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ORIGINAL ARTICLE

Impact of dietary and lifestyle factors on the prevalence of hypertension in Western populations

JM Geleijnse[1], DE Grobbee[2] and FJ Kok[1]
[1]*Division of Human Nutrition, Wageningen University, Wageningen, The Netherlands;* [2]*Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands*

The impact of dietary and lifestyle factors on the prevalence of hypertension was quantified for Finland, Italy, The Netherlands, UK and USA. For this purpose, we combined data of blood pressure (BP) and risk factors distributions in these five countries with BP estimates from randomized controlled trials of dietary and lifestyle factors to obtain population attributable risk percentages (PAR%) for hypertension. Overweight made a substantial contribution to hypertension (PAR%: 11–17%), as was the case for excessive sodium intake (9–17%), low potassium intake (4–17%), physical inactivity (5–13%), and low intake of fish oil (3–16%). PAR% were smaller for low calcium intake (2–8%), low magnesium intake (4–8%), excessive coffee consumption (1–9%) and excessive alcohol intake (2–3%). We conclude that diet and lifestyle have a major impact on hypertension in Western societies. The relative significance of different risk factors varies among populations, which is important for preventive strategies.
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Keywords: population attributable risk; dietary and lifestyle factors; prevention

Introduction

Many dietary and lifestyle factors have been implicated in the aetiology of hypertension. However, an objective scientific understanding of their relative significance in the general population is lacking. The population attributable risk percentage (PAR%) provides insight into this complex matter, as it is based not only on the strength of the risk factor–blood pressure (BP) association but also on BP and risk factor distributions in the population.[1] The impact of dietary and lifestyle factors on the prevalence of hypertension was quantified for Finland, Italy, the Netherlands, the UK and the USA. PAR% was computed for the following modifiable risk factors: body weight, physical activity, and intake of alcohol, coffee, sodium, potassium, magnesium, calcium and fish oil (eicosapentaenoic and docosahexaenoic acid). Findings from this study may indicate priorities for preventive strategies to reduce the burden of hypertension in Western populations.

Correspondence: ILSI Europe a.i.s.b.l., publications@ilsieurope.be, fax +32 2 762 0044
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Methods

First, we obtained BP estimates for each dietary and lifestyle factor by performing metaregression analysis of randomised controlled trials, as described in detail elsewhere.[2–5]

Second, BP distributions (mean $\pm$ s.d.) were obtained for five Western populations using data from population-based surveys, such as the MONICA project.[6] Mean systolic BP was 139 ± 20 mmHg for Finland, 133 ± 19 mmHg for Italy, 127 ± 19 mmHg for the Netherlands, 130 ± 20 mmHg for the UK and 125 ± 20 mmHg for the USA. Under the assumption of a normal distribution, population proportions with systolic BP $\geqslant 140$ mmHg were estimated at 48% for Finland, 36% for Italy, 25% for the Netherlands, 31% for the UK and 23% for the USA.

Third, we defined risk categories for exposure to dietary and lifestyle factors. If possible, these were based on recommended dietary allowances or dietary guidelines for adults. Overweight was defined as a body mass index $\geqslant 25$ kg/m^2. For physical inactivity, we chose a general risk group definition of 'no exercise during leisure time, exclusive of walking'. Heavy alcohol consumption was defined as $\geqslant 3$ drinks per day and heavy coffee consumption as $\geqslant 4$ cups per day (one cup ≈ 125 ml). High sodium intake was defined as $\geqslant 2.4$ g/day (equals 6 g of salt). Low intake of potassium was defined as < 3.5 g, low

intake of magnesium as <350 mg and low intake of calcium as <750 mg per day. For fish fatty-acids (eicosapentaenoic acid and docosahexaenoic acid), low intake was defined as <200 mg per day. Distributions of dietary and lifestyle factors in the five populations studied were obtained from nationwide dietary surveys, such as NHANES,[7] and salt intake from the worldwide INTERSALT study,[8] as described in detail elsewhere.[5]

Finally, PAR% was calculated for each dietary and lifestyle factor within the five populations. The PAR% is the percentage of hypertension in a population that is caused by exposure to a risk factor and thus that can be eliminated if the risk factors are negated.[1] PAR% was based on only systolic BP (cutoff: 140 mmHg) because the proportion of population with isolated diastolic hypertension is negligible. Pooled systolic BP estimates from randomised trials (Table 1) were taken as the BP reduction that may be achieved after risk factor elimination. Calculation of the expected change in the prevalence of hypertension after risk factor elimination was performed using a JAVA™ applet for the standard normal distribution.[9] PAR% was obtained after multiplying this figure with the proper population exposed to the risk factor, divided by the prevalence of hypertension in that population (detailed calculations available from the authors).

Results

Weighted BP estimates for dietary and lifestyle factors, obtained by metaregression analysis of randomised controlled trials, are presented in Table 1. Overweight had the strongest effect on BP with an average decrease of 5/3 mmHg in weight loss trials (~1 mmHg/kg). BP decreases were 2–3 mmHg systolic and 1–2 mmHg diastolic in intervention studies of physical activity, alcohol reduction, coffee reduction, sodium reduction, potassium supplementation and fish oil supplementation. The BP effects of calcium and magnesium supplementation were smaller and only borderline statistically significant.

Table 1 BP response to dietary and lifestyle interventions: metaregression analysis of randomized controlled trials

			BP change (mmHg)[a]	
Dietary of lifestyle factor	*No. of trials*	*Size of intervention*[b]	*Systolic BP*	*Diastolic BP*
Body weight	25	−6.5±2.4 kg	−4.8 (−6.5, −3.1)	−3.4 (−4.7, −2.2)
Physical activity	49	+2.5±1.1 h/wk	−2.8 (−3.9, −1.7)	−1.8 (−2.6, −1.1)
Alcohol	13	−41±17 ml	−2.6 (−3.7, −1.4)	−1.4 (−2.0, −0.7)
Coffee	10	−4.9±0.9 cups	−2.2 (−3.9, −0.6)	−1.0 (−2.1, 0.0)
Sodium	40	−2.1±1.2 g	−2.5 (−3.4, −1.6)	−2.0 (−2.6, −1.4)
Potassium	27	+2.0±1.0 g	−2.4 (−3.7, −1.2)	−1.6 (−2.6, −0.6)
Magnesium	16	+483±216 mg	−1.3 (−2.9, 0.3)	−0.9 (−1.9, 0.1)
Calcium	36	+1.2±0.4 g	−1.5 (−2.8, −0.3)	−0.7 (−1.6, 0.1)
Fish oil[c]	36	+4.1±2.7 g	−2.1 (−3.2, −1.0)	−1.6 (−2.2, −1.0)

[a]Pooled BP estimate obtained from randomized controlled trials, weighted by trial sample size, with 95% confidence interval.
[b]Average change in dietary intake (per day) or lifestyle factor in trials.
[c]Supplementation of fish fatty-acids (eicosapentaenoic acid and docosahexaenoic acid).

Table 2 Exposure to risk factors and PAR% for hypertension in five Western populations

	Finland		*Italy*		*The Netherlands*		*UK*		*USA*	
Risk factor[a]	*Exposed*[b]	*PAR%*[c]	*Exposed*	*PAR%*	*Exposed*	*PAR%*	*Exposed*	*PAR%*	*Exposed*	*PAR%*
Overweight	0.60	12%	0.40	11%	0.48	19%	0.41	13%	0.60	25%
Physical inactivity	0.41	5%	0.58	10%	0.42	10%	0.63	11%	0.52	13%
High alcohol intake	0.18	2%	0.19	3%	0.15	3%	0.19	3%	0.13	3%
High coffee intake	0.48	4%	0.03	<1%[d]	0.48	9%	0.27	4%	0.05	1%
High sodium intake	0.84	9%	0.88	13%	0.81	17%	0.82	13%	0.78	17%
Low potassium intake	0.36	4%	0.74	10%	0.46	9%	0.80	12%	0.79	17%
Low magnesium intake	0.36	4%	0.98	8%	0.62	7%	0.80	7%	0.74	8%
Low calcium intake	0.25	2%	0.35	3%	0.28	4%	0.43	4%	0.60	8%
Low intake of fish fatty-acids[e]	0.39	3%	0.75	9%	0.85	15%	0.83	11%	0.85	16%

[a]Risk group definitions for dietary and lifestyle factors are given in the text.
[b]Proportion of the general adult population in risk category, estimated from nationwide surveys.
[c]The percentage of hypertension in a population that is caused by exposure to a risk factor and thus that could be eliminated if the risk factors are negated. The PAR% depends on the blood pressure effect of the risk factor (Table 1), the prevalence of risk factor exposure in the population (Table 2) and the prevalence of hypertension in the population (given in text).
[d]Prevalence of heavy coffee consumption in Italy may be underestimated (details given in text).
[e]Accurate population-based data are lacking and prevalence figures should be interpreted with caution.

Table 2 shows population proportions with unfavourable levels of risk factors in the five populations which, combined with BP estimates from randomised trials, were used to obtain PAR% for hypertension. PAR% calculation for overweight in Finland is explained as an example. For a 4.8 mmHg decrease in systolic BP (ie 139.0–134.2 mmHg), the prevalence of hypertension (systolic BP $\geqslant$140 mmHg) would decline from 48.0 to 38.5%. It is estimated that 60% of Finnish adults are overweight (Table 2). If 6 kg of weight loss (average reduction in trials) were achieved in this segment of the population, hypertension in Finland would decline by 5.7% (ie $0.60 \times 9.4\%$). Dividing this figure by the prevalence of hypertension yields a PAR% of 12%. Overweight made a substantial contribution to the prevalence of hypertension in all populations, with PAR% between 11% (Italy) and 25% (USA). PAR% was 5–13% for physical inactivity, 9–17% for high sodium intake, 4–17% for low potassium intake and 4–8% for low magnesium intake. The impact of alcohol was small (2–3%) in all populations. PAR% for low calcium intake was also small ($<5\%$), except for the USA (8%). PAR% varied among populations with respect to inadequate intake of magnesium (2–8%), fish fatty-acids (3–16%) and coffee (0–9%).

Discussion

This study shows that diet and lifestyle have a substantial impact on the prevalence of hypertension in Western societies, with different ranking of risk factors within populations. Overweight, physical inactivity, high salt intake and low potassium intake appeared to be the major contributors to hypertension in Western societies.

BP estimates in this study were obtained from randomised trials and are likely to be causal and fully attributable to the specific risk factors. We calculated expected changes in the prevalence of hypertension after a uniform shift of the population BP distribution to a lower level. However, it should be noted that this is a simplified model. Subject characteristics may influence BP response to intervention; for example, BP sensitivity to sodium is probably larger in populations with elevated BP, which we did not take into account in our study. Also, PAR% should be interpreted with caution when based on BP estimates with wide confidence intervals, for example for magnesium, for which the number of trials in metaregression analysis was small. PAR% in our study may be too conservative since they were calculated only for risk groups, whereas other people may also benefit from prevention. To illustrate, weight loss is known to also reduce BP in normal-weight subjects. Furthermore, we would like to emphasise that PAR% for different risk factors may not be fully additive owing to, for example, risk factor interactions. In case of hypertension, which has a multifactorial aetiology, the sum of PAR% for all risk factors combined could easily exceed 100%.

The total BP effect of all dietary and lifestyle interventions in this study was more than 20 mmHg. Cardiovascular risk strongly increases with BP, even in the 'normal' range.[10] In the large MRFIT study, 20 mmHg decrease in population systolic BP was associated with a 26% reduction in mortality, meaning 56 479 lives saved in the US male population.[11] We need to point out that prevalences of hypertension in our study are overestimated due to single BP measurements in epidemiological surveys.[12] However, this is unlikely to have had a large effect on PAR% and the ranking of risk factors in the different populations. Also, there are several uncertainties with regard to uniform assessment of risk factor prevalences in different populations. Data on intake of fish fatty-acids (eicosapentaenoic acid and docosahexaenoic acid) on a population-based level were scanty and the number of people consuming less than 200 mg/day could only roughly be estimated. For coffee, uniform assessment was hampered by differences in cup size among populations. We considered a cup of coffee to be equal to 125 ml, but for Italy cup size may be only 50 ml. A study by Ferraroni *et al*[13] among 395 Italian adults (median age of 50 years) showed an average coffee intake of 100–110 ml per day, which is in line with the low intake that we report. In a case–control study by Tavani *et al*[15] in Northern Italian women, however, over 10% consumed four or more cups of coffee per day,[14] and in another case–control study in this population[15] this prevalence exceeded 20% (cup size in these studies was not reported).

From this study, we conclude that effective dietary and lifestyle interventions could make a major contribution to the prevention of hypertension in Western societies. For several risk factors, the impact on hypertension varied among populations, which is important for setting priorities in preventive strategies. Hypertension itself, however, is not the outcome of primary interest. More research is needed to assess the total impact of diet and lifestyle on (cardiovascular) morbidity and mortality. Public health research in this field may be facilitated by standardised data collection on dietary and lifestyle factors in different countries.

