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Review Article

Update on Lipid Metabolism and Thyroid Disorders

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Abstract

Thyroid hormone plays an important role in the regulation of lipid metabolism. It acts predominantly through its nuclear receptors (thyroid hormone receptor α and β) to regulate the gene expression related to lipid metabolism. Both overt hypothyroidism and hyperthyroidism result in abnormalities of lipid profile. However, changes in serum lipid profiles in patients with subclinical hypothyroidism have been inconsistent. In recent years, thyroid receptor β1-selective analogue represents a new class of hypolipidemic compound have been developed. Some of these T3 analogues are very potent in lowering serum cholesterol and triglyceride in animal models and human clinical studies. This mini review on the mechanisms that affect lipid profile under pathological thyroid conditions, and give brief touch on thyroid analogues.

Special Issue on

Role of Thyroid Hormone in Metabolic Homeostasis

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ABBREVIATIONS

TR: Thyroid Hormone Receptor; L-T4: Levothyroxine; TC: Total Cholesterol; HMGCR: 3-hydroxy-3-methyl-Glutaryl coenzyme A reductase; SREBP: Sterol Regulatory Element Binding Protein; TRE: Thyroid Hormone Responsive Element; TG: Triglyceride; LDL-R: Low Density Lipoprotein Cholesterol Receptor; HDL: High-Density Lipoprotein cholesterol; IDC: Intermediate Density lipoprotein Cholesterol; VLDL-C: Very Low Density Lipoprotein Cholesterol; CYP7A1: Cholesterol 7-Hydroxylase; HL: Hepatic Lipase; LPL: Lipoprotein Lipase; CETP: Cholesteryl-Esters Transfer Protein; LCAT: Lecithin-Cholesterol Acyltransferase; Lp (a): Lipoprotein (a); CM: Chylomicron; apo (B): Apolipoprotein (B); Free thyroxine: FT3: FT3 Free triiodothyronine; TSH: Thyrotropin

INTRODUCTION

Thyroid Hormone (TH) has multiple effects on the regulation of lipid digestion, absorption, synthesis, and catabolism [1]. Cumulative evidence shows that both overt hypothyroidism and subclinical hypothyroidism can result in hyperlipidemia, leading to increased risk of cardiovascular disease. With the elucidation of the molecular mechanism of thyroid hormone action, we have gained much understanding the influences of thyroid hormone on lipid metabolism. This article intends to update the current knowledge concerning the impact of thyroid disorders on lipid metabolism and levothyroxine (L-T4) treatment, and also reviews the effect of thyroid hormone analogue treatment on hyperlipidemia.

Effects of thyroid hormone on cholesterol metabolism

TH regulates cholesterol synthesis through multiple mechanisms. Liver is the main organ for cholesterol synthesis. 3-Hydroxy-3-Methyl-Glutaryl Coenzyme A Reductase (HMGCR) is the rate-limiting enzyme in cholesterol synthesis, which is regulated by several hormones, such as insulin, glucagon, estrogen, glucocorticoid and thyroid hormone [2]. In hypothyroid state, *HMGCR* mRNA levels are reduced and treatment with thyroid hormone restores it to normal level. Thyroid hormone stimulates *HMGCR* transcription and increases its stability [3]. TH stimulation of *HMGCR* occurs *via* Sterol Regulatory Element Binding Protein-2 (SREBP-2), a cholesterol sensing factor, low density Lipoprotein Cholesterol Receptor (LDL-R) and ATP-Binding Cassette Transporters (ABCA1 and ABCG5/8) [4-8]. When intracellular cholesterol level is low, thyroid hormone stimulates the transcription of *SREBP2* gene, leads to increasing SREBP-2-mediated *HMGCR* gene transcription [5]. Thyroid hormone-mediated *LDL-R* and *ABCA1/ABGG5/8* expression plays a major pathway for hepatic cholesterol clearance. TH also reduces cholesterol through enhancing cholesterol clearance pathway. Conversion of cholesterol into bile acids is important for maintaining whole body cholesterol homeostasis. The rate-limiting enzyme in bile acid synthesis is controlled by cholesterol 7-hydroxylase (CYP7A1), which is regulated by thyroid hormone [9]. Recent studies using ChIP-Seq found 3 putative Thyroid Hormone Responsive Elements (TREs) in human *CYP7A1* promoter. These TREs confer T3 transactivation of CYP7A1 in human hepatic cells (HepG2) [10]. In addition, thyroid hormone increases the activity of the enzymes involved in the metabolism of lipoproteins and reverse cholesterol transport, such as hepatic lipase (HL) [11], lipoprotein lipase (LPL) [12], Cholesteryl-Esters Transfer Protein (CETP) [13], and Lecithin-Cholesterol Acyltransferase (LCAT) [14].

