COMMENTARY

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Thyroid hormones regulate both cardiovascular and renal mechanisms underlying hypertension

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Physiologically, thyroid hormones are able to affect the fundamental determinants of blood pressure (BP): cardiac output, peripheral vascular resistance, and kidney function (Figure 1). The thyroid-mediated fine orchestration of cardiac contractility, vascular tone, and renal homeostasis confers to the thyroid gland a key role in the pathophysiology of hypertension. Indeed, BP is altered across the entire spectrum of thyroid diseases.[1] However, the effects of thyroid disorders on BP are very intricate, mirroring the multifactorial and disparate actions of thyroid hormones on cardiovascular system and metabolism. In fact, if on one hand thyroid hormones increase contractility, tachycardia, and basal metabolic rate, which are positive regulators of BP, on the other hand they are able to decrease systemic vascular resistance, thereby lowering BP. Ergo, the balance between these opposite actions is eventually able to achieve an optimal regulation of BP, and modifications in thyroid hormones availability, both hypo- and hyperthyroidism, can alter this fine equilibrium. A wide and consistent literature is available on the association between thyroid disorders and hypertension.[2] However, only few studies have explored the relationship between BP and thyroid hormones in healthy subjects, in order to understand whether different levels of thyroid hormones, within a physiological range, can reflect changes in BP. In this context, in the current issue of the Journal, Jamal and colleagues offer their elegant investigation conducted on 691 healthy subjects.[3] The authors elegantly show that in a physiological context, augmented serum levels of triiodothyronine (T3) and thyroxine (T4) are associated with an increase of both peripheral and central BP. A strength of the study is denoted by the choice to measure central BP, which is suggested to be a more reliable prognostic marker in cardiovascular disorder compared to conventional brachial cuff BP.[4] The authors open the scenario for a potential role of serum level of thyroid hormones as predictor of central BP, and therefore a powerful prognostic factor of hypertension and cardiovascular complications. Of course, further studies are needed to verify and better understand the proposed relationship, even to enlarge the sample population. Moreover, in future studies it could be interesting to perform a time-course assessment of thyroid hormones levels (which usually oscillate in the same subject) evaluating their effects on BP variation. Indeed, a circadian rhythm has been demonstrated for triiodothyronine (T3), with a periodicity that lags behind thyroid-stimulating

