MAARIT KORHONEN

Dietary treatment of elevated blood pressure

Doctoral dissertation

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Department of Public Health and General Practice
University of Kuopio
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ABSTRACT

The effect of salt restriction on the blood pressure and on the nutrient intakes, as well as adherence to the salt restriction were studied in a salt restriction study (I, II, III). In a separate study, the effect of intensified diet counselling on the diet and cardiovascular risk factors was investigated in a primary health care setting (IV). The diet was evaluated by 4-day food records and by 24-h urinary sodium and potassium excretions.

Altogether 39 subjects aged 28-65 y with mildly elevated blood pressure participated in a placebo controlled study examining the effects of salt restriction alone or in combination with cilazapril (I, II and III). The subjects were advised by a nutritionist to reduce salt intake to less than 5 g/day and to keep their physical activity and body weight unchanged. In the primary health care study lasting for 2 years (IV), altogether 715 hypertensive subjects aged 25-74 y were randomised into an intervention and an usual care group. The primary health care nurses educated by a study physician and a nutritionist gave intensified diet counselling to the intervention group. The main dietary goals were reduction of total fat, saturated fatty acids and salt intake, as well as weight reduction and moderation of alcohol intake if any. The usual care group continued their usual health care.

In the salt restriction study, the daily sodium chloride intake decreased significantly by an average of 4.5 g during 20 weeks. There were minor changes in the intakes of other nutrients. During the salt restriction period alone (8 wk) both systolic/diastolic blood pressure (SBP/DBP) decreased significantly by 7.1±12.7/4.2±7.5 mmHg. In the primary health care study, the proportion of fat from total energy intake and sodium intake reduced more in the intervention group than in the usual care group, and the fatty acid composition of the diet in the intervention group improved more as compared to that in the control group. Body weight decreased significantly more in the intervention group than in the usual care group (-1.8±3.7 kg vs -0.4±3.4 kg). In subjects without antihypertensive medication, the changes in SBP/DBP were significantly greater in the intervention group compared to the usual care group (-4.1±12.2/-2.9±7.3 mmHg vs +0.8±11.5/-0.1±7.5 mmHg).

In conclusion, free living hypertensive subjects can reduce salt intake in a clinical trial when they received intensive counselling. Salt restriction does not cause any nutritional imbalance, and seems to be effective in reducing mildly elevated blood pressure. The intensified diet counselling in primary health care can result in dietary changes interpreted as being of benefit in the long-term treatment of hypertension and prevention of atherosclerotic vascular diseases.
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Kuopio, January 2002

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ABBREVIATIONS

AHA  American Heart Association
ABP  Ambulatory blood pressure
BMI  Body mass index
BP   Blood pressure
CI   Confidence interval
CHD  Coronary heart disease
CVD  Cardiovascular disease
DBP  Diastolic blood pressure
E%  Percent of energy
FR   Food record
fS-Crea  Fasting serum creatinine
fS-K   Fasting serum potassium
fS-Na  Fasting serum sodium
HDL-C High density lipoprotein cholesterol
LDL-C Low density lipoprotein cholesterol
MUFA Monounsaturated fatty acid(s)
MRITT Multiple Risk Factor Intervention Trial
PUFA Polyunsaturated fatty acid(s)
RAA  Renin-angiotensin-aldosterone
SBP  Systolic blood pressure
SD   Standard deviation
SEM  Standard error of mean
SFA  Saturated fatty acid(s)
SNS  Sympathetic nervous system
U-Crea Urinary creatinine excretion
U-K   Urinary potassium excretion
U-Na Urinary sodium excretion
TC   Total cholesterol
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1. INTRODUCTION

Hypertension is usually a non-symptomatic condition, but it is a major risk factor for cardiovascular diseases (stroke, coronary heart disease (CHD), left ventricular hypertrophy, congestive heart failure) and renal diseases. In addition, it can cause retinal damage. Due to the importance of elevated blood pressure (BP) as a risk factor for cardiovascular diseases (CVDs), the primary goals of hypertension treatment are to achieve the maximum reduction in the total risk of cardiovascular morbidity and mortality (World Health Organization-International Society of Hypertension, WHO-ISH 1999) or to reduce the morbidity and mortality (The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, JNC VI 1997).

Hypertension can be prevented and treated by life-style changes (non-pharmacological treatment) and/or antihypertensive medication. The life-style modifications recommended to prevent and treat hypertension are reduced sodium intake, weight loss, moderation of alcohol intake, increased potassium intake, increased physical activity, and, most recently, an overall healthy diet that emphasizes vegetables, fruits, and low-fat dairy products (JNC VI 1997, Ramsay et al. 1999, WHO-ISH 1999).

The essential role of lifestyle modifications in hypertension has been well described in recent dietary guidelines for the general population prepared by the American Heart Association (AHA, Krauss et al. 2000). AHA states: “In nonhypertensive individuals, these lifestyle modifications have the potential to prevent hypertension by reducing BP and retarding the age-related rise in BP. Indeed, even an apparently small reduction in BP, if applied to the whole US population, could have an enormous beneficial impact on preventing cardiovascular events, including both coronary heart disease and stroke. In hypertensive individuals, these nonpharmacological therapies can serve as initial therapy in early hypertension before the addition of medication and as an adjunct to medication in persons already receiving drug therapy. In hypertensives with controlled BP, nonpharmacological therapies can facilitate medication step-down or even withdrawal in certain individuals.” In addition, the lifestyle factors also prevent and treat other diseases e.g. obesity, type 2 diabetes and osteoporosis.

In addition to weight reduction, salt reduction has been an essential part of non-pharmacological treatment of hypertension, although in the late 1990's the relationship between salt and BP has been questioned (Taubes 1998). The evidence of the efficacy and safety of sodium reduction especially for the normotensive population has been claimed to be inadequate, thus the need for salt recommendation in population level has been challenged (Swales 1999). However, the epidemiological and experimental data available are sufficiently convincing to demonstrate the beneficial effects of salt reduction on BP.

On the other hand, salt restriction has been proposed to cause harmful physiological and nutritional changes (McCarron et al. 1997, Morris 1997). Salt reduction could lead to a reduced consumption of foods that are primary sodium sources i.e. meat products, grains
and dairy products, and this could concurrently reduce the dietary intake of other nutrients even below their recommended intake (Morris et al. 1997). No particular study has been done to investigate the effects of salt restriction on the intake of other nutrients, and the analyses of dietary effects have been secondary analyses of salt restriction trials (Gillum et al. 1983, Langford et al. 1985, Ellison et al. 1989, Shah et al. 1990, Howe et al. 1991, Wylie-Rosett et al. 1993).

Hypertension is one of the most common health problems managed in primary health care. The major challenge in the diet of hypertensive subjects is the adherence to the salt restriction and other lifestyle changes. In the trials on elevated BP carried out in research centers diet changes including salt reduction have been feasible, but the feasibility of diet treatment in general clinical practice has been questioned (Margetts et al. 1999). The adherence to the recommended dietary changes seems to be somewhat weak, e.g. in Finland the diet of hypertensive subjects is similar to the diet of normotensive subjects (Silaste et al. 2000).

This doctoral thesis investigates the feasibility and effects of salt restriction on BP and other nutrient intakes in a clinical trial. In a second long-term study, the effects of intensified diet counselling on the diet, body weight and BP of hypertensive subjects were studied in a primary health care setting.
2. REVIEW OF LITERATURE

2.1. Definition of hypertension

There is a continuous relationship between the level of BP and the risk of cardiovascular events, so the definition of hypertension according to a particular BP level is arbitrary. The World Health Organization and International Society of Hypertension (WHO-ISH 1999) has defined hypertension to be systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg or greater, when measured at rest, and relaxed conditions in subjects without antihypertensive medication. The BP is classified as optimal, normal, grade 1, 2, 3 hypertension and isolated systolic hypertension (Table 1.)

Table 1. Definitions and classifications of blood pressure levels according to the WHO-ISH (1999) recommendations.

<table>
<thead>
<tr>
<th>Category</th>
<th>Systolic blood pressure, mmHg</th>
<th>Diastolic blood pressure, mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal</td>
<td>&lt;120</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Normal</td>
<td>&lt;130</td>
<td>&lt;85</td>
</tr>
<tr>
<td>High-normal</td>
<td>130-139</td>
<td>85-89</td>
</tr>
<tr>
<td>Mild hypertension, grade 1</td>
<td>140-159</td>
<td>90-99</td>
</tr>
<tr>
<td>Subgroup: borderline</td>
<td>140-149</td>
<td>90-94</td>
</tr>
<tr>
<td>Moderate hypertension, grade 2</td>
<td>160-179</td>
<td>100-109</td>
</tr>
<tr>
<td>Severe hypertension, grade 3</td>
<td>≥180</td>
<td>≥110</td>
</tr>
<tr>
<td>Isolated systolic hypertension</td>
<td>≥140</td>
<td>&lt;90</td>
</tr>
<tr>
<td>Subgroup: borderline</td>
<td>140-149</td>
<td>&lt;90</td>
</tr>
</tbody>
</table>

The target BP levels given in recommendations for treatment of hypertension differ somewhat. In the WHO-ISH (1999) recommendation, the SBP/DBP of <120/80 mmHg or <130/85 mmHg seems to be desirable to achieve in young, middle-aged or diabetic subjects. The target BP in elderly people is below 140/90 mmHg. In United States, the goal of prevention and management of hypertension is SBP below 140 mmHg and DBP below 90 mmHg according to the JNC VI (1997). In the British Hypertension Society Guidelines for Hypertension Management (Ramsay et al. 1999), the optimal BP treatment targets are SBP <140 mmHg and DBP <85 mmHg in non-diabetic hypertensive people. In diabetic individuals, the target BP is even lower, since hypertension is common in diabetics and it plays a major role in the development of diabetic macrovascular and microvascular
complications. The target SBP/DBP is <140/80 mmHg in type 2 diabetes and in type 1 diabetes if proteinuria is present.

2.2. Prevalence and trends of hypertension

Hypertension is a common problem in western societies. According to the NHANES III (Third National Health and Nutrition Examination Survey) 20% of the adult population in United States is hypertensive if the criteria is BP more than 140/90 mmHg or taking antihypertensive drug treatment (Burt et al. 1995). In Great Britain, 19.5% of adults had SBP/DBP above 160/95 mmHg or were receiving treatment for hypertension (Colhoun 1998), but if the hypertension criteria were 140/90 mmHg and/or antihypertensive treatment, 38% of British adults were hypertensive.

In Finland, the SBP levels of adults has declined since 1972 to 1997, but no further decline in DBP was found in 1997 (Vartiainen et al. 2000). In 1997, SBP was high (>160 mmHg) in 12% of men and 9% of women. Respectively high DBP (>95 mmHg) was observed in 20% of men and 9% of women. Despite the decline in BP levels in Finnish adults that has taken place in last 20 years, hypertension is a still remarkable public health problem with economical burden in Finland. At the end of 2000, a total of 464 132 citizens were using antihypertensive drugs, which were special-rate reimbursed by the Social Insurance Institution (The Social Insurance Institution 2000). The total costs of these special-rate reimbursements amounted to 516 million FIM. The total costs of elevated BP are even larger if the costs of additional diseases of hypertension are taken into account.

The control of hypertension has improved in many developed countries during the last few decades. The data from Health Examination Surveys in the United States showed that since the late 1970's to the late 1980's the prevalence of hypertensive patients who had their BP controlled (<140/90 mmHg) increased from 10% to 27% (Burt et al. 1995). In the Framingham Study, the rate of use of antihypertensive drugs increased from 2.3% to 24.6% in men and from 5.7% to 27.7% in women from 1958 to 1989 (Mosterd et al. 1999). The prevalence of hypertension increases with age, and it has been estimated that less than 20% of adults over 70 years have an optimal BP: <120/80 mmHg (Appel 1999). The ageing population structure of most of the developed countries and the increasing prevalence of CVDs in the developing countries and former socialist republics in Eastern Europe mean that hypertension is a truly global problem (WHO-ISH 1999).

2.3. Regulation of blood pressure

BP is determined by the magnitude of the cardiac output and by the vascular resistance of arteries. Kidneys, adrenal glands, brain, arteries and heart interact in a complex way to balance blood volume, cardiac output, and the contraction of the peripheral vessels, to maintain optimum BP and blood supply to each organ (A report of SBU, 1995).
Figure 1. Schematic diagram of the nervous and hormonal mechanisms that influence BP (A report of SBU 1995). Reprinted with permission from Blackwell Science Ltd.
The kidneys play a central role in BP regulation (Figure 1.). The secretion of renin from juxtaglomerular cells of kidneys is increased if salt deficiency exists, at low BP, and during sympathetic nerve activation (noradrenaline). Renin leads to the synthesis of angiotensin II, a powerful vasoconstrictor. Renin can also stimulate the secretion of aldosterone from adrenal glands, which in turn increase the reabsorption of water and sodium. This increases the blood volume and the amount of sodium in the vascular smooth muscle cells, increasing their excitability and vascular resistance.

Sensory cells (baroreceptors) in the heart, in the aorta and in the arteries which supply the head send impulses to the brain, which reacts by modifying the activity of sympathetic nervous system (SNS) to modulate the heart function and contraction of heart vessels. The increased activity of sympathetic nerves in the heart leads to a higher cardiac output. The arterial smooth muscle cells can also change their structure and function. The smooth muscle cells of the blood vessels are stimulated to contract by the noradrenaline released from sympathetic nerve endings. The increased stress caused from high BP may stimulate vascular smooth muscle cells to proliferate, leading to the thickening of the vessel walls, which reduces their inner diameter, further increasing vascular resistance. Locally vessel walls produce factors that cause vasodilatation (nitric oxide) or vasoconstriction (endothelin)(Lifton et al. 2001).

BP is regulated by a range of complicated nervous and hormonal systems, but the detailed knowledge of how BP is regulated is still unknown (Lifton et al. 2001). Several physiological mechanisms regulate BP, and if one particular BP regulating system is blocked, then compensatory systems are activated. Sustained hypertension requires the adjustment of several systems to maintain BP at a higher level (Swales 1995).

2.4 Etiology of hypertension

The etiology of hypertension is known about only in 5 % of hypertensive subjects. This form of hypertension, termed secondary hypertension, can be due to drugs, renal disease, renovascular disease, pheochromocytoma, Conn’s syndrome, coarctation or Cushing’s syndrome. In most of hypertensive subjects (95 %), the etiology of hypertension is unknown, and it is called essential hypertension or primary hypertension.

Numerous uncontrollable and controllable factors are responsible for the development of primary hypertension. Genes, age, sex, race and possibly early growth pattern are uncontrollable factors which may determine the actual level of BP as well as an individual’s ability to adapt to lifestyle factors that affect the BP.

BP has a strong genetic component. It is estimated that about 30-60 % of BP variability is genetically determined (Swales 1995). Potential candidate genes are those that affect the RAA system (renin-angiotensin-aldosterone system), the kallikrein-kinin system, and the SNS. Hypertension is a polygenic and multifactorial disorder in which several genes interact with each other and with the environment (Lander & Schork 1994). Genetic
variation can result in differing biological responses to specific nutrients and hence in differing optimum requirements for these nutrients among individuals e.g. sodium vs BP. The genes and genetic combinations that determine the hormonal and neural mechanisms that regulate BP may be revealed in the near future.

BP, especially SBP, has a tendency to rise with age in westernised societies. This has been noticed also in inter-population comparison of 32 nations (Intersalt Study Research Group 1988). The age-related rise in BP is steeper for women, so that in old age the BP level in both sexes is equal whereas in younger ages it is slightly lower in women. Blacks tend to have a higher BP than whites, and the difference increases with age (Swales 1995).

The prevalence of hypertension tends to be greater in individuals with birth weight less than 2500 grams (Ashwell 1997). Low birth weight originating from fetal undernutrition in mid to late gestation leads to changes in a variety of metabolic, physiologic and structural processes (Barker 1995). Possible mechanisms linking BP with fetal undernutrition have been proposed to be persistent changes in vascular structure, including loss of elasticity in vessel walls and effects of glucocorticoid hormones (Barker 1995).

The controllable factors (lifestyle factors) known to affect the BP are diet, stress, physical activity, tobacco smoking and alcohol consumption. Only the dietary factors affecting BP are described in more detail in this thesis.

2.5 Dietary factors and blood pressure

2.5.1 Body weight

Obesity is the most important risk factor for elevated BP: approximately 20-30% of BP variability has been attributed to obesity (Kotchen and Kotchen 1999). Consequently, weight reduction is an essential part of the non-pharmacological treatment of hypertension.

Data from cross-sectional studies indicate a direct linear association between body weight and BP. Especially, centrally located body fat (upper-body obesity) is related to BP (Mikhail et al. 1999). Data derived from NHANES III (National Health and Nutrition Examination Survey), which included approximately 30,000 people showed that SBP/DBP was higher among those with higher BMI (Ernst et al. 1997). In the Intersalt Study 10 kg lower weight was associated with 3.0/2.2 mmHg lower BP (Dyer and Elliott 1989). The relationship between obesity and hypertension is modified by demographic, genetic, hormonal, renal and hemodynamic factors. Age, ethnicity and sex also modulate the strength of the association between obesity and hypertension (Mikhail et al. 1999).

