1

Hypothyroidism on Lipid Metabolism

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1. Introduction

The thyroid gland is important in the human body because of its ability to produce the hormones triiodothyronine (T3) and tetraiodothyronine (T4), necessaries for appropriate energy levels and an active life. It has long been known that thyroid hormones are of vital importance in maintaining the initial level of phospholipids in cell membranes and fatty acids composition of the lipids (Prasad & Kumar, 2005). T3 plays a critical role in lipid metabolism by regulating genes involved in lipogenesis and lipolysis (Zhu & Chang, 2010). The underlying mechanisms, however, have only begun to be unraveled in recent years. Hypothyroidism, characterized by low serum thyroid hormone levels, is associated with reduced metabolism, reduced lipolysis, weight gain, reduced cholesterol clearance, and elevated serum cholesterol. It is known that thyroid hormone has genomic and nongenomic effects (Davis et al., 2008). Thyroid hormones exert their effects by stimulation of thyroid hormone receptors (TRs) that have different tissue distribution and metabolic targets. Thyroid hormone receptors possess two isoforms, TRα and TRβ (Nr1a1 and Nr1a2) encoded by the TRα (*NR1A1*) and TRβ (*NR1A2*) genes, and each isoform exists as two or three subtypes, respectively (α1, α 2, β1, β2, and β3). TRα plays a key role in postnatal development, adipose tissue and cardiac metabolism, whereas TRβ regulates multiple steps in hepatic metabolism as well as thyroid hormone levels (Oetting & Yen, 2007). Nuclear mechanisms of thyroid hormone action have been extensively described but an increasing number of nongenomic effects of the hormone at the cellular level have been recognized in the past 10 years (Cheng et al. 2010). Nongenomic actions of thyroid hormone are by definition independent on nuclear receptors for the hormone and have been described at the plasma membrane, various organelles, the cytoskeleton, and in cytoplasm. The actions include alterations in the transport of solutes like Ca^{++}, Na^{+} and glucose, changes in activities of several kinases, including protein kinase C, cAMP-dependent protein kinase and mitogen-activated protein kinase. Iodothyronines also can regulate nongenomically through a protein kinase C activation of neutral lipids, phospholipids and phosphatidylinositol 4, 5-bisphosphate [PtdIns (4, 5) P2] (Axelband et al., 2011).

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The objective of this review is to provide a current overview of the impact of hypothyroidism on lipid content, distribution and metabolism in serum, erytrocytes and different tissues of human and experimental animals. The molecular mechanisms involved in lipids regulation, with emphasis on the effect of hypothyroidism on liver, which is a fundamental organ responsible for controlling cholesterol metabolism, and on adipose tissue, where the role of thyroid hormone in regulating adipogenesis and lipolysis is complex and controversial, are discused. Finally, an overview of hipothyroidism and its correlation with lipid homeostasis in the liver and mammary gland during pregnancy and lactation is also given.

2. Hypothyroidism and circulating lipids

Thyroid dysfunctions are frequent (Benseñor et al., 2001). Abnormal serum thyrotropin (TSH) values and thyroid dysfunction are more prevalent in women than men and increase with age (Valeix et al., 2004). Hypothyroidism has been defined as those conditions which result from suboptimal circulating levels of thyroid hormones (Castieiras Lacambra et al., 1998). It affects 0.5-2.4% of the general population (Sawin et al., 1985). The term myxedema was formerly used as a synonym for hypothyroidism. It is now well kown that hypothyroidism is a graded phenomenon, including presentations with clinical manifestations (overt hypothyroidism) to asymptomatic states known as subclinical hypothyroidism (Evered & Hall, 1972). Subclinical thyroid dysfunction may be defined as an elevated TSH concentration in an asymptomatic patient with a normal serum free thyroxine concentration (Woeber, 1997). It is a common condition affecting 6-17% of the general population (Helfand, 2004). Moreover, subclinical hypothyroidism may progress to overt hypothyroidism. The rate of progression is higher with the concomitant presence of thyroperoxidase antibodies or higher levels of TSH (Vanderpump et al., 1995).

In 1952, Robertson & Kirkpatrick showed very high level of cholesterol in serum of patients with overt hypothyroidism which decreased after adequate hypothyroidism treatment. In 1972, Nikkilä & Kekki observed a moderate increase of serum triglycerides in hypothyroid patients, associated with a decrease in efficiency of triglyceride removal from plasma, which was attributed to a low lipoprotein lipase (LPL) activity. Fowler, in 1973, mentioned that serum cholesterol and triglycerides were increased in patients with "preclinical" hypothyroidism, condition equivalent to the actual subclinical hypothyroidism. Furthermore the author also suggested that the abnormal lipid pattern is the first change to occur as hypothyroidism develops and the last to disappear after treatment. It is now widely recognized that hypothyroidism is one of the most common causes of secondary dyslipidemia. The most common abnormalities of lipoprotein metabolism associated with hypothyroidism are elevated levels of total cholesterol and low-density-lipoprotein cholesterol (LDL-C), which are attributable to the effect of thyroid hormone on lipoprotein lipase activity (Lithell et al., 1981) and the expression of the LDL- receptor (Staels et al., 1990). These changes probably play an important role in atherogenesis.

2.1 Lipid profile in overt hypothyroidism

It is known that overt hypothyroidism is associated with increased fasting plasma cholesterol and triglyceride levels (Tulloch, 1974). Hypothyroid patients also usually have

increased lipoprotein a, Lp(a), levels (Tzotzas et al., 2000), a low-density lipoprotein (LDL)-like particle synthesized by the liver that has been reported to promote thrombosis, inflammation, and foam cell formation (Erqou et al., 2009). Trials evaluating the effects of overt hypothyroidism on LDL subfractions have shown conflicting results. A study in newly-diagnosed hypothyroid patients (n=60) showed that hypothyroidism was associated with higher prevalence of atherogenic small and dense LDL (sdLDL) (Abbas et al., 2008). By contrast, Roscini et al. (1999) found no significant differences between overt hypothyroid patients and healthy controls regarding sdLDL levels. In addition, Pearce et al. (2008) has evaluated the effects of short-term overt hypothyroidism on LDL subfractions. Patients exhibited an increase in LDL-C that was found to be primarily due to increases in the large LDL particles, while sdLDL did not significantly change (Pearce et al., 2008). A possible explanation for these dissimilar results could be the different methodology used for the measurement of LDL subparticles. Hypothyroid patients may also exhibit elevated levels of high-density lipoprotein cholesterol (HDL-C), mainly due to increased concentration of cholesterol- and phospholipid-enriched HDL-2 particles (Pearce et al., 2008). A decreased HDL_2 catabolism and cholesteryl ester transfer protein activity has been observed. This decrease leads to a reduced transfer of cholesteryl esters from HDL to very-low-density lipoprotein (VLDL), thus increasing HDL-C levels (Dullaart et al., 1990).

Hypothyroidism correction results in a decrease of serum total cholesterol, LDL-C, apolipoprotein (apo) A1, apo B and apo E. Hypothyroidism treatment may also decrease serum triglycerides (Stockigt, 2002). The apoB/apoA-1 ratio is highly valuable for detecting atherogenic risk (Millán et al., 2009). In addition, elevated levels of LDL-C have been consistently associated with an increased risk for development of cardiovascular disease (Pekkanen et al., 1990). Recently, non-HDL-C, a measure of total cholesterol minus HDL-C, has emerged as a predictor of cardiovascular disease. After levo-thyroxine replacement, a decrease in non-HDL-C has been observed in patients with overt hypothyroidism (Ito et al., 2007). The altered serum concentrations of non-HDL-C in hypothyroidism may be related to the disturbed metabolism of LDL, remnant lipoprotein, and Apo B (Ito et al., 2007).