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ORIGINAL ARTICLE

Hypertension, single sugars and fatty acids

P Valensi
Laboratory of Nutrition, Metabolic Diseases and Cardiovascular Prevention, Paris-Nord University, and Jean Verdier Hospital, AP-HP, Bondy, France

Macronutrients may induce various hemodynamic effects. In the fructose-fed rat blood pressure increase is associated with insulin resistance and enhanced sympathetic activity. In humans, oral glucose intake induces a slight and transient increase of blood pressure secondary to sympathetic activation. This increase may be higher in hypertensive subjects and followed by a significant fall in blood pressure in elderly subjects. Saturated fatty acid-enriched diet induces in male rats a significant increase in blood pressure related to sympathetic activation. Some observational and interventional studies suggest that *n*-3 polyunsaturated fatty-acids may reduce blood pressure in humans. Thus, both carbohydrates and fatty acid balance may contribute to blood pressure changes. The clinical relevance of these data should be evaluated in long-term trials, in particular in overweight and hypertensive subjects.
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Keywords: blood pressure; sugars; fatty acids; obesity; sympathetic nervous system; insulin resistance

Introduction

Hypertension is more prevalent among overweight people and may result from various mechanisms including insulin resistance, hyperinsulinaemia and, increased sympathetic activity.[1–4] Changes in food habits are also likely to contribute to the increase in blood pressure even before weight gain. The increase in caloric intake induces an augmentation of plasma catecholamines, which results from sympathetic activation.[5,6] These changes are accompanied by an increase in serum insulin and insulin resistance. The increase in serum insulin levels is probably involved for the most part in sympathetic activity enhancement, as suggested by the activation of the sympathetic nervous system during a euglycemic hyperinsulinaemic clamp.[7]

Macronutrients induce various haemodynamic changes. In this review, we examine the acute and long-term effects of single sugar and fatty-acid intake in rats and humans. Since overweight subjects are more susceptible to hypertension, we will also address the question of whether some of these effects might be relevant, in particular, to patients who are overweight and/or show insulin resistance.

Correspondence: ILSI Europe a.i.s.b.l., publications@ilsieurope.be, fax +32 2 762 0044

Haemodynamic effects of carbohydrates

Experimental data
Reaven *et al* have carried out a series of works investigating the occurrence of insulin resistance and the changes in blood pressure after single-sugar intake in rats. The introduction of fructose induces, within 10–15 days, insulin resistance, compensatory hyperinsulinaemia and a rise in blood pressure.[8,9] The introduction of glucose or sucrose in the diet without increase in total caloric intake during 2 weeks induces an increase in serum insulin without change in blood glucose, an increase in serum triglycerides and blood pressure, the latter being higher after sucrose.[10] The hypertensive effect of fructose has even been shown to be higher in rats with spontaneous hypertension.[11]

Kaufman *et al*[12] have compared the effects of diet enrichment in glucose or fat on body weight and blood pressure in normal rats. Blood pressure increased more in these rats than in normally-fed rats, whereas body weight increased similarly in glucose-fed rats as in those with a normal diet but less than in those with a fat-enriched diet.

Sympathetic activation and changes in endothelium function may be involved in the increase in blood pressure. In rats under a glucose-enriched diet, urine noradrenaline is increased as compared with rats under a normal diet.[12] In fructose-fed rats, sympathectomy prevents hyperinsulinaemia and hypertension.[13] In rats receiving fructose, rilmenidine, a central antihypertensive agent that acts

through I_1-medullar receptors of imidazoline, prevents the increase in body weight induced by fructose. Blood glucose, free fatty acids and glucose utilization become similar to that in control rats. This suggests that rilmenidine may improve the deleterious effect of fructose, in particular, on blood pressure and insulin resistance, by reducing sympathetic activity.[14] Thus, sympathetic activity is likely to play a central role in the occurrence of insulin resistance associated with single sugar enrichment. The increase in serum insulin secondary to insulin resistance is likely to contribute to sympathetic activation and the rise in blood pressure elicited by sugars.

Endothelium dysfunction has been clearly shown to be associated with obesity and insulin resistance. Insulin *per se* induces vasodilation by activating NO-synthase and nitric oxide (NO) production in smooth muscle cells. Endothelium dysfunction associated with insulin resistance may contribute to hypertension. The contribution of NO production in the prevention of hypertension in normal rats receiving a prolonged glucose infusion during 7 days has been tested using a previous treatment by L-NAME, an arginine antagonist that reduces NO synthesis. This treatment amplifies the increase in blood pressure induced by glucose infusion.[15] These data confirm the hypertensive effect of glucose and show that NO may minimise these effects. On the contrary, the hypertensive effect of glucose might be amplified if endothelium function is impaired. In addition, since NO depresses sympathetic activity, endothelium dysfunction might also elevate blood pressure by exaggerating glucose-induced sympathetic activation. Indeed alpha- and beta-adrenergic blockade prevents partly the deleterious effect of L-NAME combined with glucose on blood pressure.[16] Thus, the protective effect of NO against glucose-induced hypertension might be mediated by its depressive effect on sympathetic activity.

Data in humans

The intake of 100 g glucose has been shown to induce an acute moderate elevation (7 mmHg) in systolic blood pressure and a significant increase in heart rate.[17] We have studied the effect of 75 g glucose intake in middle-aged normal adults and observed a slight and sustained acceleration of heart rate (5 beats/min) without any significant change in mean blood pressure.[18] After a meal enriched in carbohydrates (85% of caloric intake), a significant increase in heart rate has been reported, whereas blood pressure decreased significantly by 30 min. The early increase in peripheral blood flow may have limited the increase in blood pressure.[19]

The role of sympathetic activity in the haemodynamic changes induced by carbohydrates has been investigated by various methods including serum catecholamine measurement, muscle sympathetic activity recording, and the analysis of heart rate and blood pressure variations.

Serum noradrenaline level and muscle sympathetic activity increase significantly after glucose intake, and a significant correlation has been reported between muscle sympathetic activation and serum insulin.[17]

In our experiment, sympathetic activation as evidenced by the increase in the low-frequency/high-frequency spectra ratio provided by spectral analysis of heart rate variations was probably involved in the late heart rate acceleration and might have limited the trend to a late hypotension related to splanchnic vasodilation and the peripheral vasodilation induced by insulin response.

Sympathetic activation together with vagal activity depression provoked by serum insulin increase[20] may be suspected to increase blood pressure in patients with basal hyperinsulinaemia, that is, overweight or hypertensive patients. Indeed, we have previously suggested that a high vagal activity may be protective against hypertension associated with obesity.[21] Since cardiac vagal activity is often depressed in overweight and hypertensive subjects,[22,23] the repetitive sympathetic activation induced by single-sugar intakes might together with vascular insulin resistance (resistance to the vasodilative effect of insulin) contribute to the elevation of blood pressure. However, this hypothesis should be tested in long-term experimental settings in humans. It may be mentioned that in nondiabetic overweight subjects an association was found between cardiac parasympathetic dysfunction and a higher long-term carbohydrate intake.[24]

Effects of carbohydrates on blood pressure in particular situations

Oral glucose intake has been shown to be followed by a significant acute increase in systolic blood pressure in a series of 40 subjects, 15 of them with moderate hypertension and 13 with glucose intolerance. Unfortunately, the data in the hypertensive subgroup have not been isolated.[25] Whether the effect of glucose on blood pressure increase is higher in hypertensive subjects than in subjects with normal blood pressure should be tested specifically.

We have analysed the haemodynamic changes after glucose intake in subjects older than 70 years and found a transient increase in blood pressure followed by a significant decrease (by 20 mmHg) without concomitant changes in heart rate or vagosympathetic activity. The lack of sympathetic activation might contribute to postprandial hypotension and dizziness induced by single sugars in some elderly subjects. In the same subjects, we have analysed haemodynamic parameters after a mixed meal. Blood pressure and heart rate changes were quite similar in these subjects and in younger ones.[18] Therefore glucose intake at variance with a mixed meal may induce in the elderly an inappropriate haemodynamic response with secondary hypotension.

Effects of fatty acids

Epidemiological data

Several epidemiological studies have suggested that the risk for coronary heart diseases is increased by saturated fatty-acids and decreased by mono and polyunsaturated fatty-acids (for a review, see[26]). Some studies have also reported interesting data regarding the link between fatty acids and blood pressure. In a cross-sectional Finnish study, mean blood pressure was associated with dietary intake of saturated fats and inversely with dietary intake of linolenic acid.[27] In the Health Professionals Follow-up Study, there was no significant association between fatty acids and incident hypertension after adjustment for other risk factors.[28] In the Paris Prospective Study II, the level of palmitoleic acid (a monounsaturated fatty acid) in serum cholesterol esters, which is supposed to reflect dietary saturated fats (since there is considerable mono-unsaturated endogenous synthesis from saturated fat), was associated with hypertension.[29] According to the ARIC (Atherosclerosis Risk In Communities) study, fatty-acid composition in plasma cholesterol esters has been associated with the 6-year incidence of hypertension. The results suggest that a lower plasma linoleic acid level and higher plasma levels of palmitic and arachidonic acids are associated with a higher risk of hypertension.[30] Arachidonic acid may act through changes in eicosanoid/prostaglandin metabolism, and the balance between thromboxan-A_2 (a vasoconstrictor agent) and prostacyclin (a vasodilating agent).

Experimental data in rats

Some experiments have tested the effect of lard on blood pressure in normal or castrated rats. In males a lard-enriched diet (50% of the energy content) induced a significant increase in blood pressure. However, this effect depends on gonadal function. Indeed, blood pressure increase in males was suppressed by castration and restored in castrated rats receiving testosterone supplementation. Moreover, in females lard did not induce any change in blood pressure but an increase was observed in ovariectomized females treated with testosterone.[31] Therefore, the effect of lard on blood pressure in rats depends on testosterone. In addition, Gerber *et al*[32] have shown that the sensitivity of small mesenteric arteries to noradrenaline is enhanced and endothelium function impaired in virgin rats fed with saturated fat (20% of energy content). Previous studies have reported an activation of sympathetic nervous activity in rats fed with saturated fat.[33] The impairment of insulin sensitivity in these rats together with a compensatory increase in serum insulin are likely to contribute to sympathetic activation and blood pressure increase.

Human studies

A decrease in blood pressure has been observed in hypertensive subjects after *n*-6 polyunsaturated-enriched diet. Several studies have provided evidence for protective effects of *n*-3 polyunsaturated fatty-acids against cardiovascular events and coronary restenoses. Rousseau *et al*[34] have reported that dietary *n*-3 polyunsaturated fatty-acid supplement reduces the increase in heart rate and blood pressure associated with psychological stress in rats. Similar protective effects against the rise in systolic blood pressure were found in spontaneously hypertensive rats, in rats with renovascular hypertension as well as in a hyperinsulinic rat model.[35,36] Some trials have tested the effects of *n*-3 fatty acids on blood pressure in man.

Cobiac *et al*[37] have shown that 6 g fish oil lowered blood pressure only in hypertensive subjects who consumed less than three fish meals per week. Morris *et al*[38] have reported the results of a meta analysis of 31 placebo-controlled trials including a total of 1356 subjects. After 3–24 weeks, fish oil consumption is accompanied by a blood pressure decrease. The authors were able to calculate that a supplement of 7.7 g *n*-3 fatty acids per day may lower systolic and diastolic blood pressure by 4 and 3 mmHg, respectively, in hypertensive patients.[38] Some moderate effects on blood pressure were also reported among hypercholesterolaemic patients and patients with cardiovascular disease, but little or no effect was reported among healthy normotensive subjects.

Many mechanisms may be involved in the beneficial effects of *n*-3 polyunsaturated fatty-acids on blood pressure. They improve membrane cell fluidity and prostanoic balance in favour of arterial dilation (EPA stimulates the synthesis of prostacyclin and inhibits the synthesis of thromboxan-A2). They also improve endothelium function and reduce cardiac adrenergic activity.

Conclusion

In conclusion, both carbohydrates and fatty acid balance may contribute to blood pressure changes. The experimental data on blood pressure increase are more convincing in rats than in humans. Sympathetic activation and endothelium impairment are likely to play an important role in these effects. Single sugars may induce a moderate and transient increase in blood pressure in healthy subjects but possibly more important effects in elderly subjects, and in patients with hypertension and/or overweight. Besides their atherogenic consequences, high saturated-fat diet may contribute to hypertension whereas polyunsaturated *n*-3 supplements seem to decrease blood pressure in hypertensive patients. Finally, there is lack of strong evidence for the relation between macronutrients and blood pressure over days or weeks. More human

clinical data are required to address the effects of various macronutrients on blood pressure through long-term trials, in particular, in overweight and hypertensive subjects. Such effects should also be tested in patients receiving antihypertensive treatments.

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ORIGINAL ARTICLE

Why and how to implement sodium, potassium, calcium, and magnesium changes in food items and diets?

H Karppanen, P Karppanen and E Mervaala
Institute of Biomedicine, Pharmacology, University of Helsinki, Helsinki, Finland

The present average sodium intakes, approximately 3000–4500 mg/day in various industrialised populations, are very high, that is, 2–3-fold in comparison with the current Dietary Reference Intake (DRI) of 1500 mg. The sodium intakes markedly exceed even the level of 2500 mg, which has been recently given as the maximum level of daily intake that is likely to pose no risk of adverse effects on blood pressure or otherwise. By contrast, the present average potassium, calcium, and magnesium intakes are remarkably lower than the recommended intake levels (DRI). In USA, for example, the average intake of these mineral nutrients is only 35–50% of the recommended intakes. There is convincing evidence, which indicates that this imbalance, that is, the high intake of sodium on one hand and the low intakes of potassium, calcium, and magnesium on the other hand, produce and maintain elevated blood pressure in a big proportion of the population. Decreased intakes of sodium alone, and increased intakes of potassium, calcium, and magnesium each alone decrease elevated blood pressure. A combination of all these factors, that is, decrease of sodium, and increase of potassium, calcium, and magnesium intakes, which are characteristic of the so-called Dietary Approaches to Stop Hypertension diets, has an excellent blood pressure lowering effect. For the prevention and basic treatment of elevated blood pressure, various methods to decrease the intake of sodium and to increase the intakes of potassium, calcium, and magnesium should be comprehensively applied in the communities. The so-called 'functional food/nutraceutical/food-ceutical' approach, which corrects the mineral nutrient composition of extensively used processed foods, is likely to be particularly effective in producing immediate beneficial effects. The European Union and various governments should promote the availability and use of such healthier food compositions by tax reductions and other policies, which make the healthier choices cheaper than the conventional ones. They should also introduce and promote the use of tempting nutrition and health claims on the packages of healthier food choices, which have an increased content of potassium, calcium, and/or magnesium and a lowered content of sodium. Such pricing and claim methods would help the consumers to choose healthier food alternatives, and make composition improvements tempting also for the food industry.
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Keywords: salt; sodium; potassium; calcium; magnesium; plant sterols; functional foods

Introduction

The objective of this paper is to review the role of dietary sodium, potassium, calcium, and magnesium in the pathogenesis, prevention, and treatment of elevated blood pressure (hypertension). This paper illustrates the reasons for the fact that the present average intakes of these mineral nutrients are remarkably different from the levels, which are encountered in 'Natural Diet', that is, in diets composed of unprocessed food (items). The evidence for or against the recent hypothesis that the genetic programs of man are best compatible with the intake levels, which are characteristic of diets composed of unprocessed foods ('Natural Diet'), is discussed. The current intakes of sodium, potassium, calcium, and magnesium are also compared with the levels, which are recommended by the US Department of Health and Human Services and the US Department of Agriculture.[1] On the basis of scientific evidence and current intake recommendations, it is proposed that, for the improvement of the control of hypertension in the community, the food manufacturers, governments, and other organizations should use different methods, which improve in a health-promoting manner the diets in general and the above-mentioned electrolytes in particular.

