Chapter 8

Obesity and Weight Loss: The Influence of Thyroid Hormone on Adipokines

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Additional information is available at the end of the chapter

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1. Introduction

The primary function of adipose tissue is storing energy in triacylglycerol (TG) form, neutralizing the excess of circulating lipids and saving non-adipose tissues of a fat overload. Under normal conditions, in the postprandial state, there is lipogenic endocrine system stimulation, allowing that positive energy balance can be stored as TG in adipose tissue, a process called lipogenesis. In contrast, the mobilization of fat in adipocytes occurs through the hydrolysis of TG by hormone sensitive lipase (HSL), a phenomenon called lipolysis. At the center of this interface - lipolysis and lipogenesis - is the insulin hormone, which exerts a potent inhibitory role on the HSL, allowing lower rates of lipolysis and hence, highest fat mass [1]. However, adipose tissue is not only a passive stock organ of triacylglycerol, being currently recognized as an endocrine organ with multiple functions [1, 2]. Produces several biologically active substances called adipokines, among them tumor necrosis factor-α (TNF-α), monocyte chemoattractant protein 1 (MCP-1), interleukin-6 (IL-6), leptin, resistin and adiponectin. These substances actively participate in, among others, body energy regulation, mainly, by endocrine, paracrine and autocrine signals, which allow the adipocyte play a metabolic role in other tissues [3-5].

However, in obesity there is an imbalance in adipokines production, a fact which, together with the inability to store fat in the adipocytes, results in a process of adipose tissue dysfunction [6], a known risk factor for developing obesity-associated metabolic disorders [1, 2, 6]. This fact occurs because the adipocytes (hypertrophic and hyperactive) initiates the production of adipokines and chemotactic factors (such as MCP-1), which attract macrophages into the adipose tissue [7]. Consequently there is a synergistic interaction on

proinflammatory adipokines production - mainly TNF-α - and antagonistic on adiponectin. These substances lead to insulin resistance, reducing the lipogenic action of insulin in adipocytes, which results in higher rates of lipolysis in the adipose tissue [8, 9]. On the other hand, calorie restriction affects the regulation of adipose tissue gene expression, normalizing the adipokines changes observed in obesity [10].

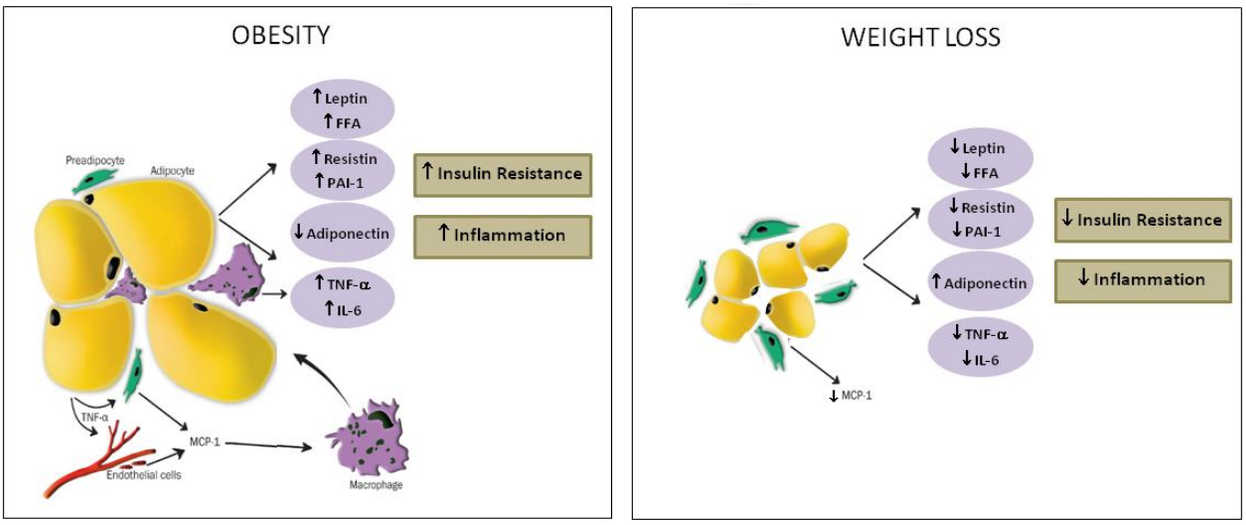

Figure 1. Adapted from van Kruijsdijk et al, 2009 [6]. In obesity the hypertrophic and hyperactive adipocytes initiate the production of MCP-1, which attract macrophages into the adipose tissue, increasing proinflammatory adipokines production (mainly TNF-α) and decreasing adiponectin production, leading to insulin resistance and inflammation. The weight loss process revert this alterations, improving insulin resistance and inflammation. FFA: fatty free acids; PAI1: Plasminogen activator inhibitor 1; TNFα: tumor necrosis factor-α; MCP1: monocyte chemoattractant protein 1; IL6: interleukin 6.

In this chapter will be revised about the influence of thyroid hormones on adipokines in obesity and weight loss. Also will be discussed the physiological role of adipokines as well as the effect of obesity and weight loss on the adipokines.

2. Adipokines physiological role

The adipose tissue is considered an endocrine organ and shows great dynamism. Since 1940 there is a hypothesis that adipose tissue has signals to communicate with other tissues [11], but only later was shown that this tissue is able to synthesize and secrete a large number of protein factors (which also act as cytokines) collectively called adipokines. These adipokines, in most part, are related, directly or indirectly, in processes involving atherosclerosis, hypertension, insulin resistance (IR) and type 2 diabetes (DM2), dyslipidemia, ie, represent the link between adiposity, metabolic syndrome and cardiovascular diseases [12-15]. Among these is Leptin, Resistin, Adiponectin, and others such as tumor necrosis factor-alpha (TNF-alpha), interleukin-6 (IL-6), plasminogen activator inhibitor-1 (PAI-1), acylation stimulating protein (ASP) and factors involved in the renin-angiotensin system (RAS).

2.1. Leptin

With its gene identified in 1994 [16] leptin is the adipokine most studied and thenceforth it has been identified more than 30 biochemical products secreted by adipocytes. Leptin is a peptidic hormone with 167 amino acids and 16kDa of molecular weight and synthesized from the "ob" gene in adipocytes, being more common in subcutaneous adipose tissue than in visceral fat [17]. Besides to be considered an important lipostate, or energy balance regulator according to body fat mass in long-term [18, 19] has been implicated in the regulation of immune, respiratory and reproductive systems [20]. The term Leptin comes from Greek "leptos" which means "thin" due to the fact that this protein lead to increased energy expenditure and act on satiety signals in hypothalamus, reducing caloric intake [21].

The expression and circulating leptin levels are controlled by a number of factors that may increase its secretion (insulin, glucocorticoids, TNF-α, estrogens, thyroid hormone and CCAAT/enhancer-binding protein-alpha) or decrease (Beta3-adrenergic activity, androgens , free fatty acids, GH, and peroxisome proliferator-activated receptor-gamma agonists) depending on the physiological assembly expressed by the body, especially on satiety and energy intake [22].

When circulating this adipokine reaches various body tissues as pancreas, increasing insulin secretion; liver, causing a satiety sensation by the increase in glucose production and increasing energy expenditure; hypothalamus, increasing stimulation of hypothalamic-pituitary-adrenal axis, and decreasing the stimulus of hypothalamic-pituitary-thyroid and hypothalamic-pituitary-gonadal axis; muscle tissue, increasing glucose uptake and metabolism [23].