2.2 Lipid profile in subclinical hypothyroidism

Unlike the relationship established between overt hypothyroidism and lipid alterations, the relationship between subclinical hypothyroidism and dyslipidemia is still controversial. Despite the fact that the Colorado study of over 25.000 subjects (Caneris et al., 2000) showed a continuous graded increase in serum cholesterol over a range of serum TSH values from <0.3 to >60mU/l, there is no consensus whether mild thyroid failure has an adverse effect on plasma lipids, or whether its T4 treatment, sufficient to normalize TSH, has a beneficial effect (Stockigt, 2002).

A recent study made in 1534 Chinese subjects shows that patients with subclinical hypothyroidism (TSH > 4,8mIU/L) have higher serum triglyceride levels and lower serum HDL-C levels than euthyroid subjects (Lai et al., 2011). Similar results were found by Iqbal et al. (2006), after performing a follow-up study in subclinical hypothyroidism male patients. Subclinical hypothyroidism was also associated to a high serum total cholesterol, LDL-C and apo B levels in the female patients, and to significantly lower apo A-1 levels when males and females were analysed together. After an appropriate treatment with

thyroxine, patients showed a significant reduction in the serum total cholesterol, LDL-C and apo B levels (Iqbal et al., 2006).

On the other hand, from a study of patients with Hashimoto thyroiditis it has been shown that subjects with subclinical hypothyroidism have significantly higher LDL-C and LDL-C to HDL-C ratio compared with euthyroid subjects. After treatment with small doses of levo-thyroxine there was a significant decrease of total cholesterol, non-HDL-C, LDL-C, and LDL-C to HDL-C values (Iqbal et al., 2006). Recent evidence also shows that T4 replacement therapy may improve lipid profile in the cases of subclinical hypothyroidism with Hashimoto thyroiditis. A marked total cholesterol reduction was inversely correlated with an increase in free T4 levels, but not correlated with changes in TSH levels (Tagami et al., 2010). However, properly controlled prospective studies with a larger sample size are neccesary to demonstrate whether replacement therapy alters several cardiovascular markers in patients with subclinical hypothyroidism and Hashimoto thyroiditis.

Ito et al. (2007) found that patients with subclinical hypothyroidism had serum concentrations of total cholesterol, non-HDL-C, remnant-like particle cholesterol, and apo B significantly decreased, without significant changes in the serum concentrations of LDL-C, HDL-C, triglycerides, apolipoprotein A-I, and Lp(a) after levo-thyroxine replacement. They also did not find changes in the serum levels of triglycerides, HDL-C, apo A-1, and Lp(a). On the other hand, in a randomized, double-blind, crossover study, it found that after levo-thyroxine therapy (100 μg/day), patients with subclinical hypothyroidism showed a decrease in total cholesterol, LDL-C, HDL-C, apo B, apo A-1, and apo B to apo A-1 ratio, but only total cholesterol and LDL-C decrease were significantly reduced (5,5% and 7,3% reduction respectively). The total cholesterol reduction was inversely correlated with an increase in free T4 levels, but was not correlated with changes in TSH levels. This would indicate that a significant increase in free T4, although within the normal reference range, may be a better marker for risk factors for cardiovascular disease in monitoring response to treatment in subclinical hypothyroidism than TSH level alone (Razvi et al., 2007). This last result contradicts what was observed by Asvold et al. (2007), who found that there is a linear increase in total cholesterol, LDL-C and triglyceride, and a linear decrease in HDL-C levels with increasing TSH, but this correlation was obtained with TSH values within the normal range. In opposition, a population-based study of 1350 participants did not show changes in mean levels of total cholesterol, triglycerides and LDL-C in both female and male subjects with subclinical hypothyroidism and euthyroid. Women with subclinical hypothyroidism had significantly lower HDL-C than those who were euthyroid. The differences remained significant after adjustment for age, sex, and body mass index. The HDL-C was not different between patients with subclinical hypothyroidism and euthyroid men. However, in this study it was also observed that the mean TSH levels were higher in subjects with dyslipidemia, indicating a relationship between TSH-total cholesterol, and TSH-LDL-C levels mainly in overweight women (Lu et al., 2011).

On the other hand, in a study conducted in patients with subclinical hypothyroidism, with normocholesterolemie and normotriglyceridemie, a decreased triglycerides and phospholipids transference to HDL, which was corrected with appropriate levo-thyroxine therapy, were observed. These results, evaluated using an artificial triglyceride-rich

emulsion labeled with radioactive triglycerides, also showed abnormalities in plasma lipid metabolism, even when these are not detected in routine laboratory tests, in patients with subclinical hypothyroidims (Sigal et al., 2011). Moreover, contradictory results may be due to patient diversity. Mild thyroid failure may be present in two types of patients: patients with untreated mild thyroid failure and patients with a history of overt hypothyroidism, whose T4 dose are not sufficient to normalize the serum TSH level. It has been observed that the change in serum total cholesterol concentration, after an appropriate T4 treatment, is much higher in the second group of patients (Danese et al., 2000). On the other hand, the TSH influence on lipids is different in the overweight and normal weight populations, as well as in men and women. The combination of serum TSH, sex, and body mass index has important effects on serum lipid parameters (Lu et al., 2011).

Hormone thyroid influences on atherogenic serum lipoproteins are attractive metabolic actions that could hypothetically be exploited to treat obesity (Danese et al., 2000) and dyslipidemia (Aronne & Thornton-Jones, 2007). However, using supraphysiological doses of the endogenous thyroid hormones, T4 and T3, for these purposes is predictably associated with risk of thyrotoxic adverse effects in other organ systems, particularly the heart (Morkin et al., 2004) and skeleton (Biondi & Cooper, 2008). A large number of hormone thyroid analogs have been synthesized and tested in experimental animal models for their lipid-lowering activity (Johansson et al., 2005). In all case of thyromimetics therapy use, potential side-effects occur in a dose-dependent fashion; therefore dosing regimens in humans will need to be tightly controlled (Tancevski et al., 2009). Further prospective studies should be carried out to stablish that patients with subclinical hypothyroidism should receive levo-thyroxine replacement.

3. Hypothyroidism and erythrocytes

There are many results indicating that thyroid hormones stimulate erythropoiesis, and also increase erythrocyte 2, 3-diphosphoglycerate concentrations, which serve to enhance the delivery of oxygen to tissues and affect steady-state levels of circulating erythropoietin, playing a major role in abrupt adjustments of erythropoietin production. Thus, hypothyroidism has been generally associated with anemia (Fein & Rivlin, 1975; Antonijević et al., 1999; Shevtsova et al., 1994). The anemia- hypothyroidism relation has even been observed in infants with congenital hypothyroidism, in who anemia has been found to be depended on the degree of neonatal hypothyroidism (Franzese et al., 1996). This anemia may be normocytic, hypochromic-microcytic, or macrocytic, although normocytic and macrocytic anaemia are the most frequent (Fein & Rivlin, 1975; Omar et al., 2010). Macrocytosis (found in up to 55% of patients) and normocytic anemia may result from the insufficiency of the thyroid hormones themselves without nutritive deficit (Antonijević et al., 1999).

A case report of haemolytic anemia induced by hypothyroidism has been described in the literature (Nomura et al., 1991). An increased osmotic fragility is generally associated with haemolytic anemia (Schröter & Eber, 1989). In erythrocytes from streptozocin diabetic rats, an increase in red cell volume and osmotic fragility was accompanied by a defect in the ouabain-sensitive Na^+ K^+-ATPase (Kowluru et al., 1989). In hyperthyroidism it has been found that there are alterations in the number and the activity of Na^+ K^+-ATPase pump in

circulating erythrocytes (Gasawara & Ishikawa, 1993). Also, under this condition, an alteration in osmotic fragility has been observed (Asl et al., 2009). In erythrocytes of hypothyroid rats, it was observed that there is an increase in osmotic fragility, demonstrated by a right shift of hemolysis curve (Dariyerli et al., 2004). However, in hypothyroid subjects these alterations have not been found (Asl et al., 2009).

