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Insulin resistance: An adaptive mechanism becomes maladaptive in the current environment — An evolutionary perspective

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ABSTRACT

Human survival has relied upon the ability to withstand starvation through energy storage, the capacity to fight off infection by a proinflammatory immune response, and the ability to cope with physical stressors by an adaptive stress response. Energy storage, mainly as glycogen in liver and triglycerides in adipose tissue, is regulated by the anabolic actions of insulin. On the other hand, mobilization of stored energy during infection, trauma or stress is served by the temporary inhibition of insulin action (insulin resistance) in target tissues by proinflammatory cytokines and stress hormones. In the current environment, high energy intake, low physical activity, and chronic stress favor the storage of surplus fat in adipose tissue depots that far exceeds their storage capacity and liporegulation. Lipid overload in central fat depots initiates an inflammatory response and adipocyte dysfunction with resultant low-grade systemic inflammation and lipid overflow to peripheral tissues. In turn, proinflammatory cytokines and non-oxidized lipid metabolites, accumulated in liver and muscle cells, activate the mechanism of insulin resistance as would occur in the case of infection or stress. The same factors together with the ensuing insulin resistance further contribute to pancreatic β -cell dysfunction and ultimately to type 2 diabetes and cardiovascular disease. The present review supports the hypothesis that insulin resistance evolved as a physiological adaptive mechanism in human survival and that the same mechanism is inappropriately activated on a chronic basis in the current environment, leading to the manifestations of the metabolic syndrome.

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Abbreviations: MS, metabolic syndrome; DM2, type 2 diabetes mellitus; CVD, cardiovascular disease; TGs, triglycerides; IRS, insulin receptor substrates; PI3K, phosphatidylinositol 3-kinase; Akt/PKB, Protein kinase B; MAPK, mitogen activated protein kinase; JNK, c-Jun amino-terminal kinase; IKK, I κ B kinase; nPKC, novel protein kinase C; FFAs, free fatty acids; AMPK, AMP-activated protein kinase; CPT-1, carnitine palmitoyl transferase-1; TNF- α , tumor necrosis factor- α ; IL-6, interleukin-6; PAI-1, plasminogen activator inhibitor -1; ANG, angiotensinogen; MCP-1, monocyte chemoattractant protein-1; MIF, macrophage inhibitory factor; LPA, lysophosphatidic acid; PA, phosphatidic acid; DAG, diacylglycerol; DGAT-1, diacylglycerol acyltransferase-1; ER, endoplasmic reticulum; LTB4, leukotrienes B4; ATMs, adipose tissue macrophages; TLR4, toll-like receptor-4; HDL-C, high density lipoprotein-C; HPA, hypothalamic-pituitary adrenal; SNS, sympathetic nervous system; GH, growth hormone; TCF7L2, transcription factor 7-like 2 (T-cell specific, HMG-box); PPAR- γ , peroxisome proliferator-activated receptor- γ ; VEGF-B, vascular endothelial growth factor-B.

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1. Introduction

The insulin resistance or metabolic syndrome (MS) is characterized by the clustering of metabolic abnormalities including central obesity, atherogenic dyslipidemia, hypertension and systemic insulin resistance that confer an increased risk for type 2 diabetes (DM2) and cardiovascular disease (CVD) [1–3].

Although there is some debate surrounding the scientific concept and the practical utility of the metabolic syndrome as a diagnostic or management tool [2,4–6], it is generally accepted that the components of the syndrome co-exist more often than might be expected by chance [7]. It is also believed that central obesity and associated resistance to the metabolic actions of insulin lie at the root of the problem [8,9]. However, the underlying pathogenic mechanisms for the development of systemic insulin resistance and the MS are still subject to debate.

In this review, we take an evolutionary approach and support the hypothesis that adaptive mechanisms, which helped our ancestors to survive in times of famine, infection and stress, may become maladaptive in the current obesogenic environment, favoring the manifestation of the MS. We argue that the mechanism of insulin resistance evolved as a physiologic adaptive response in this survival process, and that the same mechanism is inappropriately activated on a chronic basis as a consequence of our modern lifestyle.

