

WHL In Focus Statement

Can non-pharmacological interventions reduce doses of drugs needed for the treatment of hypertension?

Summary

Non-pharmacological approaches lower medication requirements in patients with hypertension. A decreased salt intake to a sodium value of about 80 mmol/d lowers blood pressure in the presence of diuretics, beta-blockers, converting enzyme antagonists and sympatholytics, but apparently not in patients treated solely with calcium antagonists. A reduced medication requirement is seen in about half of patients, suggesting that the phenomenon of "salt-sensitivity" still applies. Weight loss is an effective adjunctive therapy and simultaneously improves other cardiovascular risk factors. A high alcohol consumption is a confounding factor in the drug treatment of hypertension. Reducing the alcohol intake of hypertensive heavy drinkers significantly lowers their blood pressures and drug requirements. Aerobic exercise is an effective non-pharmacological treatment, which simultaneously fosters weight loss and improves risk factors. Potassium supplementation does not decrease medication requirements in drug-treated patients who are ingesting a low salt diet, but may do so in those eating large amounts of salt. Non-pharmacological approaches should be included in the management of all hypertensive patients, irrespective of their drug therapy. These should include weight reduction through decreased food and alcohol consumption as well as regular, programmed exercise. Patients should be instructed in a low calorie diet rich in fresh, rather than processed products and high in fruits and vegetables. Such a diet will contain relatively little salt, reduced fat, and ample amounts of potassium and calcium. However, physicians should not lose sight of the fact that cigarette smoking remains the most important risk factor to be addressed in their hypertensive patients.

Introduction

The merits of non-pharmacological approaches in the management of hypertension have been debated in numerous reviews, meta-analyses, and reports (1). The World Hypertension League itself has published three consensus statements on selected aspects of this subject, namely, on weight control (2), physical activity (3), and alcohol consumption (4). Although agreement on all aspects of non-pharmacologic treatment has not yet been attained, the evidence in support of non-pharmacologic treatment is convincing (5). The purpose of this report is not to review the entire topic of non-pharmacologic therapy as such, but rather to concentrate its specific role in augmenting pharmacological therapy and facilitating a reduction in medication requirements.

Salt reduction

Salt intake and its relationship to blood pressure continues to be a major area of investigation (see 6 for review). Recent highlights of which all clinicians should be aware include publication of the Intersalt study and meta-analyses largely engendered by the Intersalt findings (7). Salt reduction and the response to antihypertensive drugs has been the topic of an earlier review (8). Salt reduction generally results in an additional decrease in blood pressure in the presence of most, but not all antihypertensive agents. Salt reduction augmented the

hypotensive effect of chlorthalidone in two investigations, but not that of hydrochlorothiazide in another (9-11). The effect of beta-blockers was augmented by salt reduction in three studies (11-13). Angiotensin converting enzyme inhibitors lowered blood pressure even more effectively when dietary salt intake was reduced (14). The combined effect of angiotensin converting enzyme inhibitors and salt reduction was recently investigated in detail by Singer et al. (15). They performed a double-blind crossover study of the effects of moderate salt reduction in 21 patients with essential hypertension who were already being treated with the combination of a converting enzyme inhibitor and a diuretic. After one month of captopril (50 mg twice daily) and hydrochlorothiazide (25 mg once daily) therapy at their usual level of salt intake, the subjects were instructed in a reduced salt intake (80 - 100 mmol/day sodium). Their supine blood pressure was 147/96+5/2 mm Hg prior to salt reduction. After achieving a reduced salt intake, the subjects were randomized to "slow sodium" capsules or placebo. The study showed an added effect of salt reduction on mean arterial blood pressure, which was reduced by 5-7%. The decrease was correlated with the reduction in salt intake. The authors suggested that the blockade of the renin-angiotensin system afforded by captopril may augment the effects of salt reduction, since presumably increases in angiotensin II otherwise engendered by salt reduction are thereby avoided. In his commentary on this paper, Morgan (16) pointed out that salt reduction is a desirable alternative to increasing diuretics in pharmacologically treated patients. Increased diuretics could lead to further metabolic side effects, potassium losses, low magnesium levels, higher uric acid values and further cholesterol elevation. He suggested that a combination of low dose thiazide therapy and moderate salt reduction should be ideal in achieving the maximum blood pressure reduction with the minimum of side effects. Morgan suggests that moderate salt reduction (50-100 mmol/d) is readily attained by not adding salt at the table or in cooking, the use of a reduced salt bread and cereal, and avoidance of high salt-containing foods (fast foods, prepared meats). Weinberger et al. (17) reduced the dietary salt intake of 100 patients undergoing pharmacological treatment of hypertension. All had blood pressures well controlled (140/90 mm Hg) with medication. The medications regularly included a thiazide diuretic. Beta-blockers, calcium antagonists, converting enzyme inhibitors and sympatholytics were also employed. The study was designed to explore the feasibility of long-term reduced salt intake in an American clinic population. The subjects were recruited by advertisement; they expressly volunteered to be instructed in a low salt diet. The subjects were followed by physicians who were instructed to reduce their medication if mean blood pressure fell by at least 8 mm Hg. Salt intake was documented by frequent 24 hr urine collections. The subjects were instructed by expert dietitians. The food preparer in the family was identified and specifically trained in "low salt" cooking. A telephone "hot line" was provided so that questions could be quickly answered. The subjects were given chloride titrator sticks so that they could assess their level of compliance in first morning voided urine samples (18). The educational methodology to this study has been published (19).