Many of the effects of leptin result from their actions on the central nervous system, particularly in the hypothalamus, which acts in satiety and appetite regulation. Reaching these tissues after crossing the blood-brain barrier, leptin acts in the arcuate nucleus where there is a large concentration of leptin receptors, when binding to reduce the action of neurons that use neuropeptide Y (NPY) signaling and agouti-related protein (ARGP). NPY is a peptide of 36 amino acids, synthesized mainly in the arcuate nucleus, which projects to the paraventricular nucleus, ventromedial, perifornical and lateral, also involved in energy balance regulation. It is the most potent orexigenic. The ARGP also synthesized in the arcuate nucleus, also is projected to paratentricular nucleus, ventromedial and lateral, acting as a melanocortin system analogue on receptors MC-3 and MC-4, stimulating food intake. Leptin acts by decreasing the activity of these orexigenics signals, inhibiting food intake and increasing energy expenditure by activating the sympathetic nervous system [24, 25]. Also in the hypothalamus, leptin activates neurons pro-opiomelanocortin (POMC) producing alpha-melanocyte stimulating hormone (alpha-MHS). All substances expressed in this system are anorexigenics, ie, act on reducing food intake [14]. This product acts on malanocortin-4 receptors and also on neurons that express cocaine and amphetamine-regulated transcript (CART). POMC/CART neurones also have projections to the lateral hypothalamus and paraventricular nucleus, with a reciprocal innervation of these nuclei to the arcuate nucleus. Both alpha-MSH and CART are potent anorexigenic agents. The

nucleus tractus solitarius (NTS) participates in the satiety control, involved in the end of food intake process. Afferent inputs related satiety signals include neurological vagus nerve and sympathetic system associated with chemical signals such as endocrine factors of gut cholecystokinin. There are many interconnections between hypothalamic nuclei including the paraventricular nucleus and the NTS (Figure 2).

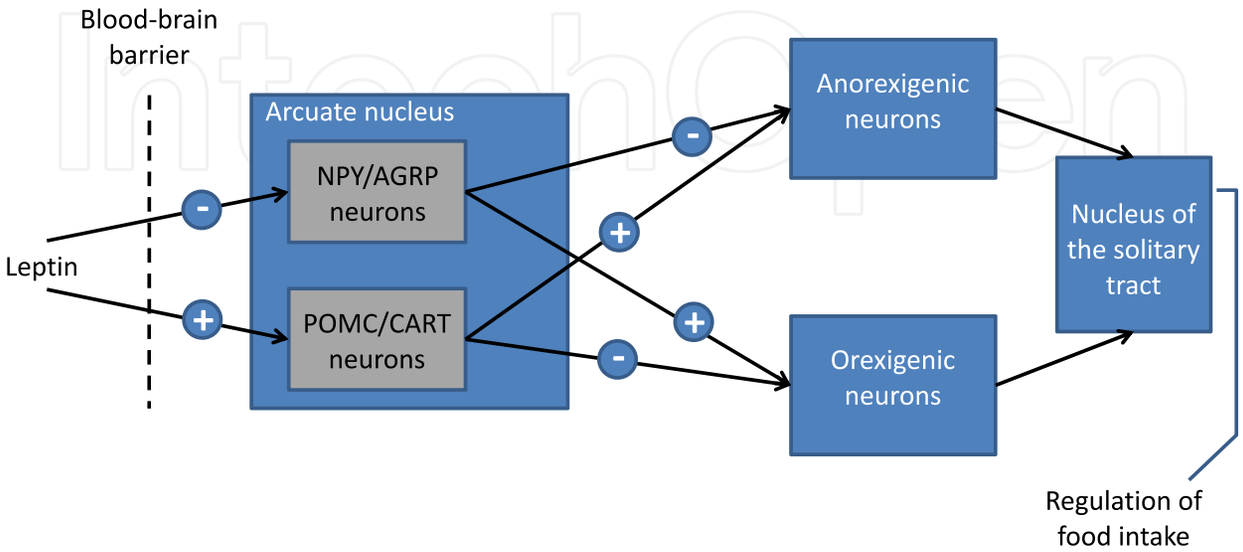

Figure 2. Food intake regulation by leptin at arcuate nucleus level. NPY: Neuropeptide Y; AGRP: Agouti-related protein; POMC: Pro-opiomelanocortin; CART: Cocaine and amphetamine-regulated transcript.

Among the actions taken by other hypothalamic nuclei in relation to energy homeostasis, can be highlight the ventromedial nucleus as a satiety center, lateral hypothalamus as the center of hunger and paraventricular nucleus on increased energy expenditure effects, as production of corticotropin releasing hormone and thyrotropin releasing hormone, activators the sympathetic nervous system. In perifornical nucleus, there is production of peptides termed orexins A and B, which act in the ventromedial nucleus and inhibits satiety and increase food intake. These areas receive nucleus axons of neurons in the arcuate nucleus, POMC/CART and NPY/ARGP, being considered as secondary action areas of leptin (downstream) [14, 26]. The leptin role in the CNS as a regulator is thus triggering mechanism (cascading effect), in order to stimulate or inhibit substances that act directly or indirectly in the hypothalamic areas involved in energy balance control.

In addition to their central effects, leptin also interacts with numerous peripheral tissues. Essentially, there are two major isoforms of leptin receptor, a long isoform which is required for full stimulation of the janus kinase-signal transducers and activators of transcription (JAK-STAT) pathway, and the short isoforms which result in the activation of JAK2 but not STAT. In skeletal muscle, for example, there are the two isoforms but the expression of short isoform is greater than the long one, making the leptin signalization in skeletal muscle activate various kinases including PI3-kinase, Akt (or PKB), PKC, MAP kinase kinase and Jun ERK [27, 28].

In the immune system the leptin receptor are expressed in hematopoietic cells, where leptin produced by adipocytes stimulates the normal growth of myeloid and erythroid [14]. In addition, leptin synergistically acts with other cytokines by increasing the proliferation of leukocytes, specifically T4 cells.

Leptin effects on reproduction are varied and the target organs range of hypothalamus, ovary and endometrial. In the hypothalamic-pituitary axis there is a stimulatory effect [29]. Its levels have a circadian and ultradian cycle, and these variations are associated with varying levels of luteinizing hormone (LH) and estradiol, informing to the brain about the critical fat stores necessary for secretion of luteinizing releasing hormone and activation of hypothalamic-pituitary-gonadal axis [30]. The amount of leptin released in the brain is greater in women than in men, suggesting that women may be more resistant to the leptin action and require higher levels to achieve an appropriate response [31]. It is known that leptin, in ovaries, may affect the menstrual cycle by a direct inhibitory effect on the follicles development [29]. Leptin may still have an important role in the early stages of cleavage and embryonic development [32], in the fetal growth regulation and development, hematopoiesis and angiogenesis, as leptin receptors were found in syncytiotrophoblast, suggesting that leptin may play an important role in fetal endocrine function of feto-placental unit [33]. In addition, leptin may play a central role in other target organs for reproduction, such as endometrial and mammary gland, influencing important functions including lactation and prevention of misbirth [34].

In the respiratory system leptin acts as a growth factor in the lung and as a modulator in the mechanisms of breathing central control. Leptin levels are elevated in patients with sleep apnea, independent of body fat, being associated with leptin resistance [14].

For hypothalamic-pituitary-thyroid axis leptin acts on the expression of thyrotropin-releasing hormone (TRH). Mice *in vitro* and *in vivo* study has demonstrated that leptin stimulates neurons directly in the paraventricular nucleus, which express TRH, increasing proTRH expression [35]. During fasting, the prohormone convertases 1 and 2 (PC1 and PC2) are decreased and leptin showed to restore PC1 and PC2 to pre-fasting levels [36]. Studies in rodents have shown that calorie restriction rapidly suppresses TRH expression in the paraventricular nucleus, leading to decreased thyroxine (T_4) and triiodothyronine (T_3) levels [37], and leptin can reverse these changes [38].

Both partial and complete deficiency of leptin is associated with hypothyroidism. Ob/ob mice exhibit hypothyroidism at birth [39] and normal mice have decreased T_4 levels during fasting [38]. Individuals with congenital leptin deficiency have a disorganized TSH secretion, suggesting that leptin may regulate the pulsatile characteristics of TSH and the circadian cycle [40]. In women with hypothalamic amenorrhea leptin treatment significantly increased free T_3 and free T_4, however did not affect TSH levels [41]. The lack of significant changes in TSH levels in many studies may be due to pulsatile nature of this hormone, but leptin can directly stimulate the T_4 release from the thyroid gland and/or increase TSH bioactivity [42, 43].

