Review

Regulation of nitric oxide production in hypothyroidism

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A R T I C L E   I N F O

A B S T R A C T

Hypothyroidism is a common endocrine disorder that predominantly occurs in females. It is associated with an increased risk of cardiovascular diseases (CVD), but the molecular mechanism is not known. Disturbance in lipid metabolism, the regulation of oxidative stress, and inflammation characterize the progression of subclinical hypothyroidism. The initiation and progression of endothelial dysfunction also exhibit these changes, which is the initial step in developing CVD. Animal and human studies highlight the critical role of nitric oxide (NO) as a reliable biomarker for cardiovascular risk in subclinical and clinical hypothyroidism. In this review, we summarize the recent literature findings associated with NO production by the thyroid hormones in both physiological and pathophysiological conditions. We also discuss the levothyroxine treatment effect on serum NO levels in hypothyroid patients.

1. Introduction

Atherosclerosis is among the significant causes of overall morbidity and mortality in the general population. Overall, the risk factors for atherosclerosis development include metabolic syndrome (MetS) components (insulin resistance, dyslipidemia, central obesity, hypertension), smoking, and sedentary lifestyle [1–3]. Despite the confusing conclusions of some studies, both MetS and atherosclerosis are strongly associated with hypothyroidism [4–7]. Thyroid hormones facilitate the normal functioning of cardiovascular physiology, while clinical or subclinical hypothyroidism leads to alterations in hemodynamics, vessels and cardiac morphology and physiology, hypertension, and accelerated atherosclerosis [8–12]. Despite numerous evidence links unbalanced thyroid hormones action with cardiovascular diseases (CVD), the molecular mechanisms of these pathologies remain poorly explored. However, literature evidence suggests that endothelial dysfunction (ED) and altered nitric oxide (NO) production are among the main factors causing these disorders.

The physiological production of NO has beneficial effects on the cardiovascular system (CVS), maintaining vascular tone, controlling

Table 1
Hypothyroidism-related complications and altered NO production.

Study group	Pathophysiological process	NO-related effects	Reference
Patients with hypothyroidism	Atherosclerosis	↓Endothelial NO production	[120]
	Dyslipidemia	↓NO	[74]
	ED and Hyperlipidemia	↓NO	[9]
	ED and Hyperlipidemia	↓eNOS expression	[112]
	ED and Chronic inflammation	↓Flow-mediated dilation	[122]
	ED and Chronic inflammation	↓NO availability	[129]
Hypothyroid rats	ED and Heart failure	↓Atrial NOS activity	[138]
	Cognitive dysfunction and Brain tissue oxidative damage	↑NO	[140,141,144–146]
HUVEC treated with ↑TSH	Atherosclerosis	↓eNOS expression	[107]
HUVEC treated with ↑T3 and ↑oxLDL	Atherosclerosis	↓NO	[135]

ED-endothelial dysfunction; eNOS-endothelial nitric oxide synthase; HUVEC-human umbilical vein endothelial cells; NO-nitric oxide; NOS-nitric oxide synthase; oxLDL- oxidized low-density lipoprotein; T3-triiodothyronine; TSH-thyroid-stimulating hormone; ↑-increased; ↓-decreased.

leukocyte adhesion, and platelet aggregation. Also, NO provide anti-inflammatory and antioxidant effects [13–16]. Moreover, NO is an endothelium-derived relaxing factor, which is critical for CVS homeostasis [17–19]. Reduced bioactivity and bioavailability of NO in the vasculature is the major contributor and a marker of ED [7,20,21]. Various hormones, including thyroid hormones [20,22–25], regulate the activity of nitric oxide synthase (NOS) and NO production, while altered NO level is associated with thyroid dysfunction [8,26].

Understanding the regulation of NO production by thyroid hormones and thyroid-stimulating hormone (TSH) may provide new and useful insight of how ED links to thyroid function alterations and diseases. Thus NO may be a potential biochemical marker of thyroid diseases.

In this review, we summarize the recent literature related to NO production and its role in hypothyroidism (Table 1) and discuss the effects of levothyroxine (LT4) treatment on NO levels in the serum of hypothyroid patients.

