The Effects of Nonpharmacologic Interventions on Blood Pressure of Persons With High Normal Levels

Results of the Trials of Hypertension Prevention, Phase I

The Trials of Hypertension Prevention Collaborative Research Group

Objective.—To test the short-term feasibility and efficacy of seven nonpharmacologic interventions in persons with high normal diastolic blood pressure.

Design.—Randomized control multicenter trials.

Setting.—Volunteers recruited from the community, treated and followed up at special clinics.

Participants.—Of 16 821 screenees, 2182 men and women, aged 30 through 54 years, with diastolic blood pressure from 80 through 89 mm Hg were selected. Of these, 50 did not return for follow-up blood pressure measurements.

Interventions.—Three life-style change groups (weight reduction, sodium reduction, and stress management) were each compared with unmasked nonintervention controls over 18 months. Four nutritional supplement groups (calcium, magnesium, potassium, and fish oil) were each compared singly, in double-blind fashion, with placebo controls over 6 months.

Main Outcome Measures.—Primary: change in diastolic blood pressure from baseline to final follow-up, measured by blinded observers. Secondary: changes in systolic blood pressure and intervention compliance measures.

Results.—Weight reduction intervention produced weight loss of 3.9 kg ($P<.01$), diastolic blood pressure change of −2.3 mm Hg ($P<.01$), and systolic blood pressure change of −2.9 mm Hg ($P<.01$). Sodium reduction interventions lowered urinary sodium excretion by 44 mmol/24 h ($P<.01$), diastolic blood pressure by 0.9 mm Hg ($P<.05$), and systolic blood pressure by 1.7 mm Hg ($P<.01$). Despite good compliance, neither stress management nor nutritional supplements reduced diastolic blood pressure or systolic blood pressure significantly ($P>.05$).

Conclusions.—Weight reduction is the most effective of the strategies tested for reducing blood pressure in normotensive persons. Sodium reduction is also effective. The long-term effects of weight reduction and sodium reduction, alone and in combination, require further evaluation.

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HIGH blood pressure (BP) is an important determinant of the incidence of coronary heart disease, stroke, congestive heart failure, renal failure, and peripheral vascular disease.[1] Antihypertensive drug treatment trials have demonstrated reduced cardiovascular morbidity and mortality in study populations with pretreatment diastolic levels of 90 mm Hg and higher.[2-4] Hence, this level constitutes a conventional definition of diastolic hypertension. Approximately 30% of the adult population in the United States have hypertension thus defined, or are already receiving antihypertensive drug treatment.[5] In addition, a continuous, monotonic relationship exists between diastolic blood pressure (DBP) or systolic blood pressure (SBP) and cardiovascular risk across a wide range within general adult populations. Indeed, as much as one third of cardiovascular disease attributable to an above-optimal BP level occurs in the nonhypertensive portion of the distribution.[6-8] This fact provides impetus for directing primary prevention efforts at high normal levels of BP.

Epidemiologic studies, mostly cross-sectional, have identified several dietary and other factors related to life-style as possible determinants of BP levels.[9] These factors include obesity, intake of monovalent and divalent cations, use of alcohol, level of physical activity, and amount or type of dietary fat. Based on studies of the sympathetic nervous system and laboratory stressors, the hypothesis has emerged that chronic stress may also be etiologically important.[10] All of these factors have been targeted in clinical trials, mostly conducted in hypertensive patients. As of the mid-

See also pp 1221 and 1256.

1980s, few trials had reported any results in subjects with BP levels in the nonhypertensive range, and almost none included long-term follow-up. For this reason, the National Heart, Lung, and Blood Institute, Bethesda, Md, initiated an integrated multicenter program of intervention research, the Trials of Hypertension Prevention (TOHP), which encompass several randomized clinical trials studying nonhypertensive subjects. This article reports the main results of Phase I of TOHP (TOHP-I), the goals of which were (1) to test the short-term effect on BP of selected nutritional and behavioral interventions, and (2) to determine the feasibility of a long-term clinical trial of methods for reducing the incidence of hypertension.

DESIGN AND METHODS

Design

A detailed description of the design of TOHP-I has been published.[11] Briefly, the design consisted of three randomized control, parallel-group trials with

A complete list of the group's participants and their affiliations appears at the end of the article.

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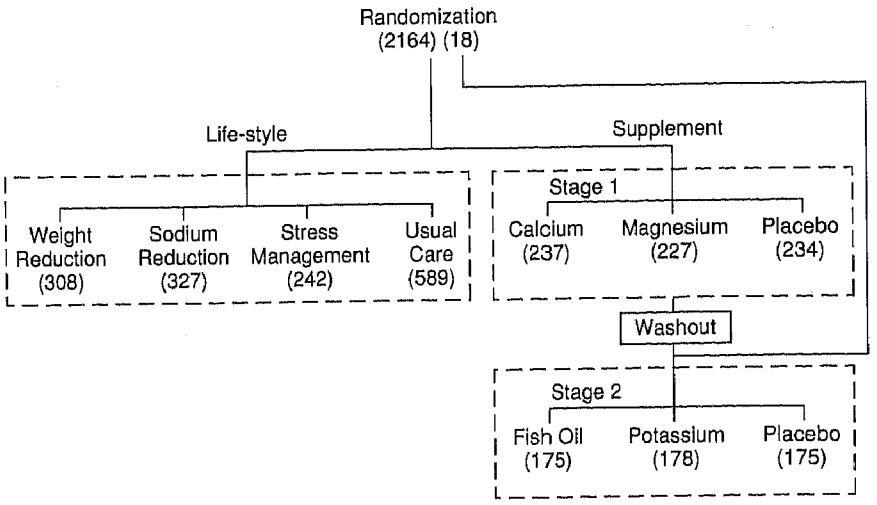


