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Review Article

Clinical and Subclinical Hypothyroidism And Its Effects on Dyslipidemia: As Narrative Review

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Abstract

The literature on the connection between dyslipidemia, clinical and subclinical hypothyroidism is critically analyzed in this narrative review. These conditions are frequently observed among adult populations and various studies and meta-analyses have assessed their association. Hypothyroidism (Clinical and subclinical) is frequently associated with higher serum levels of total cholesterol, LDL-C and triglycerides. Thyroid hormones (TH) has an effects on the production, clearance and transformation of cholesterol, however, recent studies suggest that thyroid-stimulating hormone (TSH) also participates in lipid metabolism independently of TH. Therefore, the mechanism of hypothyroidism-related dyslipidemia is associated with the decrease of TH and the increase of TSH levels. Some newly identified regulatory factors, such as proprotein convertase subtilisin/kexin type 9, angiogenin-like proteins and fibroblast growth factors are the underlying causes of dyslipidemia in hypothyroidism. HDL serum concentration changes were not consistent, and its function was reportedly impaired. The current review focuses on the updated understanding of the mechanism of hypothyroidism-related dyslipidemia.

1. Introduction

Hypothyroidism is a common endocrine disorder resulting from deficiency of thyroid hormone or its effects on peripheral tissues. According to the causes, hypothyroidism has three types. The primary hypothyroidism usually is caused by an insufficient production of thyroid hormone by thyroid gland, the secondary hypothyroidism is caused by inadequate secretion of TSH from the pituitary gland and tertiary hypothyroidism caused by inadequate secretion of TRH from the hypothalamus [1].

The cause of hypothyroidism could be (Congenital) which results from defect of hormones' synthesis and effects, or (Aquired) which include: autoimmune thyroiditis, iodide deficient diet and thyroid ablation, or (Pharmacological): iodide, propylthiouracil, methimazole, lithium, thiocyanate etc [2]. Hypothyroidism is a very common condition affecting 3-5% of the population. It is estimated that about 2% of adult women and about 0, 1-0 ,2% of men have clinical hypothyroidism.

Signs and symptoms are nonspecific and can vary in individual presentations. Diagnosis is based on blood levels of decreased FT4 , with a corresponding elevated thyrotropin (i.e., TSH) level in primary causes (thyroid source) the TSH level may be normal to low in secondary (pituitary source) or tertiary (hypothalamic source) causes. 5 Subclinical hypothyroidism describes the state of normal FT4 levels when the TSH level is elevated.

Subclinical hypothyroidism (SCH), also called mild thyroid failure, is diagnosed when peripheral thyroid hormone levels (T3 ,T4) are within normal range but serum thyroid-stimulating hormone (TSH) levels are slightly raised. This condition occurs in 3% to 8% of the general population. It is more common in women than men, and its prevalence increases with age. Of patients with SCH, 80% have a serum TSH of less than 10 mIU/L. The most important Implication of SCH is high probability of progression to clinical hypothyroidism

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[3]. Although SCH considered an asymptomatic disorder, some patients may present non-specific symptoms, which can be suggestive of hypothyroidism [4, 5].

Mild thyroid failure is a common disorder that frequently progresses to overt hypothyroidism. This condition may clearly be associated with somatic symptoms, depression, memory and cognitive impairment, subtle neuromuscular abnormalities, subtle systolic and diastolic cardiac dysfunction, raised serum levels of total and LDL cholesterol, and an increased risk for the development of atherosclerosis [6]. In fact, a growing number of studies have associated SCH with an increased number of cardiovascular risk factors, including hypertension [7], weight gain [8], insulin resistance [9] hypercholesterolemia, dyslipidemia [10], coronary and ischemic heart diseases [11].

2. Lipids and lipids metabolism

Lipids defined as biological substances that are generally hydrophobic in nature and in many cases soluble in organic solvents [12]. These chemical properties cover a broad range of molecules, such as fatty acids, phospholipids, sterols, sphingolipids, terpenes, and others [13]. The chief biological functions of lipids include storing energy, signaling, and acting as structural components of cell membranes [14].