2. Nitric oxide – mechanism of action and function

Nitric oxide is a lipophilic molecule involved in various physiological and pathophysiological processes [20,27], and also the first gaseous molecule described as a mediator in signaling pathways [28]. It is an intracellular molecule with a very short biological half-life of only a few seconds or even less [29], but despite that, NO can produce remote or long-lasting and prolonged effects [30] via generation of different S-nitrosothiols (SNO) which are carriers of NO [31]. S-nitrosylation of the reactive cysteine thiol group on different proteins forms SNO, and then the nitrosyl moiety is transferred between interacting proteins as a means of transporting the NO signal to a distant location by transnitrosylation [32]. Throughout the years it was thought that the NO molecule only diffuses freely across cell membrane phospholipid bilayer, but the discovery of new membrane transport functions exerted by membrane channel proteins such as aquaporin-1 (AQP-1) [33–35] and connexins [36] challenges this concept. Disturbance of NO transport/conduction through these channels suggests a possible alternate origin of the diseases currently explained by insufficient NO bioavailability [33,36–38].

NO is a molecule generated and/or present in many different cell types throughout the body [39], such as vascular smooth muscle cells (VSMC), endothelial cells, central and peripheral neurons, epithelial cells of various organs, pancreatic islet cells, kidney macula densa cells, macrophages, etc. [40]. It is known that NO plays an essential role in various physiological processes such as neuronal signaling, synaptic plasticity, immune and inflammatory response, ion channels regulation, phagocytic defense mechanism, penile erection, as well as cardiovascular homeostasis and atherogenesis [41]. Nevertheless, NO is generated primarily in blood vessel endothelial cells, which are the primary source of NO production in CVS under physiological conditions [42]. NO interaction with different signaling molecules initiates effects, while

its interaction with free radicals leads to multiple biological reactions [43,44], thereby influencing different metabolic and membrane transport processes [37,38].

NOS enzymes synthesize NO by converting the amino acid L-Arginine (L-Arg) and oxygen into NO and citrulline [45–47]. It has been shown that the availability of L-Arg is one of the limiting factors for NO synthesis in the vascular adventitia of rats with sepsis [48]. NOS is a family of enzymes consisting of 3 isoforms, including neuronal NOS (nNOS), endothelial NOS (eNOS), and inducible NOS (iNOS) [49]. The biological effect of NO on the CVS depends on the NOS isoform that is activated. Constitutively expressed forms in mammalian cells are nNOS and eNOS, while NO produced by iNOS has proinflammatory and defensive effects [49,50]. eNOS is the most common isozyme in the healthy vascular system, and it is activated by phosphorylation at different regulatory sites via protein kinases [51]. Stimulatory phosphorylation of eNOS at Serine^{1177} usually occurs via the activity of protein kinase A (PKA), protein kinase B (Akt), adenosine monophosphate-activated protein kinase (AMPK), or calmodulin-dependent protein kinase IIβ (CAMK2B), while the inhibitory phosphorylation of eNOS at threonine^{495} occurs via Rho-kinase and protein kinase C [52]. Another enzyme, arginase, also uses the substrate L-Arg and plays a critical role in the NO synthesis regulation by reducing the L-Arg availability for NO production [53].

In VSMC, cardiac myocytes, and platelets, NO activates soluble guanylate cyclase (sGC) and increases the level of cyclic guanosine monophosphate (cGMP), which activates protein kinase G (PKG) and its subsequent signaling pathway, which leads to cell relaxation and consequently blood vessels dilatation [54,55]. Increased cGMP level also leads to anti-inflammatory properties as it inhibits leukocytes adhesion to the endothelium and platelet aggregation [56]. Furthermore, when NO is overproduced, NO could also exert its effects through sGC-independent mechanisms [54,57]. Production of large amounts of NO and its reaction with superoxide anion, form the toxic compound peroxynitrite, that may induce nitrosative stress [58,59]. Increased nitrosative stress leads to nitration and S-nitrosylation of macromolecules, including lipids, proteins, and DNA that may cause tissue damage and dysfunction [60]. On the other hand, under physiological conditions, in the presence of a low level of reactive oxygen species, NO protects cells from further oxidative modification also by protein S-nitrosylation [31,32,61–64], which is nowadays an emerging paradigm of redox signaling [32]. Proper regulation of S-nitrosylation is vital for normal physiology, while its dysregulation leads to pathological conditions [32,65].

