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# Vitamin D Supplementation as an Adjunct Treatment for Hypertension

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by

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**Vitamin D Supplementation as an Adjunct Treatment for Hypertension**

Hypertension, also known as high blood pressure, is a major modifiable risk factor for heart disease and stroke. Elevated blood pressure is an independent risk factor for cardiovascular disease, stroke, congestive heart failure, and chronic renal disease. It is associated with a high mortality rate, accounting for an estimated 14% of cardiovascular deaths worldwide and 18% of deaths in high income countries. It is the leading cause of death in the United States. About one in three American adults has high blood pressure and yet not many people know they live with it. Hypertension (HTN) is called the "silent killer" because it often has no warning signs or symptoms (Ostchega, Yoon, Huges, & Louis, 2008). Hypertension( HTN) is the most prevalent primary diagnosis reported in ambulatory care visits and its management accounts for 30% of office visits for individuals aged 45 to 65 years and more than 40% among those aged 64 and older (Cohen, 2009). In contrast, controlled blood pressure levels are associated with higher probability of survival rate until age 85 years and also increased longevity without co-morbidities (Ostchega et. al, 2008). However, despite advances in medical treatment and public campaigns to reduce the prevalence of hypertension, the disease remains a significant cause of health problems with huge health impacts mainly due to limited knowledge of risk factors related to the condition.

Interestingly, there is a growing body of evidence that shows a link between hypertension and vitamin D deficiency. It is important to understand this link and its potential impact on health in the context of current epidemiologic and demographics of HTN and to evaluate treatment plans using vitamin D supplement as an adjunct therapy for hypertension. Primary health care providers are in a key position to promote increased awareness of the relationship between hypertension and vitamin D, and the use of supplements in reduction of hypertension and consequent complications related to it.

Vitamin D deficiency has been found worldwide across all ages, races, geographic regions and socioeconomic status. In the past, vitamin D has been extensively studied in relation to its role to skeletal development and calcium homeostasis; however, recent studies show its association with hypertension and other diseases such as diabetes, obesity cardiovascular disease,

depression, certain types of cancers and immunologic disorders. The chronic disease burden and costs of health complications associated with hypertension, especially in the aging population are expected to increase dramatically in the coming decades worldwide. Considering that vitamin D deficiency is a modifiable nutritional risk factor that could help prevent chronic diseases, it is necessary to understand its role and relationship with hypertension in order to reduce the growing global health and socioeconomic burden. Understanding the scientific link between hypertension and vitamin D has strong potential public health implications. In particular, the role of vitamin D in reducing hypertension could help bring about possible new management strategies. Compared to the cost and side effects associated with other drugs in the management of hypertension, vitamin D is a therapeutic alternative with cost effectiveness, accessibility, minimal side effects and complications.

**Definition and Classification of Hypertension**

Hypertension is defined as persistent elevation of systolic blood pressure (SBP) of 140mmHg or greater and diastolic blood pressure (DBP) of 90 mmHg or higher or taking antihypertensive medication. The Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII) classifies normal blood pressure (BP) in adults as systolic BP < 120mmHg and diastolic BP < 80 mmHg. Pre-hypertension is defined as SBP from 120-130mmHg or DBP from 80-89 mmHg. Stage 1 hypertension (HTN) is SBP from 140-159 mmHg or DBP from 90-99 mmHg. Stage 2 hypertension is SBP of 160 mmHg or greater and DBP of 100 mmHg or greater. Diagnosis is based on average two or more properly measured seated blood pressure readings taken at two or more office visits after the initial screening, and the higher BP value is selected to classify the individual's blood pressure stage (Chobanian, Bakris, Black, et. al, 2003). Table 1 illustrates the JNCVII stages of hypertension.

Table 1: JNC VII Classification of Blood Pressure in Adults 18 Years and Older

| BP classification | SBP mmHg | DBP mmHg |
|---|---|---|
| Normal | < 120 | < 80 |
| Pre-hypertension | 120-139 | Or 80-89 |
| Stage 1 hypertension | 140-159 | Or 90-99 |
| Stage II hypertension | >160 | Or > 100 |

BP = Blood pressure, SBP = systolic blood pressure, DBP = diastolic blood pressure

Adapted from The JNC 7 Report: The seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure, by Chobanian et al., 2003, *JAMA*, *289*, 2560-2572.

Furthermore, hypertension is classified into two categories: essential also known as primary hypertension which accounts for approximately 90-95% of cases, with no identifiable etiology; and secondary hypertension which is the elevation of BP from identifiable causes that include increased catecholamine, increased renin secretion, and increased sodium and water retention, all of which contribute to increased blood pressure through different mechanisms (Uphold & Graham, 2003).

**Pathophysiology of Hypertension**

The cause or causes of essential hypertension are not fully known, but several risk factors are implicated as contributory to its development. Family history of hypertension, race, and age-related increase in blood pressure are among the non-modifiable risk factors, whereas obesity, high fat and sodium intake, large alcohol intake, sedentary life style, psychogenic stress and oral contraceptives are some of the modifiable risk factors (Uphold & Graham, 2003). In addition, vitamin D has been identified as another possible modifiable risk factor, with potential protective role on the cardiovascular system. Primary care providers working in close partnership with patients can play a great role educating them and promoting healthy life styles that reduce risk factors and their complications.

The most commonly known physiological cause of hypertension is increased peripheral vascular resistance. And because blood pressure equals total peripheral resistance times cardiac output, prolonged increase in cardiac output can cause elevation in blood pressure. Any factor that produces an alteration in peripheral vascular resistance, stroke volume or heart rate affects the systemic arterial blood pressure through four control mechanisms, namely: the arterial baroreceptor and chemoreceptor systems, regulation of body fluid volume, the rennin-angiotensin system and the vascular autoregulation. Increased blood volume and marked blood viscosity can increase arterial pressure. The renin-angiotensin system is the body's main regulator of electrolyte and volume homeostasis. Inappropriate increased activation of this system causes increased vasoconstriction and in response to this there is an increase in peripheral vascular resistance which results in elevation of blood pressure (Uphold & Graham, 2003).

**Overview of Vitamin D**

Vitamin D is found in two forms: vitamin $D_2$ (ergocalciferol) and vitamin $D_3$ (cholecalciferol). Vitamin $D_2$ is found in plants, is the product of ultraviolet B (UVB) irradiation of ergosterol and can be consumed as a supplement or in fortified foods. Vitamin $D_3$ is a product of UVB irradiation of 7-dehydrocholesterol and is synthesized in the human epidermis or consumed in the form of oily fish, fortified foods, or a supplement (Martini & Wood, 2006).

