

## Review Article

# Different Adipose Depots: Their Role in the Development of Metabolic Syndrome and Mitochondrial Response to Hypolipidemic Agents

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Adipose tissue metabolism is closely linked to insulin resistance, and differential fat distributions are associated with disorders like hypertension, diabetes, and cardiovascular disease. Adipose tissues vary in their impact on metabolic risk due to diverse gene expression profiles, leading to differences in lipolysis and in the production and release of adipokines and cytokines, thereby affecting the function of other tissues. In this paper, the roles of the various adipose tissues in obesity are summarized, with particular focus on mitochondrial function. In addition, we discuss how a functionally mitochondrial-targeted compound, the modified fatty acid tetradecylthioacetic acid (TTA), can influence mitochondrial function and decrease the size of specific fat depots.

## 1. Introduction

In a modern lifestyle people are chronically exposed to elevated amounts of lipids and nutrients, potentially leading to tissue dysfunction and disease [1]. The adipose tissue is highly involved in the development of metabolic disorders such as cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM). It is the body's largest storage site for triglycerides and plays an important role as an endocrine organ in energy homeostasis [2]. The adipose tissue is divided into specific regional depots with differences in structural organization, cellular size, and biological function [3]. The distribution of fat between these depots seems to be more important than the total adipose tissue mass for the risk of developing obesity-associated diseases (Figure 1).

Normally, fat storage in the form of neutral triglycerides takes place during food intake to be replaced by fat mobilization processes during fasting or situations with elevated energy demand (Figure 2(A)). Adipocytes produce a number of endocrine hormones that contribute to the regulation of this mechanism, such as adiponectin and leptin. As adipocytes play a key metabolic role as a source of fuel, they

are required to respond acutely to changes in the nutritional levels. As a result they are tightly regulated by both hormonal (e.g., insulin) and sympathetic (e.g., adrenergic) stimulation [2].

Metabolic syndrome is a group definition on several diseases connected to obesity. Subjects will display elevated levels of glucose and nonesterified fatty acids, also called free fatty acids (FFAs), and show symptoms of one or more afflictions amongst which hypertension, hypertriglyceridemia, diabetes, and obesity are the most usual. Lipotoxicity and the accumulation of saturated fat in peripheral tissues are an important step in the development of metabolic syndrome. Fatty liver (liver steatosis) is found in a large proportion of individuals with body mass index (BMI) above 30. Liver steatosis contributes to insulin resistance and may lead to the development of nonalcoholic fatty liver diseases (NAFLDs), including nonalcoholic steatohepatitis (NASH) and cirrhosis [4].

T2DM is usually linked to obesity and lipid redistribution to nonadipose organs and tissues and is caused by a reduced sensitivity to insulin in muscle, liver, and adipose tissue [1]. During insulin resistance, an increase in insulin

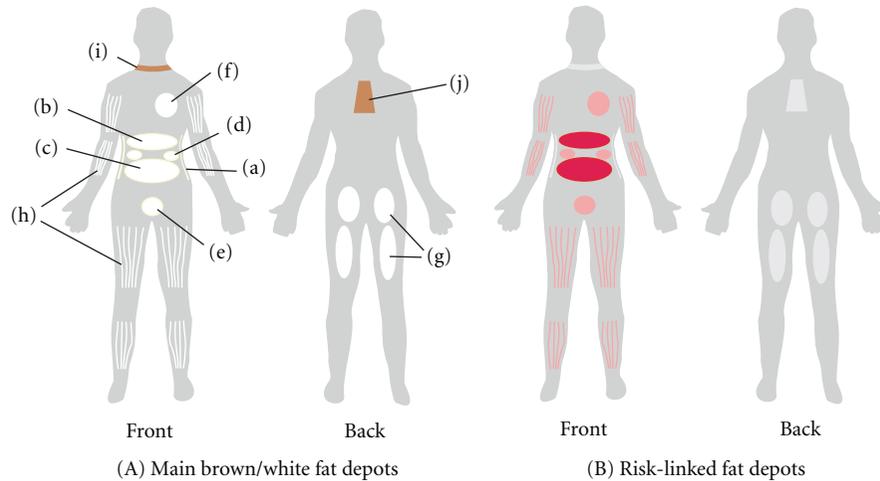


FIGURE 1: (A) The main white adipose tissues (WATs) are abdominal subcutaneous adipose tissue (SAT, (a)), and visceral adipose tissue (VAT). VAT surrounds the inner organs and can be divided in omental (b), mesenteric (c), retroperitoneal ((d): surrounding the kidney), gonadal ((e): attached to the uterus and ovaries in females and epididymis and testis in men), and pericardial (f). The omental depot stars near the stomach and spleen and can expand into the ventral abdomen, while the deeper mesenteric depot is attached in a web-form to the intestine. The gluteofemoral adipose tissue (g) is the SAT located to the lower-body parts and is measured by hip, thigh, and leg circumference. WAT can also be found intramuscularly (h). Brown adipose tissue is found above the clavicle ((i): supraclavicular) and in the subscapular region (j). Although the mentioned subcutaneous and visceral adipose tissues are found in humans, depots (d) and (e) are mostly studied in rodents. (B) The adipose tissue depots that have been linked to risk of developing obesity-related diseases are indicated in red. The best-documented link to risk is found for the omental and mesenteric VAT.