Scientists may broadly define lipids as hydrophobic or amphiphilic small molecules; the amphiphilic nature of some lipids allows them to form structures such as vesicles, multilamellar/unilamellar liposomes, or membranes in an aqueous environment. Biological lipids originate entirely or in part from two distinct types of biochemical subunits or ”building-blocks”: ketoacyl and isoprene groups. Using this approach, lipids may be divided into eight categories: fatty acids, glycerolipids, glycerophospholipids, sphingolipids, saccharolipids, and polyketides (derived from condensation of ketoacyl subunits); and sterol lipids and prenol lipids (derived from condensation of isoprene subunits) [15].

Lipids are first absorbed from the small intestine and emulsified by bile salts which are synthesized from cholesterol in the liver, stored in the gallbladder and secreted following the ingestion of fat. As an emulsion dietary fats are accessible to pancreatic lipase. The products of pancreatic lipase, i.e. free fatty acids (FFA) and a mixture of monoacylglycerols (MG) and diacyl glycerols (DG) from dietary TG diffuse into the intestinal epithelial cells where the resynthesize of triacylglycerol’s occurs. Lipids are insoluble in plasma, thus their transport is mediated by lipoproteins which differ in particle size, composition and density. These are chylomicrons (CYM), which are very low density lipoproteins (VLDL), low density lipoproteins (LDL) and high density lipoproteins (HDL). All of them have a hydrophobic core containing TG and cholesteryl ester (CE) and a polar periphery with phospholipids (PL), cholesteryl (C) and apolipoproteins [16].

3. Clinical and Subclinical Hypothyroidism and Dyslipidemia

Hypothyroidism has been found to be a very important risk factor for secondary hypercholesterolemia. According to many surveys, the prevalence of overt hypothyroidism depends on various geographical and the environmental factors which include: dietary iodide, goitrogen intake, the genetic characteristic and the age distribution of the population [17].

Several studies have showed a statistically significant increase in fasting TC, TG, and LDL-C concentrations with declining thyroid function. [18–20]. So hypothyroidism is characterized by hypercholesterolemia, and especially increased levels of LDL-C and apolipoprotein B (apo B) due to decreased fractional clearance of LDL by the reduced number of LDL receptors (LDL-R) in the liver and to diminishing control by T3 over sterol regulatory element-binding protein 2 (SREBP-2), which is crucial for the expression of the LDL-R [17, 21].

It has recently been reported that thyroid hormones (TH) emerged as a discernible hypocholesterolemia effect by affecting on bile acids (BA). Elevated levels of bile acids cause depletion of the hepatic cholesterol pool followed by an increase in the synthesis of cholesterol in the liver and the hepatic uptake of cholesterol from the circulation. It has been found that TH can promote BA synthesis by stimulating the rate-limiting enzyme cholesterol 7α hydroxylase (CYP7A1), which is a key element in cholesterol catabolism, as shown in mice and lately in humans [22].

