# 47

# *Nutritional Treatment of Blood Pressure: Nonpharmacologic Therapy*

**L. Michael Prisant**

Blood pressure is a continuous variable, like temperature and heart rate.[1] The level of blood pressure gradually increases from birth to age 18 years. The dividing line between a normal and an abnormal blood pressure is arbitrary. However, there is a continuous relationship between the level of blood pressure and various cardiovascular events, including myocardial infarction, strokes, congestive heart failure, renal failure, and mortality. An optimal blood pressure is a systolic blood pressure less than 120 mmHg and diastolic blood pressure less than 80 mmHg. Hypertension is defined by the average of multiple measurements with either a systolic blood pressure ≥140 mmHg or a diastolic blood pressure ≥90 mmHg.

The hallmark of hypertension is an elevated systemic vascular resistance. Hypertension may be caused by various adrenal tumors producing cortisol, aldosterone, and norepinephrine, hyperthyroidism, hypothyroidism, hyperparathyroidism with increased parathormone and calcium, acromegaly with increased growth hormone, renal failure, renal artery stenosis resulting in renal ischemia and increased renin, and various drugs that cause salt and water retention, increase renin, or activate the sympathetic nervous system. The majority of patients with arterial hypertension do not have a known cause.

Why the prevalence of essential hypertension increases with aging and what causes it remain an enigma. It is likely that what is called essential hypertension may be the result of diverse causes. Multiple factors alter the level of blood pressure. The sympathetic nervous system is important for modifying the tone of blood vessels. Circulating renin, angiotensin, aldosterone, norepinephrine, and endothelin are vasoconstrictors. The kidney is necessary to regulate sodium excretion and volume. Endothelial damage due to abnormal lipids, glucose intolerance, tobacco use, hyperhomocystinemia, hyperinsulinemia, and circulating vasoconstrictors is less responsive to local endogenous vasodilators such as nitric oxide. Essential hypertension is not a homogenous disease state; it is likely a polygenic trait.

Hypertension affects 24% of the U.S. adult population. Since essential hypertension accounts for 90 to 95% of all causes and the prevalence increases with each decade of life, there is an interest in the role of nutrients and foods for both the etiology and treatment of hypertension. A primary preventive approach is advocated by some epidemiologists and researchers.

## Nutrients and Blood Pressure

### Sodium

A large body of data relates salt intake to the level of blood pressure. In a study of chimpanzees that normally eat a fruit and vegetable diet (low sodium and high potassium intake), half had salt (up to 15 g/d) added gradually to their diet over 20 months.[2] Sodium chloride resulted in a blood pressure increase of 33/10 mmHg, which could be reversed within six months of removing sodium chloride from the diet. Similar studies have convinced the medical community that salt may be responsible for the higher prevalence of hypertension in modern society compared to more primitive communities. However, sodium may not be the sole culprit. Studies suggest that the chloride anion with sodium is necessary for an increase in blood pressure, since giving sodium with other anions does not increase blood pressure.[3,4]

The INTERSALT (International Study of Salt and Blood Pressure) Cooperative group examined 10,079 men and women aged 20 to 59 by urine sodium excretion and blood pressure at 52 centers throughout the world.[5] The average intake of sodium was 100 to 200 mmol (6 to 12g NaCl or 2.5 to 5g sodium). The relationship of sodium excretion and systolic blood pressure correlated positively in 33 of 52 centers after correcting for age, gender, body mass index (BMI), alcohol consumption, and urine potassium excretion, but was significant in only eight centers. Negative correlations were observed in 19 centers. For the entire cohort, the adjusted effect of sodium for systolic blood pressure was 2.17 mmHg per 100 mmol 24 hour sodium excretion ($p<0.001$). There was not a significant adjusted effect for diastolic blood pressure. Among the centers with a low BMI (21.8 kg/m$^2$) and a low sodium intake (26.7 mmol), the mean prevalence of hypertension was 1.7%. For the sites with a low BMI (22.2 kg/m$^2$) but with a high sodium intake (187.7 mmol), the prevalence of hypertension was 11.9%.[6] Alternatively, the Scottish Heart Health Study of 7354 men and women aged 40 to 59 years reported a weak positive correlation of urinary sodium excretion and either systolic or diastolic blood pressure.[7] The correlation was not significant after adjustment for age, BMI, alcohol consumption, and urinary potassium excretion.

The implication of INTERSALT is that if the population reduces daily sodium intake by 100 mmol or 1 teaspoon of salt per day, systolic blood pressure would decrease 2 to 3 mmHg.[6] This could have the potential to reduce coronary deaths by 4 to 5%, stroke deaths 6 to 8%, and total mortality by 3 to 4%. The impact would be greater over a lifetime for a whole population, reducing total, coronary, and stroke mortality by 13, 16, and 23%, respectively. The public policy sodium intake goal is 6 g per day.[8]

Not every person's blood pressure increases with salt. Salt-sensitivity refers to those individuals whose blood pressure increases with increased salt intake and decreases with reduced salt intake. Up to 50% of hypertensives may be salt sensitive. The blood pressure response to sodium chloride is determined by genetic and environmental factors. African Americans, obese patients, low-renin hypertensives, chronic renal insufficiency patients, and the elderly may benefit more than other groups by reducing sodium intake.

To assess the impact of sodium chloride on blood pressure, trials have been conducted either by restricting or supplementing sodium to the diet. Sodium supplementation trials are conducted less commonly (Table 47.1).[9] In the Study of Sodium and Blood Pressure, normotensive subjects participated in a trial, using a placebo or 96 mEq sodium capsules in 4-week treatment periods separated by a 2-week washout period.[9] Overnight urinary sodium excretion decreased 51 mEq/8 hr from baseline to 9 mEq/8 hr after the low sodium

**TABLE 47.1**

Randomized Double-Blind Trials of Sodium Supplementation

| Author, Year | Study Group | Design | n | Group Differences in Na+ Excretion (mEq/24 hr) | Sodium Effect on Pressure Δ Systolic/Δ Diastolic (mmHg) |
|---|---|---|---|---|---|
| Australian National Committee, 1989 | Hypertensive | Parallel | 103 | 43 | +4.8/+2.8 |
| Dodson, 1989 | Hypertensive Type 2 Diabetes | Parallel | 9 | 76 | +9.7/+5.1 |
| McCarron, 1997 | Hypertensive | Crossover | 99 | 55 | +4.9/+2.9 |
| MacGregor, 1982 | Hypertensive | Crossover | 19 | 146 | +10/+5 |
| MacGregor, 1989 | Hypertensive | Crossover | 20 | | |
| High intake | | | | 141 | +16/+9 |
| Moderate intake | | | | 59 | +8/+4 |
| Mascioli, 1991 | Normotensive | Crossover | 48 | 60 | +3.6/+2.3 |
| Palmer, 1989 | Elderly | Crossover | 7 | — | +11.0/+8.6 |
| Watt, 1983 | Hypertensive | Crossover | 18 | 56 | +0.5/+0.4 |

Updated and modified from Mascioli et al., *Hypertension* 17: 121; 1991.

diet run-in period, before treatment periods were initiated. Differences in systolic and diastolic blood pressure between sodium and placebo treatment periods were significant. Sodium excretion increased +20.4 mEq/8 hr ($p < 0.001$). An increase of systolic and diastolic blood pressure with the salt capsules was experienced by 65 and 69% of study participants.

A number of meta-analyses have sought to summarize the impact of sodium restriction on blood pressure.[10-15] One meta-analysis of 2635 subjects with 32 randomized trials on sodium reduction required random allocation, no confounding variables, an objective measure of a change in sodium intake (i.e., urine sodium excretion), and no adolescents,[14] updating an earlier analysis by the same authors.[11] The individual studies are listed in Tables 47.2 and 47.3. The largest meta-analysis of 4294 subjects included 58 trials of hypertensive and 56 trials of normotensive persons.[15] The mean reduction of blood pressure by sodium restriction in hypertensive individuals was –3.9/–1.9 mmHg ($p < 0.001$ for both) and in normotensives was –1.2/–0.26 mmHg ($p < 0.001$ for systolic only). Tables 47.4 and 47.5 provide a comprehensive list of the trials used in that meta-analysis. The authors conclude that the cumulative blood pressure-lowering effect of individual sodium restriction trials in both normotensive and hypertensive populations has been stable since 1985. Future trials are unlikely to change the average treatment effect noted above.

The reduction of sodium intake for primary prevention as well as nonpharmacologic treatment of hypertension has become controversial in recent years.[16-18] In one study, 2937 hypertensive men provided 24-hour urine collections for sodium determination off medication for 3 to 4 weeks.[16] After 3.8 years of average followup, 117 cardiovascular events (including 55 myocardial infarctions) occurred. There was an inverse relationship between baseline urinary sodium excretion and myocardial infarction rate. A recent meta-analysis indicated that renin, aldosterone, norepinephrine, total cholesterol, and low-density lipoprotein cholesterol increases with sodium restriction.[15] Other hazards of moderate sodium restriction suggested include a potential increase in blood pressure in 15% of patients, increased sympathetic activity and sleep disturbances, the potential of simultaneous restriction of grain products, meat, poultry, and fish, and dairy products (which contain 50% of sodium intake), decreased iodine intake, decreased susceptibility of the elderly to respond to blood loss or heat stress, the potential for fetal growth retardation during pregnancy, and unknown effects of alternative food preservatives.[19]

**TABLE 47.2**

Descriptive Summary of Sodium-Reduction Trials in Normotensive Subjects*

| Author , Year | n | Duration (mo) | Blinding | Δ Urinary Na mmol/24 h | (No)¶ Changes in Confounders | Δ Systolic mm Hg | Δ Diastolic mm Hg |
|---|---|---|---|---|---|---|---|
| *Crossover Trials* | | | | | | | |
| Skrabal, 1981 | 20 | 0.5 | NR | –170 | Wt (K) | –2.7 | –3.0 |
| Cooper, 1984 | 113 | 2 | BP obs | –68 | Wt, (K) | –0.6 | –1.4 |
| Watt, 1985 (H) | 35 | 1 | DB | –74 | (Wt), K | –1.4 | 1.2 |
| Watt, 1985 (L) | 31 | 1 | DB | –60 | (Wt), K | –0.5 | 1.4 |
| Teow, 1985 | 9 | 0.5 | BP obs | –210 | (Wt), K | –0.6 | –2.7 |
| Myers, 1989 | 172 | 1 | BP obs | –130 | (Wt), (K) | –3.5† | –1.9† |
| Hargreaves, 1989 | 8 | 0.5 | DB | –106 | (Wt), (K) | –6 .0† | –3.0† |
| Mascioli, 1991 | 48 | 1 | DB | –20.2/8h | NR | –3.6† | –2.3† |
| *Parallel Trials*‡ | | | | | | | |
| Puska , 1983 | 19, 19‡ | 0.5 | BP obs | –117 | Wt, K, Alc, (P:S) | –1.5 | –1.1 |
| HPT, 1990 | 174, 177 | 36 | BP obs (RZ) | –16 | (Wt), K | 0.1 | 0.2 |
| Cobiac, 1992 | 26, 28 | 1 | DB | –71 | (Wt), (K) | –1.7 | 0.8 |
| TOHP, 1992 | 327, 417 | 18 | BP obs (RZ) | –44 | (Wt), (K), (Ca), (mg), (alc), (fat) | –1.7† | –0.9† |
| Nestel, 993 (Females) | 15, 15 | 6 | DB | –94 | (Wt), (K) | –6.0† | –2.0† |
| Nestel, 993 (Males) | 17, 19 | 6 | DB | –76 | (Wt), (K) | –2.0† | –1.0† |

* NR, not reported; Wt, body weight; K, potassium excretion; BP obs, observers blinded; H, high blood pressure; L, low blood pressure; DB, double blind; Alc, alcohol intake; P:S, ratio of polyunsaturated to saturated fat; HPT, Hypertension Prevention Trial; RZ, random zero manometer; TOHP, Trials of Hypertension Prevention Collaborative; Ca, calcium intake; Mg, magnesium intake; fat, fat intake.

† $p < 0.05$.

‡ values are the number of subjects in the sodium-reduction treatment and control groups, respectively.

¶ Parentheses denote controlled factors; no parentheses denotes possible confounders

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**TABLE 47.3**

Descriptive Summary of Sodium-Reduction Trials in Hypertensive Subjects*

| Author , Year | n | Duration (mo) | Blinding | Δ Urinary Na mmol/24 h | (No)¶ Changes in Confounders | Δ Systolic mm Hg | Δ Diastolic mm Hg |
|---|---|---|---|---|---|---|---|
| *Crossover Trials* | | | | | | | |
| Parijs,1973 | 15 | 1 | NR | –98 | (Wt) | –6.7 | 3.2 |
| MacGregor, 1982 | 19 | 1 | DB | –76 | Wt, (K) | –10.0† | –5.0† |
| Watt,1983 | 18 | 1 | DB | –56 | (Wt), (K) | 0.5 | –0.3 |
| Richards, 1984 | 12 | 1–1.5 | NR | –105 | (Wt), K | –5.2 | –1.8 |
| Grobbee, 1987 | 40 | 1.5 | DB | –72 | (Wt), (K) | –0.8 | –0.8 |
| MacGregor, 1989 | 20 | 1 | DB | –82 | (Wt), (K) | –8 .0† | –5.0† |
| Dodson,1989 | 9 | 1 | DB | –76 | (Wt), (K) | 9.7† | –5.1 |
| ANHMRC,1989 | 88 | 2 | DB | –67 | (K) | –2.6† | –2.1† |
| Benetos, 1992 | 20 | 1 | DB | –78 | (Wt), (K), (Ca) | –6.5† | –3.7† |
| *Parallel Trials*‡ | | | | | | | |
| Morgan, 1978 | 31, 31‡ | 24 | BP obs | –27 | NR | –1.5† | –6.9† |
| Morgan,1981 | 6, 6 | 2 | BP obs | –98 | K | NR | –6.02 |
| Morgan, 1981 | 6, 6 | 2 | BP obs | –78 | K | NR | –4.0 |
| Costa, 1981 | 20, 21 | 12 | NR | NR§ | NR | –18.3† | –5.9† |
| Silman, 1983 | 10, 15 | 12 | BP obs (RZ) | –53 | (Wt), (K) | –8.7 | –6.3 |
| Puska, 1983 | 15, 19 | 1.5 | BP obs | –117 | Wt, K, Alc, (P:S) | 1.8 | 0.5 |
| Fagerberg, 1984 | 15, 15 | 2.3 | NR | –89 | (Wt), (K), (Alc) | –13.3† | –6.7† |
| Maxwell,1984 | 18, 12 | 3 | NR | –171 | Wt | –2.0 | 2.0 |
| Erwteman,1984 | 44, 50 | 6 | BP obs (RZ) | –58 | NR | –2.7 | –3.4† |
| Chalmers,1986 | 48, 52 | 3 | NR | –54 | (K) | –5.1† | –4.2† |
| Logan,1986 | 37, 38 | 6 | BP obs | –32 | Wt, (K) | –1.1 | –0.2 |
| Dodson, 1989 | 17, 17 | 3 | BP obs | –59 | (Wt). (K) | –13.0† | –1.8 |
| ANHMRC, 1989 | 50, 53 | 2 | DB | –71 | (Alc) | –5.5† | –2.8† |
| Sciarrone, 1992 | 46, 45 | 2 | DB | –84 | (Wt), (K) | –6 .0† | –1.0 |
| Parker,1990, low EtOH, | 16, 15 | 1 | DB | –80 | (Wt), (Alc), (K), (Ca), (Mg) | 2.2 | 0.5 |
| Parker ,1990, norm EtOH | 15, 13 | 1 | DB | –52 | (Wt), (Alc), (K), (Ca), (Mg) | –0.1 | 0.8 |

* NR, not reported; Wt, body weight; DB, double blind; K, potassium intake/excretion: ANHMRC, Australian National Health and Medical Research Council; Ca, calcium intake/excretion; BP obs, observers blinded: RZ, random zero manometer; Alc, alcohol intake; P:S, ratio of polyunsaturated to saturated fatty acid; Mg, magnesium excretion.

† $p < 0.05$.

‡ n values given for each study are the number of subjects in the sodium-reduction treatment and control groups, respectively.

§ –23% intracellular Na.

