Obesity and the Dysregulation of Fatty Acid Metabolism: Implications for Healthy Aging

Introduction. The population of the world is aging. In 2010, an estimated 524 million people were aged 65 years or older presenting eight percent of the global population. By 2050, this number is expected to nearly triple to approximately 1.5 billion, 16 percent of the world's population. Although people are living longer, the quality of their lives are often compromised due to ill-health.

Areas covered. Of the conditions which compromise health as we age, obesity is at the forefront. Over half of the global older population were overweight or obese in 2010, significantly increasing the risk of a range of metabolic diseases. Although, it is well recognised excessive calorie intake is a fundamental driver of adipose tissue dysfunction, the relationship between obesity; intrinsic aging; and fat metabolism is less understood. In this review we discuss the intersection between obesity, aging and the factors which contribute to the dysregulation of whole-body fat metabolism.

Expert Commentary. Being obese disrupts an array of physiological systems and there is significant crosstalk among these. Moreover it is imperative to acknowledge the contribution intrinsic aging makes to the dysregulation of these systems and the onset of disease.

Keywords: Aging, obesity, fatty acid metabolism, inflammaging, endocrine system

Introduction

The world population is aging[1,2]. However, despite the dramatic rise in life expectancy global health is on the decline. Of the clinical problems whose prevalence is increasing, obesity, a chronic condition which is underpinned by an imbalance between energy ingested versus energy expended, is the most pronounced. Globally, more than half a billion adults aged 20 years and older are obese (BMI>30kg/m^2) worldwide[3]. In 2014, 39% of the world's adult population were overweight (BMI >25kg/m^2), with 13% classed as obese, a figure which has more than doubled since 1980[3]. This problem is amplified when the data for England is considered. In England it has been estimated ~80 % of males aged 55-64 years are overweight/obese, while and ~70% of females aged between 55-64 years are overweight/ obese[4] (Figure 1).

It is projected 2.8 million people die annually as a result of being overweight or obese[3]. These fatalities are underpinned by the pathological footprint left by obesity, characterised by clinical conditions, which are the direct or indirect result of being overweight or obese. Such conditions include hypertension[5], insulin resistance[6], cardiovascular disease (CVD)[7], type-2 diabetes mellitus (T2DM)[8], rheumatoid arthritis[9], dementia[10], and certain cancers, for example, breast[11], colorectal[12], oesophageal[13], pancreatic[14] and gastric[15]. A feature of many of the diseases associated with obesity is the disruption of whole-body fatty acid metabolism; a metabolic system which is intimately coupled with adipose tissue function[16]. An elementary summary of the biological mechanisms which regulate fat metabolism is presented in figure 2. Briefly, ingested lipids are packaged intestinally and released into the blood stream as chylomicrons. Chylomicrons are hydrolysed by lipoprotein lipase (LPL), releasing free fatty acids (FFAs) into a fatty acid pool. FFAs are removed from the pool by muscle and hepatic tissue, where they are either oxidized or re-

esterified. Hepatic triacylglycerides (TAGs) can be shuttled into the blood stream as a constituent of very low density lipoproteins (VLDLs). During periods of fasting, or as a result of sustained physical activity (PA), hormone sensitive lipase (HSL) is activated, and serves to mobilize FFAs by hydrolysing TAG found in adipose tissue[16]. Conversely during the fed state, adipose tissue fat storage is stimulated and fat mobilization suppressed by insulin. The activity of HSL is regulated by insulin, via an increase or decrease in the extent of phosphorylation of HSL, depending on the respective metabolic state. Clearly, the mechanisms which regulate fat metabolism are interdependent, and subtle alterations to them can disrupt fat metabolism. For instance, adipose tissue is a key regulatory hub within fat metabolism and many of the clinical manifestations associated with obesity are a direct consequence of the enlargement of and/or an increase in the number of cells found in adipose tissue, which is the result of excessive TAG deposition[17]. However, it is important to recognise that despite this, metabolically healthy obese individuals may not have these clinical manifestations[18].

The anatomical remodeling of adipose tissue results in a pathophysiology, characterised by the release of excess FFAs; a state induced as a result of enhanced lipolysis[19]. This pernicious metabolic state is often associated with immune system dysfunction and increased hormonal secretion. For instance, T2DM is regularly accompanied by a rise in inflammatory markers in tandem with hyperinsulinemia[20]. Excess calorie intake is a key driver of adipose tissue dysfunction and concomitant metabolic dysregulation, however intrinsic aging also contributes significantly to the dysfunction of adipocytes and lipid metabolism more broadly[21,22]. In this paper we will discuss the relationship between whole body fat metabolism and the aging process. Our aim is to emphasize the contribution aging has to play

in disrupting whole-body fat metabolism homeostasis and the contribution this makes to health in addition to obesity.