Prospective studies have also shown that obesity is the most important controllable risk factor for the development of hypertension (Garrison et al. 1987, Haffner et al. 1992, Jouilahti 1995). In the Framingham Offspring Study, the occurrence of hypertension and its precursors were followed for 8 yrs in 2027 men and 2267 women aged 20-49 yrs (Garrison et al. 1987). Adiposity and relative weight were related to hypertension
occurrence controlled for age. Furthermore, the changes in body fat over 8 yrs were related
to changes in SBP and DBP. In the San Antonio Heart Study, the incidence of hypertension
was greater during the 8-yr follow-up in those subjects with higher BMI (Haffner et al.
1992). Jousilahti et al. (1995) found also in 12-yr follow-up of 15 439 middle-aged people
in Eastern Finland that BMI predicted the incidence of hypertension independently from
the baseline BP. The 6-y large MRFIT (Multiple Risk Factor Intervention Trial) in the US
revealed a direct independent association of BMI to SBP and DBP (Stamler et al. 1997).

The effect of weight reduction on BP has been studied in some large nonpharmacological hypertension treatment trials (Table 2.). In a 5-yr study by Stamler et al. (1989), 201 overweight young adults with high-normal BP were randomised to a
nutrition-hygienic intervention group or to a control group. The goals of intervention group
were weight loss, sodium reduction ≤ 1800 mg/d, alcohol intake in moderation (< 2
drinks/d) and exercise. The net decrease in body weight was -2.7 kg and in SBP/DBP
-2.0/-1.9 mmHg. The incidence of hypertension was lower in intervention group than in
control group (8.8.% vs 19.2%). In the Hypertension Prevention Trial (HPT) the weight
loss in adults with high-normal BP induced a significant decrease in SBP/DBP as
compared to control group: net change -5.1/-2.8 mmHg at 6 mo and -2.4/-1.8 mmHg at 3
y (Hypertension Prevention Trial Research Group 1990, Table 2.).

In a multicenter randomised clinical trial: the Trials of Hypertension Prevention, Phase
II (TOHP II) the effect of long-term weight loss on BP was studied with non-medicated
adults with SBP < 140 mmHg and DBP between 83-89 mmHg, and who were 110-165 %
of their ideal body weight (The Trials of Hypertension Prevention Collaborative Research
Group 1997, Stevens et al. 2001). The 3-year weight loss program consisted both of group
sessions and individual counselling (Table 2.). Mean weight changes were -4.4 kg at 6 mo,
-2.0 kg at 18 mo, and -0.2 kg at 36 mo in weight loss group (n=595). In the control group
(n=596), the weight changes at the same time points were 0.1, 0.7 and 1.8 kg. SBP and
DBP were significantly lower in the weight loss group than in the control group at all time
points, and the risk ratios for hypertension in the weight loss group compared to control
group were significant (0.58 at 6 mo, 0.78 at 18 mo and 0.81 at 36 mo).

In the Trial of Nonpharmacologic intervention in the Elderly (TONE) hypertensive,
overweight subjects mean age as 66.5±4.6 yrs were randomized to weight loss, reduced
sodium or both and to usual care group after drug withdrawal (Whelton et al. 1998). A
higher proportion from the weight loss group remained free of high BP compared to the
usual care group during follow-up (range 15-36 months). Approximately 30 % decrease
in the need for antihypertensive medication was achieved by a 3.5 kg reduction of body
weight.

The evidence from the follow-up study of one large hypertension treatment trial
supports the link between weight gain and the development of hypertension. He et al.
(2000) studied the long-term effects of weight reduction and dietary sodium reduction
on the incidence of hypertension in 181 men and women, who participated in the Trials of
Hypertension Prevention, Phase I (TOHP I) in the late 1980's (The Trials of Hypertension Prevention Collaborative Research Group 1992, Table 2.). After 7 years follow-up, the odds of hypertension were reduced by 77 % in the weight loss group and by 35 % in sodium reduction group compared with the control group. The mean body weight of the weight loss group had even slightly increased and the 24-h sodium excretion of sodium reduction group had remained at the same level during the follow-up. The changes in body weight and 24-h sodium excretion during the 7 years follow-up between the active treatment groups and control group did not differ.

The exact mechanisms whereby BP becomes elevated with an increase in body weight is unknown, but the most likely explanation is that the SNS is overactive in obese subjects (Swales 1995). Potential mechanisms how weight loss can affect BP are a) hemodynamic effects via reduction in blood volume and cardiac output; b) reduction in plasma renin activity which may be associated with a reduction in SNS activity; and c) correction of hyperinsulinaemia with reduction in renal sodium retention (Hermansen 2000).
### Table 2. Description of large non-pharmacological hypertension treatment trials.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Subjects</th>
<th>Treatment groups</th>
<th>Duration</th>
<th>Dietary method</th>
<th>Na/K, mmol⁻¹</th>
<th>Body weight, kg⁻¹</th>
<th>SBP/DBP, mmHg⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stamler et al. 1989</td>
<td>n=201, 30-44 y, DBP 80-99 mmHg, 10-49 % overweight</td>
<td>weight↓ + Na↓ + alcohol↓ + exercise↓; control group</td>
<td>5-y</td>
<td>overnight urine</td>
<td>12.0/nr</td>
<td>2.7</td>
<td>2.0/1.9</td>
</tr>
<tr>
<td>HPT 1990</td>
<td>n=841, 25-49 y, DBP 78-89 mmHg</td>
<td>weight↓; Na↓; weight↓+Na↓; Na↓+K↓, control group</td>
<td>3-y</td>
<td>overnight urine</td>
<td>Na↓:21.0/NS at 6 mo; NS/6.4 at 3 y</td>
<td>weight↓: 5.7 at 6 mo, 3.5 at 3 y</td>
<td>weight↓: 5.1/2.8 at 6 mo, 2.4/1.8 at 3 y</td>
</tr>
<tr>
<td>TOHP I 1992</td>
<td>n=2182, 30-54 y, DBP 80-89 mmHg</td>
<td>weight↓; Na↓; stress management; usual care</td>
<td>18 mo</td>
<td>24-h urine</td>
<td>Na↓:58.5/nr at 6 mo; 43.9/nr at 18 mo</td>
<td>weight↓: 5.7 at 6 mo, 3.9 at 18 mo</td>
<td>Na↓:1.7/0.9 at 18 mo; weight↓: 2.9/2.3 at 18 mo</td>
</tr>
<tr>
<td>TOHP II 1997</td>
<td>n=2382, 30-54 y, DBP 83-89 mmHg, SBP &lt;140 mmHg, 110-165 % of desirable body weight</td>
<td>weight↓; Na↓; weight↓+Na↓; usual care</td>
<td>36 mo</td>
<td>24-h urine</td>
<td>Na↓:50.4/nr at 6 mo; 40.4/nr at 36 mo; weight↓+Na↓: 36.7/nr at 6 mo, 23.6/nr at 36 mo</td>
<td>weight↓: 4.5 at 6 mo, 1.9 at 36 mo; weight↓+Na↓: 4.3 at 6 mo, 2.1 at 36 mo</td>
<td>weight↓: 3.7/2.7 at 6 mo, 1.3/0.9 at 36 mo; Na↓: 2.9/1.6 at 6 mo, 1.2/NS at 36 mo; weight↓+Na↓: 4.0/2.8 at 6 mo, 1.1/NS at 36 mo</td>
</tr>
<tr>
<td>Study</td>
<td>Sample Size</td>
<td>Age</td>
<td>Blood Pressure</td>
<td>Treatment</td>
<td>Duration</td>
<td>Outcome</td>
<td>Notes</td>
</tr>
<tr>
<td>-------</td>
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</tr>
<tr>
<td>Whelton et al. 1998 (TONE)</td>
<td>n=875, 60-80 y, SBP&lt;145 mmHg, DBP&lt;85 mmHg with one drug for hypertension</td>
<td>obese: weight i; Na; weight i+Na; usual care, nonobese: Na; usual care</td>
<td>15-36 mo</td>
<td>24-urine</td>
<td>nr/nr</td>
<td>nr</td>
<td>nr/nr</td>
</tr>
</tbody>
</table>

Na = sodium, K = potassium, SBP = systolic blood pressure, DBP = diastolic blood pressure, nr = not reported, HPT = Hypertension Prevention Trial Research Group, NS = nonsignificant, TOHP = The Trials of Hypertension Prevention Collaborative Research Group, TONE = Trial of Nonpharmacological Interventions in the Elderly. ¹ Net reduction = reduction in intervention group minus reduction in control group.
2.5.2 Dietary sodium

Sodium is a main cation in the extracellular fluid, and it has an important role in the regulation of the volume of the extracellular fluid, regulation of osmolarity, acid-base balance and the membrane potential of cells. In addition, it is involved in active transport across cell membranes (National Research Council 1989). Sodium homeostasis is maintained by the kidneys, and the ingested sodium is excreted mainly in urine. Minor amounts of sodium are excreted via faeces and sweat, though during the active sweating the loss of sodium via sweat can be multiplied. Minimum average requirement for adults without active sweating is 115 mg per day or approximately 300 mg sodium chloride per day (National Research Council 1989). A safe minimum intake of sodium according to the Recommended Dietary Allowances (National Research Council 1989) for adults is 500 mg/day.

Dietary sodium is derived mainly from sodium chloride added to foods and beverages, although sodium is also present naturally in foods. Salt (sodium chloride) is composed of 40% sodium. It has been estimated that 10% of total sodium is naturally present in foods (Pietinen 1981, Sanchez-Castillo et al. 1987). In the beginning of the 1980's, Pietinen (1981) estimated that in Finland 57% of added salt was used by food industry and catering and 43% was added by the consumer. Sanchez-Castillo et al. (1987) calculated that in Great Britain from sodium derived from salt (sodium chloride) 15% comes from salt used during cooking and at the table, and 85% of salt is added to foods during processing and manufacturing.

2.5.2.1. Epidemiological evidence - sodium and BP

The evidence from epidemiological, experimental and intervention studies has revealed the role of sodium in the regulation of BP. A part of epidemiologic evidence comes from primitive people e.g. the Yanomomo Indians in Northern Brazil, the New Guinea Highlanders of Tukisenta and the Australian aborigines, who eat little or no sodium and have little hypertension (Denton 1997). There is some doubt how these results from primitive populations can be generalized to western populations, since the diet and lifestyle of these individuals are totally different from people in western societies. However, in the primitive men of the Qash’qai tribe of southern Iran the dietary sodium intake averaged 184 mmol/24 h were related to BP (Page et al. 1981). The population sample was considered to be at a low level of acculturation.

Evidence from migration studies demonstrates that when rural populations move to urban communities and the low salt diet shifts to higher salt intake, their BP rises compared to the peers they left behind (Siani et al. 2000). When rural Kenyan men moved to urban lifestyle conditions in Nairobi, their sodium intake increased from 60 to 100 mmol/d and their BP also increased (Poulter et al. 1990). In China, the rise in BP of Yi
migrants with age was significantly higher than in Yi farmers living in a remote mountain area (He et al. 1991).

In large population studies, significant correlations between salt and BP have been found (Law et al. 1991a, Beard et al. 1997). A meta-analysis of observational data among populations by Law et al. (1991a) estimated that SBP would rise by 5-10 mmHg for every 100 mmol increase in sodium excretion; the differences in DBP were about half as great. In British adults (16-64 yrs) the 24-h urinary sodium excretion adjusted for age, obesity, alcohol intake and season of interview was significantly associated with SBP and DBP (Beard et al. 1997). The strongest evidence came from the Intersalt Study, which measured BP and 24-h urinary sodium and potassium in 10079 people aged 20-59 y in 52 places around the world (Intersalt Cooperative Research Group 1988, Elliott et al. 1996). According to the Intersalt Study, populations with low sodium excretion have both lower SBP and DBP, and this association was more clear in older age groups. Intersalt within population analyses indicated a 3-6/0-3 mmHg increase in SBP/DBP for every 100 mmol increase in 24-h sodium excretion. The association was larger for individuals in the age range 40-59 years. In cross population analyses, a difference in sodium intake of 100 mmol/day was associated with a median SBP/DBP higher on average by 5-7/2-4 mmHg, and over a 30-year period this would result in differences of approximately 10-11 mmHg in SBP and 6 mmHg in DBP (Elliott et al. 1996).

2.5.2.2. Epidemiological evidence - sodium and cardiovascular disease

In addition to the direct effect of salt on blood pressure there is evidence that a high salt intake also predicts left ventricular hypertrophy and stroke (Perry 2000), but the association is still somewhat unclear. It is also not clear, if the salt intake increases the risk of CVDs indirectly via BP or directly via alternative mechanisms (Perry 2000). Other physiological conditions such as obesity may modify the relationship between salt and hypertensive target organ damages. Obese subjects with a greater salt intake during an average of 19 years follow-up seemed to have an increased risk for CVD incidence and mortality (He et al. 1999). In that prospective cohort study, a total of 2688 overweight and 6797 nonoverweight of participants of the first National Health and Nutrition Examination Survey (1971 to 1975) were followed up in 1982-1984, 1986, 1987, and 1992. Their sodium intakes were measured by the 24-h dietary recall method.

In a few studies, the sodium intake has been found to be inversely associated to CVD morbidity and mortality. Alderman et al. (1995) showed in 3.8 years of follow-up that a low urinary sodium was associated with a greater risk of myocardial infarction among treated hypertensive men. Alderman’s study (1995) has also been criticized (Chobanian and Hill 2000). The average sodium intake in the lowest quartile of sodium excretion was unusually low. This could be due to the fact that patients had been counselled to limit their
sodium intake for 4 to 5 days before baseline 24-h urine collection, and those with the highest CVD risk may have reduced their sodium intake more than average.

In the 20-year follow-up of the first National Health and Nutrition Examination Survey (NHANES I), the reported sodium intake at baseline was inversely associated with all cause and cardiovascular mortality (Alderman et al. 1998), but for the sodium/calorie ratio, there was a weak direct relation to all cause mortality and significant relation to CVD mortality. However, a single 24-h recall used to collect dietary data in this study was unreliable for the measurement of salt intake.

The latest evidence about the direct effect of salt intake on the CVDs comes from a prospective study performed in Finland (Tuomilehto et al. 2001a). They followed the salt intake and cardiovascular events of 1173 Finnish men and 1263 women aged 25-64 years who participated in the baseline surveys in 1982 and 1987. The salt intake was measured by 24-h urinary sodium excretion. In that study, a high sodium intake predicted mortality and risk of CHD independent of other cardiovascular risk factors, including BP.

Some studies do not support any kind of relationship between sodium and CVDs. In MRFIT with a total of 11697 men aged 42-64 years followed for 6-years, there was no association between sodium intake and CVD mortality risk (Cohen et al. 1999). In that study nutrient intake data for trial years 1-6 were based on four or five 24-h recalls per subject and the data from the intervention and usual care groups were pooled for analyses. Ascherio et al. (1998) found no association between intakes of sodium and the incidence of stroke in a large 8-year follow-up study carried out in 43 738 US men aged 40-75 years. In the Scottish Heart Health Study, baseline 24-h urinary sodium excretion and incidence of myocardial infarction after 7.6 years follow-up were associated in women, but not in men (Tunstall-Pedoe et al. 1997).

### 2.5.2.3 Experimental evidence

Experimental evidence linking sodium with BP comes from studies carried out in animals and in humans. The effect of salt intake on BP has been documented e.g. in the Dahl salt-sensitive rat (Tobian 1991). Denton et al. (1995) studied the effect of low-sodium, high-potassium diet of vegetables and fruit in chimpanzees, whose genetic identity with humans is 98.4 %. Sodium was added in increasing amounts from 5 to 10 to 15 grams per day over 20 months to half of the 22 chimpanzees, while the other half had no change in sodium intake. There were no other changes in diet or social conditions. In those chimpanzees who ingested at least half of the added salt, BP rose, at week 84 SBP/DBP was 33/10 mmHg higher than at baseline. No changes in BP occurred in the control chimpanzees.