2.2. Resistin

Resistin is a polypeptide at approximately 12kDa and belongs to proteins family with cysteine-rich C-terminal domain call resistin-like molecules, which are identical to those found in inflammatory zone family, giving to resistin the alias FIZZ3 [44]. Its expression is 15 fold higher in visceral adipose tissue when compared to subcutaneous adipose tissue, in rodents [44], but it is also expressed in human macrophages [45]. Its name is due to the resistin presents a significant role in obesity-associated insulin resistance [46] and its molecular structure is very similar to adiponectin. Resistin production increases with food intake and obesity, and decreases in the presence of PPAR-gamma ligands [47].

Resistin promotes insulin resistance by increasing hepatic gluconeogenesis, and presenting rapid effect on this tissue [47]. Other *in vivo* study also found effects of administration and neutralization of resistin on glucose tolerance in skeletal muscle and adipose tissue, indicating resistin action also in these tissues by negative modulation of insulin signaling on glucose uptake [46].

Regarding the specific body fat deposits, resistin expressions 2-3 fold higher is found in visceral adipose tissue, followed by subcutaneous, abdominal and gluteal-femoral subcutaneous. Its expression is 3 fold higher in preadipocytes compared with mature adipocytes, also functioning as a potential regulator of adipogenesis [48].

Resistin deficient mice have weight and fat mass similar to wild-type mice, even when high-fat fed. However, resistin deficient mice significantly improved fasting glucose levels in control diet and improved glucose tolerance in high-fat diet. Insulin sensitivity is unaffected. The improvement in glucose homeostasis in resistin deficient mice is associated with decreased hepatic gluconeogenesis. Whereas these data support a resistin role in glucose homeostasis during fasting in rodents, a similar role in humans remains to be determined [3].

2.3. Adiponectin

Adiponectin, also known as ACRP 30 (adipocyte complement related protein of 30kDa), apM1 (adipose most abundant gene transcript 1), AdipQ or GBP28 (gelatin binding protein of 28 kDa) [49-52], is a protein exclusively expressed in differentiated adipocytes and circulates in high levels in the blood [53], presenting greater expression in subcutaneous adipose tissue than in visceral adipose tissue [54]. Unlike other factors secreted by adipose tissue, adiponectin acts as a protective factor for cardiovascular disease and increases insulin sensitivity. It is an approximately 30 kDa polypeptide that shows high homology with collagen VIII and X, and complement component C1q. A proteolytic cleavage product containing the globular domain of adiponectin circulate in physiologically significant levels and has biological activity [53].

Except for cases of severe malnutrition [55] and in neonates [56], there is a strong negative correlation between plasma adiponectin and fat mass [52].

Were identified two adiponectin receptors isoforms (Adipo-R1 and -R2) [57]. This receptors present seven transmembrane domains but are functionally different of receptors coupled to G protein. AdipoR1 is expressed mainly in muscle tissue and has high affinity for globular adiponectin, and low affinity for full-length adiponectin. AdipoR2 has high expression in liver and has intermediate affinity for both isoforms of circulating adiponectin. Thus, it is noted that the biological effects of adiponectin depends not only on circulating levels or the properties of each isoform but also receptor subtype and its expression in each tissue [3].

Adiponectin anti-inflammatory and anti-atherogenic actions occurs through decreased expression of adhesion molecule-1 (via reduced expression of TNF-alpha activity and resistin); decreased macrophage chemotaxis to fat cells formation; and inhibition of inflammatory signaling in endothelial tissue [58]. It increases insulin sensitivity via increased fatty acid oxidation and glucose uptake and utilization in skeletal muscle and adipose tissue; reduction of hepatic glucose release, leading to better control of glucose serum levels, free fatty acids and triglycerides [59]. In rat adipocytes, *in vitro*, the 60% reduction in adiponectin expression increased significantly insulin resistance. The presence of nucleotide polymorphisms in adiponectin caused by genetic or environmental factors (diet rich in fat, for example), can be a determining factor in reducing their insulin sensitizing action [60].

In the liver, adiponectin increases insulin sensitivity by reducing nonesterified fatty acids uptake, increasing fatty acid oxidation and decreasing glucose output. In muscle, adiponectin stimulates glucose metabolism and fatty acid oxidation. In the endothelium, it inhibits monocyte adherence by reducing adhesion molecules; inhibits macrophages transformation and reduces migrating smooth muscle cells proliferation in response to growth factors. Adiponectin also increases nitric oxide production by endothelial cells and stimulates angiogenesis. Taken together, these effects suggest that adiponectin is the only adipokine that present antidiabetic, anti-inflammatory and anti-atherogenic effects [3].

2.4. Others adipokines

Tumor Necrose Factor - alpha (TNF-α) – TNF-α is a cytokine expressed by adipocytes and stromovascular cells, with higher expression in subcutaneous adipose tissue compared to visceral adipose tissue, acting directly on adipocytes, promoting apoptosis induction, lipogenesis inhibition, by inhibiting lipoprotein lipase (LLP), GLUT-4 and the acetyl CoA synthetase expressions, as well as increased lipolysis, therefore exerting an important regulatory role in fat accumulation in adipose tissue [61, 62]. TNF-α is a transmembrane protein of 26 kDa, which, after being cleaved generates a portion of 17-kDa, which is biologically active and exerts its effects through TNF-α receptor type I and II. It is a cytokine initially described as an endotoxin-induced factor causing necrosis in tumors. The ability of TNF to induce cachexia *in vivo* led to an extensive evaluation of its role in energy homeostasis [3]. TNF-α alters gene expression of metabolically important tissues such as adipose tissue and liver [63] and impairs the insulin signaling by activation of serine kinases that increase the insulin receptor substrate-1 and -2 phosphorylation, increasing its

degradation [64]. Both TNF-α and triiodothyronine are involved in the tissue homeostasis maintenance of the anterior pituitary gland, however, triiodothyronine inhibit the signaling cascade that TNF-α promotes on this tissue in signaling pathways affecting MAPK p38 and nuclear factor kappaB [65].

Interleukin-6 (IL-6) – IL-6 is also a cytokine with pro-inflammatory effect in acute responses and action on carbohydrates and lipids metabolism [66, 67]. IL-6 circulates in glycosylated form ranging from 22 to 27 kDa. Its receptor (IL-6R) is homologous to the leptin receptor and exists in two isoforms, a membrane-bound and soluble. The infusion of IL-6 near physiological doses, in healthy humans, increase lipolysis independently of catecholamines, glucagon and insulin modulation [68], indicating IL-6 as an important factor in lipid metabolism. As TNF-α, it inhibits the LLP and increases free fatty acids and glycerol release. Furthermore, the increased expression may be related to leptin suppression and stimulation of C-reactive protein production, as well as in reducing IRS-1 and GLUT-4 expression in the liver and muscle [66]. IL-6 is secreted by adipocytes and macrophages, which are responsible for 30% of its secretion [67]. Catecholamines can stimulate IL-6 expression via β2-and β3-adrenoceptors in adipose tissue, when in high concentrations [69]. The IL-6 central administration increases energy expenditure and decreases body fat in rodents. Also, transgenic mice with IL-6 overexpressed showed generalized growth deficiency and reduced body mass, however, IL-6 deficient mice develop obesity and metabolic abnormalities, suggesting that IL-6 may prevent, rather than cause these conditions [70].

Monocyte chemotactic protein-1 (MCP-1) – MCP-1 is a chemokine and a member of the small inducible cytokine family, which plays a role in the recruitment of monocytes and T lymphocytes to sites of injury and infection. Its main receptor is the chemokine CC motif receptor (CCR) 2 that is expressed in various cell types including adipocytes, skeletal muscle cells and macrophages. MCP-1 was first described as a secretory product of monocytes and endothelial cells with a role in atherosclerosis. MCP-1, acting through its receptor CCR2, is now thought to play a central role in the recruitment of monocytes to atherosclerotic lesions and in the development of intimal hyperplasia after arterial injury. Owing to their crucial roles in monocyte recruitment in vascular and nonvascular diseases, MCP-1 and CCR2 have become important therapeutic targets in cardiovascular research. Furthermore, MCP-1 plays a role in inflammation in insulin-responsive tissues. As for skeletal muscle, MCP-1 is increased during myopathies and can be induced by interferon-gamma. Recently, MCP-1 has been attributed an additional role in the pathophysiology of obesity [71].

