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EFFICACY OF CALCIUM AND VITAMIN D SUPPLEMENTATION IN REDUCING DIASTOLIC BLOOD PRESSURE IN A MILD HYPERTENSIVE MALE POPULATION

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EFFICACY OF CALCIUM AND VITAMIN D SUPPLEMENTATION IN REDUCING DIASTOLIC BLOOD PRESSURE IN A MILD HYPERTENSIVE MALE POPULATION

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DEDICATION

I dedicate this thesis to my parents and brothers, Jim, Evelyn, Robert and William. Their timely advice, assistance, moral support and encouragement have enabled me to continue to master ever higher educational and professional goals.

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ABSTRACT

The blood pressure response of 11 hypertensive males (5 blacks, 4 whites and 2 Hispanics) to 1000 mg elemental calcium (as carbonate) and 500 IU vitamin D (cholecalciferol)/ day for six weeks, was assessed in a randomized, double blind, placebo controlled, crossover trial.

Single subject case analysis revealed that there were 5 significant decreases in diastolic blood pressure $p < .05$ (4 blacks and 1 white), 2 significant increases $p < .05$, with the remaining participants seeing no change with respect to supplementation (2 Hispanics and 2 whites).

Treatment with 1000 mg elemental calcium and 500 IU vitamin D/day for 6 weeks represents a safe, well tolerated non-pharmacologic intervention that lowers diastolic blood pressure in selected male participants with mild hypertension.

CHAPTER 1

INTRODUCTION

Hypertension is one of the major causes of illness and death in America today. Several population studies have reported that 20-30% of adults are hypertensives (Hawthorne, Greaves, and Beevers 1974, Kannel and McGee, 1979) with the prevalence greater in blacks within the same environment (Wilber et al. 1972, Gillum 1979), the majority of such individuals having mildly elevated blood pressure levels.

In many cases the cause of hypertension is unknown and the person is said to have primary or essential hypertension. Secondary hypertension is so named because the elevated pressure stems from a known cause; for example, it may accompany kidney disease or endocrine disorders.

Life expectancy decreases as blood pressure rises for both men and women. The higher the level of either systolic or diastolic pressure, the greater the risk of developing target organ disease secondarily. Attention is called to the 30-39 year age group of men with blood pressures of 138-147/88-95 mm Hg (mild hypertension), because these young men have a mortality ratio of 190 percent, almost twice normal (MacMahon, Blacket, Macdonald, and Hall 1984).

Target organs include the heart, kidneys, central nervous system, and major arteries. Manifestations of cardiac involvement include the development of angina pectoris, acute myocardial infarction, left ventricular hypertrophy, acute pulmonary edema, congestive heart failure and sudden coronary death. Involvement of the kidneys secondary to hypertension produces nocturia as the initial symptom and albuminuria (more than 250 mg per 24 hours) as the first objective sign. Ultimately renal involvement leads to azotemia and renal failure. Involvement of the major arteries includes the development of dissecting aneurysms and atherothrombic obstruction of the abdominal aorta and major peripheral arteries.

Physiology of Blood Pressure

There are several factors which are responsible for maintaining arterial pressure within normal ranges:

Rate and force of heart beat: The faster the rate of the heart beat, up to a certain level, and the greater its force of contraction, the higher the arterial pressure will be. The heart is a pump, and if cardiac output changes the pressure in the system is bound to change. A decrease in the rate or force of the beat of the heart leads to lowering of the arterial pressure.

Elasticity of the large arteries: The elastic recoil of the distended arterial walls is responsible for the maintenance of arterial pressure between beats of the heart (diastolic pressure). Elasticity keeps the flow steady from the arteries into the capillaries. If the large arteries lose their elasticity, the pressure is unusually high during systole and fall to a low level during diastole. With rigid arteries, the flow into the capillaries is intermittent, coming in spurts with each ventricular systole and ceasing during diastole.

Peripheral resistance: The resistance offered by arterioles to the flow of blood is called peripheral resistance. By offering resistance to flow, arterioles maintain a high pressure behind them and a lower pressure in front of them in the capillaries and the veins. The most important factor in determining the amount of resistance to blood flow is the diameter of the arterioles. If the diameters are large, there is little resistance to flow. In this case the pressure on the arterial side becomes higher and that on the venous side becomes lower than before. These changes are regulated by the autonomic nerve fibers that supply smooth muscle in the walls of vessels.

Quantity of blood: The volume of blood in the vascular system in relation to capacity of the system is exceedingly important. Normally blood not only fills the system but also distends it slightly (i.e., keeps the vessels on stretch). Thus if a large quantity of blood is lost from the system as in severe hemorrhage, there will be a reduced venous return from the heart, reduced cardiac output, and reduced arterial pressure. The walls of the arteries will not stretch, and the blood flow to the vital organs may be inadequate to maintain homeostasis.

Viscosity of Blood: The presence of red blood cells and plasma proteins gives blood its viscosity or thickness. If the number of red cells is increased in proportion to the plasma, the viscosity is increased and blood pressure is higher. This is seen in polycythemia, in which there is a very high red blood cell count. If the number of red cells is decreased as in anemia, the viscosity is low and the arteriole blood pressure is below average. If the concentration of plasma proteins is low, the blood pressure is low. If albumin solutions are injected, viscosity increases and blood pressure rises.

Blood pressure rises in patients with hypertension either because of an increase in cardiac output, or an inappropriate increase in total systemic resistance, a narrowing of the arterioles (Cohn, 1983).

Problem Statement

While there are conflicting thoughts on the long-term benefits of reducing the mild form of essential hypertension via pharmacological means, there is strong support to reduce it by non-pharmacological means.

Some of the current non-pharmacologic approaches being promoted by health practitioners include sodium restriction, weight control, and limiting substance abuse. These approaches have had varying success dependent upon the patient's medical profile. Calcium supplementation is currently being studied as an additional non-pharmacological approach to reduce high blood pressure. However, without adequate amounts of vitamin D, absorption and utilization of calcium may be impaired.

Variables such as skin pigmentation and dietary consumption patterns may adversely affect vitamin D metabolism and consequently calcium's ability to effect a blood pressure response.

Research Objectives

The major research objectives of this study are:

Research Objective 1: To determine if there is a significant difference in reducing diastolic blood pressure while supplementing a mildly hypertensive adult black male population with a calcium/vitamin D supplement as compared to a placebo treatment.

Research Objective 2: To examine the possibility of an ethnic variance to blood pressure response while supplementing with calcium/vitamin D as compared to placebo in mildly hypertensive black, white, and Hispanic adult males.

Statement of Hypothesis and Explanatory Questions

H1: Supplementation with calcium and vitamin D will reduce diastolic blood pressure in a mildly hypertensive adult black male population.

E1: Does the level of hypertension have any effect on the magnitude of response?

E2: Is there a correlation between dietary intake of calcium and blood pressure response to calcium/vitamin D supplementation?

E3: Is there a positive change in serum ionized calcium levels when the value for the calcium/vitamin D supplementation phase is compared to the placebo phase.

H2: The magnitude or type of response to calcium/vitamin D supplementation will vary based upon difering ethnic backgrounds.

E1: Is there any difference in blood pressure response to calcium/vitamin D supplementation between ethnic groups?

E2: Is there any difference in consumption patterns of calcium between ethnic groups?

Definitions

Blood pressure: Pressure of the blood on the walls of the arteries. The human heart pumps intermittently by means of a sudden contraction of the entire ventricular musculature, followed by a period of relaxation. The pressure during the contraction phase is called systolic pressure, and the pressure during the resting phase is called diastolic pressure. In recording blood pressure, the systolic pressure is written first, followed by the diastolic pressure.

Body mass index (BMI): Noted as the simplest method devised for rating accurately the degree of obesity. This index is easily computed by dividing the body weight by the square of height (W/H^2).

Calcium: A major mineral constituent of the body that makes up 1.5% to 2% of body weight. Of this amount, 99% is present in bones and teeth; the remaining 1% is

found in soft tissues and body fluids and serves a number of functions not related to bone structure. Calcium is important in blood coagulation, transmission of nerve impulses, contraction of muscle fibers, myocardial function, and activation of enzymes.

Calcium carbonate, precipitated (USP): An odorless, tasteless, fine white crystalline powder containing 40% elemental calcium.

Calcium rigor: State of tonic contraction of muscles due to elevated blood calcium levels. It is probably due to dysfunction of the parathyroid gland.

Cholecalciferol: Activated 7-dehydrocholesterol or vitamin D3.

Hypercalcemia: Excessive amounts of calcium in the blood; may occur in hyperparathyroidism. Results in vomiting, anorexia, gastrointestinal bleeding, high blood pressure, and muscular weakness.

Cornstarch placebo: A fine white flour starch made from Indian corn.

Hypertension: Also called high blood pressure; elevation of blood pressure above normal. Blood pressure varies considerably among individuals, depending on many factors such as age, physical constitution, occupation and health. For adults, the average systolic/

diastolic pressure is about 120/80 mm Hg. Hypertension in the adult is defined by most authorities and by the American Heart Association as that arterial pressure exceeding 140/90 mm Hg. It is conventional to classify hypertension based upon the level of diastolic pressure as mild (90-104 mm Hg), moderate (105-119 mg Hg), or severe (> 120 mm Hg).

Melanin: Brown or black pigment resulting from the polymerization of the oxidation products of dopa. It is deposited in the hair, skin, and choroid of the eyes.

National Health and Nutrition Examination Survey (NHANES): The National Center for Health Statistics is conducting nutritional status surveys of the United States population on a two-year cycle. The sample consists of persons from age 1 through 74 years who are not institutionalized. There is an oversampling of groups that are prone to nutrition difficulties such as poor children of preschool age, women of childbearing age, and the aged. The survey includes household interviews, questionnaires, physical examination, tests and procedures, and biochemical determinations on blood and urine samples. These examinations are done in mobile examination centers.

Parathormone (PTH): Parathyroid hormone or parathyrin, a protein consisting of a single polypeptide chain with alanine as its N-terminal amino acid. It exerts a profound effect on the metabolism of calcium and phosphorus. Administration of the hormone raises blood calcium and lowers blood phosphorus levels, increases the elimination of both minerals in the urine, causes migration of calcium from the bones if there is an inefficient supply of this element in the food, and increases the phosphatase activity of the serum.

Primary or essential hypertension: An increase in peripheral resistance which is responsible for elevated arterial pressure to which a specific cause cannot be ascribed. It is best regarded as a multifactorial disease related to abnormalities of the regulatory mechanisms normally concerned with the homeostatic control of arterial pressure.

Secondary hypertension: Hypertension which is due to a clearly definable cause, such as renal disease or endocrine disorders.

Vitamin D: Fat-soluble vitamin formed by irradiation of sterols. Ergocalciferol (vitamin D2) is obtained by irradiating the provitamin ergosterol found in plants, and cholecalciferol (vitamin D3) is produced

by irradiation of the provitamin 7-dehydrocholesterol found underneath the skin.

CHAPTER 2

LITERATURE RESEARCH

Current Strategy for the Treatment of Essential Hypertension

The current strategy for the treatment of essential hypertension is identification, confirmation, and pharmacologic intervention, usually for a lifetime. Clinical trials have demonstrated the benefits of reducing blood pressure. While these benefits have been achieved primarily by pharmacological agents, the "1984 Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure" (1984) suggested that the benefits of these agents must be balanced against the potential for long-term adverse effects by drug treatment. At moderate and severe elevations of blood pressure, benefits outweigh the risks; but these benefits may not be as compelling at the milder levels (90-104 mm Hg diastolic). Furthermore, there is no consensus on the use of drug therapy at the lowest levels of the mild range (90-94 mm Hg diastolic).

Prevailing Drug Therapy

The prevailing drug treatment utilized today for the management of hypertension is the Stepped-Care Technique.

Step 1 entails utilizing thiazide diuretics. When patients do not respond sufficiently, a so-called Step 2 drug is added to the diuretic: beta-adrenergic blockers, alpha-beta blockers, alpha-adrenergic blockers, and centrally acting alpha 2 agonists.

But now most authorities feel that therapy should be individualized rather than regimented, starting with non-drug treatment of mild hypertension. Nonpharmacologic therapy provides expanded options for blood pressure control not only for those patients with mild hypertension, but also as an adjunctive modality for those patients with higher pressures who require drug therapy. There are now many non-drug treatments which have had varying success, dependent upon the type of hypertensive patient being treated. Some of the non-pharmacologic interventions now being utilized and explored include sodium restriction, weight reduction, substance abuse and potentially calcium supplementation.

Sodium Restriction

Sodium consumption has long been thought of as a factor in the pathogenesis of essential hypertension. Several studies have described primitive societies in which hypertension is virtually nonexistent and in which blood pressure does not increase with age (Freis 1976). The lower blood pressure found in these populations could not be

ascribed to malnutrition (Page, Damon, and Moellering 1974, Prior et al. 1968). The lack of hypertension generally has been attributed to the meagerness of dietary sodium, invariably less than 50 mEq/day (1.5 g sodium or 2.9 g salt).