Correspondence: ILSI Europe a.i.s.b.l., publications@ilsieurope.be, fax +32 2 762 0044

Physiological basis for intimate connection of blood pressure with sodium, potassium, calcium, and magnesium

Among the dietary factors, which are connected to the present epidemic of high blood pressure, the mineral nutrients sodium, potassium, calcium, and magnesium are of particular interest. All of these mineral nutrients have important roles in both the control of cardiac output and peripheral vascular resistance, the main determinants of the blood pressure level.[2] On the other hand, the body uses the rise of blood pressure as the most powerful physiological mechanism in the maintenance of sodium balance to prevent sodium accumulation in the case of a high intake. By increasing the blood pressure level, the body is able to get rid of excess sodium by the pressure-natriuresis mechanism.[3,4] Interestingly, the sensitivity of the pressure-natriuresis mechanism and, hence, the excretion of excess sodium is markedly improved by increased intakes of potassium, calcium, and magnesium.[4,5] The development of sodium deficiency during very small intake or losses due to gastrointestinal causes, sweating, or blood loss can, in turn, be effectively prevented by decreasing the blood pressure. In fact, by lowering the blood pressure, the body is able to prevent renal sodium excretion completely.

Intakes of sodium, potassium, calcium, and magnesium: levels in natural diet, modern diet, and recommended diet

It has been suggested that the optimum dietary basis for good health is provided by a diet, which is in agreement with our genetic programmes. According to Eaton and Konner,[6] there is an optimum type and composition of food, which each species, including man, is genetically programmed to eat and metabolise.[6] For example, the lion is programmed to eat animal food only, while the antelope is programmed to eat plant food only. The nutrients provided by such foods are believed to provide optimum nutrition for the lion and antelope, respectively. In the case of wild animals, it is evident, *a priori*, that the genetic programming does not include any processing of food in the form of removal of, or enrichment with, any nutrient components. Human beings are believed to be programmed to eat and metabolise both plant and animal food.[6,7] It has also been suggested that the human genetic programme, which has remained essentially unchanged for at least the past 100 000 years, is best compatible with unprocessed mixed foods, that is, foods without removal of any nutrient components and without addition of any nutrients or other compounds.[6,7] According to this hypothesis, man-made changes in the composition of foods and diets would cause, or at least predispose to, a number of pathological conditions, including elevated blood pressure.

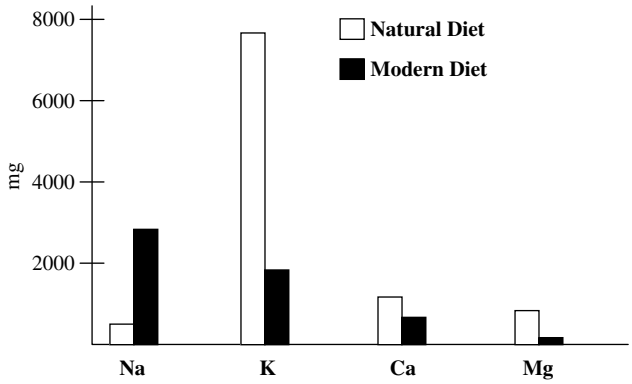

Figure 1 Sodium, potassium, calcium, and magnesium contents (calculated per 2100 kcal) in the Natural Diet and in the Modern Diet (average US diet, which served as the control diet in the DASH study; see below and Appel *et al*[8]). Data extrapolated from Eaton and Eaton III[7].

In view of the important connections of sodium, potassium, calcium, and magnesium with the physiological control of blood pressure and also many other body functions, it is interesting to compare the amounts of various mineral nutrients that are derived from the 'Natural Diet' with the amounts of nutrients that are obtained from current diets. It is also of considerable interest to evaluate the scientific data on the blood pressure effects of changes in the intakes of sodium, potassium, calcium, and magnesium away from the levels of the 'Natural Diet' on the one hand, and towards the levels encountered in the 'Natural Diet', on the other hand. Authoritative expert bodies have recently evaluated the scientific evidence on optimum intakes.[1] The levels derived from the Recommended Diet are given for comparison.

Natural diet

The levels of sodium, potassium, magnesium, and calcium in diets, which consist of unprocessed foods so that approximately two-thirds of the energy is derived from plant food and one-third from animal food, are illustrated in Figure 1 (data derived from Eaton and Konner[6] and Eaton and Eaton III[7]). If a daily energy need of 2100 kcal is satisfied by such a diet composition, the daily intake of sodium is approximately 500 mg, that of potassium about 7400 mg, that of calcium approximately 1100 mg, and that of magnesium about 800 mg.

Modern diet

The modern diets provide sodium, potassium, calcium, and magnesium in dramatically different amounts and ratios than the Natural Diet (Figure 1). In the average US diet, the energy-standardised intake (per 2100 kcal) of sodium was about 3000 mg a day, that is, approximately six-fold as compared with the genetically programmed diet.

By contrast, the potassium intake was as low as 1750 mg,[8] which is only 24% of the amount provided by the Natural Diet.

From the Modern Diet, the daily intake of calcium (about 440 mg;[8]) is remarkably lower than that from the Natural Diet, approximately 40% only.

The usual intake of magnesium (approximately 180 mg;[8]) is also very low (approximately 23% only) as compared with the amount provided by the Natural Diet.

Recommended diet

Recently, the recommended Dietary Reference Intakes (DRIs) have largely replaced the 1989 Recommended Dietary Allowances (RDAs; see US Department of Health and Human Services and US Department of Agriculture[1]).

The DRI for sodium is 1500 mg a day, while 2500 mg has been given as the maximum level of daily intake that is likely to pose no risk of adverse effects. Hence, the average current sodium intake of 3000–4500 mg a day in various westernised communities[9,10] exceeds clearly even the highest sodium intake level, which has been estimated to be safe.

The recommended intake of potassium for adolescents and adults is 4700 mg/day. Recommended intake of potassium for children 1–3 years of age is 3000 mg/day, for 4–8 years of age it is 3800 mg/day, and for 9–13 years of age it is 4500 mg/day.[1]

Hence, the current average potassium intake in USA is very low, only about 37% of the recommended level.

The DRIs for calcium are 1000–1300 mg per day. Therefore, the usual USA intakes are only 35–40% of the DRIs.

The magnesium intake recommendation is 420 mg for adult men.[1] No exact figures have been given for other groups, but the weight-based corresponding value for women would be approximately 300 mg a day. Therefore, the usual USA intake of 180 mg is only approximately 50% of the recommended level.

Pathophysiological basis for the hypertensive effect of current diets (Modern diet)

The average sodium intake is remarkably higher than the recommended or natural intake, which the body can handle without any difficulties and harms. Although suppression of the sodium-retaining renin–angiotensin–aldosterone system, together with other hormonal mechanisms, can improve the excretion of sodium to some extent, in the majority of individuals such mechanisms alone are not effective enough to increase the excretion of sodium enough to match the high intake.

Lifton *et al*[11] emphasised that, given the diversity of physiologic systems that can influence blood pressure, it is striking that all Mendelian forms of hypertension and hypotension solved to date converge on a final common pathway, altering blood pressure by changing net renal salt balance. Since most of the known Mendelian forms of high and low blood pressure have now been solved, the findings on the key role of salt in hypertension do not reflect an obvious selection bias.[11]

The elevated blood pressure levels, which are present in more than half of the population, contribute markedly to the output of sodium.[3] The estimated total number of adults with hypertension in 2000 was 972 million (957–987 million): 333 million (329–336 million) in economically developed countries and 639 million (625–654 million) in economically developing countries. The number of adults with hypertension in 2025 was predicted to increase by about 60% to a total of 1.56 billion (1.54–1.58 billion).[12]

The Intersalt study[9,10] as well as combined data from other studies[10] have shown that in the industrialised communities, the average intake of sodium is approximately 3000–4500 mg per day. The average blood pressure in various communities increases in a dose-related manner with increasing sodium intake. Moreover, weighted linear regression analyses have convincingly shown a correlation between the reduction in urinary sodium, an indicator of sodium intake, and the reduction in blood pressure.[13]

In addition to the high intake of sodium, the low intakes of potassium, calcium, and magnesium further increase the need for blood pressure rise in the maintenance of sufficient sodium output.[4,5]

Improvement of the intakes of sodium, potassium, calcium, and magnesium towards the natural levels lowers blood pressure

Effect of sodium reduction alone

In the second DASH study,[14] the rather vigorous sodium restriction alone, to approximately 40% of the usual level, during a control diet produced a fall of 6.7 mmHg in systolic blood pressure and 3.5 mmHg in diastolic blood pressure. A moderate sodium reduction to approximately 67% of the usual level produced a smaller fall in blood pressure. The average fall in systolic blood pressure was 2.1 mmHg and that in diastolic blood pressure, 1.1 mmHg.

Two recent meta-analyses[15,16] have revealed that an approximately 75 mmol a day (about 50%) reduction in the intake of sodium lowers blood pressure in both subjects with hypertension and normotensive individuals. In hypertensives, the fall in systolic blood pressure is about 5 mmHg and that in diastolic pressure, approximately 3 mmHg. In normotensives, the fall in systolic pressure is approximately 1.3–2 mmHg and that in diastolic pressure about 1 mmHg.

Effect of increased potassium intake alone

An increase of potassium intake by approximately 1.8–1.9 g a day has proved to lower the blood pressure of hypertensive subjects so that the average fall in systolic blood pressure is approximately 4 mmHg and that in diastolic pressure, about 2.5 mmHg[16,17] This increase in potassium intake is about 25% of the amount provided by a 2100 kcal Natural Diet, and not sufficient to raise the potassium intake in USA to the currently recommended level of 4.7 g per day.

Several mechanisms, such as increased natriuresis, reduced sympathetic nervous activity, and decreased pressor response to noradrenaline and angiotensin II, seem to be involved in the blood pressure lowering effect of potassium.[18]

Effect of increased calcium intake alone

Calcium supplementations, which have increased the total daily intake to more than 1000 mg a day, have produced an average fall of 1.4 mmHg in systolic and 0.8 mmHg in diastolic blood pressure.[19]

Improved sodium excretion, modulation of the function of the sympathetic nervous system, increased sensitivity to the vasodilatory action of nitric oxide, and decreased production of superoxide and vasoconstrictor prostanoids have been implicated in the antihypertensive effect of increased calcium intake.[18]

Effect of increased magnesium intake alone

According to a recent meta-analysis,[20] magnesium supplementation resulted in only a small overall reduction in blood pressure. The pooled net estimates of blood pressure change were −0.6 mmHg for systolic pressure and −0.8 mmHg for diastolic pressure. However, there was an apparent dose-dependent effect of magnesium, with reductions of 4.3 mmHg in systolic and of 2.3 mmHg in diastolic blood pressure for each 10 mmol/day increase in magnesium dose.

The antihypertensive effect of magnesium may be mainly due to its vasodilatatory effects.[21]

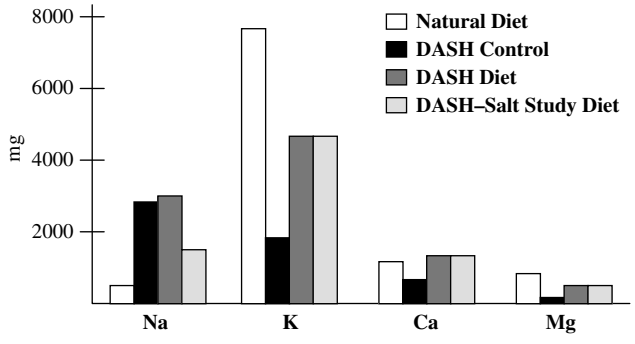

Figure 2 Sodium, potassium, calcium, and magnesium contents (calculated per 2100 kcal) in the DASH diets. For comparison, the contents in the Natural Diet and DASH control diet are also shown. Data adapted from Appel *et al*[8] and Sacks *et al*.[14]

Effect of multiple improvements

In view of the many and complex interactions between sodium, potassium, calcium, and magnesium in body physiology, one can easily realise that all deviations from the optimum levels should be simultaneously corrected for an optimum effect. However, in search for simple measures to combat high blood pressure, single-factor approaches aiming at sodium reduction only, or increase of one beneficial mineral nutrient only, have been used in most studies.

However, in the recent DASH studies,[8,14] the intakes of potassium, calcium, and magnesium increased simultaneously (Figure 2). These changes were produced through a change in the dietary pattern.