An imbalance between endothelial vasodilators (predominantly NO) and vasoconstrictors leads to ED, which is a part of numerous cardiovascular and other systemic diseases. ED is an early event in the atherosclerosis process [66–68] characterized by a decrease in NO synthesis, release, and activity [69–71]. Decreased bioavailability of NO is one of several probable causes of ED [72], and it features in hyperthyroid [73], and both subclinical [74] and clinical hypothyroid

patients [11,73,75].

3. Nitric oxide and hypothyroidism

Hypothyroidism has two-stages based on clinical manifestations and biochemical characteristics: a/ subclinical and b/ clinical hypothyroidism [76,77]. Hypothyroidism is prevalent in 20 % of the general population; moreover, at least 80 % of patients with hypothyroidism are subclinically hypothyroid [78], while the prevalence of clinical hypothyroidism is significantly lower, less than 1 % in non-endemic and more than 5 % in endemic areas [78–86].

Thyroid hormones have multiple roles in the normal CVS functioning [87,88]. Both the myocardial and vascular endothelial tissues present TSH receptors, so even slight alterations in TSH concentrations can affect CVS functioning [89]. Endothelial cells also express TSH receptors, but TSH exhibits its effect on endothelial cells independently of the peripheral thyroid hormones [90,91]. Contrary, the morphology and function of CVS are altered in subclinical and clinical hypothyroidism [92], and the development of alterations depends on the severity and duration of thyroid dysfunction [93–96]. Hypothyroidism occurs with dyslipidemia, hypertension, blood hypercoagulability, increased arterial wall stiffness, maladaptive cardiac remodeling, ED, and elevated levels of C-reactive protein (CRP). All these factors lead to an elevated risk of coronary heart disease and heart failure [8,10,92,97–100]. Also, the level of TSH is a reliable predictor of CVD in hypothyroid patients [101].

Alterations in CVS physiology in clinical hypothyroid patients include a reduced heart rate and cardiac contractility, as well as increased peripheral vascular resistance [102]. In subclinical hypothyroid patients, the most frequent CVS abnormalities include increased systemic vascular resistance and diastolic dysfunction, ED, impaired ventricular filling and relaxation [4,95,103]. Decreased endothelium-dependent vasodilatation in the aorta and renal blood vessels, with a concomitant decrease in eNOS activity, was demonstrated in hypothyroid rats [104–106]. Endothelial cells from human umbilical veins under conditions of elevated TSH levels, exhibit decreased expression of eNOS [107]. The prevalence of ED is marked up in both subclinical and clinical hypothyroid patients, implying a role for serum TSH in ED pathology [23].

Furthermore, the progression of hypothyroidism occurs with an increase in CRP [23], tumor necrosis factor-α (TNF-α), and interleukin 6 (IL-6) levels [108]. The inflammatory markers characteristic for hypothyroidism correlates with hypothyroidism etiology (chronic autoimmune thyroiditis), as well as the pulse wave velocity, a marker of endothelium-dependent dysfunction [109,110]. Additionally, multiple linear regression models showed a correlation between TSH and NO levels, after adjustment for other CVD risk factors, suggesting elevated TSH affects the progression of atherosclerosis in patients with hypothyroidism [9,111]. Hyperlipidemia presented in hypothyroid patients also causes ED by decreasing eNOS expression [112]. However, the correction of hyperlipidemia in hypothyroid patients only partially restores endothelium-dependent vasodilatation and ED [101].

During the first trimester of pregnancy, the mothers' thyroid and placenta play a pivotal role in the maintenance of thyroid hormones supply to the fetus. The increase in activity enlarges the volume of the thyroid gland as compared to the non-pregnancy state [113]. In such a period, the importance of microelements and nutrients supply required for the syntheses of thyroid hormones is cumbersome [114]. Despite that, some mothers experience the lowering of levels of peripheral thyroid hormones, especially thyroxine (T4). Nonetheless, even in the cases where the mother has low T4 levels, the adaptive responses of the placenta, changes in expression and activity of placental thyroid hormone transporters and deiodinase, ensure availability of enough triiodothyronine (T3)/T4 that is essential for fetus growth and development. Placental endothelial cells are under the close influence of thyroid hormones. These hormones may induce the synthesis and release of vasoactive mediators, such as NO and endothelin-1, and hence control the fetoplacental circulation network. Mothers frequently experience low levels of T4 with gestational diabetes, which could additionally contribute to the current and delayed vascular damage, as well as organ damage of both mother and fetus [115–117].