Effects of thyroid hormone on circulating triglyceride level

Thyroid hormone plays a role in both lipogenesis and lipolysis. Thyroid hormone regulates Lipoprotein Lipase (LPL) an essential enzyme that responsible for removing Triglycerides (TG) from circulating chylomicrons and Very Low Density Lipoproteins (VLDL). LPL catalyzes TG breakdown into non-esterfied fatty acid and transporting to adipose tissue where it re-esterfied and storage as TG [12,15,16]. Also, the fatty acids yield from LPL hydrolysis TG as energy source for heart. Additionally, TH affects TG levels involves angioprotein-like 3 (ANGPTL3), a potent LPL inhibitor. Over expression of ANGPTL3 in mice significantly enhances total cholesterol, non-esterfied fatty acid and TG. Patients carrying ANGPTL3 mutation have increased circulating TG levels [17]. Furthermore, in rats, thyroid hormone treatment reduced *ANGPTL3* mRNA expression by 70%. At transcription level, *ANGPTL3* is negatively regulated by thyroid hormone, which is mediated by TRβ but not TRα [18]. In hyperthyroid condition, TG level showed either no change or decrease, partly, due to T3 down regulate *ANGPTL3* and stimulates *PLP*, leading to hydrolysis TG. Then, T3-mediated LDLR stimulation dramatically increases clearing capacity for LDL [17]. Thyroid hormone influences TG homeostasis also involves regulating *APOA5* gene transcription. Apolipoprotein A-V (ApoA5) is associated with HDL, VLDL and chylomicrons. ApoA5 regulates TG level through stimulating LPL-mediated TG hydrolysis and inhibiting hepatic VLDL-TG formation. Patients with single nucleotide polymorphisms or mutation of APOA5 manifest markedly reduced plasma postheparin LPL activity and hypertriglyceridemia [19]. TH directly regulates AproA5 gene transcription via TRW in ApoA5 promoter and increases the protein level [20]. Animal experiment showed that *ApoA5* mRNA significantly reduced in hypothyroid rats. After T3 treatment, *ApoA5mRNA* level returned to normal. Thyroid hormone regulation of circulating TG level is more complex involving in multi-pathways and positive and negative gene regulations.

LIPID PROFILES IN OVERT HYPOTHYROIDISM

Serum Total Cholesterol (TC), LDL-C, lipoprotein (a) [Lp(a)], oxi-LDL, ApoB [1,21], remnants of VLDL and Chylomicron (CM) levels are increased in overt hypothyroidism [22], while serum levels of triglyceride, High-Density Lipoprotein Cholesterol (HDL) and VLDL are normal or slightly increased [1,2]. All of the lipid abnormalities in overt hypothyroidism are reversible with levothyroxine (L-T4) therapy unless the patient has underlying hyperlipidemia [12].

In overt hypothyroidism, thyroid hormone effects on LDL receptor expression and cholesterol absorption outweigh the effects of decreased hepatic cholesterol synthesis, leading to high serum levels of LDL, Intermediate Density Lipoprotein Cholesterol (IDC), and total cholesterol levels [23]. Additionally, LPL activity is decreased in hypothyroidism, resulted in higher level of VLDL-TG. Studies showed that Lipoprotein (a) [Lp(a)] levels are increased in patients with overt hypothyroidism and decrease after L-T4 treatment. Lp(a) is a complex of low density lipoprotein in which apolipoprotein (apo) B-100 is linked to apo(a) by a disulfied bridge. Lp(a) promotes foam cell formation and deposition of cholesterol, resulting in increased atherosclerotic and thrombogenicpotential. The mechanism may be related to the decreased clearance of LP(a) mediated by the LDL-R degradation pathway [23]. The levels of apolipoprotein (B) are higher in both overt and subclinical hypothyroidism and have been shown to decrease after L-T4 treatment [24-26].