Plasminogen activator inhibitor (PAI)-1 – Adipocytes can secrete many proteins in hemostasis and fibrinolytic system as PAI-1 [72]. PAI-1 is a member of the serine protease inhibitor family and is the primary inhibitor of fibrinolysis by inactivating urokinase-type and tissue-type plasminogen activator. PAI-1 has also been implicated in a variety of other biological processes including angiogenesis and atherogenesis. PAI-1 is expressed by many cell types within adipose tissue including adipocytes [3]. PAI-1 expression and secretion are greater in visceral adipose tissue relative to subcutaneous adipose tissue [54]. PAI-1 promotes thrombi formation and unstable atherogenic plaque rupture, and change the fibrinolytic balance by

inhibition of plasmin production, contributing to vascular architecture remodeling and atherosclerotic process [66, 73].

Adipsin and acylation stimulating protein (ASP) – Also secreted by adipose tissue it has an important effect on lipogenesis [59]. APS inhibits the lipolysis by inhibition of hormone sensitive lipase (HSL), and stimulating lipogenesis by increasing GLUT4 translocation from cytosol to membrane; increases glycerol-3-phosphate production and increases diacylglycerol acyltransferase activity, an catalyst enzyme in triglycerides synthesis [74]. Thus affects both the glucose and the lipid metabolism.

Proteins of the renin angiotensin system (RAS) – Pathogenic models have been proposed to explain the association between adiposity and the renin angiotensin system [75]. This seems to be related to fat accumulation in adipose tissue, as well as its involvement in inflammatory and atherogenic process. Adipose tissue secretes many proteins related to the RAS as renin, angiotensinogen (AGT), angiotensin I, angiotensin II, angiotensin type I receptors (AT1) and type 2 (AT2) angiotensin-converting enzyme (ACE), and other proteases capable of producing angiotensin II (chymase, cathepsins D and G) [76, 77]. The angiotensin I receptor is secretion inductor of series 2 prostaglandins which participates in preadipocytes cell differentiation, and the angiotensin II stimulates adipocytes differentiation and lipogenesis in time of angiotensin I to II conversion, indicating their involvement in the accumulation of fat mass process [78].

3. Adipokines and thyroid hormones

The thyroid gland mainly produces the thyroid hormones T_3 and T_4. However, also produces small amounts of other iodothyronines as reverse T_3 and 3,5-diiodo-L-thyronine. This gland is part of hypothalamic-pituitary-thyroid axis. Thyroid hormones secretion is regulated by the classical mechanism of negative feedback; briefly, thyroid releasing hormone (TRH), produced predominantly by neurons of the paraventricular nucleus in the hypothalamus, stimulates the release of thyroid stimulating hormone (TSH) in pituitary and this in turn, stimulates the synthesis and release of thyroid hormones. The increase in thyroid hormones serum concentrations inhibit the production of both TRH and TSH, leading to decreased thyroid function. The subsequent decrease in thyroid hormones serum levels, in turn, stimulates TRH and TSH, again increasing the concentration of hormones [79]. Thyroid hormones act in the body through the coupling to its receptor α (TRα) and β (TRβ). The thyroid hormone receptors (TRs), members of the superfamily of nuclear receptors interact with a specific DNA sequence, called responsive element in the promoter region of target gene and regulates gene transcription [80]. Generally, TRs are repressors in the absence of binding T_3 and transcriptional activators in its presence [81].

Although the thyroid hormones are essential for the survival [37], thyroid function disorder leads to changes in metabolic parameters, for example, thyroid hormone excess is associated with weight loss and reduced muscle and fat mass [82] , showing that thyroid hormones play a central role in regulating the adipose tissue metabolism [83]. Furthermore, Viguerie et

al. [84] showed by microarray that 19 genes of human white adipose tissue are regulated by thyroid hormone. These modulated genes give rise to proteins involved in transduction signal, lipid metabolism, apoptosis and inflammatory responses. The thyroid hormones inhibit proliferation and stimulate differentiation of adipocytes [85], regulate lipid metabolism by upregulation lipolytic enzymes expression, increase oxygen consumption and modulate tissue sensitivity to other hormones [84].

Since thyroid hormones affect adipose tissue metabolism, it is interesting to evaluate the relationship between thyroid hormones and adipokines in obese and weight loss, the focus of discussion in next sections.

4. Thyroid hormone effect on adipokines in obesity

4.1. Leptin

A potential interaction between leptin and thyroid hormones has been suggested since both hormones are associated with body weight and energy expenditure regulation.

Leptin deficiency leads to severe obesity, however, in humans it's usually find high levels of leptin associated with leptin-resistance state [86-91]. Although thyroid function is usually normal in obese subjects, many studies have demonstrated that TSH levels are slightly increased in obese subjects [92-94]. Several studies have suggested that leptin influences TSH release, suggesting a regulatory role by leptin on thyroid axis at least in some conditions [35, 40, 95-101]. Thyroid hormones regulate the expression of several genes in human adipocyte [84], however, the role of thyroid hormones in leptin modulation remains controversial (Figure 3).

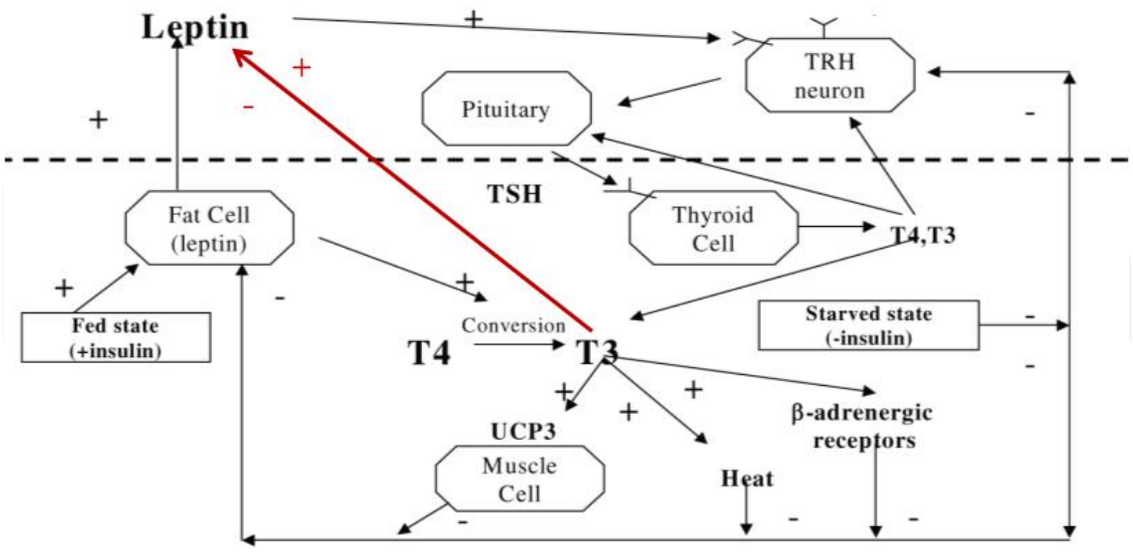

Figure 3. Adapted from Feldt-Rasmussem, 2007. Leptin can act on TRH or can directly influence T_4 – T_3 conversion, showing a regulatory role on thyroid axis. Despite contradictory data, thyroid hormone also regulates leptin levels increasing or decreasing depending on condition. TRH: thyroid release hormone; TSH: thyroid stimulating hormone; UCP3: uncoupling protein 3; T_4: thyroxine; T_3: triiodothyronine.

Studies with rodents indicate that thyroid hormones exert a negative influence on serum leptin concentrations [102-105]. Syed et al. [106] also found similar results, but report that thyroid hormones influence leptin levels indirectly through the regulation of fat mass. Wang et al. [107] reported that although leptin and thyroid hormones might affect the same pathways to regulate energy metabolism, the leptin effects on metabolism are not dependent upon the presence of thyroid hormones. In agreement, Luvizotto et al. [108] reported that T_3 administration in obese rats promotes weight loss and diminishes serum levels and gene expression of leptin and other adipokines. Contrary to these results, Yoshida et al. [109] founds increased leptin mRNA levels in 3T3-L1 cell cultures treated with T_3 at physiological and supraphysiological doses.

