

Incidence of Hypertension with Thyroid Disease

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Received: March 12, 2020; Published: May 29, 2020

Abstract

Thyroid disease increases cardiovascular risk, partly because it can be a secondary cause of hypertension. The pressure changes would be the result of the effects of thyroid hormone levels alterations in the cardiovascular system. In this review, we have described the relationship between thyroid disorders and hypertension and the studies that estimated the prevalence of hypertension related to thyroid disorders. We performed a literature search using PubMed database focusing, but not excluding, on the period 2010-2020. We observed that the prevalence of hypertension in thyroid disease in the reported studies ranged between 9-60%. Literature search indicated that hormonal changes in hypo- and hyperthyroidism can cause many hemodynamic alterations related to hypertension development. Subclinical forms are also causes of negative hemodynamic effects and increase cardiovascular risk. Since hypertension could be one of the first clinical manifestations of thyroid disorders it could be thought that thyroid disorders should be explored as potential cause of underlying secondary hypertension. Cardiovascular risk due to thyroid disorders is an important cause of morbidity and mortality and early diagnosis and treatment could be beneficial. Blood pressure is a non-invasive and economic parameter and it could be considered as an easy detection tool for subclinical forms of thyroid disease.

Keywords: Hypertension; Thyroid Disease; Cardiovascular Risk

Introduction

Hypertension is a world wide silent medical condition that affects more than 20% of the population. It is well known that long-term hypertension is associated with cardiovascular risk. Essential hypertension has no apparent cause and affects nearly 90% of the individuals with hypertension. Patients with secondary hypertension present with blood pressure elevation because of an underlying cause. These patients represent around 5 to 10% of the subjects with hypertension [1]. It has been reported that 30% of individuals with secondary hypertension are 18 to 40 years old [1,2]. Consequently, it has been proposed that patients that present with possible causes of secondary hypertension such as young age or similar suggestive history, should be further studied [2].

Some of the known secondary causes of hypertension include thyroid disorders. Notably, hypertension has been related to subclinical thyroid disease and possibly being one of the first manifestations of the disease, preceding other symptoms [3]. Thyroid disorders are highly frequent and affect 9 to 15% of women. Hypothyroidism affects nearly 5% of the population, while the subclinical form can be detected in 7.5% [4]. On the other hand, hyperthyroidism is present in 2% of the population with a female predominance, and subclinical hyperthyroidism prevalence can reach 6% in individuals over 65 years old [5].

Both, hypo- and hyperthyroidism, increase cardiovascular risk and several reports have shown that both diseases cause blood pressure elevation. The pressure changes would be the result of the effects of thyroid hormone levels alterations in the cardiovascular system [6]. In hyperthyroidism, cardiac output, pulse amplitude and heart rate are increased. An elevation of hormonal and growth factors such

as atrial natriuretic peptide and erythropoietin also occurs [5]. Thyroxine affects the contractility of the vascular smooth muscle and arterial stiffness is also observed [7].

In hypothyroidism, mild hypertension, a narrowed pulse pressure and bradycardia are usually observed [5]. The cardiac output decreases around 40% together with lower ventricular filling and cardiac contractility; which relate to the observed increased diastolic blood pressure [6].

Although several findings have shown that hypertension can be caused by thyroid diseases, some results were controversial. Furthermore, it is unclear how relevant thyroid diseases are a cause of secondary hypertension. Some reports state that it is a rare cause [1], while others would indicate a prevalence of hypertension with thyroid disorders of up to 50% [8]. In this review we will describe the relationship between overt and subclinical thyroid disorders and hypertension. We will also describe the studies that have been performed till date in order to establish this relationship and to determine the prevalence of hypertension with thyroid disorders.

Methods

A literature search has been performed using PubMed database by using the keywords “thyroid disorders”, “hypothyroidism”, “hyperthyroidism”, and “hypertension”. Articles were chosen mainly from the period 2010-2020, unless previous studies were relevant.