Half of the subjects attaining a sodium excretion of less than 80 mmol/d reduced their blood pressures sufficient to permit a reduction in their medications. Since only half of these motivated subjects were able to achieve adherence despite the presence of a dedicated team to help them do so, it appears that a reduced salt intake diet may not be as easily attained as Morgan and others have suggested (15,16). In part, the difficulty may stem from the amount of salt in processed foods. This fact has not been lost on food producers; "low salt" products are becoming increasingly available for those who need them. A few rules with respect to food preparation are generally not enough; professional help is needed. Finally, there are indications that a reduced salt intake has no additive effect with calcium antagonist drug therapy (20,21). Similarly, thiazide diuretics and calcium antagonists appear to exhibit little additive effect. The reasons for this rather unexpected result may be related to a mild

natriuretic effect of calcium antagonists (22). Further investigations of this issue are needed to clarify this issue.

Weight loss

This topic was discussed in an earlier WHL consensus statement (2). Further, the Intersalt study also addressed the relationship of body mass index to blood pressure (7). Obesity is central to a constellation of risk factors, each of which calls for its own particular dietary considerations and interventions. These are beyond the scope of this discussion. Nevertheless, clinicians must be aware of the current attention given to the "deadly quartet", or syndrome "X" as it has been termed in Europe. This controversial constellation features central obesity, insulin resistance, hyperlipemia and hypertension (23). It calls for simultaneous consideration of lipid and carbohydrate metabolism, obesity in general, and the treatment of hypertension. It underscores the complexity of these interrelationships on the one hand, while on the other offering numerous simultaneous avenues for non-pharmacological approaches. For instance, if persons featuring the "deadly quartet" can be compelled to lose weight, lower their fat intake and also exercise regularly and vigorously, it is likely that all four features of this syndrome will be addressed simultaneously. A clinical overview of dyslipidemias and their management has recently been published (24). Obesity may account for as much as one-third of all hypertension (25). Weight loss results in decrease of blood pressure, independent of other variables such as salt intake (26). Further, weight loss may cause salt sensitive individuals to become less salt sensitive (27). MacMahon et al. (28) have also shown that weight loss lowers blood pressure in hypertensive patients compared to controls, while at the same time improving their putative cardiovascular risk. In a 21 week study, weight loss reduced blood pressure as well as metoprolol, while it increased HDL-cholesterol and decreased total cholesterol. Metoprolol also decreased blood pressure, but increased total cholesterol and decreased HDL- cholesterol. Although long-term follow-up is not available, the data nevertheless emphasize the importance of weight loss. As with salt reduction, compliance is a major problem. Eliahou et al. reported on weight loss as a management strategy in over 200 subjects visiting a community clinic (29). They reported that 20% of their patients did not complete the treatment program and that 40% did not adhere to the dietary regimen. However, in the 60% remaining, more than two-thirds achieved normal blood pressure with a loss of half their excess weight, even if they remained above ideal body weight. Oberman et al. (30) conducted a multicenter trial of pharmacologic and non-pharmacologic therapy (The TAIM Study) in 692 hypertensive patients, who were 110 to 160% above ideal body weight. The diet interventions were: usual, low salt- high potassium, and weight loss. The drug interventions were: placebo, chlorthalidone, and atenolol. Nine diet plus drug combinations were studied. The degree of salt reduction achieved as reflected by 24 hr urinary sodium excretion was from 133 mmol/d to 100-110 mmol/d, while the amount of weight loss attained ranged from 3.2 to 6 kg. After six months, the chlorthalidone plus usual diet group had an increased cardiovascular risk, despite a decreased blood pressure because of undesirable plasma lipid changes. All other groups showed favorable cardiovascular risk profiles. However, the best cardiovascular risk profiles were identified in groups combining drug therapy plus weight loss. The authors concluded that weight loss was the most important adjunctive treatment in reducing overall cardiovascular risk.