¶ Parentheses denote controlled factors; no parentheses denotes possible confounders

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**TABLE 47.4**

Characteristics of Trials of Sodium Restriction and Blood Pressure in Normotensive Populations*

| Author, Year | Design | Dur. | N | Age | NU | SR | Cum SR | Effect SBP | Effect DBP | Cum. SBP | Cum DBP | Z SBP | Z DBP |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Sullivan, 1980 | Op, CO | 4 | 27 | 29 | 1 | 146 | 146 | –7.1 | –1.1 | –7.1 | –1.1 | –2.2 | –0.4 |
| Skrabal, 1981 | Op, CO | 14 | 20 | 23 | 1 | 150 | 147 | 2.7 | 3.0 | –2.7 | 0.7 | –1.0 | 0.4 |
| Myers, 1982 | Op, CO | 14 | 136 | 39 | 1 | 130 | 133 | 3.3 | 2.7 | 2.4 | 2.4 | 1.1 | 2.2 |
| Puska, 1983 | SB, P | 72 | 38 | 40 | 3 | 90 | 123 | 1.5 | 2.1 | 2.4 | 2.2 | 1.1 | 2.2 |
| Cooper, 1984 | SB, CO | 24 | 59 | 16 | 1 | 55 | 111 | 1.4 | 3.4 | 2.0 | 3.5 | 1.6 | 3.0 |
| Cooper, 1984 | SB, CO | 24 | 54 | 16 | 1 | 72 | 107 | –0.3 | –0.7 | 1.3 | 2.7 | 1.3 | 2.6 |
| Skrabal, 1984 | Op, CO | 14 | 30 | 23 | 1 | 137 | 109 | –1.4 | –0.8 | 1.2 | 2.3 | 1.0 | 2.2 |
| Skrabal, 1984 | Op, CO | 14 | 22 | 23 | 1 | 167 | 113 | 7.7 | 4.6 | 1.5 | 2.4 | 1.9 | 2.7 |
| Skrabal, 1985 | SB, CO | 14 | 34 | 23 | 1 | 144 | 115 | 0.1 | 0.6 | 0.9 | 1.9 | 1.9 | 2.8 |
| Skrabal, 1985 | SB, CO | 14 | 28 | 23 | 1 | 163 | 118 | 5.8 | 3.3 | 1.4 | 2.0 | 3.3 | 3.9 |
| Watt, 1985 | DB, CO | 28 | 31 | 23 | 4 | 60 | 114 | 0.5 | –1.4 | 1.3 | 1.4 | 3.4 | 3.3 |
| Watt, 1985 | DB, CO | 28 | 35 | 22 | 4 | 75 | 111 | 1.4 | –1.2 | 1.3 | 0.9 | 3.7 | 2.8 |
| Teow, 986 | Op, CO | 14 | 9 | 25 | 1 | 200 | 112 | 0.6 | 2.7 | 1.3 | 0.9 | 3.6 | 2.9 |
| Richards, 1986 | SB, CO | 4 | 8 | 36 | 4 | 181 | 114 | 2.0 | –7.0 | 1.3 | 0.9 | 3.5 | 2.2 |
| Fuchs, 1987 | Op, CO | 9 | 6 | 20 | 3 | 99 | 113 | 5.8 | –3.0 | 1.3 | 0.8 | 3.6 | 1.9 |
| Fuchs, 1987 | Op, CO | 9 | 11 | 20 | 3 | 93 | 111 | 1.1 | –1.0 | 1.3 | 0.8 | 3.5 | 1.8 |
| El Ashry, 1987 | SB, CO | 14 | 13 | 24 | 1 | 222 | 111 | 0.0 | 4.0 | 1.3 | 0.8 | 3.4 | 1.9 |
| El Ashry, 1987 | SB, CO | 14 | 13 | 27 | 1 | 232 | 115 | 0.0 | 1.0 | 1.3 | 0.8 | 3.3 | 1.9 |
| Lawton, 1988 | Op, CO | 6 | 13 | 24 | 1 | 313 | 119 | 2.0 | –2.0 | 1.3 | 0.8 | 3.3 | 1.7 |
| Hargreaves, 1989 | DB, CO | 14 | 8 | 23 | 2 | 106 | 119 | 6.0 | 3.0 | 1.3 | 0.8 | 3.4 | 1.7 |
| Mtabaji, 1990 | Op, P | 7 | 30 | • | 1 | 272 | 121 | 9.0 | 9.0 | 1.4 | 1.0 | 4.0 | 2.3 |
| Friberg, 1990 | Op, CO | 13 | 10 | 33 | 3 | 117 | 120 | 0.0 | 1.0 | 1.4 | 1.0 | 4.0 | 2.4 |
| Dimsdale, 1990 | Op, CO | 5 | 19 | 34 | 2 | 183 | 129 | –1.4 | –4.1 | 1.2 | 0.5 | 3.7 | 1.6 |
| Dimsdale, 1990 | Op, CO | 5 | 23 | 34 | 2 | 178 | 132 | –1.0 | –4.4 | 1.2 | 0.3 | 3.6 | 1.0 |
| HPT, 1990 | SB, P | 1100 | 228 | 40 | 1 | 23 | 125 | –0.3 | –0.1 | 1.1 | 0.3 | 3.5 | 0.9 |
| Sharma, 1990 | SB, CO | 7 | 15 | 24 | 2 | 192 | 127 | 0.9 | 3.7 | 1.1 | 0.3 | 3.4 | 1.1 |
| Schmid, 1990 | SB, CO | 7 | 9 | 32 | 1 | 190 | 128 | 3.0 | 0.0 | 1.1 | 0.3 | 3.5 | 1.0 |
| Bruun, 1990 | Op, CO | 4 | 10 | 46 | 1 | 341 | 131 | 5.0 | 1.0 | 1.1 | 0.3 | 3.6 | 1.1 |
| Ruppert, 1991 | SB, CO | 7 | 98 | 35 | 3 | 275 | 179 | –0.3 | –0.3 | 1.1 | 0.3 | 3.5 | 1.0 |
| Ruppert, 1991 | SB, CO | 7 | 24 | 36 | 3 | 275 | 190 | –6.0 | –6.0 | 0.9 | 0.1 | 2.9 | 0.4 |
| Ruppert, 1991 | SB, CO | 7 | 25 | 46 | 3 | 262 | 198 | 7.5 | 7.5 | 1.0 | 0.2 | 3.3 | 0.9 |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Sharma, 1991 | SB, CO | 6 | 13 | 25 | 3 | 246 | 198 | 3.0 | –0.5 | 1.1 | 0.2 | 3.6 | 0.9 |
| Sharma, 1991 | SB, CO | 6 | 10 | 24 | 3 | 247 | 198 | 6.4 | 5.9 | 1.1 | 0.2 | 3.7 | 1.1 |
| Mascioli, 1991 | DB, CO | 28 | 48 | 52 | 5 | 70 | 197 | 3.6 | 2.3 | 1.3 | 0.4 | 4.3 | 1.5 |
| Steegers, 1991 | SB, P | 140 | 36 | 27 | 5 | 63 | 195 | –2.0 | –2.0 | 1.3 | 0.4 | 4.1 | 1.4 |
| Cobiac, 1992 | DB, P | 28 | 52 | 66 | 2 | 75 | 194 | 3.1 | 2.8 | 1.3 | 0.4 | 4.3 | 1.8 |
| Cobiac, 1992 | DB, P | 28 | 54 | 67 | 2 | 73 | 192 | 2.7 | –0.6 | 1.3 | 0.4 | 4.4 | 1.7 |
| TOHP, 1992 | SB, P | 550 | 744 | 43 | 3 | 47 | 135 | 1.7 | 0.9 | 1.4 | 0.4 | 4.7 | 2.0 |
| Burnier, 1993 | Op, CO | 6 | 16 | 29 | 1 | 186 | 136 | 1.0 | –0.5 | 1.4 | 0.4 | 4.7 | 1.9 |
| Burnier, 1993 | Op, CO | 6 | 7 | 29 | 1 | 218 | 137 | 1.0 | –1.2 | 1.4 | 0.4 | 4.7 | 1.8 |
| Ruppert, 1993 | SB, CO | 7 | 30 | 46 | 3 | 270 | 146 | 12.6 | 5.6 | 1.4 | 0.4 | 5.1 | 2.3 |
| Ruppert, 1993 | SB, CO | 7 | 108 | 36 | 3 | 275 | 160 | 1.4 | –1.2 | 1.4 | 0.4 | 5.2 | 2.1 |
| Ruppert, 1993 | SB, CO | 7 | 25 | 35 | 3 | 280 | 165 | –5.9 | –8.0 | 1.4 | 0.3 | 4.9 | 1.5 |
| Sharma, 1993 | SB, CO | 7 | 16 | 24 | 3 | 224 | 166 | 0.8 | 0.5 | 1.4 | 0.3 | 4.9 | 1.5 |
| Fliser, 1993 | SB, CO | 8 | 8 | 25 | 2 | 190 | 167 | 1.3 | 1.3 | 1.4 | 0.3 | 4.9 | 1.5 |
| Fliser, 1993 | SB, CO | 8 | 8 | 26 | 2 | 181 | 167 | 0.6 | 0.6 | 1.4 | 0.3 | 4.8 | 1.5 |
| Nestel, 1993 | DB, P | 42 | 72 | 66 | 4 | 56 | 166 | 2.0 | 1.0 | 1.4 | 0.3 | 4.9 | 1.6 |
| Nestel, 1993 | DB, P | 42 | 60 | 65 | 4 | 73 | 165 | 6.0 | 2.0 | 1.4 | 0.4 | 5.1 | 1.7 |
| Donovan, 1993 | SB, CO | 5 | 8 | 36 | 1 | 152 | 164 | 2.0 | –1.0 | 1.4 | 0.4 | 5.1 | 1.6 |
| Grey, 1996 | DB, CO | 7 | 34 | 23 | 1 | 133 | 164 | –1.0 | –1.0 | 1.4 | 0.3 | 5.0 | 1.5 |
| Feldmann, 1996 | DB, CO | 7 | 5 | 27 | 1 | 176 | 164 | –5.0 | –5.0 | 1.2 | 0.2 | 4.5 | 1.1 |
| Schorr, 1996 | DB, CO | 28 | 16 | 64 | 2 | 61 | 162 | 1.0 | 0.0 | 1.2 | 0.2 | 4.4 | 1.0 |
| Miller, 1997 | Op, CO | 7 | 12 | 23 | 2 | 182 | 163 | 1.0 | 1.0 | 1.2 | 0.2 | 4.5 | 1.1 |
| Miller, 1997 | Op, CO | 7 | 10 | • | 2 | 194 | 163 | –1.0 | –1.0 | 1.2 | 0.2 | 4.4 | 1.1 |
| Schorr, 1997 | SB, CO | 7 | 27 | 25 | 7 | 208 | 163 | 5.6 | 5.6 | 1.3 | 0.3 | 4.6 | 1.3 |
| Schorr, 1997 | SB, CO | 7 | 76 | 25 | 7 | 208 | 165 | –2.8 | –2.8 | 1.2 | 0.3 | 4.5 | 1.2 |

* Dur.: duration of intervention, days; Op: open; SB: single blind; DB: double blind; P: parallel; CO: cross–over; N: number of persons in trial; Age: mean age of persons in trial; NU: number of urine collections per person per treatment period; SR: sodium reduction, mmol/24–h; Cum: cumulative; CI: 95% confidence interval of previous column. SBP: systolic blood pressure; DBP: diastolic blood pressure; Z: summary statistic; •: no data.

Personal Communication from NA Graudal of unpublished data from his manuscript.[15]

**TABLE 47.5**

Characteristics of Trials of Sodium Restriction in Hypertensive Populations*

| Author, Year | Design | Dur. | N | Age | NU | SR | Cum SR | Effect SBP | Effect DBP | Cum. SBP | Cum DBP | Z SBP | Z DBP |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Parijs, 1973 | Op, CO | 28 | 15 | 41 | 1 | 98 | 98 | 6.7 | –3.2 | 6.7 | –3.2 | 1.6 | –1.2 |
| Mark, 1975 | Op, CO | 10 | 6 | 28 | 1 | 305 | 216 | 13.1 | 7.7 | 9.8 | –0.1 | 2.7 | 0.4 |
| Morgan, 1978 | SB, P | 90 | 62 | 60 | 2 | 23 | 114 | 1.0 | 2.0 | 6.2 | 1.2 | 2.6 | 0.9 |
| Sullivan, 1980 | Op, CO | 4 | 19 | 27 | 1 | 153 | 121 | –1.2 | 1.2 | 4.6 | 1.2 | 2.2 | 0.9 |
| Morgan, 1981 | SB, P | 56 | 12 | 38 | 2 | 67 | 106 | • | 4.0 | • | 1.9 | • | 1.1 |
| Morgan, 1981 | SB, P | 56 | 12 | 40 | 2 | 92 | 104 | • | 8.0 | • | 3.0 | • | 1.7 |
| Ambrosioni, 1982 | SB, CO | 42 | 25 | 23 | 6 | 60 | 91 | 2.2 | 0.4 | 3.9 | 2.6 | 1.3 | 1.7 |
| MacGregor, 1982 | DB, CO | 28 | 19 | 49 | 2 | 76 | 89 | 10.0 | 5.0 | 5.4 | 3.0 | 2.0 | 2.2 |
| Beard, 1982 | Op, P | 84 | 90 | 48 | 3 | 124 | 95 | 5.2 | 3.4 | 5.4 | 3.0 | 2.2 | 2.5 |
| Watt, 1983 | DB, CO | 28 | 18 | 52 | 4 | 56 | 92 | 0.5 | 0.3 | 3.6 | 2.0 | 2.3 | 2.5 |
| Silman, 1983 | Op, P | 90 | 28 | 55 | 4 | 63 | 91 | –3.5 | –0.5 | 3.5 | 1.9 | 2.1 | 2.4 |
| Puska, 1983 | SB, P | 72 | 34 | 40 | 3 | 90 | 91 | –1.8 | –0.5 | 3.3 | 1.8 | 2.0 | 2.3 |
| Koolen, 1984 | Op, CO | 14 | 20 | 41 | 2 | 213 | 97 | 6.5 | 4.9 | 3.4 | 1.9 | 2.2 | 2.5 |
| Richards, 1984 | SB, CO | 28 | 12 | 36 | 2 | 100 | 97 | 4.0 | 3.0 | 3.4 | 2.0 | 2.4 | 2.7 |
| Erwteman, 1984 | SB, P | 28 | 94 | 46 | 4 | 58 | 91 | 2.7 | 2.5 | 3.3 | 2.0 | 2.5 | 2.9 |
| Maxwell, 1984 | Op, P | 84 | 30 | 46 | 4 | 161 | 92 | 2.0 | –2.0 | 3.3 | 1.9 | 2.5 | 2.8 |
| Fagerberg, 1984 | Op, P | 63 | 30 | 51 | 4 | 99 | 92 | 3.7 | 3.1 | 3.3 | 2.0 | 2.6 | 2.9 |
| Resnick, 1985 | Op, CO | 5 | 12 | • | 1 | 190 | 96 | 3.0 | 1.0 | 3.3 | 1.9 | 2.7 | 2.9 |
| Logan, 1986 | Op, P | 180 | 86 | 47 | 1 | 43 | 92 | 1.1 | 0.2 | 3.1 | 1.9 | 2.8 | 2.9 |
| Chalmers, 1986 | SB, P | 84 | 100 | 53 | 6 | 70 | 91 | 4.8 | 4.2 | 3.3 | 2.3 | 3.0 | 3.5 |
| Grobbee, 1987 | DB, CO | 42 | 40 | 24 | 4 | 72 | 88 | 0.8 | 0.8 | 3.1 | 2.3 | 3.0 | 3.5 |
| MacGregor, 1987 | DB, CO | 30 | 15 | 52 | 2 | 100 | 88 | 13.0 | 9.0 | 3.6 | 2.4 | 3.6 | 3.9 |
| Kurtz, 1987 | DB, CO | 7 | 5 | 58 | 2 | 217 | 91 | 16.0 | 8.4 | 4.7 | 2.6 | 4.6 | 4.3 |
| Morgan, 1987 | SB, P | 60 | 20 | 58 | 5 | 57 | 90 | 6.0 | 4.0 | 4.7 | 2.6 | 4.5 | 4.4 |
| Morgan, 1988 | SB, CO | 14 | 16 | 63 | 1 | 50 | 89 | 3.0 | 4.0 | 4.5 | 2.7 | 4.7 | 4.6 |
| Lawton, 1988 | Op, CO | 6 | 9 | 25 | 1 | 328 | 91 | 1.0 | –4.0 | 4.4 | 2.6 | 4.7 | 4.4 |
| Shore, 1988 | SB, CO | 5 | 6 | • | 5 | 97 | 91 | 9.0 | 5.6 | 4.5 | 2.6 | 4.8 | 4.4 |
| ANHMRC, 1989 | Op, P | 48 | 103 | 58 | 4 | 63 | 89 | 5.5 | 2.9 | 4.6 | 2.7 | 5.2 | 4.8 |
| MacGregor, 1989 | DB, CO | 30 | 20 | 57 | 2 | 150 | 91 | 16.0 | 9.0 | 4.8 | 2.8 | 5.6 | 5.2 |
| Dodson, 1989 | SB, P | 90 | 34 | 62 | 3 | 44 | 90 | 13.0 | 1.8 | 4.8 | 2.8 | 5.8 | 5.2 |
| Dimsdale, 1990 | Op, CO | 5 | 16 | 34 | 2 | 178 | 93 | 6.4 | –2.0 | 4.9 | 2.7 | 6.0 | 5.0 |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Dimsdale, 1990 | Op, CO | 5 | 17 | 34 | 2 | 198 | 98 | 0.1 | –0.8 | 4.6 | 2.6 | 6.0 | 4.9 |
| Parker, 1990 | DB, P | 28 | 31 | 50 | 4 | 73 | 97 | –1.9 | 0.1 | 4.3 | 2.4 | 5.8 | 4.9 |
| Parker, 1990 | DB, P | 28 | 28 | 54 | 4 | 49 | 97 | –1.9 | –1.8 | 4.1 | 2.4 | 5.6 | 4.7 |
| Schmid, 1990 | SB, CO | 7 | 9 | 36 | 1 | 181 | 99 | 6.0 | 1.9 | 4.1 | 2.4 | 5.7 | 4.7 |
| Bruun, 1990 | Op, CO | 4 | 12 | 47 | 1 | 331 | 103 | 8.0 | 4.0 | 4.2 | 2.4 | 5.8 | 4.8 |
| Egan, 1991 | DB, CO | 7 | 27 | 39 | 1 | 194 | 106 | 1.1 | 1.1 | 3.9 | 2.3 | 5.9 | 4.8 |
| Carney, 1991 | DB, CO | 42 | 11 | 54 | 4 | 102 | 106 | 1.0 | –1.0 | 3.9 | 2.3 | 5.8 | 4.8 |
| Singer, 1991 | DB, CO | 30 | 21 | 54 | 2 | 91 | 106 | 9.0 | 3.0 | 4.0 | 2.3 | 6.1 | 4.9 |
| Sciarrone, 1992 | DB, P | 56 | 91 | 54 | 1 | 82 | 104 | 5.8 | 0.4 | 4.0 | 2.2 | 6.4 | 4.9 |
| Benetos, 1992 | DB, CO | 28 | 20 | 42 | 1 | 78 | 103 | 6.5 | 3.7 | 4.1 | 2.3 | 6.5 | 5.1 |
| Del Rio, 1993 | DB, CO | 14 | 30 | 49 | 1 | 151 | 106 | 1.4 | 0.5 | 4.0 | 2.2 | 6.5 | 5.1 |
| Ruilope, 1993 | DB, P | 21 | 19 | • | 1 | 69 | 106 | 4.0 | 4.0 | 4.0 | 2.3 | 6.4 | 5.1 |
| Redon-Mas, 1993 | Op, P | 28 | 418 | 55 | 1 | 104 | 105 | –1.0 | –1.9 | 3.5 | 1.6 | 6.3 | 4.7 |
| Fotherby, 1993 | DB, CO | 35 | 17 | 73 | 2 | 79 | 105 | 8.0 | 0.0 | 3.6 | 1.5 | 6.5 | 4.7 |
| Buckley, 1994 | SB, CO | 5 | 12 | 49 | 1 | 296 | 106 | 8.7 | 8.7 | 3.7 | 1.6 | 6.8 | 5.0 |
| Jula, 1994 | Op, P | 365 | 76 | 44 | 3 | 57 | 105 | 6.7 | 3.8 | 3.7 | 1.7 | 6.9 | 5.2 |
| Zoccali, 1994 | SB, CO | 7 | 15 | 45 | 1 | 163 | 106 | 14.0 | 8.0 | 3.8 | 1.7 | 7.2 | 5.6 |
| Weir, 1995 | SB, CO | 14 | 11 | 60 | 5 | 146 | 106 | 9.0 | 7.0 | 3.8 | 1.8 | 7.2 | 5.7 |
| Weir, 1995 | SB, CO | 14 | 11 | 60 | 5 | 127 | 106 | –4.0 | –5.0 | 3.8 | 1.7 | 7.1 | 5.5 |
| Overlack, 1995 | DB, CO | 7 | 11 | 61 | 3 | 240 | 109 | 9.9 | 9.9 | 3.9 | 1.8 | 7.4 | 5.8 |
| Overlack, 1995 | DB, CO | 7 | 27 | 40 | 3 | 249 | 114 | 0.8 | 0.8 | 3.8 | 1.8 | 7.3 | 5.8 |
| Overlack, 1995 | DB, CO | 7 | 8 | 43 | 3 | 234 | 115 | –6.0 | –6.0 | 3.7 | 1.7 | 7.1 | 5.6 |
| Ferri, 1996 | DB, CO | 14 | 61 | 47 | 2 | 264 | 120 | 7.4 | 3.5 | 3.9 | 1.8 | 7.6 | 5.9 |
| Feldmann, 1996 | DB, CO | 7 | 8 | 27 | 1 | 178 | 120 | –2.0 | –2.0 | 3.8 | 1.8 | 7.4 | 5.7 |
| Mühlhauser, 1996 | DB, P | 28 | 16 | 36 | 4 | 107 | 120 | 2.0 | 0.0 | 3.8 | 1.8 | 7.2 | 5.5 |
| McCarron, 1997 | DB, CO | 28 | 99 | 52 | 1 | 56 | 119 | 4.9 | 2.9 | 3.8 | 1.8 | 7.4 | 5.7 |
| Cappuccio, 1997 | DB, CO | 30 | 47 | 67 | 2 | 83 | 118 | 7.3 | 3.2 | 3.9 | 1.9 | 7.7 | 6.0 |