Obese human subjects have high serum leptin levels as leptin concentrations are directly proportional to body fat mass, more specifically to adipocyte volume [110, 111]. Regarding to thyroid hormones, there is indications that human obesity is usually associated with increased TSH and T_3 levels [92, 112]. As in rats, studies with humans reached to controversial results about the effect of thyroid hormones over leptin concentrations. In fact, human studies present more difficulties in terms of controlling variables as patient characteristics, treatments and method for measuring leptin levels and body composition. In hypothyroid subjects serum leptin was found to be increased [83, 113], decreased [114, 115] or unchanged [116, 117] when compared with euthyroid subjects. The same controversial results are found in studies with hyperthyroid subjects [83, 113, 115-118].

These conflicting results might be explained by the existence of many factors influencing leptin levels and thyroid hormones, and more studies are needed to fully understand the relationship between leptin and thyroid hormones.

4.2. Resistin

Resistin is strongly related to insulin resistance, showing increased resistin concentrations in obese and diabetic animals [46], and additionally it has been associated with inflammatory condition [119]. There is evidence that the hyperlipidic diet-induced obesity as well as leptin gene mutations are associated with high resistin circulating levels [120]. Resistin administered intraperitoneally increases plasma glucose and induces a hepatic insulin resistance. Other studies involving administration of resistin-recombinant promoted insulin resistance and reduced glucose transport stimulated by insulin, whereas administration of anti-resistin antibodies produced the opposite effect in rats [46]. Moreover, anti-resistin antibodies decrease blood glucose levels and improve the insulin sensitivity in obese rats [121, 122]. In mice with diet-induced obesity, immunoneutralization of resistin resulted in a 20% drop in blood glucose and improved insulin sensitivity as measured by insulin tolerance testing [46].

Resistin in humans is primarily produced in peripheral blood monocytes and its levels correlate with IL-6 concentrations [120], the question of its inflammatory role has been raised [123, 124], however the physiological role of resistin is far from clear and its role in obesity and insulin resistance and/or diabetes is controversial. Janke et al. [121] describes in

adipose tissue of obese individuals, although this adipokine has been identified, there was no correlation between resistin gene expression and their body weight, adiposity and insulin resistance. In contrast, high resistin levels are related to obesity and insulin resistance [46], and since body mass index has a possible association with thyroid hormones during periods of weight gain [125], could be establish a relationship between thyroid hormones and resistin in obesity.

Thyroid hormones appear to regulate resistin, at least in rats, however, in humans, studies on resistin levels and thyroid status have produced conflicting results. Some studies report that patients with hyperthyroidism have elevated resistin concentrations when compared with euthyroid control subjects [126]. Normalization of circulating thyroid hormones was accompanied by a significant decrease in resistin concentrations [126]. Others showed that hyperthyroid patients exhibit a significant decrease in resistin levels compared with euthyroid individuals. Normalization of circulating thyroid hormones levels was not accompanied by any significant change in resistin levels [127]. After adjusting the weight by the body mass index, the resistin levels of hyperthyroid patients were similar to euthyroid individuals [128].

Azza et al. [129] in their study with hypothyroid rats found an increase in body mass index without changes in resistin levels. On the other hand, Nogueiras et al. [130], found that adipose tissue resistin mRNA levels were increased in hypothyroid rats and decreased, to almost undetectable levels, in hyperthyroid rats. These data may help to explain previous findings showing a marked improvement in insulin resistance observed in obese rats after treatment with exogenous thyroid hormones [106]. Luvizotto et al. [108] reported that administration of T_3 supraphysiological doses decreased resistin serum levels and ressitin mRNA gene expression in adipose tissue in obese rats.

Data on the effect of thyroid hormones on resistin are scarce and controversial, so more studies are needed to elucidate the exact mechanism by which thyroid hormones may influence resistin levels.

4.3. Adiponectin

The main target tissue and the precise mechanism of adiponectin action are not fully understood. The adiponectin activity is probably regulated at several levels, including gene expression, post-transcriptional modifications, oligomeric complexes formation, and proteolytic cleavage into smaller and perhaps more active fragments [131]. Some experimental models suggest that reduced adiponectin expression is associated with obesity and insulin resistance. Adiponectin expression may be activated during adipogenesis, but the feedback inhibition on its production may be involved in obesity development. It has been shown that adipogenic genes expression was suppressed during obesity and diabetes development in mice [132]. A negative correlation between obesity and circulating adiponectin has been well accepted.

Studies of a possible relationship between adiponectin and lipid metabolism changes associated with thyroid dysfunction are scarce. Hyperthyroid patients showed an increase

in body weight, body mass index and cholesterol serum levels after controlling for thyrotoxicosis. The lack of correlation between these parameters and serum adiponectin suggests that changes in body composition and lipid profile observed in hyperthyroidism are independent of adiponectin. In contrast, patients with hypothyroidism showed elevated cholesterol and triglycerides levels when compared to normal subjects. Thyroid function control was followed by a significant decrease in serum cholesterol and triglyceride concentrations. However no relationship between adiponectin and lipid profile before and after therapy was evidenced. Furthermore, after adjusting adiponectin levels for body mass index, no significant change was observed in patients with hyper- and hypothyroidism, suggesting that thyroid hormones play a small role in adiponectin levels modulation [128].

An experimental study of rats with hyperthyroidism showed an important rise in serum adiponectin [133]. However, in contrast, Cabanelas et al. [134] show reduced adiponectin gene expression in inguinal explants of normal rats. Confirming this data Luvizotto et. al. [108] demonstrate that obese animals had decreased adiponectin serum levels when compared to control animals; and the administration of T_3, interestingly, even diminishing the body fat mass, presented lower levels of adiponectin; showing that supraphysiological T_3 doses alter adiponectin expression in obesity, suggesting that T_3 may cause undesirable effects on adipose tissue.

4.4. Others adipokines

TNF-α - Fruhbeck et al. [135] in their investigations revealed a narrow molecular link between TNF-α and obesity, verifying that TNF-α expression is increased in obesity, which in turn decreased insulin sensitivity, the same way of resistin. High-fat fed rodents showed significantly increased TNF-α expression and alteration in insulin signaling pathway *in vivo* [136]. Anti-TNF-α antibodies improves insulin sensitivity in obese rats, whereas TNF-α deficient animals, even when subjected to high-fat diet, present themselves "protected" from obesity development and insulin resistance. TNF-α is a cytokine that may be involved in autoimmune thyroid disease development [137, 138]. Jiskra & Telicka [138] examined the relationship between thyroid function and cytokines, using patients with Graves' disease (characterized by hyperthyroidism), and patients with Hashimoto thyroiditis (disease characterized by hypothyroidism). The cytokine profile was assessed and patients with Hashimoto's thyroiditis present body mass index above the ideal level and TNF-α serum levels smaller than in patients with Graves' disease, who had body mass index within normal limits. Díez et al. [139] show that patients with hyperthyroidism before treatment present TNF-α serum levels higher than in control group, but hyperthyroidism treatment was accompanied by normalization of TNF-α levels. However TNF-α reduction was not observed in patients with hypothyroidism who have had the thyroid function normalized, despite a positive correlation between the TNF-α post-treatment levels and weight loss.

