Review

Thyroid Hormone and Vascular Remodeling

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Both hyperthyroidism and hypothyroidism affect the cardiovascular system. Hypothyroidism is known to be associated with enhanced atherosclerosis and ischemic heart diseases. The accelerated atherosclerosis in the hypothyroid state has been traditionally ascribed to atherogenic lipid profile, diastolic hypertension, and impaired endothelial function. However, recent studies indicate that thyroid hormone has direct anti-atherosclerotic effects, such as production of nitric oxide and suppression of smooth muscle cell proliferation. These data suggest that thyroid hormone inhibits atherogenesis through direct effects on the vasculature as well as modification of risk factors for atherosclerosis. This review summarizes the basic and clinical studies on the role of thyroid hormone in vascular remodeling. The possible application of thyroid hormone mimetics to the therapy of hypercholesterolemia and atherosclerosis is also discussed.

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Introduction

Thyroid hormone has various effects on the cardiovascular system. Many studies have shown that both hyperthyroidism and hypothyroidism cause or accelerate cardiovascular diseases. Hyperthyroidism causes a hyperdynamic cardiovascular state, such as sinus tachycardia, and increased left ventricular contraction and relaxation. Although cardiac output is increased, some hyperthyroid patients show heart failure symptoms. Hypothyroidism causes opposite cardiovascular changes. In addition, hypothyroidism is associated with an increased risk of atherosclerosis and ischemic heart disease. Epidemiological studies have suggested that patients with hypothyroidism have accelerated coronary atherosclerosis. The Rotterdam study showed a higher prevalence of myocardial infarction in women with subclinical hypothyroidism compared with euthyroid women. It has been suggested that hypercholesterolemia, hypertension, and impaired endothelial function in the hypothyroid state enhance atherogenesis. Some emerging risk factors for atherosclerosis, such as hyperhomocysteinemia and increased C-reactive protein (CRP) level, have also been shown to be associated with overt as well as subclinical hypothyroidism. In addition, recent studies have shown that thyroid hormone has direct vascular effects that may suppress atherogenesis. These studies suggest an anti-atherosclerotic effect of thyroid hormone. However, recent clinical trials failed to show an association between the thyroid function and cardiovascular events. Therefore, the causal relationship between the thyroid hormone and cardiovascular diseases remains elusive, and further studies are warranted. Although some controversies still exist, the application of thyroid hormone mimetics to cardiovascular diseases has been extensively investigated, and thyroid hormone mimetics have showed a promising effect on lipid profile and atherogenesis. This review summarizes the effect of thyroid hormone on vascular remodeling.

Hypothyroidism and Atherosclerotic Cardiovascular Diseases-Clinical Studies

The National Health and Nutrition Examination Survey (NHANES III) study showed that the prevalence of subclinical and overt hypothyroidism was 4.3% and 0.3% in the United States, respectively.
The prevalence of hyperthyroidism was 1.3%. Very limited data on the prevalence of thyroid dysfunction are available in Japan. It was reported that the prevalence of hyperthyroidism (defined as TSH < 0.15 mIU/L) was 0.61% and the prevalence of hypothyroidism (defined as TSH > 5.0 mIU/L) was 0.68% in males and 3.13% in females in Sapporo, Japan.

Old autopsy studies of patients with overt hypothyroidism revealed accelerated atherosclerosis in the coronary arteries of these patients compared with age-matched controls. Severe coronary atherosclerosis was observed in 84% \((n=25)\) in myxedema patients, whereas 46% of age-matched control cases \((n=50)\) had severe coronary atherosclerosis. A study with a small number of patients showed that treatment of hypothyroidism affects the progression of coronary atherosclerosis. Coronary angiography showed progression of coronary atherosclerosis in all patients \((n=5)\) with inappropriate treatment for hypothyroidism, whereas progression was observed in two of seven patients who were adequately treated with thyroid hormone replacement therapy.

Intima-media thickness (IMT) of the carotid artery measured by ultrasonography represents early atherosclerotic changes and is associated with future cardiovascular events. Nagasaki et al. showed that IMT in patients with overt hypothyroidism was significantly higher than that in euthyroid control subjects \((0.635 \pm 0.08 \text{ mm vs. } 0.559 \pm 0.021 \text{ mm in control, } P<0.005)\). One-year treatment of hypothyroid patients with levothyroxine reduced the increased IMT \((0.552 \pm 0.015 \text{ mm})\). Mechanistically, a role of microRNA (miRNA) in the enhanced IMT in patients with hypothyroidism was suggested. Serum level of miRNA21-5, which was shown to enhance proliferation and migration of vascular smooth muscle cells (VSMCs), was increased in patients with hypothyroidism in association with increased IMT, although the source of miRNA21-5 was not clear.

