



## **Role of Dietary Calcium in Hypertension**

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### **Authors' contributions**

*This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.*

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## **ABSTRACT**

Calcium level is an importance factor for control hypertension. This review tries to shade the light on the role of calcium in controlling blood pressure. Searching on the internet using the Google search engine was the main source of data as well as books was the method to explore this interaction. Calcium from supplementation and diets was the main focus of this paper.

**Keywords:** *Calcium; hypertension; diet; supplement.*

## **1. INTRODUCTION**

In Libya, the prevalence and incidence of non-communicable diseases have increased dramatically over the past twenty years. Cardiovascular diseases (CVD), hypertension, diabetes and cancer account for significant

morbidity and mortality and have put a lot of strain on health expenditure. Stepwise surveillance for non-communicable diseases has not started. The main cause of death (reported by national authorities) is cardiovascular diseases 37%, cancer 13%, road traffic accidents (RTA) 11%, and diabetes 5%. Collective

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evidence suggests that calcium underlies the hypertensive process, and may play a role in development, treatment and prevention of hypertension [1]. Blood pressure is a measure of fluid pressure against vessel walls. Optimal blood pressure is considered to be 110/70, while a normal acceptable blood pressure is below 120/80. The first number is the "systolic" pressure due to heart pumping, measured in millimetre of mercury. The second number represents the "diastolic" pressure between beats, when the heart rests. Although there are no precisely defines rules regarding abnormal blood pressure, as general guidelines, consistent systolic pressure of 150 to 160 or consistent diastolic readings of 99 or above signal hypertension that requires medical treatment and need to be controlled [2]. Hypertension is defined as either systolic pressure consistently at 140 or higher or a diastolic pressure consistently at 90 or higher [3]. Hypertension is classified according to its causes into three types; primary (essential) accounts for over 90% of cases and is often referred to as idiopathic, since the underlying cause is unknown. This type has an insidious onset with few, if any, symptoms, so it is often not recognised until complications have occurred. Secondary hypertension results from a number of conditions that impair blood pressure regulation, particularly renal, endocrine, vascular, and neurological disorders, hypertensive disease of pregnancy (formally known as toxemia); and use of estrogen-containing oral contraceptive and some other drugs. A severe acceleration form of hypertension, malignant hypertension, results from either type and can cause blood pressure as high as 240/150mmHg, possibly leading to coma and death [4,5]. Cerebrovascular disease and coronary artery disease are the most common cause of death, although hypertensive patients are also prone to renal failure and peripheral vascular disease. Hypertensive have a sixfold increase in stroke (both haemorrhagic and atherothrombotic). There is a threefold increase in cardiac death (due either to coronary events or cardiac failure). Furthermore, peripheral arterial disease is twice as common [6]. In clinical, antihypertensive therapy has been associated with reductions in stroke incidence average 35-40%, myocardial infarction 20-25%, and heart failure more than 50% [7]. It is estimated that in patients with stage one hypertension and additional cardiovascular risk factors, achieving a sustained 12mmHg reduction in systolic blood pressure over ten years will prevent one death for every eleven treated patients. In the presence

of (CVD) or target organ damage, only nine patients would require such blood pressure reduction to prevent a death [8]. Calcium is the most abundant mineral in the human body and body requires considerable quantities of The purpose of this review is to present research findings on the effect played by calcium, weather dietary or supplementary on hypertension. Background on hypertension and calcium along with a summary of literatures citing the link between the two will form the first part of this review, after which an explanatory approach on calcium metabolism in hypertension, and different outlooks of calcium effect on blood pressure will be presented. Under normal conditions, approximately 33% of the ingested calcium is absorbed. Once calcium is absorbed through the walls of the intestine it is transported in the plasma and released to fluids bathing the tissues of the body. From there, the cells absorb whatever calcium is needed for their normal functioning and growth. The level of calcium in plasma is maintained at about 10 mg/dl and is regulated by the endocrine system involving parathyroid hormone (PTH), calcitonin, and active form of vitamin D. as the blood plasma is filtered in the kidney about 99% of the calcium (10g/day) is reabsorbed and the remaining 1% (usually about 100-175 mg/day) is excreted in the urine [9]. Calcium is present in significant amounts in only a few foods, with milk and dairy products as the best sources. A quart of milk supplies about 1200 mg of calcium in a readily available form. Broccoli and leafy green vegetables such as turnip greens and kale have appreciable amount of calcium. Other foods relatively high in calcium salts are beans, shellfish, and fish of the sardine type in which bones are eaten. Some vegetables such as spinach contain appreciable quantities of oxalic acid, which forms insoluble calcium oxalate in the intestinal tract and lessens the absorption and utilization of calcium present [10,11,9]. The calcium requirements are based on balance studies that measure the intake and output of calcium over period of time. The food and nutrition Board of the national Academy of science in its 1997 revision recommends 1000mg/d of calcium for adults .this amount covers the basic needs and allows for a margin of safety. This allowance is on the basis that calcium losses are approximately 320mg/day. Because only a portion of the dietary calcium is absorbed, 1000 mg is suggested for maintaining balance. The RDA for infants up to 1 year old is between 210 and 270 mg/d. For children 1-8 years old. The allowance is set between 500 and