On the other hand, it has recently been reported that thyroid-stimulating hormone (TSH) may directly diminish liver bile acid synthesis by SREBP- 2/HNF-4α (hepatocyte nuclear factor 4)/CYP7A1) pathway in vivo and in vitro [23]. Since TSH is increased in all forms of primary hypothyroidism, a direct negative action of TSH in the liver may be an alternative explanation for the detrimental effect of the lack of thyroid hormone in lipid metabolism. High-density lipoprotein (HDL-C) levels are normal even elevated in severe hypothyroidism because of reduced activity of cholesteryl- ester transfer protein (CETP) and hepatic lipase (HL), which are both enzymes regulated by thyroid hormones [24, 25]. Hepatic lipase has a role in HDL regulation, through the conversion of intermediate density lipoproteins (IDL-C) to LDL–C [26]. Moreover, its diminished activity in hypothyroidism has been associated with the accumulation of remnant-like particles (RLP) in the serum of hypothyroid patients Remnant cholesterol is a contributor to residual cardiovascular risk and represents the cholesterol content of a subset of triglyceride-rich lipoproteins that include chylomicron remnants, VLDL-C and IDL-C in the nonfasting state, and VLDL-C and IDL-C in the fasting state [27]. Therefore, the accumulation of triglyceride-rich lipoproteins in hypothyroid patients may be considered as part of the atherogenic scenario in these patients. With regard to triglyceride levels in a hypothyroid condition, they tend to be high, mainly due to reduced activity of the enzymes involved as lipoprotein lipase (LPL) [28] and HL23 and/or on account of enhanced triglyceride hepatic synthesis [29].

The study of showed that of 295 hypothyroid patients, about 56% had Frederickson type IIa dyslipidemia (hypercholesterolemia), 3 4% type IIb (hypercholesterolemia+ hypertriglyceridemia), 1.5% type IV (hypertriglyceridemia), and only 8.5% had no lipid alterations. These abnormalities of lipoprotein metabolism that present in almost 90% of hypothyroid patients underscore once more the need to rule out the possible presence of hypothyroidism in every dyslipidemic patient [30].

The prevalence of SCH among patients with dyslipidemia was estimated between ranges 1.4% to 11.2% [31]. It was shown that serum TC, LDL-C and triglyceride levels were significantly elevated in patients with SCH compared with euthyroid individuals [32]. Other studies show a significant positive correlation between LDL-C level and fT3 and fT4 were negatively correlated with TC and LDL-C. Atherogenic lipid abnormalities were observed only if TSH was >10mIU/L [31, 33]. The study of show that serum cholesterol, LDL-C and apoB were high in patients with SCH, while concluded that patients with SCH did exhibit increased levels of the atherogenic parameters mainly LDL-C and Lp (a).

In SCH there have been reports of augmented oxidation of LDL-C particles [34, 35] increased postprandial lipemia impaired chemical composition with triglyceride enrichment of the LDL-C particle [36] and qualitative evidence of RLP in the fasting serum of SCH women

[37]. In addition, it was shown that the levels of these atherogenic particles decrease with levothyroxine, this probably related to increased degradation by LH [38].

References

[1] B. Vaidya and S. H. Pearce. Management of hypothyroidism in adults. *BMJ*, 337:284–289, 2008.

[2] S. McPhee and D. C. Bauer. *Pathology of disease*. New York, Lange Medical Books/McGraw-Hill, 1997.

[3] F. Fatourechi. Subclinical hypothyroidism: An update for primary care physicians. *Mayo Clin Proc.*, 84(1):65–71, 2009.

[4] D. A. Bemben, R. M. Hamm, L. Morgan, P. Winn, A. Davis, and (1994)Thyroid Barton E. disease in the elderly. part 2. predictability of subclinical hypothyroidism. *Journal of Family Practice*, 38:583–588.

[5] R. J. Bell, L. Rivera-Woll, S. L. Davison, D. J. Topliss, S. Donath, and (2007) Davis S. R. Well-being, health-related quality of life and cardiovascular disease risk profile in women with subclinical thyroid disease – a community based study. *Clinical Endocrinology*, 66: 548–556.

[6] M. T. McDermott and E. C. Ridgway. Subclinical hypothyroidism is mild thyroid failure and should be treated. *The Journal of Clinical Endocrinology and Metabolism*, 86(10):4585–4590, 2001.

[7] D. Liu, F. Jiang, Z. Shan, B. Wang, J. Wang, Y. Lai, Y. Chen, M. Li, H. Liu, C. Li, H. Xue, N. Li, J. Yu, L. Shi, X. Bai, X. Hou, L. Zhu, L. Lu, S. Wang, and Q. Xing. and teng. *W. A cross- sectional survey of relationship between serum TSH level and blood pressure. J. Hum.*, 24(2):134–138, 2010.