* Dur.: duration of intervention, days; Op: open; SB: single blind; DB: double blind; P: parallel; CO: cross-over; N: number of persons in trial; Age: mean age of persons in trial; NU: number of urine collections per person per treatment period; SR: sodium reduction, mmol/24-h; Cum: cumulative; CI: 95% confidence interval of previous column. SBP: systolic blood pressure; DBP: diastolic blood pressure; Z: summary statistic; •: no data.

Personal Communication from NA Graudal of unpublished data from his manuscript.[15]

## Potassium

Intracellular potassium is the major cation responsible for establishing the membrane potential. The blood pressure of normotensives increases with potassium depletion.[20] Observational studies suggest an inverse relationship between potassium intake and blood pressure.[21] Often there is an inverse relationship with dietary potassium and sodium or a positive relationship between urinary Na+/K+ ratio and blood pressure.[5, 21] In the Scottish Heart Health Study, the relationship between blood pressure and the urinary Na+/K+ ratio was stronger than the relationship between excretion of either sodium or potassium individually and blood pressure.[7] After adjusting for age, gender, BMI, ethanol intake, and urinary sodium intake, it was observed in the INTERSALT study that the systolic blood pressure was 2.7 mmHg lower for each 60 mmol/d higher excretion of potassium.[5] Since African Americans have a lower intake of potassium due to decreased consumption of fresh fruits and vegetables, this may explain the higher prevalence of hypertension in blacks compared to whites.[21-24] Potassium supplementation (80 mmol/d) compared to placebo reduced systolic and diastolic blood pressure (–6.9/–2.5 mmHg) significantly in African Americans consuming a diet low in potassium for 21 days.[25] Explanations for the hypotensive effects of potassium include direct vasodilatation, a direct natriuretic effect, altered baroreceptor function, increased urinary kallikrein, or suppression of the renin-angiotensin-aldosterone axis or sympathetic nervous system.[8]

Studies using the Dahl salt-sensitive rat show a protective effect of potassium supplementation, reducing mortality by 93% in the hypertensive rats.[26] In a 12-year prospective population study of 859 older persons, the relative risks of stroke-associated mortality in the lowest tertile of potassium intake, as compared with that in the top two tertiles combined, were 2.6 ($p = 0.16$) in men and 4.8 ($p = 0.01$) in women.[27] A 10-mmol increase in daily potassium decreased stroke-associated mortality by 40% ($p < 0.001$) in a multivariate analysis. In the Health Professionals Follow-up Study, a multivariate analysis demonstrated the greater the potassium intake, the lower the relative risk of stroke ($p = 0.007$) (Figure 47.1).[28] Furthermore, use of potassium supplements, especially among men

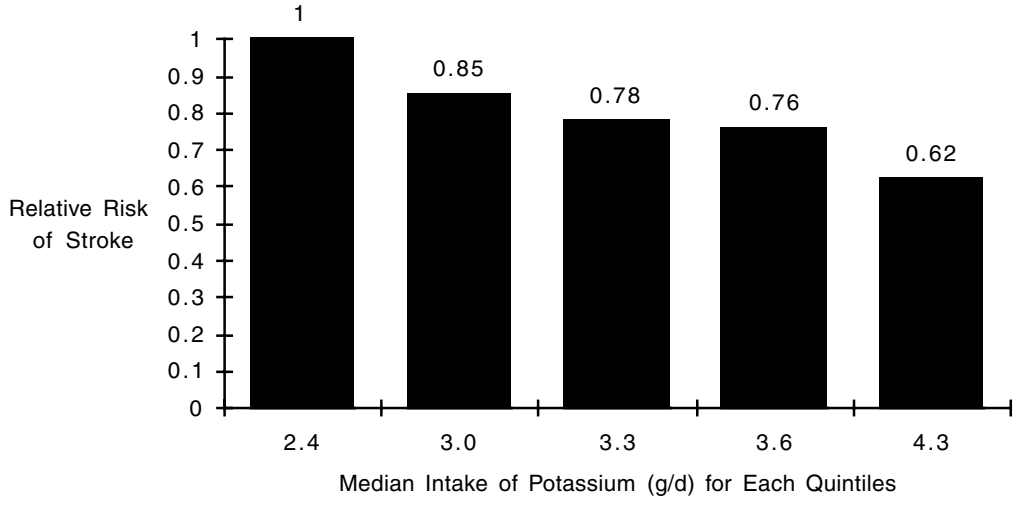


**FIGURE 47.1**
Multivariate adjusted relative risk of stroke of 43,738 United States men, 40 to 75 years by quintile of potassium intake: adjusted for age, total energy intake, smoking, alcohol consumption, history of hypertension and hypercholesterolemia, family history of premature myocardial infarction, profession, body mass index, and physical activity ($p = 0.007$ for trend). Derived from Ascherio.[28]

taking diuretics, was also inversely related to the risk of stroke. However, after further adjustment for fiber and magnesium intake, the relative risk of stroke was no longer statistically significant.

The largest meta-analysis (see Tables 47.6 and 47.7) observed a significant reduction in both systolic and diastolic blood pressure (–4.44/–2.45 mmHg, $p < 0.01$ for both) for oral potassium supplementation.[29] There was a greater decrease in blood pressure (–4.91/–2.71 mmHg, $p < 0.01$ for both) when trials were examined that achieved a net change in urinary potassium ≥20mmol/d. If trials excluded concomitant antihypertensive drugs, the change in blood pressure was –4.85/–2.71 mmHg, $p < 0.01$ for both). The change in blood pressure was lower for normotensives (–1.8/–1.0 mmHg) compared with hypertensives (–4.4/–2.5 mmHg). The change for systolic blood pressure among black subjects was greater than white subjects (–5.6 mmHg versus –2.0 mmHg, $p = 0.03$); however, the change for diastolic blood pressure was not significant (–3.0 mmHg versus –1.1 mmHg, $p = 0.19$).

Interestingly, there was no overall association between 24-hour urinary potassium excretion and change in systolic or diastolic blood pressure; however, the higher the urinary sodium excretion at followup (see Figure 47.2), the greater the decline in both systolic ($p < 0.001$) and diastolic blood pressure ($p < 0.001$).[29] This explains the lack of benefit seen in a study that combined sodium restriction and potassium supplementation in patients.[30] This randomized, placebo-controlled, double-blind trial of 287 men assessed the effect of 96 mmol of microcrystalline potassium chloride or placebo on a sodium-restricted diet. After the withdrawal of their antihypertensive medication at 12 weeks, there was no significant difference in either systolic or diastolic blood pressure between the two groups at any point in time up to an average of 2.2 years.[30]

### Calcium

Most body calcium is found in the skeleton. Calcium is important for its role in smooth muscle relaxation and contraction, especially the vascular smooth muscle that alters peripheral vascular resistance directly. An inverse relationship between water hardness and blood pressure has stimulated an interest in the role of calcium supplementation on blood pressure.[31] Paradoxically, data from the first Health and Nutrition Examination Survey found that daily calcium intake was lower in 1012 hypertensive vs. 8541 normotensive persons (608 mg vs. 722 mg, $p < 0.01$).[32] However, it was not associated with blood pressure when age and BMI were controlled. For 58,218 female nurses with a calcium intake of at least 800 mg/day, the reduction in the risk of hypertension was 22% when compared with an intake of less than 400 mg/day.[33] In men, calcium was inversely associated with baseline blood pressure but not with change in blood pressure; furthermore, intake of calcium in men was not inversely associated with an increased risk of stroke.[28,34] Other observational studies have reported both positive and negative correlations with blood pressure, but many studies did not adjust for weight and alcohol, vitamin D, sodium, and other nutrient intake, and are based on dietary recall.[35] Also, it has been suggested that calcium supplementation is important in African Americans, since intake of dairy products is especially low and the prevalence of hypertension much higher than in caucasians. In addition, sodium excretion and calcium intake interact in salt-sensitive individuals: increased ingested calcium facilitates sodium excretion.[36] Calcium supplementation is associated with controversy because of the association of hyperparathyroidism and hypertension, the pressor effect of hypercalcemia in normotensives, and the direct relationship of calcium and blood pressure.[37] However, responders to calcium supplementation may be a subset of hypertensives with a low renin level, high parathormone level, and low ionized calcium.[36]

**TABLE 47.6**

Participant and Study Design Characteristics in 33 Potassium Supplementation Trials

| Author, Year | No. of Subjects | Age, y Mean | Age, y Range | % Male | % White | % HTN† | AntiHTN Medication | Study Design* | Study Duration, wk |
|---|---|---|---|---|---|---|---|---|---|
| Skrabal, 1981 | | | | | | | | | |
| (a) | 20 | ... | 21-25 | 100 | ... | 0 | No | XO | 2 |
| (b) | 20 | ... | 21-25 | 100 | … | 0 | No | XO | 2 |
| MacGregor, 1982 | 23 | 45 | 26-66 | 52 | 78 | 100 | No | XD | 4 |
| Khaw and Thom, 1982 | 20 | ... | 22-35 | 100 | ... | 0 | No | XD | 2 |
| Richards, 1984 | 12 | ... | 19-52 | 67 | ... | 100 | No | XO | 4-6 |
| Smith, 1985 | 20 | 53 | 30-66 | 55 | 90 | 100 | No | XD | 4 |
| Kaplan, 1985 | 16 | 49 | 35-66 | 38 | 19 | 100 | Yes‡ | XD | 6 |
| Zoccali, 1985 | 19 | 38 | 26-53 | 53 | 100 | 100 | No | XD | 2 |
| Bulpitt, 1985 | 33 | 55 | ... | 45 | ... | 100 | Yes‡ | PO | 12 |
| Matlou, 1986 | 32 | 51 | 34-62 | 0 | 0 | 100 | No | XS | 6 |
| Barden, 1986 | 44 | 32 | 18-55 | 0 | ... | 0 | No | XD | 4 |
| Poulter and Sever ,1986 | 19 | ... | 18-47 | 100 | 0 | 0 | No | XD | 2 |
| Chalmers, 1986 | | | | | | | | | |
| (a) | 107 | 52 | ... | 85 | ... | 100 | No | PO | 12 |
| (b) | 105 | 52 | ... | 86 | ... | 100 | No | PO | 12 |
| Grobbee, 1987 | 40 | 24 | 18-28 | 85 | ... | 100 | No | XD | 6 |
| Siani, 1987 | 37 | 45 | 21-61 | 62 | ... | 100 | No | PD | 15 |
| Svetkey, 1987 | 101 | 51 | ... | 74 | 88 | 100 | No | PD | 8 |
| Medical Research Council, 1987 | 484 | ... | 35-64 | 56 | ... | 100 | Yes‡ | PS | 24 |
| Grimm, 1988 | 312 | 58 | 45-68 | 100 | ... | 100 | Yes‡ | PD | 12 |
| Cushman and Langford, 1988 | 58 | 54 | 26-69 | 100 | 47 | 100 | No | PD | 10 |
| Obell, 1989 | 48 | 41 | 23-56 | 44 | 0 | 100 | No | PD | 16 |
| Krishna, 1989 | 10 | ... | 20-40 | 100 | 100 | 0 | No | XD | 10d |
| Hypertension Prevention Trial, 1990 | 391 | 39 | 25-49 | 64 | 83 | 0 | No | PO | 3 y |
| Mullen and O'Connor, 1990 | | | | | | | | | |
| (a) | 24 | 25 | 22-31 | 100 | 9 | 0 | No | XD | 2 |
| (b) | 24 | 25 | 22-31 | 100 | 92 | 0 | No | XD | 2 |
| Patki, 1990 | 37 | 50 | ... | 22 | ... | 100 | No | XD | 8 |
| Valdes, 1991 | 24 | 50 | ... | 54 | | 100 | No | XD | 4 |
| Barden ,1991 | 37 | 32 | ... | 0 | | 0 | No | XD | 4 d |
| Overlack, 1991 | 12 | 37 | 25-59 | 67 | ... | 100 | No | XS | 8 |
| Smith, 1992 | 22 | 67 | _ 60 | 57 | 71 | 100 | No | XD | 4 d |
| Fotherby and Potter, 1992 | 18 | 75 | 66-79 | 28 | ... | 100 | No | XD | 4 |
| Whelton, 1995 | 353 | 43 | 30-54 | 72 | 86 | 0 | No | PD | 24 |
| Brancati, 1996 | 87 | 48 | 27-65 | 36 | 0 | 0 | No | PD | 3 |

* XO indicates crossover open; XS, crossover single blind; XD, crossover double blind; PO, parallel open; PS, parallel single blind; PD, parallel double blind; and ellipses, no data.

