Review

Lifestyle Modifications to Prevent and Control Hypertension

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Keywords. hypertension, risk factors, prevention

Hypertension is the most important, modifiable risk factor for cardiovascular disease and mortality. High salt intake may predispose children to develop hypertension later. A modest reduction in population salt intake worldwide would result in a major improvement in public health. Regarding smoking as another risk factor, there are various strategies that can be used to promote smoking cessation. Physicians are in an excellent position to help their patients stop smoking. Targeted weight loss interventions in population subgroups might be more effective for the prevention of hypertension than a general-population approach. A diet rich in high-potassium fruit and vegetables is strongly recommended. Fresh products are best; normal potassium content is reduced when foods are canned or frozen. Calcium supplementation reduces blood pressure in hypertensive individuals during chronic nitric oxide synthase inhibition and high calcium diet enhances vasorelaxation in nitric oxide-deficient hypertension. Magnesium should be considered by anyone seeking to prevent or treat high blood pressure. The foundation for a healthy blood pressure consists of a healthy diet, adequate exercise, stress reduction, and sufficient amounts of potassium and magnesium, but further investigations are required before making definitive therapeutic recommendations on magnesium use. Alcohol usage is a more frequent contributor to hypertension than is generally appreciated. For hypertensive patients in whom stress appears to be an important issue, stress management should be considered as an intervention. Individualized cognitive behavioral interventions are more likely to be effective than single-component interventions.

IJKD 2016;10:237-63
www.ijkd.org

INTRODUCTION

Hypertension is an important public health challenge worldwide because of its high prevalence and the concomitant increase in the risk of cardiovascular-renal disease.[1] Increasing age is an unmodifiable risk factor for developing hypertension. The lifetime risk for developing hypertension is therefore of significant importance. In the Framingham Heart Study, investigators reported that the lifetime risk of hypertension was approximately 90% for those patients, male and female, who were normotensive at the age of 55 or 65 years and who had survived to 80 to 85 years of age, respectively.[2] Everyone is, therefore, at risk and it is impossible to predict who will not develop hypertension with increasing age. However, there are a number of important causative factors for essential hypertension. These include obesity, increased daily sodium intake, fat and alcohol intake, and the lack of physical activity. Eating too little fruit and vegetables or whole grain foods has also been implicated. Motivating patients to achieve lifestyle modifications is probably one of the most difficult aspects of managing hypertension. Having a trustful

relationship between the healthcare provider and the patient is one of the most important aspects when motivating patients. Adherence to lifestyle interventions by the healthcare workers themselves is probably the best starting point. Long-established lifestyle modifications that effectively lower blood pressure include weight loss, reduced sodium intake, increased physical activity, and limited alcohol intake. These lifestyle modifications are recommended for nonhypertensive individuals with above-optimal blood pressure, known as "pre-hypertensives," and as initial therapy in stage 1 hypertension.[3] For individuals taking antihypertensive medication, lifestyle modification is recommended as adjunctive therapy. Randomized controlled clinical trials have repeatedly documented the benefits of antihypertensive drug treatment in the reduction of cardiovascular disease incidence and mortality.[4-6] Nonpharmacological intervention (lifestyle modification) offers an attractive alternative for preventing and treating hypertension at little cost and with minimal risk.[5] This review summarizes the evidence pertaining to lifestyle modifications and blood pressure reduction.

DIETARY SODIUM

Sodium Intake

Approximately 50% of hypertensive individuals and 25% of normotensive individuals are considered by some to be salt-sensitive—a term that describes the tendency for blood pressure to fall during salt reduction and rise during salt repletion. Salt sensitivity and salt resistance have a variety of determinants, including genetics, ethnicity, age, body mass, diet quality, and the presence of other associated comorbidities including diabetes mellitus and kidney dysfunction.[6,7]

Sodium is naturally present in a variety of different foods and accounts for about 12% of total intake. Salt used at the discretion of an individual (at the table or while cooking) provides about 11%; more than 75% is derived from salt added in food processing.[8] The current public health recommendations in most countries are to reduce salt intake from about 9 g/d to12 g/d to the lower levels of 5 g/d to 6 g/d. As raised blood pressure throughout its range is a major cause of cardiovascular disease, a reduction in salt intake, if it lowered blood pressure, would reduce cardiovascular risk.

Population-based Studies and Clinical Trials

Both prospective cohort studies and outcome trials have shown that a lower salt intake is related to a reduced risk of cardiovascular disease.[9] Recently, a meta-analysis showed that a longer-term modest reduction in salt intake of 4.4 g/d on average, causes significant and important falls in blood pressure in people with both raised and normal blood pressure. This study also showed a significant dose-response relationship between the reduction in salt intake and the fall in systolic blood pressure.[10]

A recent randomized controlled trial, conducted in rural northern China, evaluated the long-term effects of a reduced-sodium-high-potassium salt substitute compared to normal salt on blood pressure among 608 high-risk individuals. Mean overall difference in systolic blood pressure between the randomized groups was 3.7 mm Hg ($P < .001$), and systolic blood pressure was significantly lower in the salt substitute group than in the normal salt group at the 6-, 9-, and 12-month visits (all $P < .02$). The magnitude of this reduction increased over time ($P = .001$) with the maximum net reduction of 5.4 mm Hg achieved at 12 months.[11]

The effect of a chronic high-salt intake is a gradual increase in blood pressure throughout life. The International Study of Salt and Blood Pressure suggested a strong relationship between salt intake and a progressive increase in blood pressure with age, which was 0.4 mm Hg per year for a 6-g/d salt intake. A reduction in salt intake is therefore likely to attenuate the rise of blood pressure with ageing, in addition to the immediate blood pressure lowering effect.[12]

From the evidence above, it is clear that the recommendations to reduce salt to 5 g/d to 6 g/d will have a significant effect on blood pressure but are not ideal. In the United States, it is recommended that sodium intake should be reduced to less than 2.3 g/d (equivalent to about 6 g/d salt) for most adults, with a further reduction to 1.5 g/d (4 g/d salt) for about half of the population, including African Americans, all adults aged 51 and older, and individuals with hypertension, diabetes mellitus, and chronic kidney disease.[13]

Pathogenesis

When sodium salt is loaded, factors that inhibit sodium-potassium-adenosine triphosphatase

(ATPase) activity increase in the circulating blood and in some tissues. As inhibitors of sodium-potassium-ATPase activity were identified as digitalis glycosides, they are termed *endogenous digitalis-like factors* (EDLFs),[14] which include ouabain, digoxin, marinobufagenin, marinobufotoxin, telocinobufagin, proscillaridin A, bufalin, and others. There are 2 types of EDLFs that are cardenolides derived from plants and bufadienolides derived from toads. As these molecules contain a steroid nucleus and increase cardiac and vascular contractility by inhibiting sodium-potassium-ATPases in cell membranes, they are called *cardiotonic steroids*. Pharmacological evidence indicates that the circulating level of cardiotonic steroids may not be high enough to exert physiological effects because the main cardiotonic steroids-ATPase subunit, the alpha1-subunit, is resistant to ouabain. In recent years, EDLF has emerged as a key player, at least locally in the brain, in the onset of sodium-induced hypertension.[15] Continuous administration of mineralocorticoids leads to sodium retention, which in turn leads to natriuresis when the sodium level exceeds a threshold. This phenomenon is known as *mineralocorticoid escape*. The two major causes of natriuresis are increased glomerular filtration rate and decreased aldosterone levels, but neither is involved in mineralocorticoid escape. The factor involved in this phenomenon is thus referred to as 'the third factor,' and the most likely candidate for this third factor is an EDLF: suppression of renal tubular sodium-potassium-ATPase activity markedly increases sodium excretion, and EDLFs suppress that.[16] Investigation of EDLFs led to the discovery of many other factors that act in concert with EDLF in response to sodium loading in the central nervous system. The proposed theory that sodium metabolism is influenced by EDLFs and other factors in the central nervous system, and that this is essential in the genesis of hypertension has now been confirmed.[17] Molecular pathways for central effects of sodium and potassium on blood pressure can be seen in Figure 1.

When salt intake is reduced, there is a fall in extracellular volume and physiological stimulation of the renin-angiotensin-aldosterone system, as well as the sympathetic nervous system. These compensatory responses are bigger with sudden and large decreases in salt intake and much smaller or minimal with a longer-term modest salt reduction so with a longer-term modest reduction in salt intake there is only a small physiological increase in plasma renin activity, aldosterone, and noradrenaline.[18,19]

By far the most reliable estimate of the effect of reducing salt intake on blood pressure now comes from the large and well-controlled DASH-Sodium trial (Dietary Approaches to Stop Hypertension).[3] The trial was a multicenter 14-week feeding study in which 412 participants, 169 of whom hypertensive and 243 normotensive, were randomized in a parallel-group study to either consume a normal American diet or the DASH diet (ie, rich in fruits, vegetables, and low-fat dairy products). They were then randomized into a cross-over study of 3 salt intakes: approximately 8 g, 6 g, and 4 g per day. The results showed that reducing salt intake lowered blood pressure in hypertensive and normotensive individuals, both on the normal American diet and