800 mg, and for those between the ages of 8 and 18 the recommended amount is 1300 mg per day. To meet the needs of the growing fetus and the mother during pregnancy. The RDA for calcium during gestation is 1200 mg\day compared with 1000 mg for non – pregnant women. Human milk contains 25-035 mg calcium\100ml [12]. For lactating women this represents an additional 150-200 mg depending on the amount of milk produced, so to meet this demand the RDA during lactation set at 1200 mg\day [9]. Deficiency of calcium in children causes rickets whereas in adults result in osteomalacia or lead to osteoporosis. On the other hand, calcium overload causes hypocalcaemia which may cause renal stone, arrhythmias, heart failure, calcification of the arteries, muscle weakness. Tiredness, anorexia, constipation, and sluggish nervous response may also seen [13]. Physiologically, dietary salt-induced elevations of blood pressure can be explained as the consequence of salt-induced changes in calcium-regulating hormone- related tissues, directly resulting in the vasoconstriction and potentiated sympathetic nerve activity we associate with salt sensitive hyper-tension. Conversely, by revising or preventing these salt-induced calcium-hormonal changes, dietary calcium supplementation may lower calcium in these tissues, revising or preventing the cardiovascular effects of salt loading [14]. It appears however, that alterations in calcium metabolism may reflect or even mediate the phenomenon of salt sensitivity in hypertension. This is emphasized by the failure of calcium metabolism to change significantly in "normotensive individual" in which dietary salt loading did not change blood pressure [11,12]; and could explain why, epidemiologically, among calcium replete individuals, blood pressure appeared unrelated to dietary salt intake, because little stimulation of egg, 1, 25 D would be expected under calcium replete, 1, 25 D suppressed circumstances [14].

## 2. METHODOLOGY

Searching on the internet using the Google search engine was the main source of data as well as books. The keywords include Fruits, Vegetables, Consumption, Frequency, Health, and Dietary. The search has generated about 131 sources, of which 66 sources have actually been used. These 74 articles were considered relevant because they answered the aim and objectives of the review. The library database was also used during the study. All included articles and books were written in English.

## 3. CALCIUM AND HYPERTENSION

Calcium, and high blood pressure; the relation "Review of literature" the ability of increased calcium intake to lower blood pressure in patients with essential hypertension was first reported in 1924 by Addison [14]. This intriguing observation was largely ignored for over 50 years until work in experimental hypertensive models once again raised the issue of whether dietary intake of calcium could be used as a primary form of antihypertensive therapy. Numerous population studies since that time confirm an inverse relationship between dietary calcium intake and blood pressure, a lower intake of calcium being associated with higher blood pressure [15]. Recently, at least nine researches have stated that oral supplementation of calcium could lower blood pressure level in both hypertensive and normotensive groups. One hypothesis that could explain the relationship between calcium intake and hypertension is one portraying hypertension as a disease of dietary calcium deficiency, yet this hypothesis was faced with undue criticism. Whereas, several other research have portrayed hypertension is a disease of calcium excess. However, these wide spreading finding still remain controversial, and opposition has developed toward acknowledging that various clinical aspects of calcium metabolism, such as the absorption, dietary intake, excretion, and tissue distribution of calcium, are undeniably related to the therapy and path physiology of hypertension [15]. In order to identify the relation of 17 nutrients to blood pressure in adult Americans , the National Centre for Health Statistics, health and nutrition examination survey I (HANESI) database was used to perform a computer-assisted, comprehensive analysis. The study included 10,372 subjects, aged 18 to 74 years old, and who denied a history of intentional modification of their diet and hypertension. Among the nutritional factors that distinguished hypertensive from normotensive subjects were substantial decreases in the intake of calcium, potassium, vitamin C and vitamin A. with lower calcium intake being the most consistent factor in hypertensive individuals. Across the population, higher intakes of both calcium, potassium, along with sodium were associated with lower absolute risk of hypertension and lower mean systolic blood pressure [16]. In a study carried in a Indian population by Sudhakar and his colleagues, calcium was found to play an important role in the path physiology of essential hypertension, in the study; serum levels of calcium were

measured in 177 hypertensive subjects and 77 of their first-degree relatives. Study results showed that when compared to normotensive controls, serum calcium levels were significantly decreased in both males and females with essential hypertension and their first-degree relatives [17]. Furthermore, new research shows that increasing calcium consumption to at least recommended levels (1,000mg/day for adult 19-50 and 1,200mg/day for adult 51 and older) is also associated with a small, but important, reduction in blood pressure. This effect is expected to be even greater in people at high risk for both hypertension and low calcium intakes including African Americans and mature adults (ages 51+). Calcium has two "partners" that help curb high blood pressure, potassium and magnesium; they pitch in to help keep blood pressure levels in check. Luckily, milk products and ingredients such as milk minerals contain ample amounts of all three [18]. The evidence that calcium plays a role in the etiology. Prevention and treatment of pregnancy-induced hypertension (PIH) is reviewed. The precise factors involved in the pathogenesis of PIH are unclear, but several alterations in calcium metabolism have been identified. Epidemiologic data suggest an inverse correlation between dietary calcium intake and incidence of PIH. Although evidence suggests a possible beneficial effect of supplemental calcium, contradictions persist in clinical trials of pregnant women. Presently, there is insufficient evidence to support routine calcium supplementation of all pregnant women. However, high-risk groups, such as pregnant teens, populations with inadequate calcium intake, and women at risk of developing PIH, may benefit from consuming additional dietary calcium [19-21].

