

The thyroid hormone, parathyroid hormone and vitamin D associated hypertension

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ABSTRACT

Thyroid disorders and primary hyperparathyroidism have been known to be associated with increases in blood pressure. The hypertension related to hypothyroidism is a result of increased peripheral resistance, changes in renal hemodynamics, hormonal changes and obesity. Treatment of hypothyroidism with levo-thyroxine replacement causes a decrease in blood pressure and an overall decline in cardiovascular risk. High blood pressure has also been noted in patients with subclinical hypothyroidism. Hyperthyroidism, on the other hand, is associated with systolic hypertension resulting from an expansion of the circulating blood volume and increase in stroke volume. Increased serum calcium levels associated with a primary increase in parathyroid hormone levels have been also associated with high blood pressure recordings. The mechanism for this is not clear but the theories include an increase in the activity of the renin–angiotensin–aldosterone system and vasoconstriction. Treatment of primary hyperparathyroidism by surgery results in a decline in blood pressure and a decrease in the plasma renin activity. Finally, this review also looks at more recent evidence linking hypovitaminosis D with cardiovascular risk factors, particularly hypertension, and the postulated mechanisms linking the two.

Key words: Hypertension, hyperthyroidism, hypothyroidism, primary hyperparathyroidism, vitamin D

INTRODUCTION

Thyroid gland along with the parathyroid glands and heart share a close relationship arising in embryology. In ontogeny, the thyroid and heart migrate together. There is a strong physiological relationship between the two organs, which is affirmed by predictable changes in cardiovascular functions across the entire range of thyroid disease states.^[1] Many symptoms and signs recognized in patients with overt hyperthyroidism and hypothyroidism are due to increased or reduced action of thyroid hormone on the heart and the vascular system, respectively.

Increases in parathyroid hormone (PTH) have been

associated with changes in the vascular tone and renin angiotensin system. Hyperfunctioning parathyroid glandular disorders have been for long associated with an increased risk of hypertension, though a causal relationship is still not established.

Recent research has suggested a link between Vitamin D deficiency/insufficiency and a variety of chronic diseases including increase in cardiovascular disease and specifically in hypertension.

This review will focus on the association of hypertension with thyroid, parathyroid disorders and vitamin D deficiency/insufficiency and also look at the possible mechanisms linking these varied disorders to the development of hypertension.

CELLULAR MECHANISM OF THYROID HORMONE ACTION ON THE HEART

Most of the molecular and cellular mechanisms responsible for the cardiovascular effects of the thyroid hormone have

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been clarified. Thyroid hormone exerts both genomic and nongenomic effects on cardiac myocytes. Studies have confirmed T_3 as the active form of thyroid hormone that accounts for the vast majority of thyroid effects including stimulation of tissue thermogenesis, alterations in the expression of various cellular proteins and action on the heart and vascular smooth muscle cells.^[2,3] The process of the genomic effect of thyroid hormone begins with the entry of T_3 into the cardiomyocyte through specific transport proteins located within the cell membrane.^[4] Once inside the cardiomyocytes, T_3 enters the nucleus and interacts with specific transcriptional activators or repressors and transcriptionally regulates many cardiac proteins, out of which the best studied to date have been myosin heavy chain isoforms (alpha and beta). Changes in myosin heavy chain isoform expression occur in human atria in various diseases including congestive cardiac failure. The other protein whose expression is modulated at transcriptional level is the sarcoplasmic reticulum protein involved in the regulation of intracellular calcium handling, namely, calcium activated ATPase and its inhibitory cofactor phospholamban.^[5]

In addition to the well-characterized genomic effects of thyroid hormone, some cardiac responses appear to be mediated through nongenomic mechanisms.^[6] The significance of these diverse actions is yet to be established but may explain the ability of acute T_3 treatment to alter cardiovascular hemodynamics.

HYPOTHYROIDISM AND HYPERTENSION

Hypothyroidism is considered a disease that may alter blood pressure (BP) and has been recognized as a cause of secondary hypertension.^[7,8] The most common type of hypothyroidism is that caused by primary thyroid gland failure. In turn, chronic autoimmune lymphocytic thyroiditis is the most common cause of primary thyroid dysfunction. Replacement of deficient thyroid hormones reduces high BP and total cardiovascular risk.^[9] Some studies have indicated a high prevalence of systolic and diastolic hypertension in hypothyroidism,^[8,10-14] while other studies have reported no association of diastolic hypertension with hypothyroidism in geriatric patients in a primary care setting.^[15] Another study reported that diastolic BP correlated significantly with T_4 and T_3 levels in slightly hypothyroid females over 50 years of age.^[8]

Mechanisms of hypothyroid related hypertension

Increase in peripheral vascular resistance: Hypothyroidism and T_3 deficiency are associated with peripheral vasoconstriction and increased arterial stiffness.^[16,17] Arterial stiffness is an important determinant of arteriosclerosis and change

in arterial wall elasticity, and may occur before or during the early stages of atherosclerosis. This mechanism is probably not responsible for the increase in diastolic BP in hypothyroidism, but may be responsible for systolic hypertension.