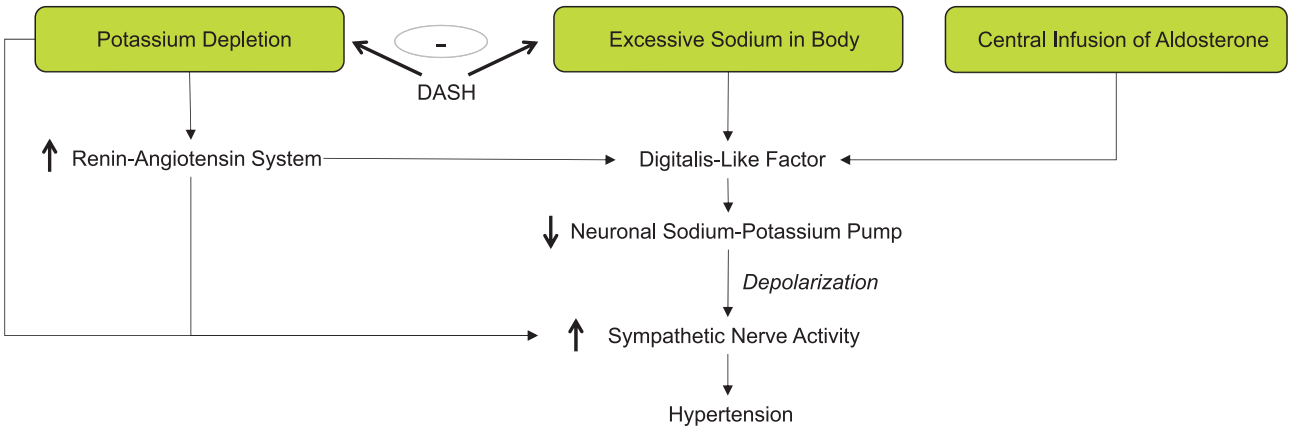

Figure 1. Molecular pathways for central effects of sodium and potassium on blood pressure.

on the DASH diet. The lower the salt intake, the lower the blood pressure. On the normal American diet, when salt intake was reduced from 8 g/d to 4 g/d, the average fall in blood pressure was 8.7/4.5 mm Hg in hypertensive and 5.3/2.6 mm Hg in normotensive individuals. On the DASH diet, blood pressure was lower, as found in the original DASH study,[10] but salt restriction still significantly lowered blood pressure in both hypertensive and normotensive individuals. The combination of salt restriction and the DASH diet reduced blood pressure by 11.5/5.7 mm Hg and 7.1/3.7 mm Hg in hypertensives and normotensives respectively.[20]

Recommendations

Currently, in most developed countries, salt is no longer added to baby foods, and salt concentrations in formula milk are very similar to those in human milk. Salt intake in children in developed countries is increased due to frequent consumption of processed foods. The restaurant foods, fast foods, and snacks are generally very high in salt, fat, and sugar. This high salt intake may predispose children to develop hypertension later.[21] A reduction in salt intake in children can be achieved by a gradual and sustained reduction in the amount of salt added to children's foods by the food industry. A comprehensive school meals program, combined with advice to parents and children, will also help reduce salt, fat, and sugar in children's diets. A modest reduction in population salt intake worldwide would result in a major improvement in public health at a low cost, as or more cost-effective than tobacco control.[22,23]

SMOKING

Impact

Smoking remains one of the most important causes of morbidity and mortality worldwide. Individuals who smoke are exposed to not only nicotine, tobacco, tar, carbon monoxide, but also to at least 50 other toxic chemicals.

Pathogenesis

Chronic cigarette smoking causes hypertension, increases oxidative stress, impairs nitric oxide bioavailability, endothelial dysfunction, and cardiac remodeling.[24,25] Nicotine acts as an adrenergic agonist, mediating local and systemic catecholamine release and possibly the release of vasopressin. In a study of 24-hour ambulatory blood pressure monitoring, smokers maintained a higher mean daytime ambulatory systolic blood pressure than nonsmokers, even though office blood pressure levels were similar.[26] These findings reflect the fact that patients do not smoke during measurement of blood pressure in office and hence the blood pressure that is recorded may not represent the subject's usual blood pressure.

Paradoxically, several epidemiological studies have found that blood pressure levels among cigarette smokers were the same as or lower than those of nonsmokers.[27] Evidence from the health survey for England showed that older male smokers had higher systolic blood pressure adjusted for age, body mass index, social class, and alcohol intake than did nonsmoking men. No such differences were seen among younger men or for diastolic blood pressure in either age group.[28] A cross-sectional study to clarify the dose-effect relationship of smoking habits with blood pressure in Japanese men showed that there was no significant difference in the adjusted systolic and diastolic blood pressure between nonsmokers and ex-smokers.[29]

Based on evidence, platelet and endothelial function, arterial stiffness, atherosclerosis, oxidative stress, inflammation, heart rate variability, and energy metabolism are sensitive to the toxins in secondhand smoke. The effects of even brief (minutes to hours) passive smoking are often nearly as large (averaging 80% to 90%) as chronic active smoking.[30] The World Health Organization released guidance on tobacco harm reduction emphasized that passive smoking compromise health not only when individuals are exposed frequently for prolonged periods of time, but also after single brief exposure. It seems that there is a dose-response relationship, with greater exposure associated with greater risk.[31]

In a study that published the impact of exposure to cigarette smoke on blood pressure of elementary school children in Kermanshah, Iran, the mean systolic and diastolic blood pressures of the exposure group were higher than those of the nonexposure group; meanwhile, difference between the two groups according to sex was not significant.[32]

In 2003 it was shown that acute exposure to passive smoking had deleterious effects on the arterial pressure waveform in healthy young males

but not in females, suggesting a possible protection of female sex from functional changes in the arteries. Passive smoking was associated with an increase in brachial and aortic systolic blood pressure at 60 minutes in the men only. The augmentation index increased from at 60 minutes only in the men.[33] In ex-smokers, duration of smoking cessation has a significant linear relationship with improvement in pulse wave velocity and arterial stiffness parameters return to nonsignificant levels after a decade of smoking cessation.[34]

Results from a survey conducted for evaluating the correlation between cigarette smoking and blood pressure and pulse pressure among teachers residing in Shiraz, southern Iran, showed the mean range of systolic and diastolic hypertension and pulse pressure was greater in heavy smokers than those who smoked less than 20 pack.years, although the difference was not significant.[35]

It has been shown clearly that the risk for high-normal urinary albumin excretion and microalbuminuria is increased in smoking compared with nonsmoking individuals of the general population.[36] These data indicate that at least in men, smoking increases the risk to reach end-stage renal failure. Of interest, the magnitude of the adverse renal effect of smoking seems to be independent of the underlying kidney disease. Death-censored kidney graft survival is decreased in smokers, indicating that smoking also damages the kidney transplant. Cessation of smoking has been shown to reduce the rate of progression of kidney failure both in patients with kidney disease and in patients with a kidney transplant.[36]

Recommendations

Despite public awareness of the health risks of smoking, millions of people worldwide continue to smoke, largely because they are physically and psychologically dependent on nicotine. There are various strategies that can be used to promote smoking cessation, including advice from a physician, nicotine replacement therapy, behavior modification, and smoking cessation programs. Physicians are in an excellent position to help their patients stop smoking. Because several of the motivating factors relate to improved physical well-being, it is important that physicians discuss the health consequences of smoking with their patients.

OBESITY

Impact

Obesity has been accepted as an established risk factor for higher systolic and diastolic blood pressures. Around the world, the incidence of overweight and obesity has increased. There is a direct positive relationship between overweight and hypertension, such that it has been estimated that the control of obesity may eliminate 48% of the hypertension in whites.[37]

Pathogenesis

Although the exact mechanism of the relationship between hypertension and obesity and the effect of weight loss on blood pressure is unknown, there are several probable biologic pathways. Renin-angiotensin-aldosterone system is overactivated in obese individuals. Furthermore, activity of the sympathetic nervous system is increased in hypertensive obese subjects, which could induce obesity-related renal effects. Alternatively, there might be inhibition of the natriuretic peptides system. Decreased insulin sensitivity and hyperinsulinemia as part of the metabolic syndrome might also form an essential link between obesity and hypertension.[37]

Recent studies have demonstrated that adipose tissue is a major endocrine organ that secrets a variety of bioactive substances, termed adipocytokines. Adipocytokines secretion is altered as obesity develops, which may induce the metabolic disorders. Accumulated visceral adipose tissue produce and secrete a number of adipocytokines, such as leptin, tumor necrosis factor-α, interleukin-6, angiotensinogen, and nonesterified fatty acids, which induce development of hypertension.[38]

Leptin is an adipocyte-derived hormone that acts in the hypothalamus to regulate appetite, energy expenditure, and sympathetic nervous system outflow. One of the major mechanisms leading to the development of obesity-induced hypertension appears to be leptin-mediated sympathetic activation. Leptin adversely shifts the renal pressure–natriuresis curve, leading to relative sodium retention. Although obesity is generally associated with resistance to the anorexic and weight-reducing actions of leptin, experimental studies showed that its sympatho-excitatory and pressor actions are preserved. This selective leptin resistance of obesity, coupled

with hyperleptinemia, may play a critical role in the cardiovascular complications of obesity.[39] Other adipocyte-derived peptides may also affect arterial pressure. Circulating adiponectin levels are decreased in obesity-induced insulin resistance, and some studies suggest that adiponectin is protective against hypertension through an endothelial-dependent mechanism.[40]

Clinical Trials

Results obtained with experimental models of obesity-associated hypertension indicate a potential role for vascular pro-inflammatory factors and oxidative stress on endothelial dysfunction in this condition. Mice with high-fat diet-induced obesity display increased blood pressure and impairment in the relaxation of the aorta in response to acetylcholine, an endothelium-dependent vasodilator. The endothelial dysfunction in this model has been proposed to be a consequence of the reduced antioxidant defense and the local activation of the nuclear factor κB pathway and increased superoxide generation in the vascular wall, indicating that these two factors may be the link between obesity and hypertension.[41]

The respiratory quotient is a parameter reflecting the utilization of the nutrients. Subjects tending to burn less fat have an increased respiratory quotient. To investigate on the relationship between the respiratory quotient and the cardiovascular risk factors, a cross-sectional study conducted in 2013 showed that high value of the respiratory quotient, is associated with high prevalence of hypertension and it is possible that in the subjects with high respiratory quotient and high body mass index, the activation of the renin angiotensin system, in concert to the reduction of endogenous fat stores utilization, could increase the risk of hypertension.[42]

