Calcium Metabolism in Hypertension

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Abstract. High blood pressure, one of the most common chronic diseases in industrialized societies, is a primary risk factor for cardiovascular disease, heart failure, renal disease and stroke. Data from both epidemiologic surveys and clinical trials have shown that calcium metabolism is altered in persons with hypertension, indicating a primary role of calcium in the etiology, prevention, and treatment of hypertension. Investigative efforts throughout the world have identified abnormalities in a number of biochemical parameters of calcium metabolism and a consistently low intake of dietary calcium in persons with high blood pressure. Calcium supplementation trials have reported varying results in terms blood pressure response, and it is generally concluded that many hypertensive patients may benefit from increased calcium intake. The blood pressure-lowering effect of calcium may be of particular benefit to the elderly, people of African origin, and pregnant women. Interactions between dietary nutrients have been shown to be critical in the effect of calcium on blood pressure, particularly sodium and potassium. Finally, based on the body of data that has accumulated in this area, calcium intake is postulated to have clinical application in the treatment of sodium-sensitive, alcohol-associated, and pregnancy-induced hypertension, and type II diabetes mellitus; and adequate, long-term calcium intake may be a means of preventing the development of hypertension. (Keio J Med 44 (4): 105-114, December 1995)

Key words: calcium, hypertension, salt

Introduction

First proposed more than 15 years ago, the hypothesis that dietary calcium deficiency and/or an abnormality of calcium metabolism is a factor in the development of human hypertension has been an issue of continuing scientific controversy. The calcium hypothesis was introduced against a backdrop of historical facts and beliefs that would appear to argue strongly against the possibility that chronic depletion of calcium and/or altered cell regulation of calcium resulting in a functional depletion of the cation causes arterial pressure to rise.

It had been demonstrated that acute hypercalcemia produced a rise in arterial pressure in normal subjects and in individuals with renal disease. An association between high blood pressure and primary hyperparathyroidism was documented in the surgical literature. By the mid-1970s, the control of vascular smooth muscle contraction was known to be related to the release of intracellular stores of calcium. In addition, it was generally believed that "salt" is the only dietary factor that contributes to hypertension. Thus, the concept of a circulating inhibitor of sodium transport dominated the explanation of how sodium intake was linked with increased intracellular calcium concentration and an obligatory increase in smooth muscle contractility. The sodium inhibitor hypothesis lead scientists to speculate that intracellular-free calcium was elevated in the vascular tissue of experimental models and humans with high blood pressure.

In the late 1970's, calcium antagonists were identified as potential antihypertensive agents. Because of the obvious paradox, ie, if a "calcium blocker" lowered blood pressure via a reduction in the intracellular concentration of calcium in vascular tissue, it was difficult to reconcile how a calcium-deficient state, particularly at a
cellular level, would contribute to an increase in arterial pressure. Finally, from a nutritional standpoint, interest in diet and heart disease focused principally on dietary excesses rather than deficiencies. In the area of hypertensive cardiovascular disease, no concept was more tightly embraced than that of excessive dietary sodium intake as a primary factor in the development of human hypertension.10

This review summarizes the data that have accumulated since the calcium hypothesis was proposed that relate calcium nutrition and metabolism to the control of arterial pressure in humans. Our understanding in this area has been expanded in recent years to recognize the critical effects of interactions between calcium and sodium that play pivotal roles in the development and treatment of human hypertension. Further, it is now reasonable to speculate on specific applications of this information to populations at high risk of developing hypertensive cardiovascular disease. Much of the content is based upon several earlier reviews by our laboratory on this subject.11–13

**Epidemiology**

*Biochemical parameters*

The first reported clinical investigation in this area characterized a small increase in circulating parathyroid hormone (PTH) levels in untreated essential hypertension compared to normotension despite similar serum total calcium.1 This increase could not be attributed to renal dysfunction, but was associated with an inappropriate increase in urinary calcium excretion (UcaV) when indexed against simultaneous urinary sodium excretion, and was characterized as a “renal calcium leak” in hypertension. Other studies have also noted an increase in UcaV in hypertension,14,15 and many have confirmed the existence of a defect in renal calcium handling.16–18 Results of a study from our laboratory, carried out under close metabolic conditions, appear to exclude an abnormal increase in intestinal calcium handling as the explanation and demonstrate that UcaV correlates very well with blood pressure.18