Latent and overt hypothyroidism induces deleterious cardiovascular effects [118,119]. Beside deranged vascular relaxation mediated by decreased endothelial NO production, coronary arteries in hypothyroid patients are prone to accelerated atherosclerosis [120]. Moreover, hypothyroidism contributes to the aggravation of the already failed heart muscle. After an acute myocardial injury occurs, the state of local hypothyroidism, i.e., decreased T3 production/activity associated with T3 deiodinase activity, promotes early as well as late heart remodeling. Cardiovascular dysfunctions caused by both types of hypothyroidism could be partially or even entirely restored by LT4 replacement [97,120,121].

4. The proposed implications of hypothyroid states on nitric oxide production

The endothelium is a target tissue of thyroid hormones, and it is sufficiently sensitive to detect changes in thyroid hormones action [9,122,123]. Both, clinical and subclinical hypothyroidism initiate CVD through disruption of the healthy endothelial function in several ways, by promoting inflammation, inducing lipid disorders and oxidative stress, and increasing blood pressure [110,122,124,125]. All these factors influence the expression and activity of different vasorelaxant and vasoconstrictor molecules, among which, those that regulate NO production are in the most critical group [7,124]. In hypothyroid states, the expression of hepatic low-density lipoprotein (LDL) receptors and activity of cholesterol-α-monooxygenase decreases, leading to reduced LDL clearance [126]. Dyslipidemia increases asymmetrical dimethylarginine (ADMA) levels and reduces the enzymatic activity of dimethylarginine dimethylaminohydrolase, which leads to decreased NO production [7,74]. Concurrently, in hypothyroid states, the inflammatory processes also promote ED by decreasing eNOS expression and increasing the level of endothelin-1 [7,127,128]. Although this process is poorly understood, evidence implicates the involvement of different inflammatory factors, such as CRP, IL-6, and TNF-α [23,122,129]. Hypothyroid states also potentiate elevation of arginase levels in endothelial cells, thus promoting oxidative stress and additional impairment of endothelial function [130]. Pretreatment of the myocardial infarction rat model with T3 and T4 reduces the level of reactive oxygen species, while increases the expression of eNOS, the total NOS activity, and NO level in the infarcted heart [131]. The thyroid hormones directly influence the renin-angiotensin-aldosterone system by stimulating the synthesis of hepatic renin substrates [11,132]. In hypothyroid states, the level of renin reduces, while the blood pressure is elevated [132].

Thyroid hormones exert their effects in CVS through genomic and non-genomic signaling pathways. These hormones affect endothelium and VSMC mostly by binding of T3 to the nuclear receptors (THR-α1 and THR-β) and regulating transcription of different genes, including the NOS3 gene that encodes for eNOS [11,133]. T3 also directly regulates vascular tone via non-genomic signaling that includes involvement of phosphatidylinositol 3-kinases (PI3K)/Akt cascade and stimulation of NO production by eNOS in endothelial cells [134–136]. Evidence suggests impaired endothelium-dependent vascular relaxation, in hypothyroid states, is caused by increases in oxidized LDL that inhibits the non-genomic action of T3 through Akt signaling [135]. T3 also induces vasorelaxation through the endothelium-independent pathway by stimulating the activation of PKG/vasodilator-stimulated phosphoprotein (VASP) signaling in VSMC [137]. Thyroid hormone stimulates L-Arg uptake to endothelial cells by upregulating L-Arg transporters. T3 may be exerting this effect through the activation of αvβ3 integrin receptor, mitogen-activated protein kinase (MAPK),

PI3K, and intracellular Ca^{2+} signaling pathways [75]. One additional proposed mechanism of thyroid hormones action on endothelium has been through the regulation of caveolin protein function [138], as in a hypothyroid state, atrial NOS activity decreases, which is associated with increased caveolin 1 expression [138]. In the subclinical hypothyroid state, elevated TSH level may be responsible for the deprivation of eNOS, since an increased TSH bind extrathyroidal TSH receptors and decrease eNOS and prostacyclin I2 expression in endothelial cells [90,107].