Alcohol Consumption

The WHL has also reviewed this topic in detail (4). Numerous epidemiological studies suggest that regular alcohol intake in excess of four drinks per day (>100 g ethanol) increases blood pressure in both men and women (31). The Intersalt study also addressed this issue (7). A pressor effect of regular alcohol consumption was demonstrated even in normotensive subjects by Puddey et al. (32) They also examined the interaction between regular alcohol intake and pharmacological therapy in hypertensive subjects (33). Forty four men with treated essential hypertension who were moderate to heavy drinkers took part in a randomized, controlled, cross-over trial of the effects of alcohol intake on blood pressure. Usual antihypertensive treatment was maintained throughout six weeks of normal drinking and six weeks of drinking only a low-alcohol beer. Estimated alcohol consumption decreased from 452 to 64 ml per week in these subjects. Systolic and diastolic blood pressures were 5 and 3 mm Hg lower respectively at the end of the low alcohol, compared to the high alcohol period. Regression analysis suggested that reduction in alcohol intake contributed to the fall in both systolic and diastolic blood pressures independently of changes in body weight. The authors conclude that curtailing alcohol intake reduces the need for antihypertensive drugs (33). Further, heavy drinking should be considered in patients whose blood pressures become difficult to control. Avoidance of heavy drinking should be included in any comprehensive management program in hypertensive patients, irrespective of their drug requirements.

Aerobic Exercise

The role of physical exercise in the management of hypertension was the subject of WHL's "In the Focus Statement" in 1991 (3). The reader is also referred to a recent exhaustive review by Tipton (34). Regular aerobic exercise is associated with a reduced risk for hypertension (35). The effect of exercise is independent of body weight, alcohol ingestion, or electrolyte intake (36). Recently, an epidemiological investigation of physical activity of male, college alumni from the University of Pennsylvania (37) has shown that physical activity is associated with reduced occurrence of non-inulin-dependent diabetes mellitus (NIDDM). These findings are immensely important, since NIDDM is closely associated with hypertension and the occurrence of both greatly add to the risk of cardiovascular events. Protection afforded by exercise (quantitated in kcal. per week from city blocks walked, stairs climbed, and calories expended in leisure time sports activities) was independent of body mass index, weight gained since college, blood pressure, family history of diabetes or hypertension, all of which were independent risk factors. Interestingly, the protective effects of exercise were greatest for those at the highest risk for developing the disease. Since exercise improves glucose tolerance, lowers insulin levels, increases peripheral sensitivity to insulin, and decreases sympathetic tone, mechanisms are at hand which may explain these findings. These mechanisms are of interest in terms of the association recently identified between disturbed carbohydrate metabolism and hypertension, even in hypertensive patients who have normal glucose tolerance (38). This association is receiving considerable attention (39). A number of well-performed prospective, randomized, clinical trials indicate that exercise decreases blood pressure in patients with hypertension to a similar degree as do salt reduction or weight loss (40-42). The effect of exercise is independent of weight loss. However, both are desirable. Exercise results in weight loss accompanied by preserved lean body mass, while diet alone decreases both body weight and lean body mass. Numerous studies on the interaction between aerobic exercise and antihypertensive agents have been performed; however, these have generally examined the effects of antihypertensive agents on exercise performance (36). An exception is the study by Ades and associates (45). These