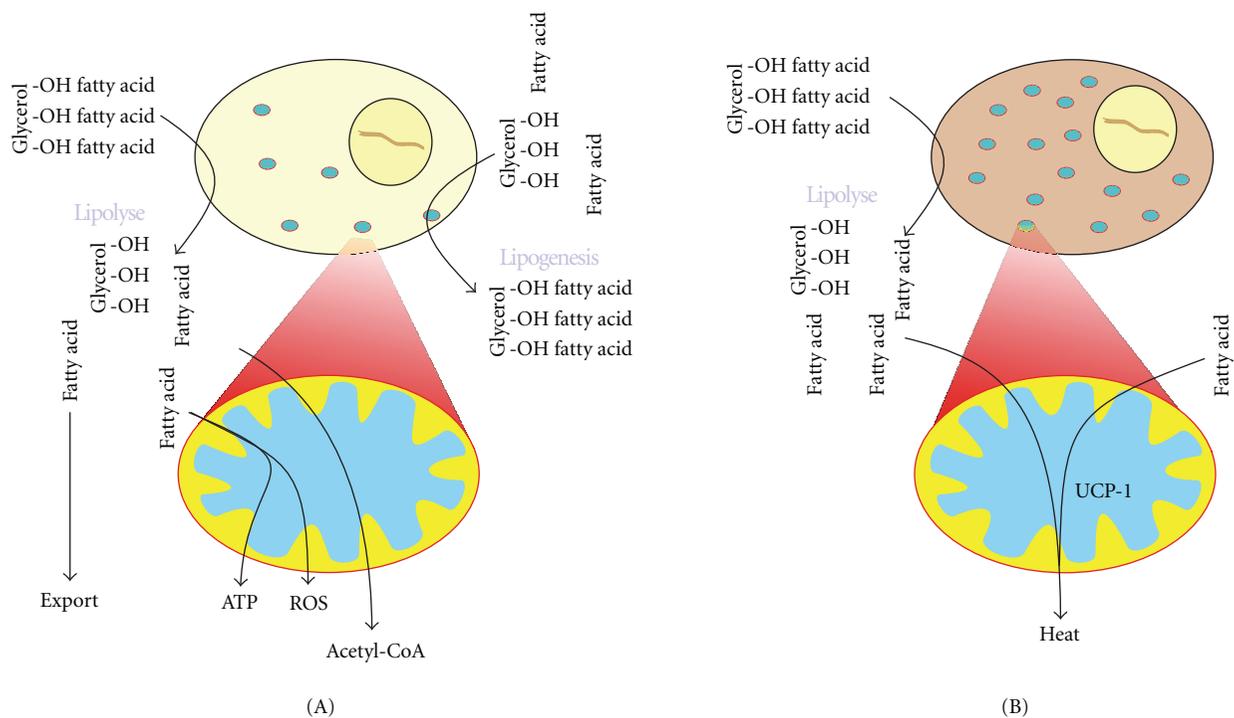


FIGURE 2: (A) The role of white adipose tissue (WAT) is to store excess dietary fat in the form of triglycerides (TGs) and to release free fatty acids (FFAs) in times of starvation or energy demand. In addition WAT releases several important factors that regulate energy homeostasis. Lipolysis takes place in the cytosol and is also dependent on processes in the mitochondria. The resulting FFA can be released to the blood or directly used as an energy source by  $\beta$ -oxidation in the mitochondria. In lipogenesis, glycerol and acyl-CoA produced in the mitochondria are used to generate TG for storage in the adipocytes. (B) In brown adipose tissue (BAT) the FFAs are  $\beta$ -oxidized, and the resulting acetyl-CoA enters the Krebs cycle. The reduction potential is used to form a mitochondrial proton gradient that instead of producing ATP is released by uncoupling protein 1 (UCP1), a process that generates heat.

does not lead to a corresponding increased uptake of glucose in muscle and liver. As a compensatory mechanism insulin production is increased in pancreatic beta cells. T2DM occurs when the increased insulin production is no longer sufficient, or when lipid-induced beta cell malfunction takes place, particularly in genetically predisposed individuals. It is believed that high levels of circulating FFA and lipotoxic mechanisms can cause damage on  $\beta$ -cell and nonislet tissues.

CVD includes hypertension, atherosclerosis, heart disease, vascular disease, and stroke. Several of the high-risk factors for CVD result directly or indirectly from obesity and a malfunctioning adipose tissue: dyslipidemia, chronic inflammation, diabetes, and hypertension. Mitochondrial dysfunction could also contribute to CVD due to their role as targets and sources of reactive oxygen species (ROS), both in the formation of vascular lesions and in their involvement in the development of insulin resistance and T2DM [5].

A well-functioning adipose tissue with capacity to neutralize and store nutritional overload is therefore necessary to protect the body from peripheral insulin resistance. Two closely linked processes in adipose tissue are important for the development of metabolic disease: adipose tissue inflammation and adipose tissue hypertrophy. Adipose tissue inflammation due to the recruitment of T-cells and macrophages has been shown to contribute to insulin resistance in obese individuals. This inflammation leads to a disturbed adipokine-balance and an uncontrolled release of free fatty acids and inflammatory cytokines [6]. As a result, lipoprotein metabolism and insulin sensitivity in other organs will be affected. During obesity, the adipocyte size increases (hypertrophy), and they are eventually unable to store excess lipids even with enhanced adipocyte proliferation (hyperplasia). This redirects fatty acids to the liver promoting dyslipidemia, characterized by elevated plasma FFA, triglycerides (TGs), and small dense low-density lipoprotein (LDL), and the reduction of high-density lipoproteins (HDL). In addition large adipocytes are characterized by an increased lipolysis, the breakdown of stored TG by lipases. This results in FFA and glycerol, which further increases plasma FFA-levels and upregulates TG synthesis in the liver [7]. A recent publication demonstrated that enlarged adipocytes in obese men had a reduced rate of FFA-delivery to the blood stream, resulting in normal systemic FFA concentrations. However, after meals the adipose tissue storage capacity was severely impaired, thus potentially causing ectopic lipid deposition [8].

How well the adipose tissue functions as a storage organ for excess energy intake and the distribution of fat and mitochondria between the different adipose depots may determine the large differences in health observed in obese individuals. Here, we will first focus on the importance of mitochondrial function in adipose tissue and then describe the different adipose tissue depots, in rodent animal models as well as humans (Figure 1), and their impact on the development of metabolic diseases. Pharmacological treatments that specifically target mitochondria have great potential in the treatment of obesity-related disorders, and their differential effect on adipose depots will be discussed.

## 2. Reactive Oxygen Species during Obesity

An elevated metabolism during obesity results in increased production of reactive oxygen species (ROS). ROS damage is most likely involved in all features of metabolic syndrome. Increased ROS production is an early event in glucose intolerance, contributing to pancreatic  $\beta$ -cell dysfunction as well as liver steatosis.  $\beta$ -cells may be specially susceptible to ROS-damage due to their relatively low expression of free-radical-detoxifying enzymes compared to most other cell types [9].