Vitamin D is converted in the liver to 25-hydroxyvitamin D {25(OH) D, the major circulating metabolite of vitamin D. In the kidney, 25(OH)D is converted by 1α-hydroxylase to its active form, 1, 25-dihydroxyvitamin D [1, $25(OH)_2$ D] which plays a vital role in maintaining bone and muscle health by regulating calcium metabolism. Although $1,25(OH)_2D$ is the active form of vitamin D, its serum level does not correlate with overall vitamin D status and thus is generally not clinically useful. To clinically assess vitamin D status, serum 25 (OH) D concentrations should be measured because it reflects both vitamin D intake and endogenous production of vitamin D. The half-life of vitamin D in the liver is approximately three weeks, which underscores the need for frequent replenishment of the body's supply (Kulie, Groff, Redmer, Hounshell & Schrager, 2009).

Vitamin D in the form of 1, 25 $(OH)_2$ D is considered a hormone, because it is produced primarily in one organ, the kidney, and then circulates throughout the body where it exerts wide-ranging effects. Vitamin D receptor (VDR) is present in most tissues including endothelium, vascular smooth muscle, and myocardium (Wang, et al., 2008). In addition, both vascular smooth muscle and endothelial cells have the ability to convert 25(OH) D to 1, 25$(OH)_2$ D. Circulatory 1, 25$(OH)_2$ D crossing the cell membrane and cytoplasm, reaching the nucleus where it binds to the VDR. The VDR-bound 1,25$(OH)_2$D in turn binds to the retinoic acid α-receptor and serves as a nuclear transcription factor, altering gene function and inducing protein synthesis. Directly or indirectly, 1,25$(OH)_2$D regulates over 200 genes, including those involved in renin production in the kidney, insulin production in the pancreas, release of cytokines from lymphocytes, production of cathelicidin in macrophages, growth and proliferation of both vascular smooth muscle cells and cardiomyocytes (Lee, O'Keefe, Bell, Hensrud & Holick, 2008). In light of its role and effect in several body tissues that involve major organs, such as kidney, pancreas and smooth muscle of cardiac system, it is vital to measure serum vitamin D levels.

A rapidly evolving body of knowledge indicates that vitamin D deficiency is much more prevalent than previously recognized and is present in up to 50% of young adults. The Third National Health and Nutrition Examination Survey (NHANES III) reported the prevalence of vitamin D deficiency in the U.S. to be between 25% and 57% of adults. The prevalence of vitamin D deficiency increases in proportion to distance from the equator because of increased atmospheric filtering of UVB radiation caused by the oblique angles of the sun's rays at higher latitudes. Additionally, ethnic groups with darker skin require proportionally more sun exposure to synthesize equivalent amounts of vitamin D compared with people with lighter skin coloration. Excessive sunlight exposure does not cause vitamin D toxicity because UVB converts excess vitamin $D_3$ to biologically inert isomers. However, excessive oral vitamin D intake can cause toxicity at very high doses, and at levels that exceed 200 nmol/L, toxicity is clearly seen with signs and symptoms of secondary hypercalcemia and present with weakness, lethargy, headaches, nausea, polyuria, ectopic calcification in tissues and possible mental status change at late stages (Moor & Kiebzak, 2007). According to the Institute of Medicine (2010)

intake of 4000 IU of vitamin D per day is established as a tolerable upper limit dose in adults age 13years and older; yet, this dose is considered to be low based on several recent studies which have shown that a healthy adult man and woman with limited sun exposure can take up to 10,000 IU/d of oral vitamin $D_3$ for 20 weeks without any adverse effects (Veith et al, 2001, Heaney, 2003).

In modern society most people produce less vitamin D cutaneously in part because of increasingly indoor lifestyles and efforts to minimize sun exposure by using sunscreens and other sun avoidance strategies. Sunscreen with a sun protection factor of 15 blocks approximately 99% of the cutaneous vitamin D production. Similarly increased skin pigmentation can reduce cutaneous vitamin D synthesis by about 99% which can explain the reason behind low vitamin D levels in dark skinned individuals. Additionally, obesity is associated with vitamin D deficiency, probably because of a decreased bioavailability of vitamin D that is sequestered in the fat of individuals with excess adipose tissue. Older age also reduces the capacity for UVB-induced cutaneous synthesis of vitamin D and lower levels of vitamin D have been associated with increased age regardless of seasonal variation. After equal doses of sunlight exposure, a 70-year-old person produces 75% less vitamin $D_3$ than a 20-year-old person. It is therefore no surprise that both blacks and the elderly have higher prevalence of vitamin D deficiency, hypertension and cardiovascular diseases. Other risk factors for vitamin D deficiency are listed in elderly, dark pigmented skin, institutionalized or homebound individuals, increased distance from equator, winter season, air pollution, cover-up clothing (for cultural or religious groups), malabsoroption, renal disease, liver disease and medications such as anticonvulsants, glucocorticoids, anti-rejection and human immunodeficiency virus medications (Lee, O'Keefe, Bell, Hensrud & Holick, 2008, Holick, 2006). These findings highly support the importance of screening for vitamin D levels in these high risk individuals

**Epidemiology of HTN and Vitamin D inadequacy and Significance of the Problem**

According to reports from the Center for Disease Control (Ostchega, et al., 2008), data from the National Health and Nutrition Examination Survey (2005-2006) shows that 29 % of all U.S. adults 18 years and older were hypertensive, and 28% had prehypertensive. Among

hypertensive adults only 78% were aware of their condition and only 64% of those with high blood pressure who took medication had their blood pressure controlled. The control rate was 46.6% among all hypertensive patients. Accordingly, over 50% of the hypertensive population remains at high risk of stroke, heart attack, heart failure and renal disease. Twenty eight percent of American adults, approximately over 50 million, have pre-hypertension which raises the risk of hypertension. In 1996 the estimated annual cost of hypertension and heart disease in the United States was 148 billion dollars (Ullah, Uwaifo, Nicholas & Koch, 2010). The cost of hypertension only is estimated at $70 billion per year and is greater than 400 billion when including coronary artery disease, cardiovascular disease, peripheral vascular disease, congestive heart failure and renal disease. Unfortunately, despite the efforts placed on education and control of the disease, 65% of the disease remains uncontrolled, thus not meeting the "Healthy people 2010" goal of blood pressure control of greater than 50%. Women are as likely as men to develop high blood pressure. However, for people under age 45 years, more men are affected than women whereas for people aged 65 years and older, more women are affected than men (Ostchega et. al, 2008). The estimated total economic burden of hypertension in the year 2010 was $ 76.6 billion (Germino, 2009), a rise from $ 73.4 billion estimated in 2009 (Cohen, 2009). Thus, increasing awareness of treatment and control of high blood pressure will reduce morbidity and mortality numbers in the population across all ages, gender, races and ethnicity.

