

# Adipose tissue dysfunction in obesity, diabetes, and vascular diseases

Gideon R. Hajer<sup>1</sup>, Timon W. van Haeften<sup>2</sup>, and Frank L.J. Visseren<sup>1\*</sup>

<sup>1</sup>Department of Vascular Medicine, University Medical Center Utrecht, PO Box 85500, 3508 GA Utrecht, The Netherlands; and <sup>2</sup>Department of Endocrinology, University Medical Center Utrecht, Utrecht, The Netherlands

Received 1 April 2008; revised 7 July 2008; accepted 14 August 2008; online publish-ahead-of-print 5 September 2008

The classical perception of adipose tissue as a storage place of fatty acids has been replaced over the last years by the notion that adipose tissue has a central role in lipid and glucose metabolism and produces a large number of hormones and cytokines, e.g. tumour necrosis factor- $\alpha$ , interleukin-6, adiponectin, leptin, and plasminogen activator inhibitor-1.

The increased prevalence of excessive visceral obesity and obesity-related cardiovascular risk factors is closely associated with the rising incidence of cardiovascular diseases and type 2 diabetes mellitus. This clustering of vascular risk factors in (visceral) obesity is often referred to as metabolic syndrome. The close relationship between an increased quantity of visceral fat, metabolic disturbances, including low-grade inflammation, and cardiovascular diseases and the unique anatomical relation to the hepatic portal circulation has led to an intense endeavour to unravel the specific endocrine functions of this visceral fat depot. The objective of this paper is to describe adipose tissue dysfunction, delineate the relation between adipose tissue dysfunction and obesity and to describe how adipose tissue dysfunction is involved in the development of diabetes mellitus type 2 and atherosclerotic vascular diseases. First, normal physiology of adipocytes and adipose tissue will be described.

## Keywords

Adipocyte dysfunction • Adipose tissue • Metabolic syndrome • Insulin resistance • Adiponectin • Type 2 diabetes mellitus • Atherosclerosis • Cardiovascular disease • Leptin • TNF- $\alpha$  • Interleukin-6 • Review

## Introduction

The classical perception of adipose tissue as a storage place of fatty acids has been replaced over the last years by the notion that adipose tissue has a central role in lipid and glucose metabolism and produces a large number of hormones and cytokines, e.g. angiotensinogen, tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-6 (IL-6), adiponectin, leptin, and plasminogen activator inhibitor-1 (PAI-1).<sup>1–3</sup>

The increased prevalence of excessive visceral obesity and obesity-related cardiovascular risk factors is closely associated with the rising incidence of cardiovascular diseases and type 2 diabetes mellitus.<sup>4,5</sup> This clustering of vascular risk factors in (visceral) obesity is often referred to as metabolic syndrome.<sup>6</sup> The close relationship between an increased quantity of visceral fat, metabolic disturbances and cardiovascular diseases, and the unique anatomical relation to the hepatic portal circulation has led to an intense endeavour to unravel the specific endocrine functions of this visceral fat depot. From a pathophysiological point of view, the 'quality' of adipose tissue is more important than the 'quantity'. Nevertheless, a major driver of adipose tissue function is the

quantity of visceral fat. The objective of this paper is to describe adipose tissue dysfunction, delineate the relation between adipose tissue dysfunction and obesity and to describe how adipocyte dysfunction is involved in the development of diabetes mellitus type 2 and atherosclerotic vascular diseases. First, normal physiology of adipocytes and adipose tissue will be described.

## Physiological role of adipocytes and adipose tissue

Adipose tissue exists in adipocytes and a vascular-stromal fraction in which macrophages, fibroblasts, endothelial cells and pre-adipocytes are present.<sup>7</sup> Pre-adipocytes originate from a multipotent stem cell of mesodermal origin and the potential to generate new fat cells persists during the entire human life.<sup>7</sup>

The primary and classical roles of adipose tissue are to insulate and cushion the body, to store free fatty acids (FFAs) after food intake and to release FFAs during the fasting state to ensure sufficient energy status. During the postprandial phase FFAs are taken up from the blood in adipose tissue after hydrolysis of triglycerides

\* Corresponding author. Tel: +31 30 2509111, Fax: +31 30 2505488, Email: f.l.j.visseren@umcutrecht.nl

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2008. For permissions please email: journals.permissions@oxfordjournals.org.

(TG) from triglyceride-rich lipoproteins (very low-density lipoprotein-cholesterol (VLDL-c), chylomicrons and their remnants) by lipoprotein lipase (LPL). Mobilization of this reserve occurs by hydrolysis of adipocyte TG by hormone sensitive lipase (HSL). Insulin is the main regulator of adipocyte fat content, since it is both a potent inhibitor of HSL and an important activator of LPL, thereby enhancing FFA uptake and triglyceride synthesis in adipocytes.

## Endocrine function of adipocytes: adipocytokines

Adipocytes and adipose tissue produce a wide range of hormones and cytokines involved in glucose metabolism (e.g. adiponectin, resistin), lipid metabolism (e.g. cholesteryl ester transfer protein, CETP), inflammation (e.g. TNF- $\alpha$ , IL-6), coagulation (PAI-1), blood pressure (e.g. angiotensinogen, angiotensin II), and feeding behaviour (leptin) thus affecting metabolism and function of many organs and tissues including muscle, liver, vasculature, and brain<sup>8-10</sup> (Table 1).<sup>132</sup> Plasma adipocytokine levels rise with an increase in adipose tissue and adipocyte volume, except for plasma adiponectin which is lower in obesity.<sup>11,12</sup>

The essential roles of adipose tissue are exemplified by the fact that total absence of adipose tissue results in non-viability as occurs in homozygous peroxisome proliferator-activated receptor gamma (PPAR- $\gamma$ ) knock-out mice.<sup>13</sup> During evolution, fat tissue presumably

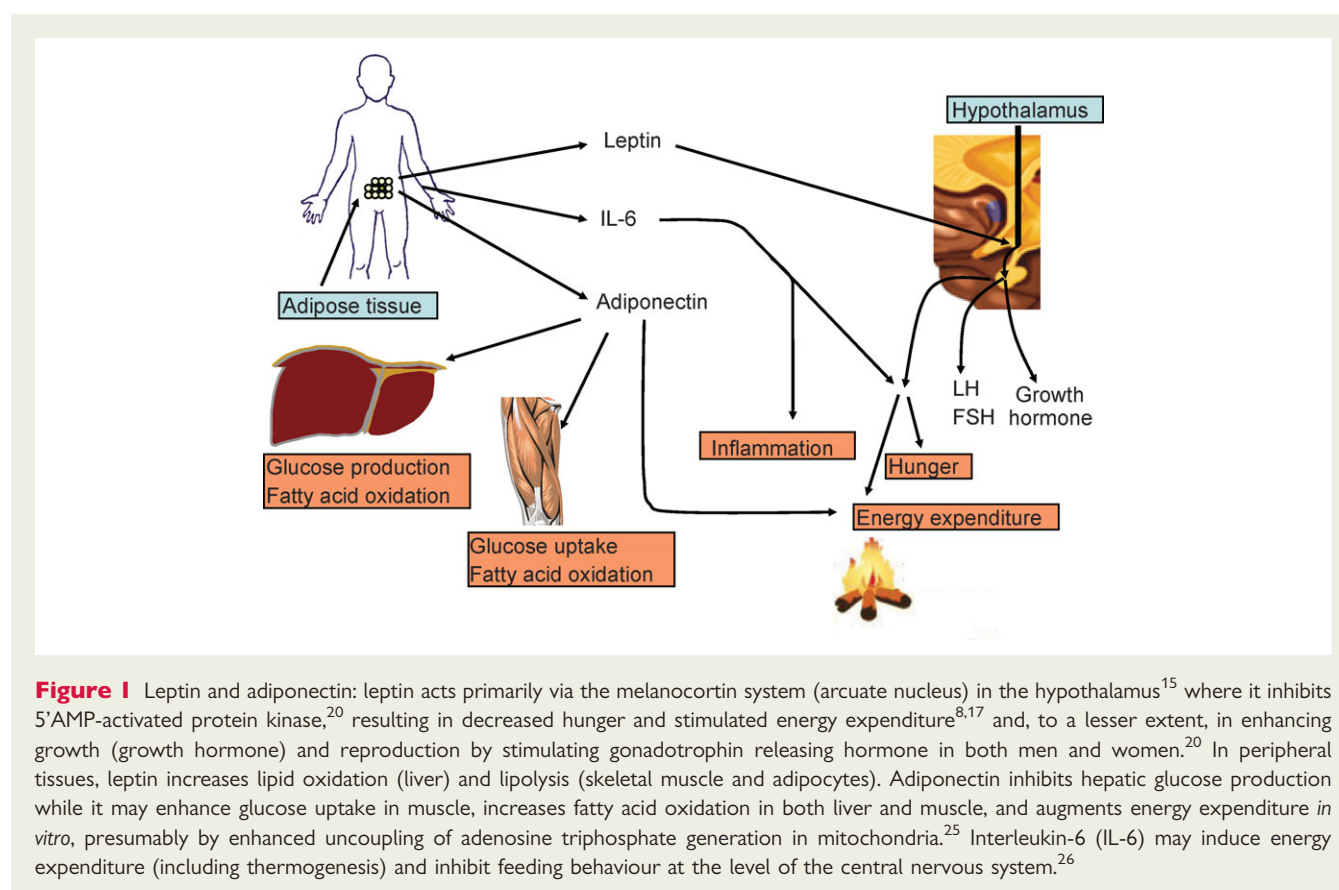
acquired an intermediary role between nutritional status and essential body functions such as feeding behaviour, growth, metabolism, and even fertility.<sup>14,15</sup> A key (co-) regulator of these functions is leptin, which is principally produced by adipocytes.<sup>16</sup>

Leptin production is markedly augmented in large adipocytes,<sup>16</sup> is stimulated by insulin and affected by TNF- $\alpha$ , estrogens, FFAs and growth hormone<sup>17,18</sup> but is not directly influenced by food uptake itself. Therefore, leptin can be considered as a signalling molecule relating the long-term nutritional and fat mass status to the brain (hypothalamus)<sup>15,19</sup> (Figure 1). Apart from central effects, leptin increases hepatic lipid oxidation and lipolysis in skeletal muscle and adipocytes.<sup>19,20</sup> In subjects with decreased fat depots, e.g. in anorexia nervosa (AN), leptin levels are low<sup>21</sup> which may contribute to complications of AN (amenorrhoea). Leptin-deficient children are not only extremely obese, but remain prepubertal while exogenous leptin substitution has resulted in the onset of puberty in these children.<sup>14</sup>

Adiponectin is exclusively produced by adipocytes<sup>2</sup> and circulates in plasma in three different full-length isoforms (trimer, hexamer, and multimers) and as globular form. Adiponectin synthesis is reduced in obesity, insulin resistance, metabolic syndrome, and type 2 diabetes.<sup>22,23</sup> Men have lower plasma adiponectin levels than women.<sup>24</sup> Adiponectin has an array of anti-atherosclerotic effects and improves insulin sensitivity through inhibition of hepatic glucose production and enhancing glucose uptake in muscle, increasing fatty acid oxidation in both liver and muscle