There are indications that mitochondrial content and function in adipose tissue might be disrupted in metabolic disorders. It has been suggested that insulin resistance is linked to mitochondrial dysfunction [10, 11]. Furthermore, it is increasingly evident that oxidative capacity and thus mitochondria are fundamental to avoid the development of toxicity during excess energy intake. For instance, increase in mitochondrial ROS is observed in adipose tissue during obesity [12–14], and in skeletal muscle, the mitochondrial  $H_2O_2$  emission is higher using fatty acids as substrates versus carbohydrate-based substrates [15, 16]. Two models of insulin resistance, induced by either tumor necrosis factor  $\alpha$  (TNF $\alpha$ ) or glucocorticoid treatment, were both shown to involve increased ROS levels [17]. Also, antioxidants attenuating mitochondrial  $H_2O_2$  emission completely restored insulin sensitivity in skeletal muscle [16]. These findings show that mitochondria play a central role in the physiology leading to insulin resistance.

In addition, the NOX family of NADPH oxidases, located to the plasma membrane, cytosol and cytosolic membranes, is a major source of ROS generation. NOX2 is an energy transporter that catalyses the reduction of oxygen to  $O_2^-$  in an NADPH-dependent reaction. The involvement of NOX enzymes in the development of metabolic syndrome has been reviewed by Krause and coauthors [18, 19]. In low concentrations, ROS participates in the cell signaling as secondary messengers [20]. In response to insulin, NOX will release ROS that activates the distal insulin-signaling cascade, mobilizing glucose transporters to the surface of adipocytes. However in higher amounts it will have serious harmful effects on the cells, including decreased glucose uptake in adipocytes [21]. Several mouse obesity models have found an increase in oxidative stress in adipose tissue associated with overexpression of NADPH oxidase and repression of antioxidant enzymes such as catalase [13]. Also, mitochondrial proliferation is inhibited by increased ROS production [22, 23], indicating that ROS can modulate adipocyte generation.

## 3. Mitochondria in Adipose Tissue

Well-functioning mitochondria are essential in adipose tissue. Mature adipocytes require large amounts of ATP to maintain their activities such as lipolysis, fatty acid  $\beta$ -oxidation, and fatty acid synthesis. In the organism, mitochondria produce energy and are central in the fatty acid metabolism since more than 98% of fatty acids are oxidized in mitochondria [24]. Recent evidence indicates

that a reduced mitochondrial function and altered biogenesis play important roles in the etiology of obesity, insulin resistance, and T2DM [25]. An impaired metabolic flexibility is the inability of an organism to adapt fuel oxidation to fuel availability. The ability to switch from fat to carbohydrate oxidation is usually impaired in subjects prone to obesity and in subjects with a family history of diabetes [26–29]. Indeed, there is strong evidence that defects in substrate switching cluster together with disturbances in mitochondrial content and/or function and might be a manifestation of an underlying mitochondrial disorder [30]. In this respect, it has been demonstrated that insulin-resistant offspring of patients with T2DM have reduced mitochondrial function, reduced ATP synthesis and accumulation of fat in skeletal muscle, the liver, and other cells [31].

**3.1. Role of White Fat Mitochondria.** The major adipose depots in the body consist of white adipose tissue (WAT). Mature white adipocytes require large amounts of ATP to maintain their diverse functions, and during adipogenesis mitochondrial biogenesis is an important process [20]. One of the main tasks of adipose tissue is to generate glycerol 3-phosphate and acetyl-CoA for esterification into TGs (lipogenesis), processes localized to the mitochondrial matrix as well as the cytosol, that require an abundant mitochondrial population [32, 33]. Mitochondria in WAT are also believed to be important for the regulation of lipolysis, the process of degrading TG into FFA and glycerol (Figure 2(A)). When inhibiting the mitochondrial respiratory chain or decreasing intracellular ATP by the use of mitochondrial uncouplers, lipolysis is inhibited [34]. Inhibition of the AMP-activated protein kinase (AMPK), which is an essential molecular sensor regulated by the ATP/AMP level in the cells, will decrease lipolysis stimulated by agonists of  $\beta$ -adrenoreceptors [35]. The FFAs produced by lipolysis can subsequently be utilized in the adipocytes as a source of energy, through  $\beta$ -oxidation in the mitochondria. Thus, mitochondria in white fat cells are involved in both *de novo* lipogenesis and lipolysis [36].

Depending on the anatomical position in the body, adipose tissue shows differences in metabolic activity due to different mitochondrial density. For example, rat epididymal (VAT) adipocytes have more mitochondria than inguinal (SAT) adipocytes [37]. The higher number of mitochondria per mg tissue in VAT than SAT is also observed in obese human individuals. Although mitochondrial respiratory flux per cell and per mitochondrial content was lower in VAT compared to SAT due to smaller cells, the visceral fat was bioenergetically more active and responsive to substrates of the electron transport chain [38]. In general, some studies show that obesity and T2DM in humans reduce mitochondrial number in white adipocytes [39], while others show a connection between mitochondrial number and lipogenesis, but not body mass index (BMI) or overall insulin sensitivity [40]. The link between mitochondrial dysfunction and T2DM is indicated by the reduced oxidative phosphorylation (OXPHOS) capacity in elderly subjects [41], and in obese subjects, where a reduced FA  $\beta$ -oxidation in several tissues including adipocytes will increase blood FFA levels and

alter glucose uptake [10, 11]. Nonalcoholic steatohepatitis, a disease caused by lipid accumulation in the liver, is associated with mitochondrial dysfunction due to increased lipid peroxidation, alterations in mitochondrial ultrastructure, depletion in mtDNA, and low OXPHOS activity. These patients also commonly display abdominal obesity, diabetes, and hypertriglyceridemia with insulin resistance [42]. In rodent genetic or high-fat fed obesity models, the expression of genes involved in mitochondrial ATP production, energy uncoupling and other genes important for mitochondrial function was downregulated compared to lean control animals [43]. This indicates a strong impairment of mitochondrial biogenesis during obesity.

**3.2. Role of Brown Fat Mitochondria.** Although brown adipose tissue (BAT) is mainly found in newborns, recent studies have demonstrated its presence in adults [44, 45]. BAT originates from a different cellular lineage than WAT [46], but they share many features. However, mature BAT contains a higher number of mitochondria and lower numbers of lipid droplets. During cold temperatures and activation of the sympathetic nervous system [47], brown adipocyte lipolysis occurs (Figure 2(B)). Instead of being released for subsequent oxidation in organs such as liver and skeletal muscle, the resulting FFAs are oxidized in the BAT mitochondria and used to generate heat (see review in [48]). This process involves transport of FFA complexed to fatty acid binding proteins (FABPs) into the mitochondria by the carnitine shuttle system, where they are oxidized and used to generate heat by uncoupling protein 1 (UCP1), a process called nonshivering thermogenesis. This process is important in newborn humans and in rodents, but appears to be almost lost in adult humans. Although UCP1 is the hallmark of BAT, increased UCP1 expression and energy expenditure can also be seen in WAT under some conditions [49] and may be a desirable effect during the treatment of obesity. The increased expression of the *Ucp1* gene in both BAT and WAT by a fat-specific *aP2* promoter generated mice partially resistant to age-related obesity, both genetically and high-fat diet induced [50, 51]. The effect of BAT on obesity is further discussed below.