A large number of clinical studies have evaluated the BP lowering effect of salt restriction in both normotensive and hypertensive subjects and several meta-analyses have been published (Table 3.). According to these meta-analyses in trials with hypertensive
subjects if a sodium reduction of an average 80-90 mmol (4.7-5.3 g as sodium chloride) is achieved this can lead to a reduction of 4-5 mmHg in SBP and 2-3 mmHg in DBP. In trials including normotensive subjects the reductions in SBP and DBP are 1-2 mmHg and 0.5-1 mmHg, respectively,
Table 3. Meta-analyses of salt restriction trials.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Studies</th>
<th>Na reduction, mmol/d</th>
<th>Duration of Na restriction</th>
<th>Change in SBP/DBP, mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grobbee and Hofman 1986</td>
<td>13 trials</td>
<td>21-113</td>
<td>from 2 wk to 2 y</td>
<td>from -10.0 to -5.0/-7.0 to 3.2</td>
</tr>
<tr>
<td>Law et al. 1991b</td>
<td>69 crossover trials, 10 RCTs</td>
<td>nr</td>
<td>from 1 wk to 2 y</td>
<td>At age 50-59 y 50 mmol lowers SBP by 5 mmHg and DBP half as much</td>
</tr>
<tr>
<td>Midgley et al. 1996</td>
<td>28 trials (hyp)</td>
<td>95 (hyp)</td>
<td>29 days (median, hyp)</td>
<td>-5.9/-3.8 (hyp)</td>
</tr>
<tr>
<td></td>
<td>28 trials (norm)</td>
<td>125 (norm)</td>
<td>14 days (median, norm)</td>
<td>-1.6/NS (norm)</td>
</tr>
<tr>
<td>Cutler et al. 1991</td>
<td>23 trials (18 hyp, 6 norm)</td>
<td>56-171 (hyp)</td>
<td>1 mo to 2 y (hyp)</td>
<td>-4.9/-2.6 (hyp)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60-170 (norm)</td>
<td>2 wk to 3 y (norm)</td>
<td>-1.7/-1.0 (norm)</td>
</tr>
<tr>
<td>Cutler et al. 1997</td>
<td>32 trials (22 hyp, 14, norm)</td>
<td>77 (hyp)</td>
<td>1 mo to 2 y (hyp)</td>
<td>-4.8/-2.5 (hyp)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>76 (norm)</td>
<td>0.5 mo to 2 y (norm)</td>
<td>-1.9/-1.1 (norm)</td>
</tr>
<tr>
<td>Graudal et al. 1998</td>
<td>58 trials (hyp)</td>
<td>118 (hyp)</td>
<td>28 days (hyp)</td>
<td>-3.9/-1.9 (hyp)</td>
</tr>
<tr>
<td></td>
<td>56 trials (norm)</td>
<td>160 (norm)</td>
<td>8 days (norm)</td>
<td>-1.2/NS (norm)</td>
</tr>
<tr>
<td>Alam and Johnson 1999</td>
<td>11 RCTs with subjects ≥60 yrs</td>
<td>nr</td>
<td>9 wk to 2 y</td>
<td>-5.6/-3.5</td>
</tr>
</tbody>
</table>

Na=sodium, RCT=randomised controlled trial, hyp=hypertensive subjects, norm= normotensive subjects, nr= not reported, NS=nonsignificant
The ability of salt restriction to reduce BP has been studied in large, randomised clinical trials in subjects with high-normal BP (Table 2.). In a trial carried out by Stamler and coworkers (1989) the sodium intake was reduced significantly by an average 12 mmol, but the effect of sodium reduction is difficult to dissect out because other changes also happened in lifestyles. In the Hypertension Prevention Trial (Hypertension Prevention Trial Research Group 1990), the sodium intake was reduced significantly only at 6 mo, and it did not reduce BP either alone or when combined with other treatment.

In the Trials of Hypertension Prevention, Phase I (TOHP I) the sodium excretion in urine was reduced by -58.5 mmol at 6 mo and at -43.0 mmol at 18 mo in the sodium reduction group as compared to control group. The sodium reduction was accompanied with a significantly greater fall in SBP/DBP at 18 mo (-1.7/-0.9 mmHg) as compared to the control group (The Trials of Hypertension Prevention Collaborative Research Group 1992).

In TOHP II, the sodium excretion was decreased by 50 mmol more in the sodium reduction group and by 37 mmol more in the combined group (sodium and weight reduction) as compared to the usual care group at 6 mo, at 36 mo the corresponding differences were 40 mmol and 24 mmol (The Trials of Hypertension Prevention Collaborative Research Group 1997). SBP/DBP decreased by 2.9/1.6 mmHg more in the sodium reduction group and by 4.0/2.8 mmHg more in the combined group at 6 mo. At 36 mo, the SBP decrease remained significantly greater in the sodium reduction than in the usual care group. Through 48 mo, the incidence of hypertension was significantly lower in the sodium reduction and in the combined group than in the usual care group (average relative risks, 0.82, 0.78).

The Trial of Nonpharmacologic Intervention in the Elderly (TONE) was conducted in four academic research centers, and it included 585 obese and 390 nonobese men and women aged 60-80 years with SBP/DBP < 145/85 mmHg with one drug for hypertension; 24% were African American (Whelton et al. 1998). The treatment was based on weight loss and sodium reduction. A moderate salt restriction, i.e. 40 mmol/d reduction in sodium excretion during 30 months follow-up, induced a decrease of 30% in the return of hypertension compared to usual hypertensive care (Whelton et al. 1998).

The long-term effects of salt restriction have been studied in Dutch children. A low-sodium or a normal sodium formula milk was given for 476 Dutch newborns in a randomised trial in 1980 (Hofman et al. 1983). Six months later SBP was 2.1 mmHg lower in low-sodium group compared to control group. After 15 years, SBP/DBP in 167 of the 476 children from the original cohort was 3.6/2.2 mmHg lower in adolescence among those who as infants had been in the low sodium group compared with the control group (Geleijnse et al. 1997).

Recently, the BP decreasing effect of reductions in salt intake was also demonstrated in conjunction with Dietary Approaches To Hypertension (DASH) diet, which emphasised fruits, vegetables, and low-fat dairy foods (Appel et al. 1997). As compared to the control
diet with a high sodium level (141 mmol/d), the DASH diet with the low sodium level (67 mmol/d) led to a 7.1 mmHg lower mean SBP in participants without hypertension, and 11.5 mm Hg lower SBP in participants with hypertension (Sacks et al. 2001).

2.5.2.4. Blood pressure regulating mechanisms of sodium

The mechanisms on how the sodium intake can affect BP are not known precisely. All theories that try to explain the mechanism how salt intake affect BP include considerations of change in the ability of kidneys to excrete sodium. The leading hypotheses are that a) renal NaCl excretory defects combined with large sodium intakes exceed excretory capacity, leading to blood volume expansion and increased cardiac output; b) excess dietary sodium intake may elevate BP through a hormonal mediator that is a natriuretic hormone; c) excess salt intake may elevate SNS activity, and d) dietary sodium loading may alter calcium and potassium metabolism and thus elevate BP (Muntzel and Drüeke 1992).

2.5.2.5. Salt sensitivity

Human responses to alterations in sodium are heterogenous (Siani et al. 2000). This phenomenon called salt sensitivity or salt resistance was determined by Luft and Weinberger (1997) as follows: “Salt sensitivity implies that some individuals respond to a high salt intake with an increase in BP and that others (salt resistant individuals) do not”. Approximately half of the hypertensive subjects and one-fourth of normotensive population have been assumed to be salt sensitive (Weinberger 1996).

The heterogeneity is due to the phenotypic expression of the interaction between multiple genetic and environmental factors that modulate the BP response to sodium intake (Siani et al. 2000). Genes modify the response of salt intake on BP. Certain polymorphisms of haptoglobin, angiotensin-converting enzyme, β2-adrenergic receptor and α-adducin have been positively related to salt sensitivity (Weinberger et al. 1987, Siani et al. 2000). In addition, salt sensitivity resulting from a chimeric mutation of the 11β-hydroxylase/aldosterone synthase gene (glucocorticoid remediable hypertension) was described by Lifton et al. (1992), and that resulting from a mutation on the β-subunit of the epithelial sodium channel (Liddle’s syndrome) by Shinkets et al. (1994).

There is no standard method to measure salt sensitivity. The salt sensitivity has been assessed by either short term dietary trial or an acute sodium and volume expansion maneuver, and the criteria for definition of salt sensitivity of BP have varied markedly. Morimoto et al. (1997) assessed salt sensitivity by measuring the difference between BP response to a high salt diet (12-15 g/day) and to a low-salt diet (1-3 g NaCl/day). If the mean difference in arterial BP (1/3 x pulse pressure + DBP) between the low-salt and high-salt diets was more than 10 %, the subject was classified as being salt sensitive.
Weinberger’s (1996) procedure to study salt sensitivity began with the intravenous administration of 2 L 0.9% saline over 4 hours in the morning. BP was measured at the completion of the infusion at noon. Next day, the sodium and volume depletion was induced by a 10 mmol sodium diet and by 120 mg furosemide. BP was measured on the following morning. The subjects were arbitrarily classified as salt sensitive if the decrease in mean arterial pressure was greater than or equal to 10 mmHg and as salt resistant if the decrease in BP was less than or equal to 5 mmHg when the two BP measurements were compared.

Salt sensitivity has been shown to be common in African Americans, hypertensive, diabetic, obese and elderly people (Falkner and Michel 1997, Weinberger 1996). Alcoholics have been also shown to be more susceptible to sodium (di Gennaro et al. 2000). Sodium sensitivity increases with age both in hypertensive and normotensive subjects (Weinberger and Fineberg et al. 1991, Overlack et al. 1993, Ishibashi et al. 1994). It has been suggested that salt sensitivity can be observed only in individuals aged 45 years or older (Overlack et al. 1995), though in younger adults the salt sensitivity has been found in obese subjects (Rocchini et al. 1989), though their salt sensitivity seems to diminish after weight loss (Rocchini et al. 1989, Tuck 1991, Rocchini 2000).

Those who are more salt sensitive have more metabolic abnormalities such as insulin resistance, proteinuria and left ventricular hypertrophy, all of which can increase their risk of cardiovascular and renal consequences of hypertension (Galletti et al. 1997, Kimura and Brenner 1997, Morimoto et al. 1997). Previous findings strongly support also the need to reduce salt intake to protect against damage to the various vital organs that accompanies sodium sensitivity (Kaplan 2000a).

The alteration in several physiological factors: renal function, the RAA system, atrial natriuretic factor, the SNS, adrenergic receptors, endothelin and nitric oxide, ion transport and insulin have all been associated with salt sensitivity (Weinberger 1996). The most obvious alteration has been the lower responsiveness of the RAA system, which is a major mechanism responsible of sodium retention and vasoconstriction. Several genetic and environmental factors may influence renal function and cause impairment in the natriuretic ability of the kidney (Cowley et al. 1997).

2.5.2.6 Possible adverse effects of salt restriction

Sodium reduction has been criticized because it has been suggested to cause harmful nutritional and physiological changes. Sodium restriction is established by reducing the intake of foods rich in sodium, and the consumption of key food groups such as meat, grain products and dairy products may decrease. This, on the other hand, could lead to the reductions in other nutrient intakes e.g. calcium, magnesium, iron and vitamin B6 intakes to levels even below their recommended values (Morris 1997).
No particular study has been done to investigate the effects of salt restriction on other nutrients, and the current knowledge is based on a secondary analyses of salt restriction trials (Gillum et al. 1983, Langford et al. 1985, Ellison et al. 1989, Shah et al. 1990, Howe et al. 1991, Wylie-Rosett et al. 1993). Changes in the intakes of other nutrients seems to be apparent, when maintaining energy intake and/or body weight constant has not been the goal (Newson and Morgan 1988, McCarron et al. 1997).

Possible physiological changes are increased plasma renin and SNS activity, insulin resistance and elevated fasting glucose, which in turn could increase the risk of CVD diseases (Alderman 2000). In a meta-analysis by Graudal et al. (1998), adverse effects of reduced sodium intake were increased levels of plasma renin, aldosterone, and serum cholesterol and low-density lipoprotein (LDL), but the sodium reduction did not affect adrenaline, triglyceride and high-density lipoprotein (HDL) levels. In the study of McCarron et al. (1997), a low urinary sodium excretion value was correlated with a decrease in plasma HDL-C and an increase in TC:HDL-C ratio. However, the duration of salt restriction (77 sodium mmol/d) was short, only 4 weeks.

2.5.2.7 Adherence to the salt restriction

Although many clinical studies have demonstrated moderate salt reductions, the adherence to the salt intake recommendation as a proportion of study population has been seldom reported. In addition, because of the dominance of salt in manufactured foods, the adherence to the salt restriction in clinical practice has been doubted.

In the study of Jeffery et al. (1984) 69 normotensive volunteers completed an eight-week study to test the feasibility and acceptability of low-sodium (< 70 mmol) diet alone or in combination with high potassium intake (>100 mmol). Urinary sodium decreased 29 mmol more in low-sodium and 39 mmol more in low-sodium+ high potassium group than in the control group.

A three-year community-based intervention program to reduce salt consumption was carried out in North Karelia in the beginning of 1980's (Pietinen et al. 1984). A random sample of about 600 subjects aged 14-64 yrs who participated in the intervention program were examined as well as the sample from a referee community. Sodium reduction succeeded only among normotensive women in both areas.

Lang et al. (1985) demonstrated the ability of free living healthy voluntary families to comply with a marked reduction in their sodium intake over a 3 month period. The women achieved a sodium excretion of 61.7 mmol/d and men of 80.8 mmol/d. The families received instructions for restricting their sodium intake by a registered dietitian in the family’s home.

In an outpatient clinic of Indiana University about 50% of 65 hypertensive patients achieved the goal of 80 mmol/d during the 6 weeks (Miller et al. 1986). The compliance
was monitored by twice-weekly 24-h urine collections and the feedback from sodium intake was given to patients.

In Eastern Finland, a study to test the feasibility and effects of intensified health education on salt restriction given by a nurse was carried out in 1983-1984 in 50 patients with mild to moderate hypertension. The sodium excretion of an intervention group decreased by 33% from the baseline value of 183 mmol/d during the 12 months, whereas there were no changes in control group (Nissinen et al. 1987).

In TOHP I (Table 2.), which was performed in clinical centers, the overall net decrease in sodium excretion at 18 mo was -43.9 mmol (40% reduction from baseline) in subjects 30 to 54 yrs subjects with DBP of 80-89 mmHg (Kumanyika et al. 1993). A total of 39% of subjects in intervention achieved the goal of 80 mmol sodium/d.

Negative results have been reported less often, but a few simple instructions given by general practitioners to the low-sodium group during the 12 months did not lead to differences in urinary sodium as compared to usual diet group in the study of Alli et al. (1992). They assessed the feasibility of long-term moderate dietary sodium restriction (≤80 mmol/d) in 56 mildly hypertensive patients (DBP 90-104 mmHg) in general practice.

2.5.3 Dietary potassium

Observational studies have documented that the intake of potassium is inversely associated with BP. In the Intersalt study, 24-h urinary potassium excretion was negatively correlated with BP in inter-population comparisons after adjustment for confounding factors: age, sex, body mass index, alcohol intake, and sodium excretion (Intersalt Cooperative Research Group 1988). The importance of potassium was seen also in urinary sodium to potassium ratio, which was positively associated with SBP and DBP, but after adjustment for body mass index and alcohol consumption, only the relation between DBP and sodium to potassium ratio remained significant. In a cross-sectional study carried out with a population of 584 men and 718 women aged 30-79 yrs in southern California age adjusted DBP correlated inversely with dietary potassium intake measured by 24-h recall (Khaw and Barrett-Connor 1988). The sodium to potassium ratio correlated even better with SBP and DBP. Potassium may modify the impact of sodium chloride on BP, and it has been claimed that the sodium to potassium ratio is a stronger correlate of BP than either sodium or potassium (Kotchen and McCarron 1998).

In some prospective studies, potassium intake has also been inversely related to the BP. In a Dutch cohort of 233 children aged 5-17 y drawn at random from participants in a population survey, dietary potassium and the dietary sodium to potassium ratio were related to the rise in BP (Geleijnse et al. 1990). In this seven year follow-up study, the levels of sodium and potassium were measured by overnight urine samples. When 58 218 US female nurses aged 34-59 yrs were followed for 4 yrs, no independent association of potassium measured by dietary questionnaire with hypertension incidence was found.
(Witteman et al. 1989). In the MRFIT, regression analyses confirmed the direct independent relationship of sodium to potassium ratio to SBP and DBP, and an inverse relationship of potassium to SBP and DBP (Stamler et al. 1997).

The effect of potassium on BP has also been investigated in clinical trials with the help of potassium supplements. Cappuccio and MacGregor (1991) reviewed 19 trials, involving a total of 586 participants. Oral potassium supplements lowered SBP/DBP by -5.9/-3.4 mmHg, and in a hypertensive subgroup the decrease was even larger: -8.2/-4.5 mmHg. Whelton et al. (1997) found in a meta-analysis of 33 randomised controlled trials that supplementation of diets with 60 to 120 mmol of potassium per day reduced SBP/DBP by 4.4/2.5 mmHg in hypertensives and by 1.8/1.0 mmHg in normotensives. The effects of potassium supplementation was enhanced in those subjects with a high intake of sodium.

The natriuretic effect of potassium may explain why potassium can reduce BP, especially if sodium intake is high. Other mechanisms may be that potassium can affect the vascular smooth muscle cells and adrenergic nerve terminals (Hermansen 2000).