On the other hand, hypothyroidism causes alterations in the lipid composition of red blood cells (Ishii & Nakao, 1968). In hypothyroid rats a 22% cholesterol and 30% phospholipid level reduction has been found, without change in fatty acid composition, in erythrocyte membranes. The simultaneous decrease in cholesterol and phospholipid levels did not alter the cholesterol/phospholipid molar ratio, thus avoiding the erythrocyte membrane abnormal function (Ruggiero et al., 1987). In a study realized in 38 patients with hypothyroidism, it was found that the level of arachidonate in erythrocyte membrane was significantly decreased both before the treatment and within the course of replacing hormonal therapy. The content of omega-3 fatty acids decreased in the course of conventional therapy (Serebriakova et al., 2008). Erythrocytes lipid changes are also found in patients with haemolytic anemia and hypothyroidism. In the red cell membrane, phosphatidylcholine and free cholesterol were increased, and the free cholesterol to phospholipid ratio was elevated. After levo-thyroxine therapy, the derangement of lipid levels was normalized with improvement of the hemolytic anemia (Nomura et al., 1991). In a hypothyroid patients group who were athyreotic as a consequence of ablation treatment for well-differentiated thyroid cancer, it was observed that the relative amounts of 18:2 omega 6 rose and those of 20:3 omega 6 fell, while the levels of all monounsaturated fatty acids increased in erythrocytes. The nature of these alterations suggests a disturbance in the delta-6 desaturase activity. The cholesterol/phospholipids ratio, polyunsaturated fatty acids content, increased intracellular Ca^{++}, protein phosphorylation, membrane protein cross-linking and membrane lipid peroxidation, among other factors, may alter the red blood cell membrane deformability (Pescarmona et al., 1983). However, in an experimental model of hypothyroidism induced in rats by methimazole addition (75 mg/100 g) to the fodder, there was no change in the erythrocyte rigidity index between control and experimental groups (Toplan et al., 2005).

Alteration in oxidative status has been observed in thyroid pathologies. Moderate hypothyroid state induced in female rabbits resulted in a significant decrease in the serum concentration of the lipid peroxidation end-product malondialdehyde. The erythrocytes of hypothyroid animals exhibited higher resistance to oxidative stress and lesser oxidative lipids damage characterized by measurement of compounds reacting with thiobarbituric acid (Brzezińska-Slebodzińska, 2003; Kowalczyk et al., 2001). Hypothyroidism induced by lithium-treatment, provoked a significant decrease in the glutathione content without change in superoxide dismutase activities, in red blood cells. This imbalance might render the erythrocytes vulnerability to oxidative stress and ultimately haemolysis (Engin et al., 2005). Alterations in the activities of catalase and glucose-6-phosphate dehydrogenase activities have been found in erythrocytes of hypothyroid patients (Sal'nikova et al., 1983; Hübner et al., 1979).

Acanthocytes are erythrocytes with several (usually 3 to 7) irregularly spaced blunted projections from the margin of the cells. These cells have increased cholesterol but normal content of phospholipids. Acanthocytes are the principal morphological abnormality in

abetalipoproteinemia and in the "spur cell anemia" associated with severe alcoholic liver disease (Horton et al., 1976; Lynch, 1990). Acanthocytosis findings in cytologic blood smear suggest hypothyroidism in about 90% of cases. Other diseases related to acanthocytes are very rare, hence hypothyroidism must be excluded in all cases where acanthocytes are observed on the blood film (Antonijević et al., 1999; Betticher & Pugin, 1991). There appears to be no correlation between any of the clinical features of the hypothyroid state and the shape red cell change but patients lacking the misshapen red cells may have a less severe disturbance of serum lipids. The abnormal red cells slowly disappear by treating the hypothyroidism (Wardrop & Hutchison, 1970).

4. Hypotyroidism and liver lipids

4.1 Cholesterol

Cholesterol is an essential constituent of most biological membranes and is also a precursor of bile acids, steroid hormones, and certain vitamins. Animals rely on two mechanisms to maintain a pool of cholesterol sufficient to meet these requirements; *de novo* cholesterol synthesis from acetyl coenzyme A and absorption of cholesterol from dietary sources (Angelin, 1995). The liver is central in cholesterol metabolism, balancing hepatic cholesterol synthesis and hepatic uptake of plasma lipoproteins from the circulation against the excretion of hepatic cholesterol and bile acids in the bile. Thyroid hormone is an important regulator of cholesterol metabolism. T3 can influence the metabolism of cholesterol at several critical steps in the liver: 1- the low-density lipoprotein receptor (LDL-R), which mediates cholesterol uptake from the circulation, 2,3-hydroxy-3-methylglutaryl coenzyme A reductase, controlling cholesterol biosynthesis, and 3-cholesterol 7α-hydroxylase (CYP7A1), the rate-limiting enzyme in the synthesis of bile acids where cholesterol is used as substrate (Gullberg, 2002). To monitor the level of membrane sterols, cells employ two sterol-sensing domain (SSD)-containing proteins, sterol regulatory element-binding protein (SREBP), cleavage-activating protein (SCAP) and 2-3-hydroxy-3-methylglutaryl coenzyme A reductase that are localized within the endoplasmic reticulum. Under low sterol conditions, SCAP binds to SREBPs to escort them from the endoplasmic reticulum to the Golgi apparatus where they are processed into functional transcription factors that activate the expression of genes involved in the synthesis of cholesterol. When sterols accumulate, the 2-3-hydroxy-3-methylglutaryl coenzyme A reductase is rapidly degraded, resulting in the termination of sterol synthesis (Eberlé, 2004; Dong & Tang, 2010).

It is known that TRβ is a major mediator of T3 effects on serum cholesterol and that it is involved in the transcriptional regulation of the CYP7A1 gene. The dependence on TRβ for T3 regulation of serum cholesterol levels was supported by the fact that TRβ-selective agonist GC-1 was is as efficient as T3 in decreasing serum cholesterol in hypothyroid mice (Trost, 2000). The molecular mechanisms controlling CYP7A1 regulation by bile acids and cholesterol metabolites have been widely studied. Liver X receptor-β (LXRβ) and farnesoid X receptor are two ligand dependent transcription factors that are receptors for derivatives of cholesterol and bile acids in the control of CYP7A1 expression (Henkel, 2011). LXRβ, an oxysterol binding transcription factor, directly activates CYP7A1 transcription in response to challenge with dietary cholesterol to mice; thus LXRβ -/- mice fed cholesterol-rich diets fail to induce enzyme activity and therefore accumulate toxic levels of cholesterol in the liver (Alberti, 2001). In addition to T3, it has been recognized that growth hormone is required for

normal CYP7A1 regulation in rats and mice. Experiments showed that in the absence of TRs (TRβ1-/- mice), neither cholesterol nor T3 stimulated CYP7A1 expression and activity. CYP7A1 mRNA expression and enzymatic activity remained on a high level in these mice regardless of the T3 status and irrespective of whether cholesterol was added to the diet or not. The blunted CYP7A1 stimulation in response to T3 confirms the importance of TRβ (Pramfalk et al., 2011). The absence of up-regulation in response to dietary cholesterol was at first unexpected, but is likely due to the critical dependence of normal CYP7A1 regulation on growth hormone and to the fact that TRβ1-/- mice have severely reduced growth hormone levels. TRβ also appears to be of major importance for the regulation of 2,3-hydroxy-3-methylglutaryl coenzyme A reductase transcription by T3 (Gullberg, 2000).

Reduced binding activity of hepatic LDL receptors is generally considered as a major mechanism of hyperlipidemia in hypothyroidism. There were clearly effects of T3 on LDL receptor mRNA, but they could not be distinctly ascribed to TRα1 or TRβ. Although T3 rapidly regulates the transcription of the LDL receptor gene no specific TRE (thyroid response element) has so far been described in the LDL receptor gene promoter. The suppression of CYP7A activity would lead to down-regulation of LDL receptor mRNA, however, it cannot be concluded that T3 directly regulates the LDL receptor transcription (Lopez et al., 2007).

