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**Author**

Martinez, Christina

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Hypertension affects more than 50 million Americans, and can lead to the development of cardiovascular disease, stroke, and renal failure (2, 9). Various methods have been used to treat hypertension, including alterations in lifestyle (exercise, stress, cigarette use and alcohol consumption) and dietary intervention (protein, fat, carbohydrate, fiber, salt and mineral intake) (1). In 1973, Langford and Watson reported that while hypertension was a direct function of sodium intake, an inverse relationship between hypertension and calcium, magnesium and potassium intake may exist; since then several epidemiological, animal, and clinical studies have attempted to clearly demonstrate this relationship between calcium and blood pressure (2, 9).

Low levels of calcium, either due to dietary deficiencies or altered calcium metabolism, have been linked by several epidemiological and laboratory studies to higher blood pressure, or hypertension (1, 2). One of the largest studies to examine this relationship was the National Health and Nutrition Examination Survey (NHANES) conducted by the National Center for Health Statistics. They found that there is a threshold of 400-600 mg/day of dietary calcium; the risk of high blood pressure increases dramatically at levels below this threshold, while the cardiovascular benefits modestly increase at higher intake (1). This threshold may vary depending on the patient population. Results of the Honolulu Heart Study indicate that this threshold would be shifted to 800-1000 mg/day for alcoholics due to impaired intestinal calcium absorption in this group (1,2). The threshold would also be increased in pregnant women, who require a higher calcium intake in order to meet fetal needs (such as bone mineralization). The Nurses Health Study, a prospective cohort study that investigated the effects of dietary calcium and magnesium on blood pressure, found that the relative risk of developing hypertension for women with a dietary calcium intake equal or above the RDA of 800 mg/day was 0.78 compared with those consuming under 400 mg/day (2). However, some clinical studies have failed to show this correlation, therefore, whether or not individuals should increase dietary calcium to prevent or treat hypertension remains somewhat controversial (1, 2).

#### ALTERED CALCIUM METABOLISM AND HYPERTENSION

Disturbances in calcium metabolism that cause calcium deficiency have been linked to abnormal blood pressure control (1). Several studies indicate that abnormal calcium metabolism is likely the cause of high blood pressure rather than resulting from cardiovascular changes associated with hypertension. In genetically hypertensive rats that received a calcium supplement during development of hypertension, blood pressure was significantly lower compared to those not receiving the supplement (5). Grobbee et. al. observed differences in calcium metabolism indices in normotensive offspring of parents with and without hypertension (the Dutch Hypertension and Offspring Study). At the ages selected, offspring in both groups had limited differences in blood pressure. Mean serum calcium levels were significantly lower, and plasma parathyroid hormone (PTH) was significantly higher in offspring having two hypertensive parents compared to those with normotensive parents, with no differences in dietary intake of calcium (5). Studies on calcium deprivation during development of animal models with a genetic pre-disposition to hypertension have also been conducted, and the majority report significantly increased blood pressure associated with low calcium intake (6). High sodium diets may reveal abnormalities in calcium metabolism that do not normally exert a noticeable effect on blood pressure, suggesting a mechanism for salt-sensitive hypertension (10).

#### INDICES OF ALTERED CALCIUM METABOLISM

Parathyroid tissue hyperplasia, elevation of plasma parathyroid hormone levels and subsequent decrease in bone mineral content (bone is the major storage site for calcium) has been associated with hypertension. Ionized serum calcium levels may be depressed or unchanged, while intracellular calcium may be increased in platelets, lymphocytes, vascular smooth muscle cells, and cardiomyocytes (1, 3). This may be due to reduced calcium extrusion via an ATP-dependant pump (8, 12). Increased intracellular calcium may also be caused by decreased vascular smooth muscle membrane stability in hypertensive individuals (12). Intracellular calcium serves as a second messenger in excitation-contraction coupling for vascular smooth muscle cells, causing contraction. This explains why abnormal cellular metabolism and subsequent elevated intracellular concentrations of calcium could contribute to hypertension (3, 12). Urinary calcium excretion, a genetically determined amount independent of dietary calcium intake, is predictive of blood pressure (1). The causes and sequence of events in altered calcium metabolism is unclear. For example,

PTH levels may rise in response to low ionized serum calcium levels, but have also been shown to increase in situations where ionized serum calcium levels are normal (3).

These observations linking hypertension to calcium disturbances in humans have also been noted and studied in animal models such as the spontaneously hypertensive rat (1). Production of the calcium-regulating hormones PTH and calcitriol, which tend to be elevated in essential hypertension, should be suppressed by supplemental dietary calcium. Since PTH and calcitriol stimulate an increase in intracellular calcium for most cells in vitro, it is presumed that suppression of these hormones would reduce intracellular calcium (3). Calcitriol may have other effects on the cardiovascular system; it has been shown to stimulate the growth of cultured vascular smooth muscle cells (3), and enhance the contractile properties of arterial smooth muscle (7). Indeed, in the spontaneously hypertensive rat, dietary calcium supplementation resulted in a lower intracellular calcium level in platelets and an anti-hypertensive effect, this effect is prevented if PTH is simultaneously administered (3).