Weight loss has been proposed as an effective nonpharmacologic means for the primary prevention of hypertension. An early meta-analysis by Staessen and colleagues in 1988 showed a reduction in systolic blood pressure and diastolic blood pressure of 2.4 mm Hg and 1.5 mm Hg per kilogram weight loss, respectively.[43] Several studies have been reported recently supporting the role of weight loss in the prevention and treatment of hypertension. Bao and colleagues examined the effects of weight reduction on ambulatory blood pressure among 63 overweight hypertensives aged 40 to 70 years in a clinical trial. Calorie restriction resulted in an average weight loss of 5.6 kg over 16 weeks in the intervention group. A significant reduction in 24-hour mean systolic (76.1 ± 2.6 mm Hg) and diastolic (74.6 ± 1.5 mm Hg) blood pressure was observed in the intervention group compared with the control group. These trials provide additional evidence that weight loss is an effective approach to the treatment and prevention of hypertension.[44]

Even modest reduction in body weight can cause a meaningful reduction in the activity of the renin-angiotensin-aldosterone systems in the circulation and in adipose tissue which makes a major contribution to the blood pressure decrease. Weight loss of 5% is associated with the reduction of angiotensinogen levels (27%), renin (43%), aldosterone (31%), angiotensin-converting enzyme activity (12%), and angiotensinogen expression in adipose tissue (20%).[45]

Huang and colleagues examined the relationship between long-term weight changes and the risk of hypertension. The incidence of hypertension was reduced by 15% for a long-term weight loss (12 to 15 years) of 5.0 ± 9.9 kg and by 26% for long-term weight loss of 10 kg or more compared with no change. Long-term weight gain, on the other hand, increased the incidence of hypertension significantly. Medium-term weight changes (2 to 14 years) had similar effects on the risk of hypertension. This study suggests that even modest adult weight gain may increase the risk of hypertension, while weight loss substantially reduces this risk.[46] A meta-analysis of aerobic exercise and blood pressure showed that blood pressure was significantly reduced even in trials in which overall weight loss was minimal because of interindividual differences in blood pressure and body weight. This suggests that exercise reduces blood pressure independent of changes in body weight.[47]

Becque and coworkers[48] reported that 80% of obese adolescents had elevated blood pressure and that 97% of obese adolescents showed elevated serum triglyceride levels, decreased high-density lipoprotein cholesterol and increased total cholesterol levels along with elevated systolic or diastolic blood pressures. Many experiments have shown that plasma cholesterol is raised by the dietary saturated fatty acids, lowered by polyunsaturated ones and slightly affected by monounsaturated fatty

acids. Plasma cholesterol falls if the percentage of dietary energy provided by fats is reduced, while diets high in starch do not increase triglycerides unless individuals are obese.[49]

Recommendations

Targeted weight loss interventions in population subgroups might be more effective for the prevention of hypertension than a general-population approach. In conclusion, weight loss makes an important contribution to the treatment of hypertension, especially in subjects taking antihypertensive medication. Prevention of weight gain is likely to have a large impact on the burden of hypertension, and consequently, cardiovascular diseases in the general population.

DIET

To date, the most definitive trials directed toward the nutritional management of hypertension are the Dietary Approaches to Stop Hypertension (DASH) and DASH-Sodium trials.[3] Briefly, DASH focused on establishing dietary patterns to lower blood pressure, with typical sodium consumption. The DASH-Sodium trial demonstrated that reducing sodium intake from 100 mmol/d to 50 mmol/d significantly reduced blood pressure in individuals, whether on the DASH diet or the typical US diet.[3] Studies suggest that an intake of fish oil at a level of approximately 4 g/d reduces systolic blood pressure by approximately 1.7 mm Hg to 2.1 mm Hg and diastolic blood pressure by 1.5 mm Hg to 1.6 mm Hg. These effects tend to be larger in individuals older than 45 years of age and in populations with blood pressure readings greater than 140/90 mm Hg.[50]

Monounsaturated fatty acids, particularly olive oil, may help to reduce blood pressure. Olive oil is a rich source of monounsaturated fatty acids and has typically been associated with the popularized Mediterranean diet, which has been promoted as a treatment for cardiovascular disease. Small clinical studies of the Mediterranean diet have shown reduced blood pressure, improved lipid profiles, and reduced markers of vascular inflammation.[51] In 2009, results of a prospective cohort of 160 adult kidney allograft recipients showed that subjects in the highest tertile of scores for the Mediterranean diet had a significantly lower odds of metabolic syndrome than those in the lowest tertile. Subjects in the highest tertile of scores for consuming fats and sugars had significantly greater odds of metabolic syndrome compared with those in the lowest tertile. This study showed that the Mediterranean dietary pattern is associated with a reduced risk of metabolic syndrome in renal transplant recipients.[52]

Prevencion con Dieta Mediterrnea was a large-scale feeding trial that assessed the effects of 2 Mediterranean diets, one supplemented with olive oil and the other supplemented with mixed nuts, compared to a low-fat diet on cardiovascular disease outcomes. Results demonstrated significant reductions in systolic blood pressure and diastolic blood pressure in the participants in the two Mediterranean diet conditions compared to low-fat diet controls. Notably, participants with hypertension showed even higher reduction in systolic blood pressure in the two Mediterranean diet conditions.[53]

The effect of the Mediterranean diet on hypertension may be mediated by lipid electrophiles such as 10-nitro-oleic acid, which inhibits hydrolase activity in a mouse model. The researchers examined whether inhibition of soluble epoxide hydrolase is associated with a reduction in blood pressure in vivo. The authors used a Cys521Ser soluble epoxide hydrolase redox-dead knock in (KI) mouse model that was resistant to this inhibition and found that in wild-type, but not KI mice, the electrophilic lipid 10-nitro-oleic acid inhibited hydrolase activity and reduced blood pressure in an angiotensin II-induced hypertension model. Following 10-nitro-oleic acid treatment, epoxyeicosatrienoic acid/dihydroxy-epoxyeicosatrienoic acid isomer ratios were increased in plasma from wild-type, but not KI mice. Inhibition of soluble epoxide hydrolase was observed in wild- type, but not KI mice, which were fed key components of the Mediterranean diet (linoleic acid and nitrites) that elevate electrophilic nitro fatty acid levels. This observation revealed that lipid electrophiles such as 10-nitro-oleic acid mediate antihypertensive signaling actions by inhibiting soluble epoxide hydrolase and suggested a mechanism accounting for protection from hypertension afforded by the Mediterranean diet.[54] Dietary fiber influences satiety and reduces energy intake. Therefore, it may influence blood pressure by a mediating effect through weight reduction.[55] Observational studies

suggest an inverse relationship between dietary fiber consumption and hypertension risk. In a meta-analysis of randomized controlled clinical trials of dietary fiber on blood pressure, results of 25 studies suggested that dietary fiber intake may reduce blood pressure in patients with hypertension with smaller reductions in normotensive participants.[55]

POTASSIUM

Impact

Everyone knows that high sodium intake can increase the risk of hypertension. Potassium also may play a role. However, the ratio of sodium to potassium may be more important than the specific amounts of sodium or potassium that a person consumes. Data support the view that an increase in potassium sodium ratio would decrease blood pressure in the general population and decrease cardiovascular mortality significantly.[56] Even in kidney transplant recipients restoring a well-balanced sodium-potassium ratio intakes could be a non pharmacological opportunity to improve blood pressure control.[57] Increasing the potassium in the diet, however, has a protective effect, reduces blood pressure in people with hypertension and has no adverse effect on blood lipid concentrations, catecholamine concentrations, or renal function in adults.[58] As compared with diets based on natural foods, diets based on processed foods are high in sodium and low in potassium. For example, 2 slices of ham (57 g) contain 32.0 mmol of sodium and 4.0 mmol of potassium. Conversely, diets containing abundant fruits and vegetables are sodium poor and potassium rich.[59] For example, an orange (131 g) contains no sodium and 6.0 mmol of potassium, and a cup of boiled peas contains 0.3 mmol of sodium and 9.8 mmol of potassium.

Population-based Studies and Clinical Trials

Population studies have shown an inverse relation of potassium intake to blood pressure, the prevalence of hypertension, or the risk of stroke. After adjusting for potentially confounding variables, the INTERSALT researchers estimated that a decrease in potassium excretion by 50 mmol/d was associated with an increase in systolic pressure of 3.4 mm Hg and an increase in diastolic pressure of 1.9 mm Hg. The urinary potassium-sodium ratio in the INTERSALT study had a significant, inverse relation with blood pressure.[60] In clinical studies, a diet low in potassium (10 mmol/d to 16 mmol/d) coupled with the participants' usual sodium intake (120 mmol/d to 200 mmol/d) caused sodium retention and an elevation of blood pressure; on average, systolic pressure increased by 6 mm Hg and diastolic pressure by 4 mm Hg in normotensive subjects, and systolic pressure increased by 7 mm Hg and diastolic pressure by 6 mm Hg in hypertensive subjects.[61]

A meta-analysis that evaluated the effects of an increased potassium intake on blood pressure concluded that potassium supplementation ($\geq$ 60 mmol/d) lowered systolic pressure by an average of 4.4 mm Hg and diastolic pressure by an average of 2.5 mm Hg in hypertensive subjects and lowered systolic pressure by an average of 1.8 mm Hg and diastolic pressure by an average of 1.0 mm Hg in normotensive subjects.[62] Potassium supplementation can reduce the need for antihypertensive medication but natural source of potassium is preferable. Currently, pharmacological potassium supplementation is not recommended as a method to obtain the advised daily intake of potassium.[63] One study showed that with an increased dietary potassium intake in hypertensive subjects, 81% of the subjects needed less than half of the baseline medication and 38% required no antihypertensive medication for blood-pressure control, as compared with 29% and 9%, respectively, in the control group at 1 year of follow-up.[64] In the DASH trial, a diet rich in fruits and vegetables, reduced systolic pressure in the 133 hypertensive subjects by 7.2 mm Hg and diastolic pressure by 2.8 mm Hg, at a constant level of sodium intake. The potassium content of the diet of fruits and vegetables was more than twice as high as that of the typical American diet; therefore, its higher potassium: sodium ratio probably accounted for most of the observed reduction in blood pressure.[65] Guidelines advise adults to consume at least 120 mmol of potassium per day (approximately 4.7 g of potassium per day). These targets would require modifications for special groups, including competitive athletes, persons working in hot environments, patients with chronic kidney disease or diabetes, and persons taking medications that affect potassium balance. Forms of potassium that do not contain chloride, such as those found naturally in fruits and vegetables, offer larger cellular entry in exchange for sodium and greater antihypertensive effects.[66,67]