### 3.1 Calcium Metabolism in Hypertension

**"The Rennin-angiotensin system"** It's widely thought that altered functions of vascular smooth muscle play an important role in the development of hypertension or maintenance of a hypertensive state, and it is also believed that calcium is crucially involved in the regulation of smooth muscle tension development including vascular muscle tone. Therefore, theories have been formed on the basis that disturbance in calcium metabolism of vascular smooth muscle might be behind altered vascular smooth muscle seen in hypertension. This concept was extended to include the possibility that alteration of whole organism calcium might be present in hypertension patient and is based on the origin

that hyper parathyroid patient are frequently hypertensive, and that the blood pressure of patient returns to normal upon removal of parathyroid gland, another support line comes from the epidemiologic studies which proved that low dietary calcium intake is often associated with elevated risk for developing hypertension [20]. In a straightforward fashion, there are only two ways of increasing pressure in a fluid-filled elastic tube such as blood vessel, regardless of the multiplicity of individual hormonal or neural contributions. One can either overload the tube by increasing the volume of a vessel of fixed diameter. Or one can squeeze more tightly, i.e., increase the vasoconstrictor tone within the walls of the vessel, which will tend to decrease the diameter of whatever amount of fluid is already present. We refer to these two elements as volume and constrictor factors. Since the rennin system presides over both volume and vasoconstrictor factors. High salt diets, by increasing the volume component of blood pressure, simultaneously and appropriately decrease constrictor elements, as evidenced by & suppression of plasma rennin activity. On the other hand, a low salt diet reciprocally stimulates plasma rennin activity. Hence, in hypertension, a suppressed plasma rennin activity indicates a greater sodium-volume dependence of the blood pressure, whereas the hypertension associated with high plasma rennin activity is rennin-dependent often sodium-volume independent [20]. The important question raised is how altered calcium metabolism can reflect on the vascular wall and alter its properties? The answer would be known when a deep understanding of the physiology of calcitropic hormones; 1, 25 dihydroxycholecalciferol, parathyroid hormone (PTH), and calcitonin and other related factors, such as rennin < ACE parathyroid hypertensive factor (PHD), and calcitonin gene related peptide (CGRP). Calcium is widely recognized as being regulated by a closely controlled endocrine system [22,23].

### 3.2 Dietary Calcium and Hypertension DASH and the Role of Dairy Products

Several studies; which will be further discussed later in this review, indicate that the intake of calcium from non-dietary sources (primarily from dairy foods) is inversely related to blood pressure regulation [24,25]. While other studies also suggest an inverse relationship between dairy product intake and insulin resistance syndrome, type 2 diabetes, and cardiovascular disease (CVD) [26]. The potential benefits of dairy food

on these conditions have generally been ascribed to the major nutrients provided by dairy including calcium, potassium, magnesium and more recently, vitamin D [27]. Substantial evidence exists from epidemiologic and randomized clinical trials showing that dietary patterns containing high amounts of fruits and vegetables in foods that are major components of the so called DASH diet, (dietary approaches to stop hypertension) are inversely and independently associated with blood pressure [28,29].

The DASH diet is rich in fruits, vegetables, whole grains, and low fat dairy food; it includes meat, fish, poultry, nuts and beans; and is limited in sugar-sweetened food and beverages, red meat, and added fats, in addition to its effect on blood pressure, it is considered a well-balanced approach to eating for the general public. It is now recommended by the US department of agriculture (USDA) as an ideal eating plan for all populations. Dairy products are also key components to the DASH diet but the independent role of dairy components on blood pressure and hypertension risk are not as well understood [27]. In the coronary artery risk development in young adults (CARDIAC) study, a prospective study of 3,157 U.S. young adults 18-30 years followed for 10 years, the incidence of elevated blood pressure (130/85) was inversely associated with total dairy food intake in subjects with a BMI > 25 but not in normal weight subjects [30]. The inverse relationship was observed for both reduced and high fat dairy products and the odds of elevated blood pressure were lowered by about 20% for each daily eating occasion of dairy products. In a subsequent follow-up study in this same cohort involving 4,304 participants followed for 15 years, total dairy food intake (i.e. milk, cheese, yogurt, and dairy desserts) was underrated to the incidence of elevated blood pressure. However, in an analysis of dairy products subgroups, inverse associations with elevated blood pressure were found for milk intake and dairy desserts but not for cheese or yogurt [31]. Thus, findings from this young adult cohort suggest some level of consistency of an inverse relationship between the intake of fluid milk and dairy desserts and elevated blood pressure. In contrast, another prospective study examined the relationship between total, low-fat and whole-fat dairy intake and risk of hypertension in 5,880 middle-aged adults (mean age: 37 yrs) over a follow-up period of 2.25 years. After multivariate adjustments, a significant reduction in the risk of hypertension in the