Fig 1.—Schematic representation of randomization of participants into the three component trials of the Trials of Hypertension Prevention, Phase I. Numbers in parentheses are sample sizes. Due to stratification by clinic and body mass index, the number of control subjects ("usual care") available for respective comparisons were sodium reduction, 417; weight reduction, 256; and stress management, 320.

common source populations, eligibility criteria, and data collection and analytic methods (Fig 1). Seven interventions were tested: three life-style change interventions with an unmasked design but with blinded measurement of BP as the end point, and four nutritional supplement interventions, with placebo-controlled, double-blind designs. The nutritional supplement component was divided into two stages, each of 6-months' duration, with an intervening washout period (Fig 1). The follow-up period for the life-style change participants was 18 months, in order to provide a reasonable test of maintenance of behavioral changes.

Each of 10 clinics tested a subset of two, four, or six interventions. All randomizations were stratified by clinic. Regardless of intervention, the main inclusion-exclusion criteria and examination procedures were identical for all clinics. Six clinics tested weight reduction; six, sodium reduction; four, stress management; and seven, the nutritional supplements. Each of the clinics involved in the life-style change trial provided a common control group ("usual care") for its two life-style interventions. In the clinics testing weight reduction, a larger sample was allocated to the control group than to either active intervention in order to provide a sufficient number of high-weight controls for comparison with the weight reduction intervention. Participants in the nutritional supplement trial were allocated equally to calcium carbonate, magnesium diglycine, or placebo groups (stage 1). After the washout period, participants were rerandomized to fish oil, potassium chloride, or placebo groups (stage 2) (Fig 1).

The primary outcome measure was change in DBP, and the major secondary outcome was change in SBP, from baseline to the last follow-up visit. Planned sample sizes were calculated to achieve at least 80% power for detecting a 1.6 mm Hg net change in DBP and a 2.5 mm Hg net change in SBP, at a significance level of .05 (two-sided test). The achieved sample sizes (Table 1) yielded 80% power for DBP effects equal to or greater than 1.3 to 1.8 mm Hg for the various interventions, and 86% through 99% power to detect changes of 2 mm Hg.[11]

Eligibility and Randomization

The target population consisted of healthy men and women, aged 30 through 54 years, who had high normal DBP and were not taking antihypertensive drugs for the prior 2 months. The BP eligibility level was based on three measurements at each of three screening visits (SV), between 10 and 30 days apart, with inclusion limits based on *cumulative* averages of all readings through that visit, as follows: SV1, 75 through 97 mm Hg; SV2, 77 through 94 mm Hg; and SV3 (baseline), 80 through 89 mm Hg. Candidates were excluded if they had (1) clinical or laboratory evidence of cardiovascular or other life-threatening or disabling diseases, (2) conditions that would require or contraindicate any of the interventions, or (3) evidence of unwillingness or inability to comply with intervention or data collection procedures. Detailed eligibility criteria have been published.[11] All participants gave informed consent following procedures approved by institutional review boards at each of the collaborating institutions.

After completion of the three screening visits and verification of eligibility by the coordinating center, candidates were asked to return for a prerandomization compliance assessment at a status review visit, using (1) completion of a food-frequency questionnaire and adequate collection of a second 24-hour urine sample, and (2) pill counts suggesting consumption of at least two thirds of nutritional supplement placebos over the previous 6-week period (candidates for the nutritional supplement trial only). At clinics participating in both the life-style change and nutritional supplement trials, candidates underwent preliminary random allocation to nutritional supplement groups or life-style change groups at SV3. At clinics using the weight reduction intervention, randomization was conducted within high- and low-weight strata, with only high-weight participants eligible for the weight reduction group. At the status review visit, randomization assignments were obtained from the coordinating center by telephone. However, when telephone contact was not possible, sealed opaque envelopes were used to convey the treatment assignment, and adherence to the appropriate assignment sequence was monitored by the coordinating center.

Intervention Methods

Life-style interventions, provided by nutritionists, psychologists, or other experienced counselors, consisted primarily of group educational sessions, supplemented by individual counseling. Group sizes averaged from 11 to 12 participants, augmented by spouses or other household members. Initial (intensive) sessions were weekly—14, 10, and 8 sessions for the weight reduction, sodium reduction, and stress management groups, respectively, with group sessions lasting 90 minutes each. Subsequently, the meetings continued at a semimonthly and then a monthly frequency throughout the trial. Demonstrations and practice were incorporated into each meeting.