Dysregulation of Fatty Acid Metabolism with Age

During aging, body fat is redistributed from subcutaneous stores to the muscles and viscera [23-26]. Redistribution of fat to visceral adipose tissue is associated with a concomitant rise in plasma FFAs[27]. However, it must be stressed this study was conducted on individuals of different ethnicities, and therefore, there may be differences in adipose tissue metabolic activity. This is pathophysiologically significant as obesity provokes the release of excess FFAs. High levels of these fatty acids are the drivers of lipotoxicity, a condition characterised by an increase in oxidative stress [28]. The coupling of dysregulated plasma fatty acid metabolism and oxidative stress is an important link connecting fat metabolism to one of the main theories of biogerontology; the free radical theory of aging. This theory proposes that the damage which accumulates with time in a biological system is a result of oxidative stress, and thus accounts for aging [29,30]. Therefore, an increase in FFAs due to age related fat redistribution could indirectly be a major contributor to the overall rise in oxidative stress; a hallmark of aging [31]. Additionally, lipid accumulation within skeletal muscle cells is correlated with insulin resistance. Moreover a change in the lipid composition of muscle tissue has been shown to have a significant impact on fatty acid metabolism, although not all muscle fibres interact with fatty acid metabolism in the same manner[32]. For instance, certain studies have found that type 1 muscle fibres have an increased response to insulin when compared to their less sensitive type II counterparts[33].

Elevated plasma fatty acids also contribute to hypertriglyceridemia by disrupting lipogenesis inhibiting the flux of TAG from the blood stream. This could explain the association between increasing age and the increase in plasma TAG observed in both males and females [34].

Insulin resistance also accompanies excess FFAs, and is likely to be induced by a decrease in the activity of the insulin receptor. It has also been proposed lipotoxic induced oxidative stress could have a role to play in this phenomenon, as demonstrated by a recent experimental study exposing cultured human hepatocytes to FA activated oxidative stress [35]. In addition, this study found that FA exposure stimulated the production of the prothrombotic marker, plasminogen activator inhibitor-1 (PAI-1). This is not surprising, as increased inflammation is also a pathophysiological response to elevated FFAs. For instance, Pararasa et al. (2016) reported fasting plasma saturated fatty acids (SFAs), monounsaturated fatty acids (MUFAs) and polyunsaturated fatty acids (PUFAs) were significantly higher in healthy middle aged men (aged 58±6.1 years) compared with their younger counterparts (aged 24±3.8 years). Furthermore, pro-inflammatory cytokines tumour necrosis factor (TNF)-α and interleukin (IL)-6 were significantly elevated in these middle aged subjects, while the anti-inflammatory IL-10 was reduced [27]. The next section will explore the relationship between inflammation, aging and fat metabolism in greater depth.

Inflammaging

Aging is associated with concomitant chronic low grade systemic inflammation. This phenomenon is referred to as inflammaging [36]. Inflammaging is considered a risk factor for both morbidity and mortality in older people [37], as it is thought the rise in inflammatory markers, such as C-reactive protein (CRP) and IL-6 are associated with physiological dysregulation and the onset of age-related disease. Stepanova et al. (2015) observed obesity was associated with age-related chronic disease, with a trend for co-occurrence. Specifically, the authors found obesity to be prevalent in 37% of individuals with one age-related chronic disease and in 58% of individuals with two or more age-related chronic diseases.

Additionally, the prevalence of hypercholesterolemia increased from 24% in healthy controls, to 34 and 52% in individuals with one and two or more chronic diseases, respectively [38].