Pathogenesis

A high-potassium diet and increases in serum potassium, even within the physiologic range, cause endothelium-dependent vasodilatation by hyperpolarizing the endothelial cell through stimulation of the sodium pump and opening potassium channels. Endothelial hyperpolarization is transmitted to the vascular smooth-muscle cells, resulting in decreased cytosolic calcium, which in turn promotes vasodilatation. Experimental potassium depletion inhibits endothelium dependent vasodilatation.[68] Experimental studies suggest that in addition to its effects on vascular tone, a potassium-rich diet decreases cardiovascular risk by inhibiting arterial thrombosis, atherosclerosis, and medial hypertrophy of the arterial wall. In addition to increased vasodilatation, other proposed mechanisms by which potassium can influence blood pressure include natriuresis, alterations in intracellular sodium and tonicity, modulation of baroreceptor sensitivity, reduced vasoconstrictive sensitivity to norepinephrine and angiotensin II, increased serum and urinary kallikrein, increased sodium-potassium ATPase activity and alteration in DNA synthesis and proliferation in vascular smooth muscle and sympathetic nervous system cells, improved insulin sensitivity, reduction in cardiac diastolic dysfunction, decrease in vascular neointimal formation, reduction in transforming growth factor-β, and decreases in nicotinamide adenine dinucleotide phosphate-oxidase, oxidative stress, and inflammation.[66-70]

In recent years, a number of previously unrecognized kinases interacting in the distal nephron have been identified as playing important roles in sodium, potassium, and blood pressure regulation. Among these are the WNKs, which regulate the renal outer medullary potassium channel (ROMK) 71, the sodium potassium chloride co transporter type 2 (NKCC2) 72, the sodium chloride cotransporter (NCC),[73,74] and the epithelial sodium channel.[75] Four WNKs are expressed in the kidney, WNK1, kidney-specific WNK1 (KS-WNK1), WNK3, and WNK4, where they are most abundant along the aldosterone-sensitive distal nephron.[76] Of these, WNK1, WNK3, and WNK4 phosphorylate SPAK and OSR1-two highly homologous kinases that are phosphorylated and activated by WNKs, which in turn phosphorylate and activate NKCC2 and NCC, WNK4 is believed to inhibit NCC activity by reducing its plasma membrane abundance.[77] WNK1 modulates NCC not only through WNK4, but also recent evidence suggested that WNK1 regulates trafficking by facilitating the final steps of NCC insertion into the plasma membrane.[78] The exact role of WNK3 in NCC regulation remains elusive, but cell studies showed that WNK3 is a positive regulator of NCC and that the net effect on NCC is determined by antagonism between WNK3 and WNK4. Phosphorylation of NKCC2 also requires an interaction between WKN3 and SPAK because catalytically inactive WNK3, prevents the activation of NKCC2.[72] WNKs also modulate ROMK by affecting clathrin-mediated endocytosis. Major renal sodium and potassium transporters are regulated by aldosterone, including NCC, epithelial sodium channel, and ROMK. When aldosterone is secreted in response to angiotensin II, its primary effect is sodium chloride retention; when it is stimulated in response to hyperkalemia, its primary effect is kaliuretic.[79] Dietary potassium intake has substantial effects on WNK abundance. Both the KS-WNK1/WNK1 ratio and the abundance of WNK4 increase on high potassium diets (hyperkalemia), but not on a low sodium diet (hypovolemia).The increase in KS-WNK1 and WNK4 would favor electro genic transport with potassium secretion. The WNK network is also modulated by angiotensin II, which is elevated when aldosterone secretion is stimulated by hypovolemia but not when it is stimulated by hyperkalemia. Indeed, angiotensin II, through WNK4, activates NCC, favoring sodium chloride reabsorption during hypovolemia.[80] Potassium deficiency increases the expression of serine/threonine-protein kinase WNK-1, which might create an imbalance between the activity of the ATP-sensitive inward rectifier potassium channel 1 and the epithelial sodium channel, which results in increased sodium retention.[81] The WNKs are a promising new link to hypertension. Several studies showed single nucleotide polymorphisms and haplotypes in the WNK1 and WNK4 genes are not only associated with blood pressure variation, but also with hypertension severity, salt sensitivity, thiazide sensitivity, and urine potassium excretion.[82-87] These findings make the WNKs obvious candidates as drug targets, and several screening strategies are already making progress.

Recommendations

In 2006, the American Heart Association issued new guidelines suggesting an increase in potassium intake to 120 mmol/d (4.7 g/d), which is the level provided in the DASH diet.[88] In 2010, the American Society of Hypertension recommended about 4.7 g/d of potassium. The most recent European Society of Hypertension guidelines also support increased potassium intake based on the DASH diet.[89] In addition, the 2003 World Health Organization statement recommends a diet high in fruits and vegetables, reduction of dietary sodium intake, and increased dietary potassium intake to reduce the incidence of hypertension. Apart from educating the public, an agreement by the food industry to limit the deviation of the cationic content of processed foods from their natural counterparts is essential.

Following these recommendations would require a comprehensive, culture-based approach, targeting both the general public and health care professionals.[90] A diet rich in high-potassium fruit and vegetables is strongly recommended. Fresh products are best; normal potassium content is reduced when foods are canned or frozen. The daily recommended allowance for potassium has been established at 3500 mg. Potassium can be found in many food, especially meat, milk, fruits, and vegetables, so people who eat a variety of foods should be able to reach the recommended amount.

CALCIUM

Impact

Calcium levels are found to be altered in essential hypertension. Elevated basal cytosolic free calcium levels, as well as defective membrane binding and transport kinetics of calcium, have been identified in platelets, erythrocytes, lymphocytes, and adipocytes of hypertensive subjects, in whom blood pressure levels were closely and directly related to the calcium content.[91] Past studies indicate that extracellular calcium concentrations also may differ between hypertensive and normotensive persons. Some researchers have found a highly significant association between serum calcium and both systolic and diastolic blood pressure in both the genders. Sudhakar and colleagues found that serum total calcium levels were significantly decreased in patients with essential hypertension and their first degree relatives.[92]

Low levels of calcium, either due to dietary deficiencies or altered calcium metabolism, have been linked by several epidemiological and laboratory studies to higher blood pressure, or hypertension. One of the largest studies to examine this relationship was the National Health and Nutrition Examination Survey conducted by the National Center for Health Statistics. They found that there was a threshold of 400 mg/d to 600 mg/d of dietary calcium; the risk of high blood pressure increases dramatically at levels below this threshold, while the cardiovascular benefits modestly increase at higher intake. This threshold may vary depending on the patient population. Several studies indicate that abnormal calcium metabolism is likely the cause of high blood pressure rather than result from cardiovascular changes associated with hypertension. In genetically hypertensive rats that received a calcium supplement during development of hypertension, blood pressure was significantly lower compared to those not receiving the supplement.[93] Studies have indicated that while increasing calcium intake might not be advantageous for the population at large with respect to hypertension, there are certain groups that do clearly benefit from increased calcium intake. Approximately 10% of pregnancies are accompanied by hypertension, preeclampsia accounting for half of these cases. Women at risk of developing pregnancy-induced hypertension are typically responsive to increased calcium, with the incidence of hypertension being reduced up to 40% to 50% in those with a 1500 mg/d to 2000 mg/d intake (there is an increased daily calcium requirement due to fetal processes that are dependent on maternal calcium stores). Maternal blood calcium levels also affect the blood pressure of the newborn infant.[94] Patients with salt-sensitive hypertension represent another group for whom increased calcium intake appears to be highly beneficial. Responses in blood pressure to salt ingestion have been shown to additionally depend on the adequacy of dietary mineral intake (calcium, magnesium, and potassium).[95] There are also considerable evidences that increased calcium intake reduces risk of hypertension in individuals with high sodium diets, and those with a increased risk of hypertension such as individuals with a family history of high blood pressure. Calcium intake required to produce an effect on blood pressure lies within the recommended dietary

allowances values (currently 800 mg/d, 1200 mg/d for those 19 to 24 years old). Therefore, the inverse correlation between calcium intake and high blood pressure provides an added reason why individuals of all ages, gender, and ethnicity should meet the recommended dietary allowances for calcium.[95] A study conducted to investigate the influence of increasing dietary calcium on the development of oral contraceptive induced high blood pressure showed that oral contraceptive administration led to significant increases in blood pressure and blood volume. Conversely, caused significant reductions in plasma levels of calcium. Increased dietary calcium attenuated the elevation in blood pressure induced by oral contraceptive and abrogated the associated changes in blood volume, plasma calcium and urinary excretion of water. The results indicate that increased calcium intake abrogated the development of high blood pressure and associated increased blood volume during the use of oral contraceptive. The beneficial effect of increased dietary calcium during oral contraceptive use may be explained by improved diuretic and preserved vasorelaxant responses.[96]