Weight reduction and sodium reduction interventions focused on shopping, cooking, and food selection behaviors aimed at reducing intakes of calories and sodium, respectively; no recommendations regarding sodium were given to weight reduction participants. The weight reduction program also encompassed a moderate increase in caloric expenditure, primarily by walking at a

Table 1.—Baseline Values for Each Life-style Change and Nutritional Supplement Groups*

	Life-style Change Groups					
	Sodium Reduction		Weight Reduction		Stress Management	
	Active (n=327)	Control (n=417)	Active (n=308)	Control (n=256)	Active (n=242)	Control (n=320)
Age, y	43.4±6.6	42.6±6.5	43.1±6.0	42.4±6.2	43.4±6.9	43.0±6.6
Male, %	70.9	71.7	72.7†	62.9	71.1	70.6
White, %	78.0	76.5	81.8	76.6	83.9	83.8
College graduate, %	54.1	56.3	50.0	43.9	56.6	50.6
Systolic blood pressure, mm Hg	124.8±8.5	125.1±8.1	124.3±8.4	124.6±8.1	125.3±8.5	124.1±8.4
Diastolic blood pressure, mm Hg	83.7±2.7	83.9±2.8	83.7±2.6	84.0±3.0	83.9±2.8	83.6±2.7
Weight, kg	82.7±14.3	82.8±14.0	90.2±13.3	89.3±13.0	83.4±12.8	83.6±13.3
Sodium, mmol/24 h	154.6±59.9	156.4±60.5	170.2±70.9	169.7±64.5	166.2±73.8	160.9±65.6

	Nutritional Supplement Groups					
	Stage 1			Stage 2		
	Magnesium (n=227)	Calcium (n=237)	Placebo (n=234)	Potassium (n=178)	Fish Oil (n=175)	Placebo (n=175)
Age, y	42.7±6.2	42.7±6.6	43.2±6.7	42.8±6.5	42.6±6.3	43.1±6.6
Male, %	69.6	69.2	67.1	74.7	70.9	69.7
White, %	86.3	87.3	83.8	88.8	88.0	84.0
College graduate, %	55.5	49.8	47.4	59.0†	58.3†	46.9
Systolic blood pressure, mm Hg	124.9±8.0	126.0±7.7	125.4±8.8	120.7±8.5†	122.9±8.8	122.6±8.3
Diastolic blood pressure, mm Hg	83.8±2.7	84.1±2.9	83.9±2.8	80.8±5.1	81.0±5.1	81.1±4.9
Weight, kg	82.7±14.3	83.6±13.6	82.0±13.9	81.6±13.7	84.1±13.4	83.6±14.2
Sodium, mmol/24 h	162.5±77.9†	155.3±64.7	146.4±63.1	149.9±74.6	144.8±67.9	156.9±71.1

*Data are presented as mean±SD unless otherwise noted.
†$P<.05$.

brisk pace for 45 minutes, four to five times per week. Stress management involved teaching four methods of relaxation (slow breathing, progressive muscle relaxation, mental imagery, and stretching), plus techniques to manage stress perceptions, reactions, and situations.

Nutritional supplements were given in doses selected to reflect daily levels of intake that could potentially be attained by diet change alone: calcium, 25 mmol or 1.0 g (two pills per day); magnesium, 15 mmol or 360 mg (six pills per day); potassium chloride, 60 mmol or 4.5 g (three pills per day); and 6.0 g of fish oil containing 3.0 g of omega-3 fatty acids (six capsules per day). Intakes were monitored by pill counts and biochemical indicators.

Follow-up Measurements

Data were collected at 3 and 6 months for both intervention groups, and for life-style change participants also at 12 and 18 months, by trained, certified observers who were blinded to participants' treatments. Blood pressure was measured with a Hawksley random-zero sphygmomanometer,[12] after the participant sat for 5 minutes at rest. Three readings (first and fifth Korotkoff's sounds) were recorded at each visit and averaged. The 6-month BP for nutritional supplement participants, and the 12- and 18-month determinations in the life-style change participants were measured at a series of three visits, between 7 and 30 days apart; thus, as for baseline values, these major follow-up determinations were the average of nine readings.

Other measurements assessed the success of interventions, as well as possible confounding factors. Participants were weighed on a balance-beam scale at the first of each series of three visits and at each individual visit. Urine was collected for 24 hours to determine sodium, potassium, and creatinine excretion at 6, 12, and 18 months (life-style change), and at 3 and 6 months (nutritional supplements). Calcium and magnesium excretion were measured twice in the respective stage 1 active and placebo groups. Food frequency questionnaires and 24-hour diet recalls were collected at final visits. The percentages of omega-3 fatty acids in plasma phospholipids were measured in a 50% sample of fish oil and placebo groups. Intermediate response to stress management was assessed by Lazarus' Hassles Scale questionnaire. Other questionnaires evaluated prescription drug use, psychological general well-being, and side effects (nutritional supplements only).