† HTN indicates hypertensive, BP indicates blood pressure; SBP, systolic BP; and DBP, diastolic BP. Sitting BP was used in the studies by Khaw and Thom, Matlou, Poulter and Sever, Chalmers, Svetkey, Grimm, Hypertension Prevention Trial, Barden, and Overlack.

‡ Study participants were treated with thiazide or thiazide-like diuretics (hydrochlorothiazide [25-75 mg/d] or chlorthalidone [50 mg/d] and in addition, clonidine [0.1 mg twice daily] in 1 subject [Kaplan]; bendrofluazide [2.5-10 mg/d], cyclopenthiazide [25-50 mg/d], hydrochlorothiazide [25 mg/d], furosemide [40-80 mg/d], and chlorthalidone [50-100 mg/d] [Bulpitt]) ; bendrofluazide [5-10 mg/d] [Medical Research Council]; chlorthalidone or hydrochlorothiazide [84%], β-blockers [43%], other medications, e.g., reserpine [6%], hydralazine [6%], and methyldopa [5%] [doses not specified] [Grimm]).

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**TABLE 47.6**

Participant and Study Design Characteristics in 33 Potassium Supplementation Trials

| Intervention | Control | Baseline Supine BP, mm Hg† SBP/DBP | Baseline Urinary Electrolytes, mmol/d K+/Na+ | Baseline K+ mmol/L |
|---|---|---|---|---|
| 200 mmol K from diet, 200 mmol NaCl | 80 mmol KCl, 200 mmol NaCl | ... | .../... | 4.7 |
| 200 mmol K from diet, 50 mmol NaCl | 80 mmol KCI,50 mmol NaCl | ... | …/... | 4.6 |
| 64 mmol KCl | Placebo | 154/99 | 68/152 | 4.0 |
| 64 mmol KCl | Placebo | 118/74 | 73/138 | ... |
| 200 mmol K from diet, 180 mmol NaCl | 60 mmol KCI,180 mmol NaCl | 140-180/90-105 | .../... | 3.8 |
| 64 mmol KCI, 70 mmol NaCl | Placebo,70 mmol NaCl | 163/103 | 72/68 | 3.9 |
| 60 mmol KCI | Placebo | 131/96 | 46/166 | 3.0 |
| 100 mmol KCI | Placebo | 154/96 | .../... | 3.8 |
| 64 mmol KCl | Usual care | 150/95 | 66/... | 3.7 |
| 65 mmol KCl | Placebo | 154/105 | 62/172 | 3.8 |
| 80 mmol KCl | Placebo | 118/71 | 50/131 | ... |
| 64 mmol KCl | Placebo | 113/69 | 39/123 | ... |
| 100 mmol K from diet | Normal diet | 150/95 | 71/155 | ... |
| 100 mmol K from diet, low Na | Low Na | 152/95 | 68/148 | ... |
| 72 mmol KCI, low Na | Placebo, low Na | 143/78 | 71/141 | 3.8 |
| 48 mmol KCI | Placebo | 145/92 | 60/190 | 4.4 |
| 120 mmol KCI | Placebo | 145/95 | .../... | 4.4 |
| 17-34 mmol KCl | Usual care | 161/98 | .../... | 4.2 |
| 96 mmol KCI, low Na | Placebo, low Na | 124/80 | 79/166 | 4.2 |
| 80 mmol KCl | Placebo | 150/95 | 52/176 | ... |
| 64 mmol KCl | Placebo | 174/100 | 59/171 | 4.0 |
| 90 mmol KCI | 10 mmol KCl | 120/77 | 70/164 | 3.2 |
| 100 mmol K from diet, low Na | Low Na | 124/82 | 64/161 | ... |
| 75 mmol KCI | Placebo | 117/69 | 77/153 | 4.2 |
| 75 mmol K citrate | Placebo | 117/69 | 77/153 | 4.2 |
| 60 mmol KCl | Placebo | 155/100 | 62/196 | 3.6 |
| 64 mmol KCl | Placebo | 147/96 | 57/155 | 3.8 |
| 80 mmol KCl | Placebo | 105/63 | 53/105 | ... |
| 120 mmol K citrate and bicarbonate | Placebo | 150/100 | 62/169 | 4.4 |
| 120 mmol KCI | Placebo | 152/87 | 70/192 | 3.9 |
| 60 mmol KCI | Placebo | 187/96 | 63/115 | 4.2 |
| 60 mmol KCI | Placebo | 122/81 | 59/153 | ... |
| 80 mmol KCl | Placebo | 125/78 | 47/147 | ... |

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**TABLE 47.7**

Urinary Electrolyte Excretion, Body Weight, and Blood Pressure during Followup in 33 Potassium Supplementation Trials*

| Author, Year | Mean Net Change in Urinary Electrolytes, mmol/d K+/Na+ | Urinary Sodium Excretion during Followup, mmol/d | Mean Net Change in Body Weight, kg | Mean Net Change, in Blood Pressure, mm Hg Systolic/Diastolic |
|---|---|---|---|---|
| Skrabal, 1981 | | | | |
| (a) | 44/-55 | 155 | -0.9 | -1.7/-4.5 |
| (b) | 107/-12 | 28 | -0.2 | 0.4/-0.5 |
| MacGregor, 1982 | 56/29 | 169 | -0.2 | -7.0/-4.0 |
| Khaw and Thom, 1982 | 52/9 | 164 | ... | -1.1/-2.4 |
| Richards, 1984 | 129/5 | 200 | 0.8 | -1.9/-1.0 |
| Smith, 1985 | 50/7 | 80 | 0.1 | -2.0/0 |
| Kaplan, 1985 | 46/1 | 168 | 0.8 | -5.6/-5.8 |
| Zoccali, 1985 | 81/13 | 195 | ... | -1.0/-3.0 |
| Bulpitt et at, 1985 | 40/10 | 149 | 1.2 | 2.3/4.8 |
| Matlou et at, 1986 | 62/35 | 165 | -0.4 | -7.0/-3.0 |
| Barden et at, 1986 | 68/5 | 130 | ... | -1.4/-1.4 |
| Poulter and Sever, 1986 | 38/1 | 114 | -0.1 | -1.2/2.0 |
| Chalmers et at, 1986 | | | | |
| (a) | 22/7 | 150 | ... | -3.9/-3.1 |
| (b) | 12/25 | 79 | ... | -1.0/1.6 |
| Grobbee, 1987 | 57/12 | 69 | 0.4 | -2.5/-0.6 |
| Siani, 1987 | 30/6 | 189 | ... | -14.0/-10.5 |
| Svetkey, 1987 | .../... | ... | ... | 6.3/-2.5 |
| Medical Research Council, 1987 | .../... | ... | ... | 0.8/-0.7 |
| Grimm, 1988 | 80/-9 | 114 | ... | 0.7/1.4 |
| Cushman and Langford, 1988 | 36/177 | 177 | ... | .../-0.1 |
| Obel, 1989 | 39/... | 172 | ... | -41.0/-17.0 |
| Krishna, 1989 | 47/44 | 144 | -0.6 | 5.5/-7.4 |
| Hypertension Prevention Trial, 1990 | 0/-6 | 155 | 0.2 | -1.3/-0.9 |
| Mullen and O'Connor, 1990 | | | | |
| (a) | 23/-12 | 141 | -0.1 | 0/3.0 |
| (b) | 34/-15 | 138 | -0.2 | -2.0/2.0 |
| Patki, 1990 | 22/-14 | 184 | ... | -12.1/-13.1 |
| Valdes, 1991 | 68/19 | 166 | -1 | -6.3/-3.0 |
| Barden, 1991 | 72/15 | 120 | ... | -1.7/-0.6 |
| Overlack, 1991 | 105/-13 | 156 | 0 | 2.8/3.0 |
| Smith et at, 1992 | 109/29 | 221 | 0.2 | -4.3/-1.7 |
| Fotherby and Potter, 1992 | 39/13 | 136 | -0.7 | -10.0/-6.0 |
| Whelton, 1995 | 42/6 | 144 | ... | -0.3/0.1 |
| Brancati, 1996 | 70/20 | 141 | -0.1 | -6.9/-2.5 |

* Ellipses indicate no data.

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In a randomized, double-blind study of 48 hypertensive persons and 32 normotensive persons, 1000 mg per day of calcium or placebo was given for 8 weeks.[38] Supine blood pressure decreased significantly 3.8/2.3 mmHg in the hypertensive subjects; 25, 23, and 13% of subjects achieved a blood pressure goal of systolic <140 mmHg, diastolic <90 mmHg and both systolic <140 mmHg and diastolic <90 mmHg, respectively. Calcium did not lower blood pressure in the normotensives. 44% of hypertensive and 19% of normotensive subjects lowered their standing systolic blood pressure >10 mmHg. There have been at least 67 randomized trials of calcium supplements in nonpregnant study popula-

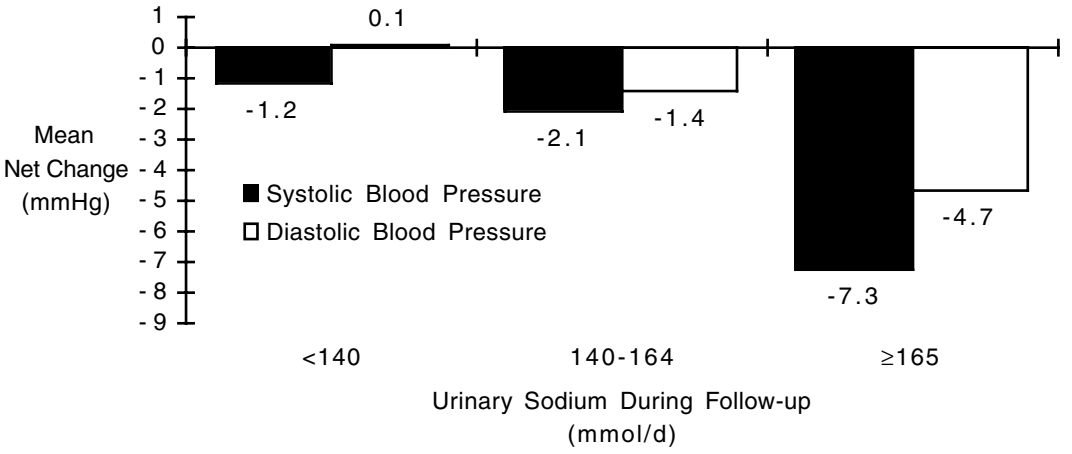


**FIGURE 47.2**
Effect of potassium supplementation on net blood pressure reduction according to urinary sodium excretion during followup: the greater the sodium excretion, the greater the blood pressure reduction with potassium supplementation ($p < 0.001$ for both systolic and diastolic blood pressure). Derived from Whelton PK, He J, Cutler JA, et al. *JAMA* 277: 1624, 1997. With permission.

tions. There have been several meta-analyses to assess the effect of dietary and nondietary interventions on blood pressure.[35,39-43] A larger effect of calcium supplementation on systolic blood pressure was observed with increasing age and among women.[41] The subgroup of hypertensive subjects had a greater reduction in blood pressure than the normotensives (–4.30/–1.50 mmHg versus –0.27/–0.33 mmHg).[42] The change in systolic and diastolic blood pressure was significant for the hypertensives, but not the normotensives.[42] The largest meta-analysis (see Tables 47.8 and 47.9) shows a reduction of blood pressure of –1.44/–0.84 mmHg ($p < 0.001$ for each).[43] There was no difference in the change in blood pressure comparing 33 nondietary trials (–1.09/–0.87 mmHg) and the 9 dietary trials (–2.01/–1.09 mmHg). The authors concluded that the small reduction in blood pressure of calcium supplements does not merit its use in mild hypertension, and further suggest that the use of calcium must weigh the benefits of reducing cardiovascular disease and increasing bone density versus the risk of nephrolithiasis.

Despite this modest benefit in nonpregnant subjects, a meta-analysis (see Tables 47.10 and 47.11) of calcium supplementation in pregnancy observed a blood pressure reduction of –5.40/–3.44 mmHg and a decrease in the rate of preeclampsia (odds ratio = 0.38 [95% CI: 0.22 to 0.65]).[44] Since the publication of the meta-analysis, the National Institutes of Health sponsored trial, Calcium for Preeclampsia Prevention, has been completed.[45] This placebo-controlled, randomized, multicenter trial assigned 4589 nulliparous women 13 to 21 weeks pregnant to 2 g of calcium carbonate or placebo. There was no benefit in the rate of preeclampsia (6.9 versus 7.3%), the prevalence of gestational hypertension (15.3 versus 17.3%), or pregnancy-associated proteinuria (3.4 versus 3.3%) in the calcium (n = 2295) and placebo (n = 2294) groups.

## Magnesium

Magnesium is a divalent intracellular cation. The adult body contains about 25 g distributed between the skeleton (60%) and soft tissues (40%).[46] It serves as a cofactor for many enzyme systems. Intracellular calcium increases and blood pressure rises as magnesium depletion occurs in rats. The hypotensive effect of magnesium is observed best when given

**TABLE 47.8**

Randomized Controlled Trials Examining the Relationship of Calcium and Blood Pressure

| Author, Year, Study Design | No. of Subjects (Intervention/ Control) | Quality Score* | Calcium Formulation | Elemental Calcium (mg/day) | Study Duration (weeks) |
|---|---|---|---|---|---|
| *Nondietary Interventions* | | | | | |
| Belizan, 1983 | 30/27 | 4 | Calcium gluconate | 1000 | 22 |
| Sunderrajan, 1984[cx] | 17/17 | 0 | Calcium carbonate | 1000 | 4 |
| Johnson, 1985 | 59/56 | 2 | Calcium carbonate | 1500 | 208 |
| McCarron, 1985[cx] | 80/80 | 3 | Calcium carbonate | 1000 | 8 |
| Grobbee, 1986 | 46/44 | 4 | Calcium citrate | 1000 | 12 |
| Nowson, 1986 | 31/33 | 3 | Calcium carbonate | 1600 | 8 |
| Resnick, 1986[cx, ci] | 8/8 | 0 | Calcium carbonate | 2000 | 8 |
| Strazzullo, 1986[cx, ci] | 17/17 | 3 | Calcium gluconate | 1000 | 15 |
| Van Berestyn, 1986 | 29/29 | 3 | Calcium carbonate | 1500 | 6 |
| Cappuccio, 1987[cx] | 18/18 | 4 | Calcium gluconate | 1600 | 4 |
| Lyle, 1987 | 37/38 | 4 | Calcium carbonate | 1500 | 12 |
| Meese, 1987[cx] | 19/17 | 3 | Calcium carbonate | 800 | 8 |
| Siani, 1987[cx] | 8/8 | 4 | Calcium gluconate | 1000 | 3 |
| Thomsen, 1987 | 14/14 | 3 | Calcium gluconate | 2000 | 52 |
| Vinson, 1987 | 4/5 | 4 | Calcium carbonate | 500 | 7 |
| Zoccali, 1987[cx, ci] | 11/11 | 3 | Calcium gluconate | 1000 | 2 |
| Siani, 1988[cx] | 14/14 | 5 | Calcium gluconate | 1000 | 4 |
| Zoccali, 1988[cx] | 21/21 | 3 | Calcium gluconate | 1000 | 8 |
| Orwoll, 1990[ci] | 34/28 | 3 | Calcium carbonate | 1000 | 156 |
| Tanji, 199l[cx] | 28/28 | 3 | Calcium carbonate | 1200 | 12 |
| Cutler, 1992 | 237/234 | 6 | Calcium carbonate | 1000 | 26 |
| Lyle, 1992 | 21/21 | 3 | Calcium carbonate | 1500 | 8 |
| Galloe, 1993[cx] | 20/20 | 4 | Calcium gluconate | 2000 | 12 |
| Jespersen, 1993[cx] | 7/7 | 5 | Calcium carbonate | 1000 | 8 |
| Pan, 1993[cx] | 14/15 | 1 | Calcium citrate and placebo Vitamin D | 800 | 11 |
| Weinberger, 1993[cx] | 46/46 | 4 | Calcium carbonate | 1500 | 8 |
| Petersen, 1994[ci] | 10/10 | 1 | Calcium gluconate | 2000 | 26 |
| Zhou, 1994 | 30/27 | 3 | Calcium carbonate | 1000 | 14 |
| Gillman, 1995 | 51/50 | 4 | Calcium citrate malate | 600 | 12 |
| Sacks, 1995[ci] | 34/31 | 5 | Calcium carbonate | 1000 | 26 |
| Lijnen, 1996[ci] | 16/16 | 5 | Calcium gluconate | 2000 | 16 |
| Davis, 1997 | 17/17 | 3 | Calcium gluconate | 1500 | 4 |
| Sanchez, 1997 | 10/10 | 4 | Calcium gluconate | 1500 | 8 |
| *Dietary Interventions* | | | | | |
| Margetts, 1986[cx, ci] | 39/39 | 3 | Other dietary manipulation | 1076 | 6 |
| Rouse, 1986 | 18/18 | 3 | Other dietary manipulation | 1177 | 6 |
| Bierenbaum, 1988[cx] | 50/50 | 1 | Milk/dairy product suppl | 1150 | 26 |
| Morris, 1988 | 142/139 | 4 | Other dietary manipulation | 1500 | 12 |
| Hakala, 1989 | 31/37 | 3 | Other dietary manipulation | 1163 | 52 |
| Van Beresteijn, 1990 | 28/25 | 3 | Milk/dairy product suppl | 1180 | 6 |
| Kynast-Gales, 1992[cx] | 7/7 | 1 | Milk/dairy product suppl | 1515 | 4 |
| McCarron, 1997 | 274/274 | 4 | Milk/dairy product suppl | 1886 | 10 |
| Appel, 1997 | 151/154 | 4 | Milk/dairy product suppl | 1265 | 8 |

[cx], cross-over study; [ci], cointervention.