Cholesteryl ester transfer protein (CETP) transfers cholesterol from HDL-cholesterol (C) to LDL-C and VLDL-C. Plasma CETP concentrations are decreased in hypothyroidism and increased in hyperthyroidism, which may lead to the higher serum HDL-C concentrations in hypothyroidism [27]. Thyroid hormone analogue (GC-1) can also increase hepatic HDL-C receptor (scavenger receptor B1) [28], and accelerate the clearance of HDL-C by the liver. HDL-C particles can be subdivided into the smaller HDL2 (primarily incorporating Apo A-I) and larger HDL3 (incorporating Apo A-I and Apo A-II) subfractions. HL can catabolize TG within HDL-C, and regulate the hydrolysis of HDL-2 to HDL3. HL is decreased in hypothyroidism, leading to the higher HDL2 levels [12,13,30,31]. Apo A-I and Apo A-II are major constituents of HDL-C. Hypothyroidism inhibits the transcription of the Apo A-I gene, but the decreased activity of HL results in slower clearance of Apo A-I, thus leading to increased Apo-AI levels. Human studies show that Apo A-I levels are decreased in hyperthyroidism and increased in hypothyroidism, whereas Apo A-II levels are not influenced by either hyperthyroidism or hypothyroidism [13,30,31].

Patients with overt hypothyroidism usually have higher LDL-C, leading to increased oxidized (oxi)-LDL. Oxi-LDLs are taken up by macrophages in the arterial walls to produce foam cells, and as such may be a risk factor for atherosclerosis. The high levels of oxi-LDL are reversible with L-T4 treatment [32,33]. Both overt hypothyroidism and subclinical hypothyroidism can levels. However, studies show that thyroid status does not affect LDL particle size [34].

Lipid profiles in subclinical hypothyroidism

The results of serum lipid levels in patients with subclinical hypothyroidism are inconsistent. The results of cross-sectional studies of serum lipid levels in patients with subclinical hypothyroidism have been inconsistent, and are well reviewed by Pearce and Duntas [1,21]. Generally, serum total cholesterol and LDL-C levels are normal or increased [1,21]; oxi-LDL [33], apo (B), remnants of VLDL and CM are increased [35]. TG and HDL may be normal [36,37], increased [38], or decreased [39]. The lipid abnormality in subclinical hypothyroidism may be related to the values of serum TSH. The lipid profile of patients with subclinical hypothyroidism with higher serum TSH level is similar to that in patients with overt hypothyroidism.

The mechanisms involved in the hypercholesterolemia resulting from subclinical hypothyroidism are the same as overt hypothyroidism. Although Free Thyroxine (FT4) and Free Triiodothyronine (FT3) levels in patients with subclinical hypothyroidism are within the normal reference range, TSH level is higher. Over time, the subclinical may develop to overt hypothyroidism. The abnormality of lipid profiles in subclinical hypothyroidism may be related to gradually decreased TH levels in the serum and tissues [35,40]. Additionally, high TSH

level stimulates *HMGCR* expression by stimulating the cyclic adenosine monophosphate/protein kinase A/cyclic adenosine monophosphate-responsive element binding protein (cAMP/PKA/CREB) cassette [41].

Overt hyperthyroidism and lipid profiles

In overt hyperthyroidism, serum levels of total cholesterol, LDL-C, and HDL-C (mainly HDL2) are decreased, while triglyceride levels are slightly elevated, normal or reduced [13,42,43], and oxi-LDL levels are increased [44,45]. Whether the decreased HDL-C levels and increased oxi-LDL levels lead to atherosclerosis in hyperthyroidism is not known. Reason for this mild hypertriglyceridemia is unclear. Lipolysis is augmented in hyperthyroidism with elevation of free fatty acids in plasma, but hepatic lipogenesis is also augmented due to increased free fatty acid flux from adipose tissue to the liver [21,46]. After treatment for hyperthyroidism, the hypertriglyceridemia caused by overt hyperthyroidism can be reversed.

ASSOCIATION OF SUBCLINICAL AND OVER HYPOTHYROIDISM WITH CARDIOVASCULAR DISEASES

The higher levels of serum total cholesterol, LDL-C, remnants of VLDL and CM, oxi-LDL, and apoB that result from subclinical hypothyroidism are risk factors for cardiovascular disease. Subclinical hypothyroidism has been associated with an increased risk of cardiovascular disease and mortality in some prospective population-based cohort studies [47-49]. By contrast, the incidence of coronary heart disease and mortality due to coronary heart disease were not increased in other prospective population-based studies [50-53]. In a meta-analysis from 11 prospective cohort studies, the risk of cardiovascular disease was negatively related to initial TH levels [54].