The effects of abnormal calcium and calcium-regulating hormone levels may extend to the blood-pressure control centers of the CNS, particularly the nucleus tractus solitarius. Calcium injected intracerebroventricularly is followed by reduced levels of plasma norepinephrine (a neurotransmitter that causes vasoconstriction), a process most likely initiated through calcium entry into neurons (7). Changes in cerebrospinal fluid concentrations of calcium in vivo would produce the same effect. In rats fed a low calcium diet, low CSF calcium levels were found along with low serum calcium concentrations despite the low cerebrovascular permeability to calcium (7). High calcium, in addition to inhibiting the release of norepinephrine, may reduce its post-synaptic effect on blood vessel constriction through modification of the  $\alpha$  1-adrenergic receptor (12).

In addition, calcium levels may regulate sodium chloride appetite, evidence for this has been found in rats. Low intake of calcium was accompanied by increased NaCl appetite, and vice versa (7). Higher sodium intake is a well-known risk factor for hypertension. Calcium-regulating hormones also appear to affect the CNS and cardiovascular regulation, as intracerebroventricular injection of PTH resulted in elevated blood pressure in hypertensive rat models (7).

## RESPONSE OF BLOOD PRESSURE TO INCREASED CALCIUM INTAKE

Administration of calcium salts (carbonate, citrate, phosphate, gluconate, lactate) have had the effect of reducing hypertension in the spontaneously hypertensive rat and also models of salt-sensitive hypertension such as the Dahl-sensitive rat (1,6). Effects of calcium salts or increasing dietary calcium in human patients have varied from study to study. In most, increased calcium results in lower blood pressure, while in the remainder no change or even increases were observed in blood pressure with calcium administration (1). In approximately two-thirds of the studies done by 1994, increases in calcium intake produced a mild anti-hypertensive response, with the average decrease of 4-7 mmHg systolic and 2-4 mmHg diastolic (1).

The majority of observational studies show a clear inverse relationship between calcium and both the prevalence of hypertension and the level of blood pressure (2). The method most commonly used for data collection has been the 24-hr diet recall. This method has been criticized on the basis that most recalls have not included information on calcium or other vitamin and mineral supplements, there is a lack of temporal association, and the 24-hr diet recall is generally not representative of overall diet patterns for an individual. However, 24-hr diet recalls may be representative of intake for the population as a whole, and data collected can encompass a broad range of ages, socioeconomic, demographic and educational backgrounds (2). In clinical trials, researchers have obtained every effect including anti-hypertensive, hypertensive, or no change in blood pressure in response to increased calcium intake. These results are similar to responses found with other common antihypertensive interventions (sodium restrictions, potassium supplementation, diuretic use). Generally, those trials of longer duration and/or larger sample size resulted in a positive correlation between increased calcium intake and lower blood pressure (2).

The interaction between calcium and other dietary nutrients (sodium, potassium) may be the complicating factor in the study of calcium and its effects on blood pressure (2, 9). Through examination of studies such as the National Health and Nutrition Examination Survey, it has been suggested that the therapeutic effect

of increasing calcium exists when sodium intake is high, and potassium intake is low, or when supplemental potassium or magnesium is also given (2). Indeed, it may be foolhardy to attempt to show a correlation between hypertension and calcium alone, since dietary sources of calcium such as dairy products are also leading sources of potassium, protein, magnesium, and Vitamin D (10). This complicates direct comparison of various studies since increases in calcium through administration of calcium salts, elemental calcium, and dietary calcium likely produce different effects due to nutrient interactions. Other components in the diet may influence the effects of dietary calcium on blood pressure. For example, fiber influences calcium absorption, and lipids interact with calcium as well (12).

Overall, these studies have indicated that while increasing calcium intake might not be advantageous for the population at large with respect to hypertension, there are certain groups that do clearly benefit from increased calcium intake (2). Approximately 10% of pregnancies are accompanied by hypertension, preeclampsia accounting for half of these cases (4). Women at risk of developing pregnancy-induced hypertension are typically responsive to increased calcium, with the incidence of hypertension being reduced up to 40-50% in those with a 1500-2000 mg/day intake (there is an increased daily calcium requirement due to fetal processes that are dependant on maternal calcium stores) (1, 4). Maternal blood calcium levels also affect the blood pressure of the newborn infant (9).

Patients with salt-sensitive hypertension represent another group for whom increased calcium intake appears to be highly beneficial. Responses in blood pressure to salt (NaCl) ingestion have been shown to additionally depend on the adequacy of dietary mineral intake (calcium, magnesium, and potassium) (10). In fact, in the NHANES I database, several individuals with high sodium intake were observed to have lower blood pressures than would be expected; upon further analysis it was found that the calcium and potassium intake of these individuals was high (10). One reason for this relationship is due to the induction of natriuresis by calcium (12). So far, there is not an accurate predictor of how an individual will respond to increased calcium intake in the treatment of hypertension, although several predictive variables (high parathyroid hormone levels, lower serum ionized calcium/total calcium concentration, increased urinary calcium excretion, old age, renin activity, pregnancy, salt intake) have been suggested (1, 3).

Adequate dietary calcium is important for all individuals. As discussed, there is considerable evidence that increased calcium intake reduces risk of hypertension, especially in such groups as pregnant women, individuals with high sodium diets, and those with an increased risk of hypertension such as individuals with a family history of high blood pressure. In addition, sufficient calcium intake can help prevent other disease processes such as osteoporosis. However, nearly all categories of individuals in the U.S. fail to attain recommended levels of calcium consumption. Calcium intake required to produce an effect on blood pressure lies within the RDA values (currently 800 mg/day, 1,200 mg/day for those 19-24 years old) (11, lecture notes). Therefore, the inverse correlation between calcium intake and high blood pressure provides an added reason why individuals of all ages, gender, and ethnicity should meet the RDA for calcium.

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