In contrast to the cross-cultural studies, findings from studies of habitual salt intake and blood pressure within industrialized populations have been almost uniformly negative (Miall 1959, Dawber, Kannell, and Gordon 1967, Oldham, Pickering, Roberts, and Sowry 1960, Bing, Thurston, and Swales 1979, Simpson et al. 1978). Even in the spontaneously hypertensive rats (SHR), which are considered to be the closest counterpart to human essential hypertension, salt sensitivity has been variable (Limas, Westrum, Limas, and Cohn 1980, Chrysant, Walsh, Kem, and Frolich 1979).

In the 1940s, the Kempner rice-fruit diet, which contained less than 10 mEq (230 mg) of sodium per day, appreciably lowered blood pressure in 20 to 60% of patients, most of whom had severe hypertension, some with renal failure (Kempner 1948). This difficult therapeutic modality has been abandoned largely with the advent of effective antihypertensive drugs.

With respect to studies of the effects of moderate sodium restriction in patients with mild hypertension (Parijis et al. 1973, Carney et al. 1975, Magnani, Ambrosioni, Agosta, and Racco 1976, Morgan et al. 1978),

most were short-term, used small sample sizes, and had many confounding variables. For these reasons, the studies are difficult to interpret. More recent trials are summarized in Tables 1-3. The studies by MacGregor et al. (1982) and Watt et al. (1983) are strikingly similar in study design, duration of trial, and number of patients. Both had a double blind, randomized crossover study design; were divided into 4-week periods of dietary sodium intake of about 80 mEq/day; and were accompanied by placebo tablets and by identical-appearing sodium chloride capsules to increase total sodium intake to 140 to 160 mEq/day. In both trials, there was heterogenicity of patient responses, so that blood pressure might increase, decrease, or stay the same. Nevertheless, in the study by MacGregor et al. (1982), mean blood pressure was significantly less on the low sodium than on the high sodium intake. In the study by Watt et al. (1983), however, there was no difference in blood pressure between high and low sodium intake, although blood pressure in both groups was significantly lower than during control period on unrestricted salt intake.

In the study by Watt et al. (1983), even when poor compliers were not included in the analysis, there was no difference in mean blood pressure between the high sodium and placebo treatment periods, although the study was designed to have had a 99% chance of detecting a difference

of 5 mm Hg in mean arterial pressure between the two periods. It should be noted that the study by MacGregor et al. (1982) had a 2-month lead-in period, whereas in the study by Watt et al. (1983) the lead-in period was 2 weeks. It is possible that part of the pressure reduction during the trial period could be attributed to regression toward the mean, or even the placebo effect (Gould et al. 1981). However, the lack of a lead-in period does not explain the lack of difference in blood pressure between the two sodium regimens.

The trial by Richards et al. (1984) was a similar randomized crossover study. In this study, 12 patients with mild hypertension were assigned randomly for 4 to 6 weeks to a control diet (180 mEq sodium and 60 mEq potassium) as compared with a sodium restricted diet (80 mEq sodium and 60 mEq potassium). In addition to frequent outpatient blood pressure and urinary electrolyte measurements, 24-hour intra-arterial blood pressures were monitored during a 4-day inpatient study at the end of each regimen. There was no difference in blood pressure at the end of the high sodium regimen or the low sodium regimen. As in the first two studies shown in Table 1 (MacGregor et al. 1982, Watt et al. 1983), there was diversity of patient responses, with a lower pressure during the low sodium dietary regimen in seven of the 12 study subjects and a higher blood pressure

Table 1. Effects of dietary sodium restriction on mild essential hypertension; studies by MacGregor et al. (1982) and Watt et al. (1983).

Reference	No. Subjects	Duration	Urinary Na^+ Excretion (mEq/24 hr)			Blood Pressure (mm Hg)		
			Control Diet	Low Na^+ Diet	High Na^+ Diet	Control Diet	Low Na^+ Diet	High Na^+ Diet
MacGregor et al.	19	4 wk	191	86	162	156/98	144/92*	154/197
Watt et al.	18	4 wk	159	87	143	150/91	136/82*	137/83*

	Study Design	Comments
MacGregor et al.	Double-blind, randomized crossover; 2-mo lead-in.	Increased BP in 6 subjects. No correlation of change in BP with PRA, plasma aldosterone, age. Mean weight lower ($p < 0.05$) with low Na^+ than high NaS diet.
Watt et al.	Double-blind, randomized crossover; 2-wk lead-in.	Decreased BP in 7 subjects. Increased BP in 11 on low Na^+ diet. Analysis of 13 "successful" sodium restrictors (U Na V, 9 mEq/day) showed no difference in blood pressure. Note significant fall in BP regardless of Na^+ intake.

Notes: BP = blood pressure; PRA = plasma renin activity; $U_{Na}V$ = urinary Na^+ excretion; OPD = outpatient.

* $p < 0.05$, compared with control diet value.

in five. Included in the study by Richards et al. (1984) was a third 4- to 6-week period of potassium supplementation (see Table 2). There was a nonsignificant, temporal trend for successively lower mean blood pressure after each of the three study periods regardless of dietary electrolyte content, which may reflect the relatively short lead-in time of 10 days. Since the order of crossover between regimens was randomized, this variables does not affect the conclusions.

In a larger, less well controlled, open study lasting only 10 days, 82 patients with mild to moderate hypertension were instructed on low sodium intake (Longworth, Drayer, Weber, and Laragh 1980). The mean daily urinary sodium excretion in these patients during the control and sodium-restricted periods was 197 and 70 mEq, respectively, and mean arterial pressures were not different (121 and 119 mm Hg, respectively). As in the other studies shown in Table 2, there were divergent results in individual patients: 30 patients demonstrated a pressure rise, and 52 patients exhibited decreased or unchanged pressures with sodium restriction.

Parfrey et al. (1981) studied 41 patients with mild essential hypertension, comparing blood pressures after 5-day regimens of 350 and 10 mEq of sodium. Mean urinary sodium excretion on these two regimens was 293 and

Table 2. Effects of dietary sodium restriction on mild essential hypertension; studies by Richards et al. (1984), Longworth et al. (1980), and Parfrey et al. (1981).

Reference	No. Subjects	Duration	Urinary Na^+ Excretion (mEq/24 hr) Control Diet	Urinary Na^+ Excretion (mEq/24 hr) Low Na^+ Diet	Urinary Na^+ Excretion (mEq/24 hr) High Na^+ Diet	Blood Pressure (mm Hg) Control Diet	Blood Pressure (mm Hg) Low Na^+ Diet	Blood Pressure (mm Hg) High Na^+ Diet
Richards et al.	12	4-6 wk	180	80	-	150/92	145/91	-
Longworth et al.	82	10 d	197	70	-	121*	119*	-
Parfrey et al.	41	5 d	145	19	293	161/102	146/96**	160/101

	Study Design	Comments
Richards et al.	Randomized crossover; no antihypertensive drugs for > 1 mo; 10-d lead-in.	OPD pressure confirmed by 24-hr intra-arterial pressure. No significant change in BP; decreased BP in 7 subjects, increased BP in 5. Changes in PRA between the diets correlated with differences in BP.
Longworth et al.	Open.	No change in mean BP; increased BP in 30 subjects. Decreased BP in 52. Comparing decreased BP patients with increased BP patients, no difference in induced changes in $U_{Na}V$, PRA, aldosterone excretion, or weight. Increased BP more common in high renin, and decreased BP more common in low renin subjects.
Parfrey et al.	Open crossover.	Parallel study in normotensive subjects and patients with severe hypertension (diastolic BP, 110-130 mm Hg) reveal significant correlation between decreased BP on decreased Na^+ and initial BP level.

Notes: BP = blood pressure; PRA = plasma renin activity; $U_{Na}V$ = urinary Na^+ excretion; OPD = outpatient.

* Mean arterial pressure.

** $p < 0.05$, compared with control diet value.

19 mEq/day, respectively. The mean arterial pressure fall from high- to low-sodium diet was 8 mm Hg ($p < 0.05$). A parallel study in normotensive subjects and subjects with severe hypertension (diastolic pressure 110-130 mm Hg) revealed a significant correlation between the fall in blood pressure on the low sodium regimen and the level of blood pressure on a normal diet (i.e., the higher the initial pressure, the greater the fall).

In the last two studies shown in Table 3, randomized parallel trials were conducted on patients in general practice groups whose diets were either not altered (controls) or changed to low sodium diets. In the study by Silman, Locke, Mitchell, and Humpherson (1983), the mean daily sodium excretion was 159 and 117 mEq in the control and low sodium groups, respectively, after 52 weeks. There was no difference in pressure between the groups, although pressure significantly declined in both groups. Poor patient compliance accounted for large standard errors in pressure and sodium excretion measurements. Furthermore, other confounding variables, such as exercise, weight reduction, and relaxation offered to the control group, may have altered their blood pressure.

In a 12-week trial by Beard, Cooke, Gray, and Barge (1982), daily sodium excretion in the low sodium group was reduced drastically from 150 to 37 mEq, but as with the

Table 3. Effects of dietary sodium restriction on mild essential hypertension; studies by Silman et al. (1983) and Beard et al. (1982).

Reference	No. Subjects	Duration	Urinary Na^+ Excretion (mEq/24 hr) Control Diet	Urinary Na^+ Excretion (mEq/24 hr) Low Na^+ Diet	Urinary Na^+ Excretion (mEq/24 hr) High Na^+ Diet	Blood Pressure (mm Hg) Control Diet	Blood Pressure (mm Hg) Low Na^+ Diet	Blood Pressure (mm Hg) High Na^+ Diet
Silman et al.								
Diet	12	52 wk	150	117	159	165/98	139/81*	139/87
Control	16		147			160/98		
Beard et al.								
Diet	45	12 wk	150	37	161	142/88	131/82*	133/83*
Control	45		175			139/86		

	Study Design	Comments
Silman et al.	Randomized, parallel trial of decreased Na + vs. general health package (exercise, weight reduction, relaxation).	Poor patient compliance. Large SE for BP and urinary sodium. Decrease in U Na V was 26 mmol/day) in intervention group. Both groups had significant fall in BP in 1 yr; no difference between groups. Elements of "general health package" may have lowered BP.
Beard et al.	Randomized, parallel trial of Na + vs. control.	Both groups had significant fall in BP; no difference between groups. Diet group greatly reduced or stopped drug therapy; need for therapy only slightly decreased in control group.

Notes: BP = blood pressure; PRA = plasma renin activity; $U_{Na}V$ = urinary Na^+ excretion; OPD = outpatient.

* $p < 0.05$, compared with control diet value.

trials reported by Silman et al. (1983) and by Watt et al. (1983), both the high and low sodium dietary groups demonstrated significant drops in pressure that did not differ between groups. However, most patients on the low sodium diet were able to discontinue or greatly reduce their hypertensive medication, which was not possible in the control group.

The conclusions thus far by the National High Blood pressure Education Program Coordinating Committee (1986) are that there have been only a few well controlled studies on the effects of moderate sodium restriction in patients with mild hypertension, all of which were short-term and had few patients. In each of these studies, there was heterogenicity of response: some patients achieved a significant fall in blood pressure with low sodium intake, while others demonstrated no change or even a slight increase. Persons whose pressures increase with high sodium intake and decrease with low sodium intake have been termed a salt sensitive subset of patients with essential hypertension (Kawasaki, Delea, Bartter, and Smith 1978). Since there is no potential for harm from moderate sodium restriction, this therapeutic modality has been proposed for trial in most patients with hypertension. Moreover, recently published results from the Dietary Intervention Study in Hypertension (Langford et al. 1985) demonstrated that sodium

restriction more than doubled the success of withdrawal of drug therapy in those whose hypertension has been controlled for five years. Sodium restriction also helps prevent hypokalemia and metabolic acidosis. When large quantities of sodium are ingested, more is available in the distal tubule for potassium exchange under the influence of aldosterone. With sodium restriction, potassium supplements or potassium-retaining drugs are less likely to be needed because hypokalemia is less likely to occur. However, the general applicability of moderate sodium restriction and its long-term effects in the entire hypertensive population are unknown, since there have been no long-term trials measuring pressure reductions in the general population.

Weight Reduction

A cause-effect relationship between obesity and hypertension has yet to be established. However, the association of hypertension with obesity is well established, and a compelling body of evidence has related the two conditions (Chiang, Perlman, and Epstein 1969, Health Implications of Obesity; National Institutes of Health Consensus Development 1985, Frolich, Masserli, Reisin, and Dunn 1983).

Many epidemiological studies have demonstrated the relationship of body weight and arterial pressure in both hypertensive and normotensive populations. This association has been observed in studies of primitive as well as

acculturated societies and was evident with systolic and diastolic pressures (Page, Damon, and Moellering 1974, Prior et al. 1968, Whyte 1963, Mann, Shaffer, Anderson, and Sandstead 1964, Lowe 1964, Epstein, Francis, and Hayner 1965, Padmavati and Gupta 1959). Evidence from studies worldwide strongly supports the conclusions that arterial pressure does not increase with age in populations in which body weight does not increase with age (Chiang, Perlman, and Epstein 1969).