Renal dysfunction and hemodynamic changes: Thyroid hormone insufficiency has been associated with deterioration of renal function which is attributed to the cardiovascular consequences of T_3 deficiency. Hypothyroidism results in reduced kidney to body weight ratio.^[18] Free water clearance and glomerular filtration rate (GFR) are reduced owing to a lowered cardiac output causing dilutional hyponatremia which is the most common electrolyte derangement in hypothyroid patients.^[19]

Hypothyroidism is a low renin hypertensive state.^[20] Renin release is minimal in the hypothyroid state because of a reduction in renal beta adrenergic activity.^[21] Hypothyroid patients have a volume-dependent, low plasma renin activity mechanism of BP elevation with an increased incidence of salt sensitivity. Oral sodium overload in these patients is followed by a volume-dependent increase in BP.^[22]

Hormonal changes: In the hypothyroid state, the density of α_1 adreno-receptors is increased but the density of beta adreno-receptors is reduced.^[23] This results in increased smooth muscle contraction causing vasoconstriction. Indirect measurements of sympathetic activity indicate that it is elevated in spite of clinical features like bradycardia suggesting that it is reduced. Plasma vasopressin levels are also elevated in the hypothyroid state, suggesting a possible role in sodium water retention. The discrepancy between vasopressin levels, serum sodium and osmolality may be the result of the lowered threshold of the hypothalamic osmoreceptors or a renal insensitivity to the hormone.^[24]

Obesity: This is another possible mechanism by which hypothyroid individuals exhibit an increase in BP. Hypothyroid individuals have been found to be significantly more overweight and obese than normal healthy volunteers and studies have reported that obesity is associated with increased 24-hour ambulatory BP values in children and adults.^[25,26]

Discussion

Large numbers of studies in the literature have reported a high prevalence of hypertension in hypothyroidism. Patients visiting a hypertension clinic for evaluation of high BP may benefit from the diagnosis of hypothyroidism as the majority of them would avoid antihypertensive therapy, as previously conducted studies have suggested replacement of deficient thyroid hormones reduces BP in

hypertensive subjects.^[9] Replacement of thyroid hormones would also reduce high cholesterol levels and consequently their total cardiovascular risk. Epidemiological community studies are needed to investigate the prevalence of thyroid disorders in large samples of hypertensive individuals and this can be best done by a single measure of thyroid stimulating hormone (TSH).

HYPERTHYROIDISM AND HYPERTENSION

Isolated systolic hypertension ($\geq 140 / < 90$ mm Hg) is the most common form of hypertension.^[27] The treatment of systolic blood pressure (SBP) has received increasing attention over the recent past because of its impact on the incidence of coronary artery disease, stroke and total mortality.^[28] Systolic arterial pressure is almost invariably increased and diastolic pressure decreased in subjects with overt hyperthyroidism, so that pulse pressure is characteristically wider and mean arterial pressure is only marginally decreased.^[29] An increase in diastolic BP is uncommon in hyperthyroidism because of reduction in systemic vascular resistance. It is estimated that the prevalence of hypertension with thyrotoxicosis is 20–30%;^[30] however, there are limited data to be certain that this statistic is accurate, since hypertension is a widely prevalent condition. Following treatment of the hyperthyroid state, SBP and cardiac output have been found to decline.^[31] There have been reports of a blunted nocturnal decline in BP in hyperthyroid patients, which in turn is associated with increased target organ damage and mortality.^[32,33]

In hyperthyroidism, T_3 dilates resistance arterioles, reducing systemic vascular resistance by 300–1000 dyne sec/cm^5 . This decline in systemic vascular resistance stimulates renin release and sodium reabsorption, resulting in an expansion of blood volume and an increase in venous return to the heart.^[34] Erythropoietin stimulation also contributes to the rise in blood volume. Heart rate and cardiac output increase significantly in the hyperthyroid state; the cardiac output may be up to 300% higher in patients with hyperthyroidism than in patients without this condition. The net effect of these hemodynamic changes is rise in SBP and widening of pulse pressure.^[30]

Mechanisms of hyperthyroid related hypertension

These mechanisms are mainly hormonal. Both renin and erythropoietin production is stimulated causing enlargement of blood volume. The levels of atrial natriuretic peptide, brain natriuretic peptide, endothelin-1 and adrenomedullin are increased while those of catecholamines are normal or decreased in hyperthyroidism.^[35,36]

Discussion

Hyperthyroidism is a common cause of isolated systolic hypertension. In hyperthyroidism, T_3 dilates resistance arterioles, reducing systemic vascular resistance, and increases cardiac output and pulse pressure. Hypertension appears to be more common in hyperthyroid patients. Treatment narrows the pulse pressure, decreases heart rate and reduces cardiac output.