## 4. Transcriptional Regulation of Lipolysis and Lipogenesis

Peroxisome proliferator-activated receptors (PPARs) are important regulators of fatty acid metabolism. They serve as lipid sensors since they are activated by metabolic derivatives of fatty acids in the body. There are three PPAR superfamily members PPAR $\alpha$ , PPAR $\gamma$ , and PPAR $\delta$  (also called PPAR $\beta$ ) that act upon ligand activation by controlling networks of target genes. It exceeds the scope of this paper to describe their function in detail, but the relevant PPARs will be mentioned briefly here. For a comprehensive review on the role of PPARs in metabolic syndrome, see Guri et al. [52].

PPAR $\alpha$  is the most important PPAR in the liver and has many important target genes involved in fatty acid  $\beta$ -oxidation. During fasting, lipolysis is stimulated while

lipogenesis is decreased. The increase in lipolysis provides FFAs that are used as energy source in other tissues [53]. The subsequent PPAR $\alpha$ -regulated metabolism of fatty acids mainly takes place in the liver, through mitochondrial and peroxisomal  $\beta$ -oxidation, but the heart, adipose tissue, and skeletal muscle can also utilize FFA for energy.

The decrease in lipogenesis is on the other hand due to downregulation of the two main lipogenic transcription factors, PPAR $\gamma$  and steroyl regulatory element binding protein 1c (SREBP1c) [54, 55]. Two isoforms of PPAR $\gamma$  exist, of which PPAR $\gamma$ 1 is expressed in a wide variety of tissues, while PPAR $\gamma$ 2 is mainly expressed in adipose tissue [56]. PPAR $\gamma$  activation stimulates preadipocyte differentiation, promotes the storage of fatty acids in mature adipocytes [56], and can activate GLUT4, facilitating increased fatty acid synthesis from glucose [57]. SREBP1c is necessary for the insulin-stimulated increase in fatty acid synthesis [58]. Its activation has been shown to create ligands for PPAR $\gamma$  [59], as well as regulate PPAR $\gamma$  expression in cultured adipocytes [60]. Lipogenesis mainly takes place in the cytosol, but the activation of PPAR $\gamma$  using rosiglitazone has been shown to alter both mitochondrial density and morphology in adipocytes suggesting that PPAR $\gamma$  also controls mitochondrial functions [36]. In obese db/db mice, the adiponectin expression and mitochondrial content of white adipocytes are reduced, and these effects are reverted by the activation of PPAR $\gamma$  by rosiglitazone [61]. It is interesting to note that rosiglitazone can increase expression of mitochondrial genes/mitochondrial biogenesis in rodent obesity models [43].

## 5. Differential Role of Fat Depots

Although the total adipose tissue is important for the development of insulin resistance, it is believed that some fat depots are more linked to risk factors for disease than others. The main adipose depots of interest are found in the abdomen and can be divided into the SAT and VAT, and the visceral tissue can again be divided into omental and mesenteric, the latter being the more deeply buried depot surrounding the intestine (Figure 1). Some studies have also included a deep subcutaneous layer (dSAT). The distribution of SAT and VAT shows person-to-person variations and is dependent on several factors such as age, nutrition, sex, and the energy homeostasis of the individual adipose tissues [62]. Both human studies and rodent obesity models will be discussed below. Although several similarities exist, the differences in rodent and human adipose tissues entail caution when choosing which depots to study and when extrapolating information between species [63].

**5.1. Visceral Fat.** Particularly, visceral fat depots, including omental and mesenteric adipose tissue, represent a risk factor for the development of CVD and T2DM. Visceral adipose tissue mass correlates with development of insulin resistance, while total or subcutaneous tissue mass does not [62, 64, 65]. It has been thoroughly confirmed that the adipocytes of visceral fat tissue are more lipolytically active

than subcutaneous adipocytes and thus contribute more to the plasma free fatty acid levels [62, 66]. This was found in particular in diabetic obese individuals, where it was linked to a significant upregulation of leptin and downregulation of adiponectin gene expression in mesenteric VAT compared to SAT and omental VAT [67].

The metabolic activity of a cell is dependent on its mitochondrial content, and it has been shown that, in rats, epididymal (VAT) adipocytes have more mitochondria than inguinal (SAT) adipocytes [37]. In adipose tissue from obese individuals undergoing bariatric surgery the relative OXPHOS activity was found to be higher in omental VAT than SAT [38]. Individuals with a polymorphism in the *UCP1* promoter reducing *UCP1* gene expression are prone to have a high BMI, in particular due to abdominal obesity [68]. Thus, the level of mitochondrial uncoupling and energy efficiency may have an effect on obesity in WAT as well as BAT. The higher expression level of beta-adrenergic receptors in VAT could contribute to the higher lipolytic activity [69]. In addition, insulin-stimulated glucose uptake was found to be higher in VAT compared to SAT [70]. As a result, excess visceral fat will enhance the level of free fatty acid delivered to the liver, thus increasing hepatic glucose and very low-density lipoprotein particles (VLDLs) output, and impair the hepatic insulin response.

The expression of *PPAR $\gamma$*  mRNA is increased in the adipose tissue of obese subjects [71], and it has been shown that while there was no difference in omental VAT and SAT, *PPAR $\gamma$*  was significantly higher expressed in mesenteric VAT and remarkably so in obese diabetic subjects [67]. This supports the involvement of PPAR $\gamma$  in mesenteric adipose tissue lipolysis. In rats, lipid synthesis is shown to be higher in internal adipose tissues compared to SAT [72]. A study comparing the gene expression pattern in rat retroperitoneal (rVAT), mesenteric VAT (mVAT), and inguinal SAT (iSAT) showed that the larger cells in rVAT expressed high amounts of the lipogenic transcription factors *Ppar $\gamma$*  and *Srebp1c* compared to mVAT and iSAT that showed a high expression of lipogenesis-related genes and a low expression of fatty acid oxidation-related genes [73]. They also showed that the genes involved in lipid metabolism changed more rapidly as a result of fasting in the internal rVAT depot compared to SAT [74].