Therefore, it is generally accepted that overt hypothyroidism accelerates atherosclerosis in an early and advanced stage. On the flip side, the role of subclinical hypothyroidism in atherogenesis remains elusive.

Higher prevalence of coronary heart disease in patients with subclinical hypothyroidism was reported (56% in patients with subclinical hypothyroidism vs 16% in euthyroid persons). It was also shown in the Rotterdam study that elderly women with subclinical hypothyroidism had a higher prevalence of myocardial infarction (odds ratio, 2.3) independently of blood pressure or high-density lipoprotein (HDL) cholesterol levels. However, Cappola et al. reported conflicting results. Cappola et al. showed no differences in the prevalence of angina or myocardial infarction between the euthyroid individuals and patients with subclinical hypothyroidism (hazard ratios, 1.07). Rodondi et al. followed 2730 persons aged 70–79 years with subclinical hypothyroidism and found that subclinical hypothyroidism was not associated with a risk of coronary heart disease or peripheral arterial diseases. Although controversial results are reported, two meta-analyses indicated that subclinical hypothyroidism was a risk factor for ischemic heart disease. Singh et al. reported that subclinical hypothyroidism was significantly associated with coronary heart disease at baseline (RR: 1.533) and death from cardiovascular causes (RR: 1.278). Another meta-analysis reported that subclinical hypothyroidism was associated with a modest increase in the risk of coronary heart diseases (RR: 1.20). Therefore, it is suggested that even mild thyroid dysfunction may affect atherogenesis. However, it remains to be determined whether normalization of TSH by thyroxine replacement therapy reduces the risk of coronary heart disease in patients with subclinical hypothyroidism. A large scale randomized clinical trial to examine the benefit of thyroid hormone replacement therapy in this population is warranted.

**Thyroid Hormone and Cardiovascular Risk Factors**

**Lipid Profile**

Thyroid hormone has various effects on lipid metabolism, such as absorption, synthesis, and degradation. Approximately 14% of hypercholesterolemic patients were reported to be in the hypothyroid state. An elevation of total cholesterol \((9.4 \pm 1.0 \text{ vs. } 6.4 \pm 0.1 \text{ mmol/L in control, } P<0.001)\), low-density lipoprotein (LDL) cholesterol \((6.3 \pm 0.8 \text{ vs. } 3.7 \pm 0.1 \text{ mmol/L in control, } P<0.001)\), and apolipoprotein B levels \((101.4 \pm 12.4 \text{ vs. } 75.2 \pm 2.2 \text{ mg/dL in control, } P<0.025)\) was reported in patients with overt hypothyroidism. The increase in LDL cholesterol levels in hypothyroidism is explained by the thyroid hormone regulation of LDL cholesterol receptor expression in the liver. LDL cholesterol receptor mRNA expression was decreased in hypothyroid rats by 50%, resulting in a prolongation of half-life of LDL cholesterol. Furthermore, LDL cholesterol from patients with hypothyroidism was more susceptible to oxidation, a modification that increases its atherogenicity. HDL cholesterol, of which concentration is inversely related to atherosclerosis, was decreased in the hypothyroid state \((1.15 \pm 0.40 \text{ vs. } 1.34 \pm 0.40 \text{ mmol/l in control, } P<0.05)\). Therefore, serum lipid profile in...
patients with overt hypothyroidism is atherosclerosis prone and is believed to be associated with thyroid hormone levels. However, HUNT study revealed a significant positive relationship between the serum TSH in normal range (0.2–4.5 mIU/L) and LDL cholesterol and triglyceride levels. Although a direct effect of TSH on serum lipid level is suggested, the detailed mechanism is not clear.

