Hypothyroidism and Atherosclerosis: From Etiology to Pathophysiology

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Abstract: Atherosclerosis is a complex multifactorial disease, which develops in the arterial wall in response to various stimuli like hyperlipidemia, hyperhomocysteinemia, hypertension, smoking, metabolic disorders and results in excessive inflammatory and fibro proliferative reactions. Hypothyroidism means deficiency of thyroid activity resulting from reduced secretion of total thyroxine (T4) and triiodothyronin (T3). Biochemical decrease in T4 and T3 lead to hyper secretion of pituitary thyroid stimulating hormone (TSH) and an amplified increases in serum TSH levels. Hyperlipidemia is a major risk factor for atherosclerosis. There is positive linear correlation between TSH and total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and triglycerides (TGs), and negative linear correlation between TSH and high-density lipoprotein cholesterol (HDL-C) levels. Alongwith hyperlipidemia, hypothyroidism is accompanied with moderately increased concentration of plasma total homocyteine (tHcy), an independent risk factor for atherosclerotic vascular disease. In subclinical hypothyroidism, there is also a significant increase in a cluster of metabolic cardiovascular disease risk factors. Thus, hypothyroidism is linked to atherosclerosis but exact molecular mechanism is yet not defined. So, present review focuses various etiological and pathophysiological aspects to link between hypothyroidism and atherogenesis.

Keywords: Hypothyroidism, Atherosclerosis, Thyroxine (T4), Triiodothyronin (T3), hyperlipidemia

INTRODUCTION
Atherosclerosis is a complex multi-factorial disease, which develops in the arterial wall in response to various stimuli like hyperlipidemia, hyperhomocysteinemia, hypertension, smoking, metabolic disorders and results in excessive inflammatory and fibro proliferative reactions [1]. Cardiovascular disease (CVD) due to atherosclerosis is the leading cause of morbidity and mortality in westernized countries[1]. In United States, 62% of man and 47% of women suffering from atherosclerotic cardiovascular disease [2].

Thyroid hormone play very important role in energy balance, metabolism of glucose and lipids [3-5]. Hypothyroidism means deficiency of thyroid activity resulting from reduced secretion of total thyroxine (T4) and triiodothyronin (T3). Biochemical decrease in T4 and T3 lead to hyper secretion of pituitary thyroid stimulating hormone (TSH) and an amplified increases in serum TSH levels [6]. Hypothyroidism is linked with an increased risk for atherosclerotic cardiovascular disease and cardiovascular morbidity [7-8]. Prevalence of hypothyroidism and subclinical hypothyroidism are 4.1% and 5.4% respectively and these disorders are also higher in females than males [9]. Many Case–control and cross-sectional studies on the association between subclinical hypothyroidism and cardiovascular disease has been done [10-14]. However, exact mechanisms by which hypothyroidism causes the development and progression of atherosclerosis is yet not defined. So, in this review, we will try to focus on different etiological and pathophysiological mechanisms to link hypothyroidism and atherosclerosis.

a) HYPOTHYRODISM AND HYPERLIPIDEMIA
Hyperlipidemia, especially hypercholesterolemia is a major risk factor for Atherosclerosis. Low-density lipoprotein (LDL) cholesterol, a major component of the total serum cholesterol associated with increased risk of atherosclerosis [15]. Thyroid function significantly affects on lipoprotein metabolism as well as some CVD risk factors[16-18]. There is positive linear correlation between thyroid stimulating hormone (TSH) and total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and triglycerides (TGs), and negative linear correlation between TSH and high-density lipoprotein cholesterol (HDL-C) levels[19]. Therefore hypothyroidism is one of the significant common causes of hyperlipidemia which linked to atherosclerosis [20-22]. One double blind, placebo-controlled study design stated that hypothyroidism significant increase in TC and LDL-C levels. One randomized trial also demonstrated that elevated serum lipid levels, mainly total and atherogenic LDL-C levels, were lowered by thyroid hormone replacement in patients with mild thyroid
failure. L-thyroxine therapy resulted in a decrease in mean serum cholesterol by 3.8% [0.24 mmol/liter] and in LDL-C by 8.2% [0.33 mmol/liter], respectively [23].