2. Adaptive role of insulin resistance

2.1. Human survival mechanisms and the adaptive role of insulin resistance

The most important processes that helped human survival are the ability to withstand starvation in times of famine by storing excess energy as fat, the capacity to fight off infection by mounting a proinflammatory immune response, and the ability to cope with physical threats (stressors) by an adaptive stress response [10–13]. The excess energy needed in these situations is provided by mobilization of stored energy substrates.

The requirement for energy storage is essentially served by the anabolic actions of insulin. Following food intake, insulin secretion by pancreatic β -cells facilitates the storage of glucose as glycogen in liver and skeletal muscles, and the deposition of fatty acids in the form of triglycerides (TGs) in adipose tissue. The stored energy can then be mobilized during fasting, infection, trauma or stress, by the action of catabolic hormones or factors with anti-insulin effects [14–18].

At the cellular level, insulin binds and activates the insulin receptor by phosphorylating key tyrosine residues on the β -chain. This is followed by tyrosine phosphorylation of insulin receptor substrates (IRS) and subsequent activation of the canonical phosphatidylinositol 3-kinase (PI3K)/AKT pathway of insulin signaling [19–21]. This pathway mediates the metabolic effects of insulin, including glucose transport and metabolism as well as lipid and protein metabolism in target tissues [19]. Specifically, insulin promotes glucose uptake in fat and muscle tissue, stimulates glycogen synthesis in liver

and muscle as well as hepatic and adipocyte lipogenesis, while inhibiting hepatic glucose production and adipocyte lipolysis [22] (Fig. 1, upper panel). At the same time, insulin is an important growth factor, promoting cell growth and inhibiting apoptosis. These “mitogenic” actions of insulin are mediated by the Ras–Raf–mitogen activated protein kinase (MAPK) signaling pathway [23,24] (Fig. 1, upper panel).

In addition to the above positive regulation of insulin signaling, nature has devised a number of ways to “tone down” insulin action in response to certain conditions, including fasting, inflammation, stress and pregnancy — in a way to allow mobilization of stored energy substrates [18,25–28]. This negative regulation of insulin action can be induced by interaction at critical nodes in signaling pathways [29]. Tyrosine phosphorylation of the insulin receptor and its substrates can be inhibited when the substrates first undergo serine phosphorylation by various serine kinases e.g. c-Jun amino-terminal kinase (JNK), I κ B kinase (IKK), and novel protein kinase C (nPKC) that are activated by inflammatory cytokines [29–32] (Fig. 1, lower panel). Disruption of the balance between the amounts of the PI3-kinase subunits, induced by overnutrition, can also terminate the insulin signal [33]. Hyperinsulinemia itself can also downregulate insulin action [29].

Negative regulation of insulin signaling could be viewed as a physiologic “adaptive mechanism” that is activated whenever the organism needs to switch from an anabolic to a catabolic or “insulin resistance” state, and mobilize energy, primarily in the form of glucose released from the liver and free fatty acids released from adipocytes, to support vital metabolic processes. In this state, insulin dependent glucose uptake in muscle and adipose tissue is inhibited while hepatic glucose production and adipocyte lipolysis are disinhibited (Fig. 1, lower panel) [22,30]. It is important to emphasize that this adaptive or protective mechanism of insulin resistance involves only the metabolic pathway of insulin signaling and not the “mitogenic” pathway, which remains intact and, in fact, in insulin resistant states may be upregulated [34].

2.2. Brain energy demand and the adaptive role of insulin resistance

Throughout human evolution, natural selection has helped our ancestors to develop a large brain. Human brain expansion must have been characterized by a diversion to more energy-dense and easy to digest diet allowing in this way the reduction in size of other energetically expensive tissues, such as the costly gut [35].