highest versus lowest intake of low fat dairy products was reported, whereas no association was found with total dairy, whole-fat dairy or total calcium. Likewise, calcium intake from low fat dairy products was significantly associated with reduced risk of hypertension, but not for whole fat dairy products [32]. Finally, in the women's health study, a prospective study of 28,886 U.S. older women ages > 45 yrs (mean age: 53.9 yrs) followed for 10 yrs, after adjustment for hypertension risk factors, the relative risk (RR) of incident hypertension was inversely associated with total dairy product and low-fat dairy product intakes, but not for high-fat dairy products [33]. The DASH multi-centre controlled-feeding trial involved 459 subjects with high-normal blood pressures (SBP/DBP = 131/84.7 mmHg), not taking hypertensive medications, and low baseline intakes of calcium, potassium and magnesium intakes (25<sup>th</sup> percentile of US consumption) [34]. Subjects consumed one of three diets for 8 weeks: 1) a control "typical American" diet low in fruits, vegetables and dairy products, 2) a diet high in fruits and vegetables (8.5 servings/d), high in dietary fibre (31g) and low in dairy products, or 3) a "combination diet" similarly high in fruits, vegetables and fiber, and that also contained 2.7 serving of dairy products (and was lower in total fat and saturated fat (DASH diet). The DASH diet lowered SBP and DBP by 5.5 and 3.0 mmHg greater than the control diet, whereas the fruit and vegetable diet (i.e., without dairy food) produced BP reductions of roughly half that of the DASH diet (SBP 2.8 mmHg : DBP -1.1 mmHg) blood pressure changes with the DASH diet were greatest in subjects with established hypertension (SBP ≥ 140 mmHg or DBP ≥ 90 mmHg; 29% of subjects). In a subgroup analysis of hypertensive subjects, the high fruits and vegetables diet reduced SAP and DBP by 7.2 and 2.8 mmHg more than the control diet. Whereas the DASH diet, with its inclusion of dairy food, resulted in decreases of 11.4 and 5.5 mmHg, respectively. It was noted that, in hypertensive, the BP improvements produced with DASH rival those observed in trials with antihypertensive medications. At study completion, 70% of the DASH diet cohort had normal BP (SBP < 140 mmHg, DBP < 90 mmHg), compared with 23% of the control group and 45% of the fruits and vegetables diet group [35]. Among certain ethnic group, like African Americans, the DASH diet resulted in blood pressure reductions of 6.9 mmHg SBP and 3.7 mmHg DBP greater than the control diet. These reductions were approximately double those

achieved with the fruits and vegetables diet that did not include dairy foods [35]. The greater reductions in blood pressure seen with the DASH diet compared to the high fruits and vegetable diet cannot be ascribed to dairy products per se because the study was not designed to identify the independent BP effects of the dietary components and because other dietary alterations besides the addition of dairy products were incorporated including a reduction in total fat and saturated fat. Nonetheless, since changes in diet related factors known to effect blood pressure such as sodium, body weight, and alcohol consumption were small and consistent across the diets, it is highly suggestive that some aspects of the DASH diet including increased calcium, potassium and magnesium or other components provided by the addition of dairy products and \or the lower level of saturated fat may play significant and possibly synergistic roles in reducing blood pressure. The blood pressure effects of the DASH diet were further examined in a second study: the DASH – sodium Trial, in which the diet was tested with various levels of sodium (high: 140 mmol/d; intermediate: 100mmol/d; low: 65 mmol/d [34]. Consistent with the first DASH blood pressure was significantly reduced in persons consuming the DASH diet compared to the control diet, and this occurred across all levels of sodium intake and in a dose-response manner with sodium reductions. This study confirmed that for most adults, with the exception of older persons with established hypertension, regular consumption of a high quality diet, rich in fruits, vegetables, and dairy products, which also is reduced in sodium, is the optimal dietary means of controlling blood pressure [36]. Following this, study authors examined the effects on blood pressure of two different self-selected diets under free-living conditions in which a low sodium, very high potassium diet, rich in fruits and vegetables (9 servings/d) (LNAHK) and a very high calcium diet rich in low fat dairy foods) 4servings/D) (HC) were compared to a DASH type diet high in potassium and calcium (3serving of low fat dairy and 8 serving of fruits and vegetables) (OD). Compared with OD, both SBP and DBP fell during the LNAHK diet period (-3.5mmHg, and -1.9 mmHg, respectively), whereas they increased during the HC diet period (-3.1 mmHg, and 0.8 mmHg, respectively). Furthermore, when compared to a low calcium , low potassium, low magnesium diet, the OD(DASH) and LNAHK (high potassium) diet resulted in significant reductions in SBP(-1.8and 4.4 mmHg, respectively), whereas no significant BP changes

were observed with the HC(high calcium) diet. These results suggest that food high in potassium effectively reduce Bp whereas this study did not observe additional BP lowering benefits from other components of the DASH type diet (e.g. increased calcium and reduced saturated fat) [36] In summary, numerous observational and some clinical studies have demonstrated a relationship between the intake of dairy products with modest but significant reductions in SBP and in some cases DBP. In some studies, these effects have been shown to be highly correlated with the intake of dairy calcium and potassium: and greater blood pressure lowering effects were sometimes reported in African American populations.