It is postulated that saturated fats in high-fat dairy products may mitigate the beneficial effects of other components of dairy products, including calcium. The capacity of calcium to form soaps is higher when fat intake is increased.[97] Therefore, high fat in foods might hinder calcium absorption and reduce the bioavailability of calcium. Experimental data also showed that intake of low-fat dairy products, calcium, and vitamin D were each inversely associated with risk of hypertension in middle-aged and older women, suggesting their potential roles in the primary prevention of hypertension and cardiovascular complications.[98]

Pathogenesis

Dietary calcium may lower the activity of renin-angiotensin system, improve sodium-potassium balance, and inhibit vascular smooth muscle cell constriction. High calcium intake facilitates weight loss and enhances insulin sensitivity, which also contribute to blood pressure reduction.[99] Calcium has direct effect on peripheral vascular tone. Alternations in intracellular calcium are thought to be involved in the common pathway mediating the secretion and action of many hormones, including the presser action of catecholamines and angiotensin II. It has been hypothesized that due to aberrant transmembrane calcium transport, lower serum ionized calcium levels in the hypertensive subjects may in fact reflect increased levels of intracellular ionized calcium, which would account for the arteriolar vasoconstriction in hypertension.[100] In vitro studies have demonstrated membrane stabilization and the consequent relaxation of the vascular smooth muscles by increasing the extracellular levels of ionized calcium.[101]

Grobbee and coworkers observed differences in calcium metabolism indices in normotensive offspring of parents with and without hypertension. At the ages selected, offspring in both groups had limited differences in blood pressure. Mean serum calcium levels were significantly lower, and plasma parathyroid hormone was significantly higher in offspring having 2 hypertensive parents compared to those with normotensive parents, with no differences in dietary intake of calcium.[102] Studies on calcium depravation during development of animal models with a genetic predisposition to hypertension have also been conducted, and the majority report significantly increased blood pressure associated with low calcium intake. Ionized serum calcium is reported to be lower in low-renin hypertensive patients and higher in high-renin hypertensive patients than in normal-renin hypertensives or in normotensives. Plasma renin activity in essential hypertension has a continuous negative correlation with serum magnesium and a positive correlation with serum ionized calcium. Hence, plasma renin in hypertension may reflect calcium and magnesium flux changes across cell membranes.[103] Besides these, there are many other factors which are, directly or indirectly, implicated in the pathogenesis of essential hypertension and are influenced by serum calcium level. Endothelial cell dysfunction is one of them which is accompanied by a decrease in the production and/or the release of nitric oxide and the increase of contracting factors with resultant increase in peripheral vascular resistance.[104]

In summary, essential hypertension is associated with a variety of perturbations in calcium physiology. It is showed that calcium supplementation reduced blood pressure in hypertensive individuals during chronic nitric oxide synthase inhibition and high calcium diet had been found to enhance the vasorelaxation in nitric oxide-deficient hypertension.

MAGNESIUM

Impact

Magnesium is a biologically active mineral found in foods rich in whole grains, green leafy vegetables, and nuts. Experimental studies have observed a close inverse relationship between dietary intake or supplementation of magnesium and blood pressure level, indicating the potential role of magnesium deficiency in the pathogenesis of essential hypertension.[105] Low serum magnesium was shown to be a cause of atherogenesis and the calcification of soft tissues.[106] A relationship has also been reported between the rennin-angiotensin system, magnesium, and blood pressure. Hypertensive patients with high renin activity have significantly lower serum magnesium levels than normotensive subjects, and plasma renin activity is inversely associated with serum magnesium.[107] Studies have shown that magnesium supplementation was associated with slight reduction of 24-hour blood pressure levels in patients with mild hypertension, which can be evaluated by ambulatory blood pressure monitoring.[108]

Pathogenesis

Magnesium modifies the vascular tone by regulating endothelium and smooth muscle cell functions along with an important role in the classical pathway of nitric oxide release. Experiments in animals have also showed increased production of prostacyclin and nitric oxide by magnesium, promoting endothelium-independent and endothelium-dependent vasodilation.[109]

One of the mechanisms by which magnesium lowers blood pressure is by acting like a natural calcium channel blocker. This mimetic effect of magnesium results in production of vasodilator prostacyclins and nitric oxide. Magnesium competes with sodium for binding sites on vascular smooth muscle cells, binds to potassium in a cooperative manner, improves endothelial dysfunction in hypertensive and diabetic patients, decreases intracellular calcium and sodium, and reduces blood pressure.[110,111] Magnesium is also an essential cofactor for the delta-6-desaturase enzyme, which is the rate-limiting step for the conversion of linoleic acid to gamma- linoleic acid. Gamma- linoleic acid, in turn, elongates to form dihomo-gamma-linoleic acid, the precursor for prostaglandin E1, is both a vasodilator and platelet inhibitor. Low magnesium states lead to insufficient amounts of prostaglandin E1, causing vasoconstriction and increased blood pressure.[112,113]

Increased magnesium efflux through altered regulation of the vascular sodium-magnesium exchanger, and decreased magnesium influx due to defective vascular and renal TRPM6⁄7 expression or activity may be important. Found in epithelial cells, TRPM7 acts as a signaling kinase involved in vascular smooth muscle cell growth, apoptosis, adhesion, contraction, cytoskeletal organization, and migration, and is modulated by vasoactive agents, pressure, stretch, and osmotic changes. Thus, TRPM7 alters intracellular magnesium levels through changes in efflux and influx, which may be related to the onset and aggravation of hypertension.[114]

Increased levels of extracellular magnesium inhibit calcium influx. Conversely, reduced extracellular magnesium activates calcium influx via calcium channels. Low intracellular magnesium concentrations stimulate inositol trisphosphate-mediated mobilization of intracellular calcium and reduce calcium ATPase activity. Thus, calcium efflux and sarcoplasmic reticular calcium reuptake are reduced, leading to cytosolic accumulation of calcium and increased intracellular calcium concentration, which is an essential factor for vasoconstriction.[115]

Clinical Trials

Some studies have shown blood pressure lowering after magnesium supplementation. The administration of magnesium oxide (400 mg daily) for 8 weeks in patients with hypertension can reduce blood pressure levels, and this reduction has already been detected in office measurements and by ambulatory blood pressure monitoring.[116] In the DASH trial, there was an increase in urinary excretion of magnesium in participants on the combination diet (low-fat dairy products and fruit and vegetables) consistent with an increase in dietary intake of this nutrient. It is not clear if the effect of the combination diet in reducing blood pressure was related to increased magnesium intake for either the hypertensive or normotensive participants.[3,117]

In addition, magnesium reduces nerve and muscle excitability, stabilizes cardiac conductivity, and

influences neurochemical transmission, and also affects circulating levels of norepinephrine and the synthesis of serotonin.[118] A study published in 1983 found that taking 600 mg of magnesium daily reduced systolic blood pressure by an average of 7.6 mm Hg and diastolic pressure by an average of 3.8 mm Hg.[104] In another double-blind placebo-controlled study published in 1997, patients who took 411 mg to 548 mg of magnesium daily experienced significant reductions in systolic and diastolic blood pressure.[119] Joosten and coworkers showed in 2013 that urinary magnesium excretion was associated with the risk of hypertension in an inverse log-linear fashion, and this association remained after adjustment for age, sex, body mass index, smoking status, alcohol intake, parental history of hypertension, and urinary excretion of sodium, potassium, and calcium. Each 1-unit increment in urinary magnesium excretion was associated with a 21% lower risk of hypertension after multivariable adjustment.[120] Also it has been shown that dietary magnesium intake inversely associated with mortality risk in Mediterranean individuals at a high risk of cardiovascular disease.[121]

Recommendations

Modern food production contributes to problems by using inadequate amounts of magnesium in plant fertilizers, as well as by employing accelerated growing techniques that reduce magnesium content. Today's dietary habits also exacerbate the problem. Colas contain large amounts of phosphates that interfere with magnesium absorption. Diets containing large amounts of fat, salt, coffee, or alcohol also interfere with magnesium absorption or cause magnesium loss. Green vegetables, whole grains, and nuts contain substantial amounts of magnesium. In summary, magnesium should be considered by anyone seeking to prevent or treat high blood pressure. The foundation for a healthy blood pressure consists of a healthy diet, adequate exercise, stress reduction, and sufficient amounts of potassium and magnesium but, before making definitive therapeutic recommendations on the use of magnesium in the management of hypertension, well controlled, long-term therapeutic trials, in carefully characterized hypertensive patients are need. Currently, magnesium supplementation is not recommended as a means of hypertensive treatment.

PHYSICAL ACTIVITY

Impact

As a single risk factor, physical inactivity is believed to be responsible for 5% to 13% of hypertension today. Available data from a recent meta-analysis showed that aerobic fitness training lowers blood pressure approximately 7/5 mm Hg in people with mild to moderate hypertension.[122]

A single episode of physical activity yields an acute lowering of the blood pressure, so-called post-exercise hypotension. Repeated bouts of physical activity are therefore a strategy for lowering blood pressure. This acute effect of increased activity is not the whole benefit, as physical activity also has a more lasting effect. These different effects of physical activity are mediated by different mechanisms, resulting in changes of total peripheral resistance, cardiac output, or both. Desirable benefits from aerobic training are summarized in Figure 2.