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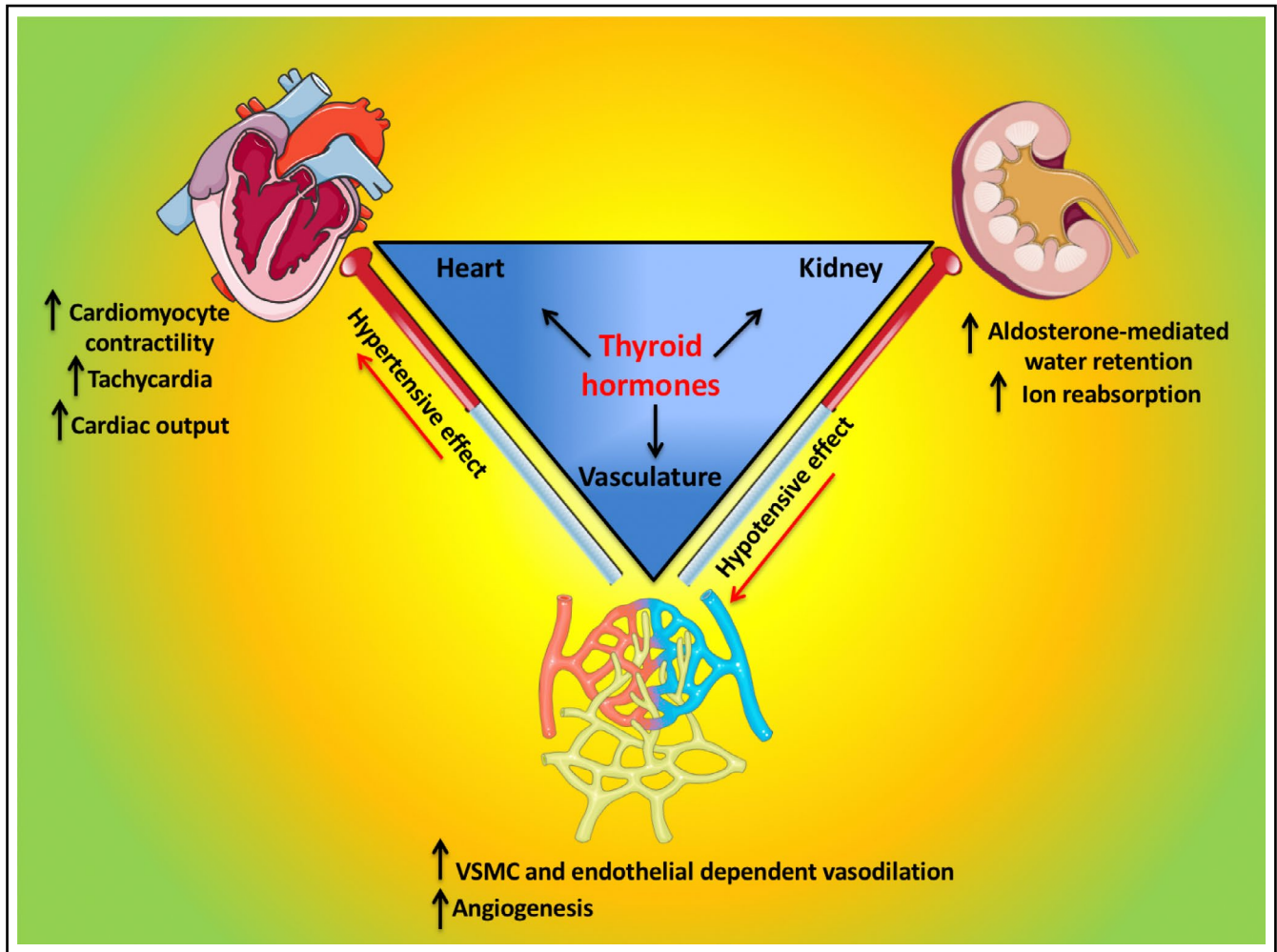
FIGURE 1 Effects of thyroid hormones on blood pressure mediated by their actions on the heart, the kidney, and the vasculature. VSMC, vascular smooth muscle cell [Color figure can be viewed at wileyonlinelibrary.com]

hormone (TSH).[5,6] Another aspect that needs to be further examined is the potential role of the effects of T3 and T4 on the intricate interaction between cardiovascular and renal systems.[7–9] To better characterize the complex context in which the study performed by Jamal and colleagues[3] fits, here we propose a summary of the central mechanisms by which thyroid hormones can affect cardiac output, vascular resistances, and kidney function. We also summarize the results of the most recent clinical studies focused on the relationship between thyroid hormones and hypertension.

1 | PHYSIOLOGICAL EFFECTS OF T3 AND T4 ON THE HEART

1.1 | Components of thyroid hormones signaling machinery in the heart

Among the numerous transporters responsible for the intracellular uptake of T3 and T4, three proteins were found to be expressed in the heart so far.[10,11] Two of them—monocarboxylate transporter

8 (MCT8) and large neutral amino acids transporter small subunit 2 (LAT2)—transport across the plasma membrane both T3 and thyroxine, whereas MCT10 is more effective in T3 transport.[12] Cardiomyocytes express also enzymes regulating thyroid hormones metabolism—type I and II iodothyronine deiodinases (DIO1, DIO2) and T4 5-deiodinase (DIO3).[13,14] DIO1 and DIO2 convert biologically inactive T4 into active T3; DIO3 catabolizes both hormones, thus ceasing their biological activity. Interestingly, local upregulation of DIO3 expression can produce a tissue-specific decrease in T3 availability.[15] Moreover, cardiomyocytes express the central element of thyroid hormone signaling—the thyroid hormone receptors α and β (THRα, THRβ).[16] THRs belong to the superfamily of nuclear protein receptors, which also includes receptors for steroid hormones, peroxisomal proliferator activator receptors (PPARs), retinoids, and other ligands. In contrast to other similar proteins, before binding their ligand, the THRs reside in the nucleus, where they are attached to specific T3 response elements (TRE) and in most cases repressing the transcription of target genes. Hence, low availability of thyroid hormones decreases the expression of particular genes and vice versa.[17] Specifically, in cardiomyocytes, the main THRs target genes include Na$^+$/K$^+$-ATPase,