### **3.3 How dose Dietary Calcium Affect Blood Pressure?**

Milk peptides are formed from milk proteins by enzymatic breakdown by digestive enzymes or by the proteinases formed by lactobacilli during the fermentation of milk. The two main milk proteins are casein and whey proteins, which are rich sources of bioactive peptides. Milk casenis comprise approximately 80% of the total protein content in bovine milk and consist of  $\alpha$ - $\beta$  and K-caseins. These milk- binding peptides stabilize calcium and phosphate ions, and upon digestion, the casin proteins yield caseinophosphopeptides (CPPs) [37]. In rats, CPPs have been shown to increase passive calcium transport in the distal small intestine and in humans, small casein phosphopeptides in the stomach , duodenum , and in the ileostomy fluid have been found following milk ingestion, indicating their ability to survive the passage down to the distal human ileum [27]. Whey protein is composed of  $\beta$  – lactoglobulin,  $\alpha$  –lactalbumin, immunoglobulin (IgGs), glycomacropptide, bovine serum albumin, and minor proteins such as lactoperoxidase, Lysosome and lactoferin. A number of whey peptides from  $\beta$ -CN terminal, were identified from Mozzarella cheese, and were found to have antiproliferative properties in human epithelial cells abstract only [38]. Novel angiotensin-I- converting enzyme (ACE) inhibitory activities were detected in synthetic peptides and some dipeptides, corresponding to sequences of  $\beta$  lactoglobulin and  $\alpha$  lactalbumin: and the tripe tide Tyr-Gly-leu also has demonstrated ACE-inhibitory activity at approximately the same concentration [27]. The most studied mechanism underlying the antihypertensive effects of milk peptides is inhibition of ACE. A number of ACE inhibitor

peptides have been found in various cheese and skim milk, however the best-known ACE-inhibitory peptides are Val-pro-pro (VPP) and Ile-Pro-pro (IPP), which have been identified from a Japanese sour milk drink. Some studies have shown that consumption of 95-150mL/d sour milk which contained these two tripeptides has reduced systolic and diastolic blood pressure over 4-8 weeks in borderline/moderately hypertensive or untreated hypertensive patients. This ingested dose would be equivalent to an ACE inhibitory peptide amount of 2.6 mg/d, much lower than the typical 1500mg/d found in blood pressure lowering medications. Other studies however have found no decrease in blood pressure in hypertensive subjects following daily consumption of 200 mL dairy drink with 14 mg lacto-tripeptide for eight weeks, or 125mL of milk drink supplemented with whey peptides for 12 weeks [27]. Milk peptides also may act via other mechanism to lower blood pressure including binding to opioid receptors (which induces nitric oxide release, therefore improving flow mediated dilatation), inhibition of ACE, and modification of antithrombotic and immune responses. However, the primary mechanisms of blood pressure regulation are thought to be explained by calcium, magnesium and potassium metabolism, as well as dairy and milk peptides, as discussed. [27].

### **3.4 Calcium and the Role of Dietary Salt in Hypertension**

Epidemiological as well as direct intervention studies repeatedly have demonstrated that altered dietary intake of mineral salts such as sodium chloride can result, in at least some "sensitive" individuals, in clinically significant differences in blood pressure. Current theories differ, however, as to how increased availability of salt to the organism as a whole results in the vasoconstrictor and other organ system responses characteristic of clinical salt-sensitive hypertension. Common to many current formulations is the proposal that an initially sodium chloride-derived signal is somehow translated at the cellular level to a calcium signal, resulting in an increased cytosolic free calcium and, thus, in increased vascular smooth muscle tone and elevated blood pressure [39]. Resnick and his colleagues studied outpatients with essential hypertension, and randomly allocated patients in to two diets for one month each, one with greater than 250 meq of sodium chloride per day, and one with less than 50 meq of sodium chloride per day, as assessed by the

average 24-hour urinary sodium excretion. The study results showed a relation between the percent changes in diastolic blood pressure on high versus low dietary and salt-induced elevated pressure, the more serum levels of calcium were suppressed. This study results were consistent with the notion that dietary salt may be stimulating cellular calcium uptake, as suggested by the so-named "molecular hypotheses" which states that calcium disappears from the extracellular space in proportion to the ability of dietary salt to raise blood pressure [20]. This disappearance of calcium can be best explained by the increasing levels of 1,25-dihydroxyvitamin D that occurs with salt loading. In Redneck and his colleagues study; the ability of dietary salt to rise blood pressure appeared proportional to its ability to stimulate circulating levels of 1,25-dihydroxyvitamin D, which is consistent with the report that a trigger for renal tubular cell synthesis of 1,25-dihydroxyvitamin D is an increasing intracellular calcium level. This same calcium metabolic response to dietary salt loading has also been observed under stricter inpatient metabolic balance diet conditions [20]. Salt sensitive individuals; in whom dietary salt loading did change blood pressure have lower plasma rennin activity, lower serum ionized calcium level, and higher 1, and 25-dihydroxyvitamin D levels than did salt-insensitive subjects [20]. On the other hand, individuals would be 'salt sensitive' if, by virtue of chronic low dietary calcium intake, an exaggerated calcium-hormonal response (or minimal rennin suppression) followed salt loading, because this would result in calcium hormone-mediated elevations of calcium and a subsequent pressor response. This is particularly common among salt-sensitive, black populations in the United States, and among pregnant women in the third trimester, in which calcium supplementation may lower blood pressure and prevent preeclampsia [40].

