INTRODUCTION

Hypothyroidism is a common endocrine disorder, which is diagnosed by estimating the thyroid hormone (TH) levels in the blood and effectively treated by the daily use of synthetic THs [1]. The prevalence of hypothyroidism according to the third National Health and Nutrition Examination Survey III is 4.6% in the general population, whereas 9.5% of Colorado prevalence study participants showed elevated levels of thyroid-stimulating hormone (TSH) [2]. Hypothyroidism is prevalent in older women, in whom autoimmune thyroiditis is common [1]. Hypothyroidism may be due to inadequate synthesis of TH or inadequate action of TH at the target tissue level [3]. Hypothyroidism ranges from mild subclinical form to overt hypothyroidism and myxedema. Depending on the time of onset hypothyroidism can be classified as congenital or acquired, depending on the level of endocrine dysfunction as primary and secondary or central hypothyroidism [1]. As thyroid function diminishes, serum TSH level begins to rise. An elevated serum TSH level is the hallmark of hypothyroidism. Subclinical hypothyroidism (SCH) or mild thyroid failure is associated with elevated TSH but a normal free thyroxin tetraiodothyronine (T4) and triiodothyronine (T3) levels [4]. Severe iodine deficiency during pregnancy decreases fetal TH synthesis causes irreparable damage to the fetal central nervous system, leading to mental retardation is termed as cretinism [5]. T3 is considered to be the metabolically active form [1]. Under normal physiological conditions, a major fraction of T3 is derived from the peripheral deiodination of T4 and only a lesser fraction is derived from direct secretion by the thyroid gland [6].

Patient presentation in hypothyroidism may vary from asymptomatic to myxedema coma. The classic symptoms and signs of hypothyroidism are weight gain, fatigue, cold intolerance, constipation, dry skin, hoarseness, goiter, mental impairment, depression, mild diastolic hypertension, narrowed pulse pressure, bradycardia, decreased appetite, or arthralgia [1]. Both overt and SCH, markedly alter lipid profile and promote cardiovascular disease (CVD) [6]. The aim of the present review is to illustrate the functions and metabolism of TH and to highlight alterations of lipid profile in hypothyroidism which may have a predisposing cardiovascular risk.

Synthesis and secretion of THs

The main function of the thyroid gland is to synthesize sufficient amount of THs to meet the demands of peripheral tissue. At least 100 µg of iodine per day is required to eliminate the signs of iodine deficiency. Synthesis of THs includes iodine uptake, trapping, iodide oxidation, organification, and coupling of iodotyrosyls (Fig. 1). Iodide trapping is accomplished by a 643 amino acid membrane glycoprotein with 13 membrane-spanning domains, sodium-iodide symporter (NIS), and encoded by the gene SLC5A5 (Solute Carrier Family 5 Member 5). Iodide transport is an active process and depends on the presence of a sodium gradient across the basolateral membrane of the thyroid cell. The downhill transport of two Na+ ions results in the entry of one iodide atom against an electrochemical gradient. Another membrane glycoprotein Pendrin, which is highly hydrophobic, is located in the apical membrane of follicular cells and functions as an apical iodide transporter in thyroid cells. It is encoded by SLC26A4. Other proteins (SLC5A8 and chloride channel 5, CLCN5) have been proposed to mediate apical iodide efflux. In addition, intracellular iodide is also synthesized by iodotyrosine dehalogenase 1, also called as iodotyrosine deiodinase. Its transcription is stimulated by cyclic adenosine monophosphate and encodes a membrane protein concentrated on the apical surface which catalyzes reduced nicotinamide adenine dinucleotide phosphate (NADPH)-dependent deiodination of monoiodotyrosine and diiodotyrosine (MIT and DIT).

Oxidation of iodide is mediated by the heme-containing protein thyroperoxidase (TPO) and requires H2O2 generated by the calcium...
and NADPH-dependent dual oxidase (DUOX) 1 and DUOX2 enzymes. DUOX maturation factor 2 is required for maturation and plasma membrane localization of DUOX2 and H$_2$O$_2$. The process of oxidation of iodide and incorporation into iodothyrosines (MIT and DIT) is termed as organification. This iodination leading to the synthesis of iodothyrosines occurs within thyroglobulins (T$_g$). TPO also catalyzes coupling of two molecules of DIT or one of DIT and MIT leading to the formation of T$_3$ and T$_4$, respectively (Fig. 2). TPO is stimulated by TSH. T$_3$ and T$_4$ are stored in the colloid as a part of T$_g$ [5]. From the follicular lumen colloid is taken in to the thyroid follicle by endocytosis (microendocytosis). The endocytic vesicles fuse with lysosomes. By the proteolytic action of lysosomal enzymes called cathepsin D and D like thiol proteases, MIT, DIT, T3 and T4 are released. MIT and DIT are metabolized by thyroid deiodinase to tyrosine and iodine which are recycled to the colloid and the iodide liberated is reincorporated into protein [7].