Studies that examined the effect of subclinical hypothyroidism on lipid profile showed inconsistent results. Vierhapper et al. reported no significant difference in serum total cholesterol, LDL, and HDL cholesterol levels in patients with subclinical hypothyroidism compared with normal subjects. In contrast, it was reported that serum TSH levels above 5.5 mIU/L were associated with an elevation of total cholesterol level (average 9 mg/dl). A recent meta-analysis that included 16 observational studies on serum lipid profile in patients with subclinical hypothyroidism revealed that LDL cholesterol and triglyceride levels but not HDL cholesterol levels were significantly increased in these patients. Another meta-analysis on the effect of thyroid hormone replacement therapy on serum lipid profile revealed a modest reduction in LDL cholesterol levels (10 mg/dL) and no change in HDL cholesterol levels in patients with subclinical hypothyroidism. These studies suggest that subclinical hypothyroidism has a small effect on serum LDL cholesterol levels but not on HDL cholesterol levels.

A recent cross-sectional study reported that the relationship between hypothyroidism and lipid profile showed gender difference and was substantially influenced by age. Although women with a TSH elevation showed a higher LDL cholesterol level, men with a TSH elevation showed an increase in the triglyceride level. However, older (> 65 year old) men with a TSH elevation showed higher triglyceride and LDL cholesterol levels. This study suggests that the data on the effects of thyroid function on serum lipid profile should be interpreted in consideration of age and gender.

**Blood Pressure**

Thyroid hormone plays an important role in the regulation of blood pressure levels. Diastolic hypertension occurred (84.6 ± 7.9 mmHg vs. 76.4 ± 6.8 mmHg in baseline, P < 0.05) after thyroidectomy in patients with normal blood pressure, indicating a role of thyroid hormone in the maintenance of the diastolic blood pressure level. Saito et al. reported a higher prevalence of hypertension in Japanese patients with overt hypothyroidism compared with euthyroid control group (14.8% vs. 5.5% in control). Conversely, 3.6% of hypertensive patients had hypothyroidism.

Adequate thyroid hormone replacement therapy successfully reduced diastolic blood pressure in these patients. Hypothyroidism also affects systolic blood pressure levels. It is suggested that development of systolic and diastolic high blood pressure in hypothyroid patients was due to an increase in peripheral vascular resistance and arterial stiffness respectively. Arterial stiffening can be evaluated by brachial-ankle pulse wave velocity. Nagasaki et al. reported that diastolic blood pressure was increased in patients with subclinical hypothyroidism (78.3 ± 2.3 mmHg vs. 67.3 ± 2.3 mmHg in normal subjects, P < 0.005) in association with an increase in brachial-ankle pulse wave velocity (1864.7 ± 78.4 cm/sec vs. 1381.2 ± 47.5 cm/sec in normal subjects, P < 0.0001).

A recent study showed that subclinical hyperthyroidism affected nocturnal blood pressure levels. Normotensive patients with subclinical hyperthyroidism showed higher systolic (109.3 ± 7.1 vs 107.1 ± 7.7 mmHg, P = 0.035) and diastolic blood pressure levels at night (66.4 ± 6.6 vs 64.8 ± 6.6 mmHg, P = 0.047). Therefore, both hyperthyroid and hypothyroid states increase blood pressure levels, indicating that euthyroid state is important for the maintenance of appropriate blood pressure levels.

**Endothelial Function**

Endothelial dysfunction characterized by a reduction in nitric oxide (NO) production from endothelial cells is believed to be the earliest step of the development of atherosclerosis. It was reported that endothelium-dependent flow-mediated vasodilatation that is principally mediated by endothelium-derived NO was impaired in patients with hypothyroidism. Vasodilation to acetylcholine was also attenuated in patients with subclinical hypothyroidism compared with euthyroid controls (358 ± 29% vs. 503 ± 19% in euthyroid controls, P < 0.0003). Endothelial function was improved by the thyroid hormone replacement therapy in patients with overt hypothyroidism and subclinical hypothyroidism. These data suggest that thyroid hormone is an important regulator of endothelial NO production and vascular tone. However, it is not clear whether the endothelial dysfunction is due to direct effects of thyroid hormone deficiency on blood vessel or indirect effects of hypercholesterolemia and high blood pressure, which are well known to cause endothelial dysfunction in patients with hypothyroidism.

**Homocysteine and CRP**

An increase in serum homocysteine and CRP levels is an emerging risk factor for atherosclerotic car-
diovascular diseases. Although the serum levels of homocysteine and CRP are increased in patients with hypothyroidism, the mechanisms by which thyroid hormone regulates these factors are elusive.