### **3.5 Oral Calcium Supplementation and Blood Pressure**

A systematic meta-analysis search for randomized trials of calcium supplementation and blood pressure in non-pregnant subjects was performed in Medline from 1966 to June 2003. Seventy-one trials were identified, 40 of which met the criteria for meta-analysis (total of 2492 subjects). Overall, calcium supplementation (mean daily dose: 1200mg) reduced systolic blood pressure by -1.86mmHg (95% confidence

interval: -2.91 to -0.81) and diastolic blood pressure by -0.99mmHg (-1.61to0.37) in people with a relatively low calcium intake (<800mg per day) somewhat larger blood pressure estimates were obtained, that is -2, 63(-4.03 to -1.24) for systolic blood pressure and -1.30(-2.13 to -0.47) for diastolic blood pressure. This study suggested that an adequate intake of calcium should be recommended for the prevention of hypertension [41]. Another study included one hundred sixteen adolescents (65 girls, 51 boys; mean age: 15.8years) who were given calcium (1.5g\|d) or placebo for 8 weeks in a randomized, double blind, crossover design. Blood pressure was measured after 2, 4 and 8 weeks. Dietary calcium was determined with a validated food-frequency questionnaire. And the results in the net effect of calcium supplementation on diastolic blood pressure was a reduction of 1.9# 1.1mm Hg. Blood pressure reduction was greater in adolescents with lower intake of calcium from the diet 24.9 #1.6, 22.3#1.6 and 1.4 #1.8 mmHg for change in the lower (0.024-0.067g ca\MJ), middle (0.069-0.091g ca\MJ), and upper (0.093-0.217g ca\MJ) tertiles, respectively. No main effect on systolic blood pressure was detected. And these findings suggested that calcium supplementation may lower diastolic blood pressure in African American adolescents with low dietary intakes of calcium [42]. Because calcium metabolism seemed relevant to the hypertensive effects of dietary salt intake, McCarron and his colleagues investigated the blood pressure effects of calcium itself. Just as salt does not raise blood pressure in all subjects as discussed previously, so the effects of dietary calcium differ in different individuals. That calcium supplementation can lower blood pressure was first reported in spontaneously hypertensive rats and extensively studied in that strain [43]. The first report of this effect in humans was also demonstrated in normotensive young adults. In a study done by Rensnick and his colleagues, essential hypertensive inpatients receiving metabolic balance diet were given 2g of calcium carbonate per day in divided doses. Blood pressure and ionic and hormonal indices were measured before and after calcium supplementation. The ability of calcium to lower average diastolic blood pressures became apparent only in those with suppressed plasma rennin activity levels. Furthermore, not only did subjects with normal plasma rennin activity fail to exhibit a significant depressor response, but those few with high-renin values actually had a presser response [44-46]. Thus, opposite blood pressure effects of the same dietary maneuver

were observed in different types of hypertension. The blood pressure responses to calcium supplementation were also predicted by pre-treatment serum ionized calcium values, where lower serum ionized calcium levels were associated with a significant hypertensive response, consistent with the lower calcium status of low- rennin subjects. Thus, the less circulating calcium present, the greater is the potential benefit from increased calcium intake [20,44]. To determine if this short-term response to calcium was relevant to the longer-term therapy of hypertensive disease under free-living conditions, resnick and his colleagues studied essential hypertensive outpatients before and one, three, and six months after they began taking calcium supplements administered as calcium carbonate, 2g per day in four divided doses. Once again, calcium lowered blood pressures, but not to the same extent in everyone, the same subgroup stood out. Subjects with lower average pre-treatment levels of ionized calcium exhibited quite significant hypertensive responses, with as much as a 10-20 percent decline in diastolic blood pressure. To the extent that calcium ultimately proves useful as a primary form of antihypertensive therapy, it would thus seem reasonable to utilize measurements of either rennin system activity or of serum ionized calcium levels to specifically target those individuals who would most benefit. This would not only help avoid possible risks in people who will not benefit, but would also protect another significant hypertensive subgroup, those with high-rennin or higher ionized calcium levels, from the potential exacerbating effects calcium might have in these individuals [45]. It was also interesting to observe that the antihypertensive efficacy of calcium was related to salt metabolism. Those subjects with the highest average urinary sodium excretion tended to have the greatest decline in blood pressure. To the extent that 24-hour sodium excretion values grossly reflect average dietary salt intake, calcium seems to lower pressure not when one is ingesting higher, rather than lower, amounts of salt. We believe these results reflect the mechanism of calcium-induced effects on pressure; we also suggest calcium as an alternative or adjunctive therapy to salt restriction in salt-sensitive patients [20,44,47]. Indeed salt-sensitive hypertensive patients have lower rennin activity and lower ionized calcium levels on a high dietary salt intake, which is exactly the metabolic pattern predictive of an enhanced hypertensive response to calcium loading. Thus, it may be that elderly and black hypertensive



population, with similar rennin and calcium metabolic patterns, are not only more likely to be salt-sensitive, but that these same groups might be most likely to benefit from calcium supplementation. Furthermore, if salt-sensitive low-rennin essential hypertension represents an inappropriate excess of sodium-volume factors, one wonders whether this imbalance might be corrected by means other than reducing dietary salt. Rather, can one compensate for what has come to be viewed as an unnecessary, high-salt diet by merely increasing dietary calcium? This exciting possibility is a focus of our current research [44].