Increasing evidence underlines the critical role of NO in damage of different tissues during hypothyroidism [115,139–143], where the brain tissue is the most exhaustively investigated [140,141,144–146]. Thyroid hormones are necessary for the period of early fetal neurodevelopment [147]. Numerous experimental studies showed that hypothyroidism is associated with learning and memory impairment [148,149]. Morphological development and functional capacity of hippocampi are under the influence of thyroid hormones [148,150]. Additionally, some results pointed out the link between NO and impairment (mentioned above) [151], as well as that such hypothyroidism-induced impairment influences the hippocampi, where the increased expression of nNOS and elevated NO levels were detected [152]. Such an increase in nNOS expression and NO levels is associated with neuronal death in the rat cortex, which suggests NO also functions as a neurogenesis inhibitor [153]. It is noteworthy that even transient maternal hypothyroidism was associated with an increase in nNOS expression and NO levels and was restored to pre-experimental levels by LT4 [152,154]. The effects of NO in hippocampi depend on local NO quantity. If the production rate is physiological, NO is acting as a neurotransmitter. In the cases of increased and extremely high production, it exhibits inhibitory and even toxic on neurons [155]. Such deleterious effects could be explained by the link between NO and mediators of oxidative stress [141,156]. Low levels of serum T4 lead to a reduction of thiol content and activity of SOD and CAT enzymes, and increased lipid peroxidation, NO metabolite levels, and neuronal apoptosis in brain tissues of hypothyroid rats [140,141,144–146]. These findings point directly to the relationship between locally disturbed NO production in hypothyroid state and brain tissue oxidative damage, including cognitive dysfunction of experimental animals [140,141,144–146].

Besides the effects on the cardiovascular and central/peripheral nervous system, thyroid dysfunction can cause damage to other organs and systems as well. Pulmonary hypertension is frequently associated with toxic multinodular goiter. A deranged balance between pulmonary vascular dilation (decreased) and constriction (increased) is the basis of pulmonary hypertension. In advanced stages of the disease, cardiorespiratory failure developed [142]. Also, autoimmune disorders predominate regarding the etiology of thyroid dysfunctions. The cytokines produced by the immune system and thyroid follicular cells favor local and systemic inflammation by promoting B and T cell stimulation and by enhancement the production of NO and various prostaglandins [143].

5. Effect of levothyroxine replacement therapy on serum nitric oxide levels

Levothyroxine (Fig. 1), the synthetic levo isomer of T4 hormone, is the most commonly used replacement therapy for the deficiency of thyroid hormones (hypothyroidism) [157,158].

Since LT4 acts as an endogenous T4, a naturally synthesized form, LT4 could also be converted peripherally to its active metabolite, T3. During LT4 therapy, the serum level of T3 also increases, T3 reaches the reference value, and by that also contributes to the decrease in the TSH level [157,158]. Oral use of LT4 reverses symptoms and signs of hypothyroidism and restores the wellbeing of hypothyroid patients with minimal side-effects such are headaches, increased appetite, and fatigue [157].
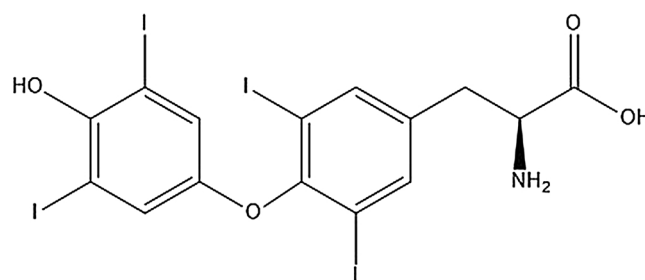

Fig. 1. Chemical structure of Levothyroxin.

Numerous interventional studies [95,103,120,159–163] report the beneficial effects of LT4 replacement regarding the improvement of cardiac and endothelial functions and the correction of some modifiable atherosclerotic risk factors in patients with hypothyroidism. LT4 replacement therapy should also be introduced in subclinical hypothyroid patients not only for the management of thyroid hormone levels but also for preventing atherosclerosis [164]. Clinical review [165] also reports the moderate beneficial effect of LT4 on numerous CVD risk factors in patients with subclinical hypothyroidism. Moreover, LT4 treated patients exhibited significant decreases in overall cholesterol, Apo-B, and LDL. As TSH and lipids levels were higher before the LT4 treatment, the decrease in these parameters level was more significant.