myosin heavy chain α (*MYH6*) and β (*MYH7*), sarcoplasmic/endoplasmic reticulum calcium ATPase 2 (SERCA2), phospholamban (*PLN*), and β_1 adrenergic receptor. It is important to note that in contrast to other genes, the expression of *MYH7* and *PLN* is negatively regulated by high T3 levels.[18,19] By affecting the expression of these genes, T3 increases the contraction force and improves lusitropy.[20]

In addition to the well-described genomic actions of thyroid hormones via THRs, T3 and T4 also exert non-genomic effects via mechanisms that to date remain mostly elusive. For instance, they can alter the activity of several plasma membrane ion transporters, including Na^+/Ca^{2+} exchanger, Na^+/K^+-ATPase, and voltage-gated K^+ channels.[21] T3 also upregulates PGC1α, TFAM, and adenine nucleotide translocator (ANT).[22,23] The first two proteins are positive regulators of mitochondrial biogenesis and the third one plays crucial roles in ATP production rate in mitochondria. As a result, T3 can trigger mitochondrial proliferation in the myocardium. Given the complex role of mitochondria within the cell, the net effect of increased mitochondria quantity on the cardiac function remains unclear and is most likely dependent on the actual metabolic context.[17,24]

Thyroid hormones can act on the heart via indirect effects as well. Indeed, T3 and T4 are able to decrease the systemic vascular resistance, thereby increasing the cardiac output. Such effect is mainly mediated by the augmented Ca^{2+} uptake in smooth muscle cells and enhanced nitric oxide production due to the activation of AKT signaling pathways.[25,26] Another mechanism of increased cardiac output is the stimulation of the renin-angiotensin-aldosterone system (RAAS), eventually resulting in increased plasma volume with subsequent increase in cardiac preload.[27]

1.2 | Hyperthyroidism and cardiac function

The most common consequences of hyperthyroidism on the heart are arrhythmias, especially tachycardia and atrial fibrillation (AF). Specifically, AF develops in 5%–15% of patients with hyperthyroid state and can be reversed in 60% of patients after bringing T3 and T4 levels back to normal.[28] Another consequence of hyperthyroidism is increased cardiac output. Combination of tachycardia, increased contractility and augmented preload due to the increased plasma volume adversely acts on the heart. Untreated thyrotoxicosis increases the risk of heart failure.[28,29] Besides, high levels of T3 and low levels of TSH have been shown to be independent predictors of mortality in patients with failing hearts.[29,30]

1.3 | Hypothyroidism and cardiac function

Cardiac symptoms of hypothyroidism include bradycardia, decreased cardiac output and contractility, and increased peripheral vascular contractility. Diastolic dysfunction caused by impaired ventricular filling and relaxation often develops in patients with hypothyroidism, accompanied by low tolerance to physical exercise;

however, cardiac performance could be ameliorated following thyroid hormones replacement therapy.[31,32] In older patients, hypothyroidism increases the risk of heart failure,[33] which is associated with hypoxia and inflammation. Both these factors downregulate the expression of Dio2 and upregulates Dio3 expression; as a result, the availability of T3 dramatically diminishes in the myocardium, further exacerbating heart dysfunction.[34] A relatively rare complication of hypothyroidism is cardiac tamponade caused by pericardial effusion. The exact mechanism underlying this condition remains unclear, although some evidence indicates increased capillary permeability and reduced lymphatic drainage from the pericardial space.[35]

2 | ACTIONS OF T3 AND T4 ON THE VASCULAR SYSTEM

The association between thyroid function and circulatory dynamism is well documented.[36] Overall, the direct effect on cardiomyocytes and on vascular compartment orchestrates the broad action of thyroid hormones on cardiovascular system. Specifically, alongside the increase in cardiomyocytes contractility, T3 exposure is able to cause arterial relaxation and reduction of systemic vascular resistance, improving cardiac output.[37] Indeed, the main regulators of vascular tone, that is, endothelium and vascular smooth muscle cells (VSMC) are both targets of thyroid hormones.