**5.2. Subcutaneous Fat.** As SAT is less metabolically active than VAT, it may have better short-term and long-term storage capacity. Thus, this depot is important to accumulate TG in periods of excess energy intake and supply the organism with FFAs in periods of fasting, starvation, or exercise. Another suggested role of SAT is to be a buffer during intake of dietary lipids, thus protecting other tissues from lipotoxic effects [75].

In humans, SAT is anatomically divided by a stromal fascia (fascia superficialis) into superficial (sSAT) and deep subcutaneous adipose tissue (dSAT), with distinct histological features. While sSAT has not been linked to risk for T2DM, the size of dSAT depots is significantly linked to the fasting insulin level and insulin-stimulated glucose

utilization, as is total fat and VAT [76, 77]. The association between dSAT and insulin resistance is particularly seen in male obese patients [77, 78]. When studying the expression and secretion of hormones and cytokines in lean subjects, dSAT was found to be more similar to VAT than sSAT [79]. Interestingly, SAT seem to have an exclusive role in leptin secretion, since it correlates with plasma leptin levels (in contrast to plasma insulin levels which correlate with inter abdominal fat [80]). Rat studies have shown that *Ppar $\gamma$ 2* expression is higher in male than in female SAT [81], indicating a gender-linked variation in this adipose depot.

**5.3. Gluteofemoral Fat.** The subcutaneous gluteofemoral fat tissue is measured by hip or thigh circumference, or leg adipose tissue mass. Accumulation of fat in this depot is believed to have a protective role against diabetes and cardiovascular disease [82]. Indeed, low amount of this tissue has been associated with an unfavorable lipid and glucose profile [83]. Likewise, an increase in gluteofemoral tissue size has been connected to increase in HDL-cholesterol and decrease in total- and LDL-cholesterol levels in several studies [83–85]. Gluteofemoral fat is also positively associated with adiponectin and leptin serum levels [86]. Tracing of specific lipid fraction in blood samples from veins draining femoral or abdominal fat showed that there was a lower metabolic flux from femoral fat [87] and that femoral fat had a preference for uptake of FFA and VLDL-TG compared to chylomicron-TG, thus accumulating recycled fat rather than dietary fat.

The gluteofemoral fat tissue may thus provide protection from ectopic deposition of excess fat. While the abdominal subcutaneous adipose tissue has a role as buffer during daily fatty acid intake [75], the gluteofemoral fat tissue may have an important role in TG storage. Since it shows less metabolic activity and is more lipolytically inert than upper-body adipose depots, it seems to be involved in the long-term sequestering of fatty acids.

**5.4. Intermuscular Fat.** Few studies have focused on intermuscular adipose tissue (IMAT), and little is known about its specific metabolic activities. However, due to its increased level in T2DM patients, IMAT has been suggested to be a risk factor along with VAT for the development of obesity-related diseases [88]. The amount of IMAT seems to be associated with age and lack of activity [89], and increases the likelihood of metabolic abnormalities in elderly subjects with normal body weight. In one study, only one third of men and less than half of women with T2DM were obese, but in the normal weight subjects, high amounts of IMAT was associated with higher fasting insulin levels [90]. Also, IMAT correlates negatively with glucose infusion rate [91], and fasting glucose and total cholesterol level in Caucasians [92], indicating its involvement in the development of insulin resistance. The amount of IMAT seem to be hereditary since African-Americans, who are also prone to develop T2DM, have more of this fat type [93].

**5.5. Epicardial Fat.** Epicardial adipose tissue (EAT) is the visceral fat layer located around the heart and is believed to be important for the buffering of the coronary arteries, and in providing fatty acids as a source of energy for the cardiac muscle. The release of adiponectin and adrenomedullin could have a protective effect on the heart during metabolic or mechanical insults [94]. On the other hand, it has recently been shown that EAT will locally influence heart and vasculature through the secretion of pro-inflammatory cytokines and will contribute to coronary atherosclerosis [95–97]. Studies indicate that the amount of EAT can be related to carotid artery stiffness in obese patients with hypertension, while waist circumference shows no statistically significant link [98]. Age seem to determine the risk associated with epicardial fat, since there is no relationship between EAT thickness and insulin resistance and metabolic syndrome in obese children [99].

A study of patients undergoing coronary artery bypass surgery showed that the fat layer closest to the heart expressed 5-fold higher *UCP1* mRNA than the more distal substernal fat, while *UCP1* expression was undetectable in subcutaneous thoracic fat [100]. The *UCP1* expression was influenced by age and body mass index, but showed no relationship to epicardial fat volume, waist circumference, metabolic syndrome or T2DM. This, along with the increased expression of brown adipocyte differentiation transcription factors *PRDM16* and *PGC-1 $\alpha$* , indicate that epicardial fat may have a function similar to brown fat. This could possibly give an additional protection of the myocardium and coronary vessels from hypothermia, but its effect on obesity-linked disease is unknown.

**5.6. Gonadal Fat.** Gonadal VAT is one of the largest adipose depots in rodents and is found around the testis of males (epididymal) and around the ovaries of females (periovarian). This depot is specifically increased in rodents fed a cafeteria diet. Gonadal VAT has been shown to express more of *Ppar $\gamma$*  and *Srebp1c* as well as another key adipogenic transcription factor, CCAAT enhancer-binding protein alpha (*C/EBP-alpha*) compared to SAT [101]. Interestingly, PPAR $\gamma$ 2 protein was found at a significantly higher level in female than in male rat perigonadal adipose tissue [81], indicating that sex hormones can affect the regulation of PPAR $\gamma$ 2 in VAT. It is possible that this could contribute to the gender differences observed with different PPAR agonists.