Several reports have extended the observation that increased UcaV characterizes specific subpopulations at risk for developing high blood pressure. Offspring of hypertensive subjects exhibit a transient hypercalciuria when ingesting a high salt diet.19,20 African-Americans with hypertension compared to normotension have significantly higher UcaV.21 Normotensive adults on a potassium-restricted diet develop a renal calcium leak at the same time mean arterial pressure rises and sensitivity to infused NaCl emerges.22 Further, Cappuccio et al23 have reported that hypertension is more prevalent in subjects with hypercalcuric nephrolithiasis, which would be anticipated if high blood pressure and hypercalciuria were pathogenetically linked to one another.

Subsequent studies have also shown an increase in PTH in hypertension.24–26 In a cross-sectional study, Grobbec et al24 documented that PTH hormone values were positively correlated with blood pressure after adjustment for weight in young males. In a separate group of individuals with early mild hypertension, these investigators found a continuous, positive relationship of PTH and blood pressure, independent of weight.25 The ratio of calcium and ionized calcium to PTH was related to blood pressure in a study by Zachariah et al26 suggesting abnormal regulation of PTH activity. A simultaneous increase in PTH, urinary cAMP, and UcaV in hypertension was confirmed by Strazzullo et al27 and by Ellison et al28 Young et al28 have documented subtle increases in PTH concentrations in hypertensive males but not females. Brickman et al29 have also reported increased PTH concentrations in essential hypertension. Krishna et al30 observed an increase in PTH levels in normal adults on low potassium diets who then express a modest increase in blood pressure when subjected to a saline infusion.

Serum ionized calcium values have been reported to be identical, modestly decreased, or increased in hypertensive as compared to normotensive subjects. We initially reported significantly lower ionized calcium levels in hypertension versus normotension;30 this was confirmed by Folsom and coworkers31 who found that ultrafiltrable calcium and serum ionized calcium tended to be lower in persons with higher blood pressure. The relationship between serum ionized calcium and blood pressure is continuous over a wide age range. An inverse correlation between ionized calcium and blood pressure has been demonstrated in the general population,32,33 as well as in adolescents34 and the elderly.35

Resnick et al26 speculated that any relationship that might exist between serum ionized calcium and blood pressure was dependent upon the simultaneous renin status; patients with low renin hypertension have lower ionized calcium as compared to patients with high renin hypertension who have higher ionized calcium values. Strazzullo et al37 noted that although baseline serum ionized calcium was virtually identical between normotensive and hypertensive subjects, serum ionized calcium concentration increased less in hypertensive than in normotensive subjects following a calcium infusion. Lower serum ionized calcium concentrations have recently been reported in women with gestational hypertension and preeclampsia.38

Some epidemiological surveys have demonstrated no relationship between blood pressure and ionized calcium levels.39–41 while others have noted an increase in serum ionized calcium in hypertensive as compared to normotensive subjects.42,43 Methodologic variations likely
explain these discrepant results. Of particular importance may be the dietary status of subjects; the results of our metabolic study are consistent with an effect of diet. In that protocol, hypertensive and normotensive persons on self-selected diets exhibited no difference in serum ionized calcium levels. However, when subjects were placed on control diets of either 400 mg or 1400 mg calcium for 9 days, a consistent difference in serum ionized calcium concentrations was observed. The importance of strict metabolic conditions to detect differences in serum ionized calcium is supported by the fact that in those studies employing such standards, differences have been consistently noted.

The relationship of serum phosphorus to high blood pressure has been quite consistent. Reports have identified lower serum phosphorus levels in subjects with hypertension and/or a continuous inverse correlation between serum phosphorus concentration and blood pressure. The depression in serum phosphorus is a predictable counterpart to the increased PTH levels noted above.