**Table 1** Adipocytokines

Adipocytokine	Full name	Effects on
Leptin	Leptin	Food intake, fat mass
Adiponectin	Adiponectin	Insulin resistance, inflammation
Resistin	Resistin	Insulin resistance, inflammation
Visfatin	Visfatin	Insulin resistance
Omentin	Omentin	Insulin resistance
Vaspin	Visceral adipose tissue-derived serpin	Insulin resistance
Apelin	Apelin	Vasodilatation
CETP	Cholesteryl ester transfer protein	Lipid metabolism
LPL	Lipoprotein lipase	Lipid metabolism
HSL	Hormone sensitive lipase	Lipid metabolism
A-FABP 4 (aP2)	Adipocyte fatty acid-binding protein 4	Lipid metabolism
Perilipin	Perilipin	Lipid metabolism
RBP <sup>4</sup>	Renitol-binding protein <sup>4</sup>	Lipid metabolism
ASP	Acylation stimulating protein	Lipid metabolism
AT II	Angiotensin II	Blood pressure
ACE	Angiotensin converting enzyme	Blood pressure
AGT	Angiotensinogen	Blood pressure
TNF- $\alpha$	Tumour necrosis factor- $\alpha$	Inflammation
IL-6	Interleukin-6	Inflammation
CRP	C-reactive protein	Inflammation
Adipsin	Adipocyte trypsin/complement factor D	Inflammation
MCP-1	Macrophage chemo attractant protein-1	Macrophage attraction
ICAM-1	Intercellular adhesion molecule-1	Macrophage activation
PAI-1	Plasminogen activator inhibitor-1	Fibrinolysis



and augmenting energy expenditure *in vitro*, presumably by enhanced uncoupling of adenosine triphosphate (ATP) generation in mitochondria.<sup>25</sup> In an insulin-resistant mouse model administration of adiponectin has been shown to ameliorate hyperglycaemia and hyperinsulinaemia.<sup>8</sup>

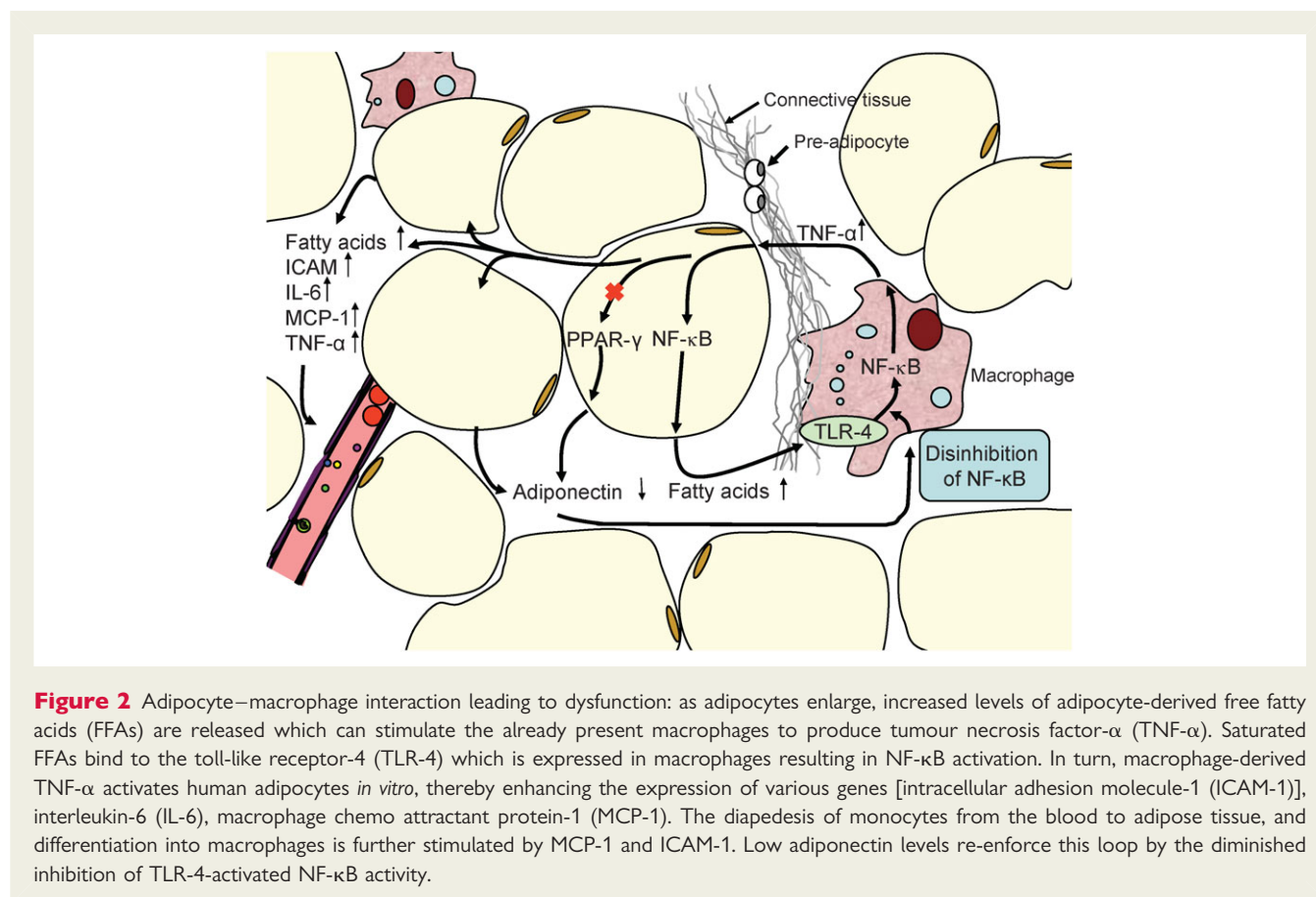
IL-6 can be produced in large quantities by abdominal adipose tissue and is a well-known pro-inflammatory cytokine. Furthermore, elevated IL-6 plasma levels are associated with insulin resistance and increased risk of diabetes, independently of body weight.<sup>11</sup> Surprisingly, IL-6-deficient mice develop obesity with increased leptin levels<sup>26</sup> although conflicting results do exist. Based on these studies it is postulated that IL-6 can induce energy expenditure (including thermogenesis) and inhibit feeding behaviour at the level of the central nervous system. However, a high dose of IL-6 given peripherally results in decreased insulin sensitivity in healthy males.<sup>27</sup> IL-6 upregulates vascular endothelial growth factor (VEGF) production by visceral and subcutaneous adipocytes *in vitro* and in mice, thus supporting angiogenesis during adipose tissue growth.<sup>28</sup> Various other hormones are produced by adipocytes, such as resistin, visfatin, omentin, retinol-binding protein 4, and others. The metabolic properties of these hormones are less clear yet and are the topic of current investigations.

### Visceral vs. subcutaneous adipose tissue

Subcutaneous and visceral adipose tissue show functional differences. For example, genes for angiotensinogen (blood pressure regulation), complement factors,<sup>29</sup> and fatty acid-binding protein 4 (involved in fatty acid trapping in adipocytes), are expressed at

higher levels in visceral adipose tissue than in subcutaneous fat.<sup>30</sup> Leptin however is mainly produced by human subcutaneous adipose tissue while TNF- $\alpha$  is equally produced by both fat depots,<sup>31</sup> although others report differently from *in vitro* studies.<sup>3</sup> In contrast to subcutaneous adipose tissue, abdominal adipose tissue drains directly onto the portal circulation.

Although it is known that during the development of obesity macrophages infiltrate in adipose tissue, it now appears that the infiltration rate of monocytes into visceral adipose tissue is higher than into subcutaneous adipose tissue (Figure 2).<sup>32</sup> A study in extremely obese patients indicates that visceral fat is the main contributor of plasma IL-6 concentration.<sup>31</sup> It is therefore conceivable that viscerally produced adipocytokines directly influence liver function because IL-6 is an inducer of liver C-reactive protein (CRP) production and proteins involved in hemostasis (PAI-1, fibrinogen, tissue plasminogen activator). IL-6 also adds to dyslipidaemia via disinhibition of microsomal TG transfer protein which controls the hepatic assembly of apolipoprotein B (ApoB)-containing lipoproteins *in vitro*.<sup>33</sup> Centrally obese women have lower adiponectin levels than women with peripheral obesity.<sup>34</sup> *In vitro*, human omental fat cells secrete more adiponectin compared with subcutaneous cells and its secretion ratio between compartments declines with increasing body mass index (BMI).<sup>35</sup> Although yet to be proven, it can be hypothesized that visceral adipose tissue is mostly responsible for the decline in adiponectin plasma levels in obese and insulin-resistant subjects while peripheral fat cells are the major adiponectin source in insulin-resistant and obese subjects.



Both visceral and subcutaneous adipose tissues are innervated by the autonomic nervous system, with different motor neurons separately for each depot and under control of neuro-endocrine feedback.<sup>36</sup> Stimulation of the parasympathetic nervous system leads to an anabolic state with decreased lipolysis, while stimulation of the sympathetic nervous system leads to a catabolic state with reduced adipogenesis and stimulated lipolysis. However, at present it is unclear whether and how these different modes of neural innervation lead to functional differences in adipose tissue.

### Transcription factors in adipocytes

Two key transcription factors in the development and metabolism of adipocytes are the PPARs and sterol regulatory element-binding proteins (SREBP).<sup>37</sup> Of the various PPAR subtypes, PPAR- $\gamma$  is expressed at high levels in adipose tissue. PPAR- $\gamma$  activates genes involved in adipocyte differentiation and fatty acid trapping, e.g. fatty acid transport protein, LPL, fatty acid-binding protein, adiponectin, and acyl-CoA synthase.<sup>38</sup> Most of the understanding of PPAR- $\gamma$  gene regulation comes from studies with thiazolidinediones (TZDs) which are PPAR- $\gamma$  ligands. Whether an endogenous, high-affinity ligand for PPAR- $\gamma$  exists is not yet clear but various unsaturated fatty acids and their metabolites have been shown to be able to bind PPAR- $\gamma$ . Activation results in adipocyte hyperplasia with a concomitant shift of TG from circulating lipoproteins and muscle tissue into adipocytes as shown in animal

models.<sup>39</sup> These changes result indirectly in improved endothelial function and in decreased plasma levels of insulin, FFAs, and cytokines.

SREBP-1c (the main SREBP-isoform) is highly expressed in most tissues, including adipose tissue. Once activated by insulin in the postprandial phase, SREBP-1c activates a cascade of genes required for endogenous lipogenesis and pre-adipocyte differentiation (fatty acid synthase, HMG-CoA synthase, LDL-receptor, adipocyte determination, and differentiation factor 1).<sup>40</sup>

### Adipose tissue dysfunction and obesity

The subsequent paragraphs will mainly deal with marked changes in the secretory function of adipocytes, and to a lesser degree of macrophages and pre-adipocytes, seen in obesity, diabetes, and vascular diseases. It has now been firmly established that obesity is associated with the appearance of a chronic, low inflammatory state<sup>41</sup> due to changes in function of adipocytes and macrophages. This indicates that there is not merely an increase in secretion of proteins but that a pathological state, i.e. inflammation, ensues from the changes in secretory function. We use the term adipose tissue dysfunction for this state of hypersecretion of pro-atherogenic, pro-inflammatory and pro-diabetic adipocytokines which is accompanied by a decreased production of adiponectin.