The Framingham Study (Kannel et al. 1967) demonstrated that relative body weight, body weight change over time, and skin fold thickness were directly related to blood pressure levels and to the subsequent rate of development of hypertension. Moreover, the risk of normotensive persons later becoming hypertensive was related to the degree of overweight. Additional longitudinal studies documented the importance of weight gain to the subsequent development of hypertension (Oberman et al. 1967, Johnson et al. 1975, Heyden, Bartel, and Hames 1969). More recently a regression analysis of nutrient data taken from the NHANES I epidemiological study had also shown that body mass index (BMI) was a significant predictor of hypertension (Harlan et al. 1984). In the Evans County, Georgia study (Tyroler, Heyden, and Hames 1975), it was shown that the relative risk of

developing hypertension with obesity or weight gain was much greater in whites than blacks.

Weight loss induced by caloric restriction lowers arterial pressure at all levels. Earlier studies on the effects of semi-starvation diet in young volunteers, all of whom were normotensive, demonstrated a fall in systolic pressure from 104 to 93 mm Hg and in diastolic pressure from 70 to 63 mm Hg. Heart rate also decreased strikingly, and oxygen consumption was reduced by almost half. With re-feeding, all values returned to pre-starvation levels (Brozek, Chapman, and Keys 1948).

Clinically, treatment of hypertension with weight reduction was reported over 60 years ago by Rose (1922), who found a lower pressure, relief of dyspnea, palpitation, headache, edema, and albuminuria in obese patients. In addition, Master and Oppenheimer (1929), in a study of obesity, reported that weight reduction resulted in a greater fall in systolic pressure than diastolic pressure, and was associated with slowing of the pulse rate and increasing exercise tolerance. Later, others reported successful treatment of hypertension with weight loss (Hovell 1982, Fagerberg, Andersson, Isaksson, and Bjorntorp 1984, Maxwell et al. 1984, Tuck, Sowers, and Dornfield 1983, Tuck, Sowers, and Dornfield 1981, Grande 1975, Brozek, Chapman, and Keys 1948, Rose 1922, Aldersberg, Coler, and

Laval 1946, Tyroler, Hayden, and Hames 1975, Ramsay et al. 1978, Stockholm, Nielson, and Quaade 1982, Stamler et al. 1980, Eliahou et al. 1981). However, not all patients demonstrated a pressure fall with slight reduction (Hovell 1982, Haynes, Harper, and Costley 1984). In one study from Israel, the investigators controlled for possible reduced dietary sodium intake by adding supplementary sodium; there was no obvious difference between the two groups (Reisin et al. 1981). Long-term evaluation by others showed that when patients regained lost weight, pressure rose to pretreatment levels (Aldersberg, Coler, and Laval 1946).

Another important intervention study in Evans County, Georgia, in which patients were randomly allocated into either a dietary treatment groups or a control group, showed that both overweight and hypertensive patients can be screened and recruited into a weight reduction program (Tyroler, Hayden, and Hames 1975). Satisfactory participation, improved patient adherence, decreased amounts of antihypertensive drugs, and lower blood pressures were achieved in this and other studies with weight reduction. In the Chicago Coronary Prevention Evaluation Program (Stamler et al. 1980), there was a considerable decrease in body weight associated with a fall in pressure, heart rate, and serum cholesterol level. Hypertensive as well as normotensive men reduced their pressure with weight loss.

More recently, another report from Israel indicated that normal pressure was achieved in most obese hypertensive patients when they had lost only half of their excess weight, even though they remained considerably obese (Eliahou et al. 1981). It was not necessary to achieve ideal body weight in order to reduce pressure, and the pressure fall persisted as long as the decreased body weight was maintained.

Thus, the evidence seems clear that weight reduction is associated with a fall in pressure in a large proportion of normotensive and hypertensive persons. A recent report showed that when weight was reduced, the decrease in blood pressure was associated with contraction of plasma volume and a decline in cardiac output, which in turn was related to a slower heart rate and decreases in plasma cholesterol, uric acid, and blood glucose (Reisin, Frolich, and Messerli 1983).

The National High Blood Pressure Education Program Coordinating Committee (1986) has thus concluded that increased body mass (i.e., overweight or obesity) is clearly related to elevated arterial pressure. Several reports have also demonstrated that a fall in arterial pressure can be expected with weight reduction. However, cardiovascular morbidity and mortality will be reduced even if pressure is not, and if the patient is receiving pharmacological

anti-hypertensive therapy, the number of dosages (or both) of these agents may be reduced. These associations do not explain why pressure is not reduced in all obese hypertensive patients who lose weight. Nevertheless, weight reduction is recommended for all obese hypertensive patients with hypertension despite the high rate of attrition that is associated with this nonpharmacological approach to treatment.

Substance Abuse

Alcohol

A significant pressor action of alcohol, even in fairly small quantities, has been identified in several epidemiological studies (Hennekens 1983). Some have found a progressive linear relationship between daily alcohol consumption and blood pressure (Cooke, Frost, and Stokes 1983), particularly for systolic levels (Arkwright et al. 1982).

In keeping with this pressor effect, epidemiological surveys, with few exceptions (Coates, Ashley, Corey, and Steele 1983, Trevisan, Farinaro, and Krogh 1984) have shown that those who consume more than 60 to 80 g ethanol per day have a significantly higher prevalence of hypertension (Hennekens 1983). By statistical analysis, from 5 to 11% of hypertension in men has been attributed to alcohol consumption (MacMahon, Blacket, Macdonald, and Hall 1984,

Friedman, Klatsky, and Siegelaub 1982), clearly incriminating regular intake of more than 1 to 2 oz of ethanol per day as the most common cause for reversible or secondary hypertension, at least among men.

In view of the foregoing findings, the National High Blood Pressure Education Program Coordinating Committee (1986) suggests that alcohol intake be assessed in all patients with hypertension. Because it is often difficult to achieve blood pressure control pharmacologically in patients with a high alcohol intake, intake should be reduced at least to 2 oz of ethanol per day (1 oz of ethanol is contained in 2 oz of 100-proof whiskey, 8 oz of wine, or 24 oz of beer). If a significant pressor effect seems likely from even that amount, abstinence should be advised. No change seems necessary for most persons who consume less than 2 oz/day.

Caffeine

Although blood pressure rises by 5 to 15 mm Hg within 15 minutes after consumption of 150 mg of caffeine (2 to 3 cups of brewed coffee) and may remain elevated for as long as 2 hours thereafter, chronic caffeine ingestion seems neither to keep the blood pressure high nor to be associated with more hypertension (Robertson, Hollister, and Kincaid 1984). The short-term effects are primarily mediated by an increase in cardiac output, with systolic

pressure usually rising more than diastolic. These effects are demonstrated both in those who are caffeine-naive and those who habitually ingest caffein, if they abstain for as long as 12 hours. The effects are not directly attributable to rises in plasma catecholamines, vasopressin, or renin activity (Izzo et al. 1983). The acute pressor effect is said to be additive to that invoked by acute physiological stress (Lane 1983) or cigarette smoking (Freestone and Ramsey 1982).

Prolonged administration of amounts of caffeine as large as 504 mg/day for 4 weeks is not associated with significant rises in blood pressure, in either normotensive (Ammon, Bick, Mandalaz, and Verspohl 1983) or hypertensive persons (Robertson, Hollister, and Kincaid 1984). This adaption or tolerance to the hemodynamic effects of caffeine may explain why most epidemiological surveys do not display a relation between coffee consumption and prevalence of hypertension (Dawber, Kannel, and Gordon 1974, Bertrand et al. 1978).

Nicotine

In many ways similar to the effects of caffeine, nicotine consumption acutely raises the blood pressure but does not seem to elevate blood pressure chronically and does not appear to be associated with more hypertension. In fact, when smokers quit, they may have a small rise in blood

pressure, possibly because they tend to gain weight (Friedman and Sieglaub 1980). The cardiovascular effects of cigarette smoking seem to be largely dependent on the inhaled nicotine (Aronow and Kaplan 1983). The rise in heart rate and in systolic and diastolic pressures that follows the smoking of two cigarettes in a 10-minute interval is dependent upon the release of epinephrine and norepinephrine (Cryer, Haymond, Santiago, and Shah 1976). When these catecholamines are blocked by alpha-blocking and beta-blocking drugs, the hemodynamic effects are largely inhibited.

As a result of the development of tolerance to those nicotine-induced effects or the lower body weight of smokers, chronic cigarette smoking is not associated with higher levels of blood pressure or greater frequency of hypertension (Ballantyne, Devine, and Fife 1978). Nonetheless, deaths due to hypertension are more common among smokers (Doll and Peto 1976), and smokers have a higher frequency of malignant hypertension (Isles, Brown, and Cumming 1975). Moreover, nicotine may influence the metabolism of antihypertensive drugs: smokers required larger doses of propranolol than did nonsmokers to achieve similar drops in blood pressure (Mann, Madhavan, and Alderman 1984).

Calcium

Epidemiological Observations

Epidemiologic evidence initially suggested a link between calcium exposure and blood pressure regulation. These observations were derived from geographic surveys that related cardiovascular death rates with water hardness (primarily determined by calcium concentration) (Neri, Mandel, and Hewitt 1972, Schroeder 1960). This reduction has been suggested to be due to lower blood pressure figures in these populations. Subsequent studies of the hard water effect have not been as supportive of an association as the initial work (Comstock 1979). It is possible that the weak association found could be related to the low amount of calcium in drinking water compared with dietary calcium. Estimates have it that calcium in drinking water represents only 10% to 15% of total calcium intake in a population with high calcium intake (Belzian et al. 1983).

In light of this theory, several recent epidemiological studies were analyzed to detect an association between dietary calcium intake and blood pressure in humans. Analysis of the 1971-1974 National Health and Nutrition Examination Survey (NHANES I) data by Harlan et al. (1984) led to the conclusion that an inverse relationship existed between dietary intake of calcium and blood pressure; however, the relationship was fragile and did not hold for

all subgroups. The one subgroup that the association did hold for was the black population. Harlan's multiple regression analysis of the NHANES I data revealed that dietary calcium had the strongest relationship for diastolic blood pressure in the black population, second only to Body Mass Index as a predictor. An additional analysis of the same data revealed that calcium intake was significantly related to systolic blood pressure among non-white men (Gruchow, Sobocinski, and Barboriak 1985).

Other studies supporting the association include analysis of the data from the second NHANES (1976-1980) (Harlan et al. 1985), the Puerto Rico Heart Health Program Study (Garcia-Palmieri 1984), an epidemiological survey of older people in a southern California community (Ackley, Barrett-Connor, Suarez 1985), and the data from the Honolulu Heart Program (Reed et al. 1985). The authors of this latter study demonstrated inverse relationships with blood pressure for potassium, protein, and milk as well as for dietary calcium. They discussed the need to be especially careful in attempting to derive inferences about the significance of any single dietary constituent without analyzing it in the context of the other dietary nutrients with which it shares a relationship and may have physiological interactions.

Clinical Studies

Belzian et al. have conducted trials assessing the effect of calcium supplementation in young normotensive subjects (1983a) and in pregnant normotensive women (1983b); diastolic blood pressures were 3 to 6 mm Hg lower in the calcium-supplemented groups. Johnson, Smith, and Freudenheim (1985) had access to data from a clinical trial on the benefits of calcium supplements (Os-Cal) in the treatment of osteoporosis, in which both resting and exercise pressures of 81 normotensive and 34 hypertensive subjects were measured annually. At the end of 4 years, there were no significant changes between the supplemented and unsupplemented normotensive women, but the calcium-supplemented hypertensive women experienced a 13 mm Hg decrease in systolic blood pressure as compared with a 7 mm Hg decrease in the unsupplemented group. McCarron and Morris (1985) conducted a double-blind, placebo-controlled, randomized crossover trial in which calcium, 1000 mg/day, was administered orally to 48 patients with mild to moderate hypertension and to 32 normotensive controls. Compared with the placebo group, the actively treated hypertensive patients experienced a mean reduction of 3.8 mm Hg in supine systolic pressure, 5.6 mm Hg in standing systolic pressure, and 2.3 mm Hg in supine diastolic pressure.

The fall in blood pressure in these trials was not experienced by all calcium-supplemented hypertensive patients. This concept of selective response to calcium supplementation was noted in a study by Resnick, Nicholson and Laragh (1984). Although neither randomized nor placebo controlled, the study indicated that hypertensive patients who were most likely to respond to orally administered calcium supplementation are those with low serum ionized calcium levels and low plasma renin activity. To confuse matters, however, other studies have suggested that (1) a direct relationship exists between serum calcium concentration and blood pressure (Kesteloot et al. 1983, Bulpitt, Hodes, and Everitt 1976, Sangal and Beevers 1982); (2) hyper-calcemic states (Earll, Kurtzman, and Moser 1966), including hyperparathyroidism (Bone, Snyder, and Pak 1977), have been associated with hypertension; and (3) induced hyper-calcemia raises blood pressure in normotensive subjects (Pak 1970).

Cellular Biochemical Research

In light of these epidemiological and clinical studies, a great deal of cellular biochemical research has been done trying to elucidate calcium's role in hypertension via its effects on smooth muscle contraction and relaxation (Rasmussen 1983).