In this context, our large brain has some unique features. It possesses a hierarchical metabolic position with the highest energy consumption rate in the body, has a limited capacity for energy storage and is protected from the general circulation by a strong blood–brain barrier [36]. Unlike other peripheral organs and tissues which metabolize glucose, fatty acids and amino acids, our brain is almost exclusively dependent on glucose metabolism (in an insulin independent way) and is the primary glucose consumer in the body [37]. In the event of even temporary disruption of energy supply, the brain can be permanently damaged with devastating implications for the survival of the whole organism [38]. For this

reason, natural selection has developed a sophisticated glucose distribution and delivery system, in order to prioritize the brain's energy requirements even at the expense of less critical functions of the body. This glucose delivery system is based on a tissue specific pattern of insulin dependent and independent glucose transporters [39], which provides the autonomic nervous system the ability to control glucose allocation to the brain by inhibiting insulin action in muscles, liver and adipose tissue [40–42]. In this way, in times of increased energy demand (e.g. fasting, infection, psychological and physical stress) the brain prioritizes its own energy supply by inducing peripheral insulin resistance: mobilization of adipose tissue-derived fatty acids occurs to cover the energy needs of the periphery, while glucose is spared for the brain (Fig. 2).

3. Adipose tissue function and insulin resistance

3.1. Role of adipose tissue function in energy storage and liporegulation

Human survival in times of famine has depended on availability of stored energy in adipose tissue. Thus, humans as well as animals developed the capacity to store fat when the opportunity to consume excess energy arose [43].

In this way, adipose tissue takes central stage in energy balance. Indeed, adipocytes have two critical roles: first to synthesize energy rich TGs from fatty acids and glucose absorbed after feeding, and second to release free fatty acids (FFAs) and concurrently regulate their metabolism in peripheral tissues during fasting or in times of high energy need [44].

In these situations, there is a dynamic equilibrium between lipolysis of TGs and release of FFAs into circulation and their uptake and oxidation in non-adipose tissues, mainly the liver and skeletal muscle. This liporegulatory function is controlled by the adipocytes themselves through the secretion of regulatory hormones such as adiponectin and leptin [44–46]. These adipokines enhance β -oxidation of FFAs in the mitochondria of the peripheral tissues by upregulation of AMP-activated protein kinase (AMPK), and activation of carnitine palmitoyl-transferase-1 (CPT-1) and the enzymes of β -oxidation [47,48]. Leptin, in addition to its peripheral effects, conveys information to the brain about the amount of fat that is stored and, in this way, regulates feeding behavior and whole-body metabolism [47–49].

It becomes obvious that dysfunction of adipose tissue, regarding its lipid storage and liporegulatory role, may change the dynamics between FFA release and their oxidation in peripheral tissues. Compared to adipocytes, non-adipose cells have a rather limited capacity for FFA storage in the form of TGs. If this storage capacity is exceeded, bioactive lipids or toxic lipid species accumulate causing insulin resistance as will be discussed below [50].

Apart from the secretion of the above liporegulatory adipokines, adipose tissue also secretes, in small amounts, inflammatory cytokines, such as tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6), thus contributing to the innate immunity. It also produces a number of other

adipokines, peptides and enzymes, including plasminogen activator inhibitor-1 (PAI-1) and angiotensinogen (ANG), in a way contributing to regulation of blood clotting and vascular tone, respectively [45,46]. The controlled secretion of these adipokines, cytokines and enzymes is dysregulated when adipose tissue becomes dysfunctional.

3.2. Dysfunctional adipose tissue — Causes and consequences

A turning point for the development of insulin resistance and its cardiometabolic consequences is when the adipose tissue cannot fulfill its normal storage and liporegulatory function [8]. This may occur under the following circumstances. a) The existing adipocytes are overwhelmed with energy surplus that exceeds their normal storage capacity, resulting in overflow of lipids into peripheral tissues. This is the extreme phenomenon of “supersizing” [51]. b) The number of adipocytes is too low to cope with normal fat intake, which then is stored in non-adipose tissues. This occurs in congenital or acquired types of lipodystrophy [52]. c) The adipocytes become dysfunctional because of their distribution in adipose tissue depots. This is the case of central or visceral adiposity that is in the root of the MS [8,9,53]. d) There is mitochondrial dysfunction, due to aging or genetic factors, resulting in reduced capacity for β -oxidation of FFAs and accumulation of non-oxidized lipids in peripheral tissues [54].