2.5.4 Dietary calcium

Animal studies have confirmed the hypothesis that calcium intake reduces BP (Hatton and McCarron 1994), and some observational studies have pointed out an inverse association between calcium and BP, but the evidence is unconvincing. McCarron et al. (1984) found that calcium was inversely associated with BP, and the analysis of NHANES I indicated an inverse relationship between dietary calcium and SBP (Dwyer et al. 1996). A recent cross-sectional study of Norwegian adults aged 25-69 y showed a significant linear decrease in SBP and DBP with increasing dairy calcium intake in both sexes (Jorde and Bonaa 2001). The difference in BP between subjects with the highest and those with the lowest calcium intake was ≤ 1-3 mmHg.

A meta-analysis of observational studies on the association between dietary calcium and BP in different populations around the world was performed by Cappuccio et al. (1995). On the basis of 23 studies suitable for overview, an inverse association between dietary calcium and BP was found. However, because of the size of estimate, the observed heterogeneity of the studies, and possible confounding and publication biases, the authors did not recommend an increase of calcium intake at the population level.

In a prospective study of nutritional factors and hypertension among 58 218 white US female nurses, the relative risk of hypertension was 0.78 for women with a calcium intake of at least 800 mg compared to women with the calcium intake of < 400 mg (Witteman et al. 1989). In the regression analyses of MRFIT, no significant association was found between calcium intake and PB (Stamler et al. 1997).

The meta-analyses of Allender et al. (1996) and Bucher et al. (1996) used pooled estimates of randomised controlled trials, using the weighted average method. The pooled data from 22 clinical trials with a total of 1231 subjects taking calcium supplements of 400
to 2160 mg/day, showed a decrease in SBP of 0.5 mmHg in normotensive and 1.7 mmHg in hypertensive subjects (Allender et al. 1996). Another meta-analysis of 33 trials involving calcium supplements of 1000 to 2000 mg/day (Bucher et al. 1996) showed a significant reduction in SBP of 1.3 mmHg in normotensive subjects. The meta-analysis of Bucher et al. (1996) was updated in 1999 and included 10 additional randomised controlled trials (Griffith et al. 1999). The pooled analysis showed a reduction of -1.4 mmHg in SBP and in DBP of -0.8 mmHg.

Evidence from meta-analyses of calcium supplementation studies has been unconvincing: calcium supplementation had a small effect on SBP in hypertensive individuals and an uncertain effect in normotensive individuals. Drüke (1999) concluded in his review that the reducing effect of calcium on BP to be 1-2 mmHg in SBP and < 1 mmHg in DBP.

The exact mechanisms of how calcium affects BP are unknown. The mechanism of action of calcium administration on BP may be via natriuresis and diuresis (Hermansen 2000). The calcium ion plays an important role in smooth muscle contraction and relaxation, and hence in the control of vascular tone and BP (Drüke 1999). Hatton and McCarron (1994) has suggested that calcium may affect by following physiological mechanisms 1) limiting the calcium influx into the cell and improving the ability of vascular smooth muscle cells (VSMC) to extrude calcium, 2) by affecting the calcium regulating hormones, which in turn may influence the BP, 3) by modulation of SNS, 4) by changing the metabolism of other electrolytes e.g. sodium, and possibly 5) by effects on the central nervous system.

2.5.5 Dietary magnesium

A review of 29 observational studies suggested an inverse association between magnesium intake and BP (Mizushima et al. 1998). Similarly, in the MRFIT study, an inverse association between magnesium intake and BP was found (Stamler et al. 1997). In a prospective 4-yr study of US female nurses, the relative risk for hypertension in subjects with magnesium intake of 300 mg/d or more compared to those with intake of < 200 mg was 0.77 (Witteman et al. 1989). However, recent controlled trials showed no effect of magnesium supplementation on BP (Sacks et al. 1998, Yamamoto et al. 1995).

Magnesium may lower BP by reduction of vascular resistance through its calcium antagonist properties, by the modulation of the activity of cell membrane sodium pump and by alterations in vascular responsiveness to vasoactive agents (Nurminen et al. 1998).

2.5.6 Dietary fat

Evidence for the effects of saturated (SFAs), monounsaturated (MUFA) and n-6 polyunsaturated fatty acids (PUFAs) on BP emerging from epidemiological and
Experimental studies are conflicting, thus the relationship between dietary fat and BP remains unsolved (Morris 1994, Pietinen 1994). The relationship between fatty acids and BP also seems to be similar according to the cross-sectional studies that have used biochemical indicators methods to evaluate the fatty acid composition of diet (Morris 1994).

Epidemiological data do not support the theory that there is any direct association between total fat intake and BP (Ascherio et al. 1992, Gruchow et al. 1985). However in Finnish (Salonen et al. 1983, Salonen et al. 1988) and in Indian subjects (Beegom et al. 1997), the SFAs has been found to correlate with high BP. The trans fatty acids, which are often paralleled to SFAs do not seem to have impact on BP (Pietinen 1994). In the MRFIT study, SFA (E%) was positively related to BP in multivariate regression models (Stamler et al. 1996a). The analyses were controlled for body weight, dietary sodium, ratio of sodium to potassium, alcohol, potassium and caffeine intake. In the large prospective Nurse's Health Study, the nutrient intakes of 58218 American females without hypertension were measured by a validated dietary questionnaire, and the incidence of hypertension was followed for 4 yrs (Wittman et al. 1989). No independent association was observed between intake of SFAs and the incidence of hypertension in multiple regression analyses adjusted for age, weight and intake of energy and other nutrients.

Some epidemiologic studies has shown an inverse association between MUFA and BP (Rubba et al. 1987, Williams et al. 1987), but others have failed to replicate their finding (Gruchow et al. 1985, Joffres et al. 1987, Wittman et al. 1989). In the prospective Nurse's Health Study no independent association was found between incidence of hypertension and intake of MUFA (Wittman et al. 1989).

The epidemiologic evidence concerning the relationship between PUFA and BP is also unconvincing, in some studies an inverse association has been reported (Stamler et al. 1996a), and in some other studies not (Gruchow et al. 1985, Joffres et al. 1987, Wittman et al. 1989). In one large prospective study, there was no relationship between intakes of PUFA and the incidence of hypertension (Wittman et al. 1989).

Numerous clinical trials have been performed to test the effect of dietary fat on BP, and a wide range of dietary fat combinations has been explored. The controlled clinical trials in normotensive and hypertensives subjects reviewed by Morris (1994) provided evidence that dietary fats did not affect BP. Only in studies done in hypertensive patients by Puska et al. (1983) and by Little et al. (1990) the very low-fat diets (27 E%, 24 E%) showed reduction in BP, but according to Morris (1994) in both studies the changes in BP could be explained by other contributing factors. Pietinen (1994) also found in her review that the effect of individual fatty acids on BP was unclear, but she concluded that a change from a high-SFA diet to a low-fat high-PUFA diet did seem to lower BP.

Dietary fat, since it is a good source of energy, can influence BP via body weight, but it is thought to also directly regulate BP. The SFAs may affect endothelial cell function and thus reduce the ability of blood vessels to dilate (Beilin 1993). Unsaturated fat is
incorporated into lipid membranes which increases membrane permeability and thereby stimulates the sodium and cation transport. PUFAs can be converted to prostaglandins, which reduce BP via effects on arterial vasodilatation -electrolyte balance, renal renin release and pressor hormones (Hermansen 2000).

Fish oils

Long-chain n-3 fatty acids of marine origin (eicosapentanoic and docosahexaenoic acids) have a mild antihypertensive effect which is seen most clearly in hypertensive subjects, in older people, and during sodium restriction. A meta-analysis of 31 controlled trials showed that a supplementation of an average 5.6 g/d of n-3 fatty acids reduced SBP/DBP in hypertensive subjects by 3.4/2.0 mmHg (Morris et al. 1993). The dose response relationship between fish oils and BP was evaluated to be linear, 1 gram fish oil decreased SBP by 0.66 mmHg and DBP by 0.35 mmHg.

Fish oils given as a supplement seem to affect BP, but also the eating of fish has been shown to lower BP. In Tanzanian villagers, consumption of freshwater fish (300-600 g/day) was associated with lower BP, and the proportions of n-3 fatty acids were higher in the fish group than in vegetarian group (Pauletto et al. 1996). In a controlled clinical trial, regular fish consumption enhanced the effects of weight reduction in hypertensive patients (Bao et al. 1998). The daily fish meal (3.65 g n-3 PUFA) combined with weight reduction in obese hypertensive subjects reduced the awake ambulatory SBP/DBP relative to the control group by 13.0/9.3 mmHg during 16 weeks. In contrast, the advice to eat two portions of fatty fish each week did not effect BP of men with CHD in a 2-y trial by Ness et al. (1999). The intake of eicosapentanoic acid was only 0.33 g/d in the active group and 0.10 g/d in men who were not especially advised to eat fish.

The mechanism by which the fish oils affect BP is uncertain. Fish oils could decrease BP by altering the balance between vasoactive prostaglandins. They may reduce the production of the vasoconstrictor agent tromboxane A2 and increase the production of the vasodilator, prostacyclin (PGI2). N-3 PUFAs have also been suspected to modulate the vasoconstrictor response to pressor hormones and to decrease blood viscosity (Appel et al. 1993). One explanation for the effects of fish oils on BP may be that changes in smooth muscle membrane composition might reduce vascular tone (Swales 1995).

2.5.7 Dietary protein

Epidemiological studies have shown an inverse relationship between protein intake and elevated BP (Stamler et al. 1996a, 1996b, Stamler et al. 1997), but the intervention studies have not found significant effects of protein on BP (Obarzanek et al. 1996). Interestingly, recently certain tripeptides produced from milk proteins in milk fermentation have been found to lower BP by their angiotensin converting enzyme (ACE) inhibitor properties (Hata et al. 1996). However, it is difficult to study the effect of a change in a specific
macronutrient e.g. protein, since if the amount of one macronutrient changes, the amount of other macronutrients must be changed concomitantly to balance the energy content.

Hermansen (2000) has suggested that dietary protein may effect BP via the following mechanisms: 1) protein may replace fats or sugars that increase BP, 2) protein can increase natriuresis, 3) some amino acids in the dietary protein may cause vasodilation through enhanced endogenous production of nitric oxide.

2.5.8 Dietary carbohydrates

The relationship between carbohydrates and BP is unclear, but there are some suggestions that sugar consumption is positively and fibre intake inversely associated with BP (Hermansen 2000). Among the 11342 middle-aged men who participated the MRFIT Study, starch was shown to have a direct relation to BP (Stamler 1996a, Stamler et al. 1997). Cross-sectional and prospective studies indicate an inverse relationship between dietary fibre intake and BP (Joffres et al. 1987, Ascherio et al. 1992), but randomized controlled trials have not confirmed this proposed relationship (He and Whelton 1999). One explanation for the beneficial effects of DASH combination diet (Lampe 1999) and vegetarian dietary pattern could be a high intake of fibre (Hermansen 2000). The possible mechanisms on how carbohydrates can affect BP remain unresolved (Nurminen et al. 1998, Hermansen 2000).

2.5.9 Alcohol

Epidemiological studies indicate that moderate alcohol intake appears to promote overall cardiovascular health in middle-aged and elderly people (McElduff and Dobson 1997, Grobbee et al. 1999). However, cross-sectional and prospective cohort studies indicate a direct relationship between alcohol intake and BP (Gordon and Kannel 1983, Salonen et al. 1983, Witterman et al. 1989, Klatsky et al. 1990). The Intersalt study revealed that alcohol drinking ≥ 36 g/d was significantly related to BP in both sexes, and the relation was independent of BMI and urinary excretion of sodium and potassium (Marmot et al. 1994).

The shape of association curve between alcohol and BP has been questioned. Some epidemiologic data suggest that the relationship between BP and alcohol intake is J-shaped, but others have reported that there is a threshold for daily alcohol intake after which BP becomes elevated (Swales 1995).

BP rises in heavy drinkers if alcohol is acutely withdrawn, but in the long-term, the withdrawal of alcohol will decrease BP (Grobbee et al. 1999). In controlled trials, moderation of alcohol intake decreased SBP/DBP by an average 4/2 mmHg (Puddey et al. 1985, Puddey et al. 1987, Ueshima et al. 1993). Alcohol is a vasodilating agent at low doses, but a vasopressor agent at higher doses (Victor and Hansen 1995), and this could
explain why “binge” drinking has been found to be associated with elevated BP (Ashwell 1997).

Neural, humoral and direct vascular mechanisms are suggested to be possible mediators of the association between alcohol and BP, but the exact mechanism is unknown (Grobbee et al. 1999). Alcohol may also affect BP via body weight, and SNS may have a role in the BP response to alcohol (Swales 1995).

According to Grobbee et al. (1999), long-term alcohol intake ≥30-60 g/d is the second most important risk factor of hypertension immediately after obesity. They estimated that from the level of alcohol intake of 30 g/d every further increment of 10 g/d will increase SBP/DBP by 1-2/1 mmHg.

2.5.10 Overall dietary pattern

Many dietary factors have been linked to the hypertension. Mostly the effect of single nutrients on BP has been investigated, but recently it has been suggested that changes in dietary pattern may be more valuable than a change in a single dietary factor. The vegetarian dietary pattern has been shown to be effective in lowering BP (Beilin et al. 1988, Melby et al. 1994, Margetts et al. 1999). In controlled trials, a vegetarian diet has reduced BP in both normotensive and hypertensive subjects (Rouse et al. 1983, Margetts et al. 1986). In the follow-up of the MRFIT, vegetarians had lower BP (Stamler et al. 1997). The superiority of vegetarian diet may be due to the high levels of fiber and minerals e.g. potassium and magnesium, and due to lower fat content. The lower body weight of vegetarians could also affect BP.

The importance of multiple factors in the diet for BP control was confirmed in Dietary Approaches to Stop Hypertension Trial (DASH), where the effects of three dietary patterns on BP were studied (Appel et al. 1997). Altogether 459 subjects with mean SBP/DBP values of 131/85 mmHg were included into this randomised controlled multicenter clinical trial. During the first 3 study weeks, participants followed a control diet that was low in fruits and vegetables (4 portions/day) and dairy products (0.5 portions/day), and had a fat content typical of the average American diet. After this run-in period, subjects were randomised for 8 weeks to receive one of three study diets: 1) the control diet, 2) a diet rich in fruit and vegetables (10 portions/day) or 3) a “combination diet” rich in fruit and vegetables (10 portions/day) with low-fat dairy products (~3 portions/day) and with reduced saturated and total fat intake (26 E%). In the combination diet, calcium intake increased to 1200 mg/day and potassium intake ranged from 4.1 to 4.4 g/day and fibre intake increased to 31 g/day. Sodium intake was equivalent in all 3 diets and remained constant, as did body weight. The fruit-and-vegetable diet reduced SBP/DBP by 2.8/1.1 mmHg more than control diet. The reduction of SBP/DBP were 5.5 and 3.0 mmHg more in the combination diet as compared to control diet. Among the hypertensive subjects, the differences between treatment groups and control group were even larger, the combination
diet reduced SBP/DBP by 11.4/5.5 mmHg more and the fruit-and-vegetable diet 7.2/2.8 mmHg more than the control diet.

2.6. Diet recommendations for prevention and treatment of hypertension

Lifestyle changes recommended in recent national and international guidelines to prevent and treat elevated BP are presented in Table 4. (Suomen Sydäntautiliiton verenpainetyöryhmän suositus 1994, JNC VI 1997, Ramsay et al. 1999, WHO-ISH 1999). All of these guidelines recommend the following dietary changes: sodium reduction, weight reduction and moderation of alcohol intake. The adequate intake of other electrolytes: potassium, calcium, magnesium are recommended by Finnish Heart Association (Suomen Sydäntautiliiton verenpainetyöryhmän suositus 1994), and by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI 1997) or their intakes of have been taken into account by recommending an overall healthy dietary pattern that emphasizes a high intake of fruit and vegetables (Ramsay et al. 1999). The reduced total fat, SFAs and cholesterol has also been recommended to treat overall cardiovascular health (Suomen Sydäntautiliiton verenpainetyöryhmän suositus 1994, JNC VI 1997, Ramsay et al. 1999). Increased oily fish consumption is recommended in the British recommendation (Ramsay et al. 1999).

Sodium intake recommendations vary somewhat between the guidelines. Finnish Heart Association (Suomen Sydäntautiliiton verenpainetyöryhmän suositus 1994) and British Hypertension Society Guidelines (Ramsay et al. 1999) recommend a reduction of salt intake to 5 grams per day, while JNC VI (1997) and WHO-ISH (1999) recommend a reduction of salt intake to 6 grams per day.
Table 4. Lifestyle changes recommended in recent hypertension treatment guidelines.