Likewise, vitamin D insufficiency affects almost 50% of the population worldwide. In the U.S. more than 40% of men and 50% of women have low vitamin D levels (<30ng/ml). Low levels in adults are associated with coronary artery disease and heart failure. Furthermore, vitamin D deficiency was more common among racial or ethnic minorities, elderly individuals, women and people with hypertension, diabetes, hypertriglyceridemia and hypercholesterolemia (Martins et al, 2007, Fiscella & Franks, 2010, Vaysman, 2010). Compared to Caucasians, African Americans and non-White Hispanics have higher prevalence of hypertension and also lower levels of 25(OH) D possibly due to their dark skin pigmentation which prevents penetration of ultraviolet B radiation from the sun. Studies that examined the relationship between vitamin D and hypertension have identified that low levels of 25-hydroxyvitamin D, the

major circulating vitamin D metabolite, are associated with elevated blood pressure and related cardiovascular diseases (Schmitz et. al, 2009).

In light of many studies suggesting an inverse relationship between blood pressure and levels of circulating vitamin D, maintaining normal vitamin D levels could prevent hypertension and other cardiovascular diseases. The main source of vitamin D is from sun exposure, however, this is limited due to previously mentioned reasons, and vitamin D from dietary source is inadequate to maintain the desired level, thus, supplementation with vitamin D therapy is required to obtain optimal vitamin D levels. Given the low cost and minimal side effects associated with vitamin D supplements, supplementation with vitamin D to deficient individuals may help reduce the burden of the disease and subsequent risk of cardiovascular disease.

The question, however, is should vitamin D supplements be used as an adjunct for the treatment of hypertension? This scholarly project discusses the relationship between vitamin D deficiency and hypertension and examines the effect of vitamin D supplements on HTN. The next section reviews the literature on the relationship between HTN and vitamin D deficiency and the effect of supplements on blood pressure.

## Literature Review

Several studies have been conducted to investigate the relationship between hypertension and vitamin D deficiency, particularly to examine the effect of vitamin D supplements on blood pressure. Many of these studies show an inverse relationship between vitamin D levels and blood pressure. Interestingly, some studies showed no relationship between the two.

### Vitamin D status and blood pressure

Forman et al (2007) examined the independent association between plasma 25(OH) D levels and risk of incident hypertension in two prospective studies that include 613 men from the Health Professionals' Follow-up Study (HPFS, 1986) and 1198 women from the Nurses' Health Study (NHS, 1989) whose vitamin D levels were followed for four to eight years. After the follow up, the multivariable relative risk of incident hypertension was 6.13 in men and 2.67 in women when comparing those whose plasma 25 (OH) D levels were < 15ng/mL to those whose

levels were > 30ng/mL. These findings show an association between vitamin D deficiency and increased risk of hypertension; thus plasma 25(OH) D levels are inversely associated with risk of incident hypertension. The authors suggest this finding be tested on other cohorts and in randomized trials for further evaluation of the hypothesis. These findings could have a significant public health implication because increasing plasma 25(OH) D is a cost effective intervention which can be obtained from high dose supplemental therapy and increased sun exposure.

In another study, Martins et al (2007) examined the cross-sectional association between serum levels of 25(OH) D and selected cardiovascular risk factors in U.S. adults from a sample of 7186 male and 7902 female adults 20 years and older drawn from available data in the Third National Health and Nutrition Examination Survey (NHANES III, 1988-94). The mean 25 (OH) D level in the overall sample was 30ng/mL which is similar to the current recommendations for optimal vitamin D status. Mean serum 25 (OH) D levels were lower in women, elderly persons >60 years of age, racial/ethnic minorities, and individuals with obesity, hypertension and diabetes mellitus. This study found the adjusted prevalence of hypertension in adults in the U.S. was 30% higher in the lowest compared to the highest quartile of serum 25 (OH) D levels. Similarly, Scragg, Sowers and Bell (2007) report on the evaluation of a cross sectional relationship between serum 25 (OH) D values and blood pressure in the NHANES III (1988-94) a national representation of non-institutionalized population in the US. The analysis of 12,644 people aged 20 years and older, none of whom were on antihypertensive medication, showed a significant inverse association between vitamin D levels and blood pressure readings even when vitamin D was adjusted for age, gender, ethnicity, and physical activities. Furthermore, the study found that mean systolic blood pressure was 3.0 mmHg lower and diastolic BP was 1.6 mmHg lower in the highest quintile of vitamin D (serum 25(OH) D > 85.7nmol/L) status than on the lower quintile (serum 25(OH) D< 40nmol/L). The authors pointed out that even this small difference in systolic blood pressure can have important health implication because it has been estimated that a decrease of 2-3 mmHg in systolic blood pressure would be associated with 10-15% reduction in mortality rate related to cardiovascular disease.

In contrast, in a population based study of 1205 older men and women from the Longitudinal Aging Study Amsterdam, Snijder et al (2007) found blood pressure in the study participants was not significantly associated with serum 25(OH) D but higher parathyroid hormone (PTH) was significantly associated with higher systolic and diastolic blood pressure. In this group, 126 (10.5%) subjects have serum 25(OH) D levels of 25nmol/ L, 442 subjects (36.7%) have serum of 25 (OH) D levels of 25-50 nmol/L/, and the remaining subjects have serum 25 (OH) D levels >50 nmol/L. Since most subjects in the study had serum 25 (OH) D levels above 50 nmol/L, it is possible that 25(OH) D only affects blood pressure at lower level and the lack of association could be relatively due to high vitamin D level in majority of these subjects.