Limited assessments of vitamin D metabolism been carried out in patients with essential hypertension. Sowers et al found a significant inverse relationship between dietary vitamin D levels and blood pressure, independent of other factors. In a subsequent report, these investigators reported that serum levels of 1,25(OH)2 vitamin D3 were directly related to blood pressure in 373 women, and could explain 7% of blood pressure variation. Young et al reported lower 1,25(OH)2 vitamin D3 levels in hypertensive compared to normal males; no differences were observed in the females. In another study, these investigators detected no difference in vitamin D3 levels between hypertensive and normotensive men. However, since the hypertensive subjects in this study exhibited increased UCA/V and low serum calcium concentrations, it could concluded that 1,25(OH)2 vitamin D3 levels were inappropriately low in the hypertensive subjects. Brickman et al observed higher 1,25 vitamin D levels in hypertensive subjects, as did Yamakawa et al in the offspring of hypertensive parents. Further assessments are necessary before conclusions can be drawn as to the state of vitamin D3 in essential hypertension.

The majority of studies of calcium metabolism in hypertension have been performed in males. Calcium metabolism differs between genders and such variations could account for the discrepancies in some surveys of calcium metabolism hypertensive populations. This potential gender difference in 1,25 vitamin D metabolism and hypertension status is consistent with the observation that preeclampsia is associated with inappropriately low vitamin D concentrations.

Resnick et al have reported that not only does ionized calcium vary by renin status, but PTH and 1,25(OH)2 vitamin D3 levels are higher in low renin hypertension, with the opposite in high renin hypertension as compared to normotension. Renin status has not been reported in most other studies, and few studies have simultaneously measured urinary calcium, ionized calcium, PTH and 1,25(OH)2 vitamin D3 in hypertension and normotension. Young et al found that hypertensive males exhibited a pattern of dysregulation of the calcium-PTH-vitamin D axis with a resultant renal leak of calcium and a failure of an appropriate up-regulation of intestinal absorption.

Overall, the subtle pattern of biochemical abnormalities is consistent with an abnormal regulation of the PTH-vitamin D axis in the clinical setting of high blood pressure, which appears to precede the emergence of hypertension. Collectively, the findings support the conclusion that within the population of subjects with high blood pressure or at risk of developing hypertension there is a subset that would likely require a greater daily intake of calcium in order to maintain their calcium balance compared to individuals with normal blood pressure.

**Dietary calcium**

In the first published study of dietary calcium intake in hypertensive as compared to normotensive individuals, we found that hypertensive subjects had significantly lower dietary calcium intake as compared to normotensive subjects. Of the nutrients measured, only calcium intake differed between the 2 groups. We subsequently confirmed this observation using the database from the National Health and Nutrition Examination Survey I (NHANES I), a population sample of the U.S. non-institutionalized civilian population conducted in 1973. Of the nutritional factors assessed in that survey, dietary calcium was the best predictor of the presence of hypertension. As the reported level of dietary calcium consumption increased, there was a lower probability of having high blood pressure. The relationship was evident in adult males at all ages; for females it was most evident above the age of fifty.

These two studies have been followed by more than 30 reports identifying an inverse relationship between calcium intake and blood pressure status. In addition to our assessment of NHANES I, six other investigate groups have utilized this same database. Although the statistical analysis varied, most but not all, reported a significant relationship between dietary calcium and blood pressure either overall or in certain subgroups. Gruchow et al, who initially reported the absence of this relationship, subsequently published an alternative analysis which indicated that the relationship between lower calcium intake and higher blood pressure was dependent on consumption of a high sodium and a low potassium diet.
This interaction between sodium and calcium has been investigated in a second database by Hamet et al and confirmed recently from China. In this study the lowest blood pressures observed were in those subjects consuming both a high sodium chloride (NaCl) and high calcium diet. Thus it appears that consumption of adequate (>800–1000 mg/day) calcium may protect against NaCl-induced hypertension.