**Fig. 1**: Synthesis of thyroid hormones [7]. AC: Adenyl cyclase, TSH: Thyroid-stimulating hormone, TSHR: Thyroid-stimulating hormone receptor, PLC: Phospholipase C, DAG: Dicacylglycerol, CAMP: Cyclic adenosine monophosphate, IP3: Inositol triphosphate, TPO: Thyroperoxidase, H$_2$O$_2$: Hydrogen peroxide, DUOX2: Dual oxidase 2, DUOX2A: Dual oxidase maturation factor 2, MIT: Monoiodotyrosines, DIT: Diiodotyrosines, DEI: Deiodinase

**Fig. 2**: Structure of monoiodotyrosine and diiodotyrosine, triiodothyronine, and tetraiodothyronine
Hypothalamo–pituitary axis
The hypothalamo–pituitary–thyroid axis is a neuroendocrine system which regulates the secretion of THs. Thyrotropin-releasing hormone, which is secreted by the hypothalamus stimulates anterior pituitary to release TSH. TSH, in turn, stimulates the thyroid gland to secrete pro-hormone thyroxin (T₄) and to lesser extent T₃ [8] (Fig. 3). T₃ is converted into T₄, which is metabolically active, by iodosyntropine deiodinase. Most TH in the blood circulates bound to thyroid binding globulin, whereas only the free form has hormonal activity. There are specific cell membrane transporters such as monocarboxylate transporter 8 which help in transport of TH across the cell membrane. T₃ interacts with nuclear receptors and activates or inactivates THs responsive gene [8].

TH and lipid metabolism
THs regulate the metabolism of lipoproteins (LP). Thyroid dysfunction is associated with various molecular and biochemical alterations. In hypothyroidism, the composition of LP and their transport is seriously disturbed. Hypothyroidism causes hypercholesterolemia characterized by increased levels of low-density lipoproteins (LDL) [9-11]. In addition to LP metabolism, thyroid function significantly affects CVD risk factors, thus influencing overall coronary artery disease (CAD) risk factors [2,6]. Hypothyroidism is a common cause of secondary dyslipidemia [1,2,13]. In a multicenter study, the prevalence of hypothyroidism was evaluated in 752 hypercholesterolemic patients; primary hypothyroidism amounted to 3.7%, SCH to 2.4%, and overt hypothyroidism to 1.4% [9]. The overall prevalence of hypothyroidism was calculated as 4.3% in patients with hypercholesterolemia [1]. The present review focuses on the impact of THs on lipid metabolism, which predisposes cardiovascular risk in hypothyroid patients.

Overview of lipid metabolism
Cholesterol synthesis is an endergonic pathway being driven by hydrolysis of the high-energy thioester bond of acetyl coenzyme A (CoA) and the terminal phosphate bond of adenosine triphosphate (ATP). The enzymes required for synthesis are present both in the cytoplasm and endoplasmic reticulum (ER). The first step in cholesterol synthesis is condensation of two molecules of acetyl CoA forming acetoacetyl-CoA, which in turn by the addition of one more molecule of acetyl CoA forms 3-hydroxy-3-methyl glutaryl-CoA (HMG-CoA). HMG-CoA is reduced to mevalonate by the rate-limiting enzyme HMG-CoA reductase, which undergoes a series of phosphorylations and cyclizations leading to the formation of squalene then finally cholesterol.

The main function of LPs is to keep their component lipids soluble as they transport them between tissues. Based on their density, the plasma LP molecules are classified into chylomicrons (CM), very LDL (VLDL), intermediate-density lipoproteins (IDL), LDL, and high-density lipoproteins (HDL). These LPs differ from each other in density, lipid and protein composition, size, and electrophoretic mobility. The CM transports exogenous or dietary fat and cholesterol, whereas VLDL transport endogenous triglycerides (TGs). Cholesterol was synthesized and secreted by the liver [1,4,15].

TGs make up 90% of CMs and 75% of VLDL by weight [14]. CMs and VLDL are hydrolyzed by LP lipase (LPL), an extracellular enzyme that is anchored by heparin sulfate to the capillary walls of most tissues, but predominantly those of adipose tissue and cardiac tissue. Thus, TG is hydrolyzed by LPL-producing smaller particles known as remnants [15]. The hepatic receptors, which contain apo (E), recognizes and removes the CMs remnants [16]. The dietary cholesterol from the chylomicron remnant particle is thought to downregulate the hepatic LDL receptors. VLDL remnants, also known as LDL, contain apo (E) and may be removed by the liver through the receptor-mediated endocytosis. The triacylglycerol concentration in LDL particles is less than their VLDL predecessor and cholesterol ester concentration is more. LDL is the major cholesterol carrier, followed by HDL [15,17]. The chief function of LDL particles is to transport cholesterol to the peripheral tissue. The level of low-density lipoprotein cholesterol (LDL-C) regulated by the amount of LDL receptors. Defects in the LDL receptor molecule leads to hypercholesterolemia and myocardial infarction [16]. HDL particles take up cholesterol from the peripheral tissues and return it to the liver as cholesterol esters by the action of lecithin cholesterol acyltransferase (LCAT). HDL cholesterol is cardioprotective (Fig. 4).