Physiopathology of the hypertension in patients with thyroid disorders

In physiological conditions, the thyroid gland secretes mainly thyroxine (T4) and less of triiodothyronine (T3). T4 is mostly transformed into T3 in the liver, kidneys and skeletal muscle. Thyrotropin (TSH) is synthesized by the hypophysis, and its serum levels depend on the negative feedback from serum free T4 and free T3 levels [9]. Genomic and non-genomic effects of T3 on vascular and cardiac smooth muscle are responsible for multiple functions of the heart and the cardiovascular system.

T3 would enter the cardiac myocyte to affect gene expression through its nuclear receptors [10]. Thus, increased levels of T3 have been related to contractility and diastolic function enhancement along with a lower vascular resistance [9]. Some of the T3-enhanced cardiac genes include the fast isoform of the myosin heavy chain, β 1-adrenergic receptor, sarcoplasmic reticulum calcium-activated ATPase (SERCA2) which cause systolic and diastolic left ventricular function enhancement. On the other hand, when thyroid hormone decreases, gene expression changes and slow isoform of myosin heavy chain is expressed while SERCA2 expression decreases, impairing cardiac function [11]. Previous studies indicate that these changes relate to the clinical manifestations present in overt and subclinical, hyper- and hypothyroidism [12,13].

Hypertension in thyroid disorders relates to many alterations in cardiovascular system, including vascular, volume, hormonal, and renal changes. In hypothyroidism, the vasodilator effect of T3 on vascular myocytes is lost resulting in vasoconstriction and a consequent higher peripheral vascular resistance [14]. Moreover, arterial stiffness reported in hypothyroidism also contributes to hypertension and atherosclerosis [15]. Fortunately, hormonal therapy can reverse arterial stiffness if adequately managed. Studies performed in hypothyroid patients indicated that they had a higher artery wall thickness than euthyroid patients, which was restored after hormonal replacement [16].

Hypertension occurs with hyper-contractility and vasodilation difficulty. Some studies indicated that T3 has vasodilatory actions, and the authors observed that, in aortas from hypertensive rats, T3 treatment was able to reduce hyper-contractility and improved vasodilation affecting vascular tone directly [17]. Another study revealed that thyroid hormones might regulate tissue renin-angiotensin system in the arterial wall and vascular smooth muscle, which has been implicated in hypertension pathogenesis [18].

The renin-angiotensin-aldosterone system (RAAS) is essential for arterial blood pressure homeostasis. In hypothyroidism, renin is low due to renal β -adrenergic activity which favors a hypertensive state and water and sodium retention [19]. Vasopressin levels would also be involved in water retention as it was found that plasma levels increase in hypothyroidism [20].

In hypothyroidism, a vascular α -adrenergic activation occurs that causes smooth muscle contraction, vasoconstriction, low cardiac output, and renin secretion resulting in tachycardia response in order to regulate consequent blood pressure increase [8]. It has been found that thyroidectomised normotensive patients increased their blood pressure after suspension of hormonal therapy in correlation with increased levels of adrenaline and noradrenaline, aldosterone and cortisol suggesting that adrenal stimulation could contribute to hypertension [21].

A state of renal dysfunction occurs in hypothyroidism that leads to weakening of renal function by lowering glomerular filtration rate. Lowered cardiac output reduces renal function and there is water retention [22]. Hormonal replacement also prevents renal disease progression [22].

Hypothyroid patients can develop atherosclerosis because of different pathophysiological mechanisms that lead to hyperlipidemia, hypercoagulability, endothelial dysfunction, arterial stiffness and consequent hypertension [23]. Hypercholesterolemia is most frequent, and appears as a consequence of a decreased LDL-cholesterol catabolism in liver. It has been proposed that thyroid hormones enhancement on cardiovascular risk would implicate their role as lipid metabolism and blood pressure regulators [24].

Hypothyroidism causes endothelial dysfunction partly by altering local vasodilatory factors. Nitric oxide's (NO), a vasodilatory molecule, production is decreased [25]. It has been demonstrated that a specific inhibitor of vasodilatory action of NO was not able to exert its effect in hypothyroid patients with respect to euthyroid patients [25]. Also, it was reported that T3 can induce ADPribosylcyclase, promoting Ca²⁺ release and subsequent vascular smooth muscle contractility [26].