4.2 LXR transcription factor

The liver X receptors, LXRα (NR1H3) and LXRβ (NR1H2), are ligand-activated transcription factors that belong to the nuclear hormone receptor superfamily. LXRs play a critical role in cholesterol homeostasis, bile acid metabolism and carbohydrate metabolism. The oral administration of LXR agonists to mice results in elevated hepatic fatty acid synthesis and steatosis and increased secretion of triglyceride-rich very low density lipoprotein resulting in hypertriglyceridemia. This increased hepatic lipogenesis has been largely attributed to the LXR-dependent upregulation of sterol regulatory element-binding protein 1c (SREBP-1c) expression. However, it has been reported that treating *Srebp-1c* null mice with the synthetic LXR agonist T0901317 still results in enhanced expression of many lipogenic genes, suggesting additional mechanisms by which LXR can enhance hepatic lipogenesis (Cha & Repa, 2007; Talukdar & Hillgartner, 2006).

LXR exists in two isoforms, LXRα and -β (also referred to as Nr1h3 and Nr1h2, respectively. LXRα is highly expressed in the liver, and expressed at lower levels in the adrenal glands, intestine, adipose tissue, macrophages, lung, and kidney, whereas LXRβ is ubiquitously expressed. The LXRs form heterodimers with the retinoid X receptor (RXR). The RXR/LXR heterodimers bind to LXR responsive elements (LXREs) consisting of direct repeats (DRs) of the core sequence AGGTCA separated by four nucleotides (DR-4). Although, the LXRs and TRs belong to two distinct receptor subgroups with respect to ligand-binding affinity, the two receptor systems show similarity with respect to molecular mechanisms, target genes, and physiological roles. Both TR and LXRs form heterodimers with RXR, and bind to DR-4 with identical geometry and polarity. Recently it has been shown that TRβ and LXRα interact on the mouse CYP7A1 gene promoter, suggesting the possibility of cross talk between the two receptors at the transcription level in the liver. There are structural similarity between LXRs and TRs. The mouse LXRα mRNA expression is positively

regulated by TR at the transcriptional level, and a cross-talk pathway between LXRα and TRβ exists in the autoregulation of the LXRα gene. The human LXRα mRNA expression and promoter activity are also positively regulated by thyroid hormone.A cross talk between TRβ and LXRα could be a therapeutic target against dyslipidemia and atherosclerosis (Hashimoto et al., 2007). LXRα plays a pivotal role in hepatic cholesterol metabolism, whereas LXRβ has not a comparable role. LXRα is inducible by thyroid hormone, whereas LXRβ is not.

There are several possible models for explaining the molecular mechanism behind the dependence or independence on TRβ for T3 regulation of target genes. One possibility is that the promoter context determines the TR isoform that regulates expression of the target gene. This implies that TRα1 and TRβ bind certain T3 response elements with different affinities. TRα1 and TRβ, respectively, govern which TR regulates a target gene in a specific cell; this assumes that the spatial expression patterns are distinct for different TRs in the liver. This would be analogous to the metabolic zonation in the liver where different metabolic processes are spatially separated along the porto-central axis of the liver units .In fact, several of the aforementioned genes are known to be zonally expressed in the liver. The CYP7A gene is expressed in a narrow zone around the central vein. It has been reported that TRβ is expressed preferentially around the central vein in the rat (Zandieh-Doulabi et al., 2004). This has supported the idea that hepatic target gene specificity by TRs may be preferentially governed by distinct zonal expression of TRs and their respective target genes, and less by promoter selection (Gullberg et al., 2000).

4.3 Sterol regulatory element-binding proteins

Sterol regulatory element-binding proteins (SREBPs) are transcription factors that belong to the basic helix-loop-helix leucine zipper family. The mammalian genome encodes three SREBP isoforms, designated SREBP-1a, SREBP-1c, and SREBP-2. SREBP-2 is encoded by a gene on human chromosome 22q13. Both SREBP-1a and -1c are derived from a single gene on human chromosome 17p11.2 through the use of alternative transcription starts sites that produce alternate forms of exon 1, designated 1a and 1c (Tarling et al., 2004). SREBP-1a is a potent activator of all SREBP-responsive genes, including those that mediate the synthesis of cholesterol, fatty acids, and triglycerides. High-level transcriptional activation is dependent on exon 1a, which encodes a longer acidic transactivation segment than does the first exon of SREBP-1c. SREBP-1c preferentially enhances the transcription of genes required for fatty acid synthesis but not cholesterol synthesis. LXRs bind to an LXR-binding site in the SREBP-1c promoter and activate SREBP-1c transcription in the presence of LXR agonists such as oxysterol (Quack et al., 2002).

There is evidence that T3 represses mouse SREBP-1c expression at the transcriptional level. The mouse SREBP-1c promoter is negatively regulated by thyroid hormone in the Hepa1–6 cells. DNA binding of TR (RXR-TR heterodimer) is required for negative regulation of the mouse SREBP-1c gene promoter. In addition, SREBP-1c mRNA levels were increased in the hypothyroid status by about 1.5-fold compared with the control, and thyrotoxic treatment reduced the mRNA levels by about 50% compared with the control level. Thus mouse SREBP-1c gene expression in the liver is negatively regulated by thyroid hormone (Berkenstam et al., 2004).

4.4 Lipid β-oxidation in TRβ$^{PV/PV}$ mice

The PV mutation has been identified in a patient with resistance to thyroid hormone. PV exhibits potent dominant-negative activity. It is due to a C-insertion at codon 448 of the TRβ1 that leads to a mutant that has complete loss of T3 binding and transcription activity (Parrilla et al., 1991). To understand the role of TRs in lipid homeostasis *in vivo*, it has been adopted the loss-of-function approach by creating knock-in mutant mice with targeted mutation in the TRα gene (TRα1PV mouse) or TRβ gene (TRβPVmouse).

The decreased β-oxidation could also contribute to lipid accumulation in the liver of wild-type and TRβ$^{PV/PV}$ mice. The β-oxidation activity in the primary hepatocytes of TRβ$^{PV/PV}$ mice was found significantly lower (24-37%) than that of wild-type mice. Simultaneously it was observed that the expression of carnitine palmitoyl-transferase Iα (Cpt1a), a rate-controlling enzyme regulating the import of fatty acids into mitochondria, was lower (37%) in the liver of TRβ$^{PV/PV}$ mice than in wild-type mice and the expression of cytochrome P450 family 4 subfamily A polypeptide 10 (Cyp4a10) involved in microsomal ω-oxidation was significantly increased in TRβ$^{PV/PV}$ mice, 40-fold higher than wild-type. These data suggest that the reduction of β-oxidation activity and the fatty liver phenotype is mainly mediated by the decreased expression of rate-determining step regulator, Cpt1a, in TRβ$^{PV/PV}$ mice. Evidence indicates that the liver of the TRα1$^{PV/+}$ mice, is smaller than the wild-type mice with paucity in hepatic fat accumulation. Further molecular analyses have indicated that the expression and activity of PPARγ are increased in the liver of TRβ$^{PV/PV}$ mice, whereas the expression of PPAR is repressed in the liver of TRα1$^{PV/+}$ mice (Araki et al., 2009).