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Salt intake</th>
<th>Other recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finnish Heart Association (Suomen Sydäntautiliiton verenpainetyöryhmän suositus) 1994</td>
<td>&lt; 5 g/day</td>
<td>adequate potassium and magnesium intake, reduced total fat intake, weight reduction, moderation of alcohol intake, increased physical activity, smoking cessation</td>
</tr>
<tr>
<td>The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) 1997</td>
<td>≤ 6 g/day</td>
<td>weight reduction, moderation of alcohol intake (≤ 30 ml ethanol/day in men and ≤ 15 ml ethanol in women), increased physical activity, adequate potassium intake (approx. 90 mmol/day), the adequate intake of calcium and magnesium for general health, and reduction of dietary saturated fat and cholesterol for cardiovascular health, smoking cessation</td>
</tr>
<tr>
<td>British Hypertension Society Guidelines (Ramsay et al. 1999)</td>
<td>≤ 5 g/day</td>
<td>weight reduction, limitation of alcohol intake (&lt; 21 portions in men and &lt; 14 portions in women per week), increased physical activity, increased fruit and vegetable consumption, reduced total fat and saturated fat, replacement of SFA with PUFA and MUFA, increased oily fish consumption, smoking cessation</td>
</tr>
<tr>
<td>World Health Organization-International Society of Hypertension Guidelines (WHO-ISH 1999)</td>
<td>&lt; 6 g/day</td>
<td>weight reduction, reduction of excessive alcohol consumption (≤ 20-30 g ethanol/d for men, ≤ 10-20 g ethanol/d for women)</td>
</tr>
</tbody>
</table>
2.7 Non-pharmacological treatment of hypertension in primary health care

Under controlled conditions e.g. in research centers, lifestyle changes have been shown to reduce BP, but the effects of lifestyles on BP in primary health care are less certain (Margetts et al. 1999). Margetts and coworkers performed a review of primary health care based diet and physical activity interventions aimed at reducing BP, and found that the results of the effectiveness of the trials varied a lot. Compliance with the dietary advice was generally not measured and the variability in the quality of the interventions made it difficult to draw any conclusions; effects if any tended to be small.

The effect of lifestyle interventions which has included dietary advice in primary health care has been reviewed by Ashenden et al. (1997), Brunner et al. (1997) and Ebrahim&Smith (1997). In the majority of the studies, the subjects were not hypertensive.

Ashenden et al. (1997) reviewed 37 trials, which investigated the effectiveness of general practitioner based lifestyle advice in a general practice setting. The dietary advice was given in 10 trials. Only two of dietary advice trials included hypertensive subjects (Koopman et al. 1990, Cohen et al. 1991). The results of these 10 trials were mixed and the dietary changes were often poorly measured or not measured at all.

The systematic review and meta-analysis of 14 multifactorial intervention trials in workforces and in primary care found the net decrease in SBP/DBP to be -4.2/-2.7 mmHg (Ebrahim and Smith1997). Especially, those risk factor interventions which included people with hypertension and other high risk groups seemed to have beneficial effects.

Brunner et al. (1997) studied the effect of dietary interventions on diet and cardiovascular risk factors in free living subjects. The mean net changes in fat intake (E%) were -2.5 % after 3-6 mo and in 24-h sodium excretion -45.0 mmol in trials of 9 to 18 month's duration. Only two of 17 randomised controlled trials in Brunner’s meta-analysis included hypertensives in primary health care (Koopman et al. 1990, Silman et al. 1983).

Table 5. lists dietary advice trials in primary health care which have included hypertensive subjects. The intervention and interveners in these studies in primary health care varied extensively, so it is difficult to draw any firm conclusions about the effect of intervention on the diet and BP. The changes in dietary intake were poorly expressed or not presented. The dietary assessment was mostly carried out by a questionnaire, the 24-h urinary sodium excretion was only used in two studies. With the exception of a small study of Silman et al. (1983), the changes in 24-h sodium excretion were non-significant. Usually weight, BP and lipid changes were reported. Net changes in serum total cholesterol varied from an average 0.1 to 0.2 mmol/l. In some studies, the changes in body weight and BP were significant, but rather minor.

According to the studies carried out among Finnish hypertensive patients in the1990's the diet of hypertensives does not seem to match the current recommendations. In the middle of 1990's, the nutrient intakes of 238 hypertensive subjects without antihypertensive drug treatment were studied by 4-d food record and 24-h urine
collections in Turku, Finland (Jula et al. 1997). The SFA and salt intake were more than recommended to hypertensive subjects, and fiber intake was less than recommended. Around 25% of the study subjects were obese (BMI >30 kg/m²).

Altogether 716 subjects with special reimbursement to antihypertensive drugs and their matched controls from the Oulu area completed the 7-d food records and their BP was measured (Silaste et al. 2000). The hypertensive subjects were heavier than control subjects, but the dietary intakes did not differ between hypertensive and control subjects. Alcohol consumption was highest among hypertensive men. Both the hypertensive subjects and their counterparts consumed more fat than recommended.

In 1995 the treatment of hypertension, but unfortunately not the diet of hypertensive patients in Finnish Primary Health Care was investigated by Kumpusalo and co-workers (1997). Doctors and hypertensive subjects from 30 primary health care centres participated in the study. Of all the patients, 83% of men and 87% of women were receiving drug treatment for hypertension. If SBP/DBP <140/90 mmHg was used as the criterion for good control, only 13% of men and 10% of women had their BP well controlled. The BMI was the only lifestyle factor studied. Of all drug-treated patients, 33% of men and 37% of women were obese (BMI >30 kg/m²). Obesity has been noticed to be a growing problem: the prevalence of obesity increased between the years 1982 and 1997 among hypertensive subjects when a randomised sample of a Finnish population was studied in eastern part of Finland (Kastarinen et al. 2000).
Table 5. Dietary interventions in primary health care including hypertensive subjects.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Subjects</th>
<th>Study groups</th>
<th>Intervener, duration</th>
<th>Dietary assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silman et al. 1983</td>
<td>nonmedicated, aged 50-64 yrs, DBP 95-104 mmHg</td>
<td>low-sodium (n=12), control (n=16)</td>
<td>nr, 1 y</td>
<td>24-h urine</td>
</tr>
<tr>
<td>Koopman et al. 1990</td>
<td>nonmedicated, DBP 90-110 mmHg</td>
<td>intervention (n=17), control group (n=18)</td>
<td>Dietitian, 3 mo</td>
<td>24-h urine</td>
</tr>
<tr>
<td>Cohen et al. 1991</td>
<td>30 obese, aged 20-75 yrs</td>
<td>weight reduction, control</td>
<td>GP, 1 y</td>
<td>discussion</td>
</tr>
<tr>
<td>Lindholm et al. 1995</td>
<td>aged 30-59 yrs with at least two CVD risk factors</td>
<td>intervention (n=339), control (n=342)</td>
<td>Nurse, GP, 18 mo</td>
<td>questionnaire</td>
</tr>
<tr>
<td>Iso et al. 1996</td>
<td>aged 35-69 yrs with SBP in 140-179 mmHg, DBP in 90-109 mmHg</td>
<td>intervention (n=56), control (n=55)</td>
<td>GP, nurse, dietitian, 1.5 yrs</td>
<td>standardized questionnaire, interview for alcohol</td>
</tr>
<tr>
<td>Roderick et al. 1997</td>
<td>aged 35-59 yrs attending CVD surgery</td>
<td>intervention (n=473), control (n=483)</td>
<td>nurse, 1 y</td>
<td>FFQ</td>
</tr>
<tr>
<td>Campbell et al. 1998</td>
<td>CHD patients under 80 yrs</td>
<td>intervention (n=673), control (n=670)</td>
<td>nurse, 1 y</td>
<td>postal questionnaire, DINE score</td>
</tr>
<tr>
<td>Pritchard et al. 1999</td>
<td>aged 25-65 yrs, at least of one of the following: overweight, hypertension, type 2 diabetes</td>
<td>doctor+dietitian (DD,n=33), dietitian (D,n=30), control (n=34)</td>
<td>GP, dietitian, 1 y</td>
<td>nm</td>
</tr>
</tbody>
</table>

TC= serum total cholesterol, BP=blood pressure, GP=general practitioner, LDL-C = low density cholesterol, CVD=cardiovascular disease, CHD=coronary heart disease, FFQ=food frequency questionnaire, DINE=dietary instrument for nutritional education, nm=not measured, nr=not reported, NS=nonsignificant, SFA=saturated fatty acids
<table>
<thead>
<tr>
<th>Dietary intakes(^1)</th>
<th>Excretion of Na/K(^1)</th>
<th>Weight(^1)</th>
<th>SBP/DBP(^1)</th>
<th>TC(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>nm</td>
<td>-53 mmol/NS</td>
<td>nm</td>
<td>NS/NS</td>
<td>nm</td>
</tr>
<tr>
<td>nm</td>
<td>NS</td>
<td>nm</td>
<td>NS/NS</td>
<td>LDL-C: -0.7 mmol/l</td>
</tr>
<tr>
<td>nm</td>
<td>nm/nm</td>
<td>NS</td>
<td>NS/NS</td>
<td>nm</td>
</tr>
<tr>
<td>fat, fibre(^1)</td>
<td>nm</td>
<td>NS</td>
<td>NS/NS</td>
<td>-0.15 mmol/l</td>
</tr>
<tr>
<td>nm</td>
<td>nr/nr</td>
<td>NS</td>
<td>-5.8 mmHg/NS</td>
<td>nm</td>
</tr>
<tr>
<td>total fat -1.4% SFA</td>
<td>nm/nm</td>
<td>-0.56 kg</td>
<td>NS/NS</td>
<td>-0.20 mmol/l</td>
</tr>
<tr>
<td>low-fat diet achieved 7.5% more</td>
<td>nm/nm</td>
<td>nm</td>
<td>management(^2) int vs cont 29.2%, 7.8%</td>
<td>management(^3) int vs cont 9.8%, 0.2%</td>
</tr>
<tr>
<td>nm</td>
<td>nm/nm</td>
<td>DD:-6.7 kg, D: -5.6 kg</td>
<td>Mean BP: DD: -12 mmHg, D: -7 mmHg</td>
<td>nm</td>
</tr>
</tbody>
</table>

\(^1\) Net change = change in intervention group minus change in control group, \(^2\) SBP/DBP ≤160/90 mmHg, \(^3\) serum TC ≤5.2 mmol/l.
3. THE AIMS OF THE STUDY

The aims of this thesis were to examine the following questions among free living hypertensive subjects:

1. How hypertensive subjects adhere to the salt restriction (I)?
2. Does the salt restriction effect on the intake of other nutrients (II)?
3. How does the salt restriction alone or in combination with an angiotensin converting enzyme (ACE) inhibitor affect on BP (III)?
4. What long-term effects has an intensified diet counselling on the diet and on the cardiovascular risk factors of hypertensive subjects in primary health care (IV)?

The data of the original publications I-III were derived from a salt restriction study, which was intended to examine the effects of salt restriction alone or in combination with cilazapril in the treatment of mildly elevated BP. The effects of intensified diet counselling was studied in a primary health care intervention study (IV), in which the feasibility, effects and cost-effectiveness of non-pharmacological treatment of hypertension were investigated.
4. SUBJECTS AND METHODS

4.1. Subjects

Salt restriction study (I, II, III)

Subjects were recruited from previous studies carried out in the Kuopio Research Institute of Exercise Medicine and from local occupational health care centers. Originally 99 hypertensive subjects were invited for screening. The main exclusion criteria were complicated hypertension, symptomatic coronary heart disease, heart failure, clinically significant hepatic, renal, gastroenterological, neurologic, haematologic, cerebrovascular disease, endocrinological or metabolic disease except for well-controlled diabetes mellitus. Other exclusions were autoimmune disease, history of allergy and angioneurotic oedema, drug or alcohol abuse and clinically significant cardiac arrhythmias and conduction disturbances.

A total of 59 subjects started the study, but due to the normalisation of BP during the run-in period, 14 subjects were excluded. There were six drop-outs during the study phase (between the weeks 4 and 24). Three subjects withdrew after they expressed their unwillingness to continue with the diet. They found the salt restriction too troublesome and one subject withdrew because of personal reasons. One subject was excluded because of side effects of cilazapril and one subject because of markedly elevated BP. Thirty nine subjects (24 men, 15 women) aged 28-65 years with a mean daytime ambulatory DBP between 90-105 mmHg and office DBP 95-115 mmHg completed the study which was carried out in free living conditions in 1993 and 1994. The baseline characteristics of the subjects who completed the study are presented in table 6.

Table 6. Basic characteristics of the subjects after the run-in period in the salt restriction study (I, II, III).

<table>
<thead>
<tr>
<th>Variable</th>
<th>All n=39</th>
<th>Men n=24</th>
<th>Women n=15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>52±8</td>
<td>51±7</td>
<td>54±9</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>29.5±3.3</td>
<td>29.0±3.2</td>
<td>30.3±3.5</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>149±12</td>
<td>149±13</td>
<td>149±11</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>101±6</td>
<td>102±7</td>
<td>100±5</td>
</tr>
<tr>
<td>Current smokers, n</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

Mean±SD.
Primary health care intervention study (IV)

Altogether 715 subjects, aged 25-74 years and with SBP 140-179 mmHg and/or DBP 90-109 mmHg and/or drug treatment for hypertension, from nine primary health care centers in the Province of North Karelia and from the primary health care center of the city of Kuopio were included in the study. The study subjects were recruited by announcements in local newspapers or from hypertension registers of health care centers. Altogether 53% of the recruited subjects were using antihypertensive drugs and they were included into the study without screening BP measurements. The exclusion criteria included secondary hypertension, mental or physical illness, which could prevent compliance with the study procedures, as well as alcoholism, type 1 diabetes mellitus, current or planned pregnancy and history of acute CVD event within the preceding 3 months. The baseline characteristics of the subjects are presented in table 7.

Table 7. Baseline characteristics of the subjects in primary health care intervention study (IV).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intervention group n=360</th>
<th>Usual care group n=355</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>54.4±10.1</td>
<td>54.2±9.9</td>
</tr>
<tr>
<td>Male/Female, (n)</td>
<td>187/173</td>
<td>190/165</td>
</tr>
<tr>
<td>Drug treatment to hypertension, %</td>
<td>52.2</td>
<td>54.4</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>81.1±15.7</td>
<td>80.0±14.8</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>28.9±4.6</td>
<td>28.5±4.5</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>149.2±16.0</td>
<td>147.7±16.3</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>90.9±8.6</td>
<td>90.7±8.4</td>
</tr>
<tr>
<td>Cigarette smoking, %</td>
<td>37077</td>
<td>37016</td>
</tr>
<tr>
<td>Serum total cholesterol, mmol/l</td>
<td>5.7±0.9**</td>
<td>5.6±0.9</td>
</tr>
<tr>
<td>Serum LDL cholesterol, mmol/l</td>
<td>3.6±0.8**</td>
<td>3.6±0.8</td>
</tr>
<tr>
<td>Serum HDL cholesterol, mmol/l</td>
<td>1.3±0.3**</td>
<td>1.4±0.4</td>
</tr>
<tr>
<td>Serum triglycerides, mmol/l</td>
<td>1.6±1.0**</td>
<td>1.5±1.0</td>
</tr>
</tbody>
</table>

Mean±SD. *No differences between the study groups at the significance level of p-value < 0.05, analysed by Student's T-test, **n=359 for serum lipids.
4.2. Study designs

Salt restriction study (I, II, III)

A randomised controlled trial was carried out to examine the effects of salt restriction alone or in combination with cilazapril (ACE inhibitor) in the treatment of mildly elevated BP (Figure 2.). During the 4-week run-in period, the subjects followed their normal-sodium diet and took one placebo tablet daily given as a control for the cilazapril arm of the study. At week 4, the subjects who still fulfilled the inclusion criteria for BP were instructed to follow a low-sodium diet for the next 8 weeks and they were given placebo tablets. At week 12, the subjects were randomised into two groups for the next 12 weeks: low sodium placebo group and low-sodium cilazapril group. Subjects were asked to maintain their physical activity and to keep their body weight unchanged during the study.

Subjects provided their written informed consent prior starting the study, and the study protocol was approved by the Ethics Committee of the University of Kuopio.
Figure 2. Study design in the salt restriction study (I, II, III). FR=food record, other abbreviations in page 7.
Primary health care intervention study (IV)
The effects of diet counselling on the diet and cardiovascular risk factors of hypertensive subjects were studied in a randomised controlled trial carried out in primary health care (Figure 3.). The main study outcome measurements were done at the baseline, and at the one and at two year examinations. Before the baseline visit, all the subjects had a group session where they received detailed information about the study and they were also given instructions on how to complete the health questionnaires, 4-d food records and how to collect the 24-h urine sample. The subjects were randomised into the intervention or the usual care group at the baseline study visit by the study physician, and they gave their written informed consent for the study protocol, which was approved by the Ethics Committee of the University of Kuopio and Kuopio University Hospital.