There are less reports regarding the mechanisms involved in cardiovascular risk in subclinical hypothyroidism [3]. Some studies indicate that there is a predisposition to endothelial dysfunction, dyslipidemia, and inflammation, all related to hypertension surge [27]. It has been proposed that TSH increase might cause the endothelial dysfunction by acting on extra TSH receptor [28] or possibly by a direct action on its receptor to stimulate angiogenesis [29], both effects related to atherosclerosis. A report showed that brain natriuretic peptide induced secretion was mediated by TSH [30]. Arterial stiffness was also observed in 83 patients with subclinical hypothyroidism [31].

In hyperthyroidism, T3 reduces systemic vascular resistance by dilating arterioles, which stimulates renin secretion with concomitant sodium reabsorption and blood volume increase [32]. Heart rate and cardiac output rise and blood pressure elevates. Many hormonal blood pressure regulators are altered such as atrial natriuretic peptide, brain natriuretic peptide, endothelin-1 and adrenomedullin [33].

Thyroid hormone stimulates renin release and liver angiotensinogen synthesis. These effects are exacerbated in hyperthyroidism and lead to plasma volume expansion and the subsequent hypertension [34]. Natriuretic peptides alterations also relate to hypertension and cardiac changes [35]. High T3 levels and cardiac overload, both present in hyperthyroidism, stimulate atrial natriuretic peptide expression. Endothelin-1 is a strong vasoconstrictor produced by endothelial cells that affects vascular smooth muscle cells. Endothelin-1 plasma levels were shown to be increased in hyperthyroidism and some reports might indicate a possible involvement in hypertension, but this point still remains unclear [36]. On the contrary, adrenomedullin is a strong vasodilator also synthesized by endothelial cells from vessels that acts on smooth muscle cells. Its circulating levels are elevated in hyperthyroidism and have been correlated to the blood pressure decrease that can be observed in the hypotensive state in thyrotoxicosis [37].

Hypertension and overt hypothyroidism

Hypothyroidism is characterized by presenting with elevated levels of TSH and decreased levels of free T4 and free T3 levels. Currently, autoimmune thyroid disease is the most commonly recognized cause of hypothyroidism [38]. Another relatively frequent cause of hypothyroidism is iatrogenic hypothyroidism which results from thyroidectomy or thyroid gland radiotherapy because of thyroid cancer.

The typical symptoms of hypothyroidism are bradycardia, diastolic hypertension, and narrowed pulse pressure, among others. Overt hypothyroidism has been associated with coronary heart disease, presenting higher incidence of atherosclerosis, increased cholesterol levels, and hypertension [39].

Evidence regarding the association between hypothyroidism and hypertension is growing. Hypertension caused by hypothyroidism is reversible once hormone replacement therapy is established but with age it increases, and then additional therapy to control blood pressure might be needed [40]. A study showed that approximately 50% of hypertensive patients with hypothyroidism were able to reduce blood pressure after hormonal therapy [40]. Previous studies showed that thyroidectomised normotensive patients with suspension of hormonal therapy presented with higher systolic and diastolic blood pressure, while therapy restitution was able to decrease blood pressure [21]. On the other hand, Kotsis, *et al.* [41] found consistent results between hypothyroid patients and euthyroid healthy volunteers. Saito, *et al.* [42] reported that hypothyroid patients over 50 years old have a higher prevalence of hypertension, and in consistency with other studies, hormone therapy was able to normalize blood pressure. New studies are assessing masked hypertension (hypertension during office hours), which also leads to cardiovascular risk. Findings show that hypothyroid patients also show a higher prevalence of masked hypertension respect to euthyroid patients [43]. However, some findings contradict these results, like the studies carried out by Bergus, *et al* [44,45].

Hypertension and subclinical hypothyroidism

It has been proposed that subclinical hypothyroidism could also be a risk factor for cardiovascular disease [46]. Subclinical hypothyroidism is characterized by showing TSH above the upper reference limit, with normal free thyroxine and free triiodothyronine levels. This form of thyroid disorder affects 4 to 10% of the population, and the prevalence increases with the age [8]. New evidence suggests that subclinical hypothyroidism would lead to hypertension and cardiovascular risk [5]. However, in a review by Manolis, *et al.* [3], no significant association between hypertension and subclinical hypothyroidism was found.