Differential regulation of lipogenic genes by apo-TRβ and apo-TRα1, in accord with the lipid phenotype, has also been observed in the liver of these two mutant mice.TRβ is known to be the major TR isoform in the liver, and many TR-mediated T_3 effects are believed to act via TRβ in this target tissue. Therefore, it is reasonable to expect that the mutation of the TRβ isoform would lead to observable phenotypic abnormalities. However, it has been shown that mutation of TRα1, which is a less abundant TR isoform in the liver, led to the repression of PPARγ and manifestation of abnormality in lipid metabolism in TRα1$^{PV/+}$ mice. The dominant-negative activity of TRβ is stronger in tissues where TRβ is the predominantly expressed isoform. Possibly, abnormal gene regulatory activity of the less abundantly expressed TRα1PV would be compensated by the predominantly expressed w-TRβ in the liver (Cheng, 2005). Thyroid hormone stimulates lipogenesis in the liver. Hepatic production of malonyl-CoA is the rate-limiting step in the synthesis of fatty acids and it is catalyzed by both acetyl-CoA carboxylase (ACC) 1 and 2. ACC1 is enriched in the liver and other lipogenic tissues and is regulated by TR, LXR and SREBP-1 at the transcriptional level through the ACC1 promoter II. SREBP-1 enhances ACC1 mRNA expression by forming a tetrameric complex with TR/RXR, which stabilizes SREBP-1 on its binding site. A PPARα agonist stimulates *ACC1* gene expression by enhancing the expression of SREBP-1c processing enzymes, which increases nuclear SREBP-1c activity .LXR directly stimulates *ACC1* gene expression (Grefhorst et al., 2005). In hypothyroidism all these processes are decreased. These findings indicate that apo-TRβ and apo-TRα1 have different effects on lipid metabolism and that both TR isoforms contribute to the pathogenesis of lipid metabolism changes in hypothyroidism.

4.5 Mitochondrial lipids

The hepatic mitochondrial lipid composition is altered significantly in hypothyroid rats. The total cholesterol increases, the phospholipids decrease and the cholesterol/phospholipid molar ratio increases (around 40%). Among the phospholipids, cardiolipin shows the greatest alteration (30% decreases in the hypothyroid rats). The phosphatidylethanolamine/ phosphatidylcholine ratio also decreases. Alterations were also found in the pattern of fatty acids. These changes in lipid composition may be responsible, at least in part, for the depression of the phosphate carrier activity in the liver mitochondria from hypothyroid rats (Hoch et al., 1981). In addition, hypothyroidism and thyroxin substitution affect the n-3 fatty acid composition of rat liver mitochondria. The n-6 and n-3 polyunsaturated fatty acids are affected differently by the hypothyroid state. The levels of linoleic (18:2n-6), gamma-linolenic (18:3n-6) and dihomo-gamma-linolenic acids (20:3n-6) have been found to be higher in hypothyroid rats than in controls, while the level of arachidonic acid (20:4n-6) was lower, which suggests an impairment of the elongase and desaturase activities. The n-3 polyunsaturated fatty acids, eicosapentaenoic (20:5n-3) and docosapentaenoic (22:5n-3) acids, were higher in hypothyroid rats, whereas the linolenic acid (18:3n-3) content remained constant. The level of docosahexaenoic acid 22:6n-3 was dramatically decreased in hypothyroid rats, while the levels of C22 n-6 fatty acids were unchanged. The differences were probably due to the competition between n-3 and n-6 polyunsaturated fatty acids for desaturases, elongases and acyltransferases. When hypothyroid rats were treated with thyroxin, the changes induced by hypothyroidism in the proportions of n-6 fatty acids were rapidly reversed, while the changes in the n-3 fatty acids were only partially reversed. After 21 days of thyroxin treatments, the 22:6n-3 content in liver mitochondria was only half as high in hypothyroid rats than in euthyroid rats. These results suggest that the conversion of 18:2n-6 to 20:4n-6 is suppressed in the hypothyroid state which favors the transformation of 18:3n-3 to 20:5n-3 (Raederstorff, 1991). The content of individual fatty acid component in mitochondria of livers from thyroidectomized and streptozotocin -induced diabetic rats has been measured to investigate how different hormones are interrelated to control the amount of a particular fatty acid in mitochondria. The results showed diabetes, in general, affected fatty acid contents more severely than hypothyroidism, regardless of the direction of the changes. Hypothyroidism and diabetes affected antagonistically the contents of C16 species and C18:1, which belong to a de novo synthesis (oleate series). However, the two pathological conditions affected synergistically those of higher unsaturated species, eg. C18:2, C20:3 and C20:4, which belong to a dietary-dependent synthesis (linoleate series). These findings strongly indicated that each desaturation site and elongation site is affected in a preferential order by either thyroid hormone or insulin, and that hypothyroidism and diabetes have their effects differently on the process of *de novo* synthesis and the pathways initiated from an essential fatty acid in mitochondria (Nishida et al., 1991).

The phospholipid composition and the in vitro incorporation of radioactive cytidine diphosphate-choline into phosphatidylcholine were studied in mitochondria and microsomal fraction obtained from liver and brain of 20 day old hyperthyroid or hypothyroid rats. The chemical composition of the subcellular membranes isolated from brain differed markedly in both conditions. In hyperthyroidism the microsomal fraction was slightly affected while the mitochondria were also affected, but not as severely as in hypothyroidism, in which the microsomal fraction showed no alterations. The incorporation

of the radioactive precursor into brain mitochondria isolated from hyperthyroid rats was markedly decreased, while no changes were observed in microsomes. However, incorporation into brain microsomal fraction obtained from hypothyroid rats was increased, while no changes were observed in mitochondria. Similar results were obtained in the studies performed with liver subcellular membranes from hyperthyroid animals while no changes were found in those from hypothyroid rats. Thus, it seems possible that both experimental conditions affect in a different way the structure and function of brain mitochondria and microsomal fractions. These findings also give further support to authors' hypothesis that mitochondria have a certain degree of autonomy for the synthesis of phosphatidylcholine (Faryna de Raveglia et al., 1982).

5. Hypothyroidism and adipose tissue

Recent evidence shows that during the adipogenesis of 3T3-L1 cells, TRα1 mRNA is constitutively expressed in preadipocytes. Its expression continues to increase during adipogenesis, concurrent with the appearance of lipid droplets. In contrast, very little, if any, TRβ1 mRNA is detectable in either preadipocytes or adipocytes. These findings suggest a critical role of TRα1 during adipogenesis of 3T3-L1 cells (Zhu et al., 2011). It is known that that thyroid hormone could also act via nongenomic action through a plasma membrane receptor. The plasma membrane receptor is located on integrin αvβ3 at the arginine-glycine-aspartic acid (RGD) recognition site important to binding by the integrin of extracellular matrix proteins. Interestingly, snake venom-derived RGD-containing disintegrin was found to inhibit adipogenesis of primary cultured fibroblastic preadipocytes (Lin et al., 2005). These cell-based studies further expanded the complexity of understanding the regulation of adipogenesis by thyroid hormone.

5.1 Peroxisome Proliferator-Activated Receptors (PPARs)

Thyroid hormone receptors regulate adipogenesis via crosstalk signaling with PPARs. Both PPARs and TRs are ligand dependent transcription receptors of the subfamily 1 (NR1) in the nuclear receptor superfamily. The NR1 group also includes retinoic acid receptors (RARs), Rev-erb, RAR-related orphan receptors (RORs), LXRs, vitamin D3 receptors (VDRs), and the nuclear xenobiotic receptor (constitutive androstane receptor (CAR). PPARs and TRs share a conserved DNA-binding domain (DBD) and exert their activity partly by heterodimerization with a common partner, the RXR, to regulate the transcription of target genes (Liu & Brent, 2010; Hunter et al., 1996).

TRs play important roles, as do PPARs, in lipid mobilization, lipid degradation, FA oxidation, and glucose metabolism. By direct or indirect effect, thyroid status influences the expression of a number of genes involved in lipid and glucose metabolism. For example, TR isoform-specific regulation of hepatic genes involved in lipogenesis and fatty acid-oxidation has been implicated by the cDNA array analysis of TRβ knockout mice treated with or without thyroid hormone (Flores-Morales et al., 2002). Among more than 200 hepatic genes responding to T3 treatment, ~60% of them are regulated by TRβ and the remaining 40% are regulated through TRα. PPARα is one of the T3-regulated genes (Flores-Morales et al., 2002).