L-T4 treatment has a hypolipemic effect on subclinical hypothyroidism. Treatment with L-T4 can prevent the progression from subclinical to overt hypothyroidism and improve hyperlipidemia, thus decreasing the risk of atherogenic disease. A number of small-scale (N=20 to100), randomized, placebo-controlled, double-blind clinical trials have recently been conducted to study the effects of L-T4 therapy on lipid profiles, and the results are inconsistent [1]. Generally speaking, the higher the initial levels of serum cholesterol and TSH, the greater the therapeutic benefit. Patients whose serum TSH levels exceed 10 mIU/L are at increased risk for heart failure and cardiovascular mortality and should be treated with L-T4 [55]. Patients whose TSH levels are greater than the upper limit of a given laboratory reference range but less than 10 mIU/L should be considered for treatment if they have symptoms of hypothyroidism, positive antithyroid antibody or cardiovascular risk factors (eg. hypertension, hypercholesterolemia, insulin resistance or diabetes) [56]. The treatment of mild subclinical hypothyroidism (serum TSH concentration of 4.5-10mIU/L) is not recommended in older patients because available evidence suggests the benefit of treatment may be reduced in patients above 65 years of age [57,58].

Perspectives of thyroid hormone analogues in treatment of hyperlipidemia

Thyroid hormone plays an important role in the regulation of lipid metabolism [59]. There are mainly two TR genes (TRα and TRβ), with different patterns of expression in different tissues. In liver, TRβ exerts approximately 80% T3 action. TRβ/T3 mediates cholesterol reduction and lipid metabolism in liver. In past decade, TRβ1 selective ligand has been one of the focal points for developing cholesterol reducing drugs. The idea is that T3 analogues should preserve the beneficial effect of T3 in reducing cholesterol levels while minimizing the harmful effects on heart and bone. The research on the selective thyroid hormone receptor β1 analogues has made significant progress. These TRβ1-selective ligands include L-9490 [60], CGS23425 [61], Triac [62], GC-1 [63], GC-24 [64], KB141 [65], KB2115 [66] and MB07811 [67]. Among them, GC-1, KB2115, and MB07811 are highly liver-selective T3 analogues and KB141 is a non-tissue selective analogue. Theoretically, these highly liver-targeting ligands have higher cholesterol-lowering potential with fewer side effects. For example, KB141 induced weight loss and an increased metabolic rate when tested in animals. Besides KB141, the liver-selective TRβ1 analogues GC-1, MB07811 and KB2115 increased expression of hepatic LDL-R and hepatic HDL receptor SR-B1, stimulated the activity of CYP7A1, and increased fecal excretion of bile acids. TRβ1 analogues also decreased levels of serum triglycerides and Lp(a) without adverse effects on heart and bone [68-71].

Presently, three selective TRβ1 analogues (KB2115, GC-1, and MB07811) reached human clinical trials for hypercholesterolemia and displayed impressive early results for this indication [66,70,71]. The studies demonstrated that the analogues took effect quickly (1-2 weeks after commencing treatment).Patients had a significant reduction in serum LDL-C levels (as high as 40% within 3 months) without side effects on heart, bone or muscle [66,70,71]. Addition of KB2115 (Eprotirome) to statin therapy resulted in further substantial reduction in levels of LDL-C, triglycerides, apolipoprotein B, and Lp(a) in human clinical trials, which suggests that these two classes of medication may work through complementary mechanisms [72].

Unfortunately, the development of KB2115 was discontinued in 2012, after a 12-month toxicology study revealed that prolonged exposure to the drug led to cartilage damage [72]. This led to termination of this trial and all other related studies (such as GC-1 and MB07811). Although the development of selective TRβ1 analogues has been halted at present, their unique lipid-lowering mechanism indicates that the selective TRβ1 may still be a potential drug to aid in lowering lipid levels and augmenting weight loss.