* A quality score of 6 corresponds to the highest quality level

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**TABLE 47.9**

Randomized Controlled Trials Studying the Effect of Calcium Supplementation and Blood Pressure

| Author, Year | Position of Blood Pressure Measurement | Mean BP at Study End* | Systolic Mean Baseline, mm Hg | Systolic Mean Difference, mmHg (SD) | Diastolic Mean Baseline, mm Hg | Diastolic Mean Difference, mm Hg (SD) |
|---|---|---|---|---|---|---|
| *Nondietary Interventions* | | | | | | |
| Belizan, 1983 | | | | | | |
| Women | Lateral | 1 | 102 | -2.40 (1.03) | 68 | -4.50 (1.46) |
| Men | Lateral | 1 | 113 | -0.80 (1.05) | 71 | -6.00 (1.94) |
| Sunderrajan, 1984 | | | | | | |
| Normotensive | Sitting | 2 | NA | 1.89 (2.78) | NA | 1.89 (2.50) |
| Hypertensive | Sitting | 2 | NA | -1.63 (5.93) | NA | -4.13 (2.50) |
| Johnson, 1985 | | | | | | |
| Normotensive | Sitting | 2 | 120 | 0.00 (3.01) | 74 | 0.00 (1.67) |
| Hypertensive | Sitting | 2 | 141 | -13.0 (6.52) | 86 | 0.00 (2.79) |
| McCarron, 1985 | | | | | | |
| Normotensive | Standing | 2 | 113 | 1.30 (2.00) | 75 | 1.00 (2.62) |
| Hypertensive | Standing | 2 | 144 | -5.60 (2.10) | 92 | -2.30 (1.40) |
| Grobbee, 1986 | Sitting | 1 | 143 | -0.40 (2.27) | 83 | -2.40 (1.90) |
| Nowson, 1986 | | | | | | |
| Normotensive | Sitting | 1 | | 0.00 (2.97) | | 0.30 (2.33) |
| Hypertensive | Sitting | 1 | 157 | 1.60 (3.83) | 92 | 1.30 (2.90) |
| Resnick, 1986 | | | | | | |
| Salt-sensitive | Sitting | 1 | NA | NA | NA | -8.0 (6.0) |
| Salt-insensitive | Sitting | 1 | NA | NA | NA | 7.0 (6.0) |
| Strazzullo, 1986 | Standing | 2 | 145 | -8.60 (4.98) | 98 | -1.70 (2.56) |
| Van Berestevn, 1986 | Supine | 1 | 115 | -1.36 (1.88) | 65 | 0.79 (1.66) |
| Cappuccio, 1987 | Standing | 2 | 156 | 2.00 (4.17) | 112 | 0.40 (2.64) |
| Lyle, 1987 | | | | | | |
| White | Sitting | 1 | 115 | -2.44 (2.00) | 75 | -1.89 (2.31) |
| Black | Sitting | 1 | 114 | -3.63 (3.85) | 71 | 4.02 (5.67) |
| Meese, 1987 | Sitting | 2 | 143 | -5.00 (4.21) | 95 | -2.00 (2.83) |
| Siani, 1987 | Supine | 2 | 154 | 5.10 (8.01) | 96 | 1.30 (4.10) |
| Thomsen, 1987 | Supine | 2 | 124 | -0.50 (6.10) | 76 | -1.30 (3.78) |
| Vinson, 1987 | Supine | 2 | 114 | 7.90 (4.93) | 74 | 2.40 (2.05) |
| Zoccali, 1987 | Sitting | 1 | 141 | 6.45 (3.35) | 88 | 4.64 (2.21) |
| Siani, 1988 | Supine | 2 | 139 | 2.20 (4.94) | 91 | 0.70 (3.68) |
| Zoccali, 1988 | Sitting | 1 | 142 | -2.80 (2.97) | 88 | -2.80 (2.47) |
| Orwoll, 1990 | Sitting | 1 | 131 | 2.60 (3.54) | 84 | 3.08 (2.63) |
| Tanji, 1991 | Sitting | 1 | 146 | 3.00 (4.20) | 95 | 2.00 (2.40) |
| Cutler, 1992 | Sitting | 1 | 126 | -0.46 (0.67) | 84 | 0.20 (0.46) |
| Lyle, 1992 | Sitting | 1 | 133 | -5.90 (1.99) | 87 | -7.20 (1.71) |
| Galloe, 1993 | Sitting | 1 | 168 | 2.20 (4.49) | 97 | 3.30 (2.75) |
| Jespersen, 1993 | Supine | 1 | 148 | -0.57 (7.20) | 93 | -0.86 (3.88) |
| Pan, 1993 | Sitting | 1 | 136 | -7.09 (7.89) | 72 | -0.87 (3.29) |
| Weinberger, 1993 | | | | | | |
| Normotensive | Sitting | 2 | 116 | 1.00 (3.00) | 72 | -1.00 (2.64) |
| Hypertensive | Sitting | 2 | 131 | -2.00 (5.68) | 87 | -1.00 (2.92) |
| Petersen, 1994 | Sitting | 2 | 145 | 4.50 (13.2) | 81 | -8.20 (5.10) |
| Zhou, 1994 | Sitting | 1 | 158 | -14.6 (4.48) | 103 | -7.11 (2.43) |
| Gillman, 1995 | Sitting | 1 | 102 | -2.20 (11.0) | 58 | -0.80 (7.16) |
| Sacks, 1995 | Sitting | 1 | NA | 3.70 (2.45) | NA | 3.60 (2.32) |
| Lijnen, 1996 | Supine | 1 | 114 | -5.70 (2.18) | 73 | -3.50 (1.79) |
| Davis, 1997 | Mean 24 h ambulatory | 1 | 125 | -1.72 (1.20) | 91 | -0.49 (0.35) |
| Sanchez, 1997 | Sitting | 1 | 166 | 1.60 (1.60) | 99 | 0.40 (1.21) |

**TABLE 47.9** *(Continued)*

Randomized Controlled Trials Studying the Effect of Calcium Supplementation and Blood Pressure

| Author, Year | Position of Blood Pressure Measurement | Mean BP at Study End* | Systolic Mean Baseline, mm Hg | Systolic Mean Difference, mmHg (SD) | Diastolic Mean Baseline, mm Hg | Diastolic Mean Difference, mm Hg (SD) |
|---|---|---|---|---|---|---|
| *Dietary Interventions* | | | | | | |
| Margetts, 1986 | Sitting | 1 | NA | -3.50 (1.75) | NA | -1.20 (1.00) |
| Rouse, 1986 | Sitting | 2 | NA | 1.90 (2.30) | NA | 2.30 (1.40) |
| Bierenbaum, 1988 | Sitting | 2 | 119 | -2.00 (2.19) | 79 | -1.00 (1.33) |
| Morris, 1988 | | | | | | |
| Normotensive | Standing | 1 | 113 | -1.00 (1.04) | 77 | -0.90 (0.80) |
| Hypertensive | Standing | 1 | 145 | -3.60 (1.50) | 94 | -1.20 (0.86) |
| Hakala, 1989 | Sitting | 1 | 129 | 3.80 (11.9) | 84 | 3.20 (4.53) |
| Van Beresteijn, 1990 | Supine | 1 | 114 | -2.82 (1.83) | 63 | 0.43 (1.89) |
| Kynast-Gales, 1992 | Supine | 1 | 136 | -8.29 (8.12) | 83 | -0.14 (6.15) |
| McCarron, 1997 | Sitting | 1 | 134 | -1.80 (0.78) | 85 | -1.20 (0.46) |
| Appel, 1997 | Sitting | 1 | 131 | -2.70 (0.83) | 84 | -1.90 (0.60) |

* For mean blood pressure at study end, 1 indicates change and 2 indicates mean.

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in preeclampsia and toxemia. Magnesium supplementation in 400 normotensive primigravida women given from 13 to 24 weeks gestation did not lower blood pressure or the incidence of preeclampsia.[47] However, among 2138 hypertensive women admitted in labor, intramuscular magnesium sulfate was superior to phenytoin in preventing eclamptic seizures (0 versus 0.92%, $p = 0.004$).[48]

Magnesium and calcium contribute to water hardness. There is an inverse relationship between water hardness and blood pressure.[49,50] However, epidemiologic studies assessing the role of magnesium and blood pressure often do not control for potential confounders, including caloric, ethanol, sodium, potassium, and calcium intake, and use of antihypertensive medication.[50] Thus, observational studies using 24-hour dietary recall, food records, and food frequency questionnaires have not always shown a consistent correlation, but generally show a negative correlation with both systolic and diastolic blood pressure after adjustment.[50] In the Health Professionals Follow-up Study, the relative risk of a stroke among 43,738 men between the lowest quintile of magnesium intake and highest quintile, after adjustment for age, BMI, various risk factors, family history, profession, and physical activity, was 0.62 ($p < 0.002$).[28] In the Atherosclerosis Risk in Communities Study of four U.S. communities ($n = 15,248$ participants), an early report suggested that low serum and dietary magnesium may be related to the etiology of hypertension; however, a subsequent report found no association between dietary magnesium intake and incident hypertension.[51,52]

The mechanism most often cited for the apparent antihypertensive effect of magnesium is a calcium antagonist property. Other mechanisms include stimulation of vascular prostacyclin release, renal vasodilation, acceleration of the cell membrane sodium pump, and alterations in vascular responsiveness to vasoactive agents.[53] One 1988 analysis concluded that there were inadequate data from the four randomized, controlled trials to suggest a hypotensive effect.[49] Since that report, there have been a number of trials reported with mixed results (see Table 47.12). It has been suggested that combinations of cations may act in concert; however, in a randomized, double-blind, multicenter trial of 125 participants, there was no hypotensive effect of magnesium in combination with either calcium or potassium.[53] In normotensive women whose reported intake of magnesium was

**TABLE 47.10**

Randomized Controlled Trials of Calcium Supplementation in Pregnancy

| Author, Year | No. of Participants, Calcium Supplementation/ Placebo | Calcium Formulation | Elemental Calcium Equivalent, mg/d | Type of Control | Weeks of Gestation | Treatment Duration, wk | Cointervention | Compliance Assessed | Quality Score† |
|---|---|---|---|---|---|---|---|---|---|
| *Trials Providing Data on Treatment Effects of Systolic and Diastolic Blood Pressure* | | | | | | | | | |
| Belizan, 1983 | 11/14 | Calcium Sandoz | 2000 | Placebo | 15 | 22 | NA* | NA | 3 |
| Marya , 1987 | 188/182 | Unknown calcium supplement | 375 | Placebo | 22 | 18 | No | Yes | 5 |
| Villar,1987 | 25/27 | Os-Cal tablets | 1500 | Placebo | 26 | 14 | Yes | Yes | 0 |
| Lopez-Jaramillo,1989 | 49/43 | Calcium gluconate | 2000 | Placebo | 23 | 17 | No | Yes | 1 |
| Repke, 1989 | 16/18 | Os-Cal tablets | 1500 | Placebo | 25 | 10 | No | Yes | 4 |
| Lopez-Jaramillo,1990 | 22/34 | Elemental calcium | 2000 | Placebo | 30 | 10 | No | No | 4 |
| Belizan, 1991 | 579/588 | Calcium carbonate | 2000 | Placebo | 20 | 20 | No | Yes | 2 |
| Felix, 1991 | 14/11 | Elemental calcium | 2000 | Placebo | 20 | 20 | No | Yes | 3 |
| Knight, 1992 | 10/10 | Os-Cal tablets | 1000 | Normal diet | 12 | 20 | Yes | Yes | 5 |
| Sanchez-Ramos, 1993 | 36/39 | Unknown calcium supplement | NA | Unknown | 22 | 18 | No | No | 6 |
| Sanchez-Ramos, 1994 | 29/34 | Calcium carbonate | 2000 | Placebo | 25 | 15 | No | Yes | 4 |
| Levine, 1997‡ | 2294/2295 | Calcium carbonate | 2000 | Placebo | 17 | 21 | No | Yes | 6 |
| *Trials Providing Data on Binary Outcomes Exclusively* | | | | | | | | | |
| Montanaro, 1990 | 84/86 | Calcium carbonate | 2000 | Placebo | 24 | 16 | No | No | 1 |
| Villar and Repke 1990 | 95/95 | Os-Cal tablets‡ | 2000 | Placebo | 23 | 20 | Yes | Yes | 2 |
| Cong, 1993 | 50/50 | Shen gu capsules | Unknown | Placebo | 22 | 18 | No | No | 0 |

* NA indicates not applicable.

† Quality scores range from 0 to 6 with 6 indicating the highest quality score

‡ Calcium for the Preeclampsia Prevention Trial (Not in the original meta-analysis)

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**TABLE 47.11**

Change in Blood Pressure in Randomized Controlled Trials of Calcium Supplementation in Pregnancy

| Author, Year | Mean Difference In Systolic Blood Pressure, mm Hg | Mean Difference in Diastolic Blood Pressure, mm Hg |
|---|---|---|
| Belizan, 1983 | -5.10 | -5.70 |
| Marya, 1987 | -6.90 | -3.40 |
| Villar, 1987 | -4.10 | -4.90 |
| Lopez-Jaramillo, 1989 | -8.70 | -6.60 |
| Repke, 1989 | -2.50 | -2.77 |
| Lopez-Jaramillo, 1990 | -13.10 | -11.80 |
| Belizan 1991 | -1.70 | -0.90 |
| Felix, 1991 | -6.30 | -5.80 |
| Knight and Keith, 1992 | | |
| Normotensive | -2.70 | 0.50 |
| Hypertensive | +4.8 | 0 |
| Sanchez-Ramos, 1993 | +4.6 | -0.82 |
| Sanchez-Ramos, 1994 | -4.08 | -3.00 |
| Levine, 1997* | -0.3 | +0.3 |

* Calcium for the Preeclampsia Prevention Trial (not in the original meta-analysis)

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between the 10th and 15th percentiles, 16 weeks' daily supplement of magnesium 14 mmol had no significant treatment effect (–0.9/–0.7 mmHg). The administration of magnesium with potassium did not enhance the effect of potassium alone.[54]

### ω-3 Polyunsaturated Fatty Acids

ω-3 polyunsaturated fatty acids refer to the fish oil, very long chain fatty acids eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids. ω-3 polyunsaturated fatty acids are thought to lower blood pressure by altering the balance of the vasoconstrictor thromboxane $A_2$ and the vasodilator prostacyclin prostaglandin $I_3$, modulating the vasoconstrictor response to pressors, or decreasing blood viscosity.[8]

A meta-analysis by Appel identified 40 studies testing the impact of ω-3 polyunsaturated fatty acids on blood pressure; however, 23 were eliminated because of design, including concurrent antihypertensive medications, no control group, unhealthy study population, concurrent use of ω-3 polyunsaturated fatty acids in the control group, or insufficient data.[55] Most trials used a combined dose of 3 g daily of EPA and DHA, which is equal to 6 to 10 capsules of commercial fish oil supplements or two 100 g servings of fish that are high in ω-3 polyunsaturated fatty acids. The overall change in blood pressure, –1.5/–1.0 mmHg, was significant. For normotensives, the change in blood pressure, –1.0/–0.5 mmHg, was significant for the systolic blood pressure only. However, the decline in blood pressure, –5.5/–3.5 mmHg, for hypertensives was significant for both systolic and diastolic blood pressure ($p < 0.001$). Interestingly, the higher the blood pressure, the greater the reduction ($p < 0.05$); however, this was not a function of the dose of the ω-3 polyunsaturated fatty acids, duration of treatment, type of intervention (food versus oil capsules), or age of participants. Side effects summarized include the unpleasant or fishy taste, gastrointes-