### **3.6 How dose Calcium Supplementations Alter Blood Pressure?**

Rennin system activity and sodium and calcium metabolism seem linked in a variety of clinical circumstances, several studies investigated whether these same systems were involved in the mechanism by which calcium exerted its effects on blood pressure. We investigated the behaviour of two different rat models of hypertension, where the mechanism of the hypertension is known: rennin-suppressed, sodium-volume-dependent DOC-saline hypertension, and rennin dependent two-kidney, one-clip gold blatt hypertension. In the study: dietary calcium supplementation resulted in lower blood pressures in DOC saline hypertension, as was found in low rennin essential hypertension. On the other hand, and in parallel to the few high-rennin hypertensive human subjects studied, the opposite effect of dietary calcium in rennin-dependent gold blatt rats was observed. Here, calcium loading elevated blood pressure, which may have been related to calcium ability to elevate plasma rennin activity, noted in all rat strains and observed in human hypertensive patients as well [46]. Hence not only this diversity exists among human "idiopathic or essential" hypertension, but also in defined, experimental hypertension [44]. Furthermore, the same dietary maneuver, calcium loading, can produce opposite blood pressure effects. This strongly suggested a linkage of the rennin-angiotensin-aldosterone system with calcium metabolism in hypertension, contributing to the effects of divalent cations on blood pressure. It may be that this system, long appreciated to regulate sodium and potassium metabolism, is also involved in calcium metabolism. Indeed, in other species, angiotensin and/or angiotensin-like peptides have pronounced effects on calcium metabolism [44]. If calcium lowered pressures because it

elevates circulating calcium levels, then one would expect that supplemental vitamin D, given in addition to calcium itself, would magnify calcium effect. However, exactly the opposite was found. In patients receiving metabolic balance diets who had already been taking calcium for five days were then given 0.25 Mg of 1,25dihydroxyvitamin D (Rocaltol) per day. Patient with low rennin hypertension, having had a depressor to calcium alone, had a presser response to calcium in the presence of 1,25dihydroxyvitamin D.

### **3.7 Calcium Channel Blocker and Their Effect on Hypertension**

"In view of serum calcium" antihypertensive drugs in different classes have similar efficacy. In uncomplicated case the recommendation is to start with an (ACE) inhibitor, angiotensin receptor antagonist, calcium channel blocker or diuretic [48]. A calcium channel blockers (CCBs) are drugs whose pharmacologic action are derived primarily from the blockage of calcium influx through calcium channels in excitable membranes. they affect the entry of calcium rather than its intracellular actions and are referred to by some authors as "calcium Entry Blockers" to make their action clearer [49]. Calcium channel blockers work by blocking voltage-gated calcium channels (VGCCs) in cardiac muscle and blood vessels. This decreases intracellular calcium leading to a reduction in muscle contraction. In the heart, a decrease in calcium available for each beat results in a decrease in cardiac contractility. In blood vessels, a decrease in calcium results in less contraction of the vascular smooth muscle and therefore an increase in arterial diameter (CCBs do not work on venous smooth muscle), a phenomenon called vasodilatation. Vasodilatation decreases total peripheral resistance, while a decrease in cardiac contractility decreases cardiac output. Since blood pressure is determined by cardiac output and peripheral resistance, blood pressure drops. Calcium channel blockers are especially effective against large vessel stiffness, one of the common causes of elevated systolic blood pressure in elderly patients [50]. Unlike beta blockers, calcium channel blockers do not decrease the responsiveness of the heart to input from the sympathetic nervous system. Since moment to moment blood pressure regulation is carried out by the sympathetic nervous system (via the bar receptor reflex), calcium channel blockers allow blood pressure to