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REFERENCES

1. Pearce EN. Update in lipid alterations in subclinical hypothyroidism. J Clin Endocrinol Metab. 2012; 97: 326-333.
2. Mullur R, Liu YY, Brent GA. Thyroid hormone regulation of metabolism. Physiol Rev. 2014; 94: 355-382.
3. Ness GC, Chambers CM. Feedback and hormonal regulation of hepatic 3-hydroxy-3-methylglutaryl coenzyme A reductase: the concept of cholesterol buffering capacity. Proc Soc Exp Biol Med. 2000; 224: 8-19.
4. Goldstein JL, DeBose-Boyd RA, Brown MS. Protein sensors for membrane sterols. Cell. 2006; 124: 35-46.
5. Shin DJ, Osborne TF. Thyroid hormone regulation and cholesterol metabolism are connected through Sterol Regulatory Element-Binding Protein-2 (SREBP-2). J Biol Chem. 2003; 278: 34114-34118.
6. Bakker O, Hudig F, Meijssen S, Wiersinga WM. Effects of triiodothyronine and amiodarone on the promoter of the human LDL receptor gene. Biochem Biophys Res Commun. 1998; 249: 517-521.
7. Lopez D, Abisambra Socarrαs JF, Bedi M, Ness GC. Activation of the hepatic LDL receptor promoter by thyroid hormone. Biochim Biophys Acta. 2007; 1771: 1216-1225.
8. Huuskonen J, Vishnu M, Pullinger CR, Fielding PE, Fielding CJ. Regulation of ATP-binding cassette transporter A1 transcription by thyroid hormone receptor. Biochemistry. 2004; 43: 1626-1632.
9. Hashimoto K, Cohen RN, Yamada M, Markan KR, Monden T, Satoh T, et al. Cross-talk between thyroid hormone receptor and liver X receptor regulatory pathways is revealed in a thyroid hormone resistance mouse model. J Biol Chem. 2006; 281: 295-302.
10. Lammel Lindemann JA, Angajala A, Engler DA, Webb P, Ayers SD. Thyroid hormone induction of human cholesterol 7 alpha-hydroxylase (Cyp7a1) in vitro. Mol Cell Endocrinol. 2014; 388: 32-40.
11. Lithell H, Boberg J, Hellsing K, Ljunghall S, Lundgvist G, Vessby B, et al. Serum lipoprotein and apolipoprotein concentrations and tissue lipoprotein-lipase activity in overt and subclinical hypothyroidism: the effect of substitution therapy. Eur J Clin Invest. 1981; 11: 3-10.
12. Kuusi T, Taskinen MR, Nikkilä EA. Lipoproteins, lipolytic enzymes, and hormonal status in hypothyroid women at different levels of substitution. J Clin Endocrinol Metab. 1988; 66: 51-56.
13. Tan KC, Shiu SW, Kung AW. Effect of thyroid dysfunction on high-density lipoprotein subfraction metabolism: roles of hepatic lipase and cholesteryl ester transfer protein. J Clin Endocrinol Metab. 1998; 83: 2921-2924.
14. Ridgway ND, Dolphin PJ. Serum activity and hepatic secretion of lecithin:cholesterol acyltransferase in experimental hypothyroidism and hypercholesterolemia. J Lipid Res. 1985; 26: 1300-1313.
15. Nikkilä EA, Kekki M. Plasma triglyceride metabolism in thyroid disease. J Clin Invest. 1972; 51: 2103-2114.
16. Abrams JJ, Grundy SM, Ginsberg H. Metabolism of plasma triglycerides in hypothyroidism and hyperthyroidism in man. J Lipid Res. 1981; 22: 307-322.
17. Korstanje R, Eriksson P, Samnegård A, Olsson PG, Forsman-Semb K, Sen S, et al. Locating Ath8, a locus for murine atherosclerosis susceptibility and testing several of its candidate genes in mice and humans. Atherosclerosis. 2004; 177: 443-450.
18. Fugier C, Tousaint JJ, Prieur X, Plateroti M, Samarut J, Delerive P. The lipoprotein lipase inhibitor ANGPTL3 is negatively regulated by thyroid hormone. J Biol Chem. 2006; 281: 11553-11559.