The intervention group was scheduled to visit the nurse of their own primary health care center four times (at 1, 3, 6 and 9 month) during the first year. During the second year, the scheduled visits were at 15, 18 and 21 months. The intervention group had a group session at six months and at 18 months with a study physician and a clinical nutritionist dealing with the non-pharmacological treatment of hypertension. Approximately half of the subjects participated in the group sessions. Apart from the annual study visits (at baseline, and at 1 y and 2 y), the control group continued their usual care in local health care centers scheduled by physicians and primary health care nurses as before the study.
Figure 3. Study design in the primary health care intervention study (IV). FR=food record, other abbreviations in page 7.
4.3. Dietary interventions

Salt restriction study (I, II, III)

Salt restriction was the only dietary intervention in this study. At week 4, the patients were advised to reduce their sodium chloride intake, but otherwise to keep the diet unchanged. Dietary instructions were given by a clinical nutritionist, who met the patients at every visit and advised them on the practical management of the diet. The patients received both oral and written instructions on how to choose and prepare food to reduce their daily sodium chloride intake to 5 grams or less per day.

The diets were composed of normal Finnish food items except for a low-salt bread (0.5%), which was supplied free of charge for the subjects during the entire salt restriction period (from the week 4 to 24). Subjects were advised to use 50% less salt than in normal Finnish cooking and baking and to flavour foods with lemon, pepper, herbs, spices, onion and garlic. Fresh vegetables and fresh fish products were recommended to be eaten instead of salted and pickled vegetables or salted and smoked fish products. The patients were also asked to eat low-sodium alternatives of meat products, fish products, cereals and dairy products, and they also participated once or twice in the group meetings during which a variety of dishes was prepared without salt. Those subjects eating lunch outside of their home were asked to order a salt-free lunch. The basic principles of the salt-restricted diet were also included in a booklet, in which the dates of future study visits were written down.

Primary health care intervention study (IV)

The goals of the dietary intervention carried out in primary health care were to reduce total fat to less than 30 E%, saturated fatty acids to less than 10 E%, salt intake to less than 5 grams per day and to maintain an adequate intake of dietary potassium (more than 2000 mg per day). The subjects were also advised to restrict their alcohol consumption to no more than two portions per day (one portion = 12 g ethanol). Other goals of the intervention were to achieve body mass index < 25 kg/m², if overweight, to have aerobic exercise at least three times (at least 30 minutes) per week and to stop smoking.

The counselling was mainly carried out by the personnel of the local primary health care centres, which participated in this intervention study. The primary health care nurses were trained by both the study physician and by a clinical nutritionist to advise the intervention group to make lifestyle changes. The nurses had a folder with information about details of foods recommended and tips on diet changes. The nurses advised the patients to eat foods which were non-fat, low-fat or contained soft vegetable fat. Patients were also advised to prepare foods without salt or with little fat. If fat was needed, vegetable oil or soft margarines were recommended. Salting less and consumption of low salt foodstuffs were preferred, and spices were advised to be used instead of salt.
The intervention group had a follow-up card for monitoring of BP and weight, which also contained the basic principles of lifestyle changes to treat hypertension. The subjects in the intervention group received a written feedback on their progress on the basis of their 4-day food record from their own primary health care nurse at the one month visit. At the one and two year follow-up visits, the study physician gave the written feedback on the diet to the intervention group.

4.4. Methods

4.4.1. Body weight and blood pressure measurements

*Salt restriction study (I, II, III)*

Body weight was measured in light clothes with the same digital scale. The BP was measured in the sitting position by the same trained nurse with a random zero sphygmomanometer between 8.00 and 12.00 a.m. after 10-15 minutes rest. Disappearance of Korotkoff's sounds (phase V) was used in the determination of the DBP. Three measurements were done, with the mean of the last two being used in the analysis. The 24-h ambulatory blood pressure (ABP) was measured with a Novacor SA device at 20 min intervals between 06.00 and 22.00 and once an hour during the night. The mean value over the registered time-period was used.

*Primary health care intervention study (IV)*

Body weight was measured in light clothes with the same digital scale, and the BP was measured with a standard mercury sphygmomanometer after five minutes of rest in the sitting position according to the WHO MONICA protocol (Kuulasmaa et al. 1998) by the same study nurse, who was unaware of the group allocation of the each study subjects. At one health center, the baseline BP measurements were done by another trained nurse. The measurement results of these two nurses did not differ significantly, when the BPs of ten volunteers were measured with a double stethoscope method. Disappearance of Korotkoff sounds (phase V) was used in the determination of the DBP, and the values were recorded to the nearest 2 mmHg. The mean of two consecutive measurements was used in the analysis.

4.4.2 Laboratory measurements

*Salt restriction study (I, II, III)*

Venous blood samples were drawn between 7.30 and 9.30 a.m. after a 12-hour fast and 10 min rest in supine position. Blood glucose was determined by the glucose dehydrogenase method (Merck, Darmstadt, Germany) and creatinine in serum and urine by the Jaffé method (Boehringer Mannheim GmbH, Germany). Serum triglycerides were
determined enzymatically (GPO-PAP method, Boehringer Mannheim GmbH). Kontron Uvikon 860 photometer (Kontron Instruments AG, Zürich, Switzerland) was used in these measurements. HDL cholesterol was measured in the supernatant obtained after precipitation of VLDL and LDL by dextran sulphate (Mr 500 000, Pharmacia, Uppsala, Sweden) and MgCl₂ (Magnesium chloride-hexahydrat, Merck, Darmstadt, Germany) (Pentilä et al. 1981). Cholesterol concentrations in serum and HDL fraction were measured enzymatically (CHOD-PAP method, Boehringer Mannheim GmbH) using Gilford Stasar III photometer (Gilford Instrument Laboratories, Oberlin, Ohio, USA). Serum LDL cholesterol was calculated using the Friedewald et al. (1972) equation modified for molar concentrations: LDL cholesterol = total cholesterol - (HDL cholesterol + 0.45 x total triglycerides). Plasma insulin was determined by radioimmunoassay based on a double antibody solid phase technique (Kabi Pharmacia Diagnostics AB, Uppsala, Sweden). The radioactivity was counted with a MiniGamma 1275 Gamma Counter (Wallac, Turku, Finland). Potassium and sodium levels in serum were determined using ion selective electrodes (Kone Microlyte Ion Selective Analyser, Kone Corporation, Espoo, Finland). Albumin in urine was analysed using Beckman micro Albumin reagent (Beckman Instruments, Inc., Ireland) on a Beckman Array Protein Analyser. The Beckman Array utilizes the measuring principle of kinetic rate nephelometry.

The 24-h urine collection was performed in free living conditions into plastic containers from 7.00 a.m. to the next morning 7.00. The correct way of collection was ascertained from the subjects when they returned the containers and urinary volume was measured. If the urine collection was incomplete, the subjects were asked to collect a new 24-h urine. The completeness of urine excretions was confirmed on the basis of the 24-h creatinine excretion by relating 24-h sodium excretions to 24-h excretion. Sodium and potassium concentrations in urine were determined using ion selective electrodes (Kone Microlyte Ion Selective Analyser, Kone Corporation, Espoo, Finland). Creatinine concentrations in urine were analysed by the Jaffé method (Boehringer Mannheim GmbH, Germany).

*Primary health care intervention study (IV)*

All the laboratory analyses were performed in the Department of Biochemistry, National Public Health Institute (KTL, Helsinki), Finland. Venous blood samples were taken at health centers after a 12-h overnight fasting. Before April 1 in 1998, enzymatic CHOD-PAP method was used for determination of total cholesterol and enzymatic GPO-PAP method for determination of total triglycerides from fasting whole serum with a commercial kit (Boehringer Mannheim GmbH, Germany) with a Olli C analyser (Kone Ltd, Espoo, Finland). High-density lipoprotein cholesterol (HDL) was determined by an enzymatic CHOD-PAP method (Boehringer Mannheim GmbH, Germany) with a Olli C analyser (Kone Ltd, Espoo, Finland) after the precipitation of β-lipoproteins with dextran sulfate and magnesium chloride. After April 1 in 1998, serum total cholesterol and
triglycerides concentrations were determined using the same enzymatic method of another company (Konelab Corporation, Espoo, Finland), and the HDL-cholesterol concentration was determined using a direct method (Konelab Corporation, Espoo, Finland). The two different laboratory methods and analysers gave similar lipid results. The regression equations between old and new methods were as follows, total cholesterol: Optima = 0.97 * Olli C + 0.18 (R² = 0.982, n = 685), HDL-cholesterol: direct method = 1.00 * precipitation method + 0.05 (R² = 0.933, n = 681) and triglycerides: Optima = 1.01 * Olli C + 0.00 (R² = 0.997, n = 679). Serum LDL cholesterol was calculated according to the formula of Friedewald et al. (1972).

The 24-h urine collection was performed in free living conditions during the last one of the four days when the food record was kept. The urine was collected in plastic containers or in throw-away containers. The completeness of collection was asked from the subjects when they returned the containers to the study nurse. Urine collections, which had been collected at least for 20 h, but no longer than 28 h, and the amount of urine lost was ≤10% of total urine, were used in analyses. Urinary sodium and potassium concentrations were determined potentiometrically using the direct ISE method (Ion-Selective Electrodes).

4.4.3. Dietary measurements

A 4-day food record was used to collect data on food consumption both in the salt restriction study (I, II, III) and the primary health care intervention study (IV). In the salt restriction study, the subjects kept the food records three times, once during the normal-sodium diet at week 4, and twice during the salt restriction period at weeks 12 and 24 (Figure 2.). The food record days were three weekdays and one weekend day. The amount of foods consumed was assessed by using a portion size booklet (Haapa et al. 1985, Pietinen et al. 1988) and household measures. Subjects also wrote the recipes of homemade dishes and pastries in the food record. The nutritionist checked the food records for completion of the data.

In the primary health care intervention study, data on the food consumption were collected at baseline, and at 1 year and at 2 year examinations. The food record days were from Thursday to Sunday. The portion sizes were assessed by using standard drawn pictures and household measures. The study subjects were given both oral and written instructions to fill in a food record. Subjects were asked to write down the recipes of homemade dishes and pastries in the food record. The food records were returned to the study nurse who checked the completion of the data.

In both studies the analysis of nutrient intake was made using the Nutrica® software package (version 2.0, Social Insurance Institution, Helsinki, Finland 1993). The daily intakes of nutrients were calculated by the composition tables based mainly on Finnish analyses and data obtained from foreign data banks (Rastas et al. 1993).
In a salt restriction study the consumption of different food groups and sodium intake from different food groups were also estimated. The food groups included food items used as such and food items present in dishes and pastries, which were first broken down into their component food items using a recipe file. Salt used in food preparation was included in the group “other food items”, which contained also baker’s yeast and vinegar. The intake of sodium was computed from all food groups. The sodium intake from the group “other food items” was indicative of the sodium intake coming from the salt used in food preparation in households or in the food industry.

4.4.4. Statistical analyses

Data were analysed using SPSS for Windows statistical package version 6.0 (I-III) and version 8.0 (III, IV) (SPSS Inc., Chicago, IL, USA). The normality of the distribution of variables was checked with Kolmogorov-Smirnov test with (I) or without (III) Lilliefors significance correction or with Shapiro-Wilk test (II) before further analyses. In the original publication IV, the distribution of the values of variables of interest was considered to normal because of the large sample size. A p-value of < 0.05 was considered statistically significant. The results for continuous variables are given as mean±standard deviation(SD), despite the 24-h urinary sodium excretion values (Figure 4.), which are given as mean±standard error of mean (SEM).

In the original publication III the mean of both office BP and ABP levels within and between the groups were tested using analysis of variance for repeated measurements (MANOVA in SPSS version 6.0). The between group analyses of BP levels at the end of the study were analysed by analysis of covariance (ANCOVA) after adjustment for baseline values. The changes in BP and dietary variables within groups were analysed by paired t-test. Student’s t-test was used for group comparisons.

Changes in dietary intake, daily urinary sodium excretion and body weight during the salt restriction period were analysed with the Friedman two-way ANOVA test, which is a nonparametric repeated measures ANOVA (I, II). In addition, differences in BP, body weight and body mass index between the study weeks 4 and 12 were analysed by Wilcoxon matched-pairs signed -ranks test in the original publication I. The difference between genders in the proportion of subjects in the different 24-h urinary sodium excretion groups was tested using Chi-square independence test (I). In the original publication II Mann-Whitney U-test was used to analyse differences in nutrient changes between the dietary and urinary sodium change groups. Linear correlations between variables were analysed with Spearman correlation coefficient (I, II).

In the original publication IV, the difference between the intervention and the usual care group in the changes in baseline characteristics, clinical and dietary variables were analysed by Student’s t-test, as well as the differences in the baseline diet between those who completed and those whose dropped out of the study.
5. RESULTS

5.1 Baseline diet

At baseline, both in the salt restriction study (I, II, III) and in the primary health care intervention study (IV), the fat and SFA(E%) intakes of subjects exceeded the level that is recommended for hypertensive subjects (fat intake < 30 E%, SFA intake < 10 E%). The daily salt intake estimated by food record and by 24-h urinary sodium excretion was markedly greater than the recommended intake (NaCl intake < 5 g per day), but the average intakes of other minerals of interest: potassium, calcium and magnesium were at an adequate level. Alcohol intake did not exceed the recommended level (less than 21 portions per week for men or 14 portions per week for women). The nutrient intakes at baseline are presented in Table 2.(I), in Table.1.(II) and in Table 2.(IV).

5.2. Adherence to the salt restriction (I)

Salt intake and 24-h urinary sodium excretion

In the salt restriction study, the subjects had the goal to reduce salt intake, but to keep their food intake and body weight constant. The daily sodium intake estimated from food records decreased statistically significantly by 1878±1338 mg in men and by 1374±786 mg in women during the salt restriction period (20 weeks) (Table 2., I). The sodium intake at the end of salt restriction period corresponded to an average salt intake of 5.2 grams per day in men and 3.2 grams per day in women. The sodium density of the diet decreased significantly in both genders; from 1837±411 mg/1000 kcal at week 4 to 1063±342 mg/1000 kcal at week 24 in men and from 1723±453 mg/1000 kcal at week 4 to 811±169 mg/1000 kcal at week 24 in women.

In men, 24-h sodium excretion decreased by 88.1±71.5 mmol (p<0.001) and in women the decrease was 82.4±51.7 mmol (p<0.001) during week 20 (Figure 4.). The mean level of 24-h sodium excretion was 132.8±65.0 mmol in men and 79.7±25.5 mmol in women at the end of salt restriction period. The 24-h sodium excretion values correspond to an average sodium chloride intake of 9.0 g per day in men and 5.4 g per day in women, if the average urinary excretion of sodium is estimated to be 86 % of total sodium intake (Holbrook et al. 1984).
Figure 4. 24-h urinary sodium excretion in salt restriction study (I, II, II). Values are mean±standard error of mean. □ men (n=24), ◆ women (n=15).

Proportion of subjects who achieved the goals

Altogether 9 of 39 subjects (23%) achieved the urinary sodium excretion level of less than 74 mmol/24 h corresponding to a salt intake of 5 grams per day at the study weeks 12 and 24. Proportionally more women than men attained the targeted sodium excretion (Figure 5.).
5.3. Effect of salt-restricted diet on food consumption and the other nutrient intakes (II)

Food consumption

Salt restriction (20 wk) was accomplished with only minor changes in the consumption of different food groups (II, Table 3). The consumption of meat products and eggs decreased significantly during the salt restriction both in men and women. Consequently, sodium intake from meat products and eggs decreased significantly in both genders (p<0.001 for men, p=0.041 for women (II, Table 4.). The use of beverages, sugars and sweets decreased in men and the consumption of other food items, including mainly salt used in food preparation in the household or by the food industry, decreased significantly in both genders. In men, the sodium intake from cereals decreased significantly, and in women the sodium intake from vegetables and fruit decreased.

Nutrient intakes

The primary goal of the study was to keep nutrient intake unchanged except for the restriction of salt intake, and therefore only a few changes were found in the intakes of other nutrients during the salt restriction (II, Table 1). In men, the total energy intake was
reduced by 252±485 kcal per day. As well as alcohol, potassium and vitamin D intakes decreased, but there were no significant changes in potassium and vitamin D intakes per energy unit. The total dietary fiber intake in men changed significantly between weeks 4 and 24, but the fiber intake per energy unit increased marginally in men (11.2±3.6 g/1000 kcal at week 4, 12.7±3.4 g/1000 kcal at week 12, 12.7±3.7 g/1000 kcal at week 24, p=0.072). In women, the total potassium intake increased, but the potassium density in the diet remained unchanged. Both total selenium intake (p=0.031) and selenium density of diet decreased significantly in women (p=0.005, data only in text).

Nutrient intakes in relation to salt restriction

To study the relationships between the changes of dietary and urinary sodium with the changes in the intakes of other nutrients, the subjects were divided into two groups according to the median of dietary sodium change and 24-h urinary sodium excretion change. The changes of energy and protein intake during the first 8 weeks of salt restriction (from week 4 to 12) were significantly greater in the group with the greater decrease in dietary sodium (>1529 mg/d). In this group, energy intake decreased by 205±447 kcal/d, while in the other group, energy intake increased by 132±421 kcal/d. (Table 2., II). During the whole 20 wk salt restriction period (from wk 4 to 24), the changes in intakes of energy and macronutrients did not differ significantly between the groups with greater or smaller decrease in dietary sodium. The changes in dietary intakes were similar in the groups divided by the median of the change in 24-h urinary sodium excretion.