Statistical Analyses

For each intervention, baseline characteristics in intervention and control groups were examined for equal allocation of variables including age, race, gender, education, SBP, DBP, 24-hour electrolyte excretion, nutrient levels, and biochemical measurements.[13] Student's t tests were used to compare changes from baseline in weight, sodium excretion, and Hassles Scale for the life-style intervention and control groups. For the nutritional supplement intervention and control groups, χ^2 tests of association were used to assess proportions of participants taking at least 95% of study medications, and Student's t tests were used to assess changes from baseline in 24-hour electrolyte excretion, weight, and blood values.

The mean difference in BP change between each intervention and control group was assessed by Student's t test. Blood pressure change was defined as the mean BP over all visits (one or three) at each follow-up minus mean BP at baseline (three visits). For participants receiving antihypertensive medications during the course of the trial, termination BP levels over three visits were obtained, insofar as possible, before starting medication. Termination BP is the last set of three (one visit), six (two visits), or nine (three visits) readings obtained for each participant while not on BP medication. In the analyses shown, participants with no follow-up visits (n=50) were assigned a zero value for BP change ("intention-to-treat" analysis). These results did not differ appreciably from those in which missing BP values were treated as missing at random and excluded from the analysis.

Table 2.—Change From Baseline in Intervention Outcome Measures for Life-style Change and Nutritional Supplement Groups

Intervention and Outcome Measure	Time, mo	Active			Control			Active-Control	
		n	Mean	SD	n	Mean	SD	Mean	95% Confidence Interval
Life-style Change Groups									
Sodium reduction Sodium excretion, mmol/24 h	6	228	−55.68	76.06	323	2.77	80.33	−58.45*	−71.80,−45.09
	18	232	−55.19	76.93	330	−11.33	77.68	−43.86*	−56.88,−30.84
Weight reduction Weight change, kg	6	294	−5.68	5.74	237	−0.01	3.24	−5.67*	−6.45,−4.90
	18	293	−3.83	6.12	235	0.07	4.01	−3.90*	−4.77,−3.03
Stress management Hassles score frequency	6	230	2.15	12.22	256	1.36	14.33	0.80	−1.57,3.16
	18	223	1.86	13.39	247	−0.49	12.36	2.35†	0.01,4.68
Hassles score intensity	6	230	0.01	0.37	256	−0.02	0.35	0.03	−0.04,0.09
	18	223	−0.01	0.39	247	0.00	0.42	−0.01	−0.09,0.06
Nutritional Supplement Groups									
Magnesium Magnesium excretion, mmol/24 h	3	162	1.31	2.41	182	−0.28	1.76	1.59*	1.14,2.05
	6	177	1.28	2.29	181	−0.03	1.85	1.31*	0.88,1.74
Serum magnesium, mmol/L	3	162	0.03	0.13	166	−0.01	0.11	0.03*	0.01,0.06
	6	173	0.02	0.12	178	−0.02	0.13	0.04*	0.01,0.07
Calcium Calcium excretion, mmol/24 h	3	179	0.87	2.56	179	−0.35	2.40	1.22*	0.70,1.73
	6	187	0.85	2.37	167	−0.05	2.27	0.91*	0.42,1.39
Potassium Potassium excretion, mmol/24 h	3	150	41.64	39.68	143	−2.40	27.60	44.04*	36.21,51.87
	6	142	37.40	38.45	144	−4.88	27.92	42.29*	34.46,50.12
Fish oil (omega-3 fatty acids) % of phospholipid fatty acids Eicosapentaenoic	3	73	2.93	1.55	75	0.04	0.89	2.90*	2.49,3.31
	6	67	2.86	1.68	72	−0.04	0.78	2.90*	2.46,3.35
Docosahexaenoic	3	73	2.10	1.32	75	0.14	0.79	1.97*	1.61,2.32
	6	67	2.24	1.51	72	0.21	0.74	2.04*	1.63,2.44

*$P<.01$.
†$P<.05$.

For termination BP, linear regression analysis was used to adjust for baseline BP, age, race, and gender.

Incidence of hypertension was compared for each intervention group and its control group. Hypertension was considered present when a mean of nine DBPs was greater than or equal to 90 mm Hg at 12 or 18 months for life-style change intervention participants, or at 6 months for nutritional supplement intervention participants, or when participants were prescribed antihypertensive medication during the trial. The relative risks of developing such events were computed along with their 95% confidence intervals.[14] Prevalence of side effects in nutritional supplement and placebo groups was compared using χ^2 tests.

RESULTS

Recruitment

Over a 12-month period, 16 821 persons were screened for possible eligibility. Of these, 2182 were ultimately randomized during a 13-month period, exceeding the target sample size of 2100. Eight of the 10 clinics met their goals of randomizing 200 or 250 participants; the numbers randomized ranged from 67 to 346 per clinic. Of the candidates excluded, at various visits 75% to 85% had DBP values outside the range of eligibility. Other common reasons for exclusion were marked obesity (body mass index≥36.1 kg/m^2), lack of interest, poor compliance, and high serum cholesterol (≥6.7 mmol/L). The numbers of participants randomized are presented by intervention group in Fig 1.