investigators randomized hypertensive patients into three groups. A non-drug-treated, but exercised control group was compared to a propranolol-treated, exercised group and a metoprolol-treated, exercised group. Exercise decreased mean blood pressure by about 8-10 mm Hg in the non-drug-treated group and in the metoprolol-treated group, but not in the propranolol treated group. It is possible that the antagonism of α -2 receptors may interfere with blood pressure-lowering effects of exercise. A weakness of this report is that no non-exercised placebo group was included. However, the study indicates that exercise may lower blood pressure in patients being simultaneously treated for hypertension. In conclusion, aerobic exercise both lowers blood pressure and has independent, desirable effects on control of weight gain, plasma lipid values, and carbohydrate tolerance. Aerobic exercise should be included in every non-pharmacological regimen, irrespective of medication requirements. A tailored program of walking, avoidance of elevators, and leisure time activity should be encouraged. The presence of underlying heart disease, left ventricular hypertrophy, and other forms of end organ damage, warrant added supervision by the physician.

Potassium

A large body of evidence suggests that potassium intake is inversely associated with blood pressure and that an increase in potassium may lower blood pressure in patients with hypertension. Numerous trials have been conducted to address the latter issue. These trials were recently subjected to a meta-analysis by Cappuccio and MacGregor (46). A total of 19 clinical trials were examined. According to their calculations, systolic blood pressure was lowered by about 6 mm Hg and diastolic blood pressure by about 4 mm Hg with potassium supplements. The magnitude of the blood pressure-lowering effect was greater in patients with higher blood pressures and appeared to be more pronounced the longer the duration of the supplementation. Meta-analyses may be misleading despite their impressive mathematics, since diverse and heterogeneous trials are frequently included, some of which are better controlled than others. However, data from intervention trials coupled with epidemiological evidence provide a compelling argument. Grimm et al. (47) conducted a randomized, placebo-controlled, double-blind clinical trial of potassium chloride supplementation in 287 hypertensive men who were treated with medication. The object of their study was to determine if potassium chloride could reduce the need of medication. A total of 142 were given potassium chloride and 145 were given placebo in addition to a low sodium diet. The patients medications were then withdrawn and they were followed for a period of 2.2 years. Patients receiving potassium chloride had higher serum and urinary potassium levels. Seventy-nine participants in each group required reinstatement of antihypertensive medication according to strict indications defined by protocol. No significant differences in systolic or diastolic blood pressure were observed between the groups. The authors concluded that potassium chloride supplementation did not reduce the need for antihypertensive medication in hypertensive men on a restricted salt diet. In their commentary on this paper, Kaplan and Ram (48) pointed out that the study by Grimm et al. (47) involved only white men and that benefits of potassium supplementation may be greater in black as compared to white subjects. Further, they argued that prevention of an increase in blood pressure may be different than initiating a decrease. In addition, a low salt diet would be expected to minimize any effects of potassium, since potassium salts seem to exert their effects by initiating natriuresis. Finally, they pointed out that evidence exists showing desirable vascular protective effects of a high potassium intake that are independent of effects on blood pressure. All of these points may be important. However, supplements are expensive and may occasionally be dangerous. Whether or not non-chloride containing potassium salts exert the same effect as potassium chloride, particularly with respect to natriuresis, is not clear. Overlack (49) was not encouraged by the

blood pressure-lowering effects of potassium combined with non-chloride anions. On the other hand, Siani et al. (50) reported highly impressive effects on blood pressure engendered by a high potassium diet consisting largely of steamed, rather than boiled vegetables. This regimen allowed a reduction of the patients' medication. The putative mechanisms of such a maneuver have recently been addressed by Krishna and Kapoor (51). These investigators performed a metabolic study on 12 patients with hypertension who received a fixed diet except for potassium (in the food), which was offered at either 16 or 96 mmol/d. Low potassium intake was associated with a 6 mm Hg increase in mean blood pressure, a decrease in sodium excretion, a decrease in renin and aldosterone, whereas arginine vasopressin and atrial natriuretic peptide values were not affected. Thus, potassium intake and sodium intake ie. excretion, appear irrevocably connected. While potassium supplementation is not a non-pharmacological intervention, it suggests the importance of a natural diet high in potassium. Such a diet is likely to contain more fresh fruits and vegetables, thereby favorably influencing salt, fat, and probably also caloric intake. From an evolutionary perspective, physiological adaptations to a naturally high potassium intake should not be casually dismissed.