The term DASH is derived from studies called 'the Dietary Approaches to Stop Hypertension'.[8,14] As compared with a typical diet in the US, the DASH diet contains more fruits, vegetables, low-fat dairy products, whole grains, poultry, fish, and nuts. It contains only small amounts of red meat, sweets, and sugar-containing beverages, and it contains decreased amounts of total and saturated fats and cholesterol. The DASH diet provides larger amounts of potassium, calcium, magnesium, dietary fibre, and protein than the typical diet. The Reduced Sodium DASH Diet, which has proved particularly effective for blood pressure reduction, also contains less sodium than the typical US diet.[14]

Although the diets in different populations may differ considerably from that used as the control diet in the DASH study, the essential features are similar in all industrialised populations. As compared with the Natural Diet, the sodium level is very high while the levels of potassium and magnesium are very low. In most populations, the level of calcium is also low, but Finland and some other 'milk countries' make an exception in this respect.

The DASH diet produced a nearly 6 mmHg average fall in systolic blood pressure, and an approximately 3 mmHg fall in diastolic blood pressure. Importantly, among the subjects with hypertension, the fall of blood pressure was even more impressive. The average fall in systolic blood pressure was 11.4 mmHg and that in diastolic blood pressure 5.5 mmHg.

When even sodium was reduced from approximately 150 mmol a day to about 60 mmol a day, the average systolic blood pressure was lowered by approximately 9 mmHg, and the fall in diastolic blood pressure was about 4.5 mmHg. The effect of sodium reduction was more pronounced during the control diet than during the DASH diet.

Increased levels of potassium, calcium, and magnesium, and decreased levels of sodium: effects beyond blood pressure

Potassium may protect against stroke and other cardiovascular diseases by mechanisms, which are not related to blood pressure.[18,22] The antiatherosclerotic properties of potassium have recently created a lot of interest.[18]

The improvement of glucose tolerance appears to be one of the beneficial effects of potassium.[22,23]

Increased intake of calcium has an established place in the prevention of osteoporosis. There is evidence that calcium may also have beneficial effects on serum lipids (for a review, see Vaskonen[18]). Recently, it has been found that increased levels of dietary calcium and magnesium enhance the cholesterol lowering effect of plant sterols.[24,25] There is also increasing evidence that an increased intake of calcium may prevent and decrease obesity (for a review, see Vaskonen[18]).

Increased intake of magnesium appears to protect against ischaemic heart disease by several different mechanisms.[26]

Decreased intake of sodium decreases the urinary loss of calcium and, hence, protects against osteoporosis.[27,28] Decreased sodium intake decreases the potentially dangerous left ventricular hypertrophy also by mechanisms that are not dependent on the lowering of blood pressure.[4,29–31]

Safety of diets with increased levels of potassium, calcium, and magnesium, and decreased levels of sodium

It would, *a priori*, appear logical that the Natural Diet[6,7] and the nutrients, which such a diet provides, are both useful and safe. In a recent evaluation of the safety of the nutrient amounts, which can be derived from the Natural Diet, it was also concluded that

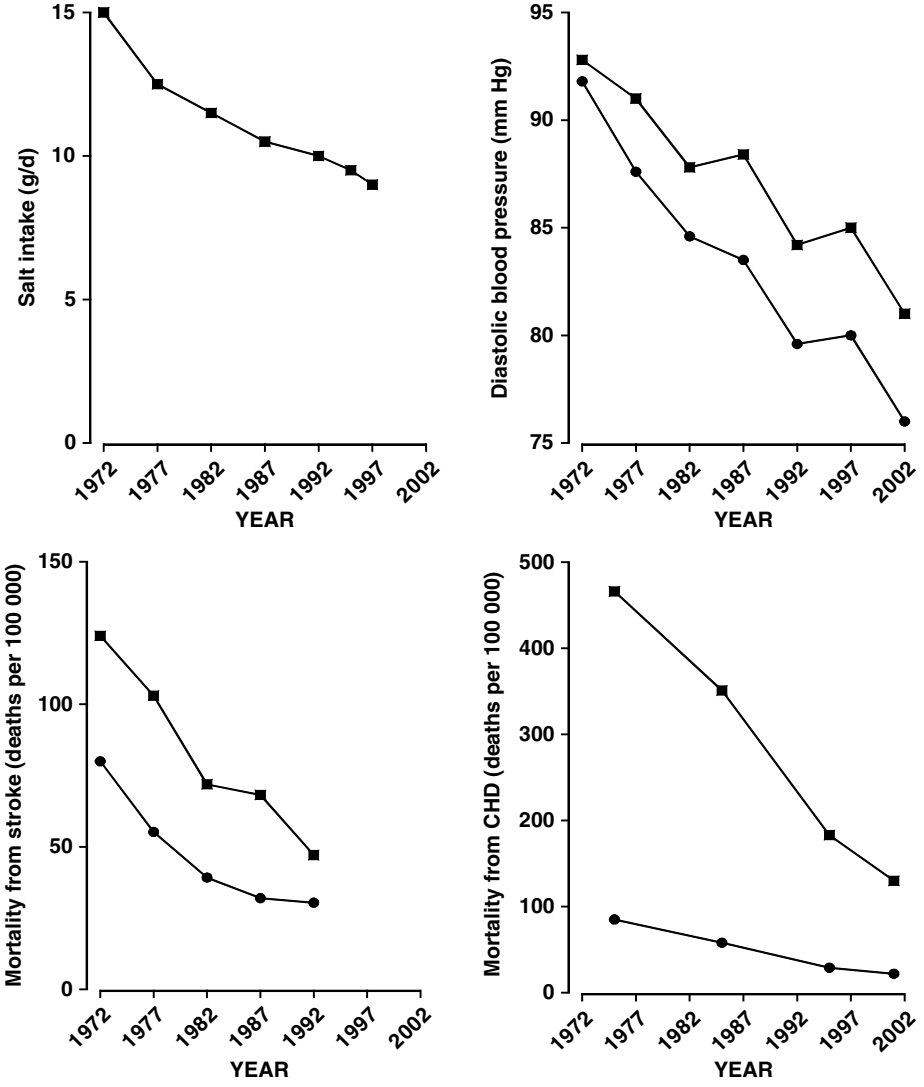

Figure 3 Decrease of salt intake, and lowering of the population blood pressure, and decrease of mortality from both stroke and ischaemic heart disease in Finland.

such amounts are safe, even though they are in some cases markedly different from the current average intakes.[32] Hence, moderate supplementation of the current diets with potassium, calcium, and magnesium can be considered safe for the population.

Unlike in most other countries, in Finland, a progressive and marked decrease in the average intake of salt has taken place during the past three decades (Figure 3).[33] During this period, there has been a remarkable 10 mmHg fall in the average diastolic blood pressure of the population. Moreover, in the middle-aged population, the death rate both from stroke and heart diseases has decreased by approximately 70% (Figure 3).[34-36] The age-adjusted overall mortality has also decreased remarkably so that the life expectancy has increased by several years both among women and men.[36]

The findings in Finland are consistent with an overall beneficial effect of a comprehensive population-wide sodium reduction.

Moreover, the conclusion of Tuomilehto *et al*[37] from a comprehensive prospective study in Finland was that high sodium intake predicted mortality and risk of coronary heart disease, independent of other cardiovascular risk factors, including blood pressure.

Magnitude of the effects on blood pressure makes improvements in the intakes of sodium, potassium, calcium, and magnesium warranted

The main thing, which determines the population impact of a blood pressure lowering factor, is the extent to which such a factor is implemented in the population. It should be noted that its importance greatly exceeds the importance of the effectiveness of a factor in an individual. The antihypertensive drugs can be used as an example to illustrate the fundamental difference between the effectiveness in individuals and the impact in preventing hypertension problems in the population. Antihypertensive drugs are the most effective agents in lowering blood pressure in the treated individuals. However, their role in the overall control of high blood pressure in the whole population is surprisingly small. The average long-term effect of antihypertensive drugs is an approximately 10 mmHg fall in the systolic blood pressure. A nationwide register kept by the Social Insurance Institution reveals that in Finland 8.5% of those aged 35–59 years were entitled to special reimbursement of antihypertensive medication at the end of 2004 (data kindly provided by professor Timo Klaukka, M.D., 2005). Since approximately nine individuals out of 10 do not receive the treatment, the average population effect of the present extensive use of antihypertensive drugs is one-tenth of 10 mmHg, that is, approximately 1 mmHg only. It is important to realise that any measure that can be implemented in all individuals, and has an average effect of 1 mmHg on systolic blood pressure, has a population impact which is equal to the effect of current antihypertensive drug therapy.

To take an example, potassium supplementation in moderate amounts lowers systolic blood pressure by 4.5 mmHg. If this is applied to the whole population, the population impact is more than four-fold as compared with the impact of blood pressure lowering drugs.

For many years, the high blood pressure guidelines have emphasised the need to decrease the sodium content of processed foods. So far, the food industries at large have failed to comply to any useful extent with this recommendation. Since up to 80% of the dietary sodium in many populations is obtained from processed, industry-produced foods, the average sodium intake shows no decreasing tendency in most populations. This shows that there are many big, unsolved problems, which are associated with the decrease in the use of salt.

One of the reasons for the reluctance of the food industries to reduce the amount of sodium, which is added in the course of the food processing, has been the opinion of some scientists. For example, Jurgens and Graudal[38] (24) stated in their recent report: 'The magnitude of the effect in Caucasians with normal blood pressure does not warrant general recommendation to reduce sodium intake.' The authors found that a reduced intake of sodium lowers systolic blood pressure by 1.27 mmHg in Caucasians with normal blood pressure. In individuals with elevated blood pressure, the fall in systolic blood pressure was remarkably greater, 4.18 mmHg. Since elevated blood pressure is present in approximately half of the population, the data of the authors indicate an average population effect, which is (1.27 mmHg + 4.18 mmHg)/2, that is, approximately 2.7 mmHg. This compares very favourably with the population impact of the antihypertensive drug treatment, which is less than half of the impact of a population-wide sodium reduction. Therefore, lack of effectiveness is not the real reason for the failure in the sodium reduction efforts.

Owing to taste habits, consumers may be reluctant to accept products with remarkably less salty taste. It is not tempting for the food industry to manufacture low-salt products, which are unacceptable for the consumers. The ions (sodium and chloride) also have good water binding and other useful technological effects on the structure of several food items. Owing to these factors, a decrease in the average intake of salt in a modern population is likely to be sluggish.

How to implement the potassium, calcium, magnesium and sodium changes in the population?

Due to the factors mentioned above, rather than focusing on salt (sodium) only, it may be wise to also

Table 1 Sodium (Na) and potassium (K) content of various food items

Food item	*Na per 100 g*	*Na per 1000 kcal*	*K per 100 g*	*K per 1000 kcal*
Tomato	2.5	139	290	16111
Tomato ketchup	1360	15111	400	4444
Sunflower seeds	3	5	690	1139
Vegetable margarine	760	1389	15	27
Milk	44	647	160	2353
Butter	650	889	18	25
Unprocessed meat	61	257	340	1435
Processed meat (ham)	920	7077	240	1846
Whole wheat flour	0.8	3	390	1322
Doughnut	210	457	120	261
Wheat flake cakes	270	740	370	1014
Orange	1.6	39	150	3659
Broccoli	7	333	400	19048

The values are expressed as mg/100 g and as mg/1000 kcal. The unprocessed food items are emphasised by bold italics. Data derived from Rastas M, Seppänen R, Knuts L-R, Karvetti R-L, Varo, P (eds). *Nutrient Composition of Foods*. Publications of the Social Insurance Institution: Finland, Helsinki, 1993.

Table 2 Calcium (Ca) and magnesium (Mg) content of various food items

Food item	*Ca per 100 g*	*Ca per 1000 kcal*	*Mg per 100 g*	*Mg per 1000 kcal*
Tomato	9	500	11	611
Tomato ketchup	28	311	18	200
Sunflower seeds	116	191	355	586
Vegetable margarine	21	38	18	33
Milk	120	1765	11	162
Butter	24	33	2,6	4
Unprocessed meat	6.7	28	22	93
Processed meat (ham)	5.7	44	15	115
Whole wheat flour	26	88	130	441
Doughnut	24	52	16	35
Wheat flake cakes	35	96	120	329
Orange	54	1317	13	317
Broccoli	48	2286	24	1143

The values are expressed as mg/100 g and as mg/1000 kcal. The unprocessed food items are emphasised by bold italics.

use the other measures, which have proved to be effective and may be more acceptable both for consumers and the industry. The best scientifically based and technically suitable possibility, which has already been shown to be useful, is offered by the known beneficial effects of increased intakes of potassium, calcium, and magnesium.

In theory, there are several possibilities to change the intakes of the important mineral nutrients towards the genetically programmed levels, which are effective and safe in the control of elevated blood pressure.

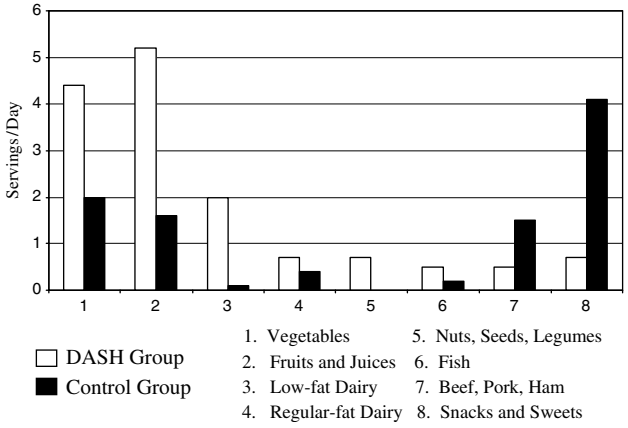

Figure 4 Consumption of different food items in the control group and the DASH group.