Calcium is the fifth most abundant element and the most abundant cation in the human body. The ionized calcium found in plasma is the physiologically active form (Schuette and Linkswiler 1984), and is one of the body's "second messengers" by relaying electrical and chemical messages that arrive at a cell's surface membrane to the biochemical machinery within the cell (Carafoli and Penniston 1985).

Initial muscle contraction is initiated by ionized calcium in response to an action potential generated at the cell membrane (Llinas 1984). The muscle fibers themselves are composed of four major proteins: myosin, actin, tropomyosin and troponin (Murray and Weber 1974). The contraction of smooth muscle arterioles is a function of their interaction when ionized calcium binds to the troponin C subunit of troponin (Cohen 1975). But if it is dilation or relaxation of the arterioles that is needed to reduce blood pressure in some cases, how can calcium play a role in muscle relaxation when it causes muscle contraction?

In order for the muscle to relax, the ionized calcium that came into the cytoplasm causing muscle contraction has to be removed, thereby causing muscle relaxation. It is theorized that when those mechanisms which remove calcium are not functioning properly, the muscle is not able to relax (McCarron 1985a). There are currently two systems thought to act as ionized calcium removers from the cell

cytosol. The first is the sodium-calcium plasma membrane co-transport system, whereby one calcium ion is exchanged for three sodium ions (Kwan 1985). It has also been theorized that the low sodium diets now prescribed for hypertensives can actually be compounding the problem by reducing the amount of sodium available to transport the excess ionized calcium out of the cell (McCarron 1985a). The second system thought to play a crucial role in the removal of ionized calcium from the cytoplasm is calcium-calmodulin activation of the calcium-magnesium pumping ATPase (Kwan 1985). This system is of great interest in that it may explain why both low and high serum ionized calcium levels seem to be related to hypertension.

Calmodulin is a small protein (18,000 molecular weight), with four calcium binding sites and no intrinsic enzyme activity. Calmodulin's only function is that of binding ionized calcium and interacting with other proteins to modify their functions, in this case activation of the calcium-magnesium pumping ATPase. The kinetics of the three components, ionized calcium, calmodulin and a response element (ATPase), is complex. One important feature is that three or four calcium binding sites on calmodulin must be occupied in order for response element activation. In order to saturate the calcium binding sites on calmodulin, the ionized calcium concentration within the cytoplasm must

change from 0.2 to 100 uM (Rasmussen 1983). If inadequate amounts of ionized calcium are bound to calmodulin, then the intracellular steps that promote relaxation will be impaired (McCarron 1985a).

Serum ionized calcium levels are normally held within narrow physiologic limits. At least three effector sites are involved in the regulation of extracellular ionized calcium concentration, the bone, kidney and GI tract.

All three effector sites are subject to control by a protein hormone called parathormone (PTH). Parathormone production is controlled directly by the calcium concentration of the extracellular fluid bathing the cells of these glands. Lower calcium concentration stimulates parathormone production, and a higher concentration does just the opposite.

PTH exerts at least four distinct affects on the above sites:

1. Increases the movement of calcium and phosphate from bone into the extracellular fluid.
2. Increases GI absorption of calcium by stimulating the active transport system which moves the ion from the gut lumen to the blood. This is an important mechanism for elevating plasma calcium concentration since under normal conditions considerable amounts

of ingested calcium are not absorbed from the intestine but are eliminated via the feces. The action of PTH here is dependent upon the presence of adequate amounts of vitamin D. Thus a major event in vitamin D deficiency is decreased gut calcium absorption resulting in decreased plasma calcium.

3. Increased renal tubular calcium reabsorption, thus decreasing urinary calcium excretion.
4. Reduces the renal tubular reabsorption of phosphate, thus raising its urinary excretion and lowering extracellular phosphate concentration; allows calcium to be released from the bone.

Calcitonin lowers plasma calcium primarily by inhibiting bone reabsorption. Its secretion is controlled directly by the calcium concentration of plasma supplying the thyroid gland; increased calcium causes increased calcitonin secretion. Thus this system constitutes a second feedback control over plasma calcium concentration, one that is opposed to the PTH system. However, its overall contribution to calcium homeostasis is minor compared to that of PTH.

Vitamin D Physiology and the Impact of Skin Pigmentation on Bioavailability

Vitamin D, by means of its active metabolite, promotes the efficient absorption of calcium from the intestine, the proper mineralization of bone, and the maintenance of normal calcium levels. The vitamin D endocrine system and parathyroid hormone play important and interrelated roles in the maintenance of calcium homeostasis in humans (Audran and Kumar 1985).

Severe deficiencies of this vitamin is most noted in the outcome of rickets in children, and osteomalacia in adults, whereas, on the other hand, hypervitaminosis D produces such symptoms as irritability, vomiting, brittle bones, hypertension, renal insufficiency, and development of a systolic heart murmur. Blood serum levels for calcium and phosphorus often become elevated in severe cases of hypervitaminosis, only to be followed by progressive calcification of the vascular system and other soft tissues (Zapsalis and Beck 1985).

In addition to being made available via dietary means, vitamin D3 is formed from a precursor, 7,dehydrocholesterol, which is present in large amounts in the skin (Holick 1984). 7,dehydrocholesterol is converted to vitamin D3 under the influence of ultraviolet light that is present in sunlight (Audran and Kumar 1985).

Vitamin D3 is made in the human skin by the photoconversion of 7,dehydrocholesterol (7-DHC) to previtamin D3, which, in turn, thermally isomerises to vitamin D3 (Holick, MacLaughlin and Doppelt 1981). It has been suggested that the presence of the chromophore melanin in high concentrations in the skin could limit vitamin D synthesis by competing with 7-DHC for ultraviolet photons (Holick 1981). As a consequence, dark-skinned individuals living in northern latitudes might be at a greater risk of vitamin D deficiency than their white-skinned neighbors. Early surveys (Hess and Unger 1917), and more recent reports (Bachrach, Fisher, and Parks 1979, Rudolf, Arulantham and Greenstein 1980) revealed a higher incidence of rickets among black children than among white children in the United States. There has also been speculation that dark skin could be a predisposing factor to vitamin D deficiency, which is common in Asian immigrants in Britain (Dunnigan et al. 1962). It has also been hypothesized that melanin pigmentation not only limits cutaneous vitamin D formation but that it is also important for controlling the amount of vitamin D3 synthesized in the skin. As a result of this theory, it has been speculated that heavily pigmented individuals living at or near the equator are protected from vitamin D toxicity, principally because the skin pigment absorbs ultraviolet-B photons (Loomis 1967).

A study to determine the effect of increased skin pigment on the cutaneous production of vitamin D3 by Clemens et al. (1982), where circulating vitamin D concentrations were determined in two lightly pigmented white and three heavily pigmented black volunteers after exposure to a single standard dose of ultraviolet radiation (UVR). Exposure of the white subjects to 1 minimal erythemal dose of UVR greatly increased serum vitamin D concentrations by up to 60-fold 24-48 hours after exposure, whereas this does did not significantly change serum vitamin D concentrations in the black subjects. Re-exposure of one black subject to a dose of UVR six times larger than the standard dose increased circulating vitamin D concentrations similar to those recorded in white subjects after exposure to the lower dose. The authors of this study concluded that increased skin pigment can greatly reduce the UVR-mediated synthesis of vitamin D3. It was also noted in this same study that the amount of 7-DHC present in pigmented skin is the same as in light skin. Therefore, the maximal amounts of pre-D3 and hence D3 produced are the same. It just takes a larger dose of ultraviolet light to convert precursor to product.

Dietary sources of vitamin D may also be limited in blacks. The NHANES I study conducted from 1971-1974 indicated that blacks had lower calcium intakes as compared to their white counterparts. McCarron (1983) has suggested

that this may be related to the reduced ingestion of dairy products, many of which are fortified with vitamin D3 in the United States because of the relatively high prevalence of lactase deficiency.

Thus reduced efficiency of the skin to synthesize vitamin D combined with lactose intolerance may place certain ethnic and geographical populations at a double risk for vitamin D3 deficiency.

Once vitamin D enters the circulation, it is bound by an alpha-2-globulin known as vitamin D binding protein (Dueland et al. 1982, Holick 1984). Vitamin D is not active as such but undergoes a series of metabolic transformations first in the liver to 25-hydroxyvitamin D and then the kidney to form the active metabolite 1,25-dihydroxyvitamin D (Kumar 1984, Audran and Kumar 1985).

The most important factor in determining the amount of 25-hydoxyvitamin D, produced by the liver, in the plasma or serum is the amount of vitamin D in the plasma from either dietary or endogenous sources. Consequently the plasma or serum 25-hydroxyvitamin D level is an accurate reflection of vitamin D reserve in the human (Audran and Kumar 1985). A competitive binding protein assay can be utilized to determine the plasma levels of 25-hydroxyvitamin D (Haddad and Chyu 1971, Belsey, DeLuca, and Potts 1974).

The formation in the kidney of 1,25-dihydroxyvitamin D is regulated by several factors, the most important of which are parathyroid hormone, serum inorganic phosphate, and perhaps serum calcium directly (Boyle, Gray, and Lemann 1971, Rasmussen et al. 1972, Tanaka and DeLuca 1973).

When hypocalcemia occurs, this perturbation is rapidly sensed by the parathyroid gland, and the secretion of parathyroid hormone is increased almost immediately (Aurbach, Marx, and Spiegel 1981). This peptide hormone increases the mobilization of calcium from bone and also decreases the fractional excretion of calcium in the kidney. These effects occur quickly and increase the concentration of calcium in the blood. In addition to these changes, parathyroid hormone causes increased activity of the 25-hydroxyvitamin D-1 alpha hydroxylase enzyme, which, in turn, enhances the synthesis of 1,25-dihydroxyvitamin D renal tubular reabsorption of calcium (DeLuca 1979).

The serum level of inorganic phosphate influences the amount of 1,25-dihydroxyvitamin D synthesized in a manner that is independent of parathyroid hormone. Hypophosatemia increases the amount of 1,25-dihydroxyvitamin D synthesized in a manner that is independent of parathyroid hormone (Tanaka and DeLuca 1973, Gray et al. 1977). The opposite series of events occurs in hyperphosphatemia. The

synthesis of 1,25-dihydroxyvitamin D is enhanced in hypophosphatemia and suppressed in hyperphosphatemia (Audran and Kumar 1985).

The major organs affected by 1,25-dihydroxyvitamin D are the intestine and bone (DeLuca 1984, Kumar 1984). In the intestine, the chief effect of this hormone is to increase the active transport of calcium (Ohdahl et al. 1971). The stimulation of calcium transport by 1,25-dihydroxyvitamin D is an energy dependent, sodium requiring process (Wasserman, Kallfelz, and Comar 1961, Martin and DeLuca 1969).

The vitamin D endocrine system is an important regulator of calcium homeostasis. To date the physiological interrelations on vitamin D activity are complex, and many aspects remain to be unraveled.

In view of the cited literature, it is the objective of this study to demonstrate that an association exists between calcium and vitamin D metabolism and blood pressure control, which may be variable based upon the diversity of skin pigmentation and dietary consumption patterns.

CHAPTER 3

METHODS AND PROCEDURES

Study Participants

Male volunteers between the ages of 26 to 49 years were drawn from the active duty outpatient clinic population stationed at Fort Huachuca, Arizona. Participants were excluded if they met any of the following criteria: morbid obesity (50% or more over average body weight for height), mental incapacitation, alcohol or drug addiction (based on participants' medical record indicating drug or alcohol problems, in addition to verbal inquiry by the investigators), congestive heart failure, myocardial infarction within 1 year, angina pectoris, kidney stone within 10 years, a history or current evidence (or blood urea nitrogen level of 35 mg/dL or more, or serum creatinine level of 1.5 mg/dL or more), of significant renal disease, or a history of cerebrovascular accident. In addition, the presence of any disease known to affect calcium balance (inflammatory bowel disease, diagnosed osteoporosis, active ulcer disease, parathyroid dysfunction, or recent bone fracture), serum cholesterol > 300 mg/dL, serum triglycerides > 200 mg/dL, or treatment with any drug known to affect calcium balance

(thiazide diuretics, steroids, cimetidine, antacids, antimicrobials, calcium channel blockers, phenytoin, or isoniazid) prohibited a participant from entering the supplemental phases of the study. Subjects with a history or current physical signs of definite or possible secondary hypertension were excluded. Withdrawal from therapy with antihypertensive agents, vitamin and mineral supplements was required 4 weeks prior to the supplemental phases of the study. Interested participants were told of the voluntary nature of the study and signed an informed consent as approved by the Human Use Committee, William Beaumont Army Medical Center, El Paso, Texas (Appendix A).

During the phase I baseline evaluation period, blood pressure was measured for 4 consecutive weeks. The blood pressures were measured on both right and left arms in the supine and sitting positions. Each participant completed a self reporting questionnaire to assess current health status, medical history (as related to calcium metabolism), current medications, and alcohol consumption (Appendix B). The first in a series of four laboratory studies was also accomplished. Height was assessed without shoes, and weight was taken while the participant was in uniform. Standardized weights for the various uniforms were subtracted. Hypertension was prospectively defined as a mean diastolic pressure of 90 mm Hg or more.