19. Calandra S, Priore Oliva C, Tarugi P, Bertolini S. APOA5 and triglyceride metabolism, lesson from human APOA5 deficiency. Curr Opin Lipidol. 2006; 17: 122-127.
20. Prieur X, Huby T, Coste H, Schaap FG, Chapman MJ, Rodríguez JC. Thyroid hormone regulates the hypotriglyceridemic gene APOA5. J Biol Chem. 2005; 280: 27533-27543.
21. Duntas LH, Brenta G. The effect of thyroid disorders on lipid levels and metabolism. Med Clin North Am. 2012; 96: 269-281.
22. Ito M, Takamatsu J, Matsuo T, Kameoka K, Kubota S, Fukata S, et al. Serum concentrations of remnant-like particles in hypothyroid patients before and after thyroxine replacement. Clin Endocrinol (Oxf). 2003; 58: 621-626.
23. Gälman C, Bonde Y, Matasconi M, Angelin B, Rudling M. Dramatically increased intestinal absorption of cholesterol following hypophysectomy is normalized by thyroid hormone. Gastroenterology. 2008; 134: 1127-1136.
24. Tzotzas T, Krassas GE, Konstantinidis T, Bougoulia M. Changes in lipoprotein(a) levels in overt and subclinical hypothyroidism before and during treatment. Thyroid. 2000; 10: 803-808.
25. Monzani F, Caraccio N, Kozakowa M, Dardano A, Vittone F, Virdia A, et al. Effect of levothyroxine replacement on lipid profile and intima-media thickness in subclinical hypothyroidism: a double-blind, placebo- controlled study. J Clin Endocrinol Metab. 2004; 89: 2099-2106.
26. Pérez A, Cubero JM, Sucunza N, Ortega E, Arcelús R, Rodriguez-Espinosa J, et al. Emerging cardiovascular risk factors in subclinical hypothyroidism: lack of change after restoration of euthyroidism. Metabolism. 2004; 53: 1512-1515.
27. Dullaart RP, Hoogenberg K, Groener JE, Dikkeschei LD, Erkelens DW, Doorenbos H. The activity of cholesteryl ester transfer protein is decreased in hypothyroidism: a possible contribution to alterations in high-density lipoproteins. European Journal of Clinical Investigation. 1991; 20: 581-587.
28. Ito M, Arishima T, Kudo T, Nishihara E, Ohye H, Kubota S, et al. Effect of levo-thyroxine replacement on non-high-density lipoprotein cholesterol in hypothyroid patients. J Clin Endocrinol Metab. 2007; 92: 608-611.
29. Johansson L, Rudling M, Scanlan TS, Lundåsen T, Webb P, Baxter J, et al. Selective thyroid receptor modulation by GC-1 reduces serum lipids and stimulates steps of reverse cholesterol transport in euthyroid mice. Proc Natl Acad Sci U S A. 2005; 102: 10297-302.
30. O'Brien T, Katz K, Hodge D, Nguyen TT, Kottke BA, Hay ID. The effect of the treatment of hypothyroidism and hyperthyroidism on plasma lipids and apolipoproteins AI, AII and E. Clin Endocrinol (Oxf). 1997; 46: 17-20.
31. Muls E, Blaton V, Rosseneu M, Lesaffre E, Lamberigts G, De Moor P. Serum lipids and apolipoproteins A-I, A-II, and B in hyperthyroidism before and after treatment. J Clin Endocrinol Metab. 1982; 55: 459-464.
32. Duntas LH, Mantzou E, Koutras DA. Circulating levels of oxidized low-density lipoprotein in overt and mild hypothyroidism. Thyroid. 2002; 12: 1003-1007.
33. Costantini F, Pierdomenico SD, De Cesare D, De Remigis P, Bucciarelli T, Bittolo-Bon G, et al. Effect of thyroid function on LDL oxidation. Arterioscler Thromb Vasc Biol. 1998; 18: 732-737.
34. Kim CS, Kang JG, Lee SJ, Ihm SH, Yoo HJ, Nam JS, et al. Relationship of