Hyperhomocysteinemia is an independent risk factor for premature atherosclerosis. It is suggested that an increase in oxidative stress, impairment of endothelial function, and induction of thrombosis are responsible for the acceleration of atherosclerosis by homocysteine. An elevation of serum homocysteine levels in patients with overt hypothyroidism was reported (12.4 vs. 8.8 mmol/L in non-hypothyroid group, \(P<0.05\)). Thyroid hormone supplementation successfully reduced serum homocysteine levels. In contrast, it was shown that subclinical hypothyroidism did not affect serum homocysteine level. A meta-analysis showed a significant association between plasma homocysteine levels and hypothyroidism severity. These studies indicate that overt but not subclinical hypothyroidism affects serum homocysteine levels.

It was reported that genetic, nutritional (vitamin B6, B12, and folate), and acquired factors (renal function and smoking) affect serum homocysteine levels. Thyroid hormone was shown to modulate the expression of genes involved in the metabolism of homocysteine and reduce serum homocysteine levels. However, changes in folate levels or renal function were reported to be the major determinants of the increased serum homocysteine level in patients with hypothyroidism.

CRP is now recognized as a useful biomarker that is associated with future cardiovascular events. An increase in high-sensitivity CRP level predicts future cardiovascular risk in a broad range of patients with cardiovascular diseases, such as stable angina, undergoing elective angioplasty, and coronary artery bypass graft. An increase in serum CRP levels in patients with overt and subclinical hypothyroidism was reported (2.8 ± 2.4 vs. 1.8 ± 1.9 mg/L in non-hypothyroid group, \(P<0.05\)). However, replacement of thyroid hormone in patients with subclinical hypothyroidism did not affect CRP levels. Another study even failed to detect any increase in CRP levels in patients with subclinical hypothyroidism. These results suggest that overt but not subclinical hypothyroidism is associated with an elevation of CRP levels. The molecular mechanism for the thyroid hormone regulation of CRP level is not clear. Therefore, further studies are needed to clarify the association of thyroid hormone with CRP and its regulatory mechanisms.

Atherosclerotic risk factors associated with hypothyroidism are listed in Table 1.

| Low Density Lipoprotein Cholesterol ↑ | Blood Pressure ↑ | C-reactive protein ↑ | Homocysteine ↑ | Plasminogen Activator Inhibitor-1 ↑ |
|--------------------------------------|-----------------|-------------------|---------------|----------------------------------|

### Table 1. Atherogenic Risk Factors Associated with Hypothyroidism

In addition to modification of atherosclerotic risk factors, recent studies have shown that thyroid hormone has direct effects on the vasculature.

Mizuma et al. showed that VSMCs expressed type II iodothyronine deiodinase that converts inactive precursor thyroxine (T4) to triiodothyronine (T3), an active thyroid hormone. The type II iodothyronine deiodinase activity is increased in the hypothyroid state and plays an important role in the maintenance of intracellular T3 level. It was also indicated that VSMCs expressed mRNA of 4 thyroid hormone receptors (TRs) designated \( \alpha 1, \alpha 2, \beta 1 \), and \( \beta 2 \). It was shown that TR\( \alpha \) was involved in the regulation of vascular tone. Contraction of coronary arteries in TR\( \alpha \) knockout mice was increased compared with that of wild type mice, which was associated with a decrease in K+ channel activity. Protective roles of TR\( \alpha \) against atherogenesis were recently reported. Mice lacking TR\( \alpha \) locus with apolipoprotein E-deficient background showed enhanced atherosclerosis and IL-1β production. These results suggest that blood vessels are targets of thyroid hormone in both physiological and pathological conditions.

Thyroid hormone is known to reduce systemic vascular resistance. Ojamaa et al. reported that thyroid hormone induced relaxation of VSMCs through a direct effect. Because the relaxation occurred within 10 min, it is suggested that the relaxation is a non-genomic effect of thyroid hormone on VSMC. The specific binding sites for triiodothyronine (T3) were also identified in the plasma membrane of VSMCs. Because Ojamaa et al. failed to detect an increase in cGMP levels after T3 stimulation in endothelial cells, it was concluded that T3 did not induce NO production. However, recent studies indicated that endothelial NO plays a critical role in thyroid hormone-induced vasodilatation. A decrease in forearm blood flow by N\( \text{G} \)-monomethyl-L-arginine (L-NMMA), a NO synthase inhibitor, was higher in patients with hyperthyroidism compared with normal subjects.
L-NMMA decreased forearm blood flow by 2.8 ± 0.6 fold and 0.61 ± 0.7 fold in patients with hyperthyroidism and normal subjects, respectively \((P<0.05)\). Another study showed that endothelium-dependent vasodilatation was impaired in patients with subclinical hypothyroidism \(^{36}\). These results suggest an important role of NO in T3-induced vasodilatation. Although the reason for the discrepant results between these recent studies and Ojamaa et al. \(^{59}\) is not clear, subsequent studies confirmed that thyroid hormone activated NO synthase through phosphatidylinositol 3-kinase/Akt pathway in endothelial cells \(^{61}\) and VSMC \(^{62}\). Therefore, it is suggested that non-genomic effects of thyroid hormone activate NO pathway.