The relationship between the changes of energy and dietary sodium intake was evaluated also by linear correlations. The correlation coefficient between the changes in energy intake and in dietary sodium intake was r=0.489 during the first 8 wk of salt restriction and r=0.448 during the whole 20 wk restriction period (Figure 6.). The changes in the 24-h urinary sodium excretion did not correlate with the changes in the intake of energy or macronutrients.
Figure 6. Changes in sodium intake and in 24-h urinary sodium excretion versus the change in energy intake from 4 to 12 week (A and C) and from 4 to 24 week (B and D) in salt restriction study (II), analysed by Spearman correlation coefficients. A: r=0.489, p=0.002; B: r=0.448, p=0.004; C: r=-0.098, p=0.555, D: r=0.333, p=0.039.

5.4. Effect of salt-restricted diet on blood pressure, body weight and serum lipids (I-III)

Blood pressure

The changes in office and ambulatory BP in placebo and cilazapril group during the salt restriction (20 wk) are presented in original publication III in Tables 4., 5. and 6. During the placebo run-in phase with normal sodium intake, no significant changes were found in the office or ambulatory BP. In the whole group (n=39) salt restriction alone (8 weeks) resulted in a decrease in SBP [-7.1 (95% CI -11.2; -3.0, p=0.001) mmHg] and in DBP [-4.2 (95% CI -6.6; -1.8, p=0.001) mmHg], whereas 24-h ABP did not change significantly during that period. During the next 12 weeks with salt restriction alone, the office and ambulatory SBP/DBP decreased further in the cilazapril group (n=19), but in placebo (n=20) group, the BP values remained at the level achieved at 12 study weeks.
Body weight

There was a small decrease in the body weight of both genders, but the change was not statistically significant. After the 4 wk run-in period in women the body weight was 78.1±9.1 kg at week 4, 77.2±8.6 kg at week 12 and 77.0±8.4 kg at week 24. Corresponding body weight values in men were 88.3±12.0 kg (wk 4), 87.4±11.0 kg (wk 12) and 87.1±11.2 kg (wk 24).

Serum lipids

Serum lipids and lipoproteins were similar in placebo and in the cilazapril groups at the beginning of the study (III, Table 7.). There was a marginal, temporary decline in HDL cholesterol in the cilazapril group during the placebo salt-restriction phase at 12 weeks, but no other changes in serum lipids were found in either group. Serum total cholesterol and LDL cholesterol declined slightly in the placebo group, but at the end of the study, no significant differences were observed in any of the lipid variables between the groups.

5.5. Follow-up rate and baseline clinical and dietary variables among completers vs dropouts (IV)

Total of 715 subjects started the primary health care intervention study and 591 (83 %) of those participated in one year and 512 (72 %) of those participated in two year study examinations. In the intervention group, the participation rates were higher than in the usual care group; at one year 88% vs 78 % (p< 0.0005) and at two years 77 % vs 66 % (p=0.002). Altogether 714 of 715 subjects filled in the food record at baseline. Three subjects from the participants at one year and four at the two year follow-up did not fill in the food record.

At baseline, the BMI of subjects who completed the study was similar to the BMI of dropouts both in intervention and in the usual care group. In the intervention group, the completers were older than the dropouts (55.9±9.7 yrs vs 49.9±10.1 yrs, p<0.0005). The baseline diet of completers was closer to the recommendations, which was particularly seen in the intervention group (IV, Table 6.). In the intervention group, the fat intake, the sodium intake per 1000 kcal and sodium to potassium ratio of completers was lower than that of the dropouts. Furthermore, the carbohydrate intake (E%) was greater and the alcohol intake as grams (7.9±14.7 g vs 12.9±21.2 g, p=0.045, data only in text) and as percentage of total energy intake was lower in completers than in dropouts. In the usual care group, the baseline diet of completers was also somewhat better than that of the dropouts; the carbohydrate (E%) and fiber intakes per 1000 kcal were greater, and the sodium to potassium ratio was lower in completers.
5.6 Effect of intensified diet counseling on the diet (IV)

The net changes i.e. the differences in the changes of nutrient intakes between the intervention and usual care groups were calculated in order to estimate the effect of intensified diet counselling on the diet of hypertensive subjects (Figure 7.). The net changes in nutrient intakes from 0 to 1 yr and from 0 to 2 yr are also shown in Table 4., IV.

The proportion of fat from total energy intake decreased and the fatty acid composition of diet improved more in the intervention group. Consequently, the proportion of carbohydrates from total energy intake increased more in the intervention group than in the control group. During the two study years, the total fat intake in grams decreased more in the intervention group (-11.5±24.8 g) than in usual care group (-3.4±21.7, p=0.006, data only in text). The reductions in SFA intake were -6.0 ±0.3 vs -1.6±3.3 g (p<0.0005, data only in text), respectively.

The net decrease in sodium intake corresponding to an average of 0.5 g sodium chloride and in sodium to potassium ratio of diet were significant (Figure 7., Table 4., IV). The decrease in sodium to potassium ratio was mainly due to reduction in sodium intake, because the potassium intake was also reduced in both study groups. However, the increase in the potassium intake per 1000 kcal was greater in the intervention group than in usual care group. The net changes in 24-h urinary sodium and potassium excretion were not significant either after the first or second year (Table 5., IV).
Figure 7. The changes in nutrient intakes and net changes (change in the intervention minus change in the usual care group) from 0 to 2 years in the primary health care intervention study (IV). P-values for differences between the intervention and the usual care group analysed by Student’s t-test, *p<0.0005, **p=0.008, ***p=0.021.

5.7. Changes in body weight, serum lipids and blood pressure during the intensified diet counselling (IV)

Body weight decreased more in the intervention group both during the first and second year. At the end of the study, the weight reduction was -1.8±3.7 kg in the intervention and -0.4±3.4 kg in the usual care group, so that the net difference between study groups was -1.4 kg (95%CI:-2.0,-0.8) (Table 8.). The net decrease in serum cholesterol and in LDL cholesterol was significantly greater in intervention group than in usual care group only at the two year examination.
### Table 8. Net differences in body weight, TC (total cholesterol) and LDL cholesterol (LDL-C) between the intervention and usual care group from 0 to 1 y and from 0 to 2 y (IV).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Net change (95%CI) from 0 to 1 y</th>
<th>P-value&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Net change (95%CI) from 0 to 2 y</th>
<th>P-value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, kg</td>
<td>-1.5(-2.1,-1.0)</td>
<td>&lt;0.0005</td>
<td>-1.4(-2.0,-0.8)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>TC, mmol/l</td>
<td>-0.02(-0.13,0.09)</td>
<td>0.696</td>
<td>-0.14(-0.27,-0.01)</td>
<td>0.039</td>
</tr>
<tr>
<td>LDL-C, mmol/l</td>
<td>-0.06(-0.15,0.04)</td>
<td>0.241</td>
<td>-0.19(-0.31,-0.07)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

<sup>a</sup> P-value for difference between the changes in the intervention and in the usual care group analysed by Student’s t-test. Sample sizes in intervention (i) and in the usual care group (u): <i>n</i>: 318, <u>: 273, 
<i>: n=27, <u>: n=233, <i>: n=312, <u>: n=269, 
<i>: n=270, <u>: n=228.

When the net changes in the whole study group in SBP and DBP were analysed from 0 to 1 yr (<i>n</i>=318 in intervention group, <u>: n=273 in usual care group) and from 0 to 2 y (<i>: n=279, <u>: n=233 in the intervention group, <i>: n=233 in the usual care group) only the net change from 0 to 2 y in DBP was significant (<i>-1.4 mmHg (95% CI: -2.7, -0.2</i>.

When those study subjects not receiving antihypertensive medication were examined separately, the change in both SBP and DBP were significantly greater in the intervention group compared to the usual care group both from 0 to 1 y and from 0 to 2 y (Table 9.).

### Table 9. Net differences in systolic (SBP) and diastolic blood pressure (DBP) in subjects without antihypertensive medication between the intervention and usual care group from 0 to 1 y and from 0 to 2 y (IV).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Net change (95%CI) from 0 to 1 y&lt;sup&gt;a&lt;/sup&gt;</th>
<th>P-value&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Net change (95%CI) from 0 to 2 y&lt;sup&gt;b&lt;/sup&gt;</th>
<th>P-value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, mmHg</td>
<td>-3.3(-6.3,-0.3)</td>
<td>0.032</td>
<td>-5.0(-8.6,-1.5)</td>
<td>0.006</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>-3.4(-5.2,-1.6)</td>
<td>&lt;0.0005</td>
<td>-2.9(-5.0,-0.7)</td>
<td>0.011</td>
</tr>
</tbody>
</table>

<sup>a</sup> P-value for difference between the changes in the intervention and in the usual care group analysed by Student’s t-test. Sample sizes in intervention and in usual care group. <i>n</i>=134, <u>: n=105, 
<i>: n= 100, <u>: n=80.
6. DISCUSSION

6.1 Methodological considerations

6.1.1. Study design and subjects

The salt restriction study (I, II, III)

The primary aim of the salt restriction study was to examine the effects of salt restriction alone or in combination with cilazapril in the treatment of mildly elevated BP. Regarding the drug treatment, it was a randomised placebo controlled trial, but with respect to the diet treatment it can be categorized as a clinical trial. The presence of a control group with “normal” salt intake would have made it possible to draw firmer conclusions about the effects of salt restriction alone on BP. However, the lack of control group is less crucial for the conclusions drawn in studies I and II.

Most subjects were middle-aged and according to the WHO-ISH criteria (1999) they had mildly to moderately elevated BP, and they had no other drug treatment for hypertension. From the 45 subjects included into the actual study phase after the run-in period, a total of thirty nine subjects (24 men, 15 women) completed the study. Three subjects of the total six drop outs withdrew because they found the salt restriction too troublesome, thus the results of salt restriction cannot be generalized to the hypertensive population, since it can be assumed that the subjects who completed the study were more willing to change their salt intake than hypertensive subjects in general. Furthermore, the compliance was improved by providing low-salt bread free of charge for the study subjects.

Primary health care intervention study (IV)

The effect of diet counselling on the diet of hypertensive subjects was studied in a randomised controlled trial carried out in a primary health care setting. Altogether 715 subjects, aged 25-74 years with mild hypertension (WHO-ISH 1999), and with or without antihypertensive drug treatment were included into the study. Altogether 53 % of the recruited subjects were using antihypertensive drugs. The study population can be considered to represent quite well ordinary Finnish hypertensive patients, since the subjects came from primary health care centers in the Province of North Karelia and from the primary health care center of the city of Kuopio. However, the subjects came from an area with a long history of cardiovascular prevention (the North Karelia project) and they had received more health education than generally is available to the Finnish population. The subjects who participated in this study, especially those recruited by newspaper announcements, may have been even more health conscious and motivated than the average hypertensive population. For instance, it has been shown among Swedish middle-
aged men, that perceived health treathe and belief in treatment efficacy predicted participation in a lifestyle intervention (Näsland et al. 1994).

6.1.2 Food record

The food record method has some advantages; it measures actual food intakes, and it does not rely on memory. Because it is open-ended, it can accommodate any level of food description in detail (Buzzard 1998). However, there are also many sources of error in using the food record to measure food intake. Buzzard has listed the sources of errors as follows: 1) memory biases due to the delay in writing down the foods eaten, 2) underreporting, because the measurement affects on the food intake, 3) lack of food description in detail, 4) quantification of portion sizes, and 5) lack of motivation of subjects.

In both studies, the subjects were advised to write down the foods eaten immediately after the meal to avoid the memory biases due to the delay in writing down. The underreporting or overreporting is one of well-known weaknesses of food record (Arab et al. 1988, Hirvonen et al. 1997). The subjects may underreport the use of unfavourable foods, while the recommended foods may be reported more than they are actually used. This has been noted to lead to overestimation of the intervention effect on nutrient intakes, since it has been shown that an intervention group in particular overreports the use of recommended foods in an intervention (Buzzard 1998). The differences in nutrient intake changes between the intervention and usual care groups could thus be overestimated in the primary health care intervention study.

The lack of food description in detail as source of error was tried to be managed in both studies in two ways. First, the subjects received written instructions to fill in a food record every time. In the salt restriction study, the subjects were given oral instructions at every recording time and in the primary health care intervention study at the beginning of the study. Secondly, the food records were checked when they were returned. In the salt restriction study (I-III), the clinical nutritionist checked the food records for completion of the data, and in the primary health care intervention study (IV) the food records were returned to the trained study nurse who checked the completion of the data.

In the salt restriction study, the amount of foods consumed was assessed by using a portion size booklet (Haapa et al. 1985, Pietinen et al. 1988) and household measures. The use of photographs for quantification of portion sizes has been found to be favorably compared with weighed food record (Buzzard 1998). The foods were described by three different portion sizes, which makes the quantification even more exact. In the primary health care intervention study, the portion sizes were assessed by using standard drawn pictures and household measures.

It has been suggested that the motivation of subjects is affected by the perceived importance and applicability of the study results (Buzzard 1998). The study personnel
should explain in detail the purpose and importance of the study to motivate the participants to provide accurate information. In the primary health care intervention study, the subjects had information about the study before they started it. In the salt restriction study, the purpose of the study and the essential role of study subjects were told to participants in individual sessions at the beginning of the study. Furthermore, receiving low-salt bread free of charge, can be considered as a motivating factor in that study.

The number of days in the food record in both studies could be assumed to be enough for estimating energy and macronutrients, but for the measurement of micronutrients: vitamins and minerals more recording days would have been needed. It has been averaged that 3 to 10 days are needed to obtain a good estimate of usual individual intake of energy and macronutrients. In general, the number of recording days required depends on the day to day variability of the nutrients of interest and on the precision desired (Buzzard 1998).

In the salt restriction study, the 4-d food record included one weekend day and in the primary health care intervention the food intake was recorded from Thursday to Sunday. The difference between the days of a week is well-known. Recently Jula et al. (1999) showed that the food intake is larger at weekends than during weekdays. The appropriate balance of the days of the week is likely to be of great importance, if the purpose is to estimate changes in absolute nutrient intakes as was the case in this study. If the aim of the study is to determine the effectiveness of intervention as in primary health care intervention study, the same combination of the days before and after intervention is more important than the balance of days (Buzzard 1998).

Food composition data for foods represent an average from a variety of samples, none of which being the food actually consumed (Arab et al. 1988). Especially, the variety of sodium sources makes it difficult to assess sodium intake accurately by food record. Dietary sodium is naturally present in foods, but in western societies sodium comes mainly from salt added to foods during manufacturing and in caterings. It has been estimated that salt from manufactured foods and in catering purchased food provide on average 85 % of the salt added to foods, and only 15 % of total salt comes from discretionary salt i.e. salt used in cooking at home or on the table (Sanchez-Castillo et al. 1987). In Finland, the salt content of the processed foods is well reported in food labels, but the salt content of foods varies especially in home-made foods, and thus we asked the patients to write down the recipes of foods their have eaten including the salt used.

6.1.3 24-h urinary sodium excretion

The 24-h urinary sodium was used as a biochemical marker of sodium intake in both studies. Holbrook et al. (1984) noticed that average absorption of sodium from foods was 98 %, and an average urinary excretion was 86 %. The amount of sodium excreted into urine varies greatly from day to day, and this may lead to an error in quantitative estimate
of salt intake (Siani et al. 1989). Liu et al. (1979) showed that the within person standard deviation of 24-h sodium excretion was 58 mmol/24 h. The 24-h urine sodium excretion is a good method to study short-term sodium intake (Hunter 1998), but at least three 24-h collections are needed to measure reliably the long-term salt intake (Liu et al. 1979).

24-h urine collection is rather troublesome to study subjects, thus being vulnerable to errors. The subjects received both oral and written instructions on how to collect the 24-h urine. In the salt restriction study, the completeness of the collection was ascertained by a nutritionist when the subjects returned the containers. If the 24-h urine collection was incomplete, the subject was asked to collect a new 24-h urine. In addition, the completeness of urine collections was confirmed on the basis of the 24-h creatinine excretion. In the salt restriction study, the creatinine excretion was related to sodium excretion, but the other way to study the completeness could have been the use of reference values for 24-h creatinine excretion as an indicator. In the primary health care intervention study, a trained study nurse checked the 24-h urine collections and the amount of urine collected was written down and the urine lost was estimated.

In the salt restriction study, the great difference between the salt intake measured by 24-h urinary sodium excretion (9.0 g in men and 5.4 g in women) and by 4-d food record (5.2 g in men and 3.2 g in women) at the end of the study may be partly explained by the fact that these estimates are from different time periods. The dietary sodium intake was the average sodium intake for 4 days, while the 24-h urinary sodium excretion was determined by a recent 24-h salt intake. The correlation coefficients between the sodium intake measured by food record and by 24-h urinary sodium excretion were weak when compared to the high correlation (r=0.61) observed by Caggiula et al. (1985), who examined the correlation between 6-d food record and a single 24-h urine measurement among 50 adults.