**5.7. BAT.** The largest region of brown adipose tissue is found in the upper back region of rodents (interscapular BAT). In humans, small areas are found in the thorax region (supraclavicular), and in the chest and abdomen [44]. There are indications that the nonshivering heat generation is important for the development of obesity [48]. Mice lacking *UCP1* demonstrates increased obesity with age when fed high-fat diets [102], and selective destruction of BAT leads to obesity and reduced energy expenditure and insulin resistance [103]. Interestingly, overnourished rat pups displayed excess weight gain, reduced thermogenic capacity, and lower levels of *UCP1* as adults [104]. It seems

that reduced amount and thermogenic capacity of BAT may contribute to a life-long predisposition for obesity. Although adult humans possess only a small percentage of BAT compared to WAT, the possibility to pharmacologically increase BAT amount or activity would be a potential treatment for obesity. Recent studies have demonstrated that the forced expression of transcription factors PRDM16 and C/EBP- $\beta$  is sufficient to generate brown fat cells from myoblastic precursors [105]. The activation of PPAR $\gamma$  by different agonists has been shown to induce the expression of brown adipose genes in white adipocytes [106], the differentiation of brown adipose progenitor cells [107], and the proliferation of BAT in rats and monkeys [108]. However, long-term activation of the sympathetic nervous system by drugs such as ephedrine and BAT proliferation with the PPAR $\gamma$  agonist the thiazolidinedione darglitazone have been linked to numerous side effects [108, 109].

## 6. Targeting Mitochondrial Function by Bioactive Components

**6.1. The Effect of Dietary Supplementation with Bioactive Lipids.** Adipose tissue plays a major role in the inflammation, insulin resistance, and dyslipidemia associated with obesity. It is therefore beneficial to use compounds that therapeutically target adipose tissue to avoid high-risk complications of obesity such as T2DM and CVD. Dietary lipids may influence the energy balance and are shown to have a differential effect on different fat depots. Studies in rats have shown that fish oil or n-3 polyunsaturated fatty acids (n-3 PUFA) intervention reduces epididymal and perirenal adipose tissues although the body weight stays constant [110, 111]. It is believed that fish oil can affect adipose tissue by the activation of PPAR $\alpha$  and  $\gamma$ , leading to decreased lipolysis, improved lipid storage capacity in subcutaneous adipose tissue, as well as anti-inflammatory effects possibly due to inhibitory action on NF- $\kappa$ B [112]. It has been shown that fish oil at 15% (w/w) level of substitution in a 35% high-fat diet prevented fat accumulation in C57BL/6 mice, preferentially in abdominal fat depots [113–115]. This dose of fish oil also induced mitochondrial biogenesis in white fat, with a stronger effect in epididymal than in subcutaneous adipose tissue [114]. AMPK could be involved in this metabolic switch that increases adipocyte fatty acid metabolism, decreases lipolysis, and upregulates mitochondrial biogenesis [116]. The anti-inflammatory effect of n-3 PUFA in mice has been associated with increased adiponectin secretion [116, 117], possibly resulting from AMPK activation. This induction of adiponectin is probably mediated by PPAR $\gamma$  and is higher in epididymal fat than in SAT [118].

The artificially made 3-thia sulphur fatty acid tetradecylthioacetic acid (TTA) has a targeted effect on mitochondria and exhibit high potency compared to fish oil, both with regard to increased fatty acid  $\beta$ -oxidation and anti-inflammatory effects [119]. TTA thus shows great promise in the treatment of metabolic syndrome (Figure 3). It is a 16-carbon saturated fatty acid where a sulfur atom is inserted between the second and the third carbon in the

$\beta$ -position, thus making it unavailable for fatty acid  $\beta$ -oxidation. The mechanism of action of TTA is based mainly on the activation of PPARs, which induce mitochondrial biogenesis and enhance fatty acid oxidation in the liver [119–121]. This has been suggested to remodel WAT tissues due to drainage of fatty acids towards the liver. TTA was shown to specifically reduce epididymal fat in young obese Zucker (fa-fa) rats and epididymal and retroperitoneal fat in male Wistar rats fed a high-fat diet for 3 weeks [122]. To further study the effect of TTA-induced adipose tissue remodelling, Wistar rats were fed a high-fat lard diet (40% energy from fat) for 7 weeks, and the distribution of fat was studied by magnetic resonance imaging (MRI). The adipose tissue mass was significantly reduced in the TTA-fed rats, particularly in the perirenal and epididymal depots [123]. Interestingly, while most of the genes involved in lipolysis, fatty acid  $\beta$ -oxidation, mitochondrial biosynthesis, and immune response were unchanged by TTA in all studied adipose tissues, *Ucp1* was highly increased at the mRNA level in epididymal and mesenteric depots [123]. Also, a *de novo* production of *Ucp3* in the liver was detected both at the mRNA and protein level along with high induction of genes involved in  $\beta$ -oxidation [123]. The possible increased energy expenditure due to uncoupling of mitochondria combined with the enhanced hepatic fatty acid  $\beta$ -oxidation supports the hypothesis of hepatic lipid drainage. As a result, TTA treatment will channel TGs to the liver for  $\beta$ -oxidation and facilitate adipose tissue lipolysis. The higher metabolic activity of the VAT tissues could explain the specific reduction of these risk-linked depots, perhaps also influenced by their increase in BAT-like features (Figure 2). Although the effect of TTA is mostly due to activation of hepatic mitochondrial genes, activation of some adipose genes involved in  $\beta$ -oxidation was observed. The lipogenic genes acetyl-CoA carboxylase alpha (*Acaca*) and fatty acid synthase (*Fasn*) were induced by TTA in perirenal and epididymal VAT [123]. In a directly comparable long-term rat study, the 3-n PUFA eicosapentaenoic acid (EPA) was found to increase *Acaca* and *Fasn* in VAT while *Cpt2* mRNA-level was increased in mesenteric VAT, indicating an increase in genes involved in fatty acid degradation also with marine oils [124]. *Ucp1* was on the other hand increased only by TTA. Similar results have been found in human adipocytes (not published results). TTA and EPA were able to significantly increase the gene expression of AMPK, *CPT2*, *UCP1*, and acyl-coA oxidase 1 (*ACOX1*), but TTA induced a higher level of AMPK and *UCP1*. Importantly, AMPK is believed to function as a metabolic switch resulting in upregulation of FA oxidation in parallel with reduced maloyl-CoA level and downregulated lipogenesis and TG biosynthesis.

The mitochondrial gene pyruvate kinase (*Pfkfb*) was upregulated by TTA specifically in perirenal VAT [123], indicating mitochondrial biogenesis in this fat depot. This is important as the generation of new mitochondria is severely compromised in several obesity-models [36, 43]. In accordance, a coactivator central for mitochondrial biogenesis, PPAR coactivator 1 $\alpha$  (*Pgc-1 $\alpha$* ) was reduced in a rodent obesity model [125] and in morbidly obese humans [126].