The detection of Type II iodothyronine deiodinase (the key enzyme for T4 - T3 conversion) in rat aorta media, in human coronary artery VSMC and in human endothelial cells as well, demonstrated local intracellular production of thyroid hormones, suggesting a decisive role for them in the regulation of vascular homeostasis.[38]

Mechanistically, thyroid hormones control vascular hemodynamic by genomic and non-genomic effects. The genomic effects are classically mediated by activation of the nuclear receptors (THRα, THRβ), which bind gene promoters containing thyroid hormone response elements (TREs) and regulate the gene expression program.[39] However, other mechanisms independent of DNA binding (non-genomic effects) contribute to the vascular effects of thyroid hormones. These non-genomic effects can involve different cellular compartments, from plasma membrane to cytosol and mitochondria[40] and interfere with a variety of signaling pathways including regulation of ion channels, and cytoskeleton organization.[41] Non-genomic effects can also occur rapidly after thyroid hormones exposure, mediating their acute vascular effects. Indeed, evidence from both experimental animals and humans shows rapid vasodilation induced by thyroid hormones administration.[42,43]

2.1 | Effects on VSMC

One of the mechanisms by which thyroid hormones induce arterial relaxation and reduction of systemic vascular resistance is the downregulation of angiotensin II type 1 receptor (AT1R) in

VSMC.[44] Indeed, with a genomic effect, T3 is able to reduce AT1R-promoter activity affecting protein expression in vitro as well as in vivo. The suppression of cytokine expression in VSMC and the inhibition of cell proliferation is another effect of T3, with potential implications in anti-atherosclerotic action of thyroid hormones.[45] Furthermore, THRα deletion in VSMC significantly increases the expression of angiotensinogen and the intracellular accumulation of cholesterol content,[46] providing further evidence of the ability of thyroid hormones in sustaining an anti-atherosclerotic gene expression program.

The exposure of VSMC to T3 can also increase the mRNA and protein levels of CD73, the enzyme involved in converting AMP to adenosine, a potent vasodilator.[47] In addition to these gene expression-dependent mechanisms, other non-genomic pathways are responsible for VSMC relaxation in response to thyroid hormones, which can occur after 10 min from cell stimulation.[25,48] This effect of a rapid relaxation is most likely the result of an endothelial independent NO production, mediated by PI3K-AKT pathway activation in VSMC.[49]

2.2 | Effects on the endothelium

Assessing cGMP content and nitrite release, Ojamaa and collaborators demonstrated in 1996 that primary cultures of vascular endothelial cells exposed to T3 did not produce nitric oxide (NO).[25] This finding suggested an endothelial independent vasodilation induced by T3. However, other studies performed ex vivo demonstrated that in intact vascular rings, thyroid hormones are able to act directly on endothelial cells to induce vasodilation.[50,51] Specifically, T3 and T4 had a dose-dependent vasodilatory effect on intact vessels which was significantly reduced but not abolished after endothelium-denudation, indicating that both endothelium-independent and endothelium-dependent components were involved. Moreover, clinical evidence supports this view; in patients with hyperthyroidism, the endothelial-dependent arterial dilation is increased but markedly reduced after thyroidectomy.[52] This phenotype may be attributable to an excessive endothelial activation and NO production, induced by intense exposure to thyroid hormones, as also shown by Napoli and colleagues.[53] Later, the same research group demonstrated that also thyrotropin (TSH) is able to induce endothelial-mediated vasodilation, even independently of thyroid hormones levels.[54] Equally important, a study led by Bernadette Biondi has shown that recombinant human T4 improves endothelial coronary flow reserve in thyroidectomized patients.[55] Thyroid hormones are also responsible for the pro-angiogenic phenotype of endothelial cells. Specifically, this effect is the result of genomic and non-genomic actions of T3 and T4. Physiological concentrations of T4 are able to induce proliferation and tubulogenesis of brain-derived endothelial cells, by increasing the expression levels of VEGF-A and FGF-2 while reducing the transcription of pro-apoptotic genes like Bcl2 and Bad.[56] The same effects on angiogenetic competence are also mediated by the T4-dependent activation of the $\alpha_v\beta_3$/PKD/HDAC5 signaling pathway.[57]