**TABLE 47.12**

Randomized Trials of Magnesium Supplementation

| Author, Year | n | Mean Age, Yr | Men, % | Cohort | BP Meds | Mg Salt, mmol Mg/d | Study Design | Duration, Weeks | Control ΔSBP/ΔDBP | Magnesium ΔSBP/ΔDBP |
|---|---|---|---|---|---|---|---|---|---|---|
| Itoh, 1997 | 33 | 65 | 33 | Mixed | ? | Hydroxide, 17-23 | DB, PR | 4 | +1/-1 | -5/-2 |
| TOHP, 1992‡ | 461 | 43 | 70 | Normotensive | No | Diglycine, 15 | DB, PR | 24 | -2.9/-2.7 | -3.0/-2.9 |
| Sacks, 1998 | 153 | 39 | 0 | Normotensive | No | Lactate, 14 | DB, PR | 16 | +0.4/+0.2 | -0.5/-0.5 |
| de Valk, 1998 | 50 | 62.5 | 56 | Diabetes (insulin) | ? | Aspartate, 15 | DB, PR | 12 | -10.4/-0.8 | -7.7/-0.3 |
| Purvis, 1994 | 28 | 53.8 | 86 | Diabetes (no insulin) | ? | Chloride, 15.7 | DB, CO | 6 | | -7.4/-2.3 |
| Cappuccio, 1985 | 17 | 52 | 53 | Hypertensive | No | Aspartate, 15 | DB, CO | 4 | -3/-3 | 0/-2 |
| Dyckner, 1983 | 20 | 65 | 33 | 90% Hypertensive | Yes | Aspartate, 15 | O,PR | 24 | -0/-4 | -12/-8 |
| Ferrara, 1992 | 14 | 47.5 | 57 | Hypertensive | No | Pidolate, 15 | DB, PR | 24 | -17/-4 | -7/-7 |
| Henderson, 1986 | 41 | 62 | ? | Hypertensive | Yes | Oxide, 12.5 | DB, PR | 24 | -3/-1 | -4/-3 |
| Kawano, 1998 | 60 | 58 | 57 | Hypertensive | Some | Oxide, 20 | CO | 8 | | -3.7/-1.7 |
| Lind, 1991 | 71 | 61 | 52 | Hypertensive | No | Mixed†, 15 | DB, PR | 24 | -2/-4.2 | +1/-2 |
| Plum-Wirell, 1994 | 39 | 39 | 62 | Hypertensive | No | Aspartate, 15 | DB, CO | 8 | -0.8/-0.4 | -2.4/-0.4 |
| Reyes, 1984 | 21 | 57 | 19 | Hypertensive | Yes | Chloride, 15.8 | DB, PR | 3 | -13/-4 | -11/-7 |
| Sanjuliani, 1996 | 15 | 36-65 | 47 | Hypertensive | No | Oxide, 25 | DB, CO | 3 | +1.7/-1.0 | -7.6/-3.8 |
| Sibai, 1989 | 374 | 18 | 0 | Pregnancy | No | Aspartate, 15 | DB, PR | 21 | +16/+18 | +15/+16 |
| Widman, 1993 | 17 | 50 | 88 | Hypertensive | No | Hydroxide, 15-40 | DB, CO | 9 | -1/0.0 | -7.9/-8.2 |
| Wirell, 1994 | 39 | 26-69 | 77 | Hypertensive | Yes | Aspartate, 15 | DB, CO | 8 | +3.2/+2.3 | -3.8//-1.7 |
| Witteman, 1994 | 91 | 57 | 0 | Hypertensive | No | Aspartate, 20 | DB, PR | 24 | +0.2/+0.1 | -3.3/-2.4 |
| Zemel, 1990 | 13 | ~49 | 86 | Hypertensive | No | Aspartate, 40 | DB, PR | 12 | -1/+1 | +3/+2 |

† 4.58 mmol Mg lactate + 0.42 Mg Citrate; ‡ TOPH, Trial of Hypertension Prevention (Phase I)

tinal symptoms, eructation, loose stool or diarrhea, and obstipation occurring in 28% of experimental subjects — 13% of the control group ($p < 0.001$).[55]

Another meta-analysis included 31 of 52 studies that included trials with a placebo group and a report of pretreatment and post-treatment blood pressures (see Table 47.13).[56] Like the previous meta-analysis, hypertensives (–3.4/–2.0 mmHg) had greater blood pressure decline than normotensives (–0.4/–0.7 mmHg), but the dose of the fish oils was higher in the hypertensive group (5.6 g/d) than the normotensive group (4.2 g/d). There also was a statistically significant dose-dependent decline in blood pressure: ≤ 3g/d, –1.3/–0.7 mmHg; >3 to 7g/d, –2.9/–1.6 mmHg; and 15g/d, –8.1/–5.8 mmHg. The effect of fish oil on blood pressure is maximally manifested by 3 to 4 weeks.

Since the completion of these meta-analyses, several new studies have supported their conclusions. In a double-blind, placebo-controlled trial of parallel design, 59 overweight, mildly hyperlipidemic men were randomized to 4 g/d of purified EPA, DHA, or olive oil (placebo) capsules and continued their usual diets for 6 weeks. Fifty-six subjects completed the study. Only DHA significantly reduced 24-hour and daytime ambulatory blood pressure ($p < 0.05$).[57] In 63 overweight hypertensives, combining a daily fish meal with a weight-reducing regimen led to additive reduction on ambulatory blood pressure and decreased heart rate.[58]

### Dietary Protein

Cross-sectional studies show that dietary protein intake is inversely related to blood pressure, although a direct relationship was considered to exist.[59] Protein intake was thought to increase blood pressure due to adverse effects on renal function in partially nephrectomized rats. The mechanism of action of high dietary protein intake is not clear, but multicollinearity (multiple nutrient intake that correlated with one another) is a problem. Amino acid production (e.g., tryptophan, tyrosine, and arginine) may affect hormones or neurotransmitters that ultimately alter blood pressure. For instance, the sulfonic amino acid taurine given 6 g for 7 days in 19 young hypertensive subjects decreased blood pressure –9.0/–4.1 mm Hg compared with to –2.7/–1.2 mmHg in the placebo-treated subjects in a double-blind, placebo-controlled trial.[60] Perhaps other protein metabolites have natriuretic or diuretic activity.

Human observational studies on protein and blood pressure are displayed in Table 47.14. These studies show in aggregate that increased protein intake, determined by food records or recall or by urine studies of sulfate and urea nitrogen, is associated with decreased blood pressure. The relationship of blood pressure and vegetable protein versus animal protein is unclear. After adjustment for age, BMI, alcohol consumption, urinary sodium excretion, dietary intake, and resident area for each one standard deviation higher level of dietary protein intake (39 g), a 3.55 mmHg lower systolic blood pressure was observed.

Most intervention trials (Table 47.15) have been conducted in normotensive subjects, were not designed to assess the relationship between protein and blood pressure or determine a dose relationship, and were not powered adequately or randomized.[59,61]

### Dietary Fiber

Vegetarians and other persons with high fiber intakes have lower average blood pressures than persons with low fiber intakes do. In the Coronary Artery Risk Development in Young Adults (CARDIA) Study, fiber intake predicted insulin levels, weight gain, and other cardiovascular risk factors more potently than did fat consumption.[62] High intake of fiber was associated with lower systolic and diastolic blood pressure in whites but not African-

**TABLE 47.13**

Characteristics of the 31 Trials used for the Meta-Analysis of Fish Oil and Blood Pressure*

| Study, Year | Study Design* | Blinding Subject | Blinding Observer§ | Study Length | n, Treatment* | ω-3 Dose (g/d)‡ | Gender (Age Range) | Baseline Pressure¶ | BP Effect SBP/DBP¶ |
|---|---|---|---|---|---|---|---|---|---|
| *Health Subjects* | | | | | | | | | |
| Mortensen, 1983 | XO | + | + | 4 | 20 Fish oil<br>20 Mixed oil | 3.3 | Men<br>(25-40 y) | 120/76 | -4.0/-4.0 |
| Bruckner, 1987 | PG | + | - | 3 | 10 Fish oil<br>11 Olive oil | 3.9 | Men<br>(19-40 y) | 119/80 | +5.0/+1.0 |
| v Houwelingen, 1987 | | | | | | | | | |
| Maastricht | PG | - | + | 6 | 19 Fish<br>20 Meat | 4.7 | Men<br>(20-45 y) | 121/77 | +1.1/-0.9 |
| Tromso | PG | - | + | 6 | 11 Fish<br>12 Meat | 4.7 | Men<br>(20-45 y) | 118/77 | +0.1/-0.9 |
| Zeist | PG | - | + | 6 | 10 Fish<br>10 Meat | 4.7 | Men<br>(20-45 y) | 115/73 | -3.7/-3.0 |
| Flaten, 1990 | PG | + | + | 6 | 27 Fish oil<br>29 Olive oil | 6.5 | Men<br>(35-45 y) | 119/80 | +1.5/+0.8 |
| Ryu, 1990 | PG | NS† | NS | 4 | 10 Fish oil<br>10 Wheat germ | 3 | Men<br>(20-39 y) | 124/73 | -4.3/-2.0 |
| TOHP, 1992 | PG | + | + | 24 | 175 Fish oil<br>175 Olive oil | 2.4 | Men & Women<br>(30-54y) | 123/81 | -0.2/-0.6 |
| *Hypertensive Subjects* | | | | | | | | | |
| Norris, 1986 | XO | + | + | 6 | 16 Fish oil<br>16 Placebo | NS | Men & Women<br>(45-74 y) | 161/95 | -10.0/-2.0 |
| Knapp, 1989 | PG | - | - | 4 | 8 Fish oil<br>8 Saturated mix | 3 | Men<br>(age NS) | 137/94 | -2.6/-0.1 |
| Meland, 1989 | PG | + | + | 6 | 20 Fish oil<br>20 Mixed oil | 6 | Men<br>(26-66 y) | 149/101 | +1.0/-1.0 |
| Bonaa, 1990 | PG | NS | NS | 10 | 78 Fish oil<br>78 Corn oil | 5.1 | Men & Women<br>(34-60 y) | 144/95 | -6.4/-2.8 |

**TABLE 47.13** *(Continued)*

Characteristics of the 31 Trials used for the Meta-Analysis of Fish Oil and Blood Pressure*

| Study, Year | Study Design* | Blinding Subject | Blinding Observer§ | Study Length | n, Treatment* | ω-3 Dose (g/d)‡ | Gender (Age Range) | Baseline Pressure¶ | BP Effect SBP/DBP¶ |
|---|---|---|---|---|---|---|---|---|---|
| Levinson, 1990 | PG | + | + | 6 | 8 Fish oil<br>8 Saturated mix | 15 | Men & Women (18-75 y) | 147/94 | -8.0/-9.0 |
| Wing, 1990 | XO | + | + | 8 | 20 Fish oil<br>20 Olive oil | 4.5 | Men & Women (32-75 y) | 139/81 | +0.6/-0.3 |
| Radack, 1991 | PG | + | + | 12 | 16 Fish oil<br>17 Safflower | 2 | Men & Women (mean, 46 y) | 136/95 | -7.2/-6.7 |
| Margolin, 1991 | PG | + | + | 8 | 22 Fish oil<br>24 Corn oil | 4.7 | Men & Women (60-80 y) | 164/94 | +1.1/+0.1 |
| Morris, 1992 | XO | + | + | 6 | 18 Fish oil<br>18 Olive oil | 4.8 | Men & Women (32-64 y) | 130/87 | -2.4/-1.8 |
| *Hypercholesterolemic Subjects* | | | | | | | | | |
| Demke, 1988 | PG | + | + | 4 | 13 Fish oil<br>18 Safflower | 1.7 | Men & Women (18-60y) | 119/74 | -3/+1.0 |
| Bach, 1989 | PG | + | + | 5 | 30 Total saturated | 2.5 | Men & Women (mean, 31 y) | 130/85 | -9.0-4.0 |
| Dart, 1989 | XO | NS | NS | 8 | 21 Fish oil<br>21 Olive oil | 6 | Men & Women (mean, 46 y) | 125/77 | -5.3/-2.0 |
| Wilt, 1989 | XO | NS | NS | 12 | 38 Fish oil<br>38 Safflower | 6 | Men (mean, 42 y) | 124/84 | -2.7/-1.8 |
| Kestin, 1990 | PG | + | + | 6 | 11 Fish oil<br>11 Linoleic | 3.4 | Men (mean, 46 y) | 124/75 | -5.1/0.0 |
| Cobiac, 1991 | PG | - | - | 5 | 12 Fish<br>13 Fish oil<br>6 Saturated mix | 4.5 | Men (30-60 y) | 128/79 | -0.6/+1.3 |
| Davidson, 1986 | PG | + | + | 4 | 30 Total olive oil | 6 | Age, sex: NS† | 142/88 | -9.8/-3.2 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| *Cardiovascular Disease Subjects* | | | | | | | | | |
| Mehta, 1988 | XO | + | + | 4 | 8 Fish oil<br>8 Placebo | 5.4 | Men<br>(52-73 y) | 138/80 | -10.0/-4.0 |
| Solomon, 1990 | PG | + | + | 12 | 5 Fish oil<br>5 Olive oil | 4.6 | Men & Women<br>(42-64y) | 142/87 | -16.8/-9.6 |
| Gans, 1990 | PG | + | + | 16 | 16 Fish oil<br>16 Corn oil | 3 | Men & Women<br>(mean, 66 y) | 148/80 | +9.0/+1.0 |
| *Diabetic Subjects* | | | | | | | | | |
| Haines, 1986 | PG | - | - | 6 | 19 Fish oil<br>22 Olive oil | 4.6 | Men & Women<br>(30-59 y) | 136/82 | +1.0/+1.7 |
| Jensen, 1989 | XO | + | + | 8 | 18 Fish oil<br>18 Olive oil | 4.6 | Men & Women<br>(22-47 y) | 148/89 | -9.0/-4.0 |
| Hendra, 1990 | PG | + | + | 6 | 40 Fish oil<br>40 Olive oil | 3 | Men & Women<br>(mean, 56 y) | 143/83 | +0.4/-0.6 |
| *Mixed Sample†* | | | | | | | | | |
| Rogers, 1987 | PG | + | + | 4 | 30 Fish oil<br>30 Olive oil | 3.3 | Men<br>(22-65 y) | 130/76 | -3.1/-5.0 |

* The number of subjects in each treatment period is listed for crossover studies. XO, Crossover, PG, Parallel Group. The number of subjects in each treatment group was not reported for Davidson, 1986 and Bach, 1989. Saturated mix is a mixture of saturated and other oils; mixed oil is a mixture of corn and olive oils.

† NS, not specified. Mixed sample indicates that there were no inclusion criteria for health of the sample.

‡ ω–3 Dose represents eicosapentaenoic acid plus docosahexaenoic acid. The ω–3 dose for Bruckner, 1987, reported as 1.5 g/10 kg body wt, is estimated based on a mean weight of 85 kg.

¶ Average blood pressure at baseline for active and control groups for parallel group studies and blood pressure during the placebo period for crossover studies. SBP, systolic blood pressure; DBP, diastolic blood pressure; NS, not specified. Change in BP attributed to fish oil treatment.

§ Blinded to treatment status.