Population-based Studies and Clinical Trials

In a meta-analysis involving 72 trials, 105 study groups, and 3936 participants, the authors reported reductions in systemic vascular resistance, plasma norepinephrine, and plasma renin activity as the main reasons for the decrease in blood pressure following exercise.[123] In the past 2 decades, several

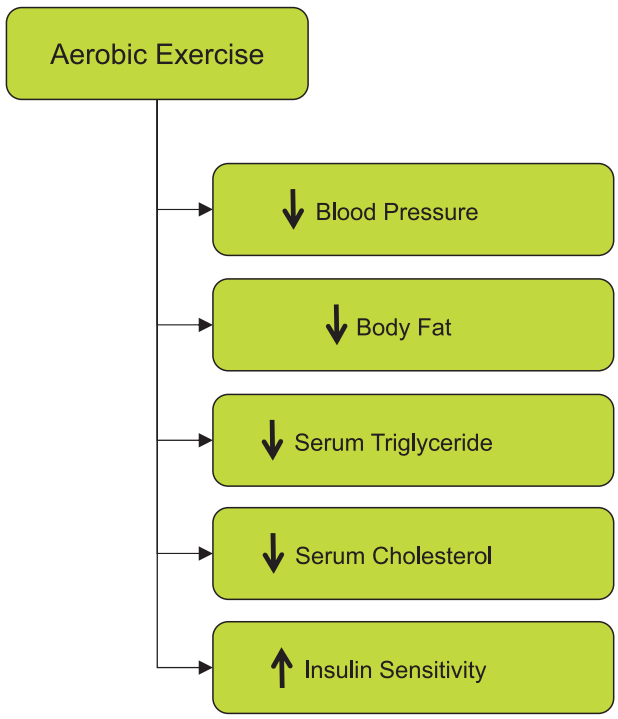

Figure 2. Desirable effects of aerobic training.

studies have shown that endothelial function is impaired in hypertensive patients. Improved endothelial function is another possible mediator of the hypotensive response observed with exercise training. During dynamic physical activity in healthy persons, such as running, systolic blood pressure normally rises during the exercise itself. In people with hypertension, the elevation in blood pressure can be more pronounced. The diastolic pressure remains the same or increases slightly during exertion, mainly due to reduced vasodilating capacity.[124] After dynamic physical activity, the blood pressure falls by about 10 mm Hg to 20 mm Hg for the next few hours, compared to the person's normal resting blood pressure. This effect is called "post-exercise hypotension." How long this lowered blood pressure lasts after the exercise seems to depend on factors such as the duration and intensity of the physical activity, and whether the activity was continuous or not. The same total physical activity, divided into smaller sessions, had a greater pressure-lowering effect than one long session. It is believed that the blood pressure-lowering in the 24 hours following physical activity is mediated mainly via a transient reduction in stroke volume or modulation of the sympathetic nervous tone.[124]

When it comes to heavy static training, there is a stronger increase in systolic and diastolic blood pressure during the training itself, than in dynamic exercise. According to a new meta-analysis, strength training can reduce both systolic and diastolic blood pressure by approximately 3 mm Hg to 4 mm Hg.[125] These studies concluded that moderate-intensity strength training is not contraindicated in hypertension and can even lead to a lowering of blood pressure, although more studies are needed with respect to the long-term effects.

A meta-analysis also showed that dynamic endurance training lowers blood pressure by approximately 7/5 mm Hg in people with mild to moderate essential hypertension.[126] The blood pressure-lowering effect of physical activity is, not surprisingly, highest in people with established hypertension compared to those with normal blood pressure (2/2 mm Hg). The effects appear to be the same in people taking antihypertensive drugs. The blood pressure-lowering effect of dynamic training is not lasting and requires continually maintained regular activity in order to remain. Regular physical activity not only lowers the resting blood pressure, but also decreases the blood pressure response during both physical exertion and mental stress.[126] The effects usually apply regardless of age, sex, and ethnicity. It has been suggested that the reduction in blood pressure was lower in older individuals, who have often had suffered from hypertension for a longer time and can thus be expected to have more established vascular changes. One study seems to confirm this, by showing that 6 months of exercise training produced lower diastolic, but not systolic blood pressure in people aged 55 to 75 years, while no measurable improvement in aorta stiffness was seen.[127] On the other hand, Fagard and Cornelissen's meta-analysis did not show any reduced efficacy of physical activity in older hypertensive patients.[128]

The efficacy of physical activity in the reduction of elevated blood pressure is no longer in question; the challenge now is to verify the amount and the frequency of exercise that will produce the maximum health benefits at a relative low risk for injury. In this regard, low-to-moderate intensity exercise (approximately 60% to 85% of age-predicted maximum heart rate) is more effective in lowering blood pressure when compared to higher intensities. A review published in 2010 evaluated the effects of regular aerobic exercise on blood pressure levels assessed throughout the full 24-hour period.[129] Aerobic training was shown to reduce most ambulatory blood pressure outcomes among individuals with hypertension in most studies. Nevertheless, it was noted that the responses were highly variable among individuals. The effect of walking programs on blood pressure was reviewed in 2010. Nine of 27 trials reported significant reductions in systolic or diastolic blood pressure. Trials that demonstrated a significant effect used more intense and frequent (36.5-minute sessions performed 4.4 d/w) exercise regimens for longer durations (19 weeks). Among the positive studies, the overall mean reduction in blood pressure between the intervention and control groups from the baseline to the end of the follow-up ranged from 5.2 mm Hg to 11.0 mm Hg and from 3.8 mm Hg to 7.7 mm Hg for systolic and diastolic blood pressures, respectively.[130]

Results of one study performed in 2012 showed that combining intermittent high-intensity (>80% to 90% of maximal heart rate) with moderate-intensity

(>60% maximal heart rate) aerobic training, was more effective than continuous training in stage 1 hypertension (mean ambulatory blood pressure, 153/93 mm Hg). Ambulatory systolic blood pressure was reduced by 12 mm Hg ($P < .001$) and 4.5 mm Hg ($P = .05$) by continuous training. Improved endothelial function as measured by flow-mediated dilation was observed only in the combined intermittent group.[131]

Aerobic exercise may also positively affect blood pressure and left ventricular mass among individuals with borderline hypertension. In a controlled study of 52 middle-aged men with high normal or mildly elevated blood pressure, 16 weeks of stationary cycling 3 times per week for 45 minutes at 60% to 80% of maximum heart rate resulted in a highly significant reduction in resting blood pressure (-12/-6.5 mm Hg) compared with individuals in the control group (-3/-1.1 mm Hg).[132] In a randomized study, the effects of aerobic versus resistance exercise in men and postmenopausal women with prehypertension or stage 1 essential hypertension were evaluated.[133] Among women, there were greater blood pressure reductions after resistance compared with aerobic exercise. Men, on the other hand, had comparable blood pressure effects after either exercise mode, confirm the beneficial effects of both types of exercise for men and women. Results of another study performed in 2012 provided evidence that aerobic exercise training could effectively lower blood pressure even among individuals with resistant hypertension, defined as a blood pressure of 140/90 mm Hg and higher on 3 medications or a blood pressure controlled by 4 medications and more. Compared with individuals in the control group, 24-hour systolic (-5.4 ± 12.2 mm Hg versus 2.3 ± 7.3 mm Hg; $P = .03$) and diastolic (-2.8 ± 5.9 mm Hg versus 0.9 ± 4.1 mm Hg; $P = .01$) blood pressure levels were significantly reduced by aerobic training.[134] Later, most studies have shown that exercising at 40% to 70% of maximal oxygen uptake (corresponding to 50% to 85% of maximal individual heart rate) lowers the blood pressure at least as well as more intensive exercise.[135] Finally, in 2013, the American Heart Association recommended to perform moderate- or high-intensity exercise (reaching more than 40% to 60% of maximum heart rate) for at least 30 minutes on most days per week to achieve a total of at least 150 minutes per week to blood pressure lowering.[136] In practice, it has been shown that an activity that makes one breathless, but still able to carry on a conversation relatively easily, corresponds to a medium intensity activity. For many untrained people with hypertension, relatively simple activities, such as walking, are therefore sufficient to achieve a reduction in blood pressure.[137] Episodes of physical activity of short duration, such as 3 to 20 minutes, can reduce blood pressure, but longer durations appear to be connected with greater and more lasting lowering of blood pressure; 30- to 45-minute sessions are therefore recommended as suitable for achieving a good pressure-lowering effect.[138]

To take maximum advantage of the acute blood pressure-lowering effect of physical activity, which lasts up to 24 hours, it is usually recommended that exercising be performed on most days of the week. The increased physical activity will need to be kept up on a continual basis in order for the blood pressure-reducing effect to be maintained. After 4 to 6 months, the maximal effect on blood pressure, with respect to pressure-lowering, seems to be attained. If the individual stops exercising, the blood pressure returns to the same level as before exercising began. This can occur as quickly as within 10 days, possibly depending on how long the individual exercised regularly.[139]

There have been a few meta-analyses on the blood pressure-lowering effects of isometric exercise. In 1 review published in 2010, the effect of isometric handgrip exercise training lasting at least 4 weeks was evaluated.[140] The main outcome showed 10% decrease in both systolic and diastolic blood pressures. Another meta-analysis published in 2011 also evaluated the impact of several different resistance training modalities.[141] A subgroup analysis of isometric handgrip exercise alone showed larger decreases in systolic (-13.5 mm Hg) and diastolic (-7.8 mm Hg) blood pressures compared with dynamic resistance training (-2.7/-2.9 mm Hg). In 2 studies, the mean peak pressure during the double leg-press for the group reached 320/250 mm Hg in individuals with normal blood pressure at rest, with pressures in one subject exceeding 480/350 mm Hg. In these studies, the enormous increase in blood pressure can be attributed to the lifting of a heavy weight to exhaustion and to the effect of the Valsalva maneuver.[142] However, next studies

did not observe the tremendous increase in blood pressure reported by previous studies, partly by avoiding the Valsalva effect, but still their findings regarding blood pressure reduction are inconsistent. Some suggested a possible antihypertensive effect of strength training, whereas others found none. In 2 of the studies, a small (5 mm Hg), but significant reduction was observed in diastolic blood pressure.[143] No changes in blood pressure were noticed after 6 months of strength training in a group of 70- to 79-year-old men and women, or in a group of previously sedentary middle-aged men after 20 weeks of strength training.[144]