Study Design

This study was designed to detect a 3-4 mm Hg decrease in the diastolic blood pressure in black hypertensives, by using a double blind, placebo controlled, cross-over study design (Figure 1). Medications were prepackaged by randomization number for each participant and dispensed weekly. Two supplemental regimens were used: 6 weeks of calcium and vitamin D (phase II), followed by a washout period of 3 weeks of cornstarch placebo (phase III), and then 6 additional weeks of cornstarch placebo (phase IV); or 6 weeks of cornstarch placebo (phase II), followed by 3 weeks of cornstarch placebo (phase III), and then 6 weeks of calcium and vitamin D (phase IV). One gram of elemental calcium and 500 international units (I.U.) vitamin D3 were provided in capsule form.[1] Prior to encapsulation, the vitamin D3 (Cholecalciferol, U.S.P, Spectrum Chemical Manufacturing Corporation, Gardena, California), was serially diluted 8 times with the calcium (Calcium Carbonate, U.S.P./NF, Spectrum Chemical Manufacturing Corporation, Gardena, California), and intimally mixed after each dilution. Each participant was provided with six capsules, each containing 415 mg calcium carbonate and 85 I.U. vitamin

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1. Gelatin Coni-Snap TM Capsules provided, at no cost, by Capsugel, a Division of Warner-Lambert Company, Greenwood, South Carolina.

	Phase I	Phase II	Phase III	Phase IV
Group A	Baseline	1000 Mg Elemental Calcium & 500 IU Vitamin D Supplementation	Corn starch Placebo	Corn starch Placebo
	4 Weeks	6 Weeks	3 Weeks	6 Weeks
Group B	Base Line	Corn Starch Placebo	Corn Starch Placebo	1000 Mg Elemental Calcium & 500 IU Vitamin D Supplementation
	4 Weeks	6 Weeks	3 Weeks	6 Weeks

Figure 1. Double-blind crossover study design.

D3, taken twice daily, three each morning and three each evening. Placebo capsules consisted of cornstarch (Argo Corn Starch, Best Foods CPC International Incorporated, Englewood Cliffs, New Jersey, and Cream Corn Starch, Distributed by Purex Corporation, Lakewood, California), and were identical in taste and appearance to the calcium and vitamin D capsules. Participants and members of the investigative staff were blinded. A copy of the key to break the capsule code was provided to the chief pharmacist in the event of a medical emergency.

Analytical Methods

Blood pressure was measured weekly by a nurse practitioner in the Hypertension Clinic, Raymond W. Bliss Army Community Hospital, Fort Huachuca, Arizona. A random-zero sphygmomanometer (Tycos, Asheville, North Carolina) was used for measurement of blood pressure after each patient was supine for 5 minutes and after sitting for 2 minutes. The American Heart Association recommendations (Kirkendall, 1981) were followed. A cuff was selected that was at least 20% wider than the diameter of the arm. The cuff was deflated at a rate of 2 mm Hg per heartbeat, and the readings were made to the nearest 2 mm Hg interval on the scale. The first consecutive Korotkoff sounds (phase 1) was used for recording systolic pressure and disappearance of the Korotkoff sounds (phase V) for recording diastolic

pressure. Weight was measured three times during the course of the study: at the beginning of the baseline period (phase 1), the end of phase II, and at the end of phase IV. Each participant was queried weekly for adverse effects of the supplemental capsules. Routine laboratory chemistry tests, complete blood count (CBC), urinalysis, serum ionized calcium and total calcium were done four times during the course of the study; the beginning of the baseline period (phase I) and the end of phases II, III, IV. An electrocardiogram was performed at the beginning of the baseline period (phase I). Twenty-four-hour diet diaries were collected three times: the beginning of the baseline period (phase I) and at the end of phases II and IV. Prior to laboratory determinations for the routine chemistry tests, CBC, urinalysis, serum ionized calcium and total calcium, the participants were required to fast for twelve hours.

Compliance was assessed at each visit by pill counts from the returned bottles of supplements.

Serum levels of calcium were measured utilizing the Cresolphalein Complexone Colorometric method (Technicon SMAC Analyzer, Terrytown, New York). Serum ionized calcium concentration was determined by using a modified Zeisler formula (Pottgen and Davis 1976). Measurements of Chemistry III (glucose, blood urea nitrogen, creatinine, uric acid, sodium, potassium, chloride, carbon dioxide, phosphate,

total protein, albumin and alkaline phosphatase) and Chemistry VI (cholesterol and triglycerides) were done on the DACOS TM (Discrete ANalyzer with Continuous Optical Scanning) Autoanalyzer. The DACOS analyzer is a quantitative automated chemistry analyzer for in vitro diagnostic use, to analyze blood serum samples, and to quantify their constituents.

Diet diaries were collected for a weekday. Participants were instructed not to alter their dietary habits on the days they recorded their food intakes. A detailed instruction pamphlet complete with a sample daily intake was provided to each participant (Appendix C), each time diet diaries were to be completed. This instruction pamphlet was closely patterned after a similar pamphlet developed for the Western Regional Research Project W-153 entitled Food Supplement Usage and Effects on Nutritional Status. A registered dietitian reviewed the completed diet record with each participant for accuracy and completeness. The diet diaries were analyzed with the Evrydiet (Evryware, 1950 Cooley Avenue, Palo Alto, California 94303) computerized nutrient data base; over 1,000 foods are contained in the data base, and each food is analyzed for 24 nutrients.

CHAPTER 4

RESULTS AND DISCUSSION

Thirty-four participants were entered into the baseline phase of the study. Eleven were taking no medication at the time, and twenty-four were either taking a Step I diuretic or combination Steps I and II anti-hypertensive medications. Eleven of the twenty-three users of prescription medications were dropped from the study after the baseline period. This was due to the fact that their blood pressures, without their medications, were below those required to remain in the study. A brief interview with these participants revealed that most had made one or more significant lifestyle changes such as weight reduction, sodium restriction and reduced alcohol consumption. This information suggests that the need for pharmacologic intervention may have to be periodically reviewed in the mild hypertensive population.

Fourteen participants had blood pressures high enough, after the baseline period, to be entered into the supplementation phases of the study. Three participants were subsequently dropped from the study, one for probable angina, one for moderate hypertension, and one for suspected alcohol abuse.

Descriptive Data

Demographic and Baseline Blood Pressure Characteristics

Each of the participants involved in the study was an active duty soldier stationed at Fort Huachuca, Arizona. Ft. Huachuca is an army post located approximately 70 miles southeast of Tucson, Arizona. This population was chosen in an effort to reduce some of the confounding variables of essential hypertension such as weight, age and physical fitness.

The younger age grouping of this hypertensive population as compared to the group studied by McCarron and Morris (1985) is targeted since MacMahon, Blacket, Macdonald and Hall (1984) revealed that the 30-39 year age group of men with diastolic blood pressures of 88-95 mm Hg, have a mortality ratio of 190 percent, almost twice normal. In addition, during the aging process the arteries tend to become less elastic due to calcification. Therefore, calcium's ability to induce arteriole muscle relaxation (Kwan 1985, McCarron 1985a) may be more effective in the younger hypertensive population.

The three groups did not differ significantly in demographic characteristics (see Table 4), but the white ethnic group was slightly older and heavier. Two of the eleven participants had been untreated. Of the 9 treated patients, 7 were taking diuretics, 3 were taking beta

blockers, 1 was taking an alpha-adrenergic argonist, and one other was taking a direct vasodilator. Four participants were taking two anti-hypertensive medications simultaneously.

Diastolic Blood Pressure to Calcium/Vitamin D Supplementation

Table 5 summarizes by ethnic group the overall response to calcium/vitamin D supplementation. There were no significant changes in blood pressure between the calcium/vitamin D and placebo phases for the grouped data. This was due to the small number of participants and the great heterogenicity of response within each group. These results are consistent with the sodium restriction studies conducted by the MacGregor et al. (1982) and Watt et al. (1983), and the calcium supplementation study conducted by McCarron and Morris (1985) whereby there was a heterogenicity of patient responses, so that blood pressure might increase, decrease or stay the same.

In contrast to the grouped data, the individual response to calcium/vitamin D supplementation is provided in Tables 6 through 16. Again, heterogenicity of response is evident. Five of the eleven participants or 45% of the tested population had significant reductions in their diastolic blood pressures. This was also the case in the study by McCarron and Morris (1985) where 44% of the

Table 4. Demographic characteristics and mean blood pressure values of 11 hypertensive male participants in three ethnic groups at Ft. Huachuca.

	Black	Hispanic	White	All Groups
Age, years	33.4 ± 2.3	35.0 ± 9.0	41.0 ± 5.4	36.4 ± 6.3
N*	5	2	4	11
Height, inches	70.6 ± 3.0	69.5 ± 1.5	72.7 ± 2.2	71.2 ± 2.8
Weight, lbs	176.2 ± 24.8	202.5 ± 3.5	222.5 ± 20.2	197.8 ± 29.5
Baseline (Mean Diastolic BP, mm Hg:				
Supine	88.7 ± 9.1	86.6 ± 5.0	88.3 ± 4.6	88.2 ± 7.1
Sitting	90.9 ± 8.3	89.7 ± 7.3	91.5 ± 8.1	90.9 ± 8.1

Note: Values are mean +/- SD; BP's are all diastolic.

* N = number of participants

Table 5. Mean blood pressure values during baseline, placebo, crossover, and calcium/vitamin D supplementation phases, of 11 hypertensive male participants at Ft. Huachuca.

	N*	mm Hg			
		Baseline	Placebo	Crossover	Calcium Vit D
Black Adults:	5				
Supine diastolic		88.8 ± 9.0	92.6 ± 9.8	86.9 ± 10.1	88.7 ± 8.5
Sitting diastolic		90.9 ± 8.2	93.2 ± 8.3	87.7 ± 9.2	88.4 ± 8.9
White adults:	4				
Supine diastolic		88.3 ± 4.5	86.3 ± 5.5	89.3 ± 6.3	85.1 ± 5.2
Sitting diastolic		91.5 ± 8.1	86.6 ± 8.5	88.0 ± 10.6	89.2 ± 10.8
Hispanic adults:	2				
Supine diastolic		86.6 ± 5.0	84.2 ± 4.7	84.7 ± 4.7	84.8 ± 3.9
Sitting diastolic		89.7 ± 7.3	83.7 ± 9.6	88.7 ± 8.0	86.3 ± 6.6
All groups:	11				
Supine diastolic		88.2 ± 7.0	88.9 ± 8.5	87.4 ± 8.1	86.6 ± 6.9
Sitting diastolic		91.0 ± 8.1	89.1 ± 9.2	88.0 ± 9.6	88.3 ± 9.4

Note: Values are mean +/- SD.

* N = number of participants

Table 6. Single subject case analysis: Participant No. 17, Black, Test Group A, 35 Years of Age, 188 Pounds; 70 Inches.

	Phase I Baseline		Phase II With Calcium		Phase III Crossover		Phase IV Without Calcium	
	Mean[a]	Range (Low-High)	Mean	Range (Low-High)	Mean	Range (Low-High)	Mean	Range (Low-High)
Diastolic								
Supine	101.5	(96-100)	99.0	(96-100)	100.0	(100-100)	107.7	(100-112)
Sitting	104.0	(98-100)	99.0	(94-104)	100.0	(100-100)	105.0	(100-110)
Diet calcium (mg)	1087		634				825	
Serum								
Total calcium (mg/dl)	9.6		N/A*		9.4		9.4	
Ionized calcium (mg/dl)	4.1		N/A*		4.1		4.1	
Compliance**			80%		0%		100%	

[a] Mean = mean values of blood pressures taken weekly for each phase.

* N/A = Data not available

** % Compliance = $\frac{\text{Estimated Intake}}{\text{Total Prescribed}}$

Conclusion: A mean 8.7 mm Hg supine ($p < .001$) and a mean 6 mm Hg sitting ($p < .005$) reduction in diastolic blood was achieved during the supplementation phase as compared to placebo levels.

Discussion: It would appear that calcium/vitamin D supplementation for this participant has a beneficial therapeutic effect on his diastolic pressure. Adequate to near adequate dietary levels of calcium would suggest that vitamin D may be the limiting factor for optimum calcium metabolism.

Table 7. Single subject case analysis: Participant No. 44, Black, Test Group A, 33 Years of Age, 131 Pounds; 67 Inches.

	Phase I Baseline		Phase II With Calcium		Phase III Crossover		Phase IV Without Calcium	
	Mean[a]	Range (Low-High)	Mean	Range (Low-High)	Mean	Range (Low-High)	Mean	Range (Low-High)
Diastolic								
Supine	86.0	(80-104)	86.0	(76-96)	90.0	(90-90)	92.7	(76-100)
Sitting	84.5	(78-90)	80.7	(70-90)	84.7	(84-86)	88.3	(80-98)
Diet calcium (mg)	258*		220*				558	
Serum								
Total calcium (mg/dl)	9.6		10.1		10.6		10.0	
Ionized calcium (mg/dl)	4.3		4.2		4.5		4.3	
Compliance**			95%		95%		100%	

[a] Mean = mean values of blood pressures taken weekly for each phase.
* Value < 50% Recommended Dietary Allowance

** % Compliance = $\frac{\text{Estimated Intake}}{\text{Total Prescribed}}$

Conclusion: A mean 6.7 mm Hg supine ($p < .05$) and a 7.6 mm Hg sitting ($p < .01$) reduction in diastolic blood pressure was achieved during the supplementation phase as compared to placebo levels.