Thyroid hormone activates cholesterol ester transfer protein (CETP) activity which converts VLDL to HDL. It also activates lipoprotein lipase (LPL) activity which converts VLDL to IDL and IDL to LDL. Along with CETP and LPL it also enhance activity of hepatic lipase (HL) which convert intermediate density lipoprotein (IDL) to LDL, LDL to sdLDL&HDL2 to HDL3. Activities of thyroid responsive element (TRE), sterol regulatory binding protein (SREBP-2), apolipoprotein AV (ApoAV) which all activates LDL receptors are increased. HMG-CoA which is principle enzyme in cholesterol biosynthesis is also activated. It inhibits oxidation of LDL and TGs formation [24].

Hypothyroidism is accompanied by reduced activity of HMG-CoA reductase and increased levels of TC and LDL-C levels [25-29] result into the decrease LDL-receptors activity, which decrease catabolism of LDL and IDL [25-27]. It also decreases in lipoprotein (LPL) activity result into the decrease the clearance of TG-rich lipoproteins [28]. Therefore, it may also elevate TG levels associated with increased levels of very low density lipoprotein (VLDL) and occasionally fasting chylomicronemia [23, 28-33]. The VLDL and IDL particles in hypothyroidism are rich in cholesterol and apolipoprotein E, thus resembling β-VLDL particles of type III hyperlipoproteinemia [25]. It is also exhibit elevate levels of HDL-C [25] result of increased concentration of HDL2 particles which due to a reduction of hepatic Lipase activity a decrease in HDL2 catabolism [34]. It also decreases activity of the cholesterol ester transfer protein (CETP) results in reduced transfer of cholesteryl esters from HDL to VLDL in opposite direction [35]. It also increase lipoprotein [a] (Lpa) levels [36-37] which are associated with increased CVD risk mainly atherosclerosis [37-38] (Figure 1).

**(Fig 1. Hypothyroidism and lipid metabolism[24])**

**b) HYPOTHYROIDISM AND HYPERHOMOCYSTEINEMIA**

Several cross-sectional, case control and prospective studies have concluded that
hyperhomocysteinemia is an independent risk factor for progression of atherosclerosis [39]. Hyperhomocysteinemia induce endothelial injury, oxidative stress, smooth muscle hypertrophy, oxidation of LDL-C and also alter platelet aggregation as well as anticoagulant functions; these all leads to atherosclerosis [40]. Evidence indicated that approximately about 5% to 7% of general population has hyperhomocysteinemia [41]. Hypothyroidism is accompanied with moderately increased concentration of plasma total homocysteine (tHcy) [42]. One already published report indicated that patients with subclinical hypothyroidism had higher level of homocysteine than control subjects and improved significantly after levothyroxine treatment [43].

Homocysteine produces from methionine in presence of flavoprotein methylene tetrahydrofolatereductase (MTHFR) by methylation process. Vitamin B12 acts as a cofactor in this process [44].

Hypothyroidism affects on Hcy metabolism via affecting on enzymes mainly MTHFR which involved in the remethylation of Hcy to methionine due to decrease its hepatic activity [45]. Defective conversion of riboflavin to the active coenzyme flavin adenine dinucleotide is also observed in hypothyroid status [46]. Hypothyroidism reduces Glomerular Filtration Rate (GFR) and reduced GFR leads to increment in tHcy [47]. Vitamin B12 levels also decreased in hypothyroidism due to alteration in rate of metabolism [48]. Thus, hypothyroid-induced altered homocysteine metabolism will finally lead to hyperhomocysteinemia and thereby progression of atherosclerosis (Figure 2).

(Fig. 2 Hypothyroidism and Hyperhomocysteinemia. [↓] = decrease [44])

c) HYPOTHYROIDISM AND OXIDATIVE STRESS

There is well known correlation between oxidative stress and atherosclerotic lesion development. Taddei et al., 2006 revealed that hypothyroidism increased production of oxidative stress [50].

Oxidative stress means the imbalance between the generation of reactive oxygen species (ROS) and antioxidant defense system. Oxidative stress modulates oxidation of LDL, reduction of NO bioavailability, and vascular inflammation. In atherosclerosis large amounts of ROS are released by inflammatory cells, as well as other constituents of atherosclerotic plaque. Reactive oxygen species may affect more than one fundamental mechanism that induce atherogenesis like oxidation of lipids, endothelium dysfunction, proliferation of vascular smooth muscle cells (SMCs), increased adhesion of monocytes to endothelial cells, and hyperlipidemia [51]. Oxidized LDL (Ox-LDL) is a significant proatherosclerotic mediator [52] which causes the alteration of endothelial cells lining the arterial wall, resulting in expression of several monocytes/macrophages, which release a number of growth factors [53-55]. Ox-LDL induces formation of matrix metalloproteinase (MMPs) in vascular endothelial cells and fibroblasts and up regulates the expression of endothelial receptors which is responsible for the formation of foam cells, which is an initial step in atherogenesis [53]. Very small fraction (3%) of T4 is...
bound to plasma lipoproteins, with a relative distribution of 0.8% to very low density lipoprotein, 6.7% to LDL, and 92% to HDL [56-57]. This lipoprotein-bound T4 could be involved in protecting LDL from oxidation. Reduced T4 level in hypothyroidism may favor the oxidative modification of LDL [58].