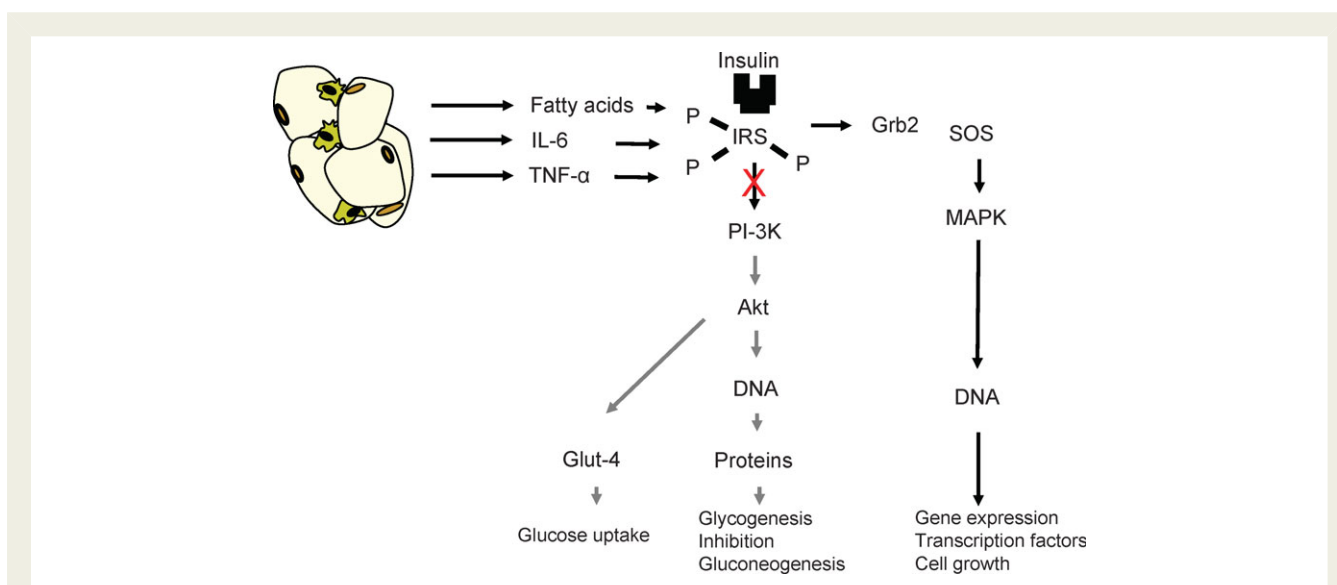
## Obesity leads to adipose tissue dysfunction

Obesity has a strong genetic predisposition, and results from an excess energy intake and/or too little energy expenditure. Obesity is in most, but not all, subjects, associated with marked changes in the secretory function of adipocytes and macrophages, together with chronic low-grade inflammation and an increased risk to develop insulin resistance, diabetes, and/or vascular disease.<sup>42</sup>

Macrophages are more prevalent in adipose tissue of obese subjects than in adipose tissue of lean subjects and the macrophage quantity correlates with measures of insulin resistance.<sup>7</sup> Adipose tissue harbours two types of macrophages, i.e. M1-macrophages (predominant in obesity<sup>43</sup> secreting TNF- $\alpha$  and IL-6 thereby enhancing inflammation), and type M2-macrophages secreting anti-inflammatory cytokines such as IL-10, which has a function in tissue repair.<sup>44</sup> Both macrophages and adipocytes are capable of accumulating lipids and secreting cytokines. Interestingly, the number of macrophages in adipose tissue is reduced after weight loss.<sup>45</sup> Interplay between macrophages and adipocytes by paracrine effects are presumably central in initiating and maintaining adipocyte dysfunction. Adipocytes enlarge as a consequence of hyperalimentation. Large adipocytes release more (saturated) FFAs which can bind to macrophage toll-like receptor-4 (TLR-4) resulting in NF- $\kappa$ B activation ultimately leading to augmented TNF- $\alpha$  production.<sup>46,47</sup> In turn, macrophage-derived TNF- $\alpha$  activates human adipocytes, thereby further inducing lipolysis and enhancing the expression of various genes [intracellular adhesion molecule-1 (ICAM-1), IL-6, macrophage chemo attractant protein-1 (MCP-1)].<sup>48,49</sup> The diapedesis of monocytes from the blood to

adipose tissue and differentiation into macrophages is further facilitated by MCP-1 and ICAM-1. This local paracrine loop involving adipocyte-derived FFAs and macrophage-derived TNF- $\alpha$  establishes a gradual vicious cycle that presumably leads to a pro-inflammatory state of both macrophages and adipocytes. It is of note that large adipocytes produce less adiponectin. Since adiponectin normally inhibits TLR-activated NF- $\kappa$ B activity, it is assumed that low adiponectin levels re-enforce the previously described loop (Figure 3). Interestingly, diet-derived saturated fatty acids activate TLR-4 also directly, while poly-unsaturated fatty acids impede TLR-4.<sup>50</sup>

To ensure a sufficient supply of nutrients and oxygen and to transport fatty acids and adipocytokines, an extended microvasculature is mandatory for adipose tissue.<sup>51</sup> Adipogenesis and angiogenesis are two closely related processes during adipose tissue enlargement, as shown in animal studies and *in vitro* models.<sup>52,53</sup> As adipocyte hypertrophy endures, local adipose tissue hypoxia may occur due to hypoperfusion since the diameter of fat cells overgrows the diffusion limit of oxygen ( $\sim 100 \mu\text{m}$ ).<sup>54</sup> As a result hypoxia-inducible transcription factors are expressed triggering the expression of angiogenic factors (VEGF, hepatocyte growth factor, PAI-1). They elicit the inhibition of adiponectin gene transcription illustrated by decreased adiponectin promoter and PPAR- $\gamma$  activity, by reduced adiponectin mRNA (messenger ribonucleic acid) stability and finally by a decline in adiponectin expression as shown in obese mice.<sup>53,55</sup> Simultaneous induction of leptin and PAI-1 gene transcription in adipose tissue suggests that the dysregulation of adipocytokine secretion is part of cellular mechanisms responding to local hypoxia and associated cellular stress.<sup>56</sup>



**Figure 3** Adipocyte dysfunction leads to insulin resistance: tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-6 (IL-6), and free fatty acids (FFAs) induce serine phosphorylation of insulin receptor substrate-1 and insulin receptor substrate-2, which reduces the capacity of insulin receptor substrate proteins to be phosphorylated by the insulin receptor *in vitro* and may even inhibit insulin receptor autophosphorylation (tyrosine kinase) activity, thereby further attenuating the insulin signalling cascade. FFAs presumably act via activation of protein kinase-c isoforms (PKC) after formation of diacylglycerol, while TNF- $\alpha$  acts via activation of c-Jun N-terminal kinase-1. In muscle, FFA-related generation of acyl-coA derivatives (e.g. ceramide) can diminish Akt1 activity and hence insulin action. In liver, insulin receptor substrate-2 is involved in inhibition of gluconeogenesis, which is often augmented in an insulin-resistant state, possibly via activation of both PKC and c-Jun N-terminal kinase-1 by FFA and TNF- $\alpha$ .<sup>129–131</sup>

Not only may the amount of fatty acids be relevant for mediating adipocyte function, but also the quality of the fatty acids. For example, dietary fish-oil, rich in long-chain unsaturated FFAs, increases activity and mRNA levels of FA oxidation enzymes in peroxisomes and mitochondria and is associated with increased adiponectin levels in mice presumably through PPAR- $\gamma$  activation.<sup>57</sup> Indeed, it has been reported that poly-unsaturated fatty acids reduce mortality and morbidity in patients who suffered from a myocardial infarction.<sup>58</sup>

### Adipose tissue dysfunction leads to obesity

In leptin-deficient humans and in animal models, leptin administration results in reduced body mass and decreased hyperphagia. Although obese subjects have high levels of leptin, their energy expenditure and appetite are not sufficiently regulated, which has led to the concept of hypothalamic leptin resistance,<sup>59</sup> which may be responsible for the persistent hunger and the difficulty to lose weight in obese subjects. Since insulin has similar properties as leptin in the hypothalamus, brain insulin resistance in obesity presumably adds to these effects of leptin resistance.<sup>60</sup> This may imply the existence of vicious circles of leptin resistance and insulin resistance which both lead to hunger and less energy expenditure thereby augmenting obesity.

### Adipose tissue dysfunction and insulin resistance and type 2 diabetes mellitus

Both FFAs and TNF- $\alpha$ , secreted at high quantities by enlarged adipocytes play a prominent role in the development of insulin resistance<sup>61</sup> (Figure 3). Since insulin is the main regulator of HSL, the rate controlling enzyme for triglyceride hydrolysis, the inhibitory effect of FFAs on insulin sensitivity leads to enhanced lipolysis in adipocytes. This effect is augmented by the upregulation of triglyceride hydrolysis by TNF- $\alpha$  in adipose tissue. Besides, TNF- $\alpha$  also contributes to insulin resistance by inhibiting the expression of genes which are essential for insulin signalling and adipocyte differentiation (CCAAT-enhancer-binding protein- $\alpha$ , PPAR- $\gamma$ , glucose transporter type 4, insulin receptor substrate-1 protein, adiponectin, and long-chain fatty acid acyl-CoA synthase) providing another molecular basis for insulin resistance.<sup>49</sup>

Adiponectin increases insulin sensitivity by inhibiting hepatic glucose production and increasing fatty acid oxidation in both liver and muscle as a result of improved 5'AMP-activated protein kinase activity.<sup>62</sup> Single-nucleotide polymorphisms (SNPs) of the promoter region of the adiponectin gene may relate to the development of insulin resistance, obesity, and type 2 diabetes.<sup>63,64</sup> In a study of morbidly obese subjects, SNPs in the adiponectin promoter gene were associated with a doubling of the risk of type 2 diabetes.<sup>65</sup>

The high prevalence of non-alcoholic fatty liver disease in obese, insulin-resistant, and diabetic subjects may, at least in part, be due to adipose tissue dysfunction. The increased flux of fatty acids and IL-6 through the portal circulation results in increased hepatic lipid accumulation. Leptin is considered to be a mediator of liver fibrosis after chronic liver injury in mouse models. However, this action of

leptin may be reduced in leptin resistance.<sup>66</sup> Substitution of adiponectin ameliorates hepatomegaly and steatosis in mouse models of fatty liver disease in part due to antagonistic effects against TNF- $\alpha$ .<sup>67</sup>

### Type 2 diabetes

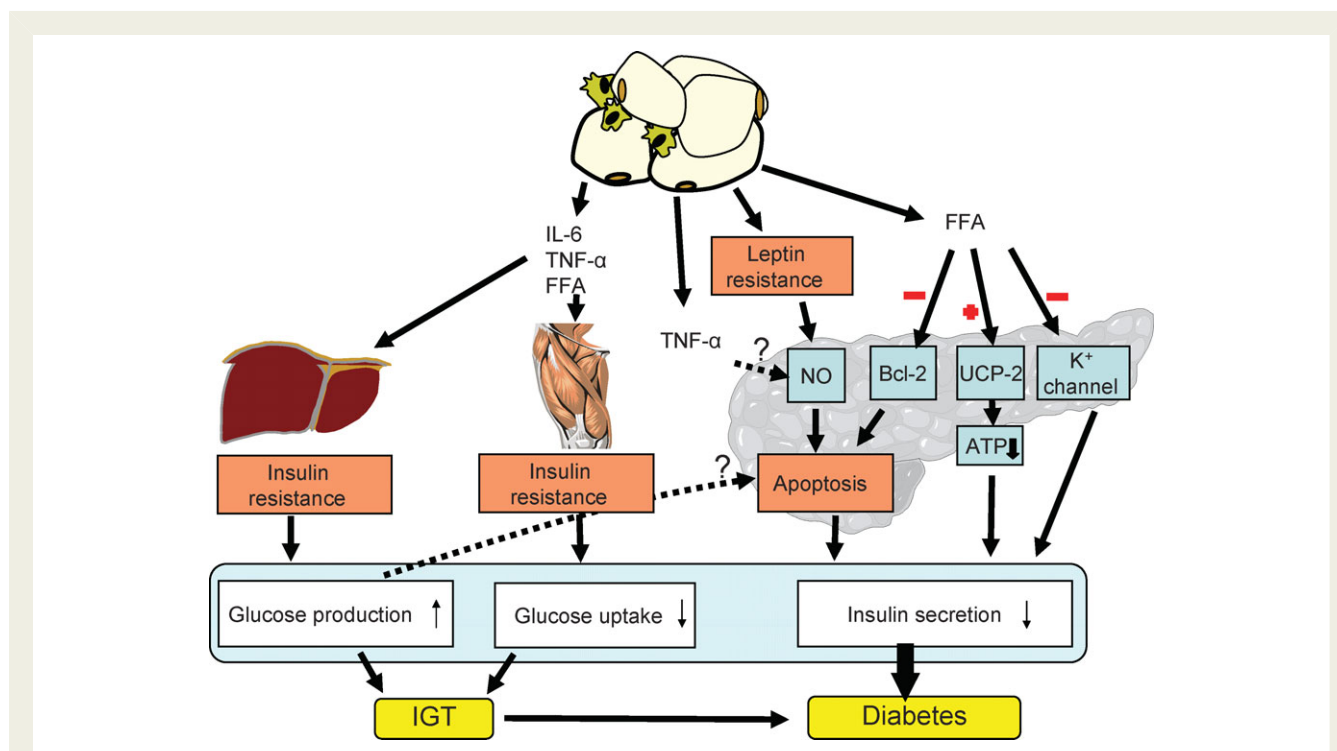
In a prospective cohort study of women, 61% of the acquired cases of type 2 diabetes could be attributed to overweight and obesity.<sup>68</sup> Already a mild increase in BMI increases the risk of type 2 diabetes: e.g. women with a BMI between 23 and 25 kg/m<sup>2</sup> have an almost three-fold increased risk of developing diabetes compared with women with a BMI below 23 kg/m<sup>2</sup>. This relative risk increases to 20 for women with BMIs  $\geq 35$ .<sup>68</sup>