Tabulated from Tables 2 and 3 from Morris.[56]

**TABLE 47.14**

Observational Studies on Protein and Blood Pressure*

| Study | Number, Age | Protein Measurement | Results |
|---|---|---|---|
| *Cross-Sectional Studies* | | | |
| Yamori, 1981 | 1120, NS* | Spot urine: sulfate:urea nitrogen ratio | ↓ SBP with ↑ animal protein |
| Kihara, 1984 | 1120, 30-70+ y | Spot urine: sulfate:urea nitrogen ratio | ↓ SBP in men with ↑ animal protein |
| Reed, 1981 | 6496 men, NS | Single 24-h recall: g/d | ↓SBP, ↓DBP with ↑ total protein |
| Pellum, 1983 | 61, 22-25 y | 3-d food record: g/d | ↓ SBP with ↑ total protein |
| Elliott, 1991 | 1190, 20-59 y | 24-h urine: total nitrogen, urea nitrogen, sulfate | ↓ SBP with ↑ total and animal protein |
| Dyer, 1992 | 2325, 20-59 y | 24-h urine: total nitrogen, urea nitrogen | ↓ SBP with ↑ total protein |
| Stamler, 1992 | 11342 men, 35-57 y | Four or five 24-h recalls: % energy intake | ↓ SBP with ↑ total protein |
| Eliott, 1992 | 1922, mean age 39 y | 7-d weighed food record: g/d, % energy intake | ↓ SBP in women, ↓ DBP in men and women with ↑ total protein |
| Liu, 1992 | 3809, 18-30 y | Interviewer-administered food-frequency questionnaire: % energy intake | ↓ DBP in white women, black women, and black men with ↑ vegetable protein only |
| Zhou, 1989 | 2672, 35-50 y | Three 24-h recalls: percentage energy intake | ↓ SBP with ↑ animal protein only |
| Zhou, 1994 | 705, 40-59 y | Three 24-h recalls: % energy intake | ↓ SBP, ↓ DBP with ↑ animal protein only |
| Havlik, 1990 | 402 male twins, 42-56 y | Interviewer-administered food-frequency questionnaire: % energy intake, g/d, g/d adjusted for energy | ↑ DBP with ↑ total protein |
| He, 1995 | 827 men, mean 31-45 y | Three 24-h recalls: % energy intake | ↓ SBP with ↑ total protein |
| Stamler, 1996 | 10020, 20-59 y | 24-h urine: total nitrogen, urea nitrogen, sulfate | ↓SBP, ↓DBP with ↑ total protein |
| Stamler, 1996 | 11342 men, 35-57 y | Four or five 24-h recalls: % energy intake | ↓ DBP with ↑ total protein |
| *Longitudinal Studies* | | | |
| Liu, 1993 | 1804 men, 40-56 y | Quantitative diet history: % energy intake | ↓ SBP with ↑ vegetable protein only |
| Liu, 1995† | 3809, 18-30 y | Interviewer-administered food-frequency questionnaire: % energy intake | No change, with ↑ total, animal, or vegetable protein |

* SBP indicates systolic blood pressure; DBP, diastolic blood pressure; NS, not stated

† Personal communication

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**TABLE 47.15**

Human Intervention Studies on Protein and Blood Pressure*

| Study | Number, Age, Cohort | Study Design | Results | Conclusion |
|---|---|---|---|---|
| Chapman, 1950 | 8 men, 31-58 y, hypertensive protein | Sequential: (1) control, (2) rice-fruit; (3) rice-fruit + 40 g milk (animal) | ↓SBP and ↓DBP, but both NS | Compared with rice-fruit diet, no effect of animal protein on BP |
| Hatch, 1954 | 9, 36-66 y, hypertensive | Sequential: (1) low-sodium control; (2) low-sodium + 30-50 g milk and meat protein | ↓SBP and ↓DBP, but both NS | No effect of ↑animal protein on BP |
| Brussaard, 1981 | 69, 18-30 y, normotensive | Parallel, randomized, each for 4 wk: (1) control; (2) casein protein; (3) soy protein | Casein: ↓SBP and ↑ DBP, but both NS; Soy: ↑ SBP and ↑ DBP, but both NS | No effect of animal or vegetable protein on BP |
| Sacks , 1981 | 21, 20-55 y normotensive vegans | Sequential: (1) 2 wk control vegetarian diet; (2) 4 wk 250 g of added beef | ↑ SBP ($p<0.05$), ↓DBP (NS) | Animal protein ↑ SBP |
| Sacks, 1984 | 18, 22-41 y, normotensive vegans | Crossover, randomized each for 6 wk (1) high protein (58 g soy and wheat protein); (2) low protein (7 g rice protein) | Compared with low protein, high protein: ↑ SBP and ↑ DBP, but both NS | No effect of ↑ vegetable protein on BP |
| Sacks, 1984 | Study 1 — 19, 14-54 y normotensive | Study I — Sequential: (1) 3 wk at baseline (2) 3 mo lactovegetarian diet | Study 1 — Low-fat vegetarian protein diet: ↑ SBP and ↑ DBP, but both NS | Study 1 — No effect of vegetarian diet on BP |
| | Study 2 — 17, 18-24 y, normotensive vegetarians | Study 2 — Crossover, randomized, each for 3 wk: (1) no eggs; (2) 1 egg/d | Study 2 — 1 egg/d: ↑ SBP and ↑ DBP, but both NS | Study 2 — No effect of eggs on BP |
| Prescott , 1987 | 50, 18-60 y, normotensive | Parallel, randomized, each for 12 wk: (1) meat protein (93 g of protein) (2) vegetable protein (84 g protein) | Compared with meat protein diet, vegetable protein: ↓SBP and ↑ DBP, but both NS | No difference in BP between vegetable and animal protein |
| Sacks, 1988 | 13, 21-41 y, normotensive vegans | Crossover, randomized, each for 3 wk: (1) 27 g casein protein; (2) 27 g soy protein | Compared with casein protein; soy protein: ↓SBP, and ↓DBP, but both NS | No difference in BP between vegetable and animal protein |
| Kestin, 1989 | 26 men, 28-64 y, normotensive | Crossover, randomized, each for 6 wk: (1) lean meat (high animal protein); (2) lactoovovegetarian (high vegetable protein) | Lactoovovegetarian diet: No change in SBP and ↑ DBP, but both NS | No difference in BP between low-fat animal and low-fat vegetable protein diet |

* SBP indicates systolic blood pressure; DBP, diastolic blood pressure; BP, blood pressure; and NS, not significant.

Americans. Among 30,681 white male health professionals, only dietary fiber had an independent inverse association with hypertension after four years of follow up.[34] The relative risk of hypertension was 1.57 times greater for men with a fiber intake of less than 12 g/day versus greater than 24 g/day. In the Health Professionals Follow-up Study (43,738 men), high intakes of cereal fiber and magnesium were inversely associated with the risk of all strokes after 8 years.[28] Among 827 Chinese men, a 10 g higher intake of dietary fiber was significantly associated with a reduced systolic and diastolic blood pressure (–2.2/–2.1 mmHg).[63]

The explanation for lower blood pressure with fiber is unclear. Suggestions include an increased intake in dietary potassium and Vitamin C and/or a decreased sodium intake.[64] Among controlled studies the average intake of fiber (primarily cereal) was increased by 14 g, resulting in an average reduction of blood pressure of –1.6/–2.0 mmHg.[65] Better studies need to be conducted to understand the relationship of fiber with blood pressure.

### Ascorbic Acid (Vitamin C) and Antioxidant Combinations

Ascorbic acid is an antioxidant and a free radical scavenger. Low vitamin C levels might decrease the production of nitric oxide and increase blood pressure by increasing free radical formation.[66] Other mechanisms include decreased vasodilating prostaglandin formation, modified leukotriene metabolism, altered vascular sodium content, or nutrient multicollinearity.[67] Several studies suggest an inverse relationship between blood pressure or stroke and vitamin C levels. Differences in nutritional consumption between hypertensives and normotensives are shown in Figure 47.3.[68]

It has been observed that a low potassium could also explain this association.[69] In 722 Eastern Finnish men in the Kuopio Ischaemic Heart Disease Risk Factor Study, both plasma ascorbic acid and serum selenium concentrations had independent inverse associations with the blood pressure.[66] However, neither vitamin E nor vitamin C supplements

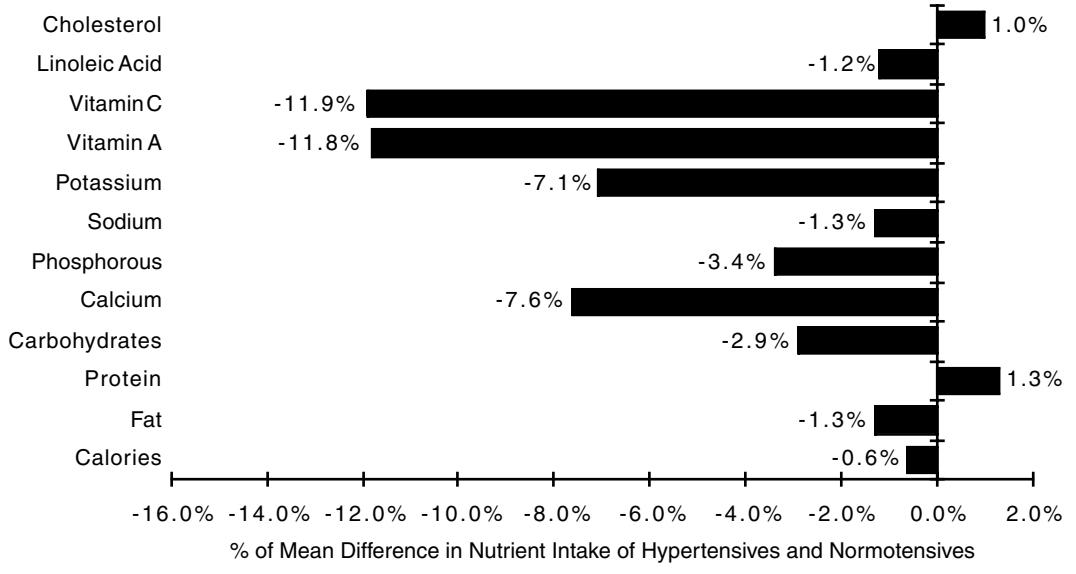


**FIGURE 47.3**
Health and Nutrition Examination Survey I: % mean difference in average nutritional consumption between hypertensive and normotensive persons, adjusted for age. Derived from McCarron DA, Morris CD, Henry HJ, Stanton JL. *Science* 224(4656), 1392, 1984. With permission.

**TABLE 47.16**

Trials of Ascorbic Acid and Blood Pressure

| Study | Patient Number | Design | Duration | Intervention | Blood Pressure (mm Hg) Systolic/Diastolic |
|---|---|---|---|---|---|
| Osilesi O, 1991 | 20 | Crossover | 6 wks | 1000 mg/d | -6.3 /0.6 |
| Feldman EB, 1992 | 21 | Single Blind | 4 wks | 1000 mg/d | -4.2/-2.9 |
| Lovat LB, 1993 | 27 | Crossover | 4 wks | 400 mg/d | -·2 to -5·3 /-0.2 to -1.9 |
| Ghosh SK,1994 | 48 | Controlled | 6 wks | 500 mg/d | -2.5/-1.2 |
| Duffy SJ, 1999 | 39 | Controlled | 4 wks | 2000 mg bolus 500 mg per day | -11/-6 |

Table modified from Ness A, Sterne J. *Lancet* 335(9211), 1271, 2000.

reduced the risk of stroke in the Health Professionals Follow-up Study of 43,738 men.[70] In 168 healthy subjects, plasma concentrations of ascorbic acid (but not α-tocopherol, selenium, or taurine) were significantly inversely related to systolic and diastolic blood pressure.[67] Intravenous vitamin C, thiopronine, and glutathione (all antioxidants) individually demonstrated an acute decrease in blood pressure in 20 unmedicated hypertensive and 20 diabetic subjects.[71] Few studies assess the impact of ascorbic acid supplementation alone. Ascorbic acid — 500 mg twice daily in 21 subjects — lowered blood pressure 4.2/2.9 mmHg in a pilot study.[72] In a double-blind randomized crossover study, ascorbic acid 200 mg twice daily or placebo for four weeks was given to 27 elderly hypertensives.[73] No significant treatment effect was observed. Following a 2-week run-in phase, 48 untreated elderly hypertensive subjects in a randomized, double-blind, placebo-controlled six week study received ascorbic acid 250 mg twice daily or placebo.[74] The change in blood pressure in the vitamin C group was –10.3/–5.9 mmHg, and in the placebo group –7.7/–4.7 mmHg (p = nonsignificant). In a controlled trial, 20 subjects received placebo and 19 subjects received a 2 g bolus followed by 500 mg daily of ascorbic acid for 30 days.[75] Systolic blood pressure decreased 13 mmHg ($p < 0.05$); the change in diastolic blood pressure was not significant. Table 47.16 summarizes several trials of vitamin C supplementation and blood pressure.[76] The effect on systolic blood pressure is consistently greater than diastolic blood pressure.

Several studies have combined several antioxidants to assess an effect on blood pressure. In a randomized, placebo-controlled, clinical trial of 297 retired teachers randomly assigned to 2 to 4 months of the combination of 400 IU/day vitamin E, 500 mg/day vitamin C, and 6 mg/day β-carotene or placebo, the antioxidant combination capsule had no significant hypotensive effect.[77] In a randomized, double-blind, crossover design placebo-controlled study of 21 hypertensives and 17 normotensives, participants were assigned to receive either 8 weeks of placebo followed by 2 weeks washout, then 8 weeks antioxidants 200 mg of zinc sulfate, 500 mg of ascorbic acid, 600 mg of α-tocopherol and 30 mg of β-carotene daily, or the opposite sequence. Only systolic blood pressure (–5.3 mmHg) decreased significantly at the end of the antioxidant phase compared with the placebo phase (+3.7 mmHg) in hypertensive subjects ($p < 0.01$).[78]

## Garlic (Allium Sativum)

Garlic has been reported to decrease blood pressure and attenuate age-related increased aortic stiffness, which could alter blood pressure rise with aging.[79-83] Allicin is believed to be the component responsible for the medicinal effects of garlic. In rabbits and dogs, garlic elicits a dose-dependent diuretic-natriuretic response.[84,85] In a randomized, placebo-con-

trolled, double-blind trial, 47 subjects with mild hypertension (diastolic blood pressures from 95 to 104 mmHg) took either garlic powder or a placebo of identical appearance for 12 weeks.[79] The supine diastolic blood pressure in the garlic treatment group decreased 13 mmHg after 12 weeks ($p < 0.01$) compared with no significant changes in the placebo group. In a double-blind crossover study of 41 moderately hypercholesterolemic men assessing the effect of aged garlic extract versus placebo on blood lipids, there was a 5.5% decrease in systolic blood pressure and a modest reduction of diastolic blood pressure.[81] Another study of 40 hypercholesterolemic men treated with 900 mg of garlic powder observed a similar finding.[80] In a randomized, double-blind study, 42 healthy adults took either 300 mg three times a day of standardized garlic powder in tablet form, or placebo for 12 weeks.[86] There was no significant change in blood pressure.

A meta-analysis of 8 trials (415 subjects) using dried garlic powder 600 to 900 mg observed a decrease for systolic blood pressure of –7.7 (95% CI –11.0 to –4.3) and diastolic blood pressure of –5.0 (95% CI –7.1 to –2.9) mmHg, which represented the overall pooled difference in the absolute change (baseline to final measurement) in blood pressure relative to placebo (see Table 47.17).[87] The same analysis for hypertensive subjects reported an –11.1/–6.5 mmHg decline in blood pressure. The authors observe that blinding may have been difficult due to the odor of garlic. Furthermore, they emphasize that their quality assessment of the trials was poor because the authors did not state their technique to achieve effective randomization. Side effects appear to be rare. A recent randomized, multicenter, double-blind, placebo-controlled, 12-week parallel treatment study in hypercholesterolemic subjects using garlic powder (Kwai) 300 mg 3 times per day found no benefits in lowering blood pressure.[88] The authors of this paper emphasize that negative studies tend not to be submitted or published, suggesting that the current literature on garlic represents a publication bias.[87,88] Despite the suggested benefit, more trials need to be conducted to assess the benefit in hypertensives.

### Ethanol

Alcohol consumption increases the risk of the development of hypertension.[89,90] The risk increases above 28 g of ethanol per day (which is equivalent to 24 oz of beer, 10 oz wine, and 3 oz of distilled spirits).[91] The maximum addition to the prevalence of hypertension of alcohol usage greater than two drinks daily is estimated to be 5 to 7%; however, the 11% risk in men is greater than in women because of greater alcohol intake.[92] In another study, alcohol consumption greater than 20 g per day gradually increases the risk of hypertension among women.[93] The relationship of alcohol intake to blood pressure is graded and continuous with the effect clearer in men than in women and more consistent in whites than in blacks (see Figure 47.4).[94] The effect of alcohol consumption on systolic blood pressure is independent of the effects of age, obesity, cigarette smoking, and physical activity.[95] In the INTERSALT Study (n = 10,079), both BMI and heavy alcohol consumption were significantly and independently correlated with both systolic and diastolic blood pressure ($p < 0.001$).[5] The effect of alcohol consumption on blood pressure is independent of and additive to BMI and urinary excretion of sodium and potassium.[96] The effect of alcohol on change in blood pressure independent of other risk factors is displayed in Figure 47.4.[94] In the Scottish Health Heart Study, alcohol consumption showed a weak positive correlation with blood pressure among 7354 men, but the correlation was greater than for sodium.[7]

Resting plasma concentrations of norepinephrine, epinephrine, renin activity, angiotensin II, aldosterone, and cortisol are similar in drinkers and nondrinkers.[97] In a prospective study of 7735 middle-aged British men, the prevalence of measured hypertension and

**TABLE 47.17**

Randomized Controlled Trials of Garlic and Blood Pressure*

| Reference | Participants | Dose per day (mg) | Control | Blinding | Number of Subjects | Duration | Position | Heart Rate | Analysis |
|---|---|---|---|---|---|---|---|---|---|
| Kandziora, 1988 | Hypertensives | 600 | Reserpine-diuretic | Single | 40 | 12 weeks | Sup/St | UC | ITT |
| Kandziora, 1988 | Hypertensives | 600 | Placebo | Double | 40 | 12 weeks | Sup/St | UC | ITT |
| Auer, 1990 | Hypertensives | 600 | Placebo | Double | 47 | 12 weeks | Sup/St | NS | NS |
| Vorberg, 1990 | Hyperlipidemics | 900 | Placebo | Double | 40 | 16 weeks | Sup | NS | NS |
| Kiesewetter, 1991 | SWISA | 800 | Placebo | Double | 60 | 4 weeks | NS | NS | NS |
| Holzgartner, 1992 | Hyperlipidemics | 900 | Bezafibrate | Double | 94 | 12 weeks | NS | UC | ITT |
| Santos, 1993 | NS | 900 | Placebo | Double | 60 | 6 months | NS | NS | ORT |
| Jain, 1993 | Hyperlipidemics | 900 | Placebo | Double | 42 | 12 months | NS | NA | NS |

* Sup, supine; St, standing; UC, unchanged; ITT intention to treat; NS, not stated; SWISA, subjects with increased spontaneous aggregation; ORT, on randomized treatment; NA. not available. Crossover study.