Reverse cholesterol transport
Reverse cholesterol transport pathway includes efflux of cholesterol from peripheral cells to HDL, esterification of cholesterol by LCAT binding of HDL-2 to the liver and steroidogenic cells, transfer of cholesterol esters into these cells, and release of HDL-3 [17,18]. The major constituents of reverse cholesterol transport are HDL, apolipoprotein A-1 (Apo-A1), enzymes like LCAT phospholipid transfer protein, hepatic lipase (HL), and cholesterol ester transfer protein (CETP) [17-19] (Fig. 5). ATP-binding membrane cassette transporter (ABCF1) mediates the efflux of cholesterol from the peripheral tissue and cell surface receptor and scavenger receptor class B Type 1 (SR-B1) mediates the uptake of cholesterol [18,19].

Apolipoproteins, or apoproteins, are proteins associated with LP molecules. They have different functions such as providing a recognition site for cell-surface receptors or acts as activators or coenzymes for enzymes involved in LP metabolism. Apo B-100 is necessary for the secretion of hepatic-derived VLDL, LDL, and LPL. Apo B-48 is a truncated form of ApoB100, which is required for secretion of CMs from the small intestine. Apo-A1 is a major component of the HDL and acts as a cofactor for LCAT [14].

Cholesterol homeostasis is maintained by multiple feedback controls which act through transcriptional and post-transcriptional mechanisms. The transcription factors sterol regulatory element-binding proteins (SREBP) play an important role in sterol synthesis and uptake. The SREBP are sterol-sensing transcription factors of the basic helix-loop-helix-leucine zipper (bHLH-Zip) family [20].
SREBP regulates the expression of the LDL receptor and cholesterol synthesis. When stores are abundant SREBPs are bound to the ER by SREBP-cleavage-activating protein (SCAP) and insulin-induced gene 1 [21,22]. When sterol levels fall, SCAP allows site-1 cleavage to occur by site-1 protease, which separates the functional domain of SREBP from the regulatory domain [23]. SREBP moves to the Golgi where site-2 protease cleavage frees the NH2-terminal bHLH-Zip domain and allows for its migration to the nucleus for transcriptional regulation of target genes [24]. There are three main SREBPs encoded by 2 genes: SREBP-1a and SREBP-1c are produced from a single gene and SREBP-2 is produced from a separate gene [24]. SREBP-1 has been shown to regulate genes involved in fatty acid metabolism, while SREBP-2 is known to regulate genes involved in cholesterol metabolism [25]. The SREBP-2 gene is regulated by TH. In a study on rats, it was

Fig. 4: Cholesterol transport [14]. TG: Triglycerides, HDL: High-density lipoproteins, LDL: Low-density lipoproteins, VLDL: Very low-density lipoproteins, IDL: Intermediate-density lipoproteins, TH: Thyroid hormones, CETP: Cholesterol ester transfer protein, LPL: Lipoprotein lipase, FC: Free cholesterol, LCAT: Lecithin cholesterol transfer protein

Hypothyroidism and lipid metabolism

THs influence all major metabolic pathways. The well-known action of THs is an increase in basal energy expenditure obtained by acting on carbohydrate, protein, and lipid metabolism [26]. In addition, thyroid disorders, including overt and SCH, significantly alters the lipid profile and promote CVD [11]. TH is known to play a role in regulating the synthesis, metabolism, and mobilization of lipids [4]. Alterations in thyroid function also result in a change in the composition and transport of LPs [2,9,10]. Studies consistently demonstrate elevated serum levels of total cholesterol (TC), LDL-C, apolipoprotein B, lipoprotein (a), and possibly TGs in individuals with subclinical and overt hypothyroidism, all of which are reversible with levothyroxine therapy [4,27,28]. Increased serum TG levels are associated with proatherogenic changes and promote CVD [11]. TH is known to play a role in regulating the oxidation of plasma cholesterol mainly because of an altered pattern of binding, which presents a substrate for the oxidative stress [9]. Hypothyroidism increases the oxidation of plasma cholesterol mainly because of an altered pattern of binding, which presents a substrate for the oxidative stress [9]. THs cause vascular smooth muscle relaxation resulting in decreased arterial resistance and diastolic blood pressure. Overt hypothyroidism is associated with increased systemic vascular resistance, diastolic hypertension, decreased cardiac contractility, decreased cardiac output, and accelerated atherosclerosis and CAD [41]. In addition, hypothyroidism is also associated with antioxidant imbalance. Increased production of free radicals and decreased antioxidant defense mechanisms leads to oxidative stress [40]. 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REFFERENCES