SUBCLINICAL HYPOTHYROIDISM AND HYPERTENSION

Subclinical hypothyroidism (SH), defined by elevated serum TSH level in the presence of normal levels of free thyroid hormone, is common in the adult population, especially in women above 60 years of age. Majority of these patients have serum TSH levels ranging between 5 and 10 mIU/L and also have circulating thyroid autoantibodies.^[37] Various studies have suggested that subclinical abnormalities in TSH levels are associated with detrimental effects on the cardiovascular system.^[38] Subclinical forms of hypothyroidism are of increasing interest as they exhibit the same consequences as clinical hypothyroidism, although to a lesser extent.

In general, the resting heart rates are normal in SH subjects.^[39] However, significant hypofunctional abnormalities in the parasympathetic nervous system and an increased prevalence of systemic hypertension have been reported in patients with SH.^[40] A recent meta-analysis of six large studies investigating the prevalence of hypertension in patients with SH has revealed a sensitivity analysis showing a higher BP level in these patients compared with euthyroid subjects.^[41]

Hemodynamic changes in subjects with SH which contributes to hypertension include rise in peripheral resistance and endothelial dysfunction.^[42] Mild thyroid dysfunction is associated with impaired left ventricular (LV) function and LV systolic dysfunction.^[43] Acceleration of arterial stiffness has also been reported, while restoration to the euthyroid state has been found to decrease arterial thickness and improve prognosis.^[44] A rise in total cholesterol levels and increased carotid artery intimal medial thickness has also been reported in SH, both of which improve after normalization of TSH levels.^[45,46]

All these data suggest that SH may play a crucial role on the deterioration of the atherogenic profile and total cardiovascular risk, and may represent an independent risk factor for coronary artery disease.

SUBCLINICAL HYPERTHYROIDISM AND HYPERTENSION

Subclinical hyperthyroidism is characterized by subnormal thyrotropin (TSH) serum levels in the presence of circulating thyroid hormones in the normal range for the general population.^[47] It may be due to an intrinsic pathology of the thyroid gland (endogenous subclinical hyperthyroidism) or a consequent suppressive or replacement L-thyroxine therapy (exogenous subclinical hyperthyroidism).^[47] Exogenous subclinical hyperthyroidism is the condition more frequently seen in clinical practice.

A number of studies have investigated the effects of subclinical hyperthyroidism on the heart, showing that this condition may be associated with various abnormalities of cardiac structure and function. The cardiovascular disorders associated with subclinical hyperthyroidism may be a direct effect of thyroid hormone disturbance or may reflect an increased arterial pressure level in these patients. There are no consistent studies proving that arterial BP rises in such patients. Recent meta-analyses of five large studies evaluating the incidence of hypertension in these patients did not reveal increased BP levels in individuals with suppressed serum TSH levels and free thyroid hormones within the reference range.^[41]

The more consistent abnormalities found in patients with subclinical hyperthyroidism are increased heart rate, prevalence of supraventricular arrhythmias, endothelial dysfunction and increased LV mass.^[48,49] This enhancement of LV mass is often associated with rise in systolic function and impaired myocardial relaxation.^[49] The rise in LV mass is due to concentric remodeling and is related to the duration of subclinical hyperthyroidism rather than to levels of circulating thyroid hormones. Cardiac involvement in subclinical hyperthyroidism is reversible.

Compelling evidence indicated that subclinical hyperthyroidism is associated with increased cardiovascular mortality, and therefore the current opinion is to avoid or correct subclinical hyperthyroidism in all patients affected with benign thyroid disease.^[47,50]

VITAMIN D AND HYPERTENSION

Evidence accumulated in the last decades has suggested a relationship between sunlight exposure, vitamin D and BP. As ultraviolet irradiation is essential for the cutaneous synthesis of vitamin D, circulating 25-hydroxyvitamin D levels are greatly influenced by geographic location and seasonal changes. Incidence of hypertension in the general

population rises with the increase in latitude which in turn is associated with low UV irradiation levels.^[51] Dark skin pigmentation in the black population which affects an efficient UV light penetration has been associated with a higher BP.^[52]