3 | THYROID HORMONES AND THE KIDNEY

3.1 | Components of thyroid hormones signaling machinery in the kidney

The kidney is another target tissue of thyroid hormones. Since renal function is highly sensitive to the changes in systemic hemodynamics, the effects of T3 and T4 on the kidney are partially mediated by an altered cardiovascular function. Nonetheless, thyroid hormones signaling machinery is also present in the kidney and T3 exerts direct actions on this tissue. Renal cells are able to uptake thyroid hormones via LAT2, MCT8 and MCT10.[58,59] MCT8 and MCT10 play an essential role not only in renal responsiveness to thyroid hormones, but also in regulating circulating levels of T3 and T4.[59] DIO1, DIO2, and DIO3 are expressed in the kidney, affecting the local levels of T3 and partially affecting the general thyroid status.[58,60] A tight feedback relation exists between these proteins. For example, the knockout of *Mct8* is associated with a marked increase in *Dio1* expression and decrease in *Dio3*.[58] Both THRα and THRβ are found in the kidney.[39,60]

Thyroid hormones play paramount roles in the regulation of tubular function. For instance, expression and activity of Na$^+$/K$^+$-ATPase, which is essential in Na$^+$ reabsorption, are both augmented by T3;[61] Na$^+$/H$^+$ antiporter is downregulated in hypothyroidism and upregulated in hyperthyroidism;[62] Na/Pi cotransporter type II (NaPi-2) is positively affected by T3.[63] Thyroid hormones also affect Ca^{2+} reabsorption[64] and the expression of voltage-gated chloride channel CLC-2 in the nephron is also under T3 control.[65]

As mentioned above, thyroid hormones have profound effects on the RAAS. T3 induces renin expression in juxtaglomerular cells.[66] Since renin secretion is positively regulated by β-adrenergic receptors, this effect might be mediated by a thyroid hormones-dependent increase in sensitivity to β-adrenergic stimuli.[67] Additionally, T3 potentiates local RAAS in the kidney augmenting the activity of angiotensin-converting enzyme.[68] The expression of angiotensin receptors is also controlled by the thyroid status, with angiotensin II receptor type 1 (ATR1) being regulated positively and angiotensin II receptor type 2 (ATR2) negatively by thyroid hormones; ATR1 is known to mediate the pro-fibrotic and vasopressive effects of angiotensin II whereas ATR2 counteracts them.[69] As seen in the heart, a number of mitochondrial enzymes in the kidney are regulated thyroid hormones.[70]

3.2 | Hyperthyroidism and renal function

T3 mediates increase in cardiac output, systemic vasodilation, and aldosterone-mediated water retention as a result of RAAS activation.

All these hemodynamic modifications increase blood flow in afferent arterioles with a subsequent rise in the glomerular hydrostatic pressure; the filtration through glomerular capillaries increases thus causing a significant increment in the glomerular filtration rate (GFR).[71] High levels of thyroid hormones enhance resorption of Na^+ and Cl^- in the proximal nephron, thereupon decreasing their concentration in a distal part. The *macula densa* reacts to low levels of Na^+ and Cl^- activating the tubule-glomerular feedback, further increasing the already high GFR.[72] Patients with hyperthyroidism lose ability to concentrate urine.[73] Increased activity of NaPi-2 might provoke hyperphosphatemia, which in turn would affect the secretion of FGF23 and parathyroid hormone with subsequent effects on mineral metabolism.[74]