Although several target genes of T3 have been identified in cardiac myocytes \(^{63}\), relatively little is known about the target genes of T3 in the blood vessel. A recent report showed that T3 at physiological concentrations increased matrix Gla protein in VSMCs by 3-8 fold \(^{64}\). Because matrix Gla protein is known to act as an inhibitor of vascular calcification \(^{65}\), it is suggested that thyroid hormone may prevent vascular calcification, one of the markers of advanced atherosclerotic lesion.

It was reported that T3 induced expression of adrenomedullin, a potent vasodilator peptide, in rat endothelial cells \(^{66}\). The induction of adrenomedullin may be one of the mechanisms by which T3 reduces vascular resistance. T3 also induced adrenomedullin expression in VSMC \(^{67}\).

T3 was reported to affect the metabolism of extracellular nucleotide \(^{68}\). T3 increased hydrolysis of AMP but not ATP or ADP in VSMC, suggesting that T3 increases production of adenosine that is an important local vasodilator molecule. The increase in AMP hydrolysis was due to an increase in the expression level of ecto-5’-nucleotidase (ecto-5’-NT) that converts AMP to adenosine. Induction of ecto-5’-NT may be another possible mechanism for T3-induced vascular relaxation. These studies suggest that thyroid hormone dilates blood vessels through multiple mechanisms involving upregulation of NO, adrenomedullin, and adenosine.

Downregulation of angiotensin II type 1 receptor (AT1R) expression in VSMCs by T3 at a relatively high concentration was reported (47% reduction at 1 \(\mu\)M of T3, \(P<0.05\)) \(^{69}\). Intraperitoneal administration of T3 decreased aortic AT1R expression. The downregulation of AT1R may play a role in the sustained vasodilatation in the hyperthyroid state. In addition, Fukuyama et al. showed that T3 inhibited AT1R signaling \(^{70}\). T3 inhibited angiotensin II-induced activation of cAMP response element binding protein (CREB), a 43-KDa nuclear transcription factor involved in a broad range of gene expression, such as cell cycle and metabolism. Although a previous study suggested that angiotensin II-induced CREB activation was dependent on extracellular signal-regulated protein kinase (ERK) and p38 mitogen-activated protein kinase \(^{71}\), T3 did not affect phosphorylation of these kinases. Instead, TR directly interacted with CREB. Although the precise mechanism for the inhibition of CREB activity by TR is not clarified, structural changes induced by binding of T3 to TR is supposed to inhibit the activation of CREB. Balloon injury-induced neointimal formation in the rat carotid artery was attenuated in hyperthyroid rats with decreased BrdU incorporation and phosphorylation of CREB in the neointima.

Recently, Kasahara et al. reported that T3 as well as T4 inhibited platelet-derived growth factor (PDGF)-induced DNA synthesis of VSMC \(^{72}\). This may be explained by that T4 is converted to T3 through type II deiodinase in VSMC \(^{56}\). Although, molecular mechanism for thyroid hormone inhibition of PDGF-induced VSMC growth is not clear, these studies suggest that T3 inhibits VSMC growth through blunting the effect of angiotensin II and PDGF, which may be a novel anti-atherosclerotic mechanism of thyroid hormone.