Baseline Characteristics

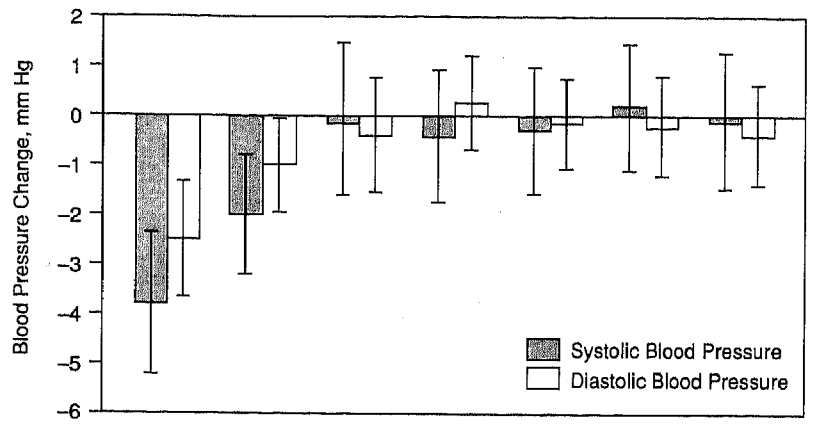
The average age of study participants was 43 years. Seventy percent were male; 82% were white, and 15% were black. Participants were generally well-educated (53% college graduates) and employed (91%). The mean BP at entry was 125/84 mm Hg. Mean body mass index was 27.6 kg/m^2 (29.5 kg/m^2 in the weight reduction and control groups), and average alcohol intake was 45.3 g per week (about three to four drinks). Indexes of 24-hour cation intakes were as follows: sodium, 158.5 mmol (3644 mg), and potassium, 62.0 mmol (2423 mg), by urinary excretion; calcium, 21.6 mmol (864 mg), and magnesium, 10.7 mmol (260 mg), estimated from 24-hour dietary recalls.

Comparisons of key characteristics across randomized groups are shown in Table 1, and further details on baseline characteristics have been published.[18] Active and control groups were generally similar. The most important imbalance was in the percentage of males in the weight reduction group and its corresponding control group (73% vs 63%, respectively, $P=.016$).

Life-style Intervention Results

Attendance at group intervention meetings, including make-up contacts, was high, particularly for initial intensive interventions: 88% or greater for each of the 14 weight reduction sessions; 70% or greater for each of the 10 sodium reduction meetings; and 86% or greater for each of the eight stress management weekly meetings. Table 2 presents the findings for the principal group measures of intervention outcomes: weight change from baseline (SV3), change in 24-hour sodium excretion from the mean of determinations at SV3 and the randomization visit, and change in Hassles score (collected only from stress management and corresponding control participants). Only unadjusted data are shown because adjusting for age, race, gender and baseline values of each outcome variable had no substantial effect.

In the sodium reduction intervention group, the mean decrease in sodium excretion was constant at about 55 to 60 mmol/24 h at 6, 12 (not shown), and 18 months. Due to a slight decline in control participants, the net difference was 44 mmol at the end of the follow-up ($P<.01$). There was also about a 1.2-kg net weight reduction during the first 6 months; by 18 months, the difference between groups was only 0.4 kg and was not significant. There were no consistent, significant differences in potassium excretion, or intakes of alcohol, calcium, or magnesium (data not shown). For the weight reduction group, weight loss was maximal at 6 months (5.7 kg, $P<.01$) compared to the control group. This difference declined to 3.9 kg at 18 months ($P<.01$). There were no significant differences in sodium excretion between the weight reduction and control groups (data not shown). Net potassium excretion increased in the treated group due to slight declines in the control group; however, these differences were of small magnitude (6.2 to 9.0 mmol/24 h). There were no consistent, significant differences in changes in intakes of alcohol, calcium, or magnesium. In the stress management group, there were no differences in changes in the Hassles scores for intensity, but at 18 months only there was a significant increase in frequency (Table 2). There were no consistent significant differences in weight, sodium or potassium excretion, or intakes of alcohol, calcium, or magnesium (data not shown).



No. of Participants	WR	Na	SM	Ca	Mg	K	FO
Active	299	305	236	221	206	161	161
Control	239	397	306	224	224	157	157

Fig 2.—Net mean changes in systolic and diastolic blood pressure (baseline minus follow-up), with 95% confidence intervals. WR indicates weight reduction; Na, sodium reduction; SM, stress management; Ca, calcium supplementation; Mg, magnesium supplementation; K, potassium supplementation; and FO, fish oil supplementation.

Nutritional Supplement Intervention Results

Compliance with nutritional supplement and placebo protocols was monitored by pill counts. The percentage of subjects taking 95% or more of the study medications ranged from 69% to 83% for active treatments and from 72% to 83% for placebos. Only for the fish oil intervention did they differ, with compliance about 10% less in the actively treated group at 6 weeks, 3 months, and 6 months ($P<.05$ at 3 months) (data not shown).