Reactive oxygen species formation can be induced by action of xanthine oxidase, NAD[P]H oxidase, cytochrome P450 (CYP450), autoxidation of catecholamines and uncoupling of NO synthase (NOS), or by mitochondrial leakage and also by cytokines and growth factors, Angiotensin II, PDGF and TNF-α [59] (Figure 3).

![Diagram of Hypothyroidism and oxidative stress]

Hypothyroidism and oxidative stress [60]


Hypothyroidism is accompanied with production of oxidative stress due to lower TH [61-63]. Hypothyroidism blocks the conversion of β-carotene to Vitamin E due to lack of TH which significantly reduces Vitamin E content and causes the elevation of β-carotene level [64]. The oleic to linoleic acid ratio is inversely proportional to oxidative stress [65] and lower oleic to linoleic acid ratio is observed in hypothyroidism. Hypothyroidism inhibits relaxation of vascular smooth muscle cells (VSMCs) by decreasing production of NO which occurs rapidly by the deactivation of iNOS and nNOS via mechanism of the PI3K/Akt-signalling pathway [66-68].

d) HYPOTHYROIDISM AND INFLAMMATION

Atherosclerosis is considered to be a chronic inflammatory disorder, where both innate and adaptive immune responses influence disease progression [69]. Inflammatory mediators in atherosclerosis are mainly various cytokines like interleukin 1 (IL-1), IL-6, monocyte chemo attractant protein (MCP-1), tumor necrosis factor-α (TNF-α), highly sensitive C-reactive protein (hsCRP), interferon-γ (IFN-γ) [70]. IL-6 produce by smooth muscle cells which is main stimulus for C-reactive protein (CRP) production [71]. C-reactive protein may contribute to the proinflammatory state of the plaque both by mediating monocytes recruitment and by stimulating monocytes to release IL-1, IL-6, and TNF-α [72]. These all pro-inflammatory mediators damage endothelium which allows the passage of lipids into the sub endothelial space which is first step in the atherosclerotic process (Figure 4). It was found that subclinical hypothyroidism associated with elevated CRP levels [39, 73-75].
High level TSH in body cause endothelial dysfunction and increased serum levels of IL-6, TNF-α, CRP and several indices of oxidative stress which link to atherosclerosis [76-77]. Moreover, these pro-inflammatory mediators regulate the mRNA expression of osteopontin and altered osteopontin expression may be associated with atherosclerosis [78-79].

e) HYPOTHYROIDISM AND METABOLIC SYNDROME

Metabolic syndrome is a cluster of obesity, hyperglycemia, dyslipidemia and hypertension. The prevalence of metabolic syndrome in western countries is about 20% to 30% [80-82]. There is a high prevalence of metabolic syndrome in an urban Indian population about 31.6% [83].

Metabolic syndrome is a risk factor for cardiovascular disease [84]. In subclinical hypothyroidism, there is significant increase in cardiovascular disease risk factors of metabolic syndrome [85]. Yaxin et al., 2011 revealed that elevation of TSH stimulates secretion of pro-inflammatory cytokines which leads to increase component of metabolic syndrome and atherosclerosis [86].

CONCLUSION

Atherosclerosis is cardiovascular disease occur due to various factors like hyperlipidemia, hyperhomocysteinemia, oxidative stress and inflammatory mediators. Females are at higher risk of atherosclerotic lesions than male in postmenopausal phase. Moreover, females are more prone to have hypothyroidism than male. Hypothyroidism-induced hyperlipidemia, hyperhomocysteinemia, oxidative stress, and alteration in inflammatory mediators might be responsible for development and progression of atherosclerotic lesions. Thus, hypothyroidism along with estrogen deficiency, potentiate development and progression of atherogenesis in female in postmenopausal phase. Correction of hypothyroidism along with hormone replacement therapy or anti-hyperlipidemic agents might be a new therapeutic approach to minimize the risk of atherosclerosis in females.

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