**Vitamin D supplementation and blood pressure**

A study conducted by Pfeiffer, Begerow, Minne, Nachtigall and Hansen (2001) to evaluate the effect of vitamin D supplement on blood pressure found a significant reduction in blood pressure with calcium and calcium plus vitamin D supplementation. In this double-blind, randomized, controlled trial evaluation of the impact of vitamin D supplement on blood pressure, Pfeiffer and colleagues (2001) enrolled 148 elderly women age 70 years or older with vitamin D deficiency, 25 (OH) D <25ng/ml and who were assigned to receive either calcium 1,200 mg or calcium 1,200mg plus vitamin D 800 IU daily. After eight weeks of treatment, both groups showed significant reductions in systolic and diastolic blood pressure reading which account for approximately 9.3% reduction in blood pressure. The study found the reduction in systolic blood pressure was 7.4 mmHg greater in the vitamin D plus calcium group than in the calcium only group and there was no significant difference in the diastolic blood pressure in both groups.

Interestingly, the results of another randomized double blind clinical trial conducted by Margolis et al (2008), showed no difference in blood pressure with supplemental calcium plus vitamin D and placebo. In the Women's Health Initiative Calcium/Vitamin D Trial (Margolis et al, 2008), 36282 postmenopausal women were randomly assigned in a double blind fashion to receive elemental calcium 1000mg and vitamin D3 400 IU daily or a placebo. After a follow up time of seven years the study found no significant decrease in the incidence of hypertension or

risk for developing hypertension. The authors state the lack of association in this population could be due to bias in results related to non-adherence with treatment. It was reported that only 60% of the participants consumed greater than 80% of treatment. In addition the dose of 400 IU of vitamin D used was low, as this was identified as inadequate in prevention of incidence of hip fracture and colorectal cancer. The authors concluded this study cannot be generalized to men or younger women as only postmenopausal women were included in the study.

Furthermore, Forman, Bischoff-Ferrari, Willett, Stampfer and Curhan (2005) studied the effect of vitamin D supplements on blood pressure and found no difference in blood pressure results based on variable vitamin D doses. The study examined the association between vitamin D intake and risk of incident hypertension of participants in three large cohort studies from Nurses' Health Study I (NHS I, 1977, women age 30-55years), Nurses' Health Study II (NHS II, 1989, women age 25-42 years) and Health Professionals' Follow-up Study (HPFS, 1986, men age 40-75years) followed up for eight and more years. The study found no association between amounts of daily supplemental vitamin D intake and incident hypertension when comparing participants who received greater than 1600 IU of vitamin D to those who received less than 400 IU and comparing those who received greater than 1000 IU of vitamin D to those who received below 200 IU of vitamin D. Thus there was no association between incidents of hypertension and taking minimal recommended doses or exceeding higher recommended doses.

**Vitamin D and Blood Pressure: Control mechanism**

As discussed above many of the studies and some clinical trials support the role of vitamin D in blood pressure regulation. Therefore it is vital to understand the mechanism by which the differences in levels of vitamin D affect blood pressure.

**Renin-angiotensin cascade and blood pressure regulation:**

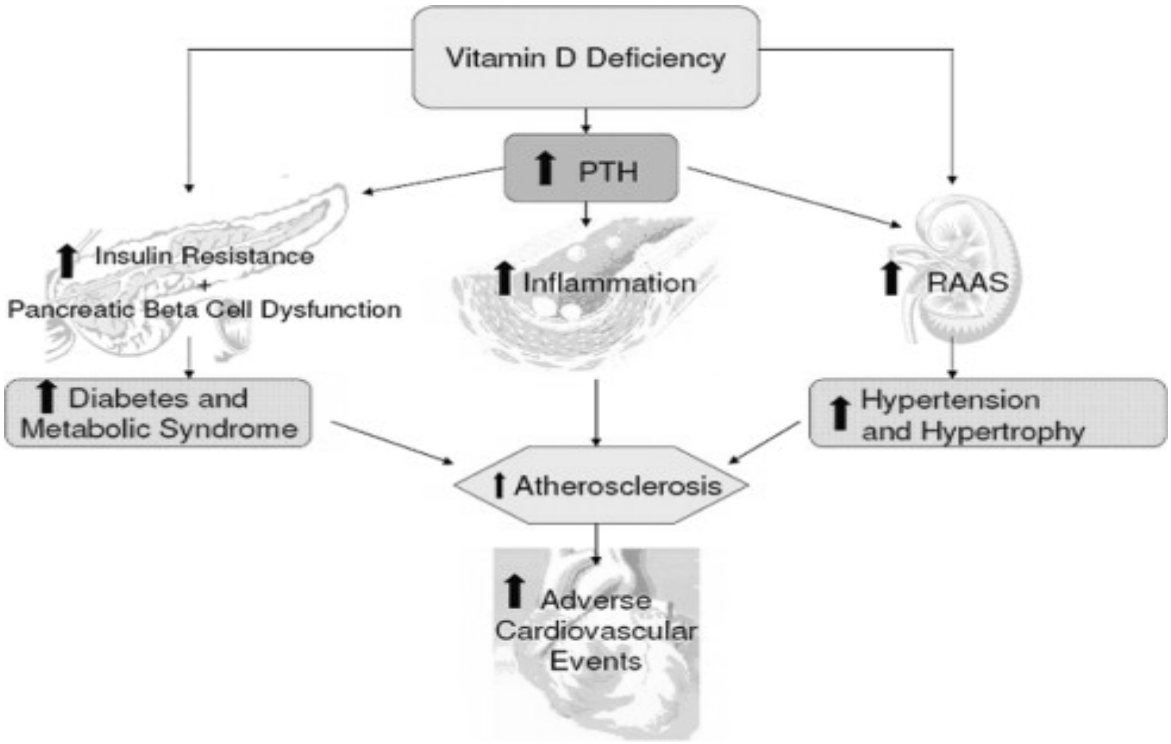
The renin-angiotensin-aldosterone system is the main regulator of electrolyte and volume homeostasis. Increased activation of this system may contribute to a major risk factor of hypertension, heart attack, and stoke. Evidence from several clinical studies shows an inverse relationship between circulating vitamin D levels, blood pressure and plasma renin activities;

however, the mechanism in this process is not understood. Renin is an enzyme synthesized and secreted by the juxtaglomerular cells of the kidney. Renin converts angiotensinogen into angiotensin I, and angiotensin I is converted to Angiotensin II by Angiotensin Converting Enzyme (ACE). The production of angiotensin II and aldosterone increases blood pressure directly by vasoconstriction and indirectly by salt and water retention and other mechanisms (Pilz, Tomaschitz, Ritz, & Pieber, 2009). Several animal studies have been conducted to support the hypothesis that vitamin D status may control blood pressure by regulating the renin-angiotensin system activities.