IL-6 - IL-6 levels are increased in obesity [140], and is also a marker of insulin resistance [141, 142]. According Nonogaki et al [143], metabolic impact produced by increased expression of

IL-6 in the body fat deposits can be very importante in the obesity pathogenesis. The increase in IL-6 plasmatic could stimulate the hepatic synthesis of triacylglycerol, contributing to hypertriglyceridemia associated with visceral obesity. Data on relationship of thyroid hormones and IL-6 in obesity are scarce, but the association between reduction of T_3 circulating levels and increasing pro-inflammatory cytokines, particularly IL-6, is described in the literature in both animals' models and human studies - septic patients and in patients with systemic inflammatory response [144, 145]. The acute subcutaneous administration of IL-6 (5 mg) in rats was associated with decrease in T_4,T_3 and TSH serum concentrations, while the T_4/T_3 ratio decreased, suggesting that T_4 deiodination was not affected [144]. Changes in serum thyroid hormone concentrations could effectively be ascribed to IL-6, since they could be prevented by IL-6 preincubation with its neutralizing antibody [144]. The continuous IL-6 intraperitoneal infusion (15 mg/day for 7 consecutive days) in rats was associated with a transient decrease in serum T_4 and TSH, although less than that caused by IL-1 [145]. In latter study, pro-TRH mRNA hypothalamic and pituitary TSH-b mRNA were unaffected by IL-6, suggesting that the effects of IL-6 on TSH might not necessarily be associated with a decreased synthesis of thyrotropin [145]. On the other hand, the observation that the intracerebroventricular IL-6 administration to rats was followed by a decrease in serum TSH and an increase in serum adrenocorticotropin (ACTH) concentrations, while these changes could be reproduced in hemipituitaries only for ACTH, but not for TSH, suggested that the action of IL-6 on TSH might be exerted predominantly at the hypothalamic levels [146]. Increased concentrations of cytokines, especially IL-6, are often found in nonthyroidal illness patients and correlate with changes in thyroid hormone concentrations [144].

MCP-1 - Expression in adipose tissue and plasma MCP-1 levels have been found to correlate positively with the degree of obesity [7, 147-149]. Elevated circulating levels of MCP-1 as well as MCP-1 mRNA have been reported in obese mice [149, 150]. The possibility that MCP-1 formation in adipose tissue is due to macrophage infiltration must be considered since obesity is associated with various degrees of macrophage accumulation in adipose tissue [7, 147]. No data on this adipokines and thyroid hormone have been published.

PAI-1 - Adipose tissue PAI-1 gene expression and serum concentration have been reported in several pathological conditions, such as obesity, hyperinsulinemia, and hyperglycemia [151, 152]. The thyroid hormones T_4 and T_3 also have cardiovascular effects, probably through the regulation of circulating clotting proteins and fibrinolytic activity [153]; however, the mechanisms leading to cardiovascular and thromboembolytic diseases in thyroid dysfunction are controversial. Some reports have described an increase in serum PAI-1 concentration in hyperthyroidism, whereas others did not detect any differences [154, 155]. Biz, et al. [158] determined the effects of *in vivo* treatment of rats with the thyroid hormone T_4 on gene expression and the serum concentration of PAI-1. Additionally, the effects of T_3 and T_4 on PAI-1 gene expression in 3T3-L1 adipocytes were also evaluated. The

results demonstrated that adipocytes present different responses to thyroid hormones when considering *in vivo* and *in vitro* experiments. Other investigations have also demonstrated different *in vivo* and *in vitro* responses. The diverse *in vivo* and *in vitro* effects of thyroid hormones on PAI-1 gene expression regulation are not related to the inhibitory effect of T_4 on thyroid-stimulating hormone (TSH) secretion, since the literature has not shown any relationship between TSH and PAI-1 serum concentration [157]. However, it could be suggested that the lower amount of thyroid hormone receptors and deiodinase present in white adipose tissue than in brain, liver, brown adipose tissue, and kidney may be involved in this process. In addition, the low blood flow in white adipose tissue in comparison to other tissue types [158] could contribute to hormone distribution *in vivo*, suggesting that lower amounts of T_4 and T_3 were achieved in adipocytes *in vivo* in comparison to the *in vitro* study. Thyroid hormones have different effects in relation to PAI-1 gene expression in adipocytes in the intact rat (*in vivo* study) and in cultured adipocytes (*in vitro* study). Further studies are required to better elucidate the diverse *in vivo* and *in vitro* effects of thyroid hormone on adipocytes PAI-1 gene expression [156].

ASP - In a number of studies, ASP has been demonstrated to be increased in obesity, diabetes and cardiovascular disease [159-161]. Plasma ASP levels correlate positively with body mass index, as well as with plasma lipids. Study using culture of human adipocytes revealed increased secretion of chylomicrons induced by ASP [162]. There is evidence that circulating lipids also stimulate the expression of ASP after drinking large quantities of these nutrients [163]. There is no data available regarding the effect of thyroid hormones on ASP levels in obesity.

RAS- Adipose tissue synthesizes and secretes the major components of RAS [164]. There is evidence for overactivation of adipose tissue RAS in obesity in rodents [165], and for a positive correlation between adipose tissue angiotensinogen levels and BMI in humans [166]. Also Ang II secretion from adipose tissue is increased in obese, but not lean, individuals [167]. Increased production of angiotensinogen with excess gain in white adipose tissue contributes to glucose intolerance development, insulin resistance, cardiovascular and renal diseases [76, 168, 169]. In addition, increased RAS activity contributes to inflammation in fat tissue [170]. The interaction of RAS with other adipokines also contributes to the development of metabolic syndrome. Ang II appears to stimulate leptin production by adipocytes [76]; which in turn, hyperleptinemia may further hyperactivity of RAS by stimulating renin release by the kidney. Ang II may also regulate negatively adipocyte production of adiponectin in both rodents and humans [171, 172]. Thyroid hormones are important regulators of cardiac and renal functions while RAS components act systemically and locally in individual organs also to control cardiovascular and renal functions. Several studies have implicated the systemic and local RAS in the mediation of functional and structural changes in cardiovascular and renal tissues due to abnormal thyroid hormone levels [173, 174]. Thyroid hormones also appear to stimulate expression and synthesis of RAS components [175-177].

5. Thyroid hormone effects on adipokines in weight loss

5.1. Leptin

After weight loss, leptin levels decrease [178-180], as well TSH and T_3 reduces to normal levels [92, 93, 112]. In starvation conditions, serum leptin levels decrease and thyroid hormones levels are quickly supressed, leading to a consequent reduction in energy expenditure [83].

Varady et al. [181] studying severely obese women have suggested that a minimum weigh loss of 5% is required to improve adipokines profile, including the reduction of leptin levels. Not only a minimal weight loss is required but a maximal weigh loss beyond which further improvements in circulating adipokine levels are no longer observed has been suggested [179, 182]. The method or diet content by which weigh loss is achieved seems to be less important than the overall weight loss [179, 183].

As mentioned before, studies investigating the correlation between thyroid hormones and leptin levels present conflicting results. Luvizotto et al. showed that administration of physiologic levels of T_3 increases leptin mRNA expression with no influence on body weight in calorie-restricted obese rats [108], while administration of supraphysiological T_3 dose promotes weight loss and diminishes serum levels and gene expression of leptin [108] (Figure 3). Again, as Syed et al. [106] reported, the effects of thyroid hormones in leptin concentrations might be indirect trough the regulation of fat mass (Figure 4). The decline of TSH release and T_3 concentrations associated with decrease in leptin levels after weight loss may contribute to the compensatory reductions of energy expenditure and catabolism that typically accompany weight loss [184].

As both thyroid hormones and leptin have major roles in energy balance and regulation of body weight, an interaction between these hormones could not be discarded to achieve or maintain weight loss but further studies are necessary to elucidate the relationship between leptin and thyroid hormones.

5.2. Resistin

Since obesity is considered a global epidemic and one of majors public health problem, affecting developed and developing countries [185, 186], and obese subjects may presente increased resistin levels [46], which can worse insulin resistance and inflammation [119], one of the most used strategies is the weight loss by reduction of caloric intake [187]. Caloric restriction affects the regulation of adipose tissue gene expression, normalizing the adipokines changes caused by obesity [10], while thyroid hormones play a central role in regulating adipose tissue metabolism [83], being related to body weight changes, thyroid hormones may therefore play a key role in the normalization of resistin in weight loss.

Nogueiras et al. [130] show a decrease in resistin mRNA expression in epididymal adipose tissue of pregnant and nonpregnant rats that were subjected to food restriction. Kim et al. [188] showed that resistin mRNA levels were decreased during fasting, but increased considerably

when the animals were refed or after insulin infusion. T_3 had no effect on resistin mRNA levels in adipose tissue of obese animals submitted to calorie restriction [189].

Normalization of circulating thyroid hormones was accompanied by a significant decrease in resistin concentrations [126]. Others showed that hyperthyroid patients exhibit a significant decrease in resistin levels compared with euthyroid individuals, and the normalization of circulating thyroid hormones was not accompanied by any significant change in resistin levels [127]. After adjusting the weight by the body mass index, the resistin levels in hyperthyroid patients were similar to euthyroid subjects [128] (Figure 4).