Crique et al added a second interactive term, besides sodium, to the blood pressure-calcium relationship. In their analysis from the Honolulu Heart Study they noted that the protective effect of dietary calcium was absent in males consuming large quantities of alcohol. Furthermore, in men on higher levels of dietary calcium, the well-recognized pressor action of alcohol was not observed. They concluded that calcium metabolism was unique among other mineral nutrients as it appeared that a higher alcohol intake would require a higher calcium intake to maintain calcium balance. They speculated that alcohol impaired intestinal calcium absorption, thereby necessitating a greater daily calcium intake.

In a prospective population study of more 58,218 females followed for four years, the Nurses’ Health Study, Wittelman et al reported that dietary calcium and magnesium had independent inverse associations with hypertension. The relative risk for the development of hypertension was significantly lower, by 23%, when calcium intake was >800 mg/day compared to <400 mg/day. They also identified an important interaction with alcohol. In a similar study in 30,681 males, the Health Professionals Follow-up Study, Ascherio et al reported that calcium intake was inversely associated with hypertension only in men with low relative weight, and with baseline blood pressure but not with change in blood pressure.

McGarvey et al added a potentially critical new dimension to the issue of calcium intake effects on blood pressure. They studied women during the third trimester of pregnancy, and found higher levels of dietary calcium to be associated with lower maternal blood pressure at term, higher infant birth weight, and lower offspring blood pressure. The latter beneficial effect of maternal calcium intake during gestation was still observed at one year of age. Confirming the beneficial impact of dietary calcium from dairy products on maternal pressure, Marcoux et al reported a 40% reduction in the risk of gestational hypertension in women in the upper quartile of calcium intake versus those women in the lowest quartile.

We conducted a prospective evaluation of dietary intake in hypertensive and normotensive men and women who were randomized to receive placebo, increased dietary calcium, or calcium supplements for 12 weeks. Baseline dietary data in subjects with high blood pressure indicated a pattern of underconsumption of essential nutrients including calcium, potassium, magnesium, phosphorus and several vitamins. In those hypertensive individuals randomized to the increased dietary calcium group, underconsumption of these nutrients was corrected. Thus, dietary alterations to increase the amount of calcium in the diet resulted in concomitant increases in other nutrients.

There is remarkable consistency in these epidemiologic reports. The association between dietary calcium intake and blood pressure appears to be independent of age, gender, race, socioeconomic status, geography, and weight, though each of these factors may modify the effect under specific circumstances. In addition the impact of dietary calcium is in part dependent on the potassium, magnesium and sodium content of the food source. This correlation of dietary calcium with blood pressure in virtually all of these studies has been stronger with systolic than diastolic pressures.

Most importantly, there is a suggestion that this relationship with blood pressure may be more pronounced below a threshold of 400–500 mg calcium/day. The threshold may be lower in females (300–400 mg/day) than in males (500–600 mg/day). If the Nurses Health Study, the Honolulu Heart Study, and our experience with NHANES are correct about a threshold, then this could be an important factor in targeting populations and interpreting results of intervention trials. Two independent assessments of the published epidemiological studies have relating dietary calcium to blood pressure: Harlan et al of the National Heart, Lung and Blood Institute (NHLBI) have characterized the calcium/blood pressure association as a consistent strong relationship with impressive numbers, and these conclusions were echoed by Grobbee and Waal-Manning in their review of studies in this area.

Blood Pressure Response to Increased Calcium

While epidemiologic studies have demonstrated that dietary calcium intake is lower in humans with hypertension and that some of these individuals exhibit evidence of subtle biochemical and metabolic abnormalities, the critical test is whether changes in calcium intake will influence blood pressure in humans. There are now more than 25 published trials of calcium supplementation. Although a number of these studies lacked a placebo phase or a control group, others included both random allocation and a placebo control. While 1.0–1.5 g/day of calcium supplementation has been the most common intervention, from 0.4 to 2.0 g/day has been used. In addition to the carbonate salt, the studies have utilized calcium citrate, gluconate and lactogluconate, yeast, and in five studies, dietary calcium. Length of supplementation has ranged from 5 days to 1 year.