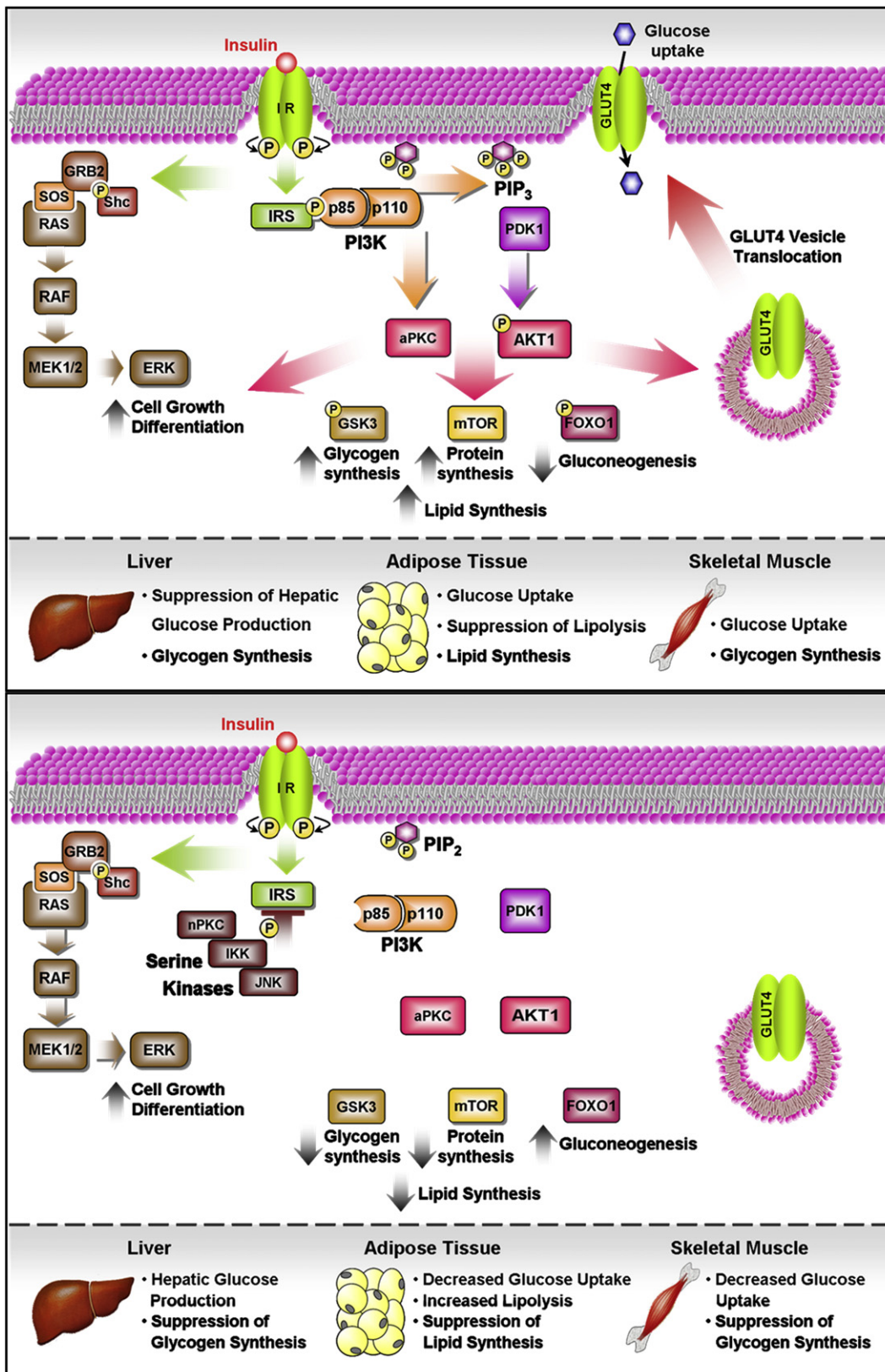
Focusing on the issue of body fat distribution, it has become increasingly evident that topography matters [55–57]. Lower or peripheral body fat deposition is a unique human female feature. It consists of small functional adipocytes capable of undergoing hyperplasia when needed, to store excess fat, and secretes the appropriate amounts of the liporegulatory adipokines. It has a less active lipolytic and a more active antilipolytic program and can be mobilized at the time of pregnancy and nursing but is less readily available for every-day-energy needs [58].