Several markers of inflammation are associated with the accumulation of visceral adipose tissue including, the pro-inflammatory cytokines IL-6, TNF-α, TFG-β1, monocyte chemotactic protein-1 (MCP-1), iNOS, coagulation factors, fibrinogen, PAI-1, and acute phase proteins serum amyloid A (SAA) and CRP [39-44]. These biomarkers have a broad range of physiological roles in the promotion of inflammation (Figure 3). For example, MCP-1 induces the migration of monocytes to the area [45], while the pro-inflammatory cytokine IFN-γ induces monocyte polarisation to M1 macrophages [46]. This is accompanied by progressive lipid accumulation and foam-like cell formation within the adipose tissue [47]. An increased M1:M2 ratio inflammatory profile is associated with the further release of pro-inflammatory cytokines, TNF-α, IL-1β, IL-6, and IL-12, in addition to an increase in the expression of pattern recognition receptors, such as TLR [48]. Moreover, elevated mitochondrial superoxide generation, and significantly reduced plasma glutathione were associated with this inflammatory profile [27]. The resulting inflammation has been associated with the promotion of insulin resistance, mitochondrial dysfunction, ROS accumulation and the pathogenesis of T2DM [49]. Additionally, inflammation affects fatty acid metabolism in a variety of ways. For example, Zhang et al. (2002) demonstrated TNF-α promotes the lipolysis of TAG in human adipocytes via the activation of mitogen activated protein kinase (MEK) and extracellular signal related kinase (ERK) and elevation of intracellular cAMP [50]. Moreover, TNF-α activation of the MEK1/2-ERK1/2 pathway has been implicated in the phosphorylation and concomitant increase in activity of HSL, stimulating lipolysis, contributing to increased hepatic production of glucose [51]. In

addition, TNF-α inhibits the maturation of adipocytes by selectively activating TNF receptor 1 [52].

Interestingly, it appears a bi-directional relationship exists between fatty acid metabolism and the immune response, as FFAs can modulate the inflammatory response. However, it is important to note FFAs exert different effects on the inflammatory status. For example, Pararasa et al. (2016) demonstrated elevated palmitic acid (C16:0) was related to an increase in TNF-α and mitochondrial superoxide generation, while high levels of the SFAs stearic acid (C18:0) and lignoceric acid (C24:0) have been associated with reduced transforming growth factor (TGF)-β1 levels [27]. Furthermore, the PUFA punicic acid (C18:3 (n-5)) has been observed to ameliorate the mitochondrial dysfunction and insulin resistance associated adipocyte TNF-α expression [53]. Importantly, inflammation induced by aging and obesity can be ameliorated by diet [54,55]. For example, Bashir et al. (2016) demonstrated fish oil supplementation resulted in a reduction in adiposity index, serum cholesterol, serum TAG and insulin resistance in obese insulin-resistant mice fed a high fat diet. Moreover, this supplementation resulted in a reduction in M1 phenotype markers, while M2 phenotype markers increased in a dose-dependent manner [56]. In addition, fish oil has been observed to reduce a range of inflammatory-related genes in humans, including the gene encoding for matrix metalloprotease MMP9, which plays an important role in macrophage infiltration [33]. Gironés-Vilaplana et al. (2014) describe several Latin-American fruits that exhibit good antioxidant capacities, and α-glucosidase and pancreatic lipase inhibitory activities, which could be utilised in the treatment of obesity and T2DM [57]. Additionally, it has been demonstrated inflammation can also be ameliorated by weight loss. For instance, Aron-Wisnewsky et al. (2009) reported a 15% total body weight loss 3 months post-bariatric surgery, resulted in a 2-fold reduction in the M1:M2 ratio [58].

The Endocrine System: Age related Modulation and Obesity

As outlined in figure 4, the endocrine system has a significant role to play in the regulation of fatty acid metabolism[59]. For instance, hormones such as insulin and glucagon interact with fatty acid metabolism to remove glucose from the plasma. Post prandial insulin secretion, not only induces the transportation of GLUT4 to the plasma membrane, but increases non esterified fatty acids (NEFA) synthesis in addition to inhibiting lipolysis[60,61]. Conversely, glucagon stimulates the release of glucose, decreases NEFA synthesis and upregulates lipolysis to increase the concentration of plasma glucose[62]. These straightforward examples provide an insight into how the endocrine system intersects with these metabolic systems. However, hormone production diminishes with age[63], which has an inevitable impact on fatty acid metabolism. In this section we will explore in detail some of the hormones that are key regulators of fat metabolism and how they change with age and obesity.