Specific objective measures of compliance were also obtained for each supplement (Table 2). In the magnesium group at 3 and 6 months, changes in serum concentrations and urinary excretion were increased compared with controls ($P<.01$); net increase in excretion was 1.3 to 1.6 mmol. Calcium excretion was increased at both visits in the active calcium supplement group by a net of 0.9 to 1.2 mmol ($P<.001$). In stage 2, plasma phospholipid levels of omega-3 fatty acids were consistently increased in the fish oil group ($P<.0001$), about sixfold for eicosapentaenoic acid and twofold for docosahexaenoic acid over the baseline levels of 0.6% and 2.0%, respectively. Potassium excretion increased by a net of 44 and 42 mmol/24 h in the potassium group at the two visits ($P<.0001$). There were no consistent changes in potassium excretion, body weight, or sodium excretion, or in intakes of alcohol, calcium, magnesium, or potassium, other than by the prescribed supplements (data not shown).

Blood Pressure Results

Data on BP changes are presented in Fig 2 for 6-month visits and in Table 3 for termination visits. These data were 91% to 96% complete at all follow-up visits, and the percentage missing at the last scheduled visits did not differ significantly between intervention and control groups. In the sodium reduction and weight reduction groups, both DBP and SBP were consistently reduced in the active intervention groups compared to controls. Net changes for both interventions were similar at 3 and 6 months of follow-up, and generally maximum at these times (Fig 2). At termination, the effects in the sodium reduction group were 0.9 mm Hg diastolic ($P<.05$) and 1.7 mm Hg systolic ($P<.01$), while for weight reduction, they were 2.3 mm Hg diastolic and 2.9 mm Hg systolic ($P<.01$ for both). These values remained similar when adjusted for age, race, gender, and baseline BP. Changes in BP for stress management were small and inconsistent in direction. Differences at termination (Table 3) were larger than at 6 months (Fig 2), but none reached statistical significance. Among the nutritional supplements, there were no significant effects on diastolic or systolic BP at 6 months (Fig 2) or at termination (Table 3). Only for potassium at the 3 months' follow-up was the change in DBP (1.2 mm Hg) statistically significant ($P=.04$).

Other Effects

There were three deaths during the trial, one each in the active weight reduction, active magnesium nutritional supplement, and life-style change control groups; causes of death were thrombotic occlusion of the right coronary artery, undetermined, and pancreatic cancer, respectively. A 21-item symptom checklist was administered to nutritional supplement and placebo participants at their 3- and 6-month visits. Few significant differences were observed. In stage 1, there was increased prevalence of loose or frequent stools (23.1% vs 11.7%; $P=.002$), and of diarrhea (15.8% vs 9.1%, $P=.04$) in the magnesium group. In stage 2, fish oil was associated with an increase in unpleasant oral taste (26.4% vs 5.7%, $P<.001$) and in belching (35.6% vs 11.4%, $P<.001$). Significant improvements on the Psychological General Well-Being scale were observed only in the sodium reduction and weight reduction groups ($P<.05$, at both 6 and 18 months) (data not shown).

Incidence of Hypertension

Table 4 presents data on the occurrence of hypertension during follow-up, defined as a mean of nine DBP readings of 90 mm Hg or greater at any of the three-visit follow-ups (12 and 18 months

Table 3.—Changes From Baseline in Diastolic Blood Pressure and Systolic Blood Pressure, mm Hg

Intervention Group	Active n	Active Mean	Active SD	Control n	Control Mean	Control SD	Active-Control Mean	Active-Control 95% Confidence Interval
Diastolic Blood Pressure								
Life-style change groups*								
Sodium reduction	327	−4.12	5.71	417	−3.27	5.73	0.85†	−1.68,−0.02
Weight reduction	308	−6.16	5.88	256	−3.91	6.12	−2.28‡	−3.25,−1.26
Stress management	242	−5.53	6.48	320	−4.71	6.00	−0.82	−1.86,0.22
Nutritional supplement groups§								
Magnesium	227	−3.00	4.54	234	−2.95	5.21	−0.05	−0.94,0.84
Calcium	237	−2.75	4.87	234	−2.95	5.21	0.20	−0.71,1.11
Potassium	178	−0.27	4.56	175	0.14	4.64	−0.42	−1.38,0.55
Fish oil	175	−0.48	4.83	175	0.14	4.64	−0.62	−1.62,0.38
Systolic Blood Pressure								
Life-style change groups*								
Sodium reduction	327	−4.86	7.81	417	−3.16	8.11	−1.69‡	−2.85,−0.54
Weight reduction	308	−5.35	7.19	256	−2.45	7.37	−2.90‡	−4.11,−1.70
Stress management	242	−4.20	9.32	320	−3.72	8.27	−0.47	−1.96,1.01
Nutritional supplement groups§								
Magnesium	227	−2.67	6.60	234	−2.67	7.24	−0.20	−1.47,1.07
Calcium	237	−3.12	7.29	234	−2.67	7.24	−0.46	−1.77,0.86
Potassium	178	−0.78	5.88	175	−0.84	5.82	0.06	−1.17,1.28
Fish oil	175	−1.05	6.64	175	−0.84	5.82	−0.22	−1.53,1.10

*Maximum of 18 months follow-up.
†$P<.05$.
‡$P<.01$.
§ Maximum of 6 months of follow-up.

for life-style change, 6 months for nutritional supplement interventions), or ever having been on antihypertensive drugs during the trial. Most of the relative risks are less than one, particularly for sodium reduction, weight reduction, and magnesium supplementation. However, only for weight reduction does the 95% confidence interval not include 1.0; ie, a relative risk of 0.66 (95% confidence interval, 0.46, 0.94).