[8] C. Fox, M. Pencina, R. D'Agostino, J. Murabito, E. Seely, and E. Pearce. Relations of thyroid function to body weight: cross-sectional and longitudinal observations in a community-based sample. *Arch Intern Med*, 168:587–592, 2008.

[9] S. Stanicka, K. Vondra, T. Pelikanova, P. Vlcek, M. Hill, and V. Zamrazil. Insulin sensitivity and counter-regulatory hormones in hypothyroidism and during thyroid hormone replacement therapy. *Clin Chem Lab Med*, 43:715–720, 2005.

[10] A. Asranna, R. S. Taneja, and B. Kulshreshta. Dyslipidemia in subclinical hypothyroidism and the effect of thyroxine on lipid profile. *Indian J Endocrinol Metab.*, pages S347–S349, 2012.

[11] B. Biondi, E. A. Palmieri, G. Lombardi, and S. Fazio. Subclinical hypothyroidism and cardiac function, thyroid;12:505–10. 2002.

[12] A. Smith. *Oxford Dictionary of Biochemistry and Molecular Biology*. Oxford University Press, Oxford, UK, 2nd edition, 2000.

[13] M. Christ-Crain, C. Meier, M. Guglielmetti, P. R. Huber, W. Riesen, and J. J. Staub. l. elevated c-reactive protein and homocysteine values: cardiovascular risk factors in hypothyroidism? a cross- sectional and a double-blind, placebo controlled trial. *Atherosclerosis.*, 166:379–386, 2003.

[14] D. Subramanian, V. Laketa, R. Muller, C. Tischer, S. Zarbakhsh, R. Pepperkok, and C. (2010) Schultz. Activation of membrane-permeant caged ptdins(3)p induces endosomal fusion in cells. nat chem biol. 2010; 6:324–326. substitution beneficial? eur j endocrinol 2001; 145: 705-10. syndrome. *Saudi Med J*, 30:907–11, 2009.

[15] E. Fahy, S. Subramaniam, R. C. Murphy, M. Nishijima, C. R. Raetz, T. Shimizu, F. Spener, G. van Meer, M. J. Wakelam, and E. A. (2009) Dennis. Update of the lipid maps comprehensive classification system for lipids. j lipid res. 50 suppl: S9-14. failure: a quantitative review of the literature. *J Clin Endocrinol Metab*, 85:2993–3001.

[16] K. Mathews, K. E. Holde van, and K. G. Ahem. Biochemistry, 3d ed., addison, wesley, longman. 2000.

[17] L. H. Duntas. Thyroid disease and lipids. *Thyroid.*, 12(4):287–293, 2002.

[18] A. A. Al-Tonsi, A. A. Abdel-Gayoum, and M. Saad. The secondary dyslipidemia and deranged serum phosphate concentration in thyroid disorders. *Exp Mol Pathol.*, 76(2):182–187, 2004.

[19] W. Y. Lee, J. Y. Suh, E. J. Rhee, J. S. Park, K. C. Sung, and S. W. Kim. Plasma crp, apolipoprotein a-1, apolipoprotein b and lp(a) levels according to thyroid function status. *Arch Med Res.*, 35(6):540–545, 2004.

[20] E. N. Pearce, Wilson Pwf, Q. Yang, R. S. Vasan, and L. E. (2008) Braverman. Thyroid function and lipid subparticle sizes in patients with short- term hypothyroidism and a population-based cohort. *J Clin Endocrinol Metab.*, 93(3):888–894.

[21] D. J. Shin and T. F. Osborne. Thyroid hormone regulation and cholesterol metabolism are connected through sterol regulatory element-binding protein-2 (srebp-2). *J Biol Chem*, 278:34114–34118, 2003.