PPARs have been shown to affect the thyroid hormone functions in thermogenesis in vivo. Administration of the PPARγ agonist rosiglitazone to male rats shifts the energy usage to an

anabolic state and markedly reduces plasma thyroid hormones. Rosiglitazone also decreases mRNA levels of the TRα1and TRβ in brown adipose tissue, and the TRα1 and TRα2 in retroperitoneal white adipose tissue (WAT). These findings explain the functions of PPARγ in up-regulating thermogenesis-related genes in WAT and brown adipose tissue, while balancing the whole body thermogenesis by down-regulating the transcription activity of TRs in these processes (Festuccia et al., 2008). PPARδ exerts an inhibitory effect on T3-induced transcription activation by TRβ on the TRE-CAT reporter gene even in the presence of overexpressed RXRα protein in cells. PPARδ could inhibit the transcriptional activity of TR action by competing for the heterodimerized partner RXR in the nucleus (Meier-Heusler et al., 1995).

5.2 Leptin

Leptin, a recently discovered protein produced in adipocytes, regulates body weight by suppressing food intake and/or increasing energy expenditure. Thyroid hormones, which increase the basal metabolic rate and thermogenesis, have been reported to be one of leptin's regulating factors because alternations in thyroid status might lead to compensatory changes in circulating leptin. Plasma leptin is significantly elevated in hypothyroid subjects, to levels similar to those seen in obese euthyroid subjects. Treatment of hypothyroidism results in a reduction in the raised plasma leptin levels. The data are consistent with the hypothesis that leptin and the pituitary-thyroid axis interact in the euthyroid state, and that hypothyroidism reversibly increases leptin concentrations. Thyroid status modifies leptin secretion independently of adiposity and noradrenaline. The data suggest leptin-thyroid interactions at hypothalamic and adipocyte level (Pinkney et al., 2000).

Hypothyroidism is clearly related to body weight gain and greater adiposity, but the range of hormonal change in serum TSH concentration associated with weight gain remains a focus of debate. It has been shown that in hypothyroidism: 1) glucose uptake in muscle and adipose tissue is resistant to insulin; 2) the suppression of lipolysis by insulin is not impaired; 3) plasma levels of triglycerides are elevated due to decreased clearance by the adipose tissue; 4) a major finding to explain most of the metabolic defects is the decrease in adipose tissue blood flow rates. These findings, taken together with published data on hyperthyroidism suggest that thyroid hormone excess and deprivation do not make a consistent story: in hypothyroidism the decrease of blood flow in adipose tissue and muscle may be considered as part of the pathogenetic mechanism of insulin resistance explaining most of the metabolic defects in these tissues; in contrast, in hyperthyroidism the increase of blood flow seems to correct the intrinsic metabolic defects in muscle and adipose tissue (Dimitriadis et al., 2006). Moreover, in hypothyroidism the targets of insulin action are not uniformly impaired: glucose uptake and proteolysis are resistant to insulin, but lipolysis is not; the latter may be necessary to relieve tissues from the burden of unsatured fatty acids surplus after meals. Low normal free T4 levels were significantly associated with increased insulin resistance. These findings are consistent with an increased cardiovascular risk in subjects with low normal thyroid function (Ross et al., 2007). In female patients with primary hypothyroidism, plasma levels of leptin were found to be increased (Hsieh et al., 2002; Teixeira et al., 2009). Thyroid hormone plays a relevant role in regulating leptin metabolism independent of body mass index and body fat (Hsieh et al., 2002). These results

may explain, at least in part, low blood flow rates and insulin resistance in the forearm and adipose tissue in overt hipothyroidism.

5.3 Lipoprotein lipase

LPL is a central enzyme in lipid metabolism, and adipose LPL activity is increased in rats that are deficient in thyroid hormone. LPL is synthesized and secreted by adipocytes, and is important for the transfer of triacylglycerol fatty acids from the circulating blood into adipocytes. The cellular regulation of LPL is complex. Previous studies have described the effects of numerous hormones and physiologic conditions on the level of LPL catalytic activity, and more recent studies have identified a number of different mechanisms of LPL cellular regulation (Wang & Eckel, 2009). Among the hormonal regulators of LPL is thyroid hormone. Adipose tissue levels of LPL have consistently been increased in hypothyroid rats, although plasma triglycerides have been either decreased or unchanged during hypothyroidism**.** Triglyceride-derived fatty acid uptake was found to be increased in WAT in association with increased LPL activity but unaffected in oxidative tissues and decreased in liver (Klieverik et al., 2009).

Studies by Saffari et al. (1992) have shown that WAT LPL is increased in hypothyroidism via a postranslational mechanism. This finding was amply confirmed by Klieverik et al. (2009) that in three WAT depots, fatty acid uptake from VLDL particles was increased in proportion to the LPL activity. The WAT fatty acid uptake in hypothyroidism is quite significant, amounting to approximately 3 nmol/mg tissue in 2 h, comparable to the combined (VLDL plus albumin) uptake by thyrotoxic muscle. The biological meaning of these observations is also intriguing. WAT only stores triglycerides so the fat is there to stay. Then, some questions have been raised ¿is the stimulation of lipoprotein lipase in WAT of hypothyroid animals a way to protect the liver from massive steatosis? Or do these depots contribute to the thermal insulation of these thermogenic deficient mice? After all, fat is an excellent thermal insulator. However, the hypothyroid rat does not obese, even after months of hypothyroidism. It is possible that as hypothyroidism extends, lipogenesis is progressively reduced and a new steady state with only moderate obesity is reached (Silva, 2010). In adipose tissue, hypothyroidism results in a decreased responsiveness of lipolysis to catecholamines even though there is no change in beta adrenergic receptor levels. This impairment in lipolytic responsiveness is reflected in decreased cellular cAMP levels due to an increase in cAMP phosphodiesterase, which degrades cAMP. In addition, some studies have suggested some impairment in adenylate cyclase activity in hypothyroid adipose tissue. Thus, the decreased responsiveness of LPL to epinephrine in cells from hypothyroid rats is consistent with previous data on adipocyte lipolysis, and suggests that a second messenger common to both hormones, such as cAMP, is important for LPL translation (Carvalho et al., 1996; Germack et al., 2000).

5.4 Adipose tissue of TR knockout mice

Studies using TR subtype knockout mice have shown that TRα1 is essential for maintaining proper thermogenesis and that TRβ is important in regulating cholesterol metabolism. These findings suggest tissue-dependent T3-mediated TR isoform action in the maintenance of metabolic homeostasis. In hypothyroidism, however, TRs function as aporeceptors. Studies

of mice deficient in all TRs (TRα1$^{-/-}$ and TRβ$^{-/-}$ mice) have shown that they exhibit a milder overall phenotype than the debilitating symptoms of severe hypothyroidism, highlighting the important role of apo-TRs in the pathogenesis of hypothyroidism. Indeed, knock-in mutant mice harboring different mutations in the TRα gene exhibit abnormalities in lipid metabolism. The TRα1PV mouse that harbors a frameshift mutation in the C-terminal 16 amino acids displays a lean phenotype, partly due to the reduction in white fat mass. The TRα1R384C knock-in mutant mouse also exhibits a lean phenotype with reduction in fat mass. The TRα1P398H knock-in mutant mouse, interestingly, has increased body fat accumulation and elevated serum levels of leptin, glucose, and insulin. These results indicate that apo-TRα1 severely perturbs lipid metabolism and energy balance but in a mutation-site-dependent manner (Liu et al., 2003).

The creation of knock-in mutant mice with an identical mutation in the TRβ (TRβPV mouse) or TRα gene (TRα1PV mouse) at the same corresponding C terminus of receptors allowed to clarify whether apo-TRβ with the same mutation as the TRα1 mutant could lead to a similar or a distinct impairment in lipid metabolism. The TRβPV mouse faithfully reproduces human RTH with dysregulation of the pituitary-thyroid axis, whereas the TRα1PV mouse has normal thyroid-pituitary functions (Kaneshige et al., 2000). Although both the homozygous (TRβ$^{PV/PV}$) and heterozygous (TRβ$^{PV/+}$) mice are viable with no severe fertility defects, homozygous TRα1$^{PV/PV}$ mice die shortly after birth, and heterozygous TRα1$^{PV/+}$ mice are dwarfs with reduced fertility (Kaneshige et al., 2001). Recently, it has been found that the reduction in the WAT contributes to the dwarfism of TRα1$^{PV/+}$ mice and that apo-TRα1 (TRα1PV) acts to repress adipogenesis of WAT by inhibition of the expression and by repression of the transcriptional activity of PPARγ. It has been found that in contrast to TRα1$^{PV/+}$ mice, no abnormality in the WAT of TRβPV mice was detected. The transcription activity of PPAR γ was repressed by TRα1PV. The dual repression effects of TRα1PV reduce the expression of several PPARγ downstream target genes involved in adipogenesis, resulting in reduced fat mass. In addition to these *in vivo* findings, it has been shown that the overexpression of TRα1PV blocked the T3-dependent adipogenesis of 3T3-L1 cells (Ying et al., 2007).