COMMENT

Phase I of TOHP succeeded in establishing the feasibility of a large-scale prevention trial and testing most of the currently promising nonpharmacological interventions for ability to affect BP favorably in the short term. Although recruitment lasted 13 instead of 9 months, enrollment exceeded the planned sample size. Randomization resulted in groups well balanced in key sociodemographic, biological, and behavioral characteristics, and large enough to provide good power for detecting DBP differences of about 1.5 to 2.0 mm Hg. Follow-up rates were high, so that collection of BP measurements was nearly complete (93% at final visits).

Compliance with the three life-style interventions was satisfactory, both in terms of attendance at counseling sessions and in reaching specific goals. The mean net weight loss of 5.7 kg achieved at 6 months' follow-up was the maximum attained and was associated with a significant BP-lowering effect of 3.8/2.5 mm Hg. However, both net weight loss and BP differences diminished somewhat during longer follow-up, even though SBP and DBP changes remained significant at the end of the trial. There was no evidence of confounding by differences in other factors influencing BP, especially sodium or alcohol intake.

Results were generally similar in the sodium reduction group, although not quite as definitive. The group difference was maximal (58 mmol/24 h) at 6 months, although the mean reduction was well maintained. At this visit, the BP effect was −2.0/−1.0 mm Hg ($P=.001$ and .04, respectively). At all subsequent visits, both systolic and diastolic differences were also significant. Although weight fell significantly more in sodium reduction participants than in control participants over 12 months, the differences were small (0.4 to 1.2 kg) and adjustment of BP effects for weight change had little effect.

These results for weight reduction and sodium reduction are concordant with previous evidence, including that from clinical trials. MacMahon et al[15] summarized five randomized trials of weight reduction in hypertensive patients and reported that a mean 9.2-kg (20-lb) weight loss decreased BP on the average by 6.3/3.1 mm Hg. In the only previous large trial of weight reduction alone in normotensive subjects, the Hypertension Prevention Trial,[16] net weight losses at 6 and 36 months—5.8 and 3.5 kg, respectively—were similar to our results, as were net BP reductions at these points: approximately 5/3 and 2/2 mm Hg, respectively. The Hypertension Prevention Trial also studied sodium reduction, but the changes in urinary sodium excretion were small; eg, 13% at 6 months, at which time SBP was lowered by 1.7 mm Hg ($P=.13$). However, in an overview of sodium reduction trials, Cutler et al[17] pooled Hypertension Prevention Trial results with those of five other trials in normotensive subjects and found a statistically significant effect of −1.7/−1.0 mm Hg, a result similar to that in TOHP. Mascioli et al[18] recently reported the results of a 10-week double-blind crossover trial in normotensive subjects, in which BP was significantly reduced by 3.6/2.3 mm Hg, with a difference in overnight sodium excretion corresponding closely to the 24-hour difference in TOHP.

In contrast to the weight reduction and sodium reduction results, there was no indication of a favorable effect on BP by stress management. Also, findings from the Hassles questionnaire showed no beneficial effect. In retrospect, perhaps this was not a good choice of instruments, because frequency and intensity of perceived "hassles" may not decrease, but only one's reaction to them. Although there are no standard objective measures for success of stress reduction techniques, we collected data

Table 4.—Incidence of Hypertension in Each Life-style and Nutritional Intervention Group*

Intervention Group	Active			Control			
	n	Hypertensive Events Total (Median)	%	n	Hypertensive Events Total (Median)	%	RR† (95% CI)
Sodium reduction	327	28 (4)	8.6	417	47 (20)	11.3	0.84 (0.62, 1.13)
Weight reduction	308	20 (7)	6.5	256	34 (16)	13.3	0.66 (0.46, 0.94)
Stress management	242	25 (10)	10.3	320	31 (16)	9.7	1.04 (0.77, 1.42)
Magnesium	227	8 (3)	3.5	234	13 (2)	5.6	0.77 (0.44, 1.33)
Calcium	237	12 (3)	5.1	234	13 (2)	5.6	0.95 (0.63, 1.45)
Potassium	178	8 (3)	4.5	175	9 (0)	5.1	0.93 (0.56, 1.56)
Fish oil	175	10 (2)	15.7	175	9 (0)	5.1	1.06 (0.68, 1.64)

*A hypertensive event is defined as a mean of nine diastolic blood pressures greater than or equal to 90 mm Hg at either the 12-month or 18-month follow-up for life-style change participants, or at the 6-month follow-up for nutritional supplement participants, or those ever on antihypertensive medication during follow-up.
†RR indicates relative risk; CI, confidence interval.

on cardiovascular reactivity and urinary excretion of catecholamines and cortisol, which will be reported elsewhere. These negative BP results were not explained by increases in weight, alcohol use, or sodium intake in the intervention group.