Data from large epidemiological studies have also confirmed the association between vitamin D deficiency and hypertension.^[53,54] Numerous clinical studies have demonstrated clear cardiovascular benefits of vitamin D supplementation, including significant reduction in the risk of cardiovascular death in patients on hemodialysis.^[55,56] However, not all reported studies support a role of vitamin D in BP control.^[57]

Vitamin D regulation of the renin angiotensin system

The mechanism underlying the inverse relationship between 1,25-dihydroxy vitamin D and plasma renin activity was unclear until it was recently demonstrated that 1,25-dihydroxy vitamin D functions as a negative endocrine regulator of renin gene expression *in vivo*.^[58] Cyclic AMP is long known to be a major intracellular signal that stimulates renin production in the juxtaglomerular cells. Intracellular cAMP is thought to be critically involved in the stimulation of renin expression by sympathetic nerve activity or by low tubular sodium chloride concentration.^[59] It is hypothesized that by targeting the cAMP signaling pathway, 1,25-dihydroxy vitamin D may function as a gatekeeper to counterbalance the other renin stimulating factors and prevent the detrimental overproduction of renin. The finding that 1,25-dihydroxy vitamin D suppresses renin biosynthesis provides a molecular basis to explore the use of vitamin D analogues as renin synthesis inhibitors for therapeutic purposes. A few vitamin D analogues have been approved for clinical use; low calcemic vitamin D analogues that have potent vitamin D inhibiting activity are particularly valuable.^[60] Recent data have demonstrated that vitamin D analogues used in combination with classic renin angiotensin inhibitors can block the unwanted compensatory renin increase and thus increase the therapeutic efficacy of these drugs.^[61]

HYPERPARATHYROIDISM RELATED HYPERTENSION

Sporadic primary hyperparathyroidism (PHPT) is a disease characterized by persistent elevated levels of serum calcium attributable to an autonomous production of PTH from a diseased parathyroid gland. PHPT is associated with increased incidence of hypertension. In a number of recent studies, majority (ranging from 40 to 65%) of patients of PHPT have been reported to have high BP values. Lower prevalence of hypertension has been reported in Indian

series on primary hyperparathyroidism [Table 1].^[62-68] Elevated PTH levels have also been reported in patients with essential hypertension.^[69] Thus, the association of high concentration of PTH with hypertension need not imply a causal relationship as both conditions may coincide in patients older than 50 years. Consistent with the above observation is the fact that more than 50% of PHPT patients remain hypertensive in spite of successful parathyroidectomy.

Mechanism of hyperparathyroid hypertension

Multiple factors contribute to parathyroid hypertension though the exact mechanism is still not clear. Serum calcium and intracellular calcium are important components that determine vascular tone in smooth muscles. Patients with hypertension and PHPT have commonly been shown to have an increased total peripheral resistance.

The proposed factors which have been held responsible for producing hypertension in patients with PHPT include activation of the rennin–angiotensin–aldosterone axis which produces vasoconstriction.^[70] The evidence for the same comes from studies showing that administration of PTH in dogs led to an increase in plasma renin activity;^[70] plasma renin activity was found to be high in patients with PHPT and fell to normal after surgery; administration of PTH in normotensive healthy humans also resulted in rise of plasma renin activity.^[71] The second factor which may contribute to the rise in BP is the upregulation of the sympathetic nervous system as norepinephrine levels have been shown to be high in patients with PHPT.^[72] Alteration of arterial tone because of impaired endothelial vasodilatory function may also be a contributing factor.^[73] Hyperuricemia, which occurs with an increased frequency in hyperparathyroidism, may also lead to a rise in BP levels.^[74] Lastly, PHPT is known to cause renal damage and renal calculi, which has also been held responsible for hypertension.^[75]

Table 1: Prevalence of hypertension in patients with primary hyperparathyroidism in various different studies

Author and reference	No. of patients	Prevalence of hypertension (%)	Country
Feldstein <i>et al.</i> ^[62]	46	56.35	Argentina
Heylinger <i>et al.</i> ^[63]	292	50.35	USA
Letizia <i>et al.</i> ^[64]	53	47.2	Italy
Politz <i>et al.</i> ^[65]	150	62	USA
Tordjman <i>et al.</i> ^[66]	113	62	Israel
Bhansali <i>et al.</i> ^[67]	52	42	India
Gupta ^[68]	11	27.3	India

CONCLUSION

This review looks at the mechanisms of hypertension associated with common endocrine conditions which are not classically considered to be etiologies involved in the work up of a patient with suspected secondary hypertension. The causality of the disorder and the reversibility of elevated blood pressure are not as clear-cut and concrete as in a patient with a classical endocrine hypertension. But because these disorders are far more common, they should be routinely sought and a practicing endocrinologist needs to be aware of the underlying mechanisms for the hypertension to be able to manage these patients more scientifically.

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