Type 2 diabetes is now generally accepted to be due to a combination of insulin resistance and relatively diminished insulin secretory function of pancreatic  $\beta$ -cells.  $\beta$ -cell dysfunction is the most important risk factor for type 2 diabetes as shown in normoglycemic subjects.<sup>69,70</sup> Expansion of  $\beta$ -cell mass has been reported from pancreata of obese subjects and is related to increased intake of nutrients (glucose and FFAs). When insulin resistance increases, insulin production by pancreatic  $\beta$ -cells also increases but if this adaption fails diabetes will ensue. In most studies low adiponectin and elevated levels of other adipocytokines (e.g. leptin, TNF- $\alpha$ , IL-6) are associated with an increased risk of diabetes. This presumably relates not only to their effects on insulin sensitivity but also to their effects in the pancreas leading to  $\beta$ -cell failure<sup>60,71,72</sup> (Figure 4).

Although FFAs acutely raise insulin secretion, chronically elevated plasma FFA levels as seen in obesity inhibit secretion.<sup>73</sup> Various proposed mechanisms have been put forward. In the presence of hyperglycaemia oxidation of FFA is inhibited, resulting in accumulation of long-chain fatty-acyl-coA.<sup>73,74</sup> Long-chain fatty-acyl-CoA and FFA can open  $\beta$ -cell potassium channels which diminishes insulin secretion.<sup>73</sup> FFAs also enhance expression of uncoupling protein 2, which would diminish ATP production necessary for insulin secretion. In addition, FFA can induce  $\beta$ -cell apoptosis via an endoplasmic stress response<sup>73</sup> and by inhibiting expression of the anti-apoptotic factor Bcl-2.

Since leptin has a restraining effect on normal insulin secretion by the pancreas, it has been proposed that in obesity leptin resistance might occur in  $\beta$ -cells, thus adding to hyperinsulinaemia observed in obese subjects. Moreover, leptin's anti-apoptotic effects in  $\beta$ -cells could be diminished in the leptin-resistant state. Anti-apoptotic effects of leptin may include inhibition of nitric oxide (NO) production via reduction of triglyceride content. NO has been proposed to induce apoptosis via depletion of calcium stores in the endoplasmic reticulum (ER) leading to the ER stress response with induction of C/EBP homologue protein expression.<sup>73</sup>

TNF- $\alpha$  inhibits glucose-induced insulin secretion *in vitro* possibly via NO synthesis, which may cause damage to the insulin DNA (deoxyribonucleic acid) strand,<sup>75</sup> and may enhance apoptosis in  $\beta$ -cells via Bcl-2.<sup>76</sup> Insulin signalling in the  $\beta$ -cell via  $\beta$ -cell insulin receptors is in itself of great importance for normal insulin secretory function, and TNF- $\alpha$  is capable of inhibiting insulin signalling. However, whether these *in vitro* phenomena are of real importance for obesity-related mechanisms in type 2 diabetes is unclear since plasma TNF- $\alpha$  levels are lower than levels necessary to obtain the above effects.



**Figure 4** Adipocyte dysfunction leads to type 2 diabetes: chronically elevated free fatty acid (FFA) levels inhibit insulin secretion.<sup>73</sup> *In vitro*, long-chain fatty-acyl-CoA and FFA can open  $\beta$ -cell potassium channels which diminish insulin secretion. FFAs enhance expression of uncoupling protein 2 (UCP-2), which diminishes adenosine triphosphate production necessary for insulin secretion. FFAs can also induce  $\beta$ -cell apoptosis via an endoplasmic stress response<sup>73</sup> and by inhibiting expression of the anti-apoptotic factor Bcl-2. Leptin has been shown to have anti-apoptotic effects in  $\beta$ -cells, which may also be diminished in the (obese) leptin-resistant state. Anti-apoptotic effects of leptin include inhibition of nitric oxide (NO) production via reduction of triglyceride content. NO has been proposed to induce apoptosis via depletion of calcium stores in the endoplasmic reticulum (ER) leading to the ER stress response.<sup>73</sup> By inhibiting insulin signalling in the  $\beta$ -cell and by induction of NO synthesis, tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) may reduce insulin secretion *in vitro*. At the same time NO may cause deoxyribonucleic acid (DNA) damage enhancing  $\beta$ -cell apoptosis.<sup>76</sup>

Finally, adiponectin has no effect on normal insulin secretion, but diminishes the pro-apoptotic effects of cytokines and FFA on  $\beta$ -cells.<sup>73</sup> In the presence of insulin resistance in mice (due to high fat diet) adiponectin augments insulin secretion in response to high glucose while inhibiting insulin secretion at low glucose plasma concentrations.

## Adipose tissue dysfunction and vascular diseases

Atherosclerotic vascular disease may also be an important clinical result of adipose tissue dysfunction. Dysfunctional adipocytes contribute directly and indirectly (through insulin resistance) to the development of vascular risk factors and vascular disease.

### Adipose tissue dysfunction and common vascular risk factors

Elevated blood pressure, low plasma HDL-c (high density lipoprotein cholesterol) and elevated TG, all independent vascular risk factors, are closely associated with abdominal obesity and can often be controlled by dietary changes and weight reduction.

A growing body of evidence suggests that an activated renin-angiotensin-aldosterone system (RAS) and leptin are involved in obesity-associated hypertension by influencing the salt-fluid homeostasis and vascular tone. In obese subjects, plasma angiotensinogen (AGT) and renin concentrations are elevated and angiotensin converting enzyme (ACE) activity is increased.<sup>77</sup> Dysfunctional adipocytes of obese subjects produce AGT and angiotensin II,<sup>1</sup> contributing to systemic blood pressure levels.<sup>78</sup> Weight loss of only 5% and especially a decrease in waist circumference is associated with reduced activity of all RAS components and accompanied with a 7 mmHg decrease in blood pressure.<sup>77</sup> Remarkably, treatment with RAS inhibitors prevents or delays the development of type 2 diabetes.<sup>79</sup> Angiotensin II may impair intracellular insulin signalling similarly to TNF- $\alpha$  and FFAs leading to reduced glucose uptake and diminished adipocyte differentiation.<sup>9,80</sup> Secondly, adiponectin gene expression may be directly increased by RAS blockade, independently of body mass, as shown in essential hypertensive patients in whom ACE-inhibition and angiotensin II receptor blockers lead to improvements in insulin sensitivity without affecting adiposity.<sup>80</sup> Indeed treatment with RAS inhibitors increases plasma adiponectin levels, improves whole body insulin sensitivity and decreases adipocyte size.

Leptin-deficient subjects are normotensive despite the presence of considerable obesity.<sup>81</sup> Indeed, weight loss (resulting in decreased leptin levels) in obese subjects with hypertension by a calorie restricted diet resulted in lower blood pressure.<sup>78</sup> The concept of leptin-provoked hypertension is based on the findings that leptin upregulates  $\text{Na}^+/\text{K}^+$ -ATPase in the renal cortex and medulla.<sup>82</sup> In the brain leptin leads to an increased sympathetic nerve activity directed to the kidneys and peripheral vasculature which leads to increased heart rate and elevated blood pressure levels in mice, a response that is preserved in leptin resistance.<sup>83</sup> In addition to leptin, renal sodium reabsorption is enhanced under insulin-resistant conditions and associated hyperinsulinaemia.<sup>84</sup>

A combination of elevated plasma TG levels and decreased plasma HDL-c due to release of large quantities of FFAs and CETP by adipocytes is the typical dyslipidaemia seen in obesity and insulin resistance. The increased fasting and postprandial FFA flux into the portal circulation contributes directly to the development of insulin resistance, endothelial dysfunction, and increased VLDL-c synthesis in the liver. Elevated levels of FFAs are independently associated with an increased vascular risk<sup>85</sup> although other studies show conflicting results. CETP facilitates the cholesteryl ester transfer from HDL-c to ApoB-containing lipoproteins and the counter flux of TG resulting in elevated plasma levels of TG-rich HDL-c particles.<sup>86</sup> These TG-rich HDL-c particles are rapidly hydrolysed and cleared from the circulation resulting in low HDL-c levels.<sup>86</sup> CETP-deficient subjects have high HDL-c levels and are at low vascular risk.<sup>86</sup> However, pharmacological inhibition of CETP activity increases HDL-c plasma levels with 63% but fails to reduce progression of atherosclerosis as measured with carotid intima media thickness in patients with mixed dyslipidaemia.<sup>87</sup> Insulin resistance contributes to chronic hypertriglyceridaemia due to less suppression by insulin of HSL and a reduction in insulin-activated LPL activity, both leading to an enhanced flux of TGs from adipocytes to the liver.<sup>88</sup>

### Adipose tissue dysfunction in visceral fat and vascular disease

Waist-to-hip ratio (WHR) and waist circumference, good indicators of abdominal obesity, are more closely associated with atherosclerosis and the risk of myocardial infarction than BMI<sup>5,89</sup> noting that different cut-off values should be applied in different populations.<sup>90</sup> After controlling for cardiac risk factors, including BMI, women with a WHR of at least 0.76 were more than twice as likely to develop coronary heart disease compared with women with a WHR <0.72. Women with a WHR >0.88 were even more than three times as likely to develop coronary heart disease.<sup>91</sup> Visceral adipose tissue showed a more close relationship with inflammatory and oxidative stress biomarkers compared with the subcutaneous fat depot based on CT measurements.<sup>92</sup> Presence of metabolic syndrome is associated with lower adiponectin plasma levels; reflecting adipose tissue dysfunction<sup>22</sup> and a two- to four-times increased risk of both the development of type 2 diabetes and vascular disease.<sup>93</sup>

### Adipocytokines and vascular disease

Being solely produced by adipocytes, a low plasma adiponectin concentration is a good representative of adipocyte dysfunction.