Based on these data, the American College of Sports Medicine concluded that studies have not been consistent in demonstrating that strength training lowers blood pressure in hypertensive individuals. Accordingly, the American College of Sports Medicine, the European Society of Hypertension, and the European Society of Cardiology recommend that the primary type of exercise for the management of blood pressure should be aerobic, supplemented by resistance training. High intensity isometric exercise, such as heavy weightlifting, should be avoided. Although weight loss has been shown to lower blood pressure, some studies found that that the blood pressure response to training is not dependent on body mass changes.[144,145]

In a recent study conducted in 2014, physical activity attenuated the positive association between weight and risk of hypertension, especially for obese women. Compared to normal-weight highly active women, risk of hypertension in obese highly active women was 3.4 times greater and in obese inactive women, it was 4.9 times greater. It means that both physical activity and maintenance of a healthy body weight are associated with lower risk of hypertension. Physical activity reduced but did not remove the effect of obesity on hypertension risk.[146]

Exercise has the most potent effect on endothelium-dependent vasodilatation, and the endothelium-derived nitric oxide is thought to be necessary to maintain an adequate vascular response to increased blood-flow demands during exercise. Shear stress is an important component of exercise, and it affects vascular nitric oxide concentration, and increases the velocity of the endothelial high-affinity/low-capacity transport system for L-arginine. This ensures substrate availability, as the rate-limiting step of endothelial nitric oxide synthase, which generates reactive oxygen species in the absence of L-arginine.[144-147] Thus, exercise training may correct endothelium-dependent vasodilatation by a variety of mechanisms. First, shear stress augments the expression of nitric oxide synthase in endothelial cells. Second, shear stress induces upregulation of the cytosolic copper-and-zinc containing superoxide dismutase, a free-radical scavenger. The inactivation of nitric oxide by a vascular superoxide or other reactive oxygen species may thereby be attenuated. Third, shear-stress-mediated suppression of angiotensin-converting enzyme may influence endothelium dependent relaxation by affecting local concentration of bradykinin by keeping it active.[147,148]

In summary, considering the increasing prevalence of sedentary lifestyle in most communities, the implementation of recommendations regarding physical activity given by expert committees should receive high priority. If only population exercise levels can be improved and sustained, the cardiovascular risk burden can be controlled.

CAFFEINE CONSUMPTION

Impact

Caffeine is widely consumed by people of all ages. Men and women aged 35 to 64 years are among the highest consumers of caffeine.[149] Although a link between caffeine consumption (particularly coffee) and hypertension may exist, the effects of coffee drinking on blood pressure appear to be dependent on the time of consumption and subsequent determination of blood pressure values. Generally, the relationship between caffeine intake and development of hypertension has plenty of paradoxes.[150] Narkiewicz and colleagues found higher systolic blood pressure in Italian men who took 4 or more cups of coffee per day compared to nondrinkers, but only for daytime ambulatory blood pressure and not for office blood pressure.[151] However Balk and Hoekstra showed that moderate and high (2 cups per day) coffee consumption was significantly associated with lower high-density lipoprotein cholesterol in women. For men, coffee consumption was not associated with any of the components of the metabolic syndrome.[152]

Two large united States cross-sectional studies showed a negative correlation of coffee with blood

pressure.[153,154] Coffee was also weakly inversely correlated with systolic and diastolic blood pressure in the Danish MONICA cohort after multivariable adjustment.[155] Lopez-Garcia and colleagues in a cross-sectional analysis of 730 healthy and 663 diabetic women studied caffeinated and decaffeinated coffee in relation to endothelial function and found no association. In these data, an inverse U-shaped relation between coffee intake and presence of hypertension was seen in healthy women.[156]

A systematic review and meta-analysis of publications identified in PubMed search up to 30 April 2011 on the effect of caffeine or coffee intake on blood pressure change showed that in 5 trials, the administration of 200 mg to 300 mg caffeine produced a mean increase of 8.1 mm Hg in systolic blood pressure and of 5.7 mm Hg in diastolic blood pressure. The increase in blood pressure was observed in the 1st hour after caffeine intake and lasted 3 hours. In 3 studies of the longer-term effect (2 weeks) of coffee, no increase in blood pressure was observed after coffee was compared with a caffeine-free diet or was compared with decaffeinated coffee.[157]

A Japanese research group demonstrated a beneficial effect of chlorogenic acid from green bean coffee extract on vasoreactivity and blood pressure in mild hypertensives, with reduction around 3 mm Hg to 4 mm Hg.[158] A meta-analysis suggested larger blood pressure elevations in the case of prolonged coffee use (> 6 weeks), younger age (< 40 years), and high levels of coffee intake (> 5 cups per day).[159]

A large cohort study in 2013 showed a positive association between coffee consumption and all-cause mortality in men and in men and women younger than 55 years. On the basis of these findings, it seems appropriate to suggest that younger people avoid heavy coffee consumption (ie, averaging > 4 cups per day).[160]

Pathogenesis

A number of mechanisms have been proposed by which caffeine could raise blood pressure, including sympathetic overactivation, antagonism of adenosine receptors, increased norepinephrine release via direct effects on the adrenal medulla, renal effects, and activation of the renin-angiotensin system.[161]

Another group showed enhanced endothelium-dependent vasodilatation after acute caffeine administration in young healthy men, a mechanism by which caffeine could lower blood pressure.[162] Shechter showed that acute caffeine ingestion significantly improved endothelial function assessed by brachial artery flow-mediated dilation in subjects with and without coronary artery disease and was associated with lower plasma markers of inflammation.[163]

From experimental research, it has become clear the caffeine administration acutely raises blood pressure, but tolerance to this effect develops rapidly and heavy coffee drinkers are less likely to show a blood pressure response after caffeine intake.[164] It is shown that espresso contains high amounts of soluble fibre and associated antioxidant polyphenols and it is possible that blood pressure-lowering minerals and polyphenols in coffee outweigh potential adverse effects of caffeine.[165]

In summary, there are many possible biological pathways through which a variety of bioactive substances in coffee may influence blood pressure, either resulting in an overall blood pressure-lowering or a blood pressure-raising effect of coffee. It is at present unclear whether habitual coffee drinking is related to risk of hypertension, although most evidence suggest that this is not the case. The precise nature of the relation between coffee and blood pressure is not yet clear. More prospective studies of coffee intake and incident hypertension are needed, as are long-term randomized placebo-controlled trials.

Recommendations

In the absence of definitive scientific data, it would seem prudent to recommend moderation when it comes to the ingestion of caffeine containing beverages such as coffee, tea, and cola drinks. There is little evidence to suggest that habitual consumption at the current average of the equivalent of 2 to 4 cups of coffee per day causes an increase in blood pressure of any clinical importance. Ingesting larger amounts (eg, > 5 to 6 cups of coffee per day) should be discouraged if increases in blood pressure are a concern, such as in patients with hypertension or in those individuals having a prehypertensive state.[164]

ALCOHOL CONSUMPTION

Impact

A large number of cross-sectional and

prospective epidemiological studies have repeatedly demonstrated that alcohol consumption is one of the most important modifiable risk factors for hypertension among populations from a variety of geographic regions, including North America, Europe, and Asia.[166] The positive association between alcohol intake and blood pressure generally persists after adjustment for important confounders such as age, body mass, smoking, exercise, and sodium and potassium intake. It has been suggested that blood pressure-reduction effect of a reduced intake of alcohol is smaller in long-term than in short-term intervention trials because study participants continually adapt to the depressor effects of alcohol withdrawal.[166,167]

The natural history of alcoholism in hypertension can be divided into 5 distinct phases. In phase 1, the consumption of alcohol is associated with an increase in blood pressure. This effect is independent of age, sex, race, cigarette smoking, and coffee consumption and is dependent on the amount of ingestion. In this phase, alcohol consumption increases sympathetic nervous system activity. In phase 2, an abstinence from alcohol reduces both the systolic and diastolic blood pressure. The blood pressure effect occurs in days to months. In phase 3, resumption of drinking invariably increases blood pressure and toxic effects of alcohol emerge in this phase. In phase 4, the alcohol-dependent patient with hypertension is at high risk of liver damage. Phase 5 occurs with the onset of end-stage liver disease when the blood pressure is usually high.[168]

It is shown that a reduction in alcohol intake among heavy drinkers significantly reduces systolic and diastolic blood pressure. Studies of alcoholics during detoxification also support this association with findings of blood pressures of 140/90 mm Hg or higher in more than 50% of alcoholics admitted for detoxification, and blood pressures of 160/95 mm Hg or higher in one-third of alcoholics admitted for detoxification without delirium tremens. Blood pressure returns to normal in approximately 70% of alcoholics after detoxification and remains normal, if patients remain abstinent. Upon reintroduction of alcohol use, blood pressures again become elevated.[166]

In addition, it has been suggested that the protection against coronary heart disease afforded by moderate alcohol consumption may be mediated by an increase in high-density lipoprotein cholesterol and a decrease in low-density lipoprotein cholesterol, but counterbalanced by an increase in risk due to increased systolic blood pressure and alcohol reduction should be recommended as an important component of lifestyle modification for the prevention and treatment of hypertension.[169]

In some epidemiological studies, a linear dose-response relationship has been established, sometimes starting with a consumption threshold of 3 drinks per day (30 g of ethanol) and at higher levels of consumption, higher triglyceride levels, increased plasma homocysteine and increased risk of type 2 diabetes mellitus are seen.[170] In others, the relationship has been nonlinear, especially in women.[171] The elderly make up a group of the general population with specific traits. Comorbid conditions and medical interactions are expected to make any alcohol use harmful. Only a few studies have addressed the relationship between alcohol and hypertension in the elderly, and most of them have shown a strong association between hypertension prevalence and alcohol intake.[172]

The Coronary Artery Risk Development in Young Adults Study was a longitudinal cohort of African-American and European-American men and women designed to recruit individuals with a wide range of incomes and education from four urban areas. In this diverse cohort the relation between baseline alcohol use and incident hypertension over 20 years of follow-up were examined. No association was found between baseline alcohol consumption and incident hypertension, except among European-American women in whom any alcohol consumption was associated with lower risk of incident hypertension.[173] These discrepancies may reflect differences in investigational design, methods, and populations.