Glucagon and the regulation of Acetyl CoA Carboxylase

NEFA synthesis is hormonally regulated at the irreversible conversion of acetyl CoA to malonyl CoA by acetyl CoA carboxylase[43]. Glucagon perturbs NEFA synthesis by phosphorylating acetyl CoA carboxylase by cAMP-dependent protein kinase, which in turn inactivates the enzyme, while insulin activates enzyme activity by promoting its dephosphorylation[64]. Additionally, it has been demonstrated epinephrine downregulates acetyl CoA carboxylase activity[64]. However, it has been found in isolated hepatocytes from rats, the ability of glucagon to stimulate phosphorylase activity and cAMP generation decreases with increasing age[65].

Lipolysis: Hormone Sensitive Lipase and Lipoprotein Lipase

Langin et al. (2005) determined obesity induced a 60% decline in HSL expression in differentiated human preadipocytes. This under-expression of HSL may contribute to the defect in lipolysis often observed in obesity[66], For example, insulin inhibits HSL, and hence lipolysis via the activation of cAMP phosphodiesterase; increased degradation of cAMP; and inhibition of cAMP dependent protein kinase. Insulin may also inhibit HSL independently of cAMP via the activation of protein phosphatase [67]. Conversely, glucagon; epinephrine; and growth hormone (GH) enhance HSL activity and lipolysis[68].

The hydrolysis of TAG to FFA and glycerol by LPL is influenced by insulin. LPL activity in adipose tissue is greatest following feeding, and lowest during fasting [69], however, the effect of hormonal interactions appears to be site dependent. For instance, it has been demonstrated LPL activity is elevated by insulin in human adipose tissue, while a decrease is observed in skeletal muscle [70,71]. Glucagon has been observed to elevate LPL activity in rat myocardial tissue and human plasma [72,73], and decrease LPL activity in rat adipose tissue [74]. Additionally, Ricart-Jané et al. (2005) observed that chronic stress reduced LPL activity in adipose tissue, while limb muscle, myocardial, adrenal, plasma and total LPL activity increased. These findings suggest catecholamines also interact with LPL in a site specific manner [75]. GH has also been observed to increase heart and skeletal muscle LPL activity [76]. Obesity has been associated with the elevation of insulin and glucagon, while epinephrine and GH have observed to decline [77-79]. Moreover, aging has been associated with significant reduction in both peak day and night secretion of GH [80]. Furthermore, Esler et al. (1995) reported aging is associated with a 40% decline in epinephrine secretion. It is important to note the concomitant 20% reduction in plasma epinephrine clearance [81]. From the perspective of aging the activity of LPL has been reported to reduce by as much as 55–60%[82,83]. This could in part be explained by the decline in physical activity with age,

as Bey and Hamilton describe physical inactivity has been observed to decrease heparin releasable LPL activity by 90-95% in rats, with ambulatory activity accounting for ~95%.of the variation between muscle fibres[84].

The HPA Axis

The hypothalamic-pituitary-adrenal (HPA) axis is affected by aging[85]. It has been shown the HPA axis becomes increasingly hyper-responsive as a result of this metabolic change in middle aged women[86]. Moreover, Roelfsema et al. (2012) observed that basal; pulsatile; and total ACTH secretion was 1.4, 1.6 and 1.5 times greater, respectively in obese premenopausal women, when compared to their normal weight counterparts. However, despite this increase in ACTH secretion, cortisol levels remained unaffected. This is thought to be due to the significant decline in sensitivity to ACTH, in addition to a decrease in this hormones efficacy [87]. Although it has been repeatedly observed that plasma cortisol is not elevated in obese individuals, there is a greater generation of cortisol within the adipose tissue, in addition to a rise in cortisol metabolite excretion [86-88]. This may be due to 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), a bidirectional enzyme, which acts as a reductase to convert cortisone to cortisol, and as a hydrolase for the reverse reaction [89]. While obesity is related to impaired hepatic 11β-HSD1 activity, it has been demonstrated that a 5.5kg/m^2 increase in BMI reflected a 65% increase in adipose 11β-HSD1 activity in middle aged females [86]. This increase in adipose 11β-HSD1 resulted in an elevated generation of cortisol within the adipose tissue, which may play a role in the pathogenesis of obesity and obesity related disease.