The association between thyroid hormone and resistin in weight loss present conflicting data, requiring further studies to evaluate this relation.

5.3. Adiponectin

Negative correlation between obesity and circulanting adiponectin has been well accept, and adiponectin concentration increases concomitantly to weight loss [190].

Experimental study on caloric restriction showed increased levels of circulating adiponectin [191]. Accordingly, Zhu et al. [194] showed that calorically restricted animals exhibited a significant increase in plasma adiponectin levels accompanied by significant decline in triglyceride levels, showing that adiponectin levels are inversely proportional to the degree of adiposity [192, 193].

Thyroid hormones perform a central role in adipose tissue metabolism regulation [83], which produces the biologically active substances adipocytokines, or adipokines, that include adiponectin [127, 194], indeed thyroid hormones share some physiological actions with adiponectin, such as reduction of body fat by increased thermogenesis and lipid oxidation [194].

The interaction between thyroid hormones and adiponectin concentration remains unclear. In humans, hyperthyroidism has been associated with both similar [128, 195] and elevated adiponectin concentrations [196], while experimental study with hyperthyroid rats found an increase in adiponectin serum concentration [133]. In agreement, some data shown that therapy to normalize hyperthyroidism significantly reduced circulating adiponectin levels [197]. In contrast Luvizotto et al. [189] show that thyroid hormone, at the doses of 5 and 25 μg T_3 / 100 g BW, diminishes adiponectin gene expression, suggesting that thyroid hormone modulates negatively adiponectin expression in calorie-restricted obese rats (Figure 4).

5.4. Others adipokines

TNF-α - The first information about the TNF-α biological effects indicated an involvement in insulin resistance, weight loss and anorexia. The increase in lipolysis result from TNF-α stimulus in hormone-sensitive lipase expression, leading to decreased activity of lipoprotein lipase. However, more recent investigations have revealed a molecular mechanism of weight loss on TNF-α levels, showing TNF-α expression is increased in obesity and

decreases with weight loss, thereby improving insulin sensitivity [135, 198]. After weight loss there is a decrease of macrophages number in adipose tissue [199], this can lead to decreased TNF-α levels, since both adipose tissue and macrophages produce this cytokine. There are few studies correlating the thyroid status with TNF-α levels in weight loss. Patients with HIV tend to lose weight and in some cases it is observed a decrease in T_3 levels accompanied by increased TNF-α levels, when these individuals are compared to patients with HIV with normal T_3 levels. These results corroborate to other study linking the sick euthyroid syndrome to high TNF-α levels in cachectic patients with HIV [200].

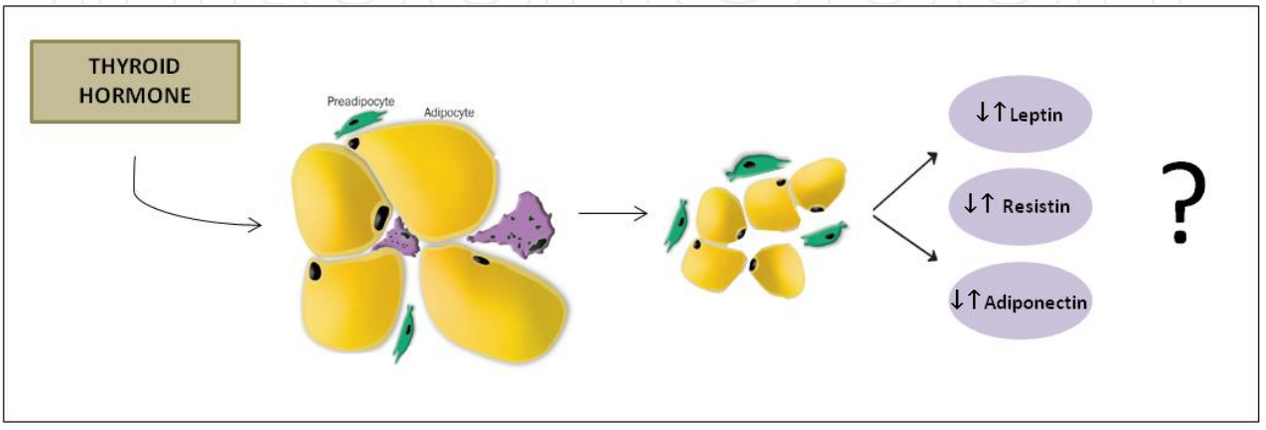

Figure 4. Thyroid hormone may modulate adipokines concentration by regulating adipose tissue metabolism by, *i.e.*, increasing lipid oxidation leading to body fat decreased. The exact influence of thyroid hormone on adipokines remains unclear.

IL-6 - IL-6 levels decrease with weight loss [140-142]. The intracerebroventricular administration of this cytokine can decrease body fat [201]. Association studies between thyroid hormones and IL-6 in weight loss are scarce, but studies in critically patients demonstrated a direct association between decreased T_3 levels and high IL-6 plasma levels, demonstrating that approximately 28% of T_3 fall could be directly related to increased IL-6 [202]. In another study, of 270 patients admitted to intensive care unit, serum T_3, T_4 and IL-6 were measured and again was observed a negative correlation between T_3 and T_4 levels and IL-6 levels, demonstrating that this cytokine could be an important factor associated with decreased circulating thyroid hormones levels [203].

MCP-1 - Chronic inflammation associated with obesity exists in dogs, and it is evident that weight loss decreases this inflammation as observed by decreasing MCP-1 after weight loss [204]. In agreement, Kanda et al. [205] demonstrated that MCP-1 deficient mice have reduced adipose tissue macrophage infiltration. Few studies correlate weight loss and MCP-1 levels, and no data was found regarding weight loss, MCP-1 and thyroid association.

PAI-1 - Weight loss secondary to calorie restriction is associated with reduced PAI-1 activity in adults [206, 207]. However, in children no significant change in PAI-1 levels was observed in 43 obese children after a physical training program [208]. This may be explain by the increase in fibrinolytic activity due to a decrease in PAI-1 antigen levels in obese children after weight loss, and a significant positive correlation was observed between variations in

body mass index and variations in PAI-1 levels. Moreover, the largest decrease in PAI-1 levels was observed in the obese children with the highest previous PAI-1 levels [209]. Weight loss induced by a low calorie diet causes a decrease in plasma PAI-1 levels especially among obese individuals [210, 211], and these increase once again if weight is regained [212]. Surgically removing fat confers the same beneficial effect [212]. Antidiabetic drugs such as thiazolidinediones, metformin, and AT1-receptor antagonists reduce adipose PAI-1 expression [211]. Interestingly, waist-to-hip ratio, a reflection of central fat accumulation, has been found in women to be the only independent predictor of circulating PAI-1 activity [213]. In individuals subjected to a calorie restricted diet, PAI-1 levels were more closely related to changes in the central fat deposit than in the subcutaneous fat deposit [214]. Thus, the visceral fat deposit may be importante for the occurrence of increased plasma PAI-1 levels. There is few data available regarding the thyroid hormones and PAI-1. Studies have been focused on serum measurements, in severe hypothyroidism was found decreased PAI-1 levels [215], while in hyperthyroidism some studies show increased [113, 216, 217], other decreased [83, 218] as well as unaffected PAI-1 levels [219, 220].

RAS - Studies with RAS manipulation (deletion) showed that function loss in any single component of RAS tested so far, provides protection from diet-induced obesity and insulin resistance [221-224]. Therefore, RAS seems to play a role in obesity development; however systemic RAS overactivation via gene overexpression or chronic Ang II infusion also induces insulin resistance, but not necessarily obesity [225]. Weight loss in humans results in decreases in circulating components of the RAS [226]. In fact, Engeli et al. [226] suggest that a 5% reduction in body fat mass can reduce meaningfully the RAS in plasma and adipose tissue, which may contribute to reduce blood pressure. Genetic polymorphisms of RAS may also play a role in response to weight loss in obese individuals [227]. Decrease of RAS leads to improvement in insulin sensitivity, blood pressure, and renal function. As RAS interacts with others adipokines, reduction in RAS concentrations followed weight loss may also contributes to improvement of other adipokines levels and, consequently, improve other metabolic disorders [226, 228]. As mentioned, thyroid hormones appear to stimulate expression and synthesis of RAS components [175-177]. However, precise interaction between thyroid hormones and RAS components in weight loss process are scarce in the literature.