**Vitamin D and renin expression in BP regulation**

Li et al (2002) reported an inappropriate increase in the activations of the RAAS in Vitamin D receptor (VDR) and 1 alpha-hydroxylase receptors knockout mice. In this study it was observed that renin expression and plasma angiotensin II production were increased several fold in vitamin D receptor–null (VDR-null) mice, leading to hypertension, left ventricular hypertrophy and increased water intake. However, the salt- and volume-sensing mechanisms that control renin synthesis were still intact in the mutant mice. In wild-type mice, inhibition of 1, 25-dihydroxyvitamin $D_3$ [1, $25(OH)_2 D_3$] synthesis also led to an increase in renin expression, whereas $1,25(OH)_2D_3$ injection led to renin suppression. The findings of this study show vitamin D regulation of renin expression was independent of calcium metabolism and that 1, $25(OH)_2D_3$ markedly suppressed renin transcription by a VDR-mediated mechanism in cell cultures. Thus, 1, $25(OH)_2$ $D_3$ is a unique negative endocrine regulator of the renin-angiotensin system. Vitamin $D_3$ plays an apparent critical role in electrolytes, volume and blood pressure homeostasis and the idea of vitamin D suppressing renin expression and blood pressure suggests that vitamin D analogues could help prevent or could be used as an intervention to control hypertension. Since it is unclear what degree of vitamin D deficiency activates the renin-angiotensin system (RAS) and triggers an increased in blood pressure, it is essential to conduct studies to identify those levels. Figure 2 illustrates the relationship of vitamin D and cardiovascular disease.

Figure 2: Overview of vitamin D regulation and its association with cardiovascular disease




PTH= parathyroid hormone; RAAS = renin-angiotensin-aldosterone system

Adopted from "Vitamin D deficiency an important, common, and easily treatable cardiovascular risk factor" by Lee, J.H., O'Keefe, J.H., Bell, D., Hensrud, D.D., & Holick, M.F., 2008, *Journal of American College of Cardiology* , *52*(24), 1949-56.

In contrast to the action of vitamin D in the renin-angiotensin system and BP control by suppressing renin expression, the angiotensin converting enzyme inhibitor (ACEI) therapy used in treatment of hypertension, acts by inhibiting the conversion of angiotensin-I to angiotensin-II, thus helping to relax blood vessels and lower blood pressure. Less angiotensin-II means less aldosterone release, a decrease in sodium re-absorption and ultimately decreases in extra cellular fluid volume. All these responses contribute to lowering blood pressure. In a state of vitamin D deficiency there is increase in renin expression which ultimately increases angiotensin I and II, thus causing hypertension. However, adequately supplementing this deficiency to optimal level could result in renin suppression and ultimate reduction in blood pressure.

**Classification of Vitamin D Values**

Although a consensus regarding the optimal level of serum 25(OH) D is still debatable, the following values are currently the most used classification by many experts. As indicated in Table 2, levels of 25(OH) D >30ng/ml (>75nmol/l) is considered sufficient, levels of 25(OH) D 21-29ng/ml (50-75nmol/l) is insufficient and levels of 25(OH) D less than 20ng/ml (50nmol/l) is considered deficient and levels of greater than 150ng/ml to be toxic and severe deficiency as less or equal to 10ng/ml (Pilz, Tomaschitz, Ritz & Pieber, 2009). The Nichols Advantage Assay (chemiluminescence protein-binding assay) and the DiaSorin radioimmunoassay are the most commonly used assays to determine vitamin D status. Other clinical assays of 25(OH) D include the benchmark high-performance liquid chromatography assays and liquid chromatography mass spectroscopy assays. Variations between assays and laboratories even when the same assay is used have been a concern of reliability in evaluating serum 25(OH) D. However, monitoring of serum vitamin D levels in those at risk should not be deterred by controversies in assay variability and imprecise definitions of deficient and insufficient status (Holick, 2006).

Table 2: Recommended Vitamin D Serum Level Standards

| **Vitamin D levels** | **Ng/mL** | **Nmol/L** |
|---|---|---|
| Deficient | <20 | <50 |
| Insufficient | 21-29 | 50-75 |
| Sufficient | >/= 30 | >75 |
| Toxic | >150 | >375 |

**Treatment of Vitamin D Deficiency**

Treatment options to maintain optimal vitamin D value is based on lab results of serum 25(OH)D levels and classification of deficient and insufficient vitamin D status. However, there is a controversy regarding what the safe dose for vitamin D supplement is. Although sun exposure is the main source of vitamin D, vitamin D is also obtained from other natural dietary sources such as salmon, sardines, tuna, cod liver oil, shitake mushrooms and egg yolk, and

fortified foods including milk, yogurts, butter, orange juice, margarine, cheeses and cereals. Several food sources of vitamin D are listed in Table 3.

Table 3: Selected Food Sources of Vitamin D

| Food | IUs per serving* | Percent DV** |
|---|---|---|
| Cod liver oil, 1 tablespoon | 1,360 | 340 |
| Salmon (sockeye), cooked, 3 ounces | 447 | 112 |
| Mackerel, cooked, 3 ounces | 388 | 97 |
| Tuna fish, canned in water, drained, 3 ounces | 154 | 39 |
| Milk, nonfat, reduced fat, and whole, vitamin D-fortified, 1 cup | 115-124 | 29-31 |
| Orange juice fortified with vitamin D, 1 cup (check product labels, as amount of added vitamin D varies) | 100 | 25 |
| Yogurt, fortified with 20% of the DV for vitamin D, 6 ounces (more heavily fortified yogurts provide more of the DV) | 80 | 20 |
| Margarine, fortified, 1 tablespoon | 60 | 15 |
| Liver, beef, cooked, 3.5 ounces | 49 | 12 |
| Sardines, canned in oil, drained, 2 sardines | 46 | 12 |
| Egg, 1 large (vitamin D is found in yolk) | 41 | 10 |
| Ready-to-eat cereal, fortified with 10% of the DV for vitamin D, 0.75-1 cup (more heavily fortified cereals might provide more of the DV) | 40 | 10 |
| Cheese, Swiss, 1 ounce | 6 | 2 |

* IUs = International Units. ** DV = Daily Value. DVs were developed by the U.S. FDA to help consumers compare the nutrient contents among products within the context of a total daily diet.