6.1.4 Blood pressure measurement

BP varies all the time to assure a suitable blood supply to the organs. Due to this large physiological variation, the BP measurement should be performed in a standardized way to obtain reliable BP values. In both studies, the subjects were given written instructions to avoid tobacco smoking, coffee drinking, eating and exercise just before the BP measurement. In the salt restriction study, BP was measured by the study nurse after 10-15 minutes rest and in the primary health care intervention study after five minutes of rest. All the BP measurements were done in a separate room, where only the nurse and study subjects were present.

The BP of most people decrease when they become accustomed to the BP measurement, so it was good that in salt restriction study the actual study BP measurements began after the 4-wk run-in period. In the primary health care intervention study, only the subjects with antihypertensive drug treatment had become accustomed to
BP measurement in the screening visits. In the salt restriction study, also the 24-h ABP was measured. Ambulatory measurement provides a more representative description of the BP, since there is no pressor response to clinic measurement (Swales 1995). In addition, the ABP measurement also covers the diurnal variation of BP.

6.2. Adherence to the salt restriction

In the salt restriction study, the daily salt intake decreased by 4.8 grams in men and by 3.5 grams in women as estimated by 4-d food record (1). According to the 24-h urinary sodium excretion, the decrease in daily salt intake was 5.1 grams in men and 4.8 grams in women.

The salt reduction achieved in the present study is comparable with the salt reduction reported in other studies where salt restriction has been the only dietary goal (Grobbee and Hofman 1986, Cutler et al. 1991, Kumanyika et al. 1993, Graudal et al. 1998, Midgley et al. 1996, Cutler et al. 1997). However, the heterogeneity in the duration of trials and in the dietary advice given make it difficult to compare the results of these different trials. All studies have not been able to demonstrate that dietary instructions about salt restriction in hypertensive subjects actually resulted in a reduction of salt intake (Alli et al. 1992). The study by Alli et al. (1992) differed from most of the other studies in that the dietary advice was given by general practitioners and not by nurses or nutritionists.

At the end of the 20 wk salt restriction period, only 9 of 39 subjects (23 %) had the 24-h urinary sodium excretion corresponding to a salt intake of less than 5 grams per day. In most of the studies, only the amount of sodium reduction has been reported, not the attainment of the recommendation for salt intake. In a randomised clinical trial by Kumanyika et al. (1993), 39 % of free living subjects with high-normal BP achieved a urinary sodium excretion level of less than 74 mmol/24 h corresponding to a salt intake of 5 grams or less per day.

In the present study, more women than men achieved the goal of salt intake (< 5 grams per day). Our results demonstrate that recommended salt restriction of 5 grams per day is more difficult to achieve in men who need more energy and consequently consume more food than women. Use of processed foods containing a substantial amount of salt also makes it hard to achieve a low-salt diet in practice. To achieve a salt intake goal of less <5 grams per day in the western diet, the average salt intake should be diminished on average by half. In the present study, the acceptance of salt restriction was strengthened by the supply of low-salt bread.

The preference for the taste of salt among western people should have to change markedly to make the reduction of salt intake possible in the long-term. In food preparation the taste preference seems to be an important predictor of added salt, and health aspects did not play a major role (van der Veen et al. 1999). However, Witschi et
al. (1985) found in young people that the sodium content of a variety of food products can be decreased by an average of 50% without the foods losing their appeal.

Single short counselling sessions with advice on salt restriction have not been successful in producing dietary changes (Elmer et al. 1991), and thus more comprehensive nutrition and behavior oriented programs that provide follow-up contacts are needed to achieve a significant sodium reduction in clinical settings. In the salt restriction study, the acceptance of salt restriction was strengthened by regular follow-up contacts. Also the motivation of the patients plays a role, and it can be considered that in the present study, the subjects who completed the study were highly motivated. Nevertheless, the results show that salt restriction is feasible in free living conditions, but because of the small sample size and the experimental study design, the results should be cautiously generalized to hypertensives treated in clinical practice.

6.3 Effects of salt-restricted diet on the intake of other nutrients

Only minor changes were found in the intake of other nutrients in the salt restriction study (II) confirming earlier findings that salt restriction do not lead to harmful changes in nutrient intakes, when there has been a goal to maintain energy intake and to keep body weight constant (Nowson and Morgan 1988, McCarron et al. 1997). However, in most trials it has been difficult to determine the potential effects of salt restriction on the intakes of other nutrients. These difficulties are due to the combination of sodium restriction with other dietary interventions, poor compliance with sodium restriction, lack of analysis of changes in patterns of food intake, or interventions which have been too short to attain new stable dietary patterns (Morris 1997).

The only significant reductions in addition to the sodium intake, were seen in potassium and vitamin D intakes in men and in selenium intake in women. In men, the daily potassium intake (3807 mg) was still at the level recommended for hypertensives by The Sixth Report of the Joint National Committee 1997 (JNC VI 1997). In general, when the nutrient intakes were adjusted for energy intake, only the selenium density of diet decreased significantly in women. The fiber intake adjusted for energy intake was even slightly increased in both genders, although the change was not significant.

Decreased consumption of meat products and eggs were the most marked changes occurring in food consumption during the salt restriction. In Finland meat products are one of the main sources of sodium. Thus the subjects reduced their consumption of this food group, and they did not eat the same amount of processed low-salt meat products. However, reducing the overall consumption of meat products may have beneficial effects on the overall quality of the diet, for instance by decreasing the saturated fat intake and energy intake.

In the present salt restriction study, the sodium density of the diet also decreased, indicating that the patients had eaten foods with a lower sodium content. This shows clearly
that in this study the subjects did not reduce sodium intake simply by reducing their energy intake. However, in our study there was also some evidence that an attempt to reduce salt intake decreased the total consumption of foods and so affected the energy intake. The significant correlation between the change in energy intake and the change in dietary sodium provides evidence that salt restriction had influenced the energy intake and vice versa. It should be pointed out that in clinical practice, where most of the hypertensive subjects are overweight, the patients are advised to reduce energy intake and thus to lose weight. The decrease in energy intake simultaneously reduces also sodium intake.

6.4 Effects of diet counselling on the diet

The 2-year dietary intervention in primary health care induced beneficial changes in the diet of hypertensive subjects. The total fat intake reduced, and the quality of dietary fat improved more in the intervention group than in control group. Furthermore, the decrease in sodium intake and sodium to potassium ratio of the diet was significantly greater in the intervention compared to usual care group. Finally, the decrease in body weight was 1.4 kg greater in the intervention group.

Weight reduction and dietary changes have been greater in some previous large scale non-pharmacological intervention studies, where the interventions have been more intensive (Stamler et al. 1989, Hypertension Prevention Trial Research Group 1990, The Trials of Hypertension Prevention Collaborative Research Group 1992, 1997). These studies have been usually carried out in academic research centers with well motivated individuals to test the effect of a single life-style regimen or the combinations of two regimens, e.g. weight reduction and sodium reduction on BP. Recently, the Finnish Diabetes Prevention Study showed that it is possible to obtain a greater weight loss and more significant improvements in cardiovascular risk factors including BP, when the diet counselling is more intensive (Tuomilehto et al. 2001b) than that in the present study.

The dietary results in present study are comparable to many other lifestyle interventions carried out in primary health care (Table 5., p. 44-45), although the variability of life style interventions makes it difficult to compare the dietary changes achieved in different studies. In addition, the actual effect of the lifestyle intervention on the diet has not been quantitatively well documented in all studies, mostly the diet changes were assessed by dietary questionnaires only covering selected topics of diet. In primary health care intervention study the diet changes achieved by diet counselling was estimated in detail.

At the baseline the diet of hypertensive subjects was similar to the diet of Finnish adults (The 1997 Dietary Survey of Finnish adults) or hypertensive subjects in other recent Finnish studies (Jula et al. 1997, Silaste et al. 2000). However, diet changes achieved in the present study by intensified diet counselling cannot be generalized; the study was based on voluntary participation, and it could be assumed that most of the patients were well motivated. Patients who are willing to participate in studies are usually more health
conscious and cooperative than other patients. This could have been seen also from the baseline diet: the diet of completed subjects were better than the diet of the drop outs (IV).

On the other hand, the diet changes achieved in the present study could be feasible also in usual clinical practice in Finland, since the study was carried out in primary health care centers. Primary health care nurses provided the intensified diet counselling as a part of their normal work, but the time for counselling may have been quite short. The fact that the same primary health care nurses advised also subjects of the control group may have diluted the difference between the groups.

6.5 Effects of diet changes on blood pressure

Salt intake

In the salt restriction study, the 4.8 g decrease in salt intake measured by 24-h urinary sodium resulted in the -7.1/-4.2 mmHg decrease in SBP/DBP during the 8 wk salt restriction (from wk 4 to 12). This result is in line with those from many well-controlled studies showing sodium-restriction as an effective means to lower elevated BP in different study populations (Cutler et al. 1991, Midgley et al. 1996, Cutler et al. 1997, Graudal et al. 1998). BP reduction is also comparable to reductions estimated in the different hypertension treatment recommendations. In the British Hypertension Society Guidelines (Ramsay et al. 1999), the reduction of daily sodium chloride intake from 10 to 5 grams is estimated to produce a reduction of 5/3 mmHg in SBP/DBP. According to the WHO guidelines (WHO-ISH 1999) reducing sodium intake by 80-100 mmol (4.7-5.8 g sodium chloride) per day from an initial intake of around 180 mmol per day will reduce SBP by an average of 4-6 mmHg. Correspondingly, in the AHA Dietary Guidelines (Krauss et al. 2000) the 80 mmol reduction in sodium is assumed to lead to a 4/2 mmHg reduction in SBP and DBP.

The reduction in BP achieved by decreased salt intake (III) is highly comparable to the effect of a single antihypertensive drug. Cappuccio et al. (1997) also observed that the effect of salt restriction in older hypertensives was similar to that which could be attained with the use of thiazide diuretics.

The 8 week salt restriction period was not blinded, but it should be noted that before the salt restriction there was a 4 wk normal-sodium run-in period with placebo, during which the subjects became accustomed to the BP measurement.

The other dietary variables, which could have had an impact on BP were monitored carefully. In the placebo group, the intake of total fat and saturated and monounsaturated fatty acids slightly decreased, but this did not explain the BP reduction, and the cilazapril group showed comparable changes in BP during the salt restriction phase although the diet of this group remained unchanged. The 24-h potassium excretion did not change during the study. There was a trend towards a reduction in the reported alcohol intake during the study, but this did not account for
the lowered BP values either. Thus, there is good indication to believe that sodium restriction alone was responsible for the reduction of BP observed.

**In the primary health care intervention study**, the net decrease of 0.5 g of sodium chloride and decrease in the sodium to potassium ratio may also has affected the BP. However, the effect of salt restriction is difficult to estimate, because of weight loss and other dietary changes. At the population level, this minor change in salt intake when combined with other diet changes, could decrease BP. Kotchen et al. (1998) also concluded in AHA’s Statement of Dietary Electrolytes and BP for Healthcare Professionals that the beneficial effect of diet on BP can be maximized by avoiding high intake of NaCl and ensuring adequate intake of fruits, vegetables, and fat free and low-fat dairy products.

Recently there has been much debate of the relationship between salt intake and BP (Taubes 1998, Swales 1999, Kaplan 2000b). It has been suggested that the link between sodium and BP remains controversial because of the inconsistency between the strong positive epidemiological evidence and only modest positive evidence from experimental human studies (Chrysant et al. 1999). The heterogenous BP responses to the changes in dietary salt intake in experimental studies could be due to the low compliance rate or due to the differences in salt sensitivity. Variation in the degree of adherence is frequently observed in nutrition counselling intervention trials (Obarzanek and Moore 1999). The difference in responses to salt intake may be a problem when one wishes to evaluate the effect of salt restriction among normotensives, since only one in four is considered to be salt sensitive (Weinberger 1996).

*Body weight and other dietary factors*

**In the primary health care intervention study**, in a subgroup of subjects without antihypertensive medication the decrease in SBP/DBP was significantly greater (-5.0/-2.9 mmHg) in the intervention group compared to that of the usual care group. The BP reduction achieved is similar or even better than in the large hypertension treatment trials, where there has also been the intention to change many lifestyle factors (Table 2., p. 22-23). Only few of the previous dietary interventions on hypertensives carried out in primary health care have reported significant decrease in BP (Table 5., p. 44-45).

The observed BP change in the present primary health care intervention study has to be considered as a conservative estimate of the true effect because of a number of reasons. The study may have underestimated the effect of intensified diet counselling. The same nurses treated hypertensives both in the intervention and the usual care group, thus the training of primary care nurses may have influenced also the care of the usual care group. The frequency of BP measurements in the intervention and usual care groups were similar during the first and second study year. In addition, the less motivated subjects and those with worse baseline diet dropped out of the study, especially in the usual care group, and that could have been lead to overestimation of effect of diet counselling.
Weight loss has been shown to be an effective measure to lower elevated BP (Hypertension Prevention Trial Research Group 1990, The Trials of Hypertension Prevention Collaborative Research Group 1997, Whelton et al. 1998). In the present study, the weight reduction was apparently an important contributor to the decrease of BP. However, the effects of weight loss and changes in other lifestyle factors could be estimated in more detail in further subgroup analysis.

The improvement in the quality of fat in the diet may have contributed to reduction of BP. Morris (1994) and Pietinen (1994) concluded that the individual fatty acids do not affect BP, but Vartiainen et al. (2000) suggested that BP decrease in Finland during the last thirty years could be partly due to the reduction in intakes of salt and SFAs, and an increase in intake PUFAs. The increase in the use of hypertension drug treatment has also proposed to account for the BP decrease in Finland, but the shift of the entire BP distribution argues against this proposal. Surprisingly, both the alcohol intake and the incidence of obesity, which both are strongly associated with BP, have increased at the same time (Vartiainen et al. 2000).

The effect of a single nutrient on BP cannot be surely determined, if we keep in mind the multifactorial origin of BP. In addition, an individual’s response in BP to nutrients will vary depending on age, race, genes, drugs, intake of other nutrients, and the duration of exposure. The ability of diet to lower BP may result from the additive contributions of multiple components (Resnick et al. 2000). Beilin (1988) has calculated that beneficial changes in diet, alcohol intake and physical activity could produce a fall of 10-20 mmHg in the mean SBP of population, which would result in an 80-90 % reduction in the prevalence of hypertension (SBP/DBP <140/90 mmHg). The aim of the present primary health care intervention study to change multiple factors in the diet was in line with a recent finding in the DASH trial (Dietary Approaches to Stop Hypertension trial), which revealed the efficacy of an overall healthy dietary pattern in decreasing BP (Appel et al. 1997). Diet changes, which decrease BP, also affect other cardiovascular risk factors: elevated blood cholesterol and increased blood coagulation. For instance, Obarzadek et al. (2001) calculated that 10-y risk of CHD decreased by 12.1 % in those who consumed the DASH diet.

In present primary health care intervention study, the BP decrease (-5.0/-2.9 mmHg) achieved in subjects not being treated with antihypertensive medication were clinically meaningful. A reduction of 5-6 mmHg in DBP induced by drugs has been estimated to reduce CHD events by 20-25 % and stroke events by 35-40 % (Collins et al. 1990). A decrease in DBP induced by non-pharmacological means was supposed by Collins et al. (1990) to lead similar declines in incidence of CHD and stroke.
7. SUMMARY AND CONCLUSIONS

This doctoral thesis consists of two different studies. The first study examined the adherence to the salt restriction and the effect of salt restriction on the BP and on the nutrient intakes in 39 free living subjects with mildly elevated BP. In the second study, the long-term effects of intensified diet counselling on the diet and cardiovascular factors of hypertensive subjects were investigated in a primary health care setting among 715 hypertensive subjects.

The result can be summarized as follows:

1. In the salt restriction study, the daily sodium chloride intake evaluated by 24-h urinary sodium excretion decreased by an average 5.0 g and when evaluated by food record by 4.1 g.
2. During the salt restriction diet, there were only minor changes in the intakes of other nutrients.
3. Salt restriction alone (8 wk) decreased SBP/DBP significantly (-7.1/-4.2 mmHg).
4. In the primary health care intervention study, intensified diet counselling improved the diet and decreased BP of hypertensive subjects. The proportion of fat from total energy intake and sodium intake reduced significantly, and the fatty acids composition of the diet improved, as well as body weight and serum lipid levels decreased significantly. In particular, in those subjects without antihypertensive medication, there occurred a significant reduction on SBP/DBP levels.

In conclusion, free living hypertensive subjects can reduce salt intake in a clinical trial with intensive counselling. The salt restriction does not cause any nutritional imbalance, if the salt reduction is made by eating foods which contain less salt instead of eliminating foods from diet. The salt restriction seems to be effective in reducing mildly elevated BP. The intensified diet counselling in primary health care can result in dietary changes interpreted as being of benefit in the long-term treatment of hypertension and prevention of atherosclerotic vascular diseases.
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