Clinical trials have shown that subclinical hypothyroidism can increase diastolic blood pressure in correlation with TSH increase within the reference range [47]. A large scale study performed in adolescents and children also indicated an association between TSH levels and blood pressure, but the authors did not review its hypertension correlation [48]. However, another population study that recruited 30,000 patients found that TSH levels (within the reference range) were correlated with blood pressure and hypertension [47],

while in a report in an adult population the latter correlation has also been detected, but mainly in the female population [47]. Many recent studies have been summarized to study the effect of hormonal replacement therapy in hypertension in subclinical hypothyroid patients [49]. The results from over 25 clinical trials and prospective studies indicated that hormone therapy was able to reduce blood pressure in a significant manner.

New studies are relating subclinical hypothyroidism with hypertension in pregnancy. A study case report indicated that a female subject 25 years old showed hypertension during her pregnancy. Further analysis indicated that the patient presented with subclinical hypothyroidism and treatment with levothyroxine normalized her blood pressure [50]. The prevalence of subclinical hypothyroidism in

pregnant women is 2% and the disorder can be asymptomatic. In fact, hypertension in pregnancy is not usually explored as a possible cause of another disease, including thyroid disorder. According to previous studies, hypertension prevalence in pregnancy increases in the presence of subclinical hypothyroidism [51]. In contrast, a systematic review that gathered data from almost 4,000 pregnant women indicated that pregnancy with subclinical hypothyroidism revealed a worse pregnancy outcome but not gestational hypertension; while supplementation with levothyroxine did not show any significant improvement in such patients [52].

Hypertension in overt hyperthyroidism

Hyperthyroidism is characterized by exposure to exogenous or endogenous increased levels of T3. Primary causes of hyperthyroidism are autoimmune Grave's disease, goiter and thyroid cancer. T3 excess causes hemodynamic changes such as ventricular contractility, systemic vascular resistance increase, and elevation of cardiac output [5]. Hyperthyroidism is associated with decreased systemic vascular resistance and lower blood pressure, but in some patients hypertension is observed because of the presence of increased cardiac output [5].

Cardiovascular risk is significantly higher in hyperthyroid patients with both increased morbidity and mortality [53]. Additionally, pulmonary hypertension (increased pulmonary artery pressure) is a common and serious complication of hyperthyroidism that can be fatal [54]. According to a previous report, the prevalence of pulmonary hypertension in untreated hyperthyroid patients was 41%, but it was avoided with hormonal therapy [55]. The mechanism laying behind pulmonary hypertension in hyperthyroidism is still unknown.

Hypertension and subclinical hyperthyroidism

Subclinical hyperthyroidism takes place when TSH reaches the lower reference limit and free T4 and free T3 are still within their reference range. When the subclinical form of hyperthyroidism is sustained for long term, cardiovascular system is altered [5]: systolic function is enhanced, diastolic function is impaired, arrhythmias appear, and heart rate increases [56]. Many studies have well established correlation between subclinical hyperthyroidism and cardiovascular risk [7]. However, it still remains unclear whether subclinical hyperthyroidism is in fact related to hypertension, since prospective cohort studies have not shown such association [57].

Prevalence of hypertension with thyroid disorders

To our knowledge, no recent large scale studies have been performed to evaluate the prevalence of thyroid disorders in hypertensive patients [8].

An early study showed that hypertension was present in 1,061 individuals, patients with hypothyroidism showed a hypertension incidence that ranged from 9 to 60% increasing with age, while controlled hypertension incidence ranged from 3 to 33%, also increasing with the age [58]. Another study performed in 1988 indicated that 40% of patients with induced hypothyroidism after radio-iodine ablative therapy developed an increase in blood pressure, while hormonal restoration was able to reduce blood pressure in most cases [59]. Interestingly, the authors showed that the study of 688 hypertensive patients revealed that 3.6% presented with hypothyroidism, and hormonal therapy was able to restore blood pressure in 32% of them [59].