Obesity and disorders of lipid metabolism are major health issues. The findings that the apo-TR isoforms act differentially in a target-tissue-dependent manner, could help direct the design and development of T3 analogs to treat these disorders. One could envision that if fatty liver were detected in patients with hypothyroidism, it would be more beneficial to treat them with a TRβ-specific analog such as GC-1 without a major undesirable effect in other organs such as the heart. As additional advances are made in better understanding the actions of TR isoforms in lipid metabolism, novel T3 analogs for improved treatment strategies would certainly be forthcoming. The finding that TRα1PV was more effective than TRβ1PV in blocking adipogenesis suggests that TRα1 could be considered as a potential therapeutic target for decreasing adipose tissue and reducing serum fatty acids. Moreover, 3T3-L1 cells stably expressing *TRa1PV* or *TRβ1PV* could be used as model cell lines to further elucidate the role of T3 via TR in adipogenesis (Baxter & Webb, 2009).

5.5 Fatty acid-beta oxidation

The role of thyroid hormone in regulating lipolysis is also complex and controversial. It has been shown that in the fed state adipocytes from hypothyroid rats had markedly reduced

sensitivity to catecholamine-induced lipolysis, whereas there was no change in catecholamine-induced lipolysis in adipocytes from hyperthyroid rats (Ben Cheikh et al., 1994). Thyroid hormones play a major role in regulating oxygen metabolism. Thyroid hormones increase both coupled and uncoupled respiration, and thyroid dysfunction impacts resting energy expenditure (REE). The underlying mechanisms are not clear, but uncoupling proteins (UCP) that produce heat instead of ATP may be involved. A positive correlation between thyroid hormones and UCP2 mRNA expression has been shown by Barbe et al. (2009). In addition, increased UCP2 mRNA expression has been demonstrated in fat biopsies from hyperthyroid patients (Hoffstedt et al., 2000). UCP2 levels in adipose tissue have been found to be significantly lower in patients in the hypothyroid state compared with the euthyroid state. The levels increased during treatment and became similar to those of healthy controls. The precise function of UCP2 in adipose tissue is not settled, but several theories exist. UCP2 may be involved in fatty acid metabolism, and UCP2 expression has been shown to be regulated by free fatty acids. UCP2 has also been suggested to be involved in the production of reactive oxygen species. Finally, UCP2 has been suggested to function as a genuine uncoupling protein, involved in lipid metabolism, since a positive association between basal free fatty acids and UCP2 expression has been demonstrated (Davis et al., 2008). The gene expression of other mitochondrial proteins participating in lipid oxidation, namely ACC and carnitine palmitoiltransferase-1, has not shown any significant changes in patients before and after treatment nor in healthy controls (Gjedde et al., 2010). These findings support the notion of UCP2 as a specific target for T3- mediated gene regulation in human adipose tissue.

6. Hypothyroidism and lipid during pregnancy and lactation

Pregnancy is a state of significant dynamic changes in metabolism, with accumulation of lipids and nutrients during about the first half; whereas during late pregnancy and lactation, these accumulated reserves are used for fetal growth and subsequently for milk synthesis (Hapon et al., 2003). The regulation and coordination of lipid metabolism on pregnancy and lactation are very important because of the sudden and profound physiological changes occuring during these physiological states (Hapon et al., 2003, 2005). It is known that undiagnosed hypothyroidism during pregnancy will lead to irreparable central nervous system defects in the newborn because the development of the child *in utero* is critically affected by the mother's thyroid status (Gartner, 2009). The prevalence of subclinical hypothyroidism in women of childbearing ages is 4-5% (Glinoer, 1997). Furthermore, at least in two population-based surveys carried out in areas with different iodine intake, suggest a 2.5% overall prevalence of compensated or uncompensated hypothyroidism during pregnancy (Parrot et al., 1960), making it a significant risk for gestational outcome.

6.1 Liver and mammary lipids in pregnancy

During the last decade there has been an increasing appreciation for the incidence of thyroid dysfunction during pregnancy as well as the resultant adverse maternal and fetal effects (Okosieme & Lazarus, 2010; Lazarous, 2011). Pregnancy is accompanied by profound alterations in thyroidal economy, resulting from a complex combination of factors that are specific to the pregnant state: the rise in T4-binding globulin concentrations as a result

of estrogenic stimulation, the effects of chorionic gonadotropin on the maternal thyroid, alterations in the requirement for iodine, modifications in autoimmune regulation, and the role of the placenta in deiodination of iodothyronines (Glinoer, 1997, 2004). In rats, hypothyroidism has been associated with delayed paturition, subnormal number of fetuses, increased pup mortality, decreased pup growth, altered circulating hormones (Parrot et al., 1960, Hapon et al., 2003) and also, altered functioning of the mammary gland during lactation (Hapon et al., 2003). A clinical state of hypothyroidism during late pregnancy may limit the capacity of the maternal organism to sustain itself and the fetus adequately and to prepare the mammary tissue for the subsequent lactation, thus compromising delivery and nutrition of the newborn (Hapon et al., 2003). A linear correlation between maternal and fetal plasma triglycerides has been described to have an important implication in newborn weight (Herrera, 2002). It contributes to provide circulating triglycerides in the form of lipoprotein to the mammary gland for milk lipid synthesis (Ramos & Herrera, 1996).

Fatty acid synthesis is an important metabolic pathway that is controlled by nutrients and hormones. Thyroid hormones are involved in the regulation of hepatic lipogenesis by altering levels of fatty acid synthase and acetyl-CoA carboxylase mRNAs, and their activities (Radenne et al., 2008; Kim et al., 2005). It is known that pregnancy stimulates fatty acid synthase and glycerol-3-phosphate acyltransferase expressions in the rat liver, while a state of clinical hypothyroidism during pregnancy shows decreased hepatic triglyceride synthesis in terms of ^{14}C[glucose] incorporation and subsequently, decreases in triglycerides and enhanced cholesterol in the circulation (Bonet & Herrera, 1991; Lopez Luna & Morales, 1985). A decrease in the liver lipid synthesis has been also evidenced by the diminished incorporation of $^{3}H[H_2O]$ into triglycerides and by the expression and activity of fatty acid synthase and acetyl-CoA carboxylase in pregnant hypothyroid rats, which may be responsible for the decrease in circulating triglycerides (Hapon et al., 2005). Congenitally hypothyroid mice show alterations in apoB RNA editing that switch hepatic production from apoB-100 to apoB-48 isoform (Mukhopadhyay et al., 2003), and whose conformational competence directs the assembly of hepatic VLDL more effectively.

The liver also plays a central role in the maintenance of whole body cholesterol homeostasis by integrating the regulation of a group of hepatic enzymes, receptors, and other proteins that are important for cholesterol, lipoprotein, and biliary metabolism (Smith et al., 1998). Changes in thyroid state indirectly modify the biosynthesis of cholesterol by its effects on metabolism and on the coefficient of intestinal absorption of cholesterol (Mathe & Chevallier, 1976). The mRNA levels of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, which is the rate-limiting enzyme for de novo cholesterol biosynthesis, is increased in the liver during late gestation, but the change of 3-hydroxy-3-methylglutaryl-coenzyme A reductase is not modified by hypothyroidism (Hapon et al., 2005). The mRNA levels of 7α-hydroxylase are not modified by pregnancy or by hypothyroidism. In addition, the LDL receptor mRNA, a factor involved in cholesterol uptake that is increased during late gestation, is decreased in the pregnant hypothyroid rats, contributing to the increased circulating (LDL+VLDL)-C (Hapon et al., 2005). It is well known that hypothyroidism increases cholesterol through an enhancement of LDL.