Overall, a significant blood pressure reduction was
observed in at least a segment of the population in 75% of these trials. This assessment has been confirmed by a meta-analysis from the Epidemiology Branch of the NHLBI. Blood pressure reduction with calcium supplementation has ranged from 2 to 10 mmHg. Based on the NHLBI analysis, the blood pressure lowering effect of increasing calcium intake is equally as great or even greater in normotensive subjects as in the hypertensive subject, and a dose-dependent effect was identified. Primarily a systolic blood pressure effect is observed. The conclusion from the NHLBI analysis is consistent with the graphic portrayal of Grobbee's meta-analysis and the conclusions of Mikami et al.

The studies that have reported the most significant blood pressure reductions have included more than 50 subjects overall, and were randomized, placebo-controlled studies. In other reports, including many of the negative studies, the sample size was insufficient to detect the small blood pressure reductions observed with nonpharmacologic interventions such as calcium supplementation, and in some cases only one blood pressure determination during the intervention phase was recorded. The length of supplementation may be very important to determine a positive effect on blood pressure. In our first clinical trial, we noted a significant blood pressure reduction only after 8 weeks of supplementation, though not after 6 weeks. Contrary to this, two negative trials by Bloomfield et al. and Cappuccio et al. used only 4 weeks of calcium supplementation. Although two trials were only 1–2 weeks in duration, significant blood pressure reductions were detected either because of a higher level of supplementation or more intensive observation on a metabolic ward.

Since the epidemiological data indicate that a threshold may exist for the effect of dietary calcium on blood pressure, it follows that studies employing subjects whose normal intakes exceed this threshold would be unlikely to reveal an impact of increased calcium. Several of the trials intervened in populations where baseline calcium intake was already very high; not surprising, none of them showed a positive outcome. Specifically, the results from the TOHP Study are consistent with that trend. In that study subjects with high normal blood pressures who received calcium supplementation failed to have a statistically significant fall in their blood pressure. Based on the information in the published report, the majority of the subjects were already consuming levels of dietary calcium exceeding the 400–600 mg/day threshold. Our own report of supplementation in young normotensive subjects is consistent with the TOHP outcome; the normotensive participants reported average dietary calcium 3–15 mmHg, when projected across the population, these changes could represent significant benefits in overall cardiovascular morbidity and mortality. The response to calcium supplementation is Gaussian, representing larger changes in blood pressure for some individuals. Similarly, as with most antihypertensive interventions, some individuals are either resistant to the treatment or actually experience a blood pressure rise. This heterogeneous response to increased calcium is similar to that observed in clinical trials for sodium restriction, potassium supplementation, and diuretic use. Clearly, even where large trials have failed to demonstrate an overall effect, the existence of calcium-sensitive subpopulations is evident and must be explored.

**Predictors of a Blood Pressure Response**

A variety of demographic, biochemical, and nutritional parameters have been assessed in an endeavor to predict blood pressure response to calcium supplementation. Although male subjects appear to be slightly more sensitive than females, this difference is not firmly established. In a trial with both African-American and Caucasian subjects, there was no difference in blood pressure response based on race. However, the clinical experience of Zemel et al. suggests that, indeed, African-Americans more than Caucasians would benefit from the cardioprotective effects of increased calcium intake.

Of the biochemical parameters, serum ionized calcium has not been a predictor of a blood pressure response although in our initial trial those subjects who had the
smallest change in ionized calcium had the largest drop in blood pressure. Resnick et al. have reported that blood pressure reduction is dependent on renin status. Low-renin (sodium expanded) hypertensive subjects have the greater blood pressure reductions and high-renin hypertensive subjects may experience a pressor effect, although this has not been confirmed in other studies. If this is ultimately demonstrated to be the case, it would provide a critical piece of evidence to support a relationship between sodium-sensitivity and calcium supplementation.

Grobbee and Hofman reported that subjects below the median for serum total calcium had a greater blood pressure response compared to those above the median. Similarly, subjects in their study who were above the median PTH level had greater reductions in blood pressure. Lyle et al. observed an identical pattern is relationship for PTH as well as for serum total calcium values, and the blood pressure response to calcium supplementation. Repke et al. have also observed that low serum calcium and elevated PTH appear to be predictive of a blood pressure reduction in gestation.