Based on the anti-atherosclerotic properties *in vitro* adiponectin may be an important causal link between dysfunctional adipocytes and the development of vascular diseases.<sup>62,94</sup> In various populations of healthy subjects and high risk patients, low plasma levels of adiponectin are independent predictions of future vascular disease.<sup>24,95–97</sup> However, other studies of both women in a primary care setting and patients with clinical evident vascular disease show discrepant results.<sup>22,98</sup> The discrepancy may be explained by functional differences between adiponectin isoforms and their ratios in plasma.<sup>99,100</sup> The high molecular weight (HMW)-form has better correlations with insulin sensitivity in subjects with and without type 2 diabetes compared with total or LMW-adiponectin levels, suggesting that HMW-adiponectin is the most active form.<sup>99</sup> Indeed, HMW-adiponectin levels were selectively suppressed in obese patients with ischaemic heart disease and were restored after weight loss.<sup>101</sup>

Two adiponectin receptors (AdipoR1 which mainly binds globular adiponectin and AdipoR2 which predominantly binds the full-length isoforms) have been identified which differ in part in distribution and potential actions. Although both receptors are expressed throughout the body, AdipoR1 is highly present in muscle tissue while AdipoR2 is abundantly expressed on liver cells.<sup>102</sup> On human adipocytes and muscle cells both types are expressed.<sup>103</sup> In the setting of both insulin resistance and obesity the expression of these receptors is reduced enhancing insulin resistance,<sup>104</sup> while after physical training the expression of adiponectin receptors is enhanced.<sup>105</sup>

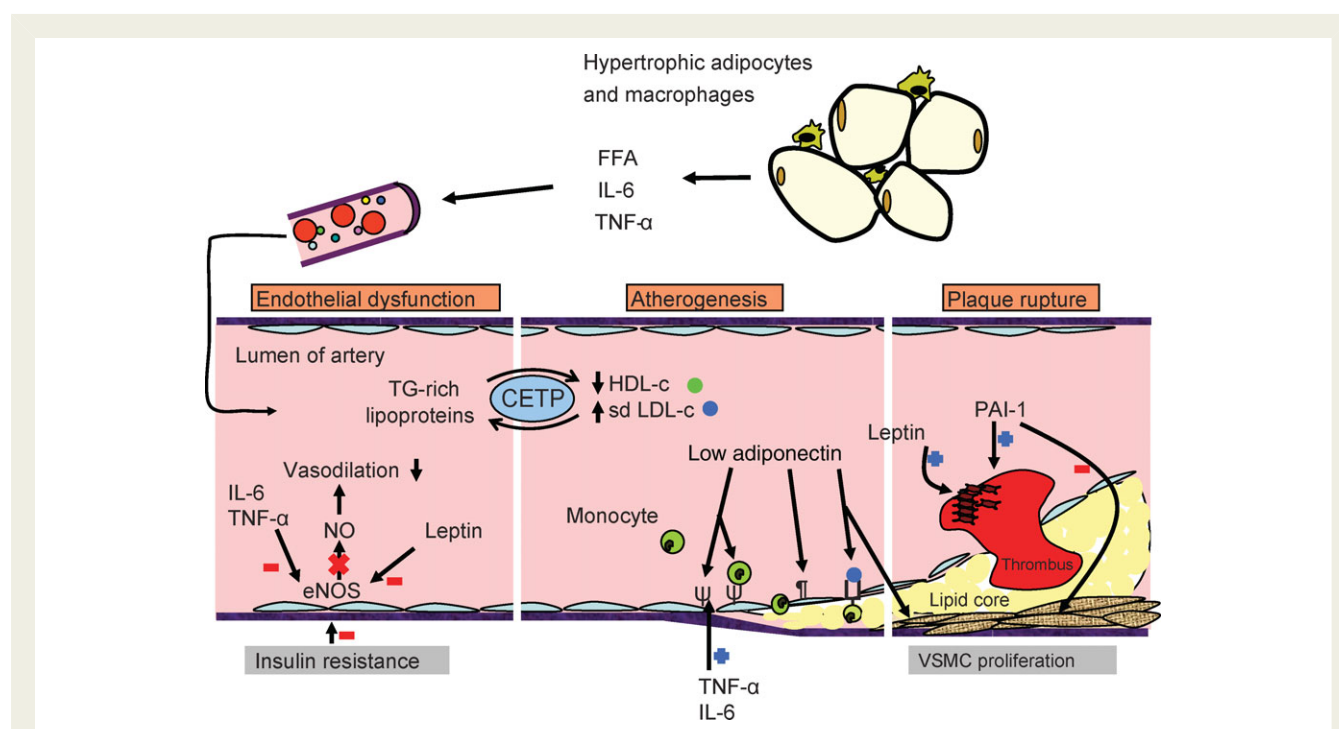
Results from prospective and Case–Control studies have pointed towards a possible contribution of coagulation factors and proteins of the fibrinolytic system in the development of vascular events.<sup>106</sup> PAI-1 is a primary regulator of fibrinolysis and is largely produced by visceral<sup>107</sup> adipocytes under influence of  $\text{TNF-}\alpha$ , insulin, FFAs and glucocorticoids *in vitro*.<sup>108</sup> Elevated plasma PAI-1 levels (due to genetic polymorphisms or to obesity) are associated with an increase in vascular risk.<sup>109,110</sup> This is due to a shift in the balance between fibrinolysis and thrombosis towards thrombosis facilitating the formation of microthrombi<sup>10</sup> and by PAI-1's ability to inhibit plasminogen-induced migration of vascular smooth muscle cells (VSMCs) resulting in plaques prone to rupture with thin fibrous caps, necrotic cores and rich in macrophages (Figure 5).

Elevated plasma levels of leptin are associated with adipocyte dysfunction, the presence of risk factors [increased BMI, CRP, LDL-c (low density lipoprotein cholesterol), and TG]<sup>111,112</sup> and increased vascular risk, although prospective studies on the relationship between leptin and vascular disease show inconsistent results. In older adults leptin was indeed associated with the extent of coronary artery calcifications however this relationship was dependent of other risk factors (blood pressure, lipid levels, and insulin resistance).<sup>113</sup>

### Interventions affecting adipose tissue function

Increasing physical activity and weight reduction are two important lifestyle changes to reduce insulin resistance and visceral obesity





**Figure 5** Adipocyte dysfunction leads to atherosclerosis (trident mark: ICAM-1, paragraph mark: vascular cell adhesion molecule-1, beaker symbol: scavenger receptor class A-1; platelets). Elevated levels of interleukin-6 (IL-6), tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ), and presence of insulin resistance lead to a decrease in production and availability of endothelial nitric oxide synthase resulting in endothelial dysfunction. Increased adipocyte-derived cholesteryl ester transfer protein (CETP) plasma concentrations lead to lower levels of high density lipoprotein cholesterol (HDL-c) and an increased number of small dense low density lipoprotein cholesterol (sdLDL-c) particles. Adiponectin has inhibitory effects on the development of atherosclerosis by inhibiting the expression of adhesion molecules [intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1] (induced by IL-6 and TNF- $\alpha$ ) on endothelial cells by activating 5'AMP-activated protein kinase (AMPK) (*in vitro*), by inhibiting NF- $\kappa$ B and by the inhibition of scavenger receptor class A-1. The latter leads to reduction of cholesterol uptake in macrophages and to transformation of macrophages into foam cells.<sup>94</sup> Furthermore, adiponectin reduces vascular smooth muscle cell proliferation (VSMCs), migration and apoptosis by attenuating DNA synthesis inducing effects of growth factors including platelet-derived growth factor and fibroblast growth factor.<sup>62</sup> Increased levels of plasminogen activator inhibitor-1 (PAI-1) can inhibit plasminogen-induced migration of VSMCs leading to plaques prone to rupture with thin fibrous caps, necrotic cores and rich in macrophages. Leptin is capable to induce ADP-dependent platelet activity and aggregation in healthy subjects.

(mainly by decreasing the size of existing adipocytes) and are therefore central in modifying adipose tissue dysfunction. After 12 weeks of restricted caloric intake and increased exercise TNF- $\alpha$ , leptin, and IL-6 levels decreased while anti-inflammatory cytokines (adiponectin and IL-10) were significantly increased in obese subjects with metabolic risk factors.<sup>114</sup> Even before weight reduction, insulin sensitivity improved and adiponectin plasma levels increased suggesting that adipocyte function has improved.<sup>115,116</sup> However, changes in lifestyle are difficult to achieve and to maintain in clinical practice, but are required for a constant improvement of a patient's metabolic profile.<sup>117</sup> Statins have anti-inflammatory properties which may point towards an influence of statins on adipocyte function.<sup>118</sup> Nevertheless, short-term treatment with simvastatin and ezetimibe alone or in combination did not result in changes in adiponectin, leptin, and resistin levels in healthy subjects and obese patients with metabolic syndrome.<sup>119,120</sup> Moreover, lower (instead of higher) levels of adiponectin have been observed after simvastatin treatment in patients with manifest vascular diseases.<sup>121</sup> In large randomized statin trials a lower incidence of type 2 diabetes has been observed in

patients on a statin compared with the placebo group.<sup>122</sup> The underlying mechanism is unclear, since insulin sensitivity and adiponectin levels did not improve after 9 weeks of simvastatin treatment in subjects with metabolic syndrome.<sup>123</sup>

Fibrates, which act as agonists of PPAR- $\alpha$ , stimulate cellular fatty acid uptake, and  $\beta$ -oxidation pathways predominantly in liver, kidney, heart, and muscle. Recent research shows that PPAR- $\alpha$  may also be involved in adipocyte gene regulation specific for fatty acid metabolism.<sup>124</sup> Combined with a reduction in fatty acid and triglyceride synthesis, a decrease in VLDL production is observed.<sup>125</sup>

TZDs are ligands of the nuclear transcription factor PPAR- $\gamma$  and have been shown to regulate the expression of numerous genes affecting glycemic control, lipid metabolism, and inflammation in (pre-) adipocytes. TZDs improve insulin sensitivity in type 2 diabetes patients and are proposed to have favourable effects on other metabolic alterations seen in metabolic syndrome and adipocyte dysfunction. Although currently available TZDs (rosiglitazone and pioglitazone) have similar effects on insulin action, they differ in their effects in the occurrence of vascular events and carotid artery

intima-media thickening in patients with type 2 diabetes<sup>126</sup>. In patients with abdominal obesity there is evidence that the endocannabinoid system is hyperactive leading to increased food intake and weight gain; offering a new therapeutic option.<sup>127,128</sup> Rimonabant is an antagonist of the endocannabinoid-1 receptor (CB1), a receptor present on cells of the central nervous system, the liver, and adipocytes. Treatment with rimonabant leads to reduction in body weight and waist circumference, and a 15% reduction in plasma TG and a 25% increase in HDL-c levels have been reported<sup>128</sup>. Adiponectin, as a marker of adipose tissue dysfunction, increased 58% when compared with that at the start of the treatment. This increase may not only be explained by changes in body weight, leaving the suggestion that direct CB1 receptor blockade in adipocytes results in changes in adipocytes function.<sup>128</sup>

## Conclusions

The classical perception of adipose tissue as a storage depot of FFAs has now been replaced by the notion that adipose tissue is an active endocrine organ playing a central role in lipid and glucose metabolism and produces a large number of hormones and cytokines involved in the development of metabolic syndrome, diabetes mellitus, and vascular diseases. As adipose tissue expands, macrophages infiltrate adipose tissue and the production of adipocytokines involved in glucose and lipid metabolism and in hemostasis and inflammation increases, except for the production of adiponectin which decreases. In daily clinical practice, the concept of adipocyte dysfunction may provide a pathophysiological framework for understanding the clustering of vascular risk in close relation to abdominal obesity and insulin resistance in individual patients. The concept of adipose tissue dysfunction may raise awareness among patients and physicians on the importance of abdominal obesity in vascular risk and risk of developing type 2 diabetes mellitus. Weight reduction and increasing physical activity are effective interventions for improving adipose tissue function. Further knowledge of the underpinnings of adipose tissue dysfunction may provide new targets for drug development for the management of obesity and prevention of vascular diseases and type 2 diabetes mellitus.