3.3 | Hypothyroidism and renal function

Hypothyroidism adversely affects kidneys. Due to the generalized vasoconstriction and impaired myocardial contractility, the kidney suffers from hypoperfusion and the reduced hydrostatic pressure in glomerular capillaries decreases GFR. As a result, less Na^+ and Cl^- can reach the *macula densa*. The subsequent activation of the tubule-glomerular feedback triggers a more robust vasoconstriction of the preglomerular arterioles, exacerbating the already low blood supply. Such a discrepancy between renal supply and demand in O_2 and nutrients could predispose patients with hypoparathyroidism to the development of acute kidney injury.[75] A prolonged hypothyroid state could also provoke irreversible damage to the kidney. Population-based studies reveled the association between thyroid-stimulating hormone (increased during hypothyroidism) with higher prevalence of chronic kidney disease.[76] Hypothyroidism also contributes to a reduced GRF in patients with CKD. However, these alterations appeared to be reversible with thyroid hormone replacement therapy;[77] thyroid hormone therapy slowed down the rate of decline in GFR in patients with subclinical hypothyroidism and stage 2–4 chronic kidney disease.[78]

Both hypothyroidism and upper-normal TSH levels are associated with higher mortality in hemodialysis patients.[79] Of note, mortality from cardiovascular reasons is the most prevalent cause of mortality in patients requiring dialysis. Studies held in patients on peritoneal dialysis revealed that low levels of T3 predict higher mortality in such patients and high levels of T3 decrease the risk of death.[80] T4 demonstrated the same trend in another study on peritoneal dialysis patients.[81]

3.4 | Clinical evidence

Hypothyroidism is widely recognized as a cause of secondary hypertension. In 1878, Ord described left ventricular hypertrophy and thickening of the arteries in an autopsy of a woman with hypothyroidism.[82] In 1983, Suito and coworkers suggested a close

association between hypertension and hypothyroidism[83] reporting a higher prevalence of hypertension (systolic BP over 160 and/or diastolic BP above 95 mmHg) in hypothyroid patients (*n* = 169) than in euthyroid patients (*n* = 308). The authors found a significant correlation between diastolic (but not systolic) BP and the circulating levels of T3 or thyroxine T4 hormones; moreover, an adequate T3 and T4 replacement therapy for an average of 14.8 months in 14 patients resulted in a normalization of thyroid function and a reduction of BP.[83] An association between hypothyroidism and diastolic hypertension was later determined by measuring serum concentrations of T4 and TSH in 688 hypertensive patients: Hypothyroidism was found in 25 (3.6%) subjects, and the restoration of normal T4 and TSH serum levels by replacement therapy lowered diastolic BP below 90 mmHg in 32% of subjects.[84] Subsequent studies corroborated the link between hypothyroidism and elevated BP and added more pieces of information to this functional association. For instance, patients with hypertension and hypothyroidism were shown to have increased aortic stiffness[85]; patients with hypothyroidism had significantly higher values of 24-h systolic BP, pulse pressure, and systolic BP variability compared with gender and age-matched healthy volunteers.[86]

In contrast to these results, some clinical trials did not find a significant association between hypertension and hypothyroidism. In 1996, Bergus and collaborators published a cross-sectional study conducted on 707 postmenopausal women aged 50 years or older, of which 45.4% had hypertension and 10.9% had hypothyroidism; in this population, the authors did not find a meaningful association between hypertension and hypothyroidism.[87] A similar conclusion was reported by the same group in a subsequent study, conducted on a group of 122 geriatric patients with elevated TSH levels and a control group including an equal number of euthyroid geriatric individuals; the authors did not find differences in the mean diastolic BP between euthyroid and hypothyroid groups, and no significant association between hypertension and TSH levels was found.[88]