In young healthy female humans, combined SFA, MUFA, and PUFA lipid–heparin infusion inhibited ACTH and cortisol secretion [90]. Another study demonstrated that by increasing serum FFA, both ACTH and cortisol decreased initially, before increasing after 120 minutes. Interestingly, the decline in ACTH was more pronounced in anorexic subjects, while cortisol levels were unaffected [91]. The profile of the FFA may be an important factor in determining the response of the HPA axis, as determined by Katoh et al. (2004), who demonstrated that the SFAs butyric acid (C4); caprylic acid (C8); lauric acid (C12); palmitic acid (C16); and stearic acid (C18) significantly reduced the CRH-induced basal ACTH release, whereas the unsaturated fatty acids oleic acid (C18:1); linoleic acid (C18:2); linolenic acid (C18:3); and arachidonic acid (C20:4) significantly increased CRH-induced basal ACTH release in primary cultured rat anterior pituitary cells [92]. Interestingly, a bidirectional relationship between the HPA axis and adipose tissue may exist. Arad et al. (2015) found that elevated cortisol, due to ACTH injection, may result in the development of central obesity and insulin resistance [93]. However, as this study was conducted *in vitro*, and using cells from rodents, one needs to be cautious when considering the implications of these findings for humans. It has also been demonstrated that aging affects the HPA axis. Basal morning concentrations of dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DS), and androstenedione (A4) were significantly reduced in older females aged 55-68 when compared to younger females aged 20-35 years old, while cortisol levels were similar in both groups. In addition, the decline in DHEA, A4 and DS with overnight dexamethasone treatment was more pronounced in the older group [94]. Intriguingly, it has been found that DHEA replacement did not correct the alterations in meal fat partitioning and post absorptive lipolysis associated with ageing, while testosterone only partially ameliorated these changes [95].

Adipocytokines: Leptin and Adiponectin

It has been observed, that increased adiposity may lead to elevated levels of the satiety hormone leptin [39]. Amouzou et al. (2016) report leptin increased from 14.7ng/ml in non-obese controls to 44.6 and 44.7ng/ml, respectively in insulin sensitive and insulin resistant obese post-menopausal women, aged between 50 and 64 years old [96]. Interestingly, males appear to be more sensitive to the effects of leptin, and therefore exhibit lower concentrations compared with females; with leptin concentration and leptin receptor inversely correlated with serum testosterone [97]. The increase in adiposity observed with age and the concomitant elevation in leptin and leptin resistance, has been associated with enhanced lipolysis, reduced β-oxidation of fatty acids in addition to a reduction in glucose tolerance [98]. Moreover, it has been postulated that leptin resistance may contribute to the pathogenesis of CVD [99]. In contrast, the adipocytokine adiponectin decreases as a result of being obese [39]. Adiponectin promotes glucose utilisation and fatty acid oxidation, and reduction of this adipocytokine is associated with insulin resistance [100]. For example, Amouzou et al. (2016) reported a decrease in adiponectin from 17.4ng/ml in non-obese controls to 12.1 and 9.3ng/ml in insulin sensitive and insulin resistant obese post-menopausal women, respectively [96]. Kim et al (2015) suggests the inhibition of adiponectin amongst the obese may be due to, obesity-induced pro-inflammatory cytokines inducing the hypermethylation of compact chromatin structures in the adiponectin gene promoter by the methyl transfer enzyme DNA methyltransferase 1 (DNMT1), impeding the expression of adiponectin [101]. Interestingly, inhibition of DNMT1 activity, or supplementation with adiponectin or adiponectin receptor ameliorated induced insulin resistance [101-103].

Mathematical Modeling of Lipid Metabolism

From our discussion of obesity, fatty acid metabolism and its interaction with aging, it is apparent this is a complex system with many interacting biological components. Therefore, studying these interactions is challenging. In recent years biological research has benefited significantly from using mathematical modeling to help improve our understanding of multifaceted biological systems (reviewed in[104-107]). This approach provides a flexible framework which enables hypothesis exploration and enables the dynamics of a biological system to be predicted. Recently, we used mathematical modeling to explore how aging impacts the biological mechanisms responsible for the regulation of whole-body cholesterol metabolism[108-110], and to explore the impact of acute and chronic levels of cortisol on brain aging[85]. This model could be extended to include some of the interactions between fat metabolism and cortisol regulation discussed in this paper. More specific to fatty acid metabolism, we also developed a mathematical model of microtubule growth and shrinkage for differential actions of short chain fatty acids in the gut[111]. Other groups, have also used mathematical modeling as conduit for understanding adipose tissue regulation. For instance, Kim et al. (2008) developed a mathematical model of adipose tissue metabolism. The model was able to simulate physiological responses from the different expression levels of lipases and found that during epinephrine infusion, lipases are differentially activated, such that DAG breakdown is approximately four times faster than triglyceride breakdown[112].