### Thyroid Hormone and Angiogenesis

Angiogenesis plays a crucial role in vascular remodeling. T3 induces cardiac hypertrophy in association with coronary angiogenesis. The T3-induced angiogenesis took place at the capillary level and was dependent on the upregulation of basic fibroblast growth factor (FGF) \(^{73}\). A subsequent study showed that thyroid hormone-induced angiogenesis was inhibited by PD98059, an ERK kinase inhibitor \(^{74}\). Bergh et al. showed that the angiogenic effect of T3 was mediated by \(\alpha v \beta 3\) integrin that worked as a receptor for T3 \(^{75}\). In the downstream of \(\alpha v \beta 3\) integrin, protein kinase D/histone deacetylase 5 pathway was activated, resulting in the induction of FGF2 \(^{76}\). Therefore, it is suggested that thyroid hormone induces angiogenesis through non-genomic effects. An imbalance between angiogenesis and cardiac hypertrophy is suggested as one of the causes that induce heart failure in the pressure-overloaded heart. T3 restored the capillary density of the pressure-overloaded heart and thereby improved left ventricular function \(^{77}\). It was also shown that TR\(\beta\) was involved in the maintenance of capillary density in the hypertrophied heart.

Hypoxia inducible factor (HIF), a transcription factor induced by hypoxia, plays an important role in...
angiogenesis through the upregulation of vascular endothelial growth factor (VEGF). Thyroid hormone increased the expression of HIF protein through activation of $\alpha_v\beta_3$ integrin/phosphatidylinositol 3-kinase pathway. It is well known that phosphatidylinositol 3-kinase pathway also activates eNOS and NO plays a critical role in angiogenesis. Therefore, it is suggested that VEGF and NO also may be involved in thyroid hormone-induced angiogenesis.

Angiogenesis may be a double-edged sword for the cardiovascular system. Formation of collateral arteries, which attenuates ischemia, is beneficial to patients with coronary artery diseases and peripheral vascular diseases. However, neovascularization in the atherosclerotic plaque is believed to destabilize the plaque and may predispose to plaque rupture and subsequent thrombosis, a mechanism of the development of acute coronary syndrome. It is not clear whether thyroid hormone-induced angiogenesis is beneficial or detrimental for the stability of atherosclerotic plaque. Future study is needed.

The effect of thyroid hormone on the vasculature is summarized in Fig. 1.

**Thyroid Hormone and the Renin Angiotensin System**

The renin angiotensin system (RAS) plays an important role in cardiovascular and renal function and blood pressure regulation. RAS is also critically involved in the development of cardiovascular remodeling, such as atherosclerosis and heart failure. Generally, circulating RAS components are activated in the hyperthyroid state. Renin production and secretion were increased by T3. Ichihara et al. showed that T3 induced mRNA expression and production of renin from rat juxtaglomerular cells in culture. In accordance with the *in vitro* study, it was reported that more than half of hypothyroid patients showed low plasma renin activity. T3 also increased angiotensinogen production from liver in rats. However, another report failed to detect any changes in the angiotensinogen level in the hyperthyroid dog. The differential results may be ascribed to the difference of species or duration and dosages of T3 treatment. Interestingly, both studies reported an increase in plasma angiotensin II levels, suggesting that the systemic RAS is eventually activated in hyperthyroidism regardless of angiotensinogen levels.

T3 also increased angiotensinogen production from liver in rats. However, another report failed to detect any changes in the angiotensinogen level in the hyperthyroid dog. The differential results may be ascribed to the difference of species or duration and dosages of T3 treatment. Interestingly, both studies reported an increase in plasma angiotensin II levels, suggesting that the systemic RAS is eventually activated in hyperthyroidism regardless of angiotensinogen levels.

Thysm concentrations of angiotensin converting enzyme (ACE) that produces angiotensin II from angiotensin I was also increased in hyperthyroid rats. However, thyroid hormone shows differential effects on tissue ACE activity. Carnero–Ramos et al. showed that T3 administration increased ACE expression in the kidney but reduced that in the heart and aorta, although the mechanism for the differential tissue-specific regulation of ACE expression have not been
may be suitable for treatment of hypercholesterolemia in patients with ischemic heart disease. T-0681, the liver-specific thyromimetics, reduced plasma cholesterol levels by 60% and development of atherosclerotic lesion by 80% in New Zealand white rabbit on a high-cholesterol diet. Several thyromimetics are under development for clinical use.

**Conclusion**

Thyroid hormone modulates vascular remodeling through NO production, suppression of VSMC proliferation, and angiogenesis. Thyroid hormone also improves serum lipid profile and reduces blood pressure. These effects of thyroid hormone are suitable for treatment of patients with atherosclerotic cardiovascular diseases and metabolic syndrome. Thyroid hormone mimetics may open a new avenue for treatment of hypercholesterolemia, obesity, and atherosclerotic cardiovascular diseases.

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**Conflict of Interest**

There is no conflict of interest to disclose.

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