1. Replacement of the use of processed food items with the use of unprocessed natural foods would have dramatic effects on the intake of the mineral nutrients (Tables 1 and 2). Complete replacement of the processed foods would result in intakes that are equal with those derived from the Natural Diet (Figure 1). However, one has to realise that the use of processed food items is not decreasing. A continuously increasing proportion of the daily diet in industrialised countries consists of processed foods. It is hardly possible to change this trend in the present-day world.

2. The use of the DASH diet instead of the usual diet is currently recommended by the high blood pressure guidelines.

This approach has proved to be effective in carefully designed research settings. However, one should realise that the changes, which the population ought to do from the usual diet to the DASH diet, are remarkable, as illustrated by Figure 4.

Implementation of even much smaller changes in the dietary habits of the population has proved to be very difficult and slow. The DASH diet warrants recommendation, but the impact of the recommendation remains to be seen.

3. 'Functional food' ('food-ceutical'/'nutraceutical') approach

By far the easiest way, in principle, would be to change the composition of the processed food items that the population most likes and is used to eating. In Finland and some other populations, the enrichment of foods with iodine has been used with excellent success to combat the endemic goitre problem. In USA and some other countries, the enrichment of milk with vitamin D has been a successful measure to prevent vitamin D deficiency. The high effectiveness of this kind of method is due to the fact that it does not require any efforts from the population, and still practically all individuals receive the beneficial 'treatment'.

Enrichment of processed food items with appropriate potassium, calcium, and magnesium com-

pounds would bring the levels of these mineral nutrients towards those found in natural, unprocessed foods. Such enrichment in several widely used foods would be able to improve the total intake of these nutrients to such an extent that they are able to produce remarkable beneficial effects on blood pressure. To avoid excessive increases in the intakes of potassium, calcium, and magnesium, it is not advisable to enrich all industrially processed foods with these mineral nutrients. The food items that are most suitable for such enrichments may be different in various communities with different food traditions.

Even a modest decrease in sodium would further improve the health effects of this enrichment-based approach.

Even partial application of this principle has proved successful in the control of hypertension. Replacement of common salt with potassium- and magnesium-enriched and sodium-reduced salts lowers blood pressure[23,39] and produces even other beneficial effects, such as improvement of glucose tolerance.[23]

Proposed actions

(1) Various health education and other means, which promote the replacement of high-sodium and low-potassium, low-calcium, and low-magnesium food items in the diet, should be effectively used.

The Reduced Sodium DASH- diet, which comprises high-potassium, high-calcium, and high-magnesium food items, which have a low content of sodium (salt), has proved to be highly beneficial. Therefore, this type of diet should be promoted.

Since a comprehensive change in the dietary habits of a community has proved to be a very slow process, other approaches are also needed.

(2) The so-called 'functional food/nutraceutical/food-ceutical' approach, which corrects the composition of extensively used processed foods, is likely to be particularly effective in producing immediate beneficial effects.

For the food industry this is a big challenge, but at the same time a major opportunity for innovative companies to improve the competitiveness of their products. Many processed foods could be enriched with appropriate potassium, calcium, and magnesium compounds to compensate for the losses of these important nutrients during processing. Whenever possible, the sodium levels should be decreased in the products, which have added salt or other added sodium compounds.

To further increase the competitiveness, such foods could be made even more health promoting by concomitant enrichment with other healthy compounds, such as plant sterols. Such composition changes result in foods that affect beneficially both blood pressure and serum cholesterol, the two major causative factors in heart diseases and stroke.[24,25]

It has proved to be easy to enrich products that contain added salt, with potassium and magnesium compounds by using potassium- and magnesium-enriched salt[23,39] Enrichment of different food items with potassium, calcium, magnesium, and plant sterols has also proved to be possible without adverse effects on taste or other important properties.[40] Recently, several calcium-enriched foods, such as milk products and juices, have become available.

(3) In USA, the Food and Drug Administration (FDA) encourages the production and use of foods that have a high content of calcium or potassium and a low content of sodium by allowing for such products health claims, which help in health education and are tempting for the consumers. The European Union and national governments should promote healthier food choices by allowing, on good scientific basis, various nutrition and health claims, which help the consumers to choose healthier alternatives.

(4) Tax reduction and other methods should also be used to promote the availability and use of healthier food compositions.

Conclusions

1. The present average sodium (salt) intake of approximately 3000–4500 mg per day in various industrialised populations is remarkably higher than the recommended intake and even exceeds the level of 2500 mg, which has been recently given as the maximum level of daily intake that is likely to pose no risk of adverse effects on blood pressure or otherwise.
2. The present average potassium, calcium, and magnesium intakes are remarkably lower than the recommended intake levels.
3. Decreased intake of sodium alone, and increased intakes of potassium, calcium, and magnesium each alone decrease elevated blood pressure. The most pronounced effects are brought about by a combination of several of these dietary factors.
4. The most recent US recommendations emphasise decrease in sodium, and increase in potassium, calcium, and magnesium intakes, which are characteristic of the so-called DASH (Dietary Approaches to Stop Hypertension) diets. Such changes bring the levels towards the levels that are encountered in the Natural Diet, and have an excellent blood pressure lowering effect.
5. For the prevention and basic treatment of elevated blood pressure (arterial hypertension), various methods to decrease the intake of sodium and to increase the intakes of potassium, calcium, and magnesium should be comprehensively applied in the communities.

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ORIGINAL ARTICLE

Effects of exercise, diet and their combination on blood pressure

RH Fagard
Department of Molecular and Cardiovascular Research, Hypertension and Cardiovascular Rehabilitation Unit, Faculty of Medicine, University of Leuven, KU Leuven, Leuven, Belgium

Epidemiological studies suggest an inverse relationship between physical activity or fitness and blood pressure. In a meta-analysis of 44 randomized controlled intervention trials, the weighted net change in conventional systolic/diastolic blood pressure in response to dynamic aerobic training averaged −3.4/−2.4 mmHg ($P<0.001$). The effect on blood pressure was more pronounced in hypertensives than in normotensives. This type of training also lowered the blood pressure measured during ambulatory monitoring and during exercise. However, exercise appears to be less effective than diet in lowering blood pressure ($P<0.02$), and adding exercise to diet does not seem to further reduce blood pressure.
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Introduction

Essential hypertension is undoubtedly a multifactorial 'disease' and it is very unlikely that only one causal factor is involved. Its pathogenesis is based on the interaction between genetic and environmental/lifestyle factors. Genetic variance has been shown in family and twin studies, but the exact nature of the postulated genetic defect remains largely unknown. Environmental and lifestyle factors that have been invoked to explain an elevated blood pressure include sodium, alcohol and caloric intake, stress and physical inactivity. Many epidemiological studies have analysed the relationship between habitual physical activity or physical fitness and blood pressure, but the results are not quite consistent. Whereas several studies did not observe significant independent relationships, others concluded that blood pressure or the incidence of hypertension is lower in fitter or more active subjects.[1] However, it remains difficult to ascribe differences in blood pressure within a population to differences in the levels of physical activity or fitness, because of the potentially incomplete statistical correction for known confounders and because of the possible influence of confounding factors that were not considered or that cannot be taken into account, such as self-selection. Therefore, longitudinal intervention studies are more appropriate to assess the effect of physical activity and training on blood pressure. In the present review, we will assess the effects of dynamic physical exercise on blood pressure from longitudinal intervention studies in man. The review will be restricted to studies in adults. Blood pressure was most often measured in resting conditions, but also by the use of ambulatory monitoring techniques or in response to stress, particularly during exercise testing.

Correspondence: ILSI Europe a.i.s.b.l., publications@ilsieurope.be, fax +32 2 762 0044

Blood pressure at rest

Overall results on resting blood pressure
Many longitudinal studies have assessed the effect of dynamic aerobic training on resting blood pressure, but essential scientific criteria have not always been observed. Inclusion of a control group or control phase is mandatory. To avoid selection bias, allocation to the active or control group or the order of the training and nontraining phases should be determined at random. Ideally, subjects in the control group or in the control phase should be seen regularly, preferably as frequently as those in the training program; some authors even included low-level exercise as placebo treatment. We recently presented a meta-analysis of 44 randomised controlled trials on the effect of dynamic aerobic or endurance exercise on blood pressure at rest in otherwise healthy normotensive or hypertensive individuals.[2,3] Of the 2674 participants 65% were men. Nineteen studies comprised only men, four only women, and the others included both sexes. Some studies involved several groups of subjects or applied different training regimens in the same

participants, so that a total of 68 training groups/programs are available for analysis. The average age of the groups ranged from 21 to 79 years (median: 44). Duration of training ranged from 4 to 52 weeks (median: 16) with a frequency of 1–7 weekly sessions (median: 3) of 15–70 min each, including warm-up and cool-down activities (median: 50). The exercises involved walking, jogging, running in 69% of the studies, cycling in 50%, swimming in 3% and other exercises were included in 23% of the training regimens. The average training intensity in the various groups varied between 30 and 85% of maximal exercise performance (median: 65).

Control data were collected only at the beginning and at the end of the control period in 23 studies; three control groups were subjected to light dynamic or recreational exercises, 10 were seen at least once in the research facilities and another eight were contacted regularly by the investigators. Resting blood pressure was measured by an automatic device in five of the 44 studies; when pressure was measured by the use of a random zero device ($n=15$) or by conventional (or unspecified) methodology ($n=24$), the investigator was blinded to the treatment in only five and three studies, respectively.

Table 1 summarises the overall results. In the 68 study groups, the changes of blood pressure in response to training, after adjustment for the control observations, ranged from +9 to −20 mmHg for systolic blood pressure (SBP) and from +11 to −11 mmHg for diastolic pressure. The overall net changes averaged −3.4/−2.4 mmHg ($P<0.001$), that is, after adjustment for control observations and after weighting for the number of trained participants that could be analysed in each study group, whose total number amounted to 1529. Peak oxygen uptake increased significantly, whereas heart rate and body mass index (BMI) decreased (Table 1). When expressed in net percent change, peak oxygen uptake increased by 11.8% (95% CL: 10.3; 13.4) and heart rate and BMI decreased by, respectively, 6.8% (5.5; 8.2) and 1.2% (0.8; 1.7). In 16 of 68 study groups, in which average baseline blood pressure was in the hypertensive range (SBP $\geqslant$140 or diastolic blood pressure (DBP) $\geqslant$90 mmHg), the weighted net blood pressure decrease was significant and averaged 7.4/5.8 mmHg; the blood pressure reduction was also significant and averaged 2.6/1.8 mmHg in the 52 study groups in which baseline blood pressure was normal, irrespective of antihypertensive therapy. In addition, when normotensive and hypertensive subjects followed the same training program, the blood pressure decrease was greatest in the hypertensives.[1]

In other recent meta-analyses, which included 29[4] and 54[5] randomised controlled trials irrespective of baseline blood pressure of the participants, the training-mediated decreases of SBP/DBP averaged 4.7/3.1[4] and 3.8/2.8 mmHg,[5] respectively.

Influence of other characteristics

Meta-analyses concluded that there was no significant effect of age[3] or baseline BMI[3,5] on the exercise-induced changes in blood pressure. The blood pressure response was also not related to changes in BMI,[3,5] which ranged from approximately −1.5 to +0.5 kg/m^2 among the various study groups. The influence of gender is more difficult to assess because many studies included both men and women. Kelley[6] reported a small but significant reduction of blood pressure in studies that only involved women, all of whom were normotensive at baseline. Among three ethnic groups, black participants had significantly greater reductions in SBP and Asian participants had significantly greater reductions in DBP compared with white participants;[5] however, there were only four studies in black participants and six in Asians. With regard to the characteristics of the training program, exercise frequency,[2,4,5] type,[5,7] intensity[2,4,5] and time per session[2] did not appear to have an effect on the blood pressure response. The change of blood pressure was, however, somewhat smaller in studies of longer duration,[2,5] most likely because participant adherence to the intervention program decreased over time.

Ambulatory blood pressure

Among randomised controlled trials, 12 applied ambulatory blood pressure monitoring.[8] Six reported the average 24-h blood pressure, nine the average daytime blood pressure from early morning

Table 1 Baseline data and net changes in response to dynamic exercise training

		Baseline	*Net change*	
	N	*Mean (95% CL)*	*Mean (95% CL)*	P
Blood pressure (mmHg)				
Systolic	68	126.2 (123.3; 129.0)	−3.4 (−4.5; −2.3)	<0.001
Diastolic	68	79.9 (77.9; 82.0)	−2.4 (−3.2; −1.6)	<0.001
Peak oxygen uptake (ml/min/kg)	59	31.4 (29.6; 33.2)	+3.7 (+3.2; +4.3)	<0.001
Heart rate (beats/min)	48	71.1 (69.3; 72.9)	−4.9 (−5.9; −3.9)	<0.001
Body mass index (kg/m)	64	25.6 (25.0; 26.1)	−0.34 (−0.46; −0.22)	<0.001

Values are weighted means and 95% confidence limits (CL).

to late evening, and four night time pressure. As an earlier analysis based on controlled and uncontrolled studies suggested that night time blood pressure is not or much less influenced by exercise training,[1] the current analysis is based on daytime blood pressure in nine studies and on 24-h blood pressure in the three studies, which did not report a separate full-day ambulatory pressure. Baseline blood pressure averaged 135/86 mmHg and the exercise-induced weighted net change in blood pressure −3.0 (−4.8; −1.3)/−3.2 (−4.3; −2.2) mmHg.

Exercise blood pressure

The effect of endurance training on blood pressure during exercise can be analysed, either by considering the data at a fixed workload or by considering the effect at a relative workload—that is, at a certain percentage of the pretraining maximal aerobic power and of the usually higher post-training maximal aerobic power. In the current overview, only the more relevant first approach will be used. In eight randomized controlled trials[8] blood pressure was measured during bicycle exercise at a median work load of 100 W (range: 60–140 W). Blood pressure was measured during treadmill exercise at an energy expenditure of ∼4 METS in two other studies. Baseline exercise SBP averaged 180 mmHg and heart rate 124 beats/min. The weighted net training-induced change in SBP amounted to −7 (−9.5; −4.5) mmHg and heart rate decreased by 6.0 (2.7; 9.2) beats/min.