The mechanism through which alcohol raises blood pressure remains elusive. Alcohol consumption seems to be related with blood pressure elevation, not through long-term structural alterations, but by neural, hormonal, or other reversible physiological changes. Clinical trials have demonstrated that the association between intake of alcohol and higher blood pressure is causal and occurs within a matter of weeks or less.[169-171] The validity of self-reported alcohol consumption has also been questioned. However, an underestimation of alcohol intake across the entire cohort, or selectively in heavy users,

could have resulted in an underestimation of the level of alcohol consumption at which blood pressure starts to increase, but it would not have changed the slope of the association.[171] Another consideration in evaluating studies of alcohol and disease is that drinking habits change over time.[172] If persons who consume high levels of alcohol at baseline decrease their intake during follow up to a greater extent than persons who drink less, prospective studies will underestimate the risk associated with alcohol intake. These findings strongly support recommendations for moderation of alcohol consumption as a means to prevent and treat hypertension.[174]

The effect of moderate alcohol consumption on blood pressure is not fully understood. A linear, J-shaped or threshold association between alcohol consumption and blood pressure has been reported in observational studies. Activation of the sympathetic nervous system and alteration of vascular tone have been hypothesized as the probable mechanisms explaining the relationship between heavy alcohol intake and an increased risk of hypertension. Some studies have suggested that alcohol has a direct effect on blood pressure, but others have indicated that repeated withdrawal from alcohol is at least as likely an explanation for elevated blood pressure.[175]

It has been proposed that the effect of heavy alcohol intake on blood pressure may be mediated by the actions of hormones such as norepinephrine and cortisol. In men, the relationship between alcohol consumption and average systemic blood pressure is linear over the range of moderate to heavy use. In women, however, the relationship is U-shaped.[175] Catecholamine excretion has been found to be elevated during acute and chronic alcohol administration. These patients show still further increases, especially in urinary epinephrine, with abrupt withdrawal. Plasma norepinephrine levels are highest 13 to 24 hours after alcohol cessation. These observations suggest stimulation of adrenal medullary secretion, as well as changes in sympathetic nervous system activity.[176] However, Arkwright and colleagues[177] measured basal and stimulated plasma norepinephrine and epinephrine in 30 moderate drinkers and 30 age-matched nondrinkers. Despite finding a significantly higher blood pressure in drinkers (9 to 7 mm Hg), there were no differences found in plasma catecholamines. Ibsen and colleagues[178] also compared plasma norepinephrine values in heavy and low-moderate chronic alcohol users. These investigators found no significant differences. Both blood pressures and pulse rates were higher in the higher intake group. These studies indicate that elevated blood pressures in chronic alcoholics can be maintained by mechanisms other than elevated plasma catecholamines.

Ethanol and its metabolites act initially as vasodilators, although vasoconstriction has been observed in some regional circulations following the feeding of ethanol to rats for 2 to 6 weeks. Altura and coworkers[179] observed that these animals developed increased tolerance to the vasodilating actions of ethanol. Moreover, such rats would demonstrate an exaggerated sensitivity to the vasoconstrictive effects of epinephrine. With long-term alcohol use, however, an abnormality in vascular responsiveness with vascular hyperactivity may occur, and could be responsible for the observed hypertension. Similarly, other vasoactive substances (eg, prostaglandins, angiotensin II, histamine, and intestinal and opioid peptides), a neurologic or neurohumoral mechanism could be responsible. An effect on the renin-angiotensin-aldosterone system has also been postulated.[178-180]

Beevers and colleagues[180] reported elevated plasma renin activity in 28 of 48 chronic alcoholics and raised plasma aldosterone in 8. All values returned to normal in seven days following the cessation of drinking. These investigators attributed the elevated plasma-renin activity to low sodium intake, although they also noted an increased sympathetic nervous system activity (high dopamine beta-hydroxylase values), suggesting an adrenergic mechanism. Cortisol may be in part responsible, since plasma-cortisol levels increase following acute alcohol ingestion, and a Cushing-like syndrome has been described in chronic alcoholics.[180]

In short-term, alcohol consumption is considered an appetite stimulant, influencing neurochemical and peripheral systems to control appetite, such as, leptin inhibition, glucagon-like-peptide-1, and serotonin, and enhancing the effect of gamma-aminobutyric acid, endogenous opioids, and neuropeptide Y. Hence, greater alcohol consumption, may also increase the risk for obesity.[181]

Alcohol usage is a more frequent contributor to hypertension than is generally appreciated. It

appears to be transitory in most patients, but is not benign. Hypertension might result in target-organ injury and could be the causal link to the increased incidence of stroke and coronary events observed in drinkers, as well as a contributor to the pathogenesis of alcoholic cardiomyopathy. Because of its transitory nature, alcohol-associated hypertension may go unrecognized, or may be dismissed thus, regrettably, a major potential cause of cardiovascular morbidity may go untreated.

STRESS MANAGEMENT

Impact

Psychosocial stress has been reported to influence the development and progression of atherosclerosis in the general population. Evidence indicates that chronic psychosocial stress induces excessive adrenergic activation and sympathetic hyper-responsivity, leading to carotid atherosclerosis and stress reduction with changes in diet or exercise led to statistically significant declines in blood pressure.[182] From Maharishi's point of view, stress and disease arise from a lack of integration of the various physiological systems of the body. This may result in loss of homeostasis in the cardiovascular system that could be expressed as higher blood pressure or increased atherosclerosis.[183]

Results of a meta-analysis in 2009 showed that individuals who had stronger responses to stressor tasks were 21% more likely to develop blood pressure increase when compared to those with less strong responses. Although the magnitude of effect was relatively small, but it emphasized on importance of controlling psychological stress as a nontherapeutic management of high blood pressure. In 2012, the association between blood pressure reactions to acute psychological stress and subsequent hypertension status was examined and results showed that systolic blood pressure reactivity was positively related to future hypertension but diastolic blood pressure reactivity was not significantly associated with hypertension.[184]

Data from a study in 2013 showed that endothelial dysfunction was paralleled by significant increases in circulating adrenaline levels and a substantial, dose-dependent decrease in sleep quality and an increase in systolic blood pressure. These findings indicate that hypertension observed in response to nighttime exposure to noise might be explained by increased sympathetic activation but also by the occurrence of vascular dysfunction. Accumulating data increasingly confirms that sleep disturbance of different causes might represent a novel, important health risk.[185]

Safe and effective nonpharmacologic approaches to treat hypertension are of interest and public health importance. Stress management techniques that elicit the relaxation response are safe and effective for treating essential hypertension. The relaxation response is a coordinated physiologic response characterized by decreases in volumetric oxygen consumption, heart rate and respiratory rate.[186] This is often achieved by the repetition of a word, sound, prayer, phrase, or muscular activity and disregard routine thoughts when they occur. Techniques that bring forth the relaxation response include meditation, yoga, and some stages of hypnosis. Potential implications of this method include improved control of blood pressure, decreased costs of treatment of hypertension, fewer side-effects, and increased patient adherence to antihypertensive therapy.[187]

Chronic psychological stress is associated with increased activation of the sympathetic-adrenomedullary axis and increased circulating levels of adrenaline and noradrenaline. Chronically elevated adrenaline levels have been implicated in the development and progression of hypertension, and hypertensive subjects have been demonstrated to have increased sympathetic and reduced parasympathetic tone compared to healthy controls.[187] Hypertensive patients have endothelial dysfunction and low plasma levels of nitric oxide metabolites. Since relaxation response is associated with increased nitric oxide in healthy subjects, it has been hypothesized that it may have increased endothelial nitric oxide production resulting in vascular dilatation and reduced systolic blood pressure.[188]

A meta-analysis of 75 controlled clinical trials of relaxation-based stress management treatments for hypertension showed that initial blood pressure level is strongly predictive of subsequent change, with treatments that started with high initial blood pressure levels producing greater reductions.[189]

By learning to manage stress more effectively and decrease negative emotional arousal, patients were able to self-generate measurable and significant changes in their physiology and health status.

The practice of relaxation techniques should be encouraged. One theory is that although adaptation to socioeconomic stressors may be slow, the emotional and physiological response to these stressors may be modified more rapidly by a behavioral intervention.[190]

Accumulating evidence shows that slow and regular breathing elicits acutely a number of beneficial effects via the cardiovascular reflex control system, including increased heart rate variability and baroreflex sensitivity, blood pressure reduction and an increase of oxygen saturation.[191] A double-blind randomized study was conducted to evaluate the effect of breathing modulation on blood pressure, guides the user towards slow and regular breathing by creating a musical pattern temporally-related to the breathing movements monitored by a sensor. It has been shown that daily use of this method is able to change respiration pattern. Results showed that 10 minutes of daily use, over an 8-week period elicited a clinically significant reduction in the blood pressure level, as checked weekly at the clinic.[192]

For hypertensive patients in whom stress appears to be an important issue, stress management should be considered as an intervention. Individualized cognitive behavioral interventions are more likely to be effective than single component interventions.

CONCLUSIONS

Hypertension, that is above-normal blood pressure, is the most important, modifiable risk factor for cardiovascular disease and mortality. The incidence is increasing in most countries and lifestyle factors are considered to play a decisive role in this development. Obesity, physical inactivity, unhealthy diets, increased salt intake, smoking, and psychosocial stress, in particular, have varying degrees of significance in different populations. Most cases of hypertension are currently still undetected or untreated, or have not reached therapeutic target values for treatment. This leaves much room for improved treatment, both via an increase in non-pharmacological treatment and lifestyle modification along with different pharmacological option.

CONFLICT OF INTEREST

None declared.

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Received March 2016
Accepted April 2016