Conclusions

Any antihypertensive drug therapy should be accompanied by intensive non-pharmacological treatment. Weight control, alcohol moderation, and regular aerobic exercise should be immediate goals. Ample fruits and vegetables, fresh rather than processed foods, and attention to reduced fat consumption and avoidance of added salt intake will result in a diet that would satisfy most, if not all advocates of dietary management. Investigations in which simultaneous efforts to reduce salt intake, weight, and alcohol consumption have been published by Stamler et al. (52). Their results were duly encouraging, supporting the notion that a holistic view is appropriate. Non-pharmacological approaches may enable some patients to discontinue drug treatment indefinitely. A decreased salt intake to a sodium value of about 80 mmol/d lowers blood pressure in patients treated with diuretics, beta-blockers, converting enzyme inhibitors and sympatholytic drugs, but perhaps not in those patients treated solely with calcium antagonists. A reduced medication requirement is seen in about half of patients, suggesting that salt-sensitivity plays a role as well. Weight loss is an effective adjunctive therapy and simultaneously improves other cardiovascular risk factors. Reducing the alcohol intake of hypertensive heavy drinkers significantly lowers their blood pressures and drug requirements. Regular exercise is an effective non-pharmacological treatment, which simultaneously fosters weight loss and improves risk factors. Its effects may be blunted by some pharmacological treatments. Potassium supplementation does not decrease medication requirements in drug treated patients who are ingesting a low salt diet, but may do so in those eating large amounts of salt. However, the initial step in non-pharmacological treatment should concentrate on whether or not the patient smokes cigarettes. If so, stopping this habit is more important for the patient's welfare than either pharmacological or non-pharmacological treatment. The cardiovascular risk of the smoking hypertensive patient is so high that the importance of stopping smoking overshadows all other non-pharmacological interventions. Moreover, convincing evidence has been recently published showing that smoking per se may increase blood pressure (53).

References

1. The 1984 Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med* 1984; 144:1045.
2. World Hypertension League. Weight control in the management of hypertension. *Bulletin of the World Health Organization* 1989; 67: 245-252.
3. World Hypertension League. Physical exercise in the management of hypertension. *J Hypertens* 1991; 9: 283-287.
4. World Hypertension League. Alcohol and hypertension - implications for management. *J Hypertens* 1991; 9: 227-232.
5. McCarron DA, Anderson S, Hill MN, Kurtz TW, Linas SL, Luft FC, Reusser M: Education Program On Nonpharmacologic Management Of Hypertension, National Kidney Foundation Inc. New York, NY, 1990.
6. Muntzel M, Drake T. A comprehensive review of the salt and blood pressure relationship. *Am J Hypertens* 1992; 5(Suppl. 4): 1S-42S.
7. Intersalt Cooperative Research Group. Intersalt: an international study of electrolyte excretion and blood pressure. Results for 24-hour urinary sodium and potassium excretion. *Br Med J* 1988; 297: 319-328.
8. Luft FC, Weinberger MH. Review of salt restriction and the response to antihypertensive drugs. *Hypertension* 1988; 11(Suppl I): I-229-I-232.
9. Erwteman TM, Nagelkerke N, Lubsen J, Koster M, Dunning AJ. Betablockade, diuretics, and salt restriction for the management of mild hypertension: a randomized, double-blind trial. *Br Med j* 1984; 289: 406-409.
10. Ram CV, Kaplan NM. Moderate sodium restriction and various diuretics in the treatment of hypertension. *Arch Intern Med* 1981; 141: 1015-1019.
11. Carney SL, Gillies AHB, Smith AJ, Waga S. Effect of dietary sodium restriction on patients receiving antihypertensive medication. *Clin Exp Hypertens* 1984; A6: 1095-1105.
12. Owens CJ, Brackett NC. Role of sodium intake in the antihypertensive effect of propranolol. *South Med J* 1978; 71: 43-46.
13. Pollavini G, Comi D, Grillo C, et al. Effects of moderate salt restriction in hypertensive patients treated with oxprenolol or chlorthalidone. In *J Clin Pharmacol Ther Toxicol* 1984; 22: 451-455.
14. Hollenberg NK, Meggs LG, Williams GH, Katz J, Garnic JD, Harrington DP. Sodium intake and renal responses to captopril in normal man and in essential hypertension. *Kidney Int* 1981; 20: 240-245.