be maintained more effectively than do beta blockers [51]. However, because calcium channel blockers result in a decrease in blood pressure, the baroreceptor reflex often initiates a reflexive increase in sympathetic activity leading to increased heart rate and contractility. A beta blocker may be combined with a dihydropyridine calcium channel blocker to minimize these effects [51]. Ionic calcium is antagonized by magnesium ions in the nervous system. Because of this, bioavailable supplement of magnesium, possibly including magnesium chloride, magnesium lactates and magnesium aspartate, may increase or enhance the effects of calcium channel blockade [51]. CCBs are classified in to two major groups: the dihydropyridines and the non-dihydropyridines. The dihydropyridines have greater selectivity for the vascular smooth muscle than for myocardium and have little or no action at the SA and AV nodes. Negative isotropic activity rarely occurs with dihydropyridines at therapeutic dose in normal myocardium. Isradipine, nifedipine, nifedipine have both immediate and extended release formulations. Amlodipine and bepridil is a long action drug (one daily) available as immediate release only. Because the vasodilatation and hypotension can lead to reflex tachycardia. Dihydropyridine calcium channel blockers can worsen proteinuria in patients with nephropathy [52-54]. This CCB class is easily identified by the suffix "dipine". Non-dihydropyridines (diltiazem, verapamil) have less selective vasodilator activity than dihydropyridines and have a direct effect on myocardium causing depression of SA and VA nodal conduction. Both diltiazem and verapamil have immediate and extended release formulations [52]. In order to assess the relationship between calcium channel blockers, serum calcium and hypertension, several studies were conducted. RESNICK and his colleagues studied the ability of a single dose the calcium channel antagonist, nifedipine to lower blood pressure in relation to the ambient metabolic or hormonal circumstances [20]. Among patients treated with Nifedipine, and according to the pre-treatment level of plasma rennin activity low-renin patients exhibited the biggest decline in blood pressure after administration of nifedipine [50-53]. Similarly, elderly have been reported to be more sensitive to calcium channel blockers, which is consistent with the low rennin form of hypertension more prevalent among the elderly [50-53]. Furthermore, low rennin subjects were found to have lower average ionized calcium values, which also predicted the blood pressure response to nifedipine: patient with lower serum

ionized calcium level also showed a greater hypotensive response. The long term blood pressure response to nifedipine after one month of therapy, 10 mg three times a day, was also predicted by pre-treatment ionized calcium levels [53]. This shows that a single measurement of serum ionized calcium, or of plasma rennin activity, as well as a single dose nifedipine test may be useful to predict the long term efficacy of calcium channel blocked in essential hypertension [20].

### **3.8 Hypertension: A State of Calcium Excess or Calcium Deficiency**

The higher the level of cytosolic free calcium, the higher the level of blood pressure. Similarly, screening large populations and measuring total serum calcium and blood pressure demonstrates a similar linear, positive association, the higher the serum calcium level, the higher the blood pressure, even within normotensive individuals [55]. It has been known for three decades that short-term elevation of serum calcium may acutely elevate blood pressure, whereas acute suppression of serum calcium is associated with an acute decline in pressure [56,57]. Diseases that result in more chronic elevations of calcium, such as primary hyperparathyroidism, are associated with a much higher incidence of hypertension than would otherwise be expected [58]. In the aggregate, these data suggest that higher blood pressure are associated with higher calcium levels, and that decreasing or blocking calcium might be an effective means of lowering pressure in hypertensive patients. In apparent contradiction to this group of observations its other rapidly accumulating evidence that hypertension may be associated with a calcium deficiency. As previously discussed in this review, many published studies, utilizing a variety of sampling techniques, describe the same phenomenon [20]. The hypothesis that increased dietary intake of calcium can lead to a reduction in blood pressure stems from epidemiologic data and animal models. An inverse association between stroke mortality and water hardness led to the first suggestion of an antihypertensive effect of calcium carbonate. Subsequent epidemiologic studies across several countries and age groups presented a fairly consistent pattern of inverse association between seated blood pressure and calcium intake from food. Three large prospective studies found protective relations between dietary intake of calcium and the incidence of hypertension, although this relation was limited to lean subjects in one

cohort. There is also substantial evidence from the spontaneously hypertensive rat model that dietary calcium supplementation blunts the age related rise in blood pressure that characterizes these animals. However, consistent blood pressure-lowering effects of calcium supplementation in randomized trials have not been observed. A meta analysis of trials in pregnant women found net blood pressure reductions in 10 of 12 trials. A preventive effect on the incidence of hypertension was observed in all 8 trials assessing this end point, and the magnitude of this protective effect was greatest in younger participants. Subsequently, a large multicenter preeclampsia prevention trial (n=4589) found a small reduction of 10% in the incidence of hypertension in pregnant women but no significant decreases in blood pressure with 2 g Ca/d from calcium carbonate. This reduction in incidence is comparable with that found per gram of dietary calcium in the NHANES epidemiologic follow up, but was much smaller than that expected from meta analyses of previous trials. Meta analyses of trails in non – pregnant adults found evidence for only a small effect of calcium supplementation on blood pressure. This pattern of findings suggests that although the blood pressure-lowering effect of a diet rich in calcium may be substantial, the effect of calcium supplementation is small. However, the effect may be greater in persons with calcium deficiency induced by increases requirements or low intake from the diet. In addition, there may be genetic heterogeneity in the systemic response to restricted calcium intake [59]. There is a consistent, inverse relationship between dietary calcium intake and blood pressure [59-61]. Subjects with higher blood pressures appear to be eating less calcium. At the same time, hypertensive patients may display a relative or absolute hypercalciuria [62]. Thus, for the same level of urinary sodium excretion, patients with hypertension tend to have a higher excretion of calcium.

#### 4. CONCLUSION

High blood pressure is a multifactorial disorder. One of the factors that manipulate the blood pressures is calcium level within the blood. This review concludes that dietary calcium must keep under control beside other factors to control blood pressure.

#### CONSENT

It is not applicable.

#### ETHICAL APPROVAL

It is not applicable.

#### COMPETING INTERESTS

Authors have declared that no competing interests exist.

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