**Conflict of interest:** none declared.

## References

- Engeli S, Gorzelniak K, Kreutz R, Runkel N, Distler A, Sharma AM. Co-expression of renin-angiotensin system genes in human adipose tissue. *J Hypertens* 1999;**17**:555–560.
- Scherer PE, Williams S, Fogliano M, Baldini G, Lodish HF. A novel serum protein similar to C1q, produced exclusively in adipocytes. *J Biol Chem* 1995;**270**:26746–26749.
- Winkler G, Kiss S, Keszhelyi L, Sapi Z, Ory I, Salamon F, Kovacs M, Vargha P, Szekeres O, Speer G, Karadi I, Sikter M, Kaszas E, Dworak O, Gero G, Cseh K. Expression of tumor necrosis factor (TNF)-alpha protein in the subcutaneous and visceral adipose tissue in correlation with adipocyte cell volume, serum TNF-alpha, soluble serum TNF-receptor-2 concentrations and C-peptide level. *Eur J Endocrinol* 2003;**149**:129–135.
- Ford ES. Prevalence of the metabolic syndrome defined by the International Diabetes Federation among adults in the U.S. *Diabetes Care* 2005;**28**:2745–2749.
- Yusuf S, Hawken S, Ounpuu S, Bautista L, Franzosi MG, Commerford P, Lang CC, Rumboldt Z, Onen CL, Lisheng L, Tanomsup S, Wangai P Jr, Razak F, Sharma AM, Anand SS, INTERHEART Study Investigators. Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: a case-control study. *Lancet* 2005;**366**:1640–1649.
- Executive summary of the third report of The National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *JAMA* 2001;**285**:2486–2497.
- Otto TC, Lane MD. Adipose development: from stem cell to adipocyte. *Crit Rev Biochem Mol Biol* 2005;**40**:229–242.
- Yamauchi T, Kamon J, Waki H, Terauchi Y, Kubota N, Hara K, Mori Y, Ide T, Murakami K, Tsuboyama-Kasaoka N, Ezaki O, Akanuma Y, Gavrilova O, Vinson C, Reitman ML, Kagechika H, Shudo K, Yoda M, Nakano Y, Tobe K, Nagai R, Kimura S, Tomita M, Froguel P, Kadowaki T. The fat-derived hormone adiponectin reverses insulin resistance associated with both lipodystrophy and obesity. *Nat Med* 2001;**7**:941–946.
- Ran J, Hirano T, Fukui T, Saito K, Kageyama H, Okada K, Adachi M. Angiotensin II infusion decreases plasma adiponectin level via its type 1 receptor in rats: an implication for hypertension-related insulin resistance. *Metabolism* 2006;**55**:478–488.
- Chu NF, Spiegelman D, Hotamisligil GS, Rifai N, Stampfer M, Rimm EB. Plasma insulin, leptin, and soluble TNF receptors levels in relation to obesity-related atherogenic and thrombotic cardiovascular disease risk factors among men. *Atherosclerosis* 2001;**157**:495–503.
- Wannamethee SG, Lowe GD, Rumley A, Lynne CL, Whincup PH, Sattar N. Adipokines and risk of type 2 diabetes in older men. *Diabetes Care* 2007;**30**:1200–1205.
- Skurk T, Alberti-Huber C, Herder C, Hauner H. Relationship between adipocyte size and adipokine expression and secretion. *J Clin Endocrinol Metab* 2007;**92**:1023–1033.
- Barak Y, Nelson MC, Ong ES, Jones YZ, Ruiz-Lozano P, Chien KR, Koder A, Evans RM. PPAR gamma is required for placental, cardiac, and adipose tissue development. *Mol Cell* 1999;**4**:585–595.
- Farooqi IS, Jebb SA, Langmack G, Lawrence E, Cheetham CH, Prentice AM, Hughes IA, McCamish MA, O'Rahilly S. Effects of recombinant leptin therapy in a child with congenital leptin deficiency. *N Engl J Med* 1999;**341**:879–884.
- Schwartz MW, Woods SC, Porte D Jr, Seeley RJ, Baskin DG. Central nervous system control of food intake. *Nature* 2000;**404**:661–671.
- Considine RV, Sinha MK, Heiman ML, Kriauciunas A, Stephens TW, Nyce MR, Ohannesian JP, Marco CC, McKee LJ, Bauer TL. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. *N Engl J Med* 1996;**334**:292–295.
- Saladin R, De Vos P, Guerre-Millo M, Leturque A, Girard J, Staels B, Auwerx J. Transient increase in obese gene expression after food intake or insulin administration. *Nature* 1995;**377**:527–529.
- Zhang HH, Kumar S, Barnett AH, Eggo MC. Tumour necrosis factor-alpha exerts dual effects on human adipose leptin synthesis and release. *Mol Cell Endocrinol* 2000;**159**:79–88.
- Cheung CC, Clifton DK, Steiner RA. Proopiomelanocortin neurons are direct targets for leptin in the hypothalamus. *Endocrinology* 1997;**138**:4489–4492.
- Long YC, Zierath JR. AMP-activated protein kinase signaling in metabolic regulation. *J Clin Invest* 2006;**116**:1776–1783.
- Holtkamp K, Herpertz-Dahlmann B, Mika C, Heer M, Heussen N, Fichter M, Herpertz S, Senf W, Blum WF, Schweiger U, Warnke A, Ballauff A, Remschmidt H, Hebebrand J. Elevated physical activity and low leptin levels co-occur in patients with anorexia nervosa. *J Clin Endocrinol Metab* 2003;**88**:5169–5174.
- Hajer GR, van der Graaf Y, Olijhoek JK, Edlinger M, Visseren FLJ. Low plasma levels of adiponectin are associated with low risk for future cardiovascular events in patients with clinical evident vascular disease. *Am Heart J* 2007;**154**:750.e1–7.
- Lindsay RS, Funahashi T, Hanson RL, Matsuzawa Y, Tanaka S, Tataranni PA, Knowler WC, Krakoff J. Adiponectin and development of type 2 diabetes in the Pima Indian population. *Lancet* 2002;**360**:57–58.
- Wolk R, Berger P, Lennon RJ, Brilakis ES, Davison DE, Somers VK. Association between plasma adiponectin levels and unstable coronary syndromes. *Eur Heart J* 2007;**28**:292–298.
- Kadowaki T, Yamauchi T. Adiponectin and adiponectin receptors. *Endocr Rev* 2005;**26**:439–451.
- Wallenius V, Wallenius K, Ahren B, Rudling M, Carlsten H, Dickson SL, Ohlsson C, Jansson JO. Interleukin-6-deficient mice develop mature-onset obesity. *Nat Med* 2002;**8**:75–79.
- Tsigos C, Papanicolaou DA, Kyrou I, Defensor R, Mitsiadis CS, Chrousos GP. Dose-dependent effects of recombinant human interleukin-6 on glucose regulation. *J Clin Endocrinol Metab* 1997;**82**:4167–4170.
- Rega G, Kaun C, Demyanets S, Pfaffenberger S, Rychli K, Hohensinner PJ, Kastl SP, Speidl WS, Weiss TW, Breuss JM, Furnkranz A, Uhrin P, Zaujec J,