In our trial in an older population, women whose baseline vitamin D levels were above the median were more likely to lower their blood pressure with supplemental calcium. Strazzullo et al. found that higher UCaV at baseline was inversely associated with blood pressure reduction with supplemental calcium. Baseline dietary calcium intake has not been a predictor of blood pressure response in any trials. To date, no report has assessed whether baseline calcium intake as indexed against either dietary sodium intake or alcohol consumption was predictive. One of these may be the more appropriate dietary index of blood pressure sensitivity to increasing calcium intake.

Areas of Potential Clinical Application

**Sodium-sensitive hypertension:** Understanding the pathogenesis and treatment of hypertension induced by NaCl remains a primary challenge to cardiovascular researchers. Kurtz and co-workers demonstrated that NaCl-sensitive hypertensive subjects develop increased urinary calcium similar to that observed in the DOCA-saline and Dahl sodium-chloride dependent experimental models. Oshima and colleagues have reported a remarkable relationship between salt sensitivity and increased intracellular calcium concentration. Shingu et al. reported a similar relationship in platelets of humans. Oshima et al. have documented that the impact of NaCl on platelet intracellular calcium can be reversed by increasing dietary calcium. These findings provide a subcellular link between salt sensitivity in human hypertension and cellular calcium metabolism.

The observation that calcium supplementation lowers blood pressure in various animal models of NaCl-related hypertension provides compelling laboratory evidence that provision of adequate calcium may afford protection against NaCl-induced hypertension. This proposition, first suggested in humans by Resnick et al., has been confirmed by Saito et al. in two separate studies; provision of supplemental calcium to subjects ingesting a high salt diet prevented any rise in blood pressure as well as platelet hyperaggregability, a risk factor for stroke.

In light of recent reports of adverse effects of sodium restriction for the treatment of hypertension, the interactive, and potentially protective effects of adequate calcium in this setting take on greater importance. The most compelling of these reports is the 1995 publication by Alderman et al. who found in a prospective study of more than 2,000 treated hypertensive individuals, that the incidence of myocardial infarction and total cardiovascular disease was significantly higher in those with urinary sodium excretion in the lowest quintile relative to those with sodium excretion in the highest quintile (range 35–340 mmol). After controlling for a variety of potential confounding factors, the risk remained significant. Other reported adverse effects of restricted sodium include increased serum lipids, impaired efficacy of the calcium channel blocker class of antihypertensive medications, and increased circulating insulin levels.

**Pregnancy-induced hypertension (PIH):** PIH is an important clinical problem to which the concepts outlined here may be of critical value. Disturbances of calcium metabolism have been identified in human pregnancy, many of which are similar to those observed in essential hypertension. PIH patients fail to increase circulating vitamin D3 and PTH levels and as a consequence may not be able to adequately defend their calcium homeostasis. This could be potentially harmful if their average daily calcium intake is less than adequate. Zemel et al. have reported recently that within the first 3 months of gestation, an increase in platelet free intracellular calcium strongly predicts a pathological increase in late-term blood pressure, confirming earlier suggestions of such a defect. This finding suggests that a preexisting disturbance of cell regulation of calcium underlies the pathogenesis of PIH and prematurity.

Several intervention trials have demonstrated that during the third trimester of pregnancy, calcium supplementation significantly reduces either blood pressure or the incidence of PIH. The importance of this area of clinical application is being directly tested in the current national trial by the National Institute of Child Health and Human Development to be completed in 1996. In this trial, 4500 women are receiving either 2000 mg of calcium or a placebo during the second half of pregnancy. The intent of this intervention is to lower the incidence of preeclampsia, but maternal and infant blood
pressure, prematurity, and birth weight are also being assessed.