Degradation of lipids is affected by altered thyroid state. Regulation of fatty acid oxidation is mainly through key rate limiting enzymes such as carnitine palmitoyltransferase 1α and

acyl-CoA oxidase. Carnitine palmitoyltransferase 1α catalyzes the transport of long chain fatty acids from cytosol into mitochondria for β-oxidation and acyl-CoA oxidase catalyzes the first rate limiting reaction in peroxisome oxidation. Thyroid hormones modulate carnitine palmitoyltransferase 1α and acyl-CoA oxidase gene transcription (Liu & Brent, 2010). It has been observed that hypothyroid rats on the 21th day of pregnancy decreased liver acyl-CoA oxidase mRNA levels but did not modify mitochondrial (carnitine palmitoyltransferase 1α) fatty acid β-oxidation. Because carnitine palmitoyltransferase 1 is regulated by the availability of malonyl-CoA, the diminished ACC activity may result in a decrease in malonyl CoA that may compensate for the effects of the hypothyroid state, resulting in no overall change in expression (Hapon et al., 2005). This is in accord with what is has was observed in vitro by Muller et al. (1981).

Experimental evidence indicates that pregnancy does not alter mammary lipogenesis, but that PTU treatment has a negative effect in the pregnant mammary gland. Glycerol-3-phosphate acyltransferase mRNA abundance, and that of LPL, is not modified by either gestation or PTU treatment (Hapon et al., 2005). Late pregnancy increases mammary acyl-CoA oxidase mRNA levels, suggesting a stimulation of fatty acid oxidation, while hypothyroidism produces a diminution of acyl-CoA oxidase. In addition, it has been found in pregnant rats that hypothyroidism increases triglycerides and total lipid content and decreases phospholipids, without modifying cholesterol in mammary gland. These findings have been associated to a lower proportion of mammary lobuloalveolar epithelial tissue in the hypothyroid pregnant rats (Hapon et al., 2005). Those effects may be a consequence of the hypothyroid state per se and not direct consequences of the increase of circulating prolactin (Hapon et al., 2003), since in mammary tissue, the increased prolactin should have stimulated lipid synthesis.

6.2 Lipids during lactation

Lactation is characterized by low levels of plasma thyroid hormone, triglyceride and VLDL, and elevated levels of plasma cholesterol (Denis et al., 2003; Smith et al., 1998). Triglyceride-rich particles are rapidly cleared from the circulation during the lactating phase, likely by conversion to IDL/LDL-size particles through the action of LPL in the mammary gland to supply lipids for milk production (Smith et al., 1998). Experiments in rats indicate that hypothyroidism in mothers produces a diminution in hepatic lipid synthesis due to a decrease in $^{3}H[H_2O]$ incorporation to triglycerides, and a decrease of ACC expression and activity (Hapon et al., 2007). In addition, PTU-induced hypothyroid during lactation reduces mammary ACC activity (on days 15 and 20 of lactation) and ACC and LPL mRNA on day 20. It is well known that ACC and milk synthesis are induced during lactogenesis (Martyn & Falconer, 1983). These findings suggest less secretion of triglycerides-rich particles into circulation during mid to late lactation, compromising the fulfillment of lactational triglyceride requirements (Hapon et al., 2007). Also, a drastic diminution in milk quality has been found in PTU-induced hypothyroid during lactation. A decrease in triglycerides in mid and late lactation along with a decrease of milk lactose on mid lactation, may contribute significantly to the severe growth deficit previously observed in the litters born from hypothyroid mothers (Hapon et al., 2003). Thyroid hormones also modulate the expression of various mammary proteins involved in cellular proliferation (de Launoit & Kiss, 1989; González-Sancho et al.,

1999). Administration of a moderate oral dose of T3 to lactating rats and mice dams induces a higher growth rate in the pups; this positive effect seems to be mainly due to augmented secretion of milk that, in addition, contains an elevated proportion of triglycerides (Quevedo-Corona et al., 2000; Capuco et al., 1999). The impaired growth of the litters of hypothyroid mothers can be largely attributed to the low milk quality along with the impaired milk ejection. In accordance with a reduced capacity to eject milk, the PTU-treated mothers show significantly lower circulating oxytocin concentrations after suckling compared with control mothers (Hapon et al., 2003). Because mammary gland physiology is similar across species, biological concepts developed for lactating rat model may be instructive for human lactation (Hapon et al., 2007). It can be concluded that a state of clinical or subclinical hypothyroidism may well be aggravated by the pregnant state, and that the adequate function of the mammary glands may be compromised. In particular, the availability of triglycerides to the fetus and to the mammary gland that is preparing for lactation is affected (Hapon et al., 2003). This, along with the decrease in the proportion of epithelial mammary tissue and in lipid synthesis, at the time when the initiation of milk synthesis is about to proceed, may contribute to the future lactation deficit of hypothyroid mothers.

7. Conclusion

The experimental and epidemiological evidences presented in this review indicate that hypothyroidism severely disturbs the lipid homeostasis in liver and adipose tissue contributing to the alteration of circulating lipids. Lipid metabolism of liver and mammary gland are also markedly altered during pregnancy and lactation by hypothyroidism. Therefore monitoring thyroid status and adjusting the T4 dose during pregnancy is very important due to changes in T4 metabolism throughout pregnancy. Thus both maternal and neonatal alterations can easily be prevented. Further understanding of the molecular mechanisms behind the dependence or independence on thyroid receptors for T3 regulation of target genes involved in the lipid homeostasis will entail therapeutic potentials not only for the prevention and treatment of thyroid disorders but also for prevalent diseases in the world, such as obesity and cardiovascular disease.

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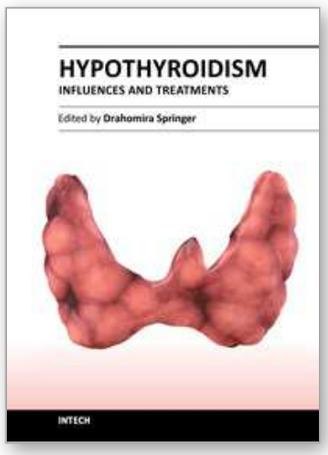

Hypothyroidism - Influences and Treatments
Edited by Dr. Drahomira Springer

ISBN 978-953-51-0021-8
Hard cover, 348 pages
Publisher InTech
Published online 08, February, 2012
Published in print edition February, 2012

Hypothyroidism is the most common thyroid disorder and it is significantly more frequent than presented - millions of people suffer from this disease without knowing it. People with this condition will have symptoms associated with slow metabolism. Estimates of subclinical hypothyroidism range between 3 to 8 %, increasing with age, whereas it more likely affects women than men. About 10% of women may have some degree of thyroid hormone deficiency. Hypothyroidism may affect lipid metabolism, neurological diseases or other clinical conditions. The book includes studies on advancements in diagnosis, regulation and replacement therapy, thyroid ultrasonography and radioiodine therapy for hypothyroidism. "Hypothyroidism - Influences and Treatments" contains many important specifications, results of scientific studies and innovations for endocrine practice.

How to reference
In order to correctly reference this scholarly work, feel free to copy and paste the following:

J. Coria Mariela, V. Carmona Yamila, B. Oliveros Liliana** and S. Giménez Maria (2012). Hypothyroidism on Lipid Metabolism, Hypothyroidism - Influences and Treatments, Dr. Drahomira Springer (Ed.), ISBN: 978-953-51-0021-8, InTech, Available from: http://www.intechopen.com/books/hypothyroidism-influences-and-treatments/hypothyroidism-on-lipid-metabolism

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