Literature on newer adipokines and thyroid disorders is scarce. No data on ASP and weight loss is available and no data on these adipokines and thyroid hormone have been published so far. Future research studying these associations is awaited.

6. The use of TRβ analogues

Thyroid hormone analogues, termed thyromimetics, are molecules with activate signaling pathway property similar to thyroid hormones, sometimes with tissue specificity or by activating a singular pathway stimulated by thyroid hormones, other with less effect, but even with a way close to thyroid hormones. The thyromimetics have a great pharmaceutical potential since they present certain specificity as intracellular signaling that stimulate and thus may have a tissue specific action. However, only the past 20 years, with increasing

resolution of three-dimensional models, docking experiments and crystallography models the specificity of thyromimetics has been revealed.

Thyroid hormone is one of the most responsible for metabolism controlling and cell oxygen consumption, affecting growth, cell differentiation and homeostasis control [229]. The thyroid hormone also has specific functions depending on tissue: in liver, controlling lipid metabolism [230-232]; in heart, regulating the calcium handling and the heart rate [233]. As for lipid deposits, the thyroid hormone acts in brown adipose tissue by controlling heating and adaptive thermogenesis during rest [234]. Under high hormone levels conditions in the organism, such as hyperthyroidism, there is an increase in metabolic rate with consequent weight loss and decrease cholesterol serum levels, desirable conditions for metabolic diseases treatment such as obesity [235] and hyperlipidemia [230-232]. In this context, the possible specificity through thyroid homone analogues may lead to desirable effects on adipokines release control and obesity, without the undesirable symptoms on heart or on TSH release.

Thyromimetics can be seen as thyroid hormone derivative or its metabolites derivative. Studies on the direct influence of these analogues on adipokines levels are scarce, but the tissue selectivity shown may be interesting in the study of non thyroid diseases, mainly involving the lipid rate control in adipose tissue and decreased cholesterol by the liver. This selectivity in many cases is related to action pathway stimulate by thyromimetics. Some of them may have actions in liver and adipose tissue through its selective binding to TR-β1, while not lead to effects such as tachycardia since there is no selectivity for the TR-α1 (most expressed isoform in the heart). Thus we can highlight some known thyromimetics and some details of their actions.

The first developed analogue, in the mid-1980s, was 3,5-dibromo-3-pyridazinone-L-thyronine (L-94901) present 50% of binding T_3 to TRs in liver, and only 1.3% effective for cardiac TRs [236, 237]. L-94901 showed an increase of oxygen overall consumption and a reduction in cholesterol serum levels in animal models submitted to low dose, sufficient to prevent cardiotoxic effects, however, also led to lower TSH, T_4 and T_3 plasma levels [236].

An analogue selectivity-related to TR-β1 is 3,5-Dichloro-4-[(4-hydroxy-3-isopropylphenoxy)-phenyl] acetic acid (KB-141), with 10-fold greater ability to reduce the cholesterol rate than increase heart rate [238, 239], stimulating metabolic rate and oxygen consumption [240]. Eprotirome (KB2115) is a thyroid hormone analogue that has a low uptake by non-hepatic tissues. It has preferential selectivity for the TRβ, leading to decreased total cholesterol, LDL and apolipoprotein B levels without apparent side-effects. It showed good results in hypercholesterolemia treatment and associated with statin was effective in reducing atherogenic lipoproteins levels without extra-hepatics effects of thyroid hormone [241].

One of the most widely studied thyroid hormone analogues is 3,5-dimethyl-4-[(4'-hydroxy-3'-isopropylbenzyl)-phenoxy] acetic acid (CG-1), with selectivity for TRβ 10-fold greater than for TR-α. Hypercholesterolemic rats models treated with GC-1 showed decrease in cholesterol, LDL and triglyceride serum levels, without significantly altering heart function or regulated-thyroid hormone gene expression as MHC-HT and α, β-MHC and SERCA2

[242]. The same results were observed with KB-141 use, but with a subtle increase in heart rate. Contributing to cholesterol serum levels reduction by GC-1 is the increased SR-BI expression, a receptor that promotes cholesterol uptake in the liver, stimulating the bile acids production [243]. Deleterious effects absence of GC-1 on cardiac structure and function [244], skeletal muscle and bone mass [245] suggests that GC-1 has potential therapeutic use for metabolic disorders such as obesity and hyperlipidemia [246].

Started studies during the mid-1990s, N-[3,5-dimethyl-4-(4'-hydroxy-3'-isopropylphenoxy)-phenyl] oxamic acid (CGS-23425) was a potent ability to decrease cholesterol in rats and dogs at dose 25 times higher than the minimum for producing lipid lowering effects [247]. In hypercholesterolemic rats, CGS-23425 had the desired effects of decreasing serum LDL and increased apoA1, with a corresponding increase in apoA1 gene transcription by TR-β1 selectively [248].

A thyroid hormone analogue currently in phase II clinical trial is the 3.5-diiodothyropropionic acid (DITPA), with affinity equivalent between TR-α1 and β1 but with 100 times less affinity than T3 [249]. In hypothyroid rats, DITPA improved cardiac performance with half the chronotropic effect and less metabolic stimulation than levothyroxine [250]. In normal volunteers, DITPA does not affect the heart rate or blood pressure, while the serum cholesterol and triglycerides were significantly decreased [251]. Observations have shown that DIPTA exerts its action by stimulating nongenomic pathways stimulated by T3 as the αVβ3 integrin receptor, activating the MAPK cascade and causing similar effects to those seen with GC-1, leading to angiogenesis, indicating that some cardiac effects may be caused by nongenomic pathway activation [252].

Although there are few studies on thyromimetics and adipokines, studies on obesity and lipid lowering show interesting results. Other compounds have been studied as thyroid hormone natural metabolic intermediates: 3-iodothyronamine (T1AM) showed effects on cardiac output, heart hate and decreased body temperature with neuroprotective action; Diiodothyronine-3.5 (T2) with effects such as increased lipid peroxidation and fatty acids oxidation, among others; 3,3 ', 5'-triiodothyronine (rT3) able to initiate actin polymerization; triiodothyroacetic acid (Triac) that increases the metabolic rate and thermogenesis, and one of the few identified analogues able to increase leptin secretion [246]. Like thyromimetics, these natural metabolites, collectively, show body weight and fat mass reduction, while thyromimetics are more specific to reduce cholesterol serum levels, but both have effects saving cardiac activity. However, before they are used in large scale, attention should be paid to non-selectivity presented by natural metabolites, and for TSH suppression showed by thyromimetics, which may lead to undesirable tissue hypothyroidism. Thus, the tissue specificity and selectivity for TR brings a good perspective for thyromimetics, however there is still a long way from its use as therapeutic agent.

7. Final considerations

Adipose tissue produces a wide range of biological active substances, named adipokines, involved in glucose metabolism, lipid metabolism, inflammation, coagulation, blood pressure, and feeding behavior, thus affecting metabolism and function of many organs and

tissues including muscle, liver, vasculature, and brain. Obesity cause imbalance in the adipokines production, while the weight loss are able to normalize these changes. In obese, the stabilization of weight loss even in calorie restricted diet has been attributed to the decrease in serum T_3 concentrations, leading to a reduction in metabolic rate. Because of this, and despite not being accepted as an obesity treatment, the administration of thyroid hormones, in isolation or in association with hypocaloric diets, is sometimes used illicitly. The thyroid hormones regulate the energetic balance and act on the adipokines, regulating several genes in adipose tissue. However, the available data on the effects of thyroid hormone on adipokines in obesity or weight loss are conflicting. A clear association has not yet been established between in obesity and calorie restriction in obesity and the effect of thyroid hormone on adipokines, requiring further studies. Despite studies of TRβ analogs show good results, the direct influence of these analogues on adipokines levels are scarce. More research is needed to fully elucidate the exact mechanism of thyroid hormone and its analogues on adipokines in obesity and weight loss.

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