low-density lipoprotein (LDL) particle size to thyroid function status in Koreans. Clin Endocrinol (Oxf). 2009; 71: 130-136.

35. Ito M, Takamatsu J, Sasaki I, Hiraiwa T, Fukao A, Murakami Y, et al. Disturbed metabolism of remnant lipoproteins in patients with subclinical hypothyroidism. Am J Med. 2004; 117: 696-699.

36. Walsh JP, Bremner AP, Bulsara MK, O'leary P, Leedman PJ, Feddema P, et al. Thyroid dysfunction and serum lipids: a community-based study. Clin Endocrinol (Oxf). 2005; 63: 670-675.

37. Bell RJ, Rivera-Woll L, Davison SL, Topliss DJ, Donath S, Davis SR. Well-being, health-related quality of life and cardiovascular disease risk profile in women with subclinical thyroid disease - a community-based study. Clin Endocrinol (Oxf). 2007; 66: 548-556.

38. Hueston WJ, Pearson WS. Subclinical hypothyroidism and the risk of hypercholesterolemia. Ann Fam Med. 2004; 2: 351-355.

39. Lai Y, Wang J, Jiang F, Wang B, Chen Y, Li M, et al. The relationship between serum thyrotropin and components of metabolic syndrome. Endocr J. 2011; 58: 23-30.

40. Staub JJ, Althaus BU, Engler H, Ryff AS, Trabucco P, Marquardt K, et al. Spectrum of subclinical and overt hypothyroidism: effect on thyrotropin, prolactin, and thyroid reserve, and metabolic impact on peripheral target tissues. Am J Med. 1992; 92: 631-642.

41. Tian L, Song Y, Xing M, Zhang W, Ning G, Li X, et al. A novel role for thyroid-stimulating hormone: up-regulation of hepatic 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase expression through the cyclic adenosine monophosphate/protein kinase A/cyclic adenosine monophosphate-responsive element binding protein pathway. Hepatology. 2010; 52: 1401-1409.

42. Abrams JJ, Grundy SM. Cholesterol metabolism in hypothyroidism and hyperthyroidism in man. J Lipid Res. 1981; 22: 323-338.

43. Heimberg M, Olubadewo JO, Wilcox HG. Plasma lipoproteins and regulation of hepatic metabolism of fatty acids in altered thyroid states. Endocr Rev. 1985; 6: 590-607.

44. Sundaram V, Hanna AN, Koneru L, Newman HA, Falko JM. Both hypothyroidism and hyperthyroidism enhance low density lipoprotein oxidation. J Clin Endocrinol Metab. 1997; 82: 3421-3424.

45. Azizi F, Raiszadeh F, Solati M, Etemadi A, Rahmani M, Arabi M. Serum paraoxonase 1 activity is decreased in thyroid dysfunction. J Endocrinol Invest. 2003; 26: 703-709.

46. Nikkilä EA, Kekki M. Plasma triglyceride metabolism in thyroid disease. J Clin Invest. 1972; 51: 2103-2114.

47. Razvi S, Weaver JU, Vanderpump MP, Pearce SH. The incidence of ischemic heart disease and mortality in people with subclinical hypothyroidism: reanalysis of the Whickham Survey cohort. J Clin Endocrinol Metab. 2010; 95: 1734-1740.

48. Walsh JP, Bremner AP, Bulsara MK, O'Leary P, Leedman PJ, Feddema P, et al. Subclinical thyroid dysfunction as a risk factor for cardiovascular disease. Arch Intern Med. 2005; 165: 2467-2472.

49. McQuade C, Skugor M, Brennan DM, Hoar B, Stevenson C, Hoogwerf BJ. Hypothyroidism and moderate subclinical hypothyroidism are associated with increased all-cause mortality independent of coronary heart disease risk factors: a PreCIS database study. Thyroid. 2011; 21: 837-843.

50. Cappola AR, Fried LP, Arnold AM, Danese MD, Kuller LH, Burke GL, et al. Thyroid status, cardiovascular risk, and mortality in older adults. JAMA. 2006; 295: 1033-1041.

51. Sgarbi JA, Matsumura LK, Kasamatsu TS, Ferreira SR, Maciel RM. Subclinical thyroid dysfunctions are independent risk factors for mortality in a 7.5-year follow-up: the Japanese-Brazilian thyroid study. Eur J Endocrinol. 2010; 162: 569-577.

52. Boekholdt SM, Titan SM, Wiersinga WM, Chatterjee K, Basart DC, Luben R, et al. Initial thyroid status and cardiovascular risk factors: the EPIC-Norfolk prospective population study. Clin Endocrinol (Oxf). 2010; 72: 404-410.

53. Rodondi N, Newman AB, Vittinghoff E, de Rekeneire N, Satterfield S, Harris TB, et al. Subclinical hypothyroidism and the risk of heart failure, other cardiovascular events, and death. Arch Intern Med. 2005; 165: 2460-2466.