Discussion: It would appear that calcium/vitamin D supplementation, for this participant, has a beneficial therapeutic effect on his diastolic blood pressure. With respect to the dietary information (suggesting low intakes of calcium), dietary counseling or calcium supplementation should be considered to improve this participant's nutritional status.

Table 9. Single subject case analysis: Participant No. 16, Black, Test Group A, 29 Years of Age, 201 Pounds; 75 Inches.

	Phase I Baseline		Phase II With Calcium		Phase III Crossover		Phase IV Without Calcium	
	Mean[a]	Range (Low-High)	Mean	Range (Low-High)	Mean	Range (Low-High)	Mean	Range (Low-High)
Diastolic								
Supine	85.5	(80-90)	83.3	(74-90)	74.0	(70-80)	86.0	(80-90)
Sitting	89.0	(80-96)	83.7	(80-90)	77.3	(66-90)	87.3	(80-92)
Diet calcium (mg)	80*		992				101*	
Serum								
Total calcium (mg/dl)	9.4		10.2		10.2		10.0	
Ionized calcium (mg/dl)	4.0		4.1		4.1		4.1	
Compliance**			93%		100%		100%	

[a] Mean = mean values of blood pressures taken weekly for each phase.

* Value < 50% Recommended Dietary Allowance

** % Compliance = $\frac{\text{Estimated Intake}}{\text{Total Prescribed}}$

Conclusion: A mean 2.7 mm Hg supine ($p < .025$) and a mean 3.6 mm Hg sitting ($p < .005$) reduction in diastolic blood pressure was achieved during the supplementation phase as compared to placebo levels.

Discussion: It would appear that calcium/vitamin D supplementation, for this participant, has a beneficial therapeutic effect on his diastolic blood pressure. With respect to the dietary information (suggesting low intakes of calcium), dietary counseling or calcium supplementation should be considered to improve this participant's nutritional status.

Table 8. Single subject case analysis: Participant No. 37, Black, Test Group A, 35 Years of Age, 198 Pounds; 73 Inches.

	Phase I Baseline		Phase II With Calcium		Phase III Crossover		Phase IV Without Calcium	
	Mean[a]	Range (Low-High)	Mean	Range (Low-High)	Mean	Range (Low-High)	Mean	Range (Low-High)
Diastolic								
Supine	88.0	(84-94)	83.0	(76-90)	85.3	(76-100)	85.3	(78-90)
Sitting	88.0	(82-90)	84.7	(78-92)	88.7	(86-90)	91.3	(78-100)
Diet calcium (mg)	681		376*				296*	
Serum								
Total calcium (mg/dl)	9.8		9.5		10.0		9.9	
Ionized calcium (mg/dl)	4.1		4.0		4.2		4.1	
Compliance**			94%		100%		98%	

[a] Mean = mean values of blood pressures taken weekly for each phase.
* Value < 50% Recommended Dietary Allowance

** % Compliance = $\frac{\text{Estimated Intake}}{\text{Total Prescribed}}$

Conclusion: A mean 2.3 mm Hg supine ($p < .05$) and a mean 6.6 mm Hg sitting ($p < .025$) reduction in diastolic blood pressure was achieved during the supplementation phase as compared to placebo levels.

Discussion: It would appear that calcium/vitamin D supplementation, for this participant, has a beneficial therapeutic effect on his diastolic blood pressure. With respect to the dietary information (suggesting low intakes of calcium), dietary counseling or calcium supplementation should be considered to improve this participant's nutritional status.

Table 10. Single subject case analysis: Participant No. 53, White, Test Group A, 39 Years of Age, 227 Pounds, 73 Inches.

	Phase I Baseline		Phase II With Calcium		Phase III Crossover		Phase IV Without Calcium	
	Mean[a]	Range (Low-High)	Mean	Range (Low-High)	Mean	Range (Low-High)	Mean	Range (Low-High)
Diastolic								
Supine	92.0	(90-96)	85.0	(80-92)	96.7	(90-102)	87.3	(82-90)
Sitting	93.0	(84-100)	85.7	(80-94)	89.3	(80-104)	87.0	(80-90)
Diet calcium (mg)	222*		167*				109*	
Serum								
Total calcium (mg/dl)	9.2		9.5		9.7		9.5	
Ionized calcium (mg/dl)	4.1		4.2		4.2		4.2	
Compliance**			100%		100%		100%	

[a] Mean = mean values of blood pressures taken weekly for each phase.
* Value < 50% Recommended Dietary Allowance

** % Compliance = $\frac{\text{Estimated Intake}}{\text{Total Prescribed}}$

Conclusion: A mean 2.3 mm Hg supine ($p < .01$) and a mean 1.3 mm Hg sitting ($p < .025$) reduction in diastolic blood presure was achieved during the supplementation phase as compared to placebo levels.

Discussion: It would appear that calcium/vitamin D supplementation, for this participant, has a beneficial therapeutic effect on his diastolic blood pressure. With respect to the dietary information (suggesting low intakes of calcium), dietary counseling or calcium supplementation should be considered to improve this participant's nutritional status.

Table 11. Single subject case analysis: Participant No. 28, Hispanic, Test Group A, 44 Years of Age, 193 Pounds; 68 Inches.

	Phase I Baseline		Phase II With Calcium		Phase III Crossover		Phase IV Without Calcium	
	Mean[a]	Range (Low-High)	Mean	Range (Low-High)	Mean	Range (Low-High)	Mean	Range (Low-High)
Diastolic								
Supine	80.0	(80-80)	83.0	(80-90)	80.0	(80-80)	83.0	(80-90)
Sitting	81.3	(80-84)	81.3	(78-90)	81.3	(80-84)	76.3	(70-88)
Diet calcium (mg)	N/A		169*				109*	
Serum								
Total calcium (mg/dl)	9.6		9.0		9.9		N/A	
Ionized calcium (mg/dl)	4.2		4.1		4.2		N/A	
Compliance**			94%		100%		98%	

[a]Mean = mean values of blood pressures taken weekly for each phase.
N/A = Data not available
* Value < 50% Recommended Dietary Allowance

** % Compliance = $\frac{\text{Estimated Intake}}{\text{Total Prescribed}}$

Conclusion: A reduction in diastolic blood pressure was not achieved during the supplementation phase.

Discussion: It would appear that calcium/vitamin D supplementation for this participant has neither a therapeutic or detrimental effect on his diastolic pressure. With respect to the dietary information (suggesting low intakes of calcium), dietary counseling or calcium supplementation should be considered to improve this participant's nutritional status.

Table 12. Single subject case analysis: Participant No. 24, Black, Test Group B, 35 Years of Age, 169 Pounds; 68 Inches.

	Phase I Baseline		Phase II Without Calcium		Phase III Crossover		Phase IV With Calcium	
	Mean[a]	Range (Low-High)	Mean	Range (Low-High)	Mean	Range (Low-High)	Mean	Range (Low-High)
Diastolic								
Supine	82.5	(80-90)	91.3	(84-100)	94.0	(86-100)	95.7	(88-100)
Sitting	89.0	(84-94)	94.0	(90-100)	96.0	(90-104)	97.3	(90-108)
Diet calcium (mg)	204*		232*				507	
Serum								
Total calcium (mg/dl)	9.5		9.8		9.5		9.7	
Ionized calcium (mg/dl)	4.3		4.4		4.4		4.2	
Compliance**			100%		100%		100%	

[a] Mean = mean values of blood pressures taken weekly for each phase.
* Value < 50% Recommended Dietary Allowance

** % Compliance = $\frac{\text{Estimated Intake}}{\text{Total Prescribed}}$

Conclusion: A mean 4.4 mm Hg supine ($p < .01$) and a mean 3.3 mm Hg sitting ($p < .025$) increase in diastolic blood pressure was achieved during the supplementation phase as compared to placebo levels.

Discussion: It would appear that calcium/vitamin D supplementation, for this participant had little effect on lowering his diastolic blood pressure. With respect to dietary information (suggesting low intakes of calcium) dietary counseling but not supplementation should be considered to improve this patient's nutritional status.

Table 13. Single subject case analysis: Participant No. 23, White, Test Group B, 34 Years of Age, 220 Pounds; 72 Inches.

	Phase I Baseline		Phase II Without Calcium		Phase III Crossover		Phase IV With Calcium	
	Mean[a]	Range (Low-High)	Mean	Range (Low-High)	Mean	Range (Low-High)	Mean	Range (Low-High)
Diastolic								
Supine	87.0	(80-90)	83.2	(80-85)	88.0	(80-94)	80.3	(74-88)
Sitting	85.5	(74.96)	77.0	(70-84)	76.0	(66-86)	76.3	(70-80)
Diet calcium (mg)	206*		473				333*	
Serum								
Total calcium (mg/dl)	9.5		9.5		9.8		10.2	
Ionized calcium (mg/dl)	4.5		4.2		4.3		4.5	
Compliance**			82%		88%		100%	

[a] Mean = mean values of blood pressures taken weekly for each phase.
* Value < 50% Recommended Dietary Allowance

** % Compliance = $\frac{\text{Estimated Intake}}{\text{Total Prescribed}}$

Conclusion: A mean 2.9 mm Hg supine (not significant) and a mean 0.7 mm Hg sitting (not significant) reduction in diastolic blood pressure was achieved during the supplementation phase as compared to placebo levels.

Discussion: It would appear that calcium/vitamin D supplementation for this participant had little effect on lowering his diastolic blood pressure. With respect to the dietary information (suggesting low intakes of calcium), dietary counseling or calcium supplementation should be considered to improve this participant's nutritional status.

Table 14. Single subject case analysis: Participant No. 34, White, Test Group B, 42 Years of Age, 198 Pounds; 70 Inches.

	Phase I Baseline		Phase II Without Calcium		Phase III Crossover		Phase IV With Calcium	
	Mean[a]	Range (Low-High)	Mean	Range (Low-High)	Mean	Range (Low-High)	Mean	Range (Low-High)
Diastolic								
Supine	85.0	(80-90)	91.0	(84-104)	88.0	(86-92)	87.7	(82-90)
Sitting	95.0	(90-100)	95.0	(90-100)	90.7	(84-96)	100.0	(90-120)
Diet calcium (mg)	695		1075				1220	
Serum								
Total calcium (mg/dl)	9.7		9.9		9.8		9.8	
Ionized calcium (mg/dl)	4.4		4.4		4.3		4.2	
Compliance**			100%		100%		99%	

[a] Mean = mean values of blood pressures taken weekly for each phase.

** % Compliance = $\frac{\text{Estimated Intake}}{\text{Total Prescribed}}$

Conclusion: A mean 3.3 mm Hg supine (not significant) reduction and a 5 mm Hg ($p < .05$) sitting increase in diastolic blood pressure was achieved during the supplementation phase as compared to placebo levels.

Discussion: It would appear that the results obtained cannot be interpreted as having either a positive or negative effect for calcium/vitamin D supplementation with respect to diastolic blood pressure. Some other variable(s) may have had an overriding effect on this participant's diastolic blood pressure response.

Table 15. Single subject case analysis: Participant No. 56, White, Test Group B, 49 Years of Age, 256 Pounds; 76 Inches.

	Phase I Baseline		Phase II Without Calcium		Phase III Crossover		Phase IV With Calcium	
	Mean[a]	Range (Low-High)	Mean	Range (Low-High)	Mean	Range (Low-High)	Mean	Range (Low-High)
Diastolic								
Supine	89.0	(84.92)	82.5	(76-90)	84.7	(80-90)	87.3	(80-94)
Sitting	92.5	(90-98)	87.5	(78-100)	96.0	(88-100)	94.7	(90-100)
Diet calcium (mg)	1148		2313				662	
Serum								
Total calcium (mg/dl)	10.1		9.5		9.9		10.0	
Ionized calcium (mg/dl)	4.3		4.3		4.3		4.2	
Compliance**			75%		83%		93%	

[a] Mean values of blood pressures taken weekly for each phase

** % Compliance = $\frac{\text{Estimated Intake}}{\text{Total Prescribed}}$

Conclusion: A mean 4.8 mm Hg supine ($p < .025$) and a 7.2 mm Hg sitting ($p < .025$) increase in diastolic blood pressure was achieved during the supplementation phase as compared to placebo levels.

Discussion: It would appear that calcium/vitamin D supplementation, for this participant, had little effect on lowering his diastolic blood pressure. With respect to the dietary information (suggesting adequate intakes of calcium), calcium supplementation should not be considered at this time.

Table 16. Single subject case analysis: Participant No. 19, Hispanic, Test Group B, 26 Years of Age, 209 Pounds; 71 Inches.