ED usually precedes atherosclerosis and correlates with an increase in the level of serum lipids in hypothyroidism [166]. The critical factor of endothelial function is the level of NO, which is directly modulated by the thyroid hormone level [164,167]. In both types of hypothyroidism, reduced NO bioavailability occurs with changes in atherosclerotic risk factors, that are reversible with LT4 replacement therapy [100]. LT4-treated hypothyroid patients [72,168,169] also exhibit normalization of the lipid profile and a partial restoration of altered endothelium-dependent vasodilation. Moreover, endothelium-dependent vasodilatation is improved by LT4 replacement via restoration and increase of NO production [72]. Also, Ozcan et al. show that an altered level of NOS inhibitor, ADMA, and consequently altered L-Arg and NO levels are significantly improved in subclinical hypothyroid patients one month after stable laboratory euthyroidism achievement by LT4 [74]. The same authors suggest that LT4, as an exogenous thyroid hormone, is beneficial for ED via lowering serum ADMA level and elevating NO production in subclinical hypothyroidism, while the precise molecular mechanism should be further investigated. The results reported by Hashemi et al. [164] does not corroborate the beneficial effect of LT4 on NO levels. They conducted a case-control study on 50 female subjects (25 control and 25 case group subjects). Serum NO levels, as well as other parameters that affect the development of ED (total cholesterol, TG, LDL, high density lipoprotein (HDL)), were measured before and two months after LT4 replacement therapy. Results show that LT4 replacement therapy did not affect the level of total cholesterol, LDL, HDL, and the level of TG decreases after two months of replacement therapy. Also, there was no significant correlation between serum NO levels in the case group before and after LT4 replacement therapy [164]. Contrary, the beneficial effects of LT4 replacement therapy on endothelial cell functions in subclinical hypothyroid patients are confirmed in a randomized, crossover trial [120]. One of the pieces of evidence that support a successful anti-atherogenic and antioxidative role of LT4 substitution is the decrease in macrophages, T lymphocytes, and proinflammatory HLA-DR cells count in the plaque. CVS alterations, like systolic and diastolic dysfunction, increased systemic vascular resistance, and decreased myocardial contractility, are almost eliminated or reduced by LT4 treatment. Also, subclinical hypothyroid patients, who had treatments switched to LT4, show significantly reduced risk of heart failure and overall mortality compared to untreated patients [170,171]. Partial or complete repair of harmful effects of hypothyroidism on CVS enabled by LT4 could be

verified either as alleviation of ischemic heart disease complaints or as improvement of ventricular rhythm disorders [84,168,172,173].

Although there are no randomized trials in patients with hypothyroidism that unequivocally pointed to beneficial effects of LT4 treatment in the reduction of cardiovascular morbidity and mortality rates after LT4 replacement and consequent laboratory euthyroidism achievement, some CVS changes such as NO production [23,72] could be at least partially restored [174]. Timely introduction of LT4 in subclinical hypothyroid patients prevents the progression of hypothyroidism and decelerates the process of atherosclerosis [72,126].

6. Conclusions

Alterations in NOS activity and NO production are involved in the cardiovascular manifestations of thyroid disorders. LT4 replacement reverses CVS changes related to NO bioavailability in both types of hypothyroidism [100]. The mechanism responsible for the regulation of NOS activity and NO bioavailability in hypothyroidism is however not fully understood, and it may be affected by various factors alone or in combination. Future studies should focus on a better understanding of the molecular mechanisms underlying the effects of NO under physiological conditions as well as in the pathophysiology of hypothyroidism and their clinical relevance. Moreover, further investigations using animal models and humans are needed to establish the best way to supplement thyroid hormones and to enhance the thyroid hormones/NO pathway. Also, more extensive clinical trials are needed to confirm the beneficial effects of LT4 treatment in the reduction of cardiovascular morbidity and mortality rates. Regulation of NO bioavailability after employing LT4 drugs is critical for developing new strategies for the treatment of cardiovascular disorders associated with hypothyroidism as NO could have both beneficial and detrimental effects. Understanding how thyroid hormones regulate NO production may provide useful knowledge about the link between thyroid diseases and ED, and may also unveil potential new treatments for cardiovascular manifestations of thyroid disorders that can prevent the onset of cardiovascular abnormalities in patients with hypothyroidism.

The literature discussed in this review, together with our published data and preliminary results related to NO regulation in hypothyroidism [12], suggest that NO levels could be a reliable marker for the assessment of thyroid dysfunction and one of the critical therapeutic molecules for improving the treatment of CVD related to thyroid dysfunction. Furthermore, the newly discovered role of thyroid hormones and the effects of LT4 on NO production may have broad implications in cardiovascular medicine.

Declaration of Competing Interest

The authors confirm that this article content has no conflict of interest.

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