[22] J. A. Lammel Lindemann, A. Angajala, D. A. Engler, P. Webb, and S. D. Ayers. Thyroid hormone induction of human cholesterol 7 alpha- hydroxylase (cyp7a1) in vitro. *Mo Cell Endocrinol*, 388:32–40, 2014.

[23] Y. Song, C. Xu, and S. Shao. Thyroid-stimulating hormone regulates hepatic bile acid homeostasis via srebp-2/hnf-4alpha/cyp7a1 axis. *J Hepatol*, 62:1171–1179, 2015.

[24] S. Valdemarsson and P. Nilsson-Ehle. Hepatic lipaseand the clearing reaction: studies in euthyroid and hypothyroid subjects. *Horm Metab Res*, 19:28–30, 1987.

[25] K. C. Tan, S. W. Shiu, and A. W. Kung. Effect of thyroid dysfunction on high-density lipoprotein sub fraction metabolism: roles of hepatic lipase and cholesteryl ester transfer protein. *J Clin Endocrinol Metab*, 83:2921–2924, 1998.

[26] A. Zambon, S. S. Deeb, A. Bensadoun, K. E. Foster, and J. D. Brunzell. In vivo evidence of a role for hepatic lipase in human apob-containing lipoprotein metabolism, independent of its lipolytic activity. *J Lipid Res*, 41:2094–2099, 2000.

[27] A. Varbo, M. Benn, and B. G. Nordestgaard. Remnant cholesterol as a cause of ischemic heart disease: evidence, definition, measurement, atherogenicity, high risk patients, and present and future treatment. *Pharmacol Ther*, 141:358–367, 2014.

[28] T. Kuusi, M. R. Taskinen, and E. A. Nikkila. Lipoproteins, lipolytic enzymes, and hormonal status in hypothyroid women at different levels of substitution. *J Clin Endocrinol Metab*, 66:51–56, 1988.

[29] S. Gjedde, L. C. Gormsen, and J. Rungby. Decreased lipid intermediate levels and lipid oxidation rates despite normal lipolysis in patients with hypothyroidism. 2010.

[30] G. Brenta, M. Vaisman, and J. A. Sgarbi. Clinical practice guidelines for the management of hypothyroidism. *Arq Bras Endocrinol Metabol*, 57:265–291, 2013.

[31] R. Shekhar, Chowdary Nvs, M. C. Das, D. Vidya, and S. (2011) Prabodh. Prevalence of subclinical hypothyroidism in coastal andhra pradesh. *Biomed Res.*, 22(4):471–474.

[32] Pearce EN. Hypothyroidism and dyslipidemia: Modern concepts and approaches. *Curr Cardiol Rep.*, 6(6):451–456, 2004.

[33] R. K. Marwaha, N. Tandon, M. K. Garg, R. Kanwar, A. Sastry, and A. Narang. Dyslipidemia in subclinical hypothyroidism in an indian population. *Clin Biochem.*, 44(14-15):1214–1217, 2011.

[34] L. H. Duntas. Thyroid disease and lipids. *Thyroid.*, 12(4):287–293, 2002.

[35] S. Arikan, M. Bahceci, A. Tuzcu, F. Celik, and D. Gokalp. Postprandial hyperlipidemia in overt and subclinical hypothyroidism. *Eur J Intern Med*, 23:e141–145, 2012.

[36] J. Boren and K. J. Williams. The central role of arterial retention of cholesterol-rich apolipoprotein-b-containingwith unnoticed hypothyroidism. *Endocr J*, 53:401–405, 2016.

[37] G. Brenta, G. Berg, P. Arias, et al. Lipoprotein alterations, hepatic lipase activity. *and insulin sensitivity in subclinical hypothyroidism: response to L-T*, 4, 2007.

[38] G. Brenta, G. Berg, and V. Miksztowicz. *Atherogenic lipoproteins in subclinical hypothyroidism and their relationship with hepatic lipase activity: response to replacement treatment with levothyroxine*. Thyroid, 2016.