	Phase I Baseline		Phase II Without Calcium		Phase III Crossover		Phase IV With Calcium	
	Mean[a]	Range (Low-High)	Mean	Range (Low-High)	Mean	Range (Low-High)	Mean	Range (Low-High)
Diastolic								
Supine	86.0	(80-94)	85.3	(80-90)	89.3	(88-90)	84.7	(80-90)
Sitting	94.7	(88-104)	91.0	(84-100)	96.0	(90-100)	91.3	(84-100)
Diet calcium (mg)	2910		5308				5161	
Serum								
Total calcium (mg/dl)	9.6		10.4		10.1		9.7	
Ionized calcium (mg/dl)	4.1		4.4		4.3		4.2	
Compliance**			100%		100%		100%	

[a] Mean = mean values of blood pressures taken weekly for each phase.

** % Compliance = $\frac{\text{Estimated Intake}}{\text{Total Prescribed}}$

Conclusion: A reduction in diastolic blood pressure was not achieved during the supplementation phase.

Discussion: It would appear that calcium/vitamin D supplementation for this participant had little effect on lowering his diastolic pressure. With respect to the dietary information (suggesting more than adequate intakes of calcium), calcium supplementation should not be considered at this time.

hypertensive persons tested had clinically significant blood pressure reductions with calcium supplementation.

A summary of the single subject analysis is provided in Table 17. For the sitting position, there were 5 significant decreases (4 blacks, 1 white), 3 significant increases (1 black, 2 whites) and 3 no significant changes (2 Hispanics, 1 white). For the supine position, there were 5 significant decreases (4 blacks, 1 white), 2 significant increases (1 black, 1 white), and 4 no significant changes (2 Hispanics, 2 whites). Of the 5 black participants involved in this study, 4 had significant mean reductions in diastolic blood pressure. This data supports the first hypothesis, which stated that supplementation with calcium and vitamin D would reduce diastolic blood pressure in a mildly hypertensive adult black male population.

It is also shown in the single subject analysis (Tables 6 though 16) and in Appendix D that the blacks in this study have, overall, lower dietary calcium intakes than their white counterparts. Blacks are often deficient in consumption of calcium-rich dairy products, probably because of lactose intolerance. Often these avoided dairy products are fortified with vitamin D. This, combined with higher levels of melanin in the cutaneous tissue, thereby reducing the skin's ability to manufacture vitamin D3 (Clemens et al.

Table 17. Grouping of mean diastolic blood pressures by direction of change for the 11 hypertensive male participants at Ft. Huachuca.

Mean Diastolic	Supine (mm Hg) With Calcium	Supine (mm Hg) Without Calcium	Supine (mm Hg) p	Sitting (mm Hg) With Calcium	Sitting (mm Hg) Without Calcium	Sitting (mm Hg) p
Significant mean diastolic blood pressure reductions						
Test group A, black, #17	99	108	<.001	99	105	<.005
Test group A, black, #44	86	93	<.05	81	88	<.01
Test group A, black, #37	83	85	<.05	85	91	<.025
Test group A, black, #16	83	86	<.025	84	87	<.005
Test group A, white, #53	85	87	<.01	86	87	<.025
Significant mean diastolic blood pressure increases						
Test group B, black, #24	96	91	<.01	97	94	<.025
Test group B, white, #34	88	91	NS*	100	95	<.05
Test group B, white, #56	87	83	<.025	95	88	<.025

Table 17--Continued

Mean Diastolic	Supine (mm Hg) With Calcium	Supine (mm Hg) Without Calcium	Supine (mm Hg) p	Sitting (mm Hg) With Calcium	Sitting (mm Hg) Without Calcium	Sitting (mm Hg) p
No significant mean change diastolic blood pressures						
Test group B, Hispanic, #19	85	85	NS*	91	91	NS
Test group B, white, #23	80	83	NS*	76	77	NS
Test group A, Hispanic, #28	83	83	NS*	81	76	NS

* NS = no significance

1982), places the black population at double risk for lowered vitamin D levels and hence impaired calcium metabolism.

Work done by Parfrey et al. in 1981 found a significant correlation between the fall in blood pressure on a low sodium regimen and the level of blood pressure on a normal diet (i.e., the higher the initial pressure, the greater the fall). This is also the case for the results obtained from this study. The individual with the highest overall mean diastolic blood pressures during the placebo phase (107.7 mm Hg supine and 105 mm Hg sitting), experienced the greatest mean drop in blood pressure (99 mm Hg supine and 99 mm Hg sitting) for the supplemental phase of the study.

Even though the small number of participants makes it difficult to interpret this data on a statistical basis, there does appear to be at least two interesting trends which warrant further study. First, it appears that blacks respond more positively to calcium/vitamin D supplementation than either whites or Hispanics. This trend may indicate that just as there is a salt-sensitive subset of hypertensive patients, there may also be a subset of calcium-sensitive hypertensive patients. This concept of selected response is also noted in a study by Resnick, Nicholson and Laragh (1984). They even went one step further by suggesting that hypertensive patients were most

likely to respond to orally administered calcium supplementation if they have low serum ionized calcium levels, and low plasma renin activity. This author would also suggest that adequate circulating levels of serum vitamin D would also be necessary for appropriate absorption and utilization of the calcium supplement. It appears that additional research needs to be conducted to support this surmise. Secondly, most of the white participants had either no response or an increase in blood pressure during the calcium/vitamin D supplementation phase. As opposed to moderate sodium restriction, which appears at this time to be a benign treatment for essential hypertension, the same may not hold for moderate calcium supplementation. This may be true, especially if the individual is ingesting adequate amounts of dietary calcium. Hypercalcemia, in some cases, is correlated with an increase in blood pressure (Kesteloot et al. 1983, Bulpitt, Hodes and Everitt 1976, Sangal and Beevers 1982). Additionally, it has also been shown that induced hypercalcemia raises blood pressure in normotensive subjects (Pak 1970).

CHAPTER 5

SUMMARY AND CONCLUSIONS

Essential hypertension is a multifactorial disease related to abnormalities of the regulatory mechanisms normally concerned with the homeostatic control of arterial pressure. Cellular biochemical research has established that calcium plays a homeostatic role in the maintenance of arterial pressure. The results of this study indicate that there is a subset of hypertensives which will respond positively to calcium/vitamin D supplementation. The following conclusions are drawn from the data collected during the course of this study:

1. Does the level of hypertensive have any effect on the magnitude of response for a calcium/vitamin D supplemented mildly hypertensive adult black male population?

   This does appear to be the case based on review of the single subject analysis. The individual with the highest overall mean diastolic blood pressures during the placebo phase (107.7 mm Hg supine and 105 mm Hg sitting), experienced the greatest mean drop

in blood pressure (99 mm Hg supine and 99 mm Hg sitting) for the supplemental phase of the study.

2. Is there a positive change in serum ionized calcium levels when the value for the calcium/vitamin D supplementation phase is compared to the placebo phase?

   The data collected on the serum ionized calcium levels showed a heterogenicity of response. This, of course, can be due to many factors, not the least of which concerns utilizing a calculated method of determining serum ionized levels as opposed to a direct measurement technique.

3. Is there any difference in blood pressure response to calcium/vitamin D supplementation between ethnic groups?

   According to the data gathered in this study, it appears that the black hypertensive population responded more positively to calcium/vitamin D supplementation than either whites or Hispanics.

4. Is there any difference in consumption patterns of dietary calcium between ethnic groups?

   The black ethnic group had the lowest overall dietary consumption of calcium when compared to the white and Hispanic ethnic groups.

Finally, the potential outcome of any dietary nutrient to effect a blood pressure change must also take into account other dietary nutrients with which it shares a relationship and physiological interactions. Therefore, if calcium is considered as a nonpharmacologic approach to alleviate mild essential hypertension, vitamin D status should also be considered.

CHAPTER 6

RECOMMENDATIONS

Study Design

1. To improve hypothesis testing and reliability of results, the sample population should be greatly increased and expanded to include women participants.
2. To minimize any drug carryover effect, withdraw anti-hypertensive agents 1 month before entry into the baseline phase of the trial.
3. Utilize a competitive binding protein assay to determine plasma levels of 25, hydroxyvitamin D in order to assess body reserves, and effects of supplementation.
4. Add 1 mg of riboflavin to the placebo and calcium/vitamin D supplements to serve as a tracer in testing for urinary fluorescence to improve assessment of patient compliance.
5. Utilize a direct measurement technique for the determination of serum ionized calcium levels.
6. Determine plasma renin activity.

Applications

1. Relative to blood pressure response, health professionals should exercise caution when counseling patients

as to calcium supplementation as there may be adverse effects as well as positive results.

2. With calcium receiving increased media and advertising attention and new products on the market such as calcium fortified margarine, orange juice and flour, some populations may be at risk for hypercalcemia, which may induce hypertension rather than alleviate it.
3. When suggesting a change in calcium consumption patterns or supplementation, the individual's vitamin D status or ability to produce vitamin D should be considered.

APPENDIX A

VOLUNTEER AGREEMENT AFFIDAVIT

VOLUNTEER AGREEMENT AFFIDAVIT

You have been asked to participate in a study to determine whether an oral supplement of 1,000 mg elemental calcium and 500 international units of Vitamin D taken orally can reduce blood pressure, compared to a placebo (sugar capsule). If true, this information could lead to a nonpharmacologic treatment for hypertension and information about the disease process.

BENEFITS: You may benefit by a reduction of your blood pressure during the supplemental phase of this study and be made aware of your individual response to calcium and Vitamin D supplementation. You will also have the knowledge that you have contributed to medical science.

ALTERNATIVES TO PARTICIPATION IN THE STUDY: Your participation is entirely voluntary. If you decide not to participate, your medical care will not be comprised and conventional treatment of your hypertension will follow with routine procedures. Conventional care involves a period of observation to prove hypertension, followed by dietary management and salt restriction.

DURATION OF STUDY: You will be involved in the study for a period of 19 weeks, during which time you will be seen weekly in the Internal Medicine Clinic.

RISKS, INCONVENIENCES AND DISCOMFORTS: On four separate occasions, blood will be drawn for the needed laboratory studies. You will also be required to take six capsules of prescribed supplement or placebo daily for 15 consecutive weeks. Bloating, constipation or nausea are occasional side effects of the calcium supplementation. No side effects are anticipated since both Vitamin D and calcium are over-the-counter supplements in these doses. If uncomfortable or severe reaction should occur, the medication will be stopped and you will be dropped from the study and receive conventional care.

SAFEGUARDS: All precautions normally undertaken for the drawing of blood will be used. You may withdraw from any part of this study at any time. The study has been reviewed and approved by the Human Use Committee at WBAMC.

ASSURANCE OF CONFIDENTIALITY OF SUBJECT'S IDENTITY: During the course of your treatment as a patient at R. W. Bliss Army Community Hospital, you have been provided with a copy of a Privacy Act Statement (DD Form 2005) which assures you

that your rights to privacy will be protected and that your name and social security number will not be released to individuals without your authorization. The results of this study may be important enough to be published in the medical journals, but the Privacy Act of 1974 assures you that you will not be identified by name, social security number or other identifying information without your express consent. These records may be reviewed by the Food and Drug Administration or the Clinical Investigation Activities Branch at HSC.

CIRCUMSTANCES UNDER WHICH YOUR PARTICIPATION MAY BE TERMINATED WITHOUT YOUR CONSENT: None are anticipated, however (a) health conditions under which your participation possibly would be dangerous; (b) other conditions which might occur that make your participation detrimental to your or your own health.

SIGNIFICANT NEW FINDINGS: Any significant new findings developed during the course of this study will be provided to you.

APPROXIMATE NUMBER OF SUBJECTS INVOLVED IN THE STUDY: 50

PRECAUTIONS TO BE OBSERVED BY SUBJECT BEFORE AND FOLLOWING THE STUDY: Since these medications are over-the-counter drugs, no side effects are anticipated. Should you develop unusual symptoms that might be related to medication, please contact Dr. Rogers. Should you develop side effects of hypertension, such as headache, shortness of breath, blurred vision, etc., please contact Dr. Rogers.

IF THERE IS ANY PORTION OF THIS EXPLANATION THAT YOU DO NOT UNDERSTAND, ASK THE INVESTIGATOR BEFORE SIGNING.

APPENDIX B

SELF-REPORTED MEDICAL HISTORY FORM

SELF-REPORTED MEDICAL HISTORY FORM

NAME LAST FIRST INITIAL SSN

QUESTIONNAIRE FOR CALCIUM IN HYPERTENSION

Circle all positive responses:

History of:

1. Kidney stones
2. Cancer
3. Sarcoidosis
4. High cholesterol
5. Kidney disease
6. Inflammatory bowel disease (Crohn's, ulcerative colitis)
7. Broken bone within the last two months
8. Thyroid or parathyroid disease

I take the following medicines (circle those drugs you now use):

Antacids, ulcer pills, steroids, antibiotics,

seizure medications, vitamins

Alcohol consumption:

I drink, on the average, _____ beers weekly

I drink, on the average, _____ ounces of hard liquor weekly

APPENDIX C

INSTRUCTIONS FOR RECORDING 24-HOUR DIETARY RECALL

INSTRUCTIONS FOR RECORDING
24-HOUR DIETARY RECALL

Please record all the foods and drink you take in the order in which they are taken throughout the day. Record them as taken so that you are less likely to forget to mark them down: Record the amounts as accurately as possible.