Adopted from “Dietary supplement fact sheet: Vitamin D” *National Institute of Health, 2011.*

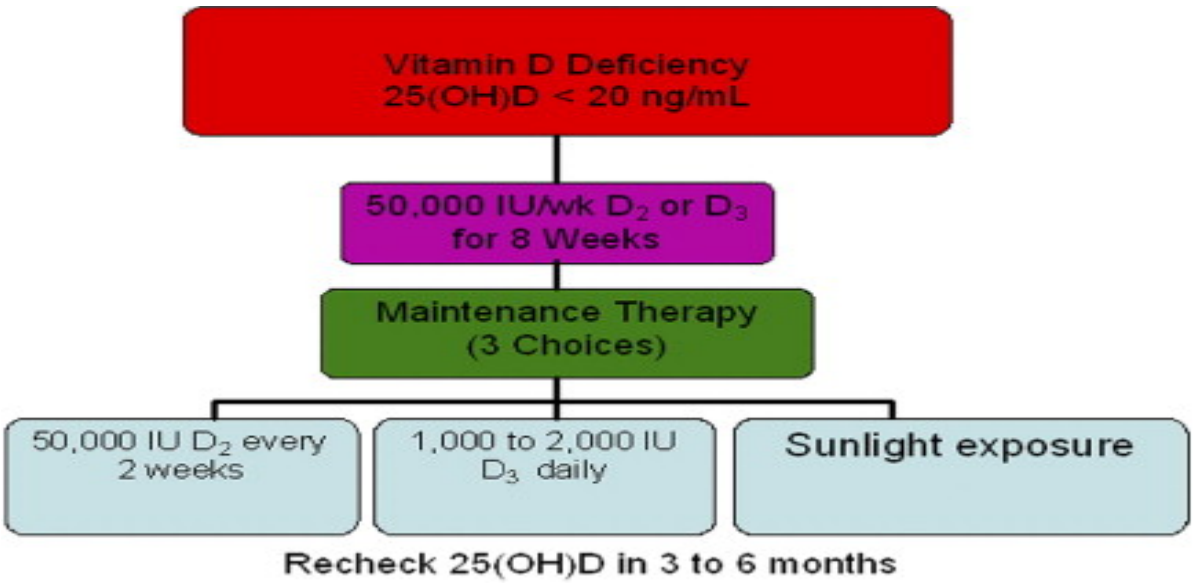
Over the counter multivitamin supplement contain 400 IU of vitamin D and over the counter vitamin $D_3$ are found in doses of 400, 800, 1000 and 2000 IU. Prescription supplementation choices include vitamin $D_2$ (ergocalciferol) in 50,000IU per capsule. It is estimated that supplemental intake of vitamin D 400 IU per day increases 25 (OH) D concentrations by only 2.8 -4.8 ng/mL (7-12nmol/L). To raise 25 (OH) D concentrations from 20–30ng/mL (50-80nmol/L), a daily intake of approximately 1700 IU is needed (Kulie, Groff, Redmer, Hounshell & Schrager, 2009).

There are varying recommendations about the correct dose of vitamin D intake, especially in view of concerns about vitamin D toxicity. According to the Institute of Medicine guidelines (2010) adequate of vitamin D in the U.S. and Canada is 600IU/day for children age one and above until adult age of 70 years, and 800 IU/day for people older than70 years and the upper limit for adults age 14years and above is 4000 IU/day. However, the U.S. Food and Drug Administration (FDA) recommended value of vitamin D is 400 IU/day regardless of age; this was considered a low intake because a dose of vitamin D up to 1000IU/day was suggested to maintain optimal 25(OH) D level of greater than 30ng/ml (75nmol/L), (Holick, 2006). There is no vitamin D toxicity from sun exposure; it is also unlikely that intakes of vitamin D from food would be high enough to cause toxicity. Toxicity is much more likely to occur from high intakes of dietary supplements containing vitamin D. No vitamin D toxicity was observed on clinical trials of vitamin D doses of up to 10,000 IU per day for up to five months. However, vitamin D toxicity and associated hypercalcemia which could cause reversible hypertension was seen when 25(OH) D levels are higher than 150ng/ml (Heanley et al 2003). In addition, given the concerns about skin cancer, many patients and clinicians are cautious in recommending sun exposure. Sun exposure to arms and legs for five to 30 minutes between hours of 10 am and 3 pm at least twice a week can be adequate to prevent vitamin D deficiency. Sun exposure of 10 minutes makes 15,000 IU of vitamin D, and individual with dark pigmentation require longer time to obtain similar effect (Kulie, Groff, Redmer, Hounshell & Schrager, 2009).

Treatment of vitamin D-deficiency should be initiated with 50,000 IU of vitamin $D_2$ or $D_3$ weekly for 8 to 12 weeks. After the initial loading dose, maintenance therapy can be continued in one of three ways: a) 50,000 IU vitamin $D_2$ or $D_3$ every two weeks; b) 1,000 to

2,000 IU vitamin $D_3$ daily; or c) sunlight exposure for five to 10 min for Caucasians (people with increased skin pigmentation require longer time) between 10 AM to 3 PM (spring, summer, and fall). The figure below illustrates the treatment plan for vitamin D therapy.

Figure 3: Vitamin D dosing to maintain adequate circulating serum vitamin D level




Adopted from Vitamin D deficiency an important, common, and easily treatable cardiovascular risk factor, by Lee, J.H., O'Keefe, J.H., Bell, D., Hensrud, D.D., & Holick, M.F., 2008, *Journal of American College of Cardiology, 52*(24), 1949-56.