Whether subclinical hypothyroidism and euthyroidism can affect BP remains controversial. In 2002, a small clinical study conducted on 57 women with subclinical hypothyroidism and 34 healthy controls revealed a significant association between hypertension and subclinical hypothyroidism in middle-aged women.[89] These results were confirmed in a larger study on 1319 participants, in which, after adjusting for age, gender, and other conditions, the risk of hypertension in subjects with subclinical hypothyroidism was significantly higher in females (but not in males) compared to the euthyroid group.[90] Modifications in serum TSH levels did not show any correlation with systolic or diastolic BP,[90] as later confirmed in a large prospective dynamic cohort study, showing that T3 and T4 levels were positively related to the normal BP and the prevalence of elevated BP in euthyroid adults whereas the relationship between TSH and elevated BP was not significant.[91] In contrast to these results, a randomized controlled trial conducted on 737 adults who were at least 65-year-old and having persisting subclinical hypothyroidism did not show any beneficial effects of T4 in the treatment group on systolic and diastolic BP compared to the placebo group.[92]

Over the years, several meta-analyses aimed to examine the relationship between subclinical hypothyroidism and hypertension. In 2011, Cai and colleagues published a meta-analysis of seven cross-sectional studies to assess whether BP levels in patients with subclinical thyroid dysfunction differ from the euthyroid subjects group; the data indicated that subclinical hypothyroidism was associated with increased systolic and diastolic BP.[93] In 2014, a meta-analysis of 20 studies including 50147 participants, of which 4690 subjects with subclinical hypothyroidism, revealed that subclinical hypothyroidism was associated with a slightly higher systolic BP[94]; however, the elevated BP could be attributed to the different ages between subclinical hypothyroidism and euthyroid groups.[94] More recently, the effects of T4 therapy on BP were assessed in a meta-analysis of 29 studies, of which 10 randomized controlled trials and 19 prospective follow-up studies: the meta-analysis of the 10 randomized controlled trials indicated that T4 could significantly reduce the systolic BP in patients with subclinical hypothyroidism by 2.48 mmHg; the analysis of the 19 prospective studies revealed that T4 significantly decreased the systolic and diastolic BP by 4.80 mmHg and 2.74 mmHg, respectively.[95]

Hyperthyroidism is a common cause of hyperkinetic circulatory disease. The hemodynamic modifications observed in hyperthyroidism, including elevated cardiac output, increased blood volume, and decreased peripheral vascular resistance, can lead to severe cases of systolic BP elevation as well as to a fall of diastolic BP.[96,97] Specifically, systolic hypertension is more frequent in young patients with hyperthyroidism, while the elevation of diastolic BP is not common in hyperthyroidism.[97] Hyperthyroidism treatment can lower systolic BP in most patients, since the increase in cardiac output, the expansion of the vascular bed volume, and the decreased peripheral resistance, are all well-established features of hyperthyroidism, alongside the enhancement of catecholamine action due to the excess of circulating thyroid hormones.[97]

Several clinical studies were designed to evaluate the effects of short- and long-term treatment of hyperthyroidism on arterial BP. In 2002, Marcisz and collaborators published a study on 51 patients with hyperthyroidism and 30 healthy controls, showing that hyperthyroid subjects had higher systolic BP and lower diastolic BP than controls; after short-term treatment with thiamazole (a medication used to treat hyperthyroidism, also known as methimazole), the systolic BP returned to normal values, while diastolic BP was normalized only after long-term treatment.[98] These results were confirmed by a subsequent study demonstrating that normotensive hyperthyroid patients, evaluated by continuously BP monitoring, exhibit higher ambulatory systolic BP throughout 24h than normotensive euthyroid subjects and therapeutic control of hyperthyroidism decreases ambulatory systolic BP values.[99] Another study has revealed an association between hyperthyroidism and mild transient pulmonary hypertension.[100] Interestingly, in contrast with these observations, the above-mentioned meta-analysis authored by Cai, examining both patients with subclinical hypothyroidism and hyperthyroidism showed that subclinical hyperthyroidism condition is not associated with increased systolic and diastolic BP,[93] emphasizing the controversy in the field.

CONFLICT OF INTEREST

None.

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