefit. In a meta-analysis of 54 randomized controlled trials including 2,419 participants, aerobic exercise was associated with a significant reduction in systolic and diastolic blood pressure of 3.8/2.6 mmHg, respectively [92]. Blood pressure reduc-

tions induced by aerobic exercise were observed in both normotensive and hypertensive individuals and in normal-weight and overweight subgroups. Although the blood pressure lowering effect of aerobic exercise can be considered clinically moderate, it constitutes, however, a valuable public health strategy for the prevention and treatment of high blood pressure. In fact, a comparable reduction in the population's blood pressure levels would translate into a significant decrease in the incidence of hypertension-related diseases.

Conversely, resistance training, also know as isometric or static exercise (e.g., weight training or body building), is not included in current recommendations for the prevention and management of high blood pressure because of the lack of conclusive evidence on its effectiveness in lowering blood pressure and the potential for long-term hypertensive effects. However, two recent meta-analyses of randomized controlled trials indicate that resistance training is not associated with chronic elevations of blood pressure and, instead, may induce a moderate reduction of blood pressure levels in healthy adults, whereas its efficacy in lowering blood pressure in hypertensive individuals and elderly is still a controversial issue [93, 94]. Currently, the evidence suggests that moderate-intensity resistance training could be performed in combination with aerobic exercise in the context of a comprehensive exercise program to prevent CVD in healthy adults [95].

Several mechanisms are likely responsible for the blood pressure lowering effects induced by regular exercise [96]. For example, a 'haemodynamic' mechanism would involve the reduction of both resting cardiac output and peripheral vascular resistance. Furthermore, a 'humoral' mechanism would determine the reduction of the activity of the renin-angiotensin-aldosterone system and of the sympathetic nervous system and an increase in prostaglandins with vasodilator effect. Finally, recent findings suggest that an enhancement in insulin sensitivity may represent a further mechanism for the beneficial effects of physical activity on blood pressure and hypertension risk [97].

COMPREHENSIVE LIFESTYLE MODIFICATIONS

A few trials have examined the efficacy of the simultaneous implementation of current lifestyle recommendations, including regular exercise, to prevent and treat high blood pressure. For example, in the Diet, Exercise, and Weight Loss-Intervention Trial (DEW-IT), forty-four overweight, hypertensive adults on mono-therapy for hypertension were randomly allocated to either a control group or a comprehensive lifestyle intervention group [28]. The intervention comprised a low-sodium and hypo-caloric version of the DASH diet, for nine weeks, along with a supervised moderate-intensity exercise program three times per week. The control group received no intervention. At the end of the trial, in the intervention group the average total weight loss was 4.9 kg and the differences in 24/h ambulatory systolic and diastolic blood pressures were 9.5/5.3 mmHg, respectively, whereas the differences in daytime blood pressures were 12.1/6.6 mmHg, respectively. Thus, this trial clearly emphasizes the efficacy of comprehensive lifestyle modifications as adjuvant therapy in hypertensive adults, who are already on drug therapy; moreover, blood pressure reductions of the magnitude observed in this study resemble blood pressure reductions obtainable by means of pharmacological therapies.

These findings were extended by recent results of the PREMIER trial, which tested the combined effects of the DASH diet with "established" recommendations, comprising weight loss, exercise, and restriction of sodium and alcohol [98]. Participants were 810 adults with above-optimal blood pressure, including stage 1 hypertension (120-159 mm Hg systolic and 80-95 mm Hg diastolic), and who were not on antihypertensive medications. They were randomly allocated to one of three intervention groups: [1] "established," a behavioural intervention that implemented established recommendations; [2] "established plus DASH," which also implemented the DASH diet; and [3] an "advice only" control group. At the end of the trial (after 6 months), in the group assigned to lifestyle modification only, the established group, the mean net reduction in blood pressure was 3.7/1.7 mmHg, compared to the control group, whereas for the group that followed the established recommendations together with the DASH diet, the mean net reduction in blood pressure was 4.3/2.6 mmHg, compared to the control group. Thus, these findings indicate the feasibility of comprehensive lifestyle modifications and their beneficial effects on blood pressure for both normotensive individuals with above-optimal blood pressure and hypertensive individuals who are not receiving medication therapy.

CONCLUSIONS

Extensive and consistent evidence provides the scientific basis for clinical and public health strategies directed to long-term lifestyle modifications to prevent and reduce the burden of disease related to high blood pressure in both individuals and populations. The current lifestyle modifications that effectively lower blood pressure include: weight reduction if overweight or obese; reduction of dietary sodium intake; increased potassium intake; moderation of alcohol consumption among regular drinkers; adoption of a dietary plan based on the DASH (Dietary Approaches to Stop Hypertension) diet; and regular aerobic exercise.

In the clinical setting, a comprehensive lifestyle intervention represents a cost-effective therapeutic option among non-hypertensive individuals with above-optimal blood pressure levels as well as among hypertensive individuals who are not receiving medication therapy and are compliant with sustained lifestyle changes. In addition, comprehensive lifestyle modifications represent an essential adjuvant therapy in hypertensive individuals who are already on drug treatment. In the public health arena, there is an urgent need to develop and implement population-wide strategies aimed at substantial "societal" changes to tackle the current epidemic of hypertension in both developed and developing countries.

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