Henley, Davis, Chen, Holick, and Barger-Lux (2003) conducted a study to establish the quantitative relation between steady state cholecalciferol input and the resulting serum 25-hydroxycholecalciferol concentration and to estimate the proportion of daily requirement during the winter season that will meet cholecalciferol reserves in body tissue reserve. The study included 67 men living in Omaha; with a mean baseline value of 70.3nmol/L, subjects were treated with cholecalciferol in controlled oral doses labeled at 0.25, 12.5, and 25.0 mcg (100, 500, and 1000 IU respectively) for approximately 20 weeks during the winter season. Results show that equilibrium concentration of serum 25 (OH) changed during winter months in direct proportion to the dose, with a slope of approximately 0.70nmol/L for each additional 1 mcg of

cholecalciferol consumption. The calculated oral intake required to sustain the serum 25-hydroxychocholecalciferol concentration present before the study (in autumn) was 12.5 mcg (500IU/d), whereas the total amount from all sources to sustain the starting level was estimated at approximately 96 mcg (3,800IU/d). Thus healthy men in this study seem to use 3,000-5,000 IU cholecalciferol to meet approximately 80% of their vitamin D need during the winter months as compared to the cutaneously synthesized levels attained from sunlight during the previous summer season. This study is an illustration that current recommendations of vitamin D intake are inadequate to maintain optimal serum 25 (OH) D concentrations in the absence of significant cutaneous production of vitamin D.

Similarly, Veith, Chan and MacFarlane (2001) assessed the efficacy and safety of prolonged vitamin D3 intake of 1000 and 4000 IU/d on 61 healthy men and women between January and February. Potential toxicity was monitored by measuring serum calcium concentration and by calculating urinary calcium/creatinine ratios. Participants' serum 25(OH) D at base line was 40.7+/-15.4nmol/L; at the end of 3 months of taking vitamin D supplements, serum 25(OH) D levels rose to 68.7+/-16.9nmol/L in the 1000IU/day group and 96.4+/-14.6nmol/L in the 4000IU/day group; with no significant change in serum calcium and urinary calcium excretion at either dose during the study. Thus, a dose of 4000 IU/d of vitamin D3 effectively and safely increased serum 25 (OH) D levels to high-normal in all adults and serum 25(OH) D was within the physiologic range, showing that vitamin D3 at 4000IU/d dose is a safe intake.

**Summary**

Based on the above literature review, it is clear there is an association between blood pressure and low vitamin D levels; however, whether the relationship is one of cause and effect is unclear. Therefore, understanding the mechanism by which vitamin D affects blood pressure is important in planning its use as an adjunct treatment for hypertension. Since the focus of this paper is on vitamin D supplement as another option for use as an adjunct therapy in the treatment plan, only a brief overview of hypertesion management needs to be mentioned. The standard treatment of HTN per JNC VII algorithm guidelines (see Appendix A) is to start with lifestyle modification, and add pharmacological therapy if the goal is not attained. The most commonly

used groups of antihypertensive drug therapies in the management of hypertension include angiotensin converting enzyme inhibitors (ACEI), diuretics, angiotensin receptor blockers (ARBs), beta blockers (BB) and calcium channel blockers (CCB). These drugs are either used as monotherapy or in combination, and choice of treatment regimen is individualized based on other co-morbid health problems.

Furthermore, in light of all the evidence that supports the relationship between vitamin D and hypertension and the effect of vitamin D supplement in reduction of blood pressure, it is evident that vitamin D supplements are appropriate for populations that are most vulnerable to vitamin D deficiency. In situations where screening is unavailable, supplementation with vitamin D 1000-2000 IU daily in the high risk population is safe and appropriate. Vitamin D supplements can be easily accessed without prescription as they are available over the counter, and toxicity at this dose is unlikely. Thus it is important to screen all high risk individuals for vitamin D levels annually and to treat them appropriately to maintain desired optimal vitamin D levels.

Studies investigating association of hypertension related to vitamin D recommend a desirable vitamin D level to be at least 30ng/mL for optimal health; however, there is no consensus on the cut-off vitamin D level, a situation which is a limiting factor for future studies. Depending on ethnic group and/or polymorphism in vitamin D receptors and their promoters which mediated vitamin D action, it is possible that each individual has a different cut-off. The degree at which vitamin D deficiency activates the renin-angiotensin system and triggers an increase in blood pressure is also unclear. Therefore, more systematic studies which incorporate genetic profiling of subjects with various levels of serum vitamin D are required to understand the most likely cutoff level that triggers clinical hypertension. The reviews of literature have confirmed the safety and efficacy of vitamin D and its importance in health maintenance. However, randomized clinical trials are recommended to evaluate the adequate dosing regimen of vitamin D that could be titrated to manage elevated blood pressure. Clinicians are encouraged to educate the public about the impact of vitamin D on hypertension and other chronic health problems, and promote a healthy life style through screening and appropriate intervention. The

next section will discuss the role of the nurse practitioner in the management of hypertension related to vitamin D deficiency.

**Should NPs and other Primary Care Providers do Routine Vitamin Screening?**

Health promotion and disease prevention is imbedded in the discipline of nursing and nurse practitioners (NPs), as primary care providers, are in the best position to implement this care model. As primary care providers, one of the roles of NPs is to provide primary prevention though counseling and education. Interventions include education on preventative care such as getting sun exposure at appropriate times for vitamin D synthesis, weight reduction and exercise, and healthy eating habits for cardiovascular health. Similarly, screening for vitamin D, as a secondary prevention, is important in the early detection and treatment of the deficiency which has been contributory to the elevation of blood pressure. Thus when nurse practitioners are evaluating patients for hypertension, it is necessary to screen them for vitamin D deficiency. Also, minimizing sun exposure is necessary for patients with the potential for skin cancer as well as those taking sun sensitive medications. Consequently education on alternative method of increasing vitamin D is needed. Dietary vitamin D intake may not be adequate to maintain optimal vitamin D levels, thus considering vitamin D supplements are safe and beneficial in the reduction of blood pressure and prevention of its complications. The main objective of these interventions is to prevent the progression of the disease; thus, routine screening can be very instrumental in prescribing an early treatment regimen to prevent complications.

Due to the increased evidence regarding an association between vitamin D deficiency and cardiovascular disease, it is sensible to screen and correct low vitamin D levels in high-risk patients such as those with resistant hypertension, nursing home residents, patients with osteoporosis, pregnant women, African Americans and other individuals with dark skin pigmentation, and women in some geographic/religious groups where covering the entire body with clothing is a custom. Screening for serum 25(OH) D in the above high risk population is most useful to identify deficiencies, plan treatment and monitor for vitamin D levels while patients are on vitamin D therapy (Holick, 2006). Vitamin D, 25(OH)D levels should be reassessed in three-six months after initiation of vitamin D supplementation, then annually, preferably at the end of the fall season to help reveal vitamin D deficiency. In patients with

increased sensitivity to vitamin D, such as those with sarcoidosis or tuberculosis, it is important to measure calcium levels in the initial phase of treatment. However, in cases where screening is not available supplemental vitamin D 1000-2000 IU daily in this population might be safe and appropriate (Ullah, Uwaifo, Nicholas and Koch, 2010).