15. Singer DRJ, Markandu ND, Sugden AL, Miller MA, MacGregor GA. Sodium restriction in hypertensive patients treated with a converting enzyme inhibitor and a thiazide. *Hypertension* 1991; 17: 798-803.
16. Morgan TO. Interaction of pharmacological and nonpharmacological therapy. *Hypertension* 1991; 17: 804-805.
17. Weinberger MH, Cohen SJ, Miller JZ, Luft FC, Grim CE, Fineberg NS. Dietary sodium restriction as adjunctive treatment of hypertension. *JAMA* 1988; 259: 2561-2565.
18. Luft FC, Sloan RS, Fineberg NS, Free AH. The utility of over-night urine collections in assessing compliance with a low sodium intake diet. *JAMA* 1983; 249:1764-8.
19. Cohen SJ, Weinberger MH, Fineberg NS, Miller JZ, Grim CE, Luft FC. The effect of a household partner and home urine monitoring on adherence to a sodium restricted diet. *Soc Sci Med* 1991; 32: 1057-1061.
20. Morgan TO, Anderson A. Interaction of slow channel calcium blocking drugs with sodium restriction, diuretics and converting enzyme inhibitors. *J Hypertens* 1988; 6(Suppl 4): S-652-S-654.
21. Morgan TO, Anderson A, Wilson D, Meyers J, Murphy J, Nowson C. Paradoxical effect of sodium restriction on blood pressure in people on slow channel calcium blocking drugs. *Lancet* 1986; i: 793.
22. Luft FC, Fineberg NS, Weinberger MH. Long-term effect of nifedipine and hydrochlorothiazide on blood pressure and sodium homeostasis at varying levels of salt intake in mildly hypertensive patients. *Am J Hypertens* 1991; 4: 752-760.
23. Jones PH. A clinical overview of dyslipidemias: treatment strategies. *Am J Med* 1992; 93: 187-198.
24. Jarrett RJ. In defence of insulin: a critique of syndrome X. *Lancet* 1992; 340: 469-471.
25. MacMahon SW, Blacket RB, MacDonald GJ, Hall W. Obesity, alcohol consumption and blood pressure in Australian men and women. The National Heart Foundation of Australia Risk Factor Prevalence Study. *J hypertens* 1984; 2: 85-91.
26. Reisin E, Abel R, Modan M, Silverberg DS, Eliahou HE, Modan B. Effect of weight loss without salt restriction in the reduction of blood pressure in overweight hypertensive subjects. *N Engl J Med* 1978; 298: 1-6.
27. Rocchini AP, Key J, Bondie D, Chico R, Moorehead C, Katch V, Martin M. The effect of weight loss on the sensitivity of blood pressure to sodium in obese adolescents. *N Engl J Med* 1989; 321: 580-585.
28. MacMahon SW, MacDonald GJ, Bernstein L, Andrews G, Blacket RB. A randomized controlled trial of weight reduction and metoprolol in the treatment of hypertension in young overweight patients. *Clin Exp Pharm Physiol* 1985; 12: 267- 271.