Limitations

Several limitations of individual studies should be mentioned. Subjects in the control group or control phase were seldom examined as regularly as those in the training program or they were not followed during control. In addition, it is difficult if not impossible to blind the participants to the treatment in training studies. Many studies did not mention that the investigator who measured blood pressure at rest or during exercise was not aware of the treatment group and automated techniques were often not used. Participants were not always advised to keep diet or lifestyle constant throughout the study periods. Other shortcomings involve methodological issues such as methods of randomization; statistical analysis; handling of drop-outs; keeping of log books; monitoring of exercise intensity; time between last exercise session and blood pressure measurement.

Mechanisms of the training-induced changes of blood pressure

Haemodynamic data

We identified 12 randomized controlled studies (17 study groups/programs) in which blood pressure, cardiac output and heart rate were measured and stroke volume and systemic vascular resistance calculated.[9] Baseline mean blood pressure ranged from 85 to 121 mmHg and averaged 101.5 mmHg. Table 2 summarizes the weighted net percent changes of haemodynamic variables. Training reduced mean blood pressure by 4.9% in these studies. On average, there was no significant effect of training on cardiac output so that the change in blood pressure could be attributed to a decrease in systemic vascular resistance. Heart rate decreased by 9% and stroke volume increased by 15%.

Basic mechanisms

Possible mechanisms linking blood pressure, physical activity and fitness have been reviewed elsewhere.[8,10,11] It is likely that the sympathetic nervous system is involved. A meta-analysis of 13 study groups from nine randomised controlled training studies showed a highly significant weighted net reduction of plasma noradrenaline of 29% (15;42) ($P<0.001$).[9] In addition, the lack of an effect on blood pressure during sleep, when sympathetic activity is low, indirectly supports the involvement of the sympathetic nervous system in the hypotensive effect of training. The renin–angiotensin–aldosterone system is also potentially important through its effects on blood volume and arterial pressure.[10] More recently, it has been suggested that improvement of endothelial function contributes to the reduction of blood pressure after training.[12–14] It is likely that the lowering of blood pressure by training is multifactorial and further studies are needed to elucidate the mechanisms.[9]

Physical training, diet and blood pressure control

We identified 10 randomized trials in which the influence of diet was compared with that of exercise alone and/or with the combined effects of diet and exercise in mostly overweight subjects.[3] Two of these studies did not include a nonexercise nondiet control group, so that the results have not been adjusted for control data in the meta-analysis. Study duration ranged from 4 to 52 week (median = 38). Table 3 summarizes the results for the paired comparison of exercise and diet (11 study groups). Only physical training increased peak oxygen

Table 2 Net haemodynamic changes (%) in response to dynamic exercise training

	N	*Mean (95% CL)*	P
Mean blood pressure	17	−4.9 (−7.0; −2.7)	<0.001
Cardiac output	17	+1.4 (−4.7; +7.5)	NS
Heart rate	16	−9.1 (−13.0; −5.2)	<0.001
Stroke volume	15	+14.9 (+5.6; +24.2)	<0.01
Systemic vascular resistance	17	−7.4 (−13.2; −1.6)	<0.05

Values are weighted means and 95% confidence limits (CL).
N = number of study groups.
NS = not significant.

Table 3 Baseline data and changes in response to exercise and to diet

	Exercise (E)		*Diet (D)*	*E vs D*[a]
	N	*Mean (95% CL)*	*Mean (95% CL)*	P
Age (year) BL	11	49.9 (45.9; 53.9)	49.3 (45.2; 53.4)	
Peak VO_2 BL (ml/min//kg)	10	31.6 (28.5; 34.8)	31.4 (28.3; 34.5)	
CH		+3.4 (+2.3; +4.4)	+1.0 (−0.2; +2.1)	<0.01
BMI BL (kg/m)	11	28.3 (26.9; 29.6)	28.6 (27.1; 30.1)	
CH		−0.42 (−0.67; −0.17)	−1.58 (−2.18; −0.97)	<0.01
SBP BL (mmHg)	11	125.6 (120.1; 131.1)	124.5 (118.8; 130.1)	
CH		−3.6 (−5.2; −2.0)	−5.9 (−7.7; −4.1)	<0.01
DBP BL (mmHg)	11	81.8 (77.5; 86.1)	80.9 (77.0; 84.8)	
CH		−2.7 (−3.8; −1.7)	−4.2 (−5.9; −2.4)	<0.05

Values are weighted means and 95% confidence limits (CL).
N = number of groups; VO_2 = oxygen uptake; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; BL = baseline; CH = change.
[a]Paired comparison of training-induced changes with exercise and with diet.

Table 4 Baseline data and changes in response to exercise plus diet and to diet alone

	Exercise+diet (ED)		*Diet (D)*	*ED vs D*[a]
	N	*Mean (95% CL)*	*Mean (95% CL)*	P
Age (year) BL	11	48.5 (45.4; 51.6)	48.7 (45.6; 51.8)	
Peak VO_2 BL (ml/min/kg)	9	29.7 (25.2; 34.2)	29.1 (24.3; 33.8)	
CH		+5.4 (+4.1; + 6.6)	+0.8 (−0.03; +1.7)	<0.001
BMI BL (kg/m)	11	28.6 (27.1; 30.1)	28.6 (27.0; 30.2)	
CH		−2.04 (−2.73; −1.35)	−1.66 (−2.37; −0.95)	<0.001
SBP BL (mmHg)	1	129.4 (120.1; 138.7)	128.3 (120.1; 136.5)	
CH		−7.1 (−9.9; −4.4)	−6.8 (−9.8; −3.9)	=0.84
DBP BL (mmHg)	11	83.1 (77.0; 89.2)	82.1 (76.6; 87.6)	
CH		−5.5 (−7.5; −3.4)	−4.2 (−6.0; −2.4)	=0.14

Values are weighted means and 95% confidence limits (CL).
N = number of groups; VO_2 = oxygen uptake; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; BL = baseline; CH = change.
[a]Paired comparison of training-induced changes with exercise+diet and with diet.

uptake. The reduction in BMI was significantly more pronounced in the diet groups than in the exercise groups. Finally, the reduction of blood pressure with diet alone (−5.9/−4.2 mmHg) was superior to that of exercise alone (−3.6/−2.7 mmHg). The results on the comparison of combined exercise and diet intervention with diet alone are shown in Table 4 (11 study groups). Only the combined intervention increased peak oxygen uptake. Diet alone was less effective in reducing BMI than the combined intervention. Nevertheless, there was no evidence that adding physical training to diet was more effective for blood pressure control than diet alone. It appears therefore that dynamic aerobic training is less effective than diet in lowering blood pressure and that exercise does not add to the blood pressure reduction by diet alone.

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ORIGINAL ARTICLE

Hypertension prevention: from nutrients to (fortified) foods to dietary patterns. Focus on fatty acids

A Grynberg
INRA-Paris 11 UMR1154, Nutrition Lipidique et Régulation Fonctionnelle du Cœur et des Vaisseaux, Faculté de Pharmacie, Châtenay-Malabry, France

Diet affects significantly the incidence and severity of cardiovascular diseases and fatty acid intake, in its qualitative as well as quantitative aspects, and influences several risk factors including cholesterol (total, LDL and HDL), triglycerides, platelet aggregation and blood pressure, as evidenced in the 2001 WHO report. This review focuses on the qualitative concern of lipid intake, the various classes of fatty acids of the lipid fraction of the diet, saturated, monounsaturated and polyunsaturated, and their effects on blood pressure. Saturated fat have a bad file and several experimental studies in the rat showed a progressive increase in blood pressure in response to a highly saturated diet. Moreover, a highly saturated diet during gestation led to offspring which, when adults, presented a gender-related hypertension. The mechanism of this effect may be related to the polyunsaturated/saturated ratio (p/s). During the past 20 years, *trans* fatty acids have been suspected of deleterious health effects, but the investigations have shown that these fatty acids display a biological behaviour close to that of saturated fatty acids (SFA). Moreover, epidemiological investigations did not confirm the relationship between *trans* fatty acids and cardiovascular pathology. Polyunsaturated fatty acids have been shown to exert a positive action on hypertension. This effect could be attributed to the alteration of the p/s, but mainly to the ω3 polyunsaturated fatty acids (PUFAs). The comparison of several animal models led to the conclusion that long-chain ω3 PUFAs (eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)) can prevent the increase in blood pressure and reduce established hypertension, but the efficient dose remains an object of discussion. Moreover, the two long-chain ω3 PUFAs, EPA and DHA, display specific effects, which vary with the aetiology of hypertension, because their mechanism of action is different. DHA acts on both blood pressure and heart function (heart rate and ECG) and interferes with the adrenergic function. Conversely, EPA, which is not incorporated in cardiac phospholipids, has no effect on the heart and its mechanism of action is largely unknown. Although it is accepted by the scientific community that the intake of EPA and DHA needs to be increased, we will have to discover new ways to do it, since marine products are the main source of these fatty acids, and this source is not inexhaustible.
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Introduction

Cardiovascular pathology represents in developed countries the first cause of mortality before cancer. Healthcare improvements and their significant effects on infectious diseases, discovery of new efficient treatments in chronic diseases and significant lifespan increase, all have contributed to this ranking. The major cardiovascular diseases such as angina, infarct or heart failure are often associated with risk factors, which belong to three main classes, physiological factors (age, gender, genetic background), pathological factors (hyperlipidemia, *hypertension*, diabetes, obesity) and life conditions (smoking, exercise, alcohol, dietary behaviour). In this context, hypertension is the cardiovascular risk factor with a very high occurrence. Rare in the developing countries, hypertension is one of the most frequent and worrying disease in western countries. In spite of significant improvements in detection and treatment, blood pressure values remain most often poorly controlled. Like hyperlipidemia, diabetes and obesity, hypertension has become dramatically common in developed countries. Defined on the basis of systolic blood pressure above 140 mmHg and/or a diastolic blood pressure above 90 mmHg, epidemiological studies reveal that approximately 10–15% of European people can be ranked as hypertensive. Due to its insidious characteristics, its high occurrence and its contribution to the development of cardiovascular diseases,

Correspondence: ILSI Europe a.i.s.b.l., publications@ilsieurope.be, fax +32 2 762 0044

hypertension is one of the major problems in public healthcare. Ageing is the main factor in the development of hypertension, partly because of the increasing arterial stiffness whose occurrence increases with age. Moreover, as a pathology related to reduced physical exercise and plethoric food intake, diabetic and obese people are more sensitive to hypertension. Although frequently based on a genetic background, hypertension is often triggered by nutritional factors (or nutritionally induced dysfunctions) including obesity, insulin resistance and excessive consumption of alcohol or salt. Some nutrients have thus been incriminated in spite of a very poor scientific file able to demonstrate the direct link between this specific consumption and the development of hypertension (excess fat intake, saturated fatty acids (SFA); excess carbohydrates, fast sugars, etc.). This is due to the difficulty to demonstrate the direct relationship between a nutrient and the onset of hypertension, mainly because of the heterogeneity of the disease and the variability among population subgroups in the responses to a specific food component.

Blood pressure is controlled by the complex interaction between cardiac output and peripheral arterial resistance. Hypertension results from the imbalance between the various mechanisms contributing to pressure regulation, such as hyperactivity of the sympathetic system or altered Renin–Angiotensine–Aldosterone system as elicited by numerous environmental factors, including nutrients or stress.[1] *Per se*, hypertension is not really a pathology of the vascular bed, but becomes a significant vascular risk factor when the increased blood pressure interacts with the biology of the vessel wall and triggers its dysfunction. When arterial tension reaches an excessive level, chronic lesions appear in the arteries and related organs (like kidneys, heart, brain and eyes). The target tissue is the arterial and arteriolar wall with significant alterations in compliance and remodelling, and the occurrence of microtrauma, which increase the arterial sensitivity to atherosclerotic plaque installation. Thus, the definition of hypertension is arbitrary and is mainly used to define the high-risk groups.[2] Hypertension is ranked moderate for constant values above 140/90 mmHg before 50 years and severe for constant values above 160/95 mmHg after 50 years,[3] but varies spontaneously with circumstances (day *vs* night, ambient temperature, exercise, stress). The treatment strategies are based on modifications of life conditions including weaning from smoking, weight control, increased exercise, decreased alcohol and salt consumption and numerous efficient pharmaceutical treatments.[4] However, as stated in the *American Heart Association* nutrition report,[5] most of the factors that contribute to the development of hypertension can be influenced by diet. For these reasons, it has become necessary to try to identify the mechanisms by which a given nutrient may prevent or trigger hypertension and also the possible interactions between different groups of nutrients.[6]

Dietary fatty acids

It is well known that in western countries, the unbalanced diet favours lipid intake, which represents approximately 45% of the daily energy intake (80–100 g for a 2000 kcal daily intake), instead of the 30–35% recommended (approximately 65 g for a 2000 kcal daily intake). However, in addition to this excess in fat consumption, the nature of these fats is a major issue, which is not sufficiently controlled. The SFA often represent 50% of the fatty acid intake, whereas they should only represent 10%. On the contrary, the proportion of the polyunsaturated fatty acids (PUFA) could be significantly increased.[7]

It is difficult to evaluate the PUFA requirement in humans, but some indications are available. In France, the requirements of ω6 PUFAs to allow optimised biological functions have been evaluated to be around 6%, supplied as linoleic acid.[8] For the ω3 PUFAs, 1% supplied as linolenic acid and 0.4% supplied as long-chain ω3 PUFAs (eicosapentaenoic acid and docosahexaenoic acid) are considered as satisfactory. However, the intake in ω3 PUFAs, and mainly in long chains, has to be higher in specific physiological circumstances like pregnancy and breast feeding, mainly for vision and nervous development of the neonates. A dietary ω3/ω6 ratio between 1/4 and 1/6 is usually recommended (Table 1).