54. Rodondi N, den Elzen WP, Bauer DC, Cappola AR, Razvi S, Walsh JP, et al. Subclinical hypothyroidism and the risk of coronary heart disease and mortality. JAMA. 2010; 304: 1365-1374.

55. Garber JR, Cobin RH, Gharib H, Hennessey JV, Klein I, Mechanick JI, et al. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. Thyroid. 2012; 22: 1200-1235.

56. Cooper DS, Biondi B. Subclinical thyroid disease. Lancet. 2012; 379: 1142-1154.

57. Gussekloo J, van Exel E, de Craen AJ, Meinders AE, Frölich M, Westendorp RG. Thyroid status, disability and cognitive function, and survival in old age. JAMA. 2004; 292: 2591-2599.

58. Surks MI, Boucai L. Age- and race-based serum thyrotropin reference limits. J Clin Endocrinol Metab. 2010; 95: 496-502.

59. Brent GA. Mechanisms of thyroid hormone action. J Clin Invest. 2012; 122: 3035-3043.

60. Ichikawa K, Miyamoto T, Kakizawa T, Suzuki S, Kaneko A, Mori J, et al. Mechanism of liver-selective thyromimetic activity of SK&F L-94901: evidence for the presence of a cell-type-specific nuclear iodothyronine transport process. J Endocrinol. 2000; 165: 391-397.

61. Taylor AH, Stephan ZF, Steele RE, Wong NC. Beneficial effects of a novel thyromimetic on lipoprotein metabolism. Mol Pharmacol. 1997; 52: 542-547.

62. Moreno M, de Lange P, Lombardi A, Silvestri E, Lanni A, Goglia F. Metabolic effects of thyroid hormone derivatives. Thyroid. 2008; 18: 239-253.

63. Chiellini G, Apriletti JW, Yoshihara HA, Baxter JD, Ribeiro RC, Scanlan TS. A high-affinity subtype-selective agonist ligand for the thyroid hormone receptor. Chem Biol. 1998; 5: 299-306.

64. Borngraeber S, Budny MJ, Chiellini G, Cunha-Lima ST, Togashi M, Webb P, et al. Ligand selectivity by seeking hydrophobicity in thyroid hormone receptor. Proc Natl Acad Sci U S A. 2003; 100: 15358-15363.

65. Grover GJ, Mellstrom K, Malm J. Development of the thyroid hormone receptor beta-subtype agonist KB-141: a strategy for body weight reduction and lipid lowering with minimal cardiac side effects. Cardiovasc Drug Rev. 2005; 23: 133-148.

66. Berkenstam A, Kristensen J, Mellström K, Carlsson B, Malm J, Rehnmark S, et al. The thyroid hormone mimetic compound KB2115 lowers plasma LDL cholesterol and stimulates bile acid synthesis without cardiac effects in humans. Proc Natl Acad Sci U S A. 2008; 105: 663-667.

67. Apriletti JW, Ribeiro RC, Wagner RL, Feng W, Webb P, Kushner PJ, et al. Molecular and structural biology of thyroid hormone receptors. Clin Exp Pharmacol Physiol Suppl. 1998; 25: S2-11.

68. Berkenstam A, Kristensen J, Mellström K, Carlsson B, Malm J, Rehnmark S, et al. The thyroid hormone mimetic compound KB2115 lowers plasma LDL cholesterol and stimulates bile acid synthesis without cardiac effects in humans. Proc Natl Acad Sci U S A. 2008; 105: 663-667.

69. Erion MD, Cable EE, Ito BR, Jiang H, Fujitaki JM, Finn PD, et al. Targeting thyroid hormone receptor-beta agonists to the liver reduces cholesterol and triglycerides and improves the therapeutic index. Proc Natl Acad Sci U S A. 2007; 104: 15490-15495.

70. Baxter JD, Webb P. Thyroid hormone mimetics: potential applications in atherosclerosis, obesity and type 2 diabetes. Nat Rev Drug Discov. 2009; 8: 308-320.

71. Ladenson PW, Kristensen JD, Ridgway EC, Olsson AG, Carlsson B, Klein I, et al. Use of the thyroid hormone analogue eprotirome in statin-treated dyslipidemia. N Engl J Med. 2010; 362: 906-916.

72. Meruvu S, Ayers SD, Winnier G, Webb P. Thyroid hormone analogues: where do we stand in 2013? Thyroid. 2013; 23: 1333-1344.

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