- Zilberfarb V, Frey M, Roehle R, Maurer G, Huber K, Wojta J. Vascular endothelial growth factor is induced by the inflammatory cytokines interleukin-6 and oncostatin m in human adipose tissue in vitro and in murine adipose tissue in vivo. *Arterioscler Thromb Vasc Biol* 2007;**27**:1587–1595.
29. Gabrielson BG, Johansson JM, Lönn M, Jernäs M, Olbers T, Peltonen M, Larsson I, Lönn L, Sjöström L, Carlsson B, Carlsson LM. High expression of complement components in omental adipose tissue in obese men. *Obes Res* 2003;**11**:699–1708.
30. Dusserre E, Moulin P, Vidal H. Differences in mRNA expression of the proteins secreted by the adipocytes in human subcutaneous and visceral adipose tissues. *Biochim Biophys Acta* 2000;**1500**:88–96.
31. Fontana L, Eagon JC, Trujillo ME, Scherer PE, Klein S. Visceral fat adipokine secretion is associated with systemic inflammation in obese humans. *Diabetes* 2007;**56**:1010–1013.
32. Cancello R, Tordjman J, Poitou C, Guilhem G, Bouillot JL, Hugol D, Coussieu C, Basdevant A, Bar Hen A, Bedossa P, Guerre-Millo M, Clément K. Increased infiltration of macrophages in omental adipose tissue is associated with marked hepatic lesions in morbid human obesity. *Diabetes* 2006;**55**:1554–1561.
33. Navasa M, Gordon DA, Hariharan N, Jamil H, Shigenaga JK, Moser A, Fiers W, Pollock A, Grunfeld C, Feingold KR. Regulation of microsomal triglyceride transfer protein mRNA expression by endotoxin and cytokines. *J Lipid Res* 1998;**39**:1220–1230.
34. Tankó LB, Bruun JM, Alexandersen P, Bagger YZ, Richelsen B, Christiansen C, Larsen PJ. Novel associations between bioavailable estradiol and adipokines in elderly women with different phenotypes of obesity: implications for atherogenesis. *Circulation* 2004;**110**:2246–2252.
35. Motoshima H, Wu X, Sinha MK, Hardy VE, Rosato EL, Barbot DJ, Rosato FE, Goldstein BJ. Differential regulation of adiponectin secretion from cultured human omental and subcutaneous adipocytes: effects of insulin and rosiglitazone. *J Clin Endocrinol Metab* 2002;**87**:5662–5667.
36. Kreier F, Fliers E, Voshol PJ, Van Eden CG, Havekes LM, Kalsbeek A, Van Heijningen CL, Sluiter AA, Mettenleiter TC, Romijn JA, Sauerwein HP, Buijs RM. Selective parasymphathetic innervation of subcutaneous and intra-abdominal fat—functional implications. *J Clin Invest* 2002;**110**:1243–1250.
37. Shimomura I, Shimano H, Korn BS, Bashmakov Y, Horton JD. Nuclear sterol regulatory element-binding proteins activate genes responsible for the entire program of unsaturated fatty acid biosynthesis in transgenic mouse liver. *J Biol Chem* 1998;**273**:35299–35306.
38. Vidal-Puig A, Jimenez-Liñan M, Lowell BB, Hamann A, Hu E, Spiegelman B, Flier JS, Moller DE. Regulation of PPAR gamma gene expression by nutrition and obesity in rodents. *J Clin Invest* 1996;**97**:2553–2561.
39. de Souza CJ, Eckhardt M, Gagen K, Dong M, Chen W, Laurent D, Burkey BF. Effects of pioglitazone on adipose tissue remodeling within the setting of obesity and insulin resistance. *Diabetes* 2001;**50**:1863–1871.
40. Kim JB, Spiegelman BM. ADD1/SREBP1 promotes adipocyte differentiation and gene expression linked to fatty acid metabolism. *Genes Dev* 1996;**10**:1096–1107.
41. Ross R. Atherosclerosis – an inflammatory disease. *N Engl J Med* 1999;**340**:115–126.
42. Iacobellis G, Ribaldo MC, Zappaterreno A, Iannucci CV, Leonetti F. Prevalence of uncomplicated obesity in an Italian obese population. *Obes Res* 2005;**13**:1116–1122.
43. Lumeng CN, Bodzin JL, Saltiel AR. Obesity induces a phenotypic switch in adipose tissue macrophage polarization. *J Clin Invest* 2007;**117**:175–184.
44. Gordon S, Taylor PR. Monocyte and macrophage heterogeneity. *Nat Rev Immunol* 2005;**5**:953–964.
45. Cancello R, Henegar C, Viguier N, Taleb S, Poitou C, Rouault C, Coupaye M, Pelloux V, Hugol D, Bouillot JL, Bouloumié A, Barbatelli G, Cinti S, Svensson PA, Barsh GS, Zucker JD, Basdevant A, Langin D, Clément K. Reduction of macrophage infiltration and chemoattractant gene expression changes in white adipose tissue of morbidly obese subjects after surgery-induced weight loss. *Diabetes* 2005;**54**:2277–2286.
46. Suganami T, Nishida J, Ogawa Y. A paracrine loop between adipocytes and macrophages aggravates inflammatory changes: role of free fatty acids and tumor necrosis factor alpha. *Arterioscler Thromb Vasc Biol* 2005;**25**:2062–2068.
47. Suganami T, Tanimoto-Koyama K, Nishida J, Itoh M, Yuan X, Mizurari S, Kotani H, Yamaoka S, Miyake K, Aoe S, Kamei Y, Ogawa Y. Role of the Toll-like receptor 4/NF-kappaB pathway in saturated fatty acid-induced inflammatory changes in the interaction between adipocytes and macrophages. *Arterioscler Thromb Vasc Biol* 2007;**27**:84–91.
48. Permana PA, Menge C, Reaven PD. Macrophage-secreted factors induce adipocyte inflammation and insulin resistance. *Biochem Biophys Res Commun* 2006;**341**:507–514.
49. Ruan H, Hacohen N, Golub TR, Van Parijs L, Lodish HF. Tumor necrosis factor-alpha suppresses adipocyte-specific genes and activates expression of preadipocyte genes in 3T3-L1 adipocytes: nuclear factor-kappaB activation by TNF-alpha is obligatory. *Diabetes* 2002;**51**:1319–1336.
50. Lee JY, Sohn KH, Rhee SH, Hwang D. Saturated fatty acids, but not unsaturated fatty acids, induce the expression of cyclooxygenase-2 mediated through Toll-like receptor 4. *J Biol Chem* 2001;**276**:16683–16689.
51. Crandall DL, Hausman GJ, Kral JG. A review of the microcirculation of adipose tissue: anatomic, metabolic, and angiogenic perspectives. *Microcirculation* 1997;**4**:211–232.
52. Rupnick MA, Panigrahy D, Zhang CY, Dallabrida SM, Lowell BB, Langer R, Folkman MJ. Adipose tissue mass can be regulated through the vasculature. *Proc Natl Acad Sci USA* 2002;**99**:10730–10735. Epub Jul 29, 2002.
53. Bell LN, Cai L, Johnstone BH, Traktuev DO, March KL, Considine RV. A central role for hepatocyte growth factor in adipose tissue angiogenesis. *Am J Physiol Endocrinol Metab* 2008;**294**:E336–E344.
54. Brahimi-Horn MC, Pouyssegur J. Oxygen, a source of life and stress. *FEBS Lett* 2007;**581**:3582–3591.
55. Hosogai N, Fukuhara A, Oshima K, Miyata Y, Tanaka S, Segawa K, Furukawa S, Tochino Y, Komuro R, Matsuda M, Shimomura I. Adipose tissue hypoxia in obesity and its impact on adipocytokine dysregulation. *Diabetes* 2007;**56**:901–911.
56. Chen B, Lam KS, Wang Y, Wu D, Lam MC, Shen J, Wong L, Hoo RL, Zhang J, Xu A. Hypoxia dysregulates the production of adiponectin and plasminogen activator inhibitor-1 independent of reactive oxygen species in adipocytes. *Biochem Biophys Res Commun* 2006;**341**:549–556.
57. Flachs P, Mohamed-Ali V, Horakova O, Rossmeisl M, Hosseinzadeh-Attar MJ, Hensler M, Ruzickova J, Kopecky J. Polyunsaturated fatty acids of marine origin induce adiponectin in mice fed a high-fat diet. *Diabetologia* 2006;**49**:394–397.
58. Von Schacky C. Omega-3 fatty acids and cardiovascular disease. *Curr Opin Clin Nutr Metab Care* 2007;**10**:129–135.
59. Munzberg H, Myers MG Jr. Molecular and anatomical determinants of central leptin resistance. *Nat Neurosci* 2005;**8**:566–570.
60. Baskin DG, Figlewicz LD, Seeley RJ, Woods SC, Porte D Jr, Schwartz MW. Insulin and leptin: dual adiposity signals to the brain for the regulation of food intake and body weight. *Brain Res* 1999;**848**:114–123.
61. Hotamisligil GS, Arner P, Caro JF, Atkinson RL, Spiegelman BM. Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance. *J Clin Invest* 1995;**95**:2409–2415.
62. Goldstein BJ, Scalia R. Adiponectin: A novel adipokine linking adipocytes and vascular function. *J Clin Endocrinol Metab* 2004;**89**:2563–2568.
63. Filippi E, Sentinelli F, Romeo S, Arca M, Berni A, Tiberti C, Verrienti A, Fanelli M, Fallarino M, Sorropago G, Baroni MG. The adiponectin gene SNP+276G>T associates with early-onset coronary artery disease and with lower levels of adiponectin in younger coronary artery disease patients (age <or=50 years). *J Mol Med* 2005;**83**:711–719.
64. Vasseur F, Helbecque N, Dina C, Lobbens S, Delannoy V, Gaget S, Boutin P, Vaxillaire M, Leprêtre F, Dupont S, Hara K, Clément K, Bihain B, Kadowaki T, Froguel P. Single-nucleotide polymorphism haplotypes in the both proximal promoter and exon 3 of the APM1 gene modulate adipocyte-secreted adiponectin hormone levels and contribute to the genetic risk for type 2 diabetes in French Caucasians. *Hum Mol Genet* 2002;**11**:2607–2614.
65. Vasseur F, Helbecque N, Lobbens S, Vasseur-Delannoy V, Dina C, Clément K, Boutin P, Kadowaki T, Scherer PE, Froguel P. Hypoadiponectinaemia and high risk of type 2 diabetes are associated with adiponectin-encoding (ACDC) gene promoter variants in morbid obesity: evidence for a role of ACDC in diabetes. *Diabetologia* 2005;**48**:892–899.
66. Leclercq IA, Farrell GC, Schriemer R, Robertson GR. Leptin is essential for the hepatic fibrogenic response to chronic liver injury. *J Hepatol* 2002;**37**:206–213.
67. Xu A, Wang Y, Keshaw H, Xu LY, Lam KS, Cooper GJ. The fat-derived hormone adiponectin alleviates alcoholic and nonalcoholic fatty liver diseases in mice. *J Clin Invest* 2003;**112**:91–100.
68. Hu FB, Manson JE, Stampfer MJ, Colditz G, Liu S, Solomon CG, Willett WC. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. *N Engl J Med* 2001;**345**:790–797.
69. Lillioja S, Mott DM, Spraul M, Ferraro R, Foley JE, Ravussin E, Knowler WC, Bennett PH, Bogardus C. Insulin resistance and insulin secretory dysfunction as precursors of non-insulin-dependent diabetes mellitus. Prospective studies of Pima Indians. *N Engl J Med* 1993;**329**:1988–1992.
70. Weyer C, Bogardus C, Mott DM, Pratley RE. The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. *J Clin Invest* 1999;**104**:787–794.
71. Morioka T, Asilmaz E, Hu J, Dishinger JF, Kurpad AJ, Elias CF, Li H, Elmquist JK, Kennedy RT, Kulkarni RN. Disruption of leptin receptor expression in the pancreas directly affects beta cell growth and function in mice. *J Clin Invest* 2007;**117**:2860–2868.