- Palmitic acid (C16:0) and stearic acid (C18:0) are the main saturated fatty acids in human food and represent 15–20 and 5–10% of total circulating fatty acids, respectively. Palmitic acid (but not stearic acid) was reported to contribute significantly to the increase in blood cholesterol level. For most of the consumers, saturated fat means animal fat. The large majority of the consumers consider that the saturated fatty acid intake results from meat or dairy products consumption, and often does not take into consideration that animal fat may also supply PUFAs, since the p/s (polyunsaturated/saturated ratio) is in the 10–12 range in beef tallow but in the 1–2 range in chicken fat. Similarly, vegetal fat is considered to supply PUFAs, whereas it largely contributes to the total saturated fatty acid intake (polyunsaturated mar-

Table 1 ω3/ω6 ratio in various diets

Population	*ω3/ω6 ratio*
Greenland	1/3
Japan	1/3
Paleolithic	1/5
EC	1/10–1/50
USA	1/30–1/50
Mean recommended ratio	1/6–1/4

garines, or food products containing 'vegetable oil', which in fact are cocoa, palm or copra).
- Oleic acid (C18:1 ω9) is the main monounsaturated fatty acid in food and also the main circulating fatty acid in human blood (30–45% of plasma fatty acids).
- PUFA of the two series (ω6 and ω3) are essential fatty acids that have to be provided by food. The 18-carbon precursors are mainly supplied by vegetable oils as linoleic acid (18:2 ω6, in corn, peanut, sunflower or soybean oil) or α-linolenic acid (18:3 ω3, in soybean or rapeseed oil). Longer chains are supplied by meat products for the ω6 PUFAs (liver, eggs) and sea products for the ω3 PUFAs (fish and sea mammals).

Some vegetable organisms contain a Δ12-desaturase able to create a group of two nonconjugated double bonds in oleic acid to give linoleic acid. Some other organisms can further desaturate to α-linolenic acid by a Δ15-desaturase. Numerous animal cells can convert these 18-carbon precursors in long-chain PUFAs, through a series of successive elongation and desaturation steps (Figure 1), but no transfer between the two series can occur. All mammals including humans possess Δ6- and Δ5-desaturases, and can thus produce the biologically active PUFAs arachidonic acid (AA, 20:4 ω6) and eicosapentaenoic acid (EPA, 20:5 ω3). In humans, this metabolic activity is highly efficient in the liver and adrenals and much less in the heart, brain and kidney. Conversely, Δ4-desaturase can be found only in algae and marine animal species. The Δ4-desaturation step leading to end products like docosahexaenoic (DHA, 22:6 ω3) involves an additional elongation step and Δ6-desaturase in a more

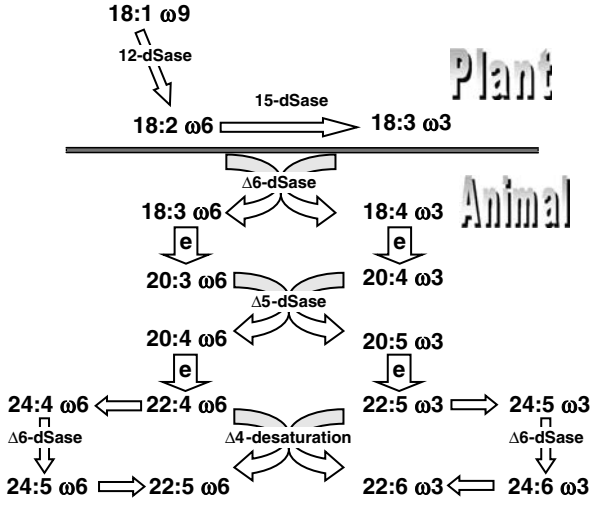

Figure 1 Metabolic pathway of the synthesis of biologically active long-chain polyunsaturated fatty acids by successive elongation and desaturation (e = elongase, dSase = desaturase). When available, the last Δ4-desaturation step includes three steps: 1 = elongation, 2 = desaturation step by Δ6 desaturase and 3 = peroxysomal β-oxidation step.

sophisticated pathway,[9] which does not take place in several organs like the brain and heart (Figure 1). However, several organs, including the heart and nervous tissue, are unable to realize this Δ4 desaturation step, which makes the exogenous supply of DHA necessary. This overall conversion process was shown to be influenced by several factors, both physiological (PUFA supply, *trans* fatty acids, ω6 to ω3 ratio, insulin, catecholamines and ageing) and pathological (alcohol, malnutrition, inflammatory bowel disease, diabetes and neuropathies). Due to multiplicity of the ω6 PUFA sources and the fact that the major biologically active ω6 PUFA (AA) is a Δ5-desaturase product, it is easy to foresee that an increase in ω6 PUFA intake will balance biological requirements in the population. On the contrary, the situation is different for ω3 PUFAs, whose main biologically active fatty acid (DHA) has to be supplied by food. The satisfactory ω3/ω6 ratio in the biological membrane can reach 1/2 in several tissues, whereas it is only 1/15 in western diet. The heart is a good example, since it is unable to produce any DHA,[10] which is the major ω3 PUFA contributing to the membrane structure. The dietary ω6/ω3 ratio appears as a very important factor. Although it is clear that it has to be increased in most populations, it is not a factor easy to handle. One reason for this is because the ω6/ω3 ratio in a given food ingredient can vary with technology or culture conditions. It is known that the ω6/ω3 ratio in eggs can vary from 1/3 in Greece to 1/50 in USA, as well as the meat of beef grown on grass (1/3) differs from the meat of grain-fed beef (1/15). Another reason is because these ratios most often refer to α-linolenic acid as ω3 PUFA and to the α-linolenic/linoleic acid ratio. The important information has also to consider the value of long-chain ω3 PUFAs, and mainly DHA, whose supply, until now, depended only on marine products. Evidently, increasing the dietary α-linolenic acid intake does not result in a significant DHA increase (unlike in the ω6 series where the most important metabolite is the product of the Δ5 desaturase). Moreover, a relative excess of ω6 PUFAs (high ω6/ω3 ratio, even with a high/ω3 content) counteracts the good metabolic utilization of ω3 PUFAs. Due to the concurrence of desaturases, the low available amount of α-linolenic acid is poorly transformed in higher metabolites, and hence in DHA. Already considered as efficient in the perinatal period for the development of neonate retina and cognition, the dietary supply in DHA is now viewed as necessary for cardiac and vascular health.

Hypertension and SFA

Due to their negative effect on cholesterol metabolism, the SFA suffer from a very bad image in the cardiovascular field. Conversely, very few data are available on the specific effect on blood pressure.

Several experimental investigations have evidenced the progressive increase in systolic blood pressure due to a highly saturated diet in animals.[11] Most of these work in animals, as well as all the investigations in humans, reported in fact the effects of high fat diets making it difficult to distinguish the consequence of lipid excess from the specific effects of SFA. SFA were reported to increase systolic blood pressure in male rats, but not in female or gonadectomized male rats.[11] Interestingly, this sensitivity to SFA was restored in castrated male rats given testosterone. On the contrary, feeding a diet rich in lard to pregnant rats also affected systolic blood pressure in adult offspring, even if fed a normal diet, but the female offspring were more sensitive than the male to this foetal nutrition-induced hypertension.[12] These results could be related to the saturated/polyunsaturated fatty acid ratio in endothelium, since it was shown that a saturated diet in rat increases catecholamine sensitivity and decreases endothelium-dependent relaxation mesenteric arteries.[13] Some epidemiological studies including a 'saturated fat' arm have focused on cholesterol, circulating lipids, atherosclerosis, coronaropathies and stroke, but not on blood pressure. However, the ARIC study (Atherosclerosis Risk in Communities) showed that in hypertensive men, the cholesterol esters are characterized by a significantly higher content in palmitic acid and lower content in linoleic acid,[14] which could be characteristic of a saturated fat diet (Figure 2). The mechanical investigations on SFA are not fully informative, because the p/s ratio is also altered, because the total fat intake is often altered and because the associated insulin resistance is *per se* a highly significant hypertension factor. However, a gender-related mechanism has been evidenced in several reports but has not yet been understood and remains to be elucidated.

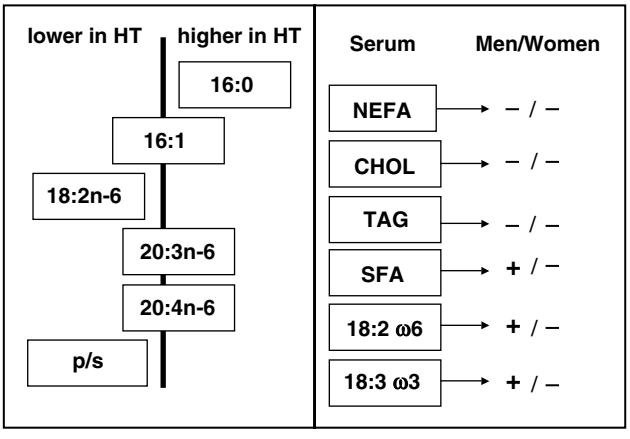

Figure 2 The ARIC study. Left panel: relationship between hypertension and plasma cholesterol ester fatty acid content. Right panel: blood predictors of vasodilation function (NEFA: nonesterified fatty acids, CHOL: cholesterol, TAG: triacylglycerol, SFA: saturated fatty acids, 18:2 ω6: linoleic acid, 18:3 ω3: α-linolenic acid).

Hypertension, monounsaturated and *trans* fatty acids

Transcultural investigations like the Seven Country Study[15] reported an inverse relationship between monounsaturated fatty acid consumption and cardiovascular mortality. These results have been confirmed by epidemiological studies like the Ireland–Boston Diet Heart Study[16] or the Lyon Heart Study.[17] The Nurse Study[18] showed that in women, a 5% increase in monounsaturated fatty acid and PUFAs decreases the cardiovascular risk by 19 and 38%, respectively. These studies demonstrated that monounsaturated fat contributes to the reduction of LDL cholesterol and the increase of HDL cholesterol (in part via the reduction in SFA), but they brought no experimental information on blood pressure and the influence of monounsaturated fatty acids on blood pressure remains largely unknown.

Dietary *trans* fatty acids are mainly produced by hydrogenation of unsaturated fatty acids in the rumen of ruminants (which leads essentially to *trans* vaccenic acid 11 *trans*-C18:1) or by technology-based partial hydrogenation of vegetable oils (which leads essentially to elaidic acid, 9 *trans*-18:1) or by high-temperature cooking of highly polyunsaturated oils. In the last two decades, nutritionists have been very suspicious of the health effects of *trans* fatty acids. Several authors reported the deleterious effect of high *trans* fatty acid intake on serum lipid profile (cholesterol), a result that deserves consideration by the cardiologist. However, no experimental evidence could be reported on the influence of *trans* fatty acids on blood pressure in spontaneously hypertensive rats,[19] and epidemiological investigations did not confirm the relationship between *trans* fatty acids intake and cardiovascular diseases.[20] In addition, the multicentric Transfair study concluded that *trans* fatty acids are not associated with an unfavourable serum lipid profile at the current European intake levels.[21] Conformational studies suggest that trans-monounsaturated fatty acids are viewed as SFA in the cell and thus display the biological behaviour of a saturated fatty acid (they are incorporated in a phospholipid structure in place of a saturated fatty acid). This is partly explained by steric features showing large similarities between *trans*-monounsaturated fatty acids and unsaturated fatty acids and between *trans*-PUFA and monounsaturated fatty acids (Figure 3).

Hypertension and PUFA

The decrease in blood pressure in moderate hypertensive patients by an increased ω6 PUFA supply, mainly linoleic acid from vegetable oils, is now well accepted in the scientific community.[5] This supplement allows a significant increase in p/s and linoleic acid and supports the conclusions of the ARIC Study showing the relationship between hyperten-

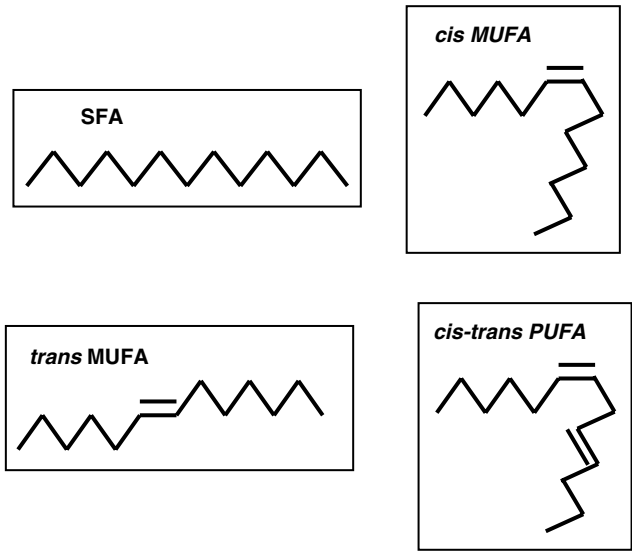

Figure 3 Conformation of the *cis vs trans* double bonds in unsaturated fatty acids.

sion and high plasma p/s and linoleic acid.[14] However, a greater part of the investigations focuses on ω3 PUFAs. Everybody knows the beneficial effects on cardiovascular disease prevention associated with the consumption of the long-chain ω3 PUFAs (EPA, DPA and DHA) provided by marine oils. Numerous studies reported outstanding results with a significant decrease (20–50%) in cardiac events and mortality. Some of these studies involved diets containing marine oils rich in these long-chain ω3 PUFAs like in the DART Study[22] and the GISSI-prevenzione Study,[23] and some other studies involved diets rich in the precursor α-linoleic acid as in the Lyon Heart Study[17] or the Indo-Mediterranean Diet Heart Study.[24] Unfortunately, only some of these studies investigated blood pressure and most of them increased both ω3 PUFAs and p/s, making it hypothetic to discuss the very effect of ω3 PUFAs on blood pressure. More recently, some investigators suggested that long-chain ω3 PUFAs can affect the pressure level and focused on the chain length specificity. Forsyth *et al*[25] reported that breast-fed infants and infants fed a DHA + AA enriched formula display at the age of 6 years a mean blood pressure significantly lower than that of the children previously fed an 18-carbon-PUFAs enriched formula. This arouses interest to investigate which ω3 PUFA can influence blood pressure and the associated mechanism.