29. Eliahou HE, Iaina A, Gaon T, Shochat J, Modan M. Body weight reduction necessary to attain normotension in the overweight hypertensive patient. *Int J Obes* 1981; 5(Suppl 1): 157-163.
30. Oberman A, Wassertheil-Smoller S, Langford HG, Blaufox MD, Davis BR, Blaszkowski T, Zimbaldi N, Hawkins CM. Pharmacologic and nutritional treatment of mild hypertension: changes in cardiovascular risk status. *Ann Intern Med* 1990; 112: 89-95.
31. MacMahon S. Alcohol consumption and hypertension. *Hypertension* 1987; 9: 111-121.
32. Puddey IB, Beilin LJ, Vandongen R, Rouse IL, Rogers P. Evidence for a direct effect of alcohol consumption on blood pressure in normotensive men: a randomized controlled trial. *Hypertension* 1985;7:707-713.
33. Puddey IB, Beilin LJ, Vandongen R. Regular alcohol use raises blood pressure in treated hypertensive subjects. *Lancet* 1987; i: 647-651.
34. Tipton CM. Exercise, training and hypertension: an update. *Exerc Sport Sci Rev* 1991; 19:447-505.
35. Paffenbarger RS, Wing AL, Hyde RT, Jung DL. Physical activity and incidence of hypertension in college alumni. *Am J Epidemiol* 1983;117: 245-257.
36. Luft FC. Hypertension and Exercise. In: *Advances in Sports Medicine and Fitness* vol. 2, Grana WA, Lombardo JA, Sharkey BJ, and Stone JA (eds.) Year Book Med Publ. Chicago, 1989.
37. Helmrich SP, Ragland DR, Leung RW, Paffenbarger RS. Physical activity and reduced occurrence of non-insulin- dependent diabetes mellitus. *N Engl J Med* 1991; 325: 147-152.
38. Ferrannini E, Buzzigoli G, Bonadonna R et al. Insulin resistance in essential hypertension. *N Engl J Med* 1987; 317: 350-357.
39. Donahue RP, Skyler JS, Schneiderman N, Prineas RJ. Hyperinsulinemia and elevated blood pressure: cause, confounder, or coincidence? *Am J Epidemiol* 1990; 132: 827-836.
40. Nelson L, Esler MC, Jennings GL, Korner PI. Effect of changing levels of physical activity on blood pressure and hemodynamics in essential hypertension. *Lancet* 1986;ii:473-476.
41. Pagani M, Somers V, Furlan R, Dell'Orto S, Conway J, Baselli G, Cerutti S, Sleight P, Malliani A. Changes in autonomic regulation induced by physical training in mild hypertension. *Hypertension* 1988; 12:600-610.
42. Hagberg JM, Goldring D, Ersani AA, et al. Effect of exercise training on the blood pressure and hemodynamics of adolescent hypertensives. *Am J Cardiol* 1983;52:763-768.
43. Soman VR, Koivisto VA, Deibert D, Felig P, DeFronzo RA. Increased insulin sensitivity and insulin binding to monocytes after physical training. *N Engl J Med* 1979; 301: 1200-1204.

44. Rauramaa R. Relationship of physical activity, glucose tolerance, and weight management. *Prev Med* 1984; 13: 37-46
45. Ades PA, Gunther PGS, Meacham CP, Handy MA, LeWinter MM. Hypertension, exercise, and beta-adrenergic blockade. *Ann Intern Med* 1988;109:629-634.
46. Cappuccio FP, MacGregor GA. Does potassium supplementation lower blood pressure? A meta-analysis of published trials. *J Hypertens* 1991; 9: 465-473.
47. Grimm RH, Neaton JD, Elmer PF, Svendsen KH, Levin J, Segal M, Holland L, Witte LJ, Clearman DR, Kofron P, LaBounty RK, Crow R, Prineas RJ. The influence of oral potassium chloride on blood pressure in hypertensive men on a low-sodium diet. *N Engl J Med* 1990; 322: 569-574.
48. Kaplan NM, Ram CVS. Potassium supplements for hypertension. *N Engl J Med* 1990; 322: 623-624.
49. Overlack A, Conrad H, Stumpe KO. The influence of oral potassium citrate/bicarbonate on blood pressure in essential hypertension during unrestricted salt intake. *Klin Wochenschr* 1991; 69(Suppl XXV): 79-83.
50. Siani A, Strazzullo P, Giorgione N, Giacco A, Mancini M. Increasing dietary potassium intake reduces the need for antihypertensive medication. *Ann Intern Med* 1992; 115: 753- 759.
51. Krishna GG, Kapoor SC. Potassium depletion exacerbates essential hypertension. *Ann Intern Med* 1991; 115: 77-83.
52. Stamler R, Stamler J, Gosch FC. Primary prevention of hypertension by nutritional-hygienic means. *JAMA* 1989; 262: 1801-1807.
54. Groppelli A, Giorgi DMA, Omboni S, Parati G, Mancia G. Persistent blood pressure increase induced by heavy smoking. *J Hypertens* 1992; 10: 495-499.