There was also no evidence for BP lowering by calcium or magnesium supplementation, with doses typical of those used in previous trials, despite excellent compliance by pill count. Biochemical markers provided semiquantitative confirmation of consumption of the calcium and magnesium salts: approximately 4% and 10%, respectively, of administered doses appeared in the urine. These levels are similar to those reported in previous trials of calcium or magnesium supplementation using the same doses.[19-23] Similarly, results for potassium and for fish oil provided little indication of BP reduction. Although there was a tendency for DBP to be reduced by potassium supplementation at 3 months, this was not seen at 6 months, nor was there any effect on SBP. Compliance with potassium supplementation was good by pill counts, and 24-hour potassium excretion indicated that about two thirds of the 60-mmol dose appeared in the urine. In the fish oil group, plasma phospholipid levels of eicosapentaenoic plus docosahexaenoic indicated an approximately threefold combined increase compared to the levels excreted by the control group. Pill counts for fish oil were significantly lower than for its placebo control, probably due to the observed gastrointestinal side effects.

The negative results for stress management and the nutritional supplements are in general accord with accumulating evidence from other clinical trials. Various techniques of stress management have been studied primarily in hypertensive patients. In one trial with 192 hypertensive subjects and an intervention apparently similar to that used in TOHP (multifaceted stress management, including relaxation, provided in group sessions), significant BP reductions were found at 8 weeks and after 4 years.[24] However, in a meta-analysis of nine randomized trials that included a total of 733 behaviorally treated and control participants, Kaufmann et al[25] found a significant effect only for DBP (about 2 mm Hg) in nonmedicated patients, but none for SBP, or any effect in concurrently medicated patients.

In a review of 19 randomized trials of calcium supplementation, Cutler and Brittain[26] reported pooled differences of −1.8/−0.7 mm Hg, but with wide confidence limits that would include the even smaller estimated effects seen in TOHP. In the nine trials that studied normotensive subjects, the pooled effect was estimated as −1.3/−1.3 mm Hg; only the diastolic change was significant. The most common dose was 1 g, the dose used in TOHP; most trials have also used calcium carbonate. Given the body of epidemiologic data that suggests an influence of dietary calcium on BP,[26] potentially susceptible subgroups, such as those with low dietary calcium and/or high sodium intake and black people may require further study.

Whelton and Klag[27] have reviewed the evidence for a BP-lowering effect of dietary magnesium. Although there is considerable literature on an inverse association between water hardness and cardiovascular mortality, the specific studies of magnesium intake and BP are inconsistent. Of four randomized clinical trials of magnesium supplementation, all in hypertensive patients, none showed a significant effect on BP. However, three of the four showed downward trends in systolic and diastolic levels, and none had sufficient power individually to detect a difference of 7/4 mm Hg or smaller. A recent trial tested whether 20 mmol (486 mg) of magnesium chloride adds to the antihypertensive effect of potassium, and found no effect.[28] In this same trial, 60 mmol of potassium chloride reduced supine BP by about 12/13 mm Hg. In a review of 25 other trials of potassium supplementation, Whelton et al[29] found pooled effects of −2.4/−1.2 overall and −0.9/−1.1 in normotensive subjects (eight trials). However, not all of the trials used satisfactory methods (including a few that were not randomized), and the more rigorous trials tended to show smaller effects. Nevertheless, dietary potassium remains one of the most consistent correlates of BP level in population studies.[30]

Hypotheses proposed to account for this paradox include the possible importance of the anion given with potassium; ie, chloride might counter some of the hypertensive effect[31] and an interaction with the level of sodium in the diet.[32]

There have been both positive and negative findings relating fish oils rich in the omega-3 fatty acids, eicosapentaenoic and docosahexaenoic acids, to BP effects,[33-35] but most of these have used large doses. Only one other trial has used a dose approaching the physiologic amount administered in TOHP—approximately 5 g of eicosapentaenoic and docosahexaenoic—and a small statistically significant effect on BP was observed, ie, 6/3 mm Hg in hypertensive patients.[36] The hypothesis that fish oils lower BP remains plausible because of the known vasoregulatory properties of prostaglandins derived from these substances, but it is unlikely that dietary intake of oily fish can be increased sufficiently to have a substantial effect on BP.

In conclusion, TOHP-I demonstrated significant BP reductions with modest reductions in weight or in sodium intake that were largely sustained through 18 months of follow-up. There was little evidence of BP effects from stress management, or from nutritional supplementation with calcium, magnesium, potassium, or fish oil. The magnitude of the BP reductions with changes in body weight and sodium intake could potentially have a substantial benefit in reducing the incidence of hypertension, and on cardiovascular morbidity and mortality, especially if these effects are additive in combination. Although the

number of participants who developed hypertension was small, the data from TOHP-I regarding incidence of hypertension underscore the likelihood that small changes in mean BP translate into large differences in hypertension incidence.[8] The possible effects of single and combined interventions, including their influence on the incidence of hypertension, as well as the ability to sustain beneficial effects for a longer period, are to be tested in Phase II of TOHP. In the interim, the results of TOHP-I support the concept of incorporating counseling on weight control and reducing sodium intake in settings where health promotion and preventive medicine are practiced.

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