Alcohol-associated hypertension: Alcohol-associated hypertension is another potentially productive area of investigation. Chronic alcohol ingestion induces several alterations in cell calcium homeostasis and ultimately results in significant bone mineral loss, the mechanisms of which are unclear. An interaction among alcohol consumption, dietary calcium intake, and blood pressure has been reported in at least four epidemiological studies.\textsuperscript{53,54,61,109} Criqui et al\textsuperscript{55} have reported that compared to other nutrient/blood pressure relations, the association of dietary calcium to blood pressure was evident only at low levels of alcohol intake, suggesting an inhibitory effect of alcohol on the blood pressure-lowering effect of calcium. We have recently demonstrated in the laboratory that maintenance of a fully adequate diet while on a high alcohol intake prevents a rise in blood pressure.\textsuperscript{110}

African-Americans: Alterations in calcium metabolism may be particularly important for the pathogenesis of hypertension in African-Americans.\textsuperscript{111,112} Dietary calcium intake among African-Americans in this country is significantly less than that observed in Caucasians.\textsuperscript{67,113} One epidemiological study has demonstrated that after correcting for differences in calcium intake, one can account for a large proportion of variation in blood pressure between adolescent Caucasian and African-American females.\textsuperscript{112} The sentinel observations of Zemel et al\textsuperscript{111,112} suggest a beneficial effect of calcium intake on blood pressure control and cardiovascular regulation in hypertensive African-American diabetic patients. Ernst et al\textsuperscript{114} reported that increasing dietary calcium intake prevents stress-induced increases in mean arterial pressure in African-Americans.

Adult-onset type II diabetes mellitus: Adult-onset type II diabetes mellitus poses a serious threat to many adults in terms of premature cardiovascular disease, both cardiac and cerebrovascular events. Hypertension is the principal co-factor in 80% of its victims. Recent experience in human subjects\textsuperscript{81} indicates a remarkable potential for intervening with dietary calcium to lower blood pressure and improve cardiac hypertrophy. This is backed by several reports in experimental animals\textsuperscript{115,116} that suggest a strong overlap among dysregulation of blood pressure, calcium metabolism, and carbohydrate metabolism. Given that African-Americans, overweight persons, and the elderly are likely to develop insulin resistant diabetes and also generally have low calcium intake, this association seems even more worthy of pursuit. Byyny et al\textsuperscript{117} have provided further cellular evidence for this link. Resetting the calcium intake threshold to a higher obligatory level would be dictated by the impaired active calcium transport in the gut that is well established in diabetes.

Hypertension prevention: Perhaps the most important application of the findings outlined above is the extent to which maintenance of the recommended daily allowance (RDA) for calcium will prevent the blood pressure increase occurring with age in industrialized societies, and the subsequent morbidity and mortality. Our current understanding in this area of investigation clearly indicates that intake of dietary electrolytes plays a major role in blood pressure regulation. This is evidenced by the most recent report of the NHLBI Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure,\textsuperscript{118} in which adequate intake of dietary nutrients including calcium, potassium, and magnesium is recommended for use in both hypertension treatment and prevention. This may be particularly beneficial in groups with chronic low consumption of dietary calcium such as women, African-Americans, undernourished infants and children, as well as many elderly individuals.

Summary
Pathological alterations in calcium metabolism are a factor in abnormal blood pressure regulation in some humans. A consistent nutrient/blood pressure association has been demonstrated in epidemiological studies, the strength of which has been acknowledged by leading authorities in the field of nutritional epidemiology. Thus, in patients with mild to moderate hypertension, dietary calcium intake should be assessed, and where appropriate, they should be encouraged to maintain intake levels of 800 to 1000 mg/day. More importantly, for normal subjects at risk of developing high blood pressure, inadequate intake of dietary calcium should be avoided. It is clear that the maintenance of the recommended daily calcium intake is essential for optimal blood pressure control as well as bone and cardiovascular health. As the accumulated evidence suggests, it is the prevention of calcium deficiency that should be strived for in patients with essential hypertension or individuals at risk of developing this all-too-common medical disorder. Adequate intake should be promoted of not only calcium, but also potassium, magnesium, phosphorus and essential fatty acids. The published scientific data summarized here support this conclusion as well as the implementation of strategies to effect such an outcome in order to improve cardiovascular health in humans.

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