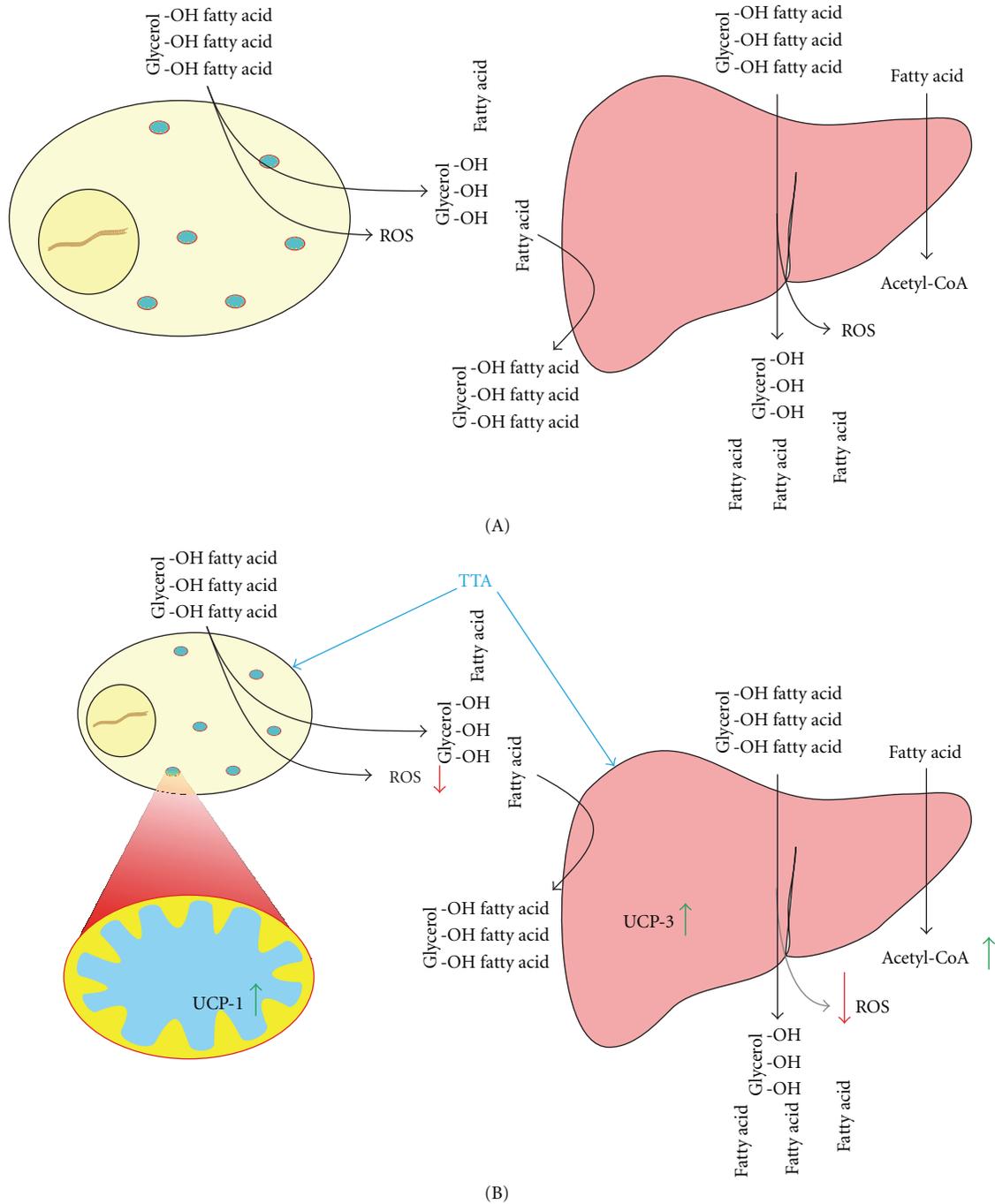


FIGURE 3: (A) During obesity, the adipocytes will have reduced lipid storage capacity, leading to increased lipolysis and release of free fatty acids (FFAs), inflammatory agents, and disturbed adipokine release. The FFAs will be repackaged to triglycerides (TGs) in the liver where they are released as very low-density lipoprotein particles (VLDL). Together this has secondary effects on organs such as skeletal muscle and pancreas, as well as liver, and can result in hyperlipidemia, tissue lipid deposition, mitochondrial malfunction, insulin resistance, increased insulin production, and pancreatic  $\beta$ -cell disruption. (B) The effect of tetradecylthioacetic acid-(TTA-) treatment on metabolic syndrome. In the liver, TTA treatment will increase the degradation of FFA, by the induction of both mitochondrial and peroxisomal genes involved in  $\beta$ -oxidation. The excess FFA released from adipose tissue during metabolic syndrome (hyperlipidemia) is drained from the blood, thereby reducing TG, cholesterol, and FFA levels. In addition the TTA-induced increase in uncoupling protein 3 (UCP3) could increase energy expenditure, as well as function as a protection from the excess ROS production observed with obesity and high levels of FA degradation. The effect of TTA on liver is probably due to PPAR $\alpha$ -mediated mechanisms, while the effect on adipose tissue may arrive from PPAR $\gamma$  as well as PPAR $\alpha$  activation. In adipose tissue, the main effect of TTA is an increase in the brown adipose tissue marker *Ucp1* in visceral adipose tissue (VAT) indicating higher energy expenditure and heat production. The higher metabolic activity of VAT compared to SAT will cause it to be the major source of FFA during increased hepatic  $\beta$ -oxidation. Together, this may explain the specific reduction of these risk-linked adipose depots with TTA-treatment.

Although TTA reduces dyslipidemia in diabetic patients [121], a direct effect on glucose metabolism and insulin sensitivity is more disputed [121, 123, 127]. A reduced amount of risk-related adipose tissue in obese individuals would however be important to reduce the likelihood of developing disease. The efficient reduction of plasma FFA and TG by TTA, seen in both human and animal studies [128], may also prevent ectopic lipid deposition and lipotoxic effects.

TTA induces mitochondrial biogenesis in liver, but the effect on mitochondrial respiration has not been fully elucidated. Although the number of mitochondria increases in the liver during TTA-treatment, the hepatocytes are enlarged, and the respiration per mg tissue stays constant (not published results). Little work has been done to measure oxygen consumption/OXPHOS in adipose tissue, probably due to the difficulties caused by a low mitochondrial density in adipocytes compared to skeletal muscle [129]. Some studies have successfully determined mitochondrial OXPHOS in cells or organelles isolated from both brown and white adipose tissues [130], and VAT and SAT have been compared using similar techniques [38]. Information on mitochondrial OXPHOS activity will be of importance when testing for improved adipose tissue function during treatment with mitochondrial-targeted compounds.