72. Rakatzi I, Mueller H, Ritzeler O, Tennagels N, Eckel J. Adiponectin counteracts cytokine- and fatty acid-induced apoptosis in the pancreatic beta-cell line INS-1. *Diabetologia* 2004;**47**:249–258.
73. Zhao YF, Feng DD, Chen C. Contribution of adipocyte-derived factors to beta-cell dysfunction in diabetes. *Int J Biochem Cell Biol* 2006;**38**:804–819.
74. Nolan CJ, Madiraju MS, Delghingaro-Augusto V, Peyot ML, Prentki M. Fatty acid signaling in the beta-cell and insulin secretion. *Diabetes* 2006;**55**(Suppl. 2): S16–S23.
75. Dunger A, Cunningham JM, Delaney CA, Lowe JE, Green MH, Bone AJ, Green IC. Tumor necrosis factor-alpha and interferon-gamma inhibit insulin secretion and cause DNA damage in unweaned-rat islets. Extent of nitric oxide involvement. *Diabetes* 1996;**45**:183–189.
76. Rabinovitch A, Suarez-Pinzon W, Strynadka K, Ju Q, Edelstein D, Brownlee M, Korbitt GS, Rajotte RV. Transfection of human pancreatic islets with an anti-apoptotic gene (bcl-2) protects beta-cells from cytokine-induced destruction. *Diabetes* 1999;**48**:1223–1229.
77. Engeli S, Böhnke J, Gorzelnik K, Janke J, Schling P, Bader M, Luft FC, Sharma AM. Weight loss and the renin-angiotensin-aldosterone system. *Hypertension* 2005;**45**:356–362.
78. Massiera F, Bloch-Faure M, Ceiler D, Murakami K, Fukamizu A, Gasc JM, Quignard-Boulangé A, Negrel R, Ailhaud G, Seydoux J, Meneton P, Teboul M. Adipose angiotensinogen is involved in adipose tissue growth and blood pressure regulation. *FASEB J* 2001;**15**:2727–2729.
79. Andraws R, Brown DL. Effect of inhibition of the renin-angiotensin system on development of type 2 diabetes mellitus (meta-analysis of randomized trials). *Am J Cardiol* 2007;**99**:1006–1012.
80. Furuhashi M, Ura N, Takizawa H, Yoshida D, Moniwa N, Murakami H, Higashiura K, Shimamoto K. Blockade of the renin-angiotensin system increases adiponectin concentrations in patients with essential hypertension. *Hypertension* 2003;**42**:76–81.
81. Ozata M, Ozdemir IC, Licinio J. Human leptin deficiency caused by a missense mutation: multiple endocrine defects, decreased sympathetic tone, and immune system dysfunction indicate new targets for leptin action, greater central than peripheral resistance to the effects of leptin, and spontaneous correction of leptin-mediated defects. *J Clin Endocrinol Metab* 1999;**84**:3686–3695.
82. Beltowski J, Jamroz-Wisniewska A, Borkowska E, Wojcicka G. Up-regulation of renal Na<sup>+</sup>, K<sup>+</sup>-ATPase: the possible novel mechanism of leptin-induced hypertension. *Pol J Pharmacol* 2004;**56**:213–222.
83. Rahmouni K, Morgan DA, Morgan GM, Mark AL, Haynes WG. Role of selective leptin resistance in diet-induced obesity hypertension. *Diabetes* 2005;**54**: 2012–2018.
84. Strazzullo P, Barbato A, Galletti F, Barba G, Siani A, Iacone R, D'Elia L, Russo O, Versiero M, Farinano E, Cappuccio FP. Abnormalities of renal sodium handling in the metabolic syndrome. Results of the Olivetti Heart Study. *J Hypertens* 2006;**24**:1633–1639.
85. Miller M, Seidler A, Moalemi A, Pearson TA. Normal triglyceride levels and coronary artery disease events: the Baltimore Coronary Observational Long-Term Study. *J Am Coll Cardiol* 1998;**31**:1252–1257.
86. Barter PJ, Kastelein JJ. Targeting cholesteryl ester transfer protein for the prevention and management of cardiovascular disease. *J Am Coll Cardiol* 2006;**47**: 492–499.
87. Bots ML, Visseren FL, Evans GW, Riley WA, Revkin JH, Tegeler CH, Shear CL, Duggan WT, Vicari RM, Grobbee DE, Kastelein JJ RADIANCE 2 Investigators. Torcetrapib and progression of carotid intima-media thickness in mixed dyslipidemia. The RADIANCE II study. *Lancet* 2007;**370**:153–160.
88. Eckel RH, Yost TJ, Jensen DR. Alterations in lipoprotein lipase in insulin resistance. *Int J Obes Relat Metab Disord* 1995;**19**(Suppl. 1):S16–S21.
89. See R, Abdullah SM, McGuire DK, Khera A, Patel MJ, Lindsey JB, Grundy SM, de Lemos JA. The association of differing measures of overweight and obesity with prevalent atherosclerosis: the Dallas Heart Study. *J Am Coll Cardiol* 2007;**50**: 752–759.
90. Li R, Lu W, Jia J, Zhang S, Shi L, Li Y, Yang Q, Kan H. Relationships between indices of obesity and its cardiovascular comorbidities in a Chinese population. *Circ J* 2008;**72**:973–978.
91. Rexrode KM, Carey VJ, Hennekens CH, Walters EE, Colditz GA, Stampfer MJ, Willett WC, Manson JE. Abdominal adiposity and coronary heart disease in women. *JAMA* 1998;**280**:1843–1848.
92. Pou KM, Massaro JM, Hoffmann U, Vasan RS, Maurovich-Horvat P, Larson MG, Keaney JF Jr, Meigs JB, Lipinska I, Kathiresan S, Murabito JM, O'Donnell CJ, Benjamin EJ, Fox CS. Visceral and subcutaneous adipose tissue volumes are cross-sectionally related to markers of inflammation and oxidative stress: the Framingham Heart Study. *Circulation* 2007;**116**:1234–1241.
93. Isomaa B, Almgren P, Tuomi T, Forsén B, Lahti K, Nissén M, Taskinen MR, Groop L. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 2001;**24**:683–689.
94. Hopkins TA, Ouchi N, Shibata R, Walsh K. Adiponectin actions in the cardiovascular system. *Cardiovasc Res* 2007;**74**:11–18.
95. Bouhali T, Brisson D, St-Pierre J, Tremblay G, Perron P, Laprise C, Vohl MC, Vissers MN, Hutten BA, Després JP, Kastelein JJ, Gaudet D. Low plasma adiponectin exacerbates the risk of premature coronary artery disease in familial hypercholesterolemia. *Atherosclerosis* 2006. Epub 22 November 2006.
96. Chen MP, Tsai JC, Chung FM, Yang SS, Hsing LL, Shin SJ, Lee YJ. Hypoadiponectinemia is associated with ischemic cerebrovascular disease. *Arterioscler Thromb Vasc Biol* 2005;**25**:821–826.
97. Pischon T, Girman CJ, Hotamisligil GS, Rifai N, Hu FB, Rimm EB. Plasma adiponectin levels and risk of myocardial infarction in men. *JAMA* 2004;**291**: 1730–1737.
98. Sattar N, Wannamethee G, Sarwar N, Tchernova J, Cherry L, Wallace AM, Danesh J, Whincup PH. Adiponectin and coronary heart disease: a prospective study and meta-analysis. *Circulation* 2006;**114**:623–629.
99. Lara-Castro C, Luo N, Wallace P, Klein RL, Garvey WT. Adiponectin multimeric complexes and the metabolic syndrome trait cluster. *Diabetes* 2006;**55**:249–249.
100. Yamauchi T, Kamon J, Minokoshi Y, Ito Y, Waki H, Uchida S, Yamashita S, Noda M, Kita S, Ueki K, Eto K, Akanuma Y, Froguel P, Foufelle F, Ferre P, Carling D, Kimura S, Nagai R, Kahn BB, Kadowaki T. Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. *Nat Med* 2002;**8**:1288–1295.
101. Kobayashi H, Ouchi N, Kihara S, Walsh K, Kumada M, Abe Y, Funahashi T, Matsuzawa Y. Selective suppression of endothelial cell apoptosis by the high molecular weight form of adiponectin. *Circ Res* 2004;**94**:e27–e31.
102. Yamauchi T, Kamon J, Ito Y, Tsuchida A, Yokomizo T, Kita S, Sugiyama T, Miyagishi M, Hara K, Tsunoda M, Murakami K, Ohnishi T, Uchida S, Takekawa S, Waki H, Tsuno NH, Shibata Y, Terauchi Y, Froguel P, Tobe K, Koyasu S, Taira K, Kitamura T, Shimizu T, Nagai R, Kadowaki T. Cloning of adiponectin receptors that mediate antidiabetic metabolic effects. *Nature* 2003;**423**: 762–769.
103. Rasmussen MS, Lihn AS, Pedersen SB, Bruun JM, Rasmussen M, Richelsen B. Adiponectin receptors in human adipose tissue: effects of obesity, weight loss, and fat depots. *Obesity* 2006;**14**:28–35.
104. Tsuchida A, Yamauchi T, Ito Y, Hada Y, Maki T, Takekawa S, Kamon J, Kobayashi M, Suzuki R, Hara K, Kubota N, Terauchi Y, Froguel P, Nakae J, Kasuga M, Accili D, Tobe K, Ueki K, Nagai R, Kadowaki T. Insulin/Foxo1 pathway regulates expression levels of adiponectin receptors and adiponectin sensitivity. *J Biol Chem* 2004;**279**:30817–30822.
105. Blüher M, Williams CJ, Klötting N, Hsi A, Ruschke K, Oberbach A, Fasshauer M, Berndt J, Schön MR, Wolk A, Stumvoll M, Mantzoros CS. Gene expression of adiponectin receptors in human visceral and subcutaneous adipose tissue is related to insulin resistance and metabolic parameters and is altered in response to physical training. *Diabetes Care* 2007;**30**:3110–3115.
106. Kohler HP, Grant PJ. Plasminogen-activator inhibitor type 1 and coronary artery disease. *N Engl J Med* 2000;**342**:1792–1801.
107. Bastelica D, Morange P, Berthet B, Borghi H, Lacroix O, Grino M, Juhan-Vague I, Alessi MC. Stromal cells are the main plasminogen activator inhibitor-1-producing cells in human fat: evidence of differences between visceral and subcutaneous deposits. *Arterioscler Thromb Vasc Biol* 2002;**22**:173–178.
108. Skurk T, Hauner H. Obesity and impaired fibrinolysis: role of adipose production of plasminogen activator inhibitor-1. *Int J Obes Relat Metab Disord* 2004;**28**: 1357–1364.
109. Wiman B, Andersson T, Hallqvist J, Reuterwall C, Ahlbom A, deFaire U. Plasma levels of tissue plasminogen activator/plasminogen activator inhibitor-1 complex and von Willebrand factor are significant risk markers for recurrent myocardial infarction in the Stockholm Heart Epidemiology Program (SHEEP) study. *Arterioscler Thromb Vasc Biol* 2000;**20**:2019–2023.
110. Sobel BE, Taatjes DJ, Schneider DJ. Intramural plasminogen activator inhibitor type-1 and coronary atherosclerosis. *Arterioscler Thromb Vasc Biol* 2003;**23**: 1979–1989.
111. Brennan AM, Li TY, Kelesidis I, Gavrilu A, Hu FB, Mantzoros CS. Circulating leptin levels are not associated with cardiovascular morbidity and mortality in women with diabetes: a prospective cohort study. *Diabetologia* 2007;**50**: 1178–1185.
112. Wolk R, Berger P, Lennon RJ, Brilakis ES, Johnson BD, Somers VK. Plasma leptin and prognosis in patients with established coronary atherosclerosis. *J Am Coll Cardiol* 2004;**44**:1819–1824.
113. Iribarren C, Husson G, Go AS, Lo JC, Fair JM, Rubin GD, Hlatky MA, Fortmann SP. Plasma leptin levels and coronary artery calcification in older adults. *J Clin Endocrinol Metab* 2007;**92**:729–732.
114. Jung SH, Park HS, Kim KS, Choi WH, Ahn CW, Kim BT, Kim SM, Lee SY, Ahn SM, Kim YK, Kim HJ, Kim DJ, Lee KW. Effect of weight loss on some serum cytokines in human obesity: increase in IL-10 after weight loss. *J Nutr Biochem* 2008;**19**:371–375.

115. Duncan GE, Perri MG, Theriaque DW, Hutson AD, Eckel RH, Stacpoole PW. Exercise training, without weight loss, increases insulin sensitivity and postheparin plasma lipase activity in previously sedentary adults. *Diabetes Care* 2003; **26**:557–562.
116. Brouwer BG, Visseren FLJ, Van der Graaf Y, for the SMART Study Group. The effect of leisure-time physical activity on the presence of metabolic syndrome in patients with manifest arterial disease. The SMART study. *Am Heart J* 2007; **154**: 1146–1152.
117. Tokmakidis SP, Volaklis KA. Training and detraining effects of a combined-strength and aerobic exercise program on blood lipids in patients with coronary artery disease. *J Cardiopulm Rehabil* 2003; **23**:193–200.
118. Jain MK, Ridker PM. Anti-inflammatory effects of statins: clinical evidence and basic mechanisms. *Nat Rev Drug Discov* 2005; **4**:977–987.
119. Gouni-Berthold I, Berthold HK, Chamberland JP, Krone W, Mantzoros CS. Short-term treatment with ezetimibe, simvastatin or their combination does not alter circulating adiponectin, resistin or leptin levels in healthy men. *Clin Endocrinol* 2008; **68**:536–541.
120. Hajer GR, Dallinga-Thie GM, van Vark-van der Zee LC, Olijhoek JK, Visseren FLJ. Lipid lowering therapy does not affect the postprandial drop in HDL-c plasma levels in obese men with metabolic syndrome. *Clin Endocrinol* 2008. Apr 3 [Epub].
121. Forst T, Pfützner A, Lübber G, Weber M, Marx N, Karagiannis E, Koehler C, Baurecht W, Hohberg C, Hanefeld M. Effect of simvastatin and/or pioglitazone on insulin resistance, insulin secretion, adiponectin, and proinsulin levels in non-diabetic patients at cardiovascular risk – the PIOSTAT Study. *Metabolism* 2007; **56**:491–496.
122. Freeman DJ, Norrie J, Sattar N, Neely RD, Cobbe SM, Ford I, Isles C, Lorimer AR, Macfarlane PW, McKillop JH, Packard CJ, Shepherd J, Gaw A. Pravastatin and the development of diabetes mellitus: evidence for a protective treatment effect in the West of Scotland Coronary Prevention Study. *Circulation* 2001; **103**:357–362.
123. Devaraj S, Siegel D, Jialal I. Simvastatin (40 mg/day), adiponectin levels, and insulin sensitivity in subjects with the metabolic syndrome. *Am J Cardiol* 2007; **100**:1397–1399.
124. Clasen R, Schupp M, Foryst-Ludwig A, Sprang C, Clemenz M, Krikov M, Thöne-Reineke C, Unger T, Kintscher U. PPARgamma-activating angiotensin type-1 receptor blockers induce adiponectin. *Hypertension* 2005; **46**:137–143.
125. Staels B, Dallongeville J, Auwerx J, Schoonjans K, Leitersdorf E, Fruchart JC. Mechanism of action of fibrates on lipid and lipoprotein metabolism. *Circulation* 1998; **98**:2088–2093.
126. Lincoff AM, Wolski K, Nicholls SJ, Nissen SE. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. *JAMA* 2007; **298**:1180–1188.
127. Blüher M, Engeli S, Klötting N, Berndt J, Fasshauer M, Bátkai S, Pacher P, Schön MR, Jordan J, Stumvoll M. Dysregulation of the peripheral and adipose tissue endocannabinoid system in human abdominal obesity. *Diabetes* 2006; **55**: 3053–3060.
128. Despres JP, Golay A, Sjostrom L. Effects of rimonabant on metabolic risk factors in overweight patients with dyslipidemia. *N Engl J Med* 2005; **353**: 2121–2134.
129. Boden G, Shulman GI. Free fatty acids in obesity and type 2 diabetes: defining their role in the development of insulin resistance and beta-cell dysfunction. *Eur J Clin Invest* 2002; **32**(Suppl. 3):14–23.
130. Hotamisligil GS, Peraldi P, Budavari A, Ellis R, White MF, Spiegelman BM. IRS-v1-mediated inhibition of insulin receptor tyrosine kinase activity in TNF-alpha and obesity-induced insulin resistance. *Science* 1996; **271**:665–678.
131. Shulman GI. Cellular mechanisms of insulin resistance in humans. *Am J Cardiol* 1999; **84**:3–10.
132. Engeli S, Böhnke J, Feldpausch M, Gorzelniak K, Janke J, Bátkai S, Pacher P, Harvey-White J, Luft FC, Sharma AM, Jordan J. Activation of the peripheral endocannabinoid system in human obesity. *Diabetes* 2005; **54**:2838–2843.