## Patient Education on Management of Hypertension and Vitamin D Deficiency

Hypertension affects the whole body system including psychosocial and emotional, therefore treatment of hypertension should be holistic. Much of the success of the treatment for hypertension depends on the individual's adherence to treatment plan and this could cause additional stress to patients and their care givers. NPs can play a great role in assisting patients and their families manage their disease process and other stressors by providing education, information on community resources and referral to appropriate interdisciplinary team. These tools empower patients to have control over their care, consequently increasing compliance and their quality of life.

Patient education and communication are imperative to the treatment and management of hypertension and vitamin D deficient states. It is essential that healthcare providers are able to discuss the aspects of hypertension, vitamin D deficiency and vitamin D supplements. In addition, clear discussion on hypertension risk factors, complications as well as treatment and management are critical to ensure that patients are able to understand and follow the established plan of care. During each visit all providers have duties to actively listen to patient concerns, and to explain the importance of life style modification, compliance, monitoring of the condition and to encourage adherence with follow up visits. If the goal to control elevated blood pressure is not attained with life style modification and vitamin D supplement, pharmacotherapy with antihypertensive drugs should be initiated based on JNC VII recommendations, in conjunction with previous management plans. Collaborative work with the patient and promoting self management of care is the key to effective management of hypertension and maintenance of optimal vitamin D level.

Research that explores benefits of vitamin D supplementation on blood pressure is promising. More clinical studies are needed to discover vitamin D analogs with minimal calcemic potential and more effect on the RAS activity. This could open new possibilities for groups of therapeutic inhibitors of the renin-angiotensin system and the potential for new antihypertensive drugs that are cost effective and with minimal side effects or complications that can be used for hypertensive patients with or without vitamin D deficiency. Management of hypertension is a lifelong commitment. The goal in hypertension management is to control blood pressure and prevent target organ damage thus reducing mortality related to hypertension induced diseases such as stroke, congestive heart failure, nephropathy, peripheral artery disease and retinopathy.

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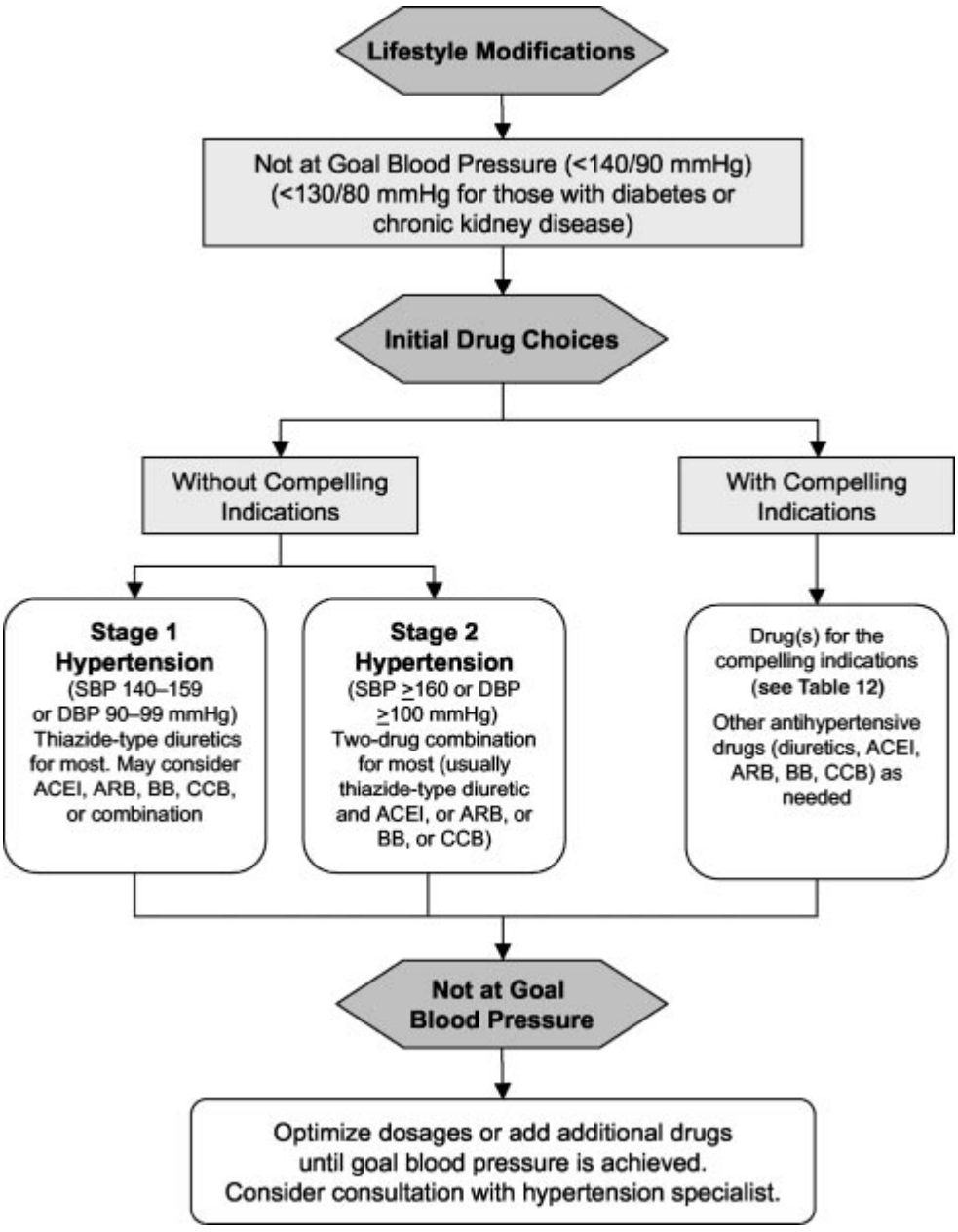
## Appendix A

JNC VII Algorithm for Treatment of Hypertension




ACEI= angiotensin converting enzyme inhibitor, ARB= angiotensin receptor blocker, BB= beta blocker and CCB= calcium channel blockers.

Adapted from The JNC 7 Report: The seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure, by Chobanian et. al., 2003, *JAMA*, *289*, 2560-2572.