Modified from Silagy CA, Neil HA. *J Hypertens* 12(4), 463, 1994. With permission.

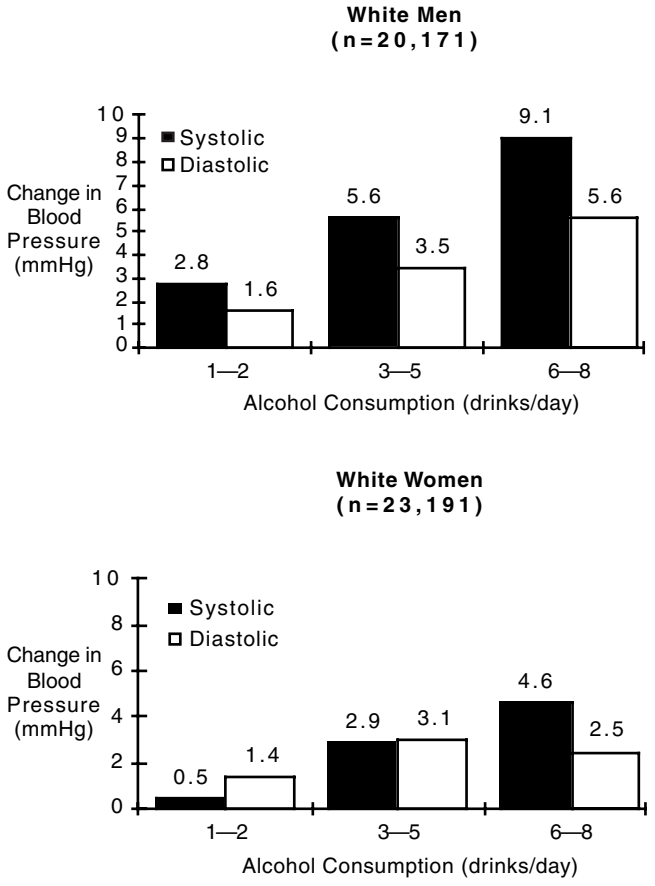


**FIGURE 47.4**
The effect of ethanol consumption on the change in blood pressure independent of other factors. Graph derived from data of Klatsky AL, Friedman GD, Armstrong MA. *Circulation* 73(4): 628, 1986.

level of blood pressure were significantly higher on Mondays and lower on Fridays than on other weekdays.[98] This suggests a withdrawal effect of weekend ethanol consumption.

Modest alcohol intake has been associated with a protective effect on ischemic heart disease events. Heavy alcohol intake has been associated with an increased rate of hemorrhagic strokes.[99,100] However, mild to moderate consumption in men reduced the risk of ischemic stroke without increasing the risk of hemorrhagic stroke.[101]

Several trials have been conducted to assess the impact of alcohol in moderation on blood pressure. These are listed in Table 47.18. Prevention and Treatment of Hypertension Study (PATHS)[91,102] was designed to assess alcohol intake reduction in nondependent moderate to heavy drinkers. 641 outpatient hypertensive and nonhypertensive veterans with a diastolic blood pressure of 80 to 99 mmHg were randomized to observation or behavioral cognitive intervention. To qualify for enrollment, self-reported alcohol intake had to be ≥294 g/week or ≥21 drinks/week for the preceding six months. The goal of behavioral cognitive intervention was to reduce alcohol intake to less than 50% of baseline intake or 14 drinks per week.

For the entire cohort, the average reduction of alcohol intake at 6 and 24 months between groups was 131 and 124 g/wk ($p < 0.001$ for each). For the 265 hypertensive subjects, the average reduction at 6 and 24 months was 157 and 135 g/wk (each $p < 0.001$). At 6 and 12 months, this translated to a nonsignificant reduction in blood pressure (i.e., treatment

**TABLE 47.18**

Randomized Controlled Trials of Alcohol Reduction on Blood Pressure

| Study, Year | n | Age, Years (Mean ± SD or Range) | Duration, Weeks | Baseline BP, mm Hg | Alcohol Intake Difference, Drinks†/Day | Blood Pressure Reduction, mm Hg | p Value |
|---|---|---|---|---|---|---|---|
| Puddey, 1985 | 46 | 35 ± 8 | 6 | 133/76 | 3.7 | 3.8/1.4 | <.001/<.05 |
| Howes, 1985 | 10 | 25-41 | 0.6 | 120/66 | 5.7 | 8/6 | <.025/<.001 |
| Puddey, 1987 | 44 | 53 ± 16 | 6 | 142/84 | 4.0 | 5/3 | <.001/<.001 |
| Ueshima, 1987 | 50 | 46 ± 7 | 2 | 148/93 | 2.6 | 5.2/2.2 | <.005/NS |
| Wallace, 1988 | 641 | 42 ± 20 | 52 | 136/82 | 1.0 | 2.1/? | <.05/NS |
| Parker, 1990 | 59 | 52 ± 11 | 4 | 138/85 | 3.8 | 5.4/3.2 | <.01/<.01 |
| Cox, 1990 | 72 | 20-45 | 4 | 132/73 | 3.4 | 4.1/1.6 | <.05/<-05 |
| Maheswaran, 1992 | 41 | 40s | 8 | 144/90 | 3.1 | Not reported | NS |
| Puddey, 1992 | 86 | 44 | 18 | 137/85 | 3.0 | 4.8/3.3 | <.01/<.01 |
| Ueshima, 1993 | 54 | 44 ± 8 | 3 | 144/96 | 1.7 | 3.6/1.9 | <.05/NS |
| PATHS, 1998‡ | 641 | 57 ± 11 | 104 | 140/86 | 1.3 | 0.9/0.6 | 0.16/0.10 |

† A standard drink is defined as 14 g of ethanol and is contained in a 12-oz glass of beer, a 5-oz glass of table wine, or 1.5 oz of distilled spirits.

‡ PATHS is Prevention and Treatment of Hypertension Study.

Modified from report of Cushman WC, Cutler JA, Bingham SF, et al. *Am J Hypertens* 7(9PT1), 814, 1994.

effect) for the entire cohort of –1.0/–0.6 mmHg and –0.9/–0.6 mmHg. For the hypertensive participants, the nonsignificant treatment effect at 6 and 12 months was –1.9/–0.6 and –1.6/–0.4 mmHg. There was no significant difference in the incidence of hypertension at 24 months: 16.6% in the intervention group and 21.8% in the control group. Weight declined more in the intervention group by –0.5 and –1.0 kg at 6 and 24 months.

PATHS was designed to achieve a 2-drink reduction in alcohol between treatments, but only achieved a reduction of 1.3 drinks per day. Furthermore, it was anticipated that 60% of the intervention group and 20% of the control group could reduce baseline alcohol intake to less than 50%; however, at 6 months the level for the control group was 23% and the intervention group was 44%.

## Caffeine

Caffeine may increase peripheral vascular resistance by blocking the adenosine receptors. There are few randomized, controlled trials assessing the impact of coffee consumption on blood pressure. A meta-analysis (see Table 47.19) reviewed 36 studies and identified 11 controlled trials with 522 subjects.[103] The median duration of the trials was 56 days. They estimated the overall pooled treatment effect attributable for a median coffee intake of 5 cups/d as +2.4 mmHg (95% CI +1.0 to +3.7) for systolic blood pressure and +1.2 mmHg (95% CI +0.4 to +2.1) for diastolic blood pressure. Only one of the 11 trials included a hypertensive cohort. This meta-analysis did not observe a treatment effect on blood pressure based on treatment duration, the type of coffee (instant or not), whether coffee was filtered, or the type of coffee control (decaffeinated or no coffee). Age, coffee consumption, and sample size were independently associated with both systolic and diastolic blood pressure. The systolic and diastolic blood pressure increased 0.8 and 0.5 mmHg per cup of coffee consumed. A recent study using ambulatory blood pressure monitoring to study nonsmoking men and women older than 50 years reported a +4.8/+3.0 mmHg higher 24-hour systolic and diastolic blood pressure comparing 14 hypertensive coffee drinkers of 5 cups/d for two weeks compared with 13 hypertensive abstainers after a mandatory period of abstention of caffeine-containing foods for two weeks.[104]

**TABLE 47.19**

Controlled Studies of Coffee Consumption

| Author, Year | No. of Subjects | Age, y Mean | Age, y Range | % Male | BP Drugs | Study Design* | Random Study | Study Duration | Baseline BP, mmHg SBP/DBP | Habitual Intake, cups/d | Run-time Time, d | Coffee Method | Coffee Filtered | No Cups of Coffee | Caffeine Content |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ammon, 1983 | 8<br>... | 27 | 20-30 | 100 | No | XO, D | No | 28 d | 123/82‡<br>126/85§ | ... | 7 | Instant | No | 504 | |
| Burr, 1989 | 54 | 35 | 18-58 | 65 | No | XO, S | Yes | 28 d | 116/69 | ... | 7 | Instant | No | 5 | ... |
| Bak, 1989a | 67 | 26 | 18-33 | 54 | No | PG, ... | Yes | 63 d | 122/71 | 5.9 | 21 | Boiled | No | 5 | 630 |
| Bak, 1989b | 68 | 26 | 18-33 | 54 | No | PG, ... | Yes | 63 d | 122/71 | 5.5 | 21 | Boiled | Yes | 5 | 670 |
| Van Dusseldorp, 1980 | 45 | 38 | 25-45 | 49 | No | XO, D | Yes | 42 d | 124/76 | .. | 0 | Drip | Yes | 5 | 435 |
| Rosmarin, 1990 | 21 | 36 | ... | 100 | No | XO, ... | Yes | 56 d | 115/72 | ... | 0 | Drip | Yes | 3.6 | ... |
| MacDonald, 1991† | 52 | 47 | 26-67 | 44 | No | XO, D | Yes | 14 d | 134/87¶ | ... | 0 | Instant | No | 3 | ... |
| Van Dusseldorp, 1992a | 43 | 39 | 17-57 | 42 | No | PG, D | Yes | 79 d | 110/69¶ | 5.5 | 17 | Boiled | No | 6 | 860 |
| Van Dusseldorp, 1992b | 42 | 39 | 17-57 | 42 | No | PG, D | Yes | 79 d | 110/70¶ | 5.5 | 17 | Boiled | Yes | 6 | 887 |
| Eggertsen, 1993 | 23 | 56 | 28-74 | 57 | Yes | XO, D | Yes | 14 d | 130/80¶ | 3.5 | 14 | Instant | No | 3.5 | ... |
| Superko, 1994 | 99 | 46 | 43-48# | 100 | No | PG, D | Yes | 56 d | 116/74 | 4.5 | 0 | Drip | Yes | 4.5 | 584 |

* BP indicates blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; XO, crossover; D, double-blind; S, single-blind; and PG, parallel group.
† MacDonald (1991): mean ambulatory BID during caffeinated coffee regimen vs caffeine-free diet.
‡ Regular coffee group.
§ Decaffeinated coffee group.
¶ Ambulatory BP measurements.
# Range of means.

Modified from Jee SH, He J, Whelton PK, et al. *Hypertension* 33(2), 647, 1999.

### Weight Reduction (Caloric Deprivation)

The relationship between obesity and hypertension is well documented. All adults with a BMI of 25 kg/m$^2$ or greater are at risk for hypertension.[105] The impact of weight reduction as a modality for preventing or reducing blood pressure is addressed in the section on major nonpharmacologic trials.

## Summary

Table 47.20 summarizes the meta-analyses on nonpharmacologic intervention and blood pressure. The importance of the amount of change in blood pressure varies with the perspective of the clinician vs. that of the epidemiologist.

**TABLE 47.20**

Meta-Analysis of Results of Studies on Nonpharmacologic Intervention and Blood Pressure

| Author, Year | Number of Trials | Nutrient | Systolic Pressure (95% CI) | Diastolic Pressure (95% CI) |
|---|---|---|---|---|
| Jee, 1999[103] | 11 | Caffeine | +2.4 (+1.0 to +3.7) | +1.2 (+0.4 to +2.1) |
| Normotensives | 10 | | +2.4 (+1.0 to +3.8) | +1.2 (+0.4 to +2.1) |
| Cappuccio, 1989[39] | 15 | Calcium | -0.13 (-0.46 to +0.19) | +0.03 (-0.17 to +0.22) |
| Hypertensives | 10 | | +0.06 (-0.59 to +0.72) | +0.03 (-0.21 to +0.27) |
| Cutler, 1990[35] | 19 | Calcium | -1.8 (-3.0 to -0.6) | -0.7 (-1.5 to +0.2) |
| Normotensives | 9 | | -1.3 (-3.2 to +0.8) | -1.3 (-2.6 to -0.1) |
| Hypertensives | 12 | | -2.1 (-3.6 to -0.6) | -0.1 (-1.3 to +1.0) |
| Allender, 1996 [41] | 22 | Calcium | -0.89 (-1.74 to -0.05) | -0.18 (-0.75 to +0.40) |
| Normotensives | 13 | | -0.53 (-1.56 to +0.49) | -0.28 (-0.99 to +0.42) |
| Hypertensives | 16 | | -1.68 (-3.18 to -0.18) | +0.02 (-0.96 to +1.00) |
| Buchner, 1996[42] | 33 | Calcium | -1.27 (-2.25 to -0.29) | -0.24 (-0.92 to +0.44) |
| Normotensives | 33 | | -0.27 (-1.80 to +1.27) | -0.33 (-1.56 to +0.90) |
| Hypertensives | 6 | | -4.30 (-6.47 to -2.13) | -1.50 (-2.77 to -0.23) |
| Griffith, 1999[43] | 42 | Calcium | -1.44 (-2.20 to -0.68) | -0.84 (-1.44 to -0.24) |
| He, 1996[65] | 20 | Fiber | -1.6 (-2.7 to -0.4) | -2.0 (-2.9 to -1.1) |
| Silagy, 1994[87] | 8 | Garlic | -7.7 (-11.0 to -4.3) | -5.0 (-7.1 to -2.9) |
| Hypertensives | 2 | | -11.1 (-17.2 to -5.0) | -6.5 (-9.6 to -3.4) |
| Appel, 1993[55] | 17 | ω-3-Fatty Acids | -1.5 (-2.4 to -0.6) | -1.0 (-1.6 to -0.4) |
| Normotensives | 11 | | -1.0 (-2.0 to 0.0) | -0.5 (-1.2 to +0.20) |
| Hypertensives | 6 | | -5.5 (-8.1 to -2.9) | -3.5 (-5.0 to -2.1) |
| Morris, 1993[56] | 31 | ω-3- Fatty Acids | -3.0 (-4.5 to -1.5) | -1.5 (-2.2 to -0.8) |
| Normotensives | 8 | | -0.4 (-1.6 to +0.8) | -0.7 (-1.5 to +0.1) |
| Hypertensives | 9 | | -3.4 (-5.9 to -0.9) | -2.0 (-3.3 to -0.7) |
| Cappuccio, 1991[106] | 18 | Potassium | -4.0 (-4.7 to -3.2) | -2.4 (-3.0 to -1.8) |
| Hypertensives | 12 | | -5.3 (-6.2 to -4.4) | -3.0 (-3.7 to -2.3) |
| Whelton, 1997[29] | 32 | Potassium | -3.11 (-4.31 to -1.91) | -1.97 (-3.42 to -0.52) |
| Normotensives | 12 | | -1.8 (-2.9 to -0.6) | -1.0 (-2.1 to 0.0) |
| Hypertensives | 20 | | -4.4 (-6.6 to -2.2) | -2.5 (-4.9 to -0.1) |
| Cutler,1991[11] | 23 | Sodium | -2.91 (-3.67 to -2.15) | -1.60 (-2.09 to -1.11) |
| Normotensives | 6 | | -1.70 (-2.68 to -0.72) | -0.97 (-1.62 to -0.32) |
| Hypertensives | 18 | | -4.92 (-6.19 to -3.65) | -2.64 (-3.46 to -1.82) |
| Midgley, 1996[13] | 56 | Sodium | -0.5 (-1.17 to -0.07) | -1.6 (-2.10 to -1.02) |
| Normotensives | 28 | | -0.1 (-0.76 to +0.63) | -0.5 (-1.16 to +0.14) |
| Hypertensives | 28 | | -2.0 (-3.57 to -0.49) | -2.7 (-3.77 to -1.58) |
| Cutler, 1997[14] | 32 | Sodium | -2.81 (-3.39 to -2.23) | -1.52 (-1.90 to -1.14) |
| Normotensives | 12 | | -1.90 (-2.62 to -1.18) | -1.09 (-1.57 to -0.61) |
| Hypertensives | 22 | | -4.83 (-5.87 to -3.79) | -2.45 (-3.13 to -1.77) |
| Graudal, 1998[15] | | Sodium | | |
| Normotensives | 56 | | -1.2 (-1.8 to -0.6) | -0.26 (-0.3 to +0.9) |
| Hypertensives | 58 | | -3.9 (-4.8 to -3.0) | -1.9 (-2.5 to -1.3) |

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