Experimental investigations: the importance of aetiology

In experimental hypertension, it is easy to decide the aetiology of hypertension and to investigate the animal before and after the onset of the mechanism leading to hypertension. Experimental hypertension results either from pressure overload (systolic overload) induced by systemic hypertension or aortic coarctation, or from volume overload (diastolic overload) induced by cardiac output increase. Numerous animal models of hypertension have been developed, particularly in the rat, including secondary renovascular hypertension (Glodblatt model), hyperaldosteronism by desoxycorticosterone overload (DOCA rat), essential hypertension (the Spontaneously Hypertensive Rat displaying hypertension of central origin, or the NEDH rat developing spontaneous catecholamine-secreting pheochromocytom), salt-sensitive models (Dahl rat) and mineralocorticoïd intoxication or glucocorticoïd administration (model of the Cushing syndrome). Moreover, in these models, cardiac hypertrophy is associated with the development of hypertension. The comparison of these various models allows a fine interpretation of the mechanisms involved, and several have been used in the investigations on the effect of ω3 PUFAs. Investigations on hypertension resulting from psychosocial stress in rats showed that EPA and DHA can delay the onset of hypertension, improve associated cardiac function impairments and increase spontaneous heart rate.[26] Other studies reported a limitation by fish oil of the systolic blood pressure increase in essential hypertension,[27] reno-vascular hypertension[28] and insulin resistance.[29]

Clinical studies

The Tromso Study revealed that the blood pressure lowering effect of ω3 PUFAs is correlated to the composition of the plasma ω3 PUFA rich phospholipids.[30] A high dose supplement with long-chain ω3 PUFAs (3–9 g/day) reduces significantly both systolic and diastolic pressure in patients with a moderate hypertension. Similarly, in an intervention study on a group declaring not to consume any fish and displaying a moderate hypertension (systolic $<$ 180, diastolic $<$ 110), a fish oil supplement (6 g/day, representing 5 g of EPA + DHA) reduced significantly both systolic and diastolic blood pressure.[31] Interestingly, the same fish oil supplement failed to elicit any hypotensive effect in the group declaring three or more fish meals per week, and in patients displaying a plasma content in phospholipid ω3 PUFA above 175 mg/l. Other studies with very low doses reported (150 mg DHA and 30 mg EPA) a positive effect on systolic pressure but no effect on diastolic blood pressure.[32] The clinical investigations in humans tend to confirm the hypothesis that ω3 PUFAs display antihypertensive properties,[25,30,32–34] in spite of some discrepancies.[35,36] In a meta-analysis, Morris *et al*[31] outlined the variability of experimental factors (dose, group size, duration of the experiment and patient selection) as a major cause of discrepancy. The biochem-

ical and physiological effects of ω3 PUFAs are evidently dose dependent, and most of the significant results in humans have been obtained with high doses.[37]

The mechanisms involved

Deeper investigations on ω3 PUFAs specific effects reveal that their effect on blood pressure is correlated to the plasma phospholipid composition in long chains EPA and DHA. These hypotensive properties appear not only related to the modification of membrane fluidity but also to their capacity to influence prostanoid balance, which affects constriction and dilation of the arterial wall.[38] The replacement of AA by either EPA or DHA in various structural phospholipids (platelets, endothelium, heart) alters the functional prostacycline/thromboxane balance towards vasodilatation. In spite of the fact that α-linolenic acid is easier to increase in the general diet, the effect of this precursor on blood pressure is poorly documented and the beneficial effects of ω3 PUFAs on blood pressure are attributed to the higher metabolites EPA and DHA. However, this known effect on prostanoids is not the single mechanism proposed. The incorporation of DHA in cardiac membrane phospholipids was shown to affect adrenergic function *in vitro*[39] and *in vivo*. In rats with metabolic syndrome (mild hypertension, hyperinsulinaemia and hypertriglyceridaemia), a pure DHA supplement (200 mg/kg per day) significantly affected the increase in blood pressure *in vivo*. Additionally, this supplement significantly lowered heart rate and reduced the QT interval length.[29] Conversely, a pure EPA supplement also lowered blood pressure but failed to affect heart rate and QT interval. DHA readily enters cardiac membrane phospholipids, but not EPA, suggesting that unlike EPA, the mechanism of action of DHA may involve the regulation of adrenergic function, like β-blockers. This model of hypertension is complex and involves several mechanisms including a contribution of catecholamines, which explains why DHA and EPA may act on different components of the pathology. A similar study was realized in patients displaying a mild hypertension and a mild dyslipidemia (Figure 4).[40] Ambulatory pressure was recorded during either DHA or EPA supplementation. DHA (4 g/day) was found to lower systolic blood pressure and heart rate, like in rats. In these conditions, EPA did not elicit any significant effect. In a model of essential hypertension in the rat (spontaneously hypertensive rat) with a high catecholamine contribution, DHA prevented the development of hypertension, but not EPA, unlike in metabolic syndrome hypertension.[41] Each long-chain ω3 PUFA has thus a specific mechanism of action, and displays variable antihypertensive properties depending on aetiology. The mechanism of DHA involves the adrenergic function and adrenergic signalling, as discussed above, and outlined by the synergic effects of fish oil and β-blockers on hypertension in humans.[42]

a

	Effect of EPA	Effect of DHA	
24h mean SyP	-2.5	-5.8	*
24h mean DiP	-1.3	-3.3	*
24h mean Rate	+2.0	-3.5	*
Day SyP	-0.6	-3.5	*
Day DiP	-0.1	-2.0	*
Day Rate	+2.7	-3.7	*

b

g/d	conditions	Sys BP	Dia BP
3-9 ω3	Mild HT, men	⇩	⇩
6 ω3	Mild HT, eating fish plasma ω3 PUFAs >175 mg/l	⇔	⇔
5 ω3	Mild HT, not eating fish plasma ω3 PUFAs <175 mg/l	⇩	⇩
0.15 DHA	Mild HT, men	⇩	⇔
4 DHA	Mild HT, men	⇩	
4 DHA	Mild HT, men	⇔	

Figure 4 Differences between EPA and DHA in mild hypertension. (a) Ambulatory blood pressure recorded during 24 h in overweight mildly hyperlipidaemic men (data from Mori *et al*[40]). (b) Effect of DHA or EPA alone on systolic and diastolic blood pressure in mild hypertension reported in various studies.

These data all confirm the relationship between ω3 PUFAs and hypertension, although animal and human investigations are in fact different in scope. The clinical studies were made with a dietary supplement given to patients with an established hypertension, in order to attribute to the dietary supplement a 'therapeutic value'. In this context, such a dietary treatment should be considered as additive to the hypotensive strategy. And this observation allows a flashback to the GISSI-prevenzione study,[23] which reported that long-chain ω3 PUFAs did not lower blood pressure in post-infarct patients. However, the number of patients receiving β-blockers was probably very high and the effect of DHA involving adrenergic function may be difficult if the patients under β-blockers are not excluded. On the contrary, preclinical investigations in animals were conducted with a dietary supplement given before the development of hypertensive pathology, in order to attribute to the dietary supplement a 'preventive value'. This 'preventive value' is difficult to assess in humans and was thus not thoroughly investigated. The results of a cross-sectional analysis on 9758 men, aged 50–59 years,

without coronary heart disease were published recently, and they demonstrated that fish oil consumers display, as compared with non-fish consumers, a lower heart rate and lower systolic and diastolic blood pressure.[43] Another concern is the specificity of EPA and DHA in this context, which questions the efficiency of the precursor α-linolenic acid. The conversion of α-linolenic acid to EPA is limited in men (and more generally in mammals) and further transformation to DHA acid is very low.[44] This ω3 PUFA may thus contribute to influence the prostanoid balance, but does not significantly affect the cardiac membrane DHA status. Moreover, the meta-analysis of the various randomised control trials did not evidence a significant effect of α-linolenic acid intake (for a few weeks) on systolic or diastolic blood pressure,[45] and the relationship between α-linolenic acid intake and blood pressure remains a question of debate. Some discussions on possible dietary strategies to help control blood pressure are ongoing, merely at the beginning of the pressure rise, when a pharmaceutical prescription is not yet necessary. Moreover, more data are required to evaluate the interaction with existing treatments, the importance of aetiology in humans and the specific mechanism in order to optimise the dietary intake.

Dietary fatty acids: research and development

Epidemiological studies have evidenced a protective effect of fish oils rich in long-chain ω3 PUFAs on the cardiovascular system, which was confirmed by secondary intervention studies.[22,23] However, the mechanism of this effect remains to be a matter of debate and more specifically in the field of hypertension, which remains an important object of experimental research. These fatty acids, as a membrane component, influence the biological and functional efficiency of membranes through the regulation of membrane-bound proteins. They contribute to the signalling processes through their metabolites (leukotrienes and prostaglandins). Moreover, these two actions can be complementary like for the platelet antiaggregating effect of EPA. The mechanisms involved in hypertension are also complex because they depend on the aetiology of the disease. However, the preventive effect of EPA and DHA appears as a constant throughout the literature and increasing their availability remains an objective in public health. The recommended intakes in western countries outline some important features. (i) There is no bad fatty acid but only bad intake levels, and this also concerns the relative intake. This statement deals with the p/s ratio and the requirements for a balanced value, which avoid the excessively low p/s (as observed in eastern EC countries) as well as the excessively high p/s (as observed in Israel for instance). (ii) The α-linolenic/linoleic ratio should be close to 1/5. The ratio is considered as representative of the ingested ω3/ω6 ratio and this value is acceptable among the different country recommendations. This highlights the importance of the balance between the two series, necessary to avoid some antagonistic effects as observed in haemostasis, platelet aggregation and inflammation. Conversely, these recommendations consider only the precursors and not the biologically active metabolites such as EPA and DHA, whose availability must be increased. The objective is difficult to reach and research and development has investigated different routes:

- Incorporation in industrial food of fish oil or purified EPA or DHA supplements (bakery, processed food, etc.), which is now accepted in various countries in spite of the elevated cost.
- Enrichment of processes food with α-linolenic using rich oils (soybean, rapeseed), or the direct use of extruded linseed (bakery) with the hope of increasing with time the long chain availability. The results are not fully positive and research is going on.
- The third route, in constant growth, is the increase of α-linolenic acid throughout the whole food chain (animal feeding) to increase the ω3 PUFA content in human food (eggs, dairy products, meat). These improvements in the fatty acid profile of the products are often associated with a decrease in saturated fatty resulting in the improvement of both the ω3/ω6 ratio and the p/s ratio in food. A study on healthy volunteers, with eggs, meat and dairy products only derived from linseed fed animals showed a significant improvement of blood lipid parameters without significant alteration of dietary habits.[46] The ω3/ω6 and p/s ratios were increased in plasma and erythrocytes, as well as EPA, but not DHA as expected.
- Another route is oriented to the genetic modification of plants already rich in Δ15 desaturase (linseed, rapeseed, soybean) to introduce the genes encoding for the other desaturase. The objective is to produce a variety able to synthesize the higher metabolites of α-linolenic acid and give oil rich in long-chain ω3 PUFAs. This route is currently investigated in several biotechnology industries.

Conclusion

Hypertension has gained a panel of therapeutic treatments more diversified and efficient than many other diseases, as shown by the reduction of hypertension-related morbidity and mortality over the past 25 years.[3] However, in spite of these significant therapeutic breakthroughs, recent studies have revealed that the incidence of hypertension (and some complications) has increased again.[3] The lifespan has increased in western countries, although the age of the onset of hypertension has not followed this progression and has tended on the contrary to decrease. This is one of the reasons why

a nutritional prevention in medical practice has been favourably considered by the NIH and WHO.[2,3] In 2001, the AHA nutrition committee considered that ω3 PUFAs can reduce blood pressure, but large quantities are needed to see only a modest effect in hypertensive individuals. The committee considered that this is not a practical treatment for lowering blood pressure. The rationale for using ω3 PUFAs in the treatment of established hypertension can be criticized by comparison with the efficiency of the available drugs, but the constant use of an adapted diet should be regarded as a powerful tool to prevent or delay the onset of hypertension. Regarding the fatty acid intake, hypertension follows the same rules as other cardiovascular diseases or risk markers and requires a decrease in saturated fatty acid intake and an increase in ω3 PUFA intake, mainly the long chains. The research tendencies indicate that both EPA and DHA could be efficient to prevent hypertension associated with metabolic syndrome or reno-vascular disease, whereas DHA alone may affect essential hypertension. Increasing the consumption of marine products in the whole population is not realistic and the efficiency of increasing the consumption of α-linolenic acid remains to be demonstrated. To clarify this debate, it is necessary to develop investigations in the direction of the 'preventive value', in contrast with the actual situation, mainly oriented towards the 'therapeutic value'. A meal is a complex thing, which contains a lot of nutrients beside lipids. Dairy products, for instance, are potentially able to prevent hypertension through the effects of calcium, but also through the bioactive peptides resulting from casein hydrolysis. The preventive effect of a given diet may thus be far beyond the fatty acid ratio and this diet should be considered for its 'overall preventive value' in hypertension. The nutritional prevention of chronic pathologies requires more research efforts and investments in research.

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