MILK AND MILK PRODUCTS: The amount taken should be recorded in ounces or by carton size. (Measure the size glass you use.) The kind of milk--while, evaporated, 2%, skim or nonfat, chocolate, buttermilk, filled milk, imitation or soya milk, yogurt or acidophilus milk etc. should be given. Please give brand.

CHEESE AND CHEESE DISHES: List kind and amount in cups or size of piece in inches: Measure cottage cheese in cups. For dishes including cheeses--such as macaroni and cheese, lasagne, pizza, etc., give recipe on page provided. Indicate the number of portions the recipe made and how many portions you ate.

EGGS: Give size (small, medium, large or extra large) and number. If combined with other foods, or omelet or scrambled, give recipe made and type of cooking fat.

MEATS, POULTRY, FISH: List kind and method of preparation, such as baked, broiled, boiled, fried. Give approximate portion size, such as 2" x 1-2/3" x 1/2". Canned, prepared or deli meats list brand and portion size. Meat spreads on sandwiches, snacks, list amount--such as 1 teaspoon. MEAT LOAF or other CASSEROLE, list recipe on page provided. Indicate the number of portions the recipe made and how many portions you ate.

LEGUMES: Kind and amount. (Dried peas, beans, lentils, etc.) List name and preparation method. Give recipe on page provided if made with other ingredients. Indicate the number or portions the recipe made and how many portions you ate.

NUTS AND PEANUT BUTTER: Nuts in pieces (6 peanuts) or in cup portions, peanut butter in tablespoons. Record brand and type of peanut butter.

BREADS: Record as whole wheat, rye, bran, 7-grain, corn, tortilla, etc. List brand and indicate if labeled enriched or fortified. If homemade, indicate if the flour used was enriched or fortified. Give recipe for homemade buns,

muffins, pancakes, or brandname if purchased mix. Give recipe for French toast or other fried or mixed breads. Indicate the number of portions the recipe made and how many portions you ate.

CEREALS: List specific name, such as Cheerios, Cream of Wheat, oatmeal, cornflakes, etc.--give brandname if applicable. Cooked: Record cup or tablespoon portions (indicate whether before or after cooking). Dry: Record by cup portions. Biscuit cereals: List brand name and number of biscuits eaten. List amount of sugar, milk cream, butter, or toppings (raisins, nuts, etc.) added to the cereals.

FRUITS AND FRUIT JUICES: List type of presentation, such as canned, frozen, dried, reconstituted, home preserved, etc., and where applicable list the brand name, and the kind, such as apple, orange, etc. Record the amount in ounces, cups, or by glass size. Record if juices indicate on the label what vitamins are added. For RAW fruits indicate kind and size, such as small, medium, or large. List whether sweetened or unsweetened.

VEGETABLES: List name and preparation method. If frozen or canned, list brand name or "Home Preserved." Record by cup portions or size--such as carrot stick 4 inches long, or potato 1/2 medium, etc.; for canned vegetables, indicate if juice is used or discarded. Fresh: List size of portions. Salads: Give kinds of vegetables, preferably list recipe on page provided and give size of serving in cups.

MIXED DISHES: Stews, soups, casseroles, homemade desserts, meatloaf, oriental vegetables, pizzas, lasagna, chile, etc. List all ingredients in recipe on page provided. Indicate the number of portions the recipe made and the number of portions you ate.

DESSERTS: Describe the size of portion in cups or measure--for example, 1-1/2" x 1-1/2" x 1-1/2", and list descriptive brand name. Indicate the number of portions you ate.

FATS: Record in teaspoons or in tablespoons, level measure, or ounces used in recipes. Include all fats used in cooking, on popcorn, and in salad dressings, sauces, dips (please include recipe of the latter). Include imitation sour cream where used in recipes or toppings. If BUTTER is used list as butter, and the amount; if MARGARINE is used, list brand name and amount. If OIL is used, indicate kind (olive, peanut, cottonseed, etc.), brand name and amount, and how used.

GRAVIES AND SAUCES: Give recipe and amount eaten.

BEVERAGES: Coffee, tea, cocoa, hot chocolate, herb teas, Ovaltine, buillon. List kind and brand--amount in cups. Include sugar, cream, milk, coffee whiteners, lemon, etc., in teaspoons. Kind or brand of beverage powders, such as Tang, Quick, Kool-Aid, etc., and how mixed if different from directions on package. List in ounces or cups taken. Soft drinks and carbonated beverages should be recorded by brand name, and bottle or ounces. Mineral water, Gatorade, etc., by ounces. Alcoholic beverages should be recorded by kind (beer, wine, whiskey, rum, etc.) and by brand--include the kind and amount of mix. Please indicate proof or percent (%) of alcohol.

SUGAR, HONEY, JAMS, SYRUPS: List the amount of sugar added to cereals, tea, and on other foods; jams and jellies on breads; syrup added to pancakes and waffles.

SNACKS: Give kind and brand name, and list size of piece of bag or container. If homemade product, list contents as a recipe on page provided. Indicate the number of portions the recipe made and the number of portions you ate.

CANDIES: List kind and exact amount, such as four large gumdrops, 12 jelly beans.

MISCELLANEOUS: List all syrups, toppings, jams, jellies (see "sugar" above), and pickles, condiments and seasonings, tomato sauce, ketchup, soy sauce, mustard, chile sauce, pepper, etc. Include chewing gum, throat lozenges, cough drops.

ON THE BLANK SPACES MARKED "RECIPE" PLEASE LIST ALL INGREDIENTS FOR MIXED FOODS, GIVE NUMBER OF PORTIONS THE RECIPE MADE, AND THE NUMBER OF PORTIONS EATEN.

AN EXAMPLE OF HOW TO FILL OUT YOUR DIETARY RECALL

Please record everything you eat and drink (except water) at the time you eat it.

	Item you eat or drink	Amount
Spell out in full teaspoon tablespoon ounce	Orange juice (frozen reconstituted) - 1/2 Toast - white bread - 2 slices Butter - 3 teaspoons Jam - strawberry - 3 tablespoons Coffee (instant) - 2 cups	Estimate quantities as nearly as possible
Brand names	Coffee Mate - 2 teaspoons Sugar - 4 teaspoons Doughnuts - 2 Coffee - 1 cup Sugar - 1 tablespoon	Cake or bread? Size?
Recipe and brand or recipe for salad dressing	Sandwich, ham and cheese - 1 Milk 2% - 8 ounce glass Boston cream pie (in restaurant) - 1 piece 4" x 3" x 4" wedge Corn chips - Fritos regular - 12 pieces Beer, Schlitz Lite - 1 12-oz bottle	Indicate amount of ham and cheese used Measure size of glass with a measuring cup
See Recipe Example	Salad, mixed green, dressing Prime rib roast - 1 slice 1" x 3" x 5" Mexican corn bread - 1 portion (recipe # EXAMPLE)	
Recipe if homemade or brand name	Baked potato - 1 large Sour cream - 2 tablespoons	Frozen Green Giant?
Recipe if homemade or brand name	Coffee - 3 cups Green peas - 3 tablespoons Cream - 6 tablespoons Sugar - 3 tablespoons Cherry pie, homemade - 1 slice, 3" wedge (1/6 of 8" diameter) Brownies - 3 (1" x 1" x 1")	List contents as on label, on back page please; an example on back page

24-HOUR DIETARY RECALL

Please record everything you eat and drink (except water) at the time you eat it.

Item you eat or drink	Amount

Recipe Example Mexican Cornbread Made 8 portions
I ate 1 portions

Flour - 1/2 cup
Cornmeal - 2 cups
Baking powder - 1 teaspoon
Salt - 1 teaspoon
Sour milk - 2 cups
Egg - 1 large
Oil - 2 tablespoons
Chopped canned chili - 1 4 oz.
Grated cheese - 1-1/2 cups

Made _____ portions
I ate _____ portions

Made _____ portions
I ate _____ portions

Made _____ portions
I ate _____ portions

Made _____ portions
I ate _____ portions

APPENDIX D

NUTRIENT INTAKE DURING CALCIUM/VITAMIN D AND PLACEBO PHASES

Mean nutrient intake for one 24-hour period for each calcium/vitamin D and placebo phase by ethnic group of 11 male hypertensive participants at Ft. Huachuca.

	Blacks		Whites		Hispanics	
	Calcium	Placebo	Calcium	Placebo	Calcium	Placebo
Calories, n	1943 ± 167	2437 ± 589	2289 ± 496	1719 ± 377	3807 ± 1926	3083 ± 1113
Protein, g/day	75 ± 20	96 ± 25	101 ± 50	64 ± 8.2	202 ± 119	160 ± 52
Total fat, g/day	62 ± 20	118 ± 33	102 ± 30	73 ± 13	80 ± 35	113 ± 66
Carbohydrate, g/day	251 ± 71	239 ± 67	246 ± 53	201 ± 74	531 ± 344	315 ± 138
Calcium, mg/day	490 ± 291	457 ± 245	1007 ± 821	602 ± 394	2738 ± 2569	2635 ± 2526
Phosphorus, mg/day	930 ± 206	953 ± 413	1601 ± 948	1060 ± 345	3803 ± 308	3114 ± 2021
Sodium, mg/day	1730 ± 579	2442 ± 850	2800 ± 1159	3132 ± 952	4016 ± 260	4152 ± 3638
Potassium, mg/day	1516 ± 681	1453 ± 722	2330 ± 1266	1725 ± 681	7004 ± 5602	3961 ± 2203
Cholesterol, g/day	242 ± 106	579 ± 144	335 ± 186	398 ± 235	185 ± 65	330 ± 34
Magnesium, mg/day	126 ± 40	118 ± 62	213 ± 209	132 ± 64	275 ± 172	419 ± 301

APPENDIX E

SERUM ELECTROLYTE AND ROUTINE BIOCHEMICAL MEAN VALUES FOR CALCIUM/VITAMIN D AND PLACEBO PHASES

Mean serum electrolyte and routine biochemical mean values for each calcium/ vitamin D and placebo phase, by ethnic group of 11 male hypertensive participants at Ft. Huachuca.

	Blacks		Whites		Hispanics	
	Calcium	Placebo	Calcium	Calcium	Placebo	Placebo
Total calcium, mg/dl	9.9 ± 0.3	9.8 ± 0.3	9.6 ± 0.2	9.9 ± 0.2	9.7 ± 0.7	9.7 ± 0.2
Ionized calcium, mg/dl	4.2 ± 0.2	4.2 ± 0.1	4.3 ± 0.1	4.3 ± 0.1	4.3 ± 0.2	4.2
Glucose, mg/dl	88 ± 10	94 ± 7.6	112 ± 21.9	95.3 ± 15.7	96 ± 7	103 ± 1.5
Blood urea nitrogen, mg/dl	13.3 ± 3.3	13 ± 3.1	16 ± 2.1	13.5 ± 3.8	17	14.5 ± 2.5
Creatinine, mg/dl	1.4 ± 0.1	1.5 ± 0.2	1.5 ± 0.2	1.4 ± 0.2	1.2 ± 0.2	1.3 ± 0.1
Phosphate, mg/dl	3.2 ± 0.1	3.4 ± 0.7	2.9 ± 0.9	2.7 ± 0.6	3.8 ± 0.3	3.2 ± 0.2
Uric acid, gm/dl	5.9 ± 0.8	6.8 ± 0.6	7.8 ± 1.9	6.9 ± 0.9	5.4 ± 0.7	7.8 ± 2.0
Protein, g/dl	6.5 ± 1.7	8.1 ± 0.6	7.2 ± 0.2	7.4 ± 0.1	7.4 ± 0.7	7.4 ± 2.0
Albumin, g/dl	4.2 ± 0.1	4.3 ± 0.2	4.3 ± 0.2	4.3 ± 0.2	4.3 ± 0.2	4.4 ± 0.1
Alkaline phosphatase, u/L	85 ± 26.4	91.2 ± 33.3	79 ± 9.6	76.2 ± 9.1	100 ± 1.5	82.5 ± 12.5
Cholesterol, mg/dl	210 ± 22.2	275 ± 35.3	183 ± 44.6	179 ± 14.3	203 ± 24	224 ± 36.5
Triglycerides, mg/dl	106 ± 67.1	138 ± 82.5	110 ± 58.3	83 ± 42.6	90 ± 6.5	165 ± 48

Continued

	Blacks		Whites		Hispanics	
	Calcium	Placebo	Calcium	Calcium	Placebo	Placebo
Sodium, mmol/L	136 ± 1.9	137 ± 2.5	140 ± 0.8	138.5 ± 1.7	138 ± 1.0	137 ± 3
Potassium, mmol/L	4.4 ± 0.3	4.3 ± 0.4	4.4 ± 0.3	4.1 ± 0.3	4.4 ± 0.2	4.2 ± 0.3
Chloride, mmol/L	104.5 ± 1.8	104.8 ± 1.1	105.7 ± 2.1	104.8 ± 1.6	104.5 ± 2.5	104.5 ± 0.5

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