**6.2. Regulation of Gene Expression in the Treatment of Obesity-Related Diseases.** PPAR is the target of many agents that restore insulin sensitivity. However, they do not necessarily decrease adipose tissue size. Thiazolidinediones (TZDs), such as pioglitazone and rosiglitazone, activate PPAR $\gamma$  and are associated with increased body weight due to the ability to stimulate preadipocyte differentiation [131, 132]. In particular the retroperitoneal VAT [133, 134] and intermuscular fat infiltration was increased by TZDs [134]. Studies show that the activation of PPAR $\alpha$  by fenofibrates or oleyletanolamide reduces adiposity and increases lipolysis [132], while a pan-PPAR ligand, LM 4156, had no effect on adipose tissue size [134]. Another study in accordance with this showed that a PPAR $\alpha$  agonist reduced feed intake and body weight gain but had less effect on glucose intolerance (GI), a PPAR $\gamma$  agonist improved GI and adiponectin release but enhanced feed intake and body weight gain, while an agent with dual PPAR-activation demonstrated a combined, more beneficial effect [135]. TTA activates both PPAR $\alpha$  and  $\gamma$ , the former with higher efficiency [136–138], and this may partly explain the effect on lipid degradation in the liver, as well as the reduced weight gain and hepatic induction of UCP3 primarily associated with PPAR $\alpha$  activation [132, 139]. However, we have shown the existence of PPAR dependent and independent induction of UCP2 by TTA [140]. Therefore, mechanisms not involving PPAR-activation may also be important for the effects seen with TTA.

**6.3. ROS Generation and TTA as an Antioxidant.** There is mounting evidence that the increased release of H<sub>2</sub>O<sub>2</sub>,

mainly originating from mitochondria, may be an important step in the development of insulin resistance in different tissues during high-fat intake [15, 16]. Mitochondrial damage is linked to insulin resistance and could be a secondary effect of the increase in ROS [141]. A number of studies have shown that treatment with antioxidants will both improve oxidative stress and restore insulin sensitivity [141–143]. While antioxidants studied so far have had little effect on human atherogenesis, it could be worthwhile to investigate mitochondrial-targeted antioxidants in the treatment of CVD [5].

TTA mainly affects mitochondrial functions and is a very potent antioxidant [144, 145] and anti-inflammatory agent [120, 146], both of which may be important for its reduction of dyslipidemia in diabetic patients [121]. TTA inhibits the lipoprotein oxidation in rats, indicating that its effects as an antioxidant may influence the development of atherosclerosis [145]. It also reduces the stenosis development after balloon angioplasty injury of rabbit iliac arteries [147]. Recently we have shown downregulated expression of PPAR target genes and reduced mitochondrial fatty acid oxidation in the liver of mice transgenic for hTNF $\alpha$  [148]. TTA enhanced the hepatic fatty acid oxidation in these animals (in preparation). Moreover, TTA reduced the hepatic gene expression of TNF $\alpha$  and visfatin [123].

## 7. Conclusions

The different adipose depots have specific roles based on their level of lipolysis and rate of TG storage. It is becoming clear that while abdominal visceral adipose tissue increases the risk of obesity-related disease, subcutaneous adipose tissue, especially located to the lower-body parts, protects from lipotoxic effects through short-term and long-term storage of TGs. In rodent studies, intake of bioactive lipids gives specific reduction of risk-related adipose tissues, and this targeted effect may be due to the higher metabolic activity of these depots. Treatments that increase energy expenditure through “mild uncoupling” of mitochondria and fatty acid  $\beta$ -oxidation show great promise in the treatment of obesity. The artificial fatty acid TTA is an inducer of these processes. Enhanced expression of uncoupling proteins together with an induction of hepatic  $\beta$ -oxidation suggests that TTA may increase energy consumption via increased uncoupling in liver and/or WAT. In addition its activity as an antioxidant and anti-inflammatory agent will have a direct positive effect on the diseases linked to obesity, such as T2DM and CVD.

## Abbreviations

- AMPK: Adenosine monophosphate-activated protein kinase
- BAT: Brown adipose tissue
- CPT: Carnitine palmitoyltransferase
- CVD: Cardiovascular disease
- DMT2: Diabetes mellitus type 2

dSAT:	Deep subcutaneous adipose tissue
EAT:	Epicardial adipose tissue
FFA:	Free fatty acid
IMAT:	Intermuscular adipose tissue
ME:	Mesenteric adipose tissue
MRI:	Magnetic resonance imaging
NOX:	NADPH oxidase
OXPHOS:	Oxidative phosphorylation
PPAR:	Peroxisome proliferator-activated receptor
PUFA:	Polyunsaturated fatty acid
ROS:	Reactive oxygen species
SAT:	Subcutaneous adipose tissue
sSAT:	Superficial subcutaneous adipose tissue
TG:	Triglyceride
TTA:	Tetradecylthioacetic acid
UCP:	Uncoupling protein
VAT:	Visceral adipose tissue
WAT:	White adipose tissue.

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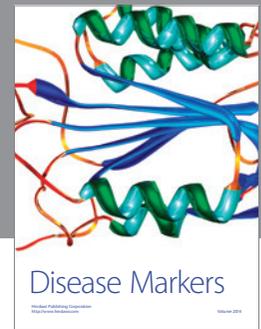
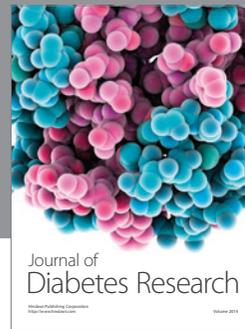
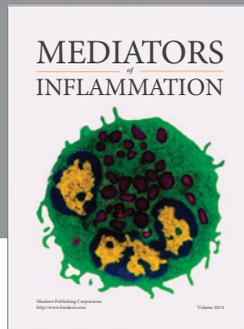
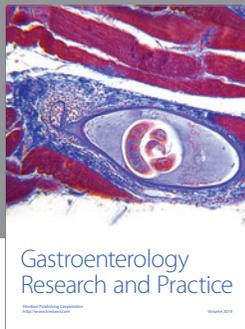
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