Up till present date, some reports have shown the percentage of patients with thyroid disease that presented with hypertension. Luboshitzky, et al. studied middle aged women with diagnosis of subclinical hypothyroidism and reported in 2002 that 20% of patients exhibited hypertension along with other cardiovascular risk alterations [60]. Denizeria, et al. [61] studied the records of 213 patients (199 female patients and 14 male patients) under thyroid medications in an Istanbul clinic and found consistent results, since 21% of these patients presented with hypertension. These authors proposed a possible relation between hypothyroidism caused by autoimmunity and hypertension. Furthermore, according to Kotsis, et al. [41], 20.2% of patients with hypothyroidism presented with hypertension.

In a pilot study performed by Piantanida, et al. [43] 64 newly diagnosed hypothyroid patients (38 were subclinical and 26 overt) were enrolled. Blood pressure was measured and masked hypertension was assessed. The results indicated a higher prevalence of masked hypertension in subclinical hypothyroid patients (26%) and in overt hypothyroid patients (15%), while true hypertension was more frequent in both groups (10-11%) with respect to controls (8 - 9%). A cross-sectional observational study reported the prevalence of hypothyroidism in patients with hypertension in 29 sites in India [62]. Out of 1,508 patients with hypothyroidism, 501 were hypertensive with a hypertension prevalence of 33%. Similarly, hypothyroidism prevalence in hypertensive patients (1,000 individuals) was 31%. In contrast, 61% of patients with subclinical hypothyroidism showed hypertension.

According to Dey, et al. [63] out of 25 subclinical hypothyroid patients of 20 to 30 years old, 20% showed hypertension along with other cardiovascular risks like dyslipidemia (92%) and obesity (24%).

Regarding hyperthyroidism, previous studies confirmed that hyperthyroid patients show higher prevalence of hypertension than euthyroid ones and that blood pressure increases with age with respect to euthyroid patients [64]. Estimated prevalence of hypertension with hyperthyroidism is 20 to 30% [32]. An early study indicated that the prevalence of hypertension in hyperthyroid patients was 26%, and another report found that untreated patients showed higher prevalence of hypertension [65].

Conclusion

In hyperthyroidism, the reported prevalence of hypertension was 26%. Regarding hypothyroidism, most studies agreed that the prevalence was around 20%. When overt and subclinical hypothyroidism were compared, the prevalence of hypertension among patients with subclinical hypothyroidism appeared to be higher (Table 1). Although the results of these prevalence studies are variable, it should be noticed that thyroid disorders are highly prevalent and a significant proportion of these patients present with hypertension, suggesting that controlling and treating this manifestation is highly relevant. Especially considering the role of hypertension in cardiovascular diseases and that cardiovascular risk due to thyroid disorders is an important cause of morbidity and mortality.

	n	Thyroid disorder studied	Hypertension prevalence
Hurxthal, et al. 1931	458	Hyperthyroidism	26%
Endo., et al. 1979	1,061	Hypothyroidism	9-60%
Streeten., et al. 1988	40	Hypothyroidism	40%
Luboshitzky, et al. 2002	57	Middle aged women with hypothyroidism	20%
Kotsis., et al. 2007	100	Hypothyroidism	20%
Denizeria., et al. 2014	213	Thyroid disorders	21%
Piantanida., et al. 2016	64	Overt and subclinical hypothyroidism	15% and 26% respectively
Talwalkar., et al. 2019	1,508	Overt and subclinical hypothyroidism	33% and 61% respectively
Dey., et al. 2019	25	Subclinical hypothyroidism	20%

Table 1: Prevalence of hypertension in thyroid disorders in different studies performed up to the date.

Considering the high prevalence of hypertension in the population with thyroid disorders, a need for consensus about early diagnosis and treatment to reduce cardiovascular risk remains unresolved. Blood pressure is a non-invasive and economic parameter and it could be considered as an easy detection tool for subclinical forms of thyroid disease.

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Volume 7 Issue 6 June 2020

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