Expert commentary

The world population is aging, and with a rise in the global population comes an increase in the prevalence of age related diseases. Many of these diseases, such as CVD and T2DM are impacted significantly by the dysregulation of fat metabolism. Overweight and obesity are central to the disruption of fat metabolism, as it is the fundamental factor which provokes a rise in plasma free fatty acids. Increased plasma free fatty acids coincide with a plethora of

metabolic changes which contribute to the pathophysiology of obesity and the eventual onset of disease. The aging process also disrupts the physiological systems and biological mechanisms responsible for the regulation of fat metabolism. Specifically, there is significant overlap between the immune aging/inflammaging and the disruption of fat metabolism. Age related hormonal changes also disrupt fat metabolism, while there is a negative impact on endocrine systems, such as the HPA axis as a result of overweight/obesity. It is also important to acknowledge the increased level of crosstalk between physiological systems as a result of aging and how it impacts the onset of disease. This is particularly relevant as the global population continues to rise, as it is predicted the prevalence of obesity will also increase across all age groups in many countries. Excess caloric intake, coupled with a demographic change in favour of older people will pose a significant challenge to healthcare in coming years. To date, public health strategies have failed to curb the increase in obesity, thus it will require innovative and imaginative initiatives to stem this global crises.

Five-Year View

- There will continue to be an increase in life expectancy
- There will be a concomitant rise in the prevalence of obesity
- Public health strategies to deal with this crises remain to developed
- Health care systems will continue to see a rise in clinical conditions associated with obesity
- It will be increasingly recognized intrinsic aging must be considered in addition to excess caloric intake when investigating the pathophysiology of obesity

Key issues

- Globally the population of the world is aging
- The prevalence of obesity is on the increase

- With an increase in obesity, there comes a increase in the metabolic condition which are associated with the dysregulation of fat metabolism
- Intrinsic aging also impacts fat metabolism
- Disturbances to fat metabolism may be related to the aging process as well as excess calorie intake
- There is a bidirectional relationship between fatty acid metabolism and inflammation
- Accumulation of visceral adipose tissue with age is associated with inflammation.
- Dysfunction of the endocrine system significantly impacts fatty acid metabolism.

Conclusions

Experimental evidence firmly suggests the dysregulation of fat metabolism plays a role in the development of metabolic conditions such CVD and T2DM. This dysregulation is at least partly driven by the disruption of adipose tissue due to excess fat accumulation, as a result of excess calorie intake. In addition, the aging process affects the biological mechanisms and physiological systems responsible for the homeostatic maintenance fat metabolism. It is important to consider the contribution of both diet and intrinsic aging when exploring the metabolic complications that accompany obesity.

Figure 1 Adult population weight by age and gender. Weight category defined by BMI; underweight <18.5kg/m^2, normal weight 18.5-25kg/m^2, overweight 25-30kg/m^2, obese 30-40kg/m^2, morbidly obese <40kg/m^2. (Data from [113]).

Figure 2 Overview of fatty acid metabolism. Abbreviations: FFA, free fatty acids; HSL, hormone sensitive lipase; LPL, lipoprotein lipase; TAG, triacylglycerol; VLDL, very low density lipoprotein. Arrows represent flux or the action of an enzyme. The Greek symbol theta represents utilisation of the metabolite.

Figure 3 Hormonal interactions with fatty acid metabolism. Abbreviations: ATGL, adipose triglyceride lipase; ATP, adenosine triphosphate; DAG, diacylglycerol; FAS, fatty acid synthase; FFA, free fatty acids; GH, growth hormone; HSL, hormone sensitive lipase; LPL, lipoprotein lipase; MAG, monoacylglycerol; MDH, malate dehydrogenase; TAG, triacylglycerol; TCA, tricarboxcylic acid. Arrows represent flux or the action of an enzyme. The Greek symbol theta represents utilisation of the metabolite.

Figure 4 Role of increased adiposity in the promotion of an inflammation, and pathogenesis of obesity-related disease. Abbreviations: FFA, free fatty acids; HSL, hormone sensitive lipase; IFN-γ, interferon-γ; LPL, lipoprotein lipase; MCP-1, monocyte chemotactic protein-1; ROS, reactive oxygen species; TAG, triacylglycerol; T2DM, type 2 diabetes mellitus; VLDL, very low density lipoprotein. Arrows represent flux or the action of an enzyme/hormone. T shaped arrows represent inhibition.