On the other hand, upper body, abdominal and mostly visceral fat, is present in every mammal. In humans, it comprises 20% of all fat in normal-weight men but only 6% in women [59]. This fat depot is metabolically more active and hypertrophic. Visceral adipocytes have greater β -adrenergic lipolytic sensitivity than femoral adipocytes [60]. When visceral adipocytes become hypertrophic, in response to excess energy intake, they also become dysfunctional. They undergo lipolysis more easily, releasing greater amounts of FFAs into the portal circulation. At the same time, they secrete less of the liporegulatory adipokine adiponectin, and more of the proinflammatory cytokines, TNF- α and IL-6, and more PAI-1 and ANG [61,62].

In addition, as visceral adipocytes become hypertrophic, they undergo necrosis and recruit macrophages from bone marrow into adipose tissue by the secretion of chemokines, such as monocyte chemoattractant protein-1 (MCP-1), macrophage inhibitory factor (MIF) and other factors [62]. These infiltrating macrophages acquire the type 1 phenotype, secreting several proinflammatory cytokines, which in turn contribute to further adipose tissue dysfunction and a low-grade inflammatory state [44,63,64].

Recently, an alternative and, in a way, complementary hypothesis was proposed by Virtue and Vidal-Puig, the “adipose tissue expandability” hypothesis [65]. According to this hypothesis, subcutaneous adipose tissue has a limited maximal capacity to increase in mass that is determined on an

individual basis by environmental and genetic factors. When an individual reaches his or her adipose tissue expansion limit, excess lipid can no longer be stored appropriately in adipose tissue and is deposited in visceral and peripheral non-adipose tissue organs, causing lipotoxicity [65].



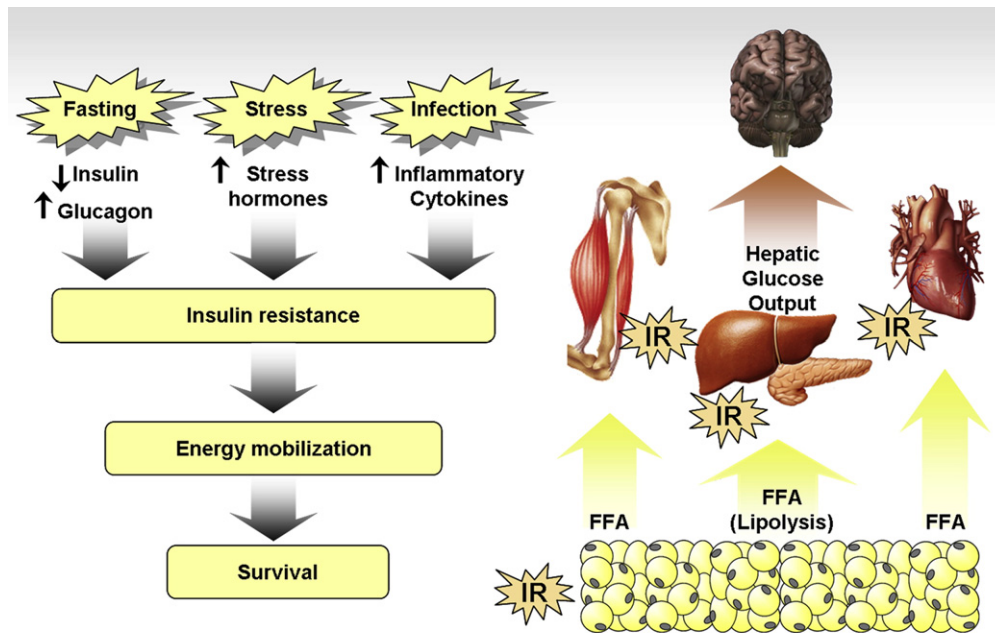


Fig. 2 – Adaptive role of insulin resistance. In conditions of increased metabolic demand of the organism such as fasting, stress and infection, different hormones and cytokines promote a state of “insulin resistance” (IR), resulting in mobilization of stored energy to support survival. Insulin resistance in adipocytes stimulates lipolysis and free fatty acid (FFA) release into circulation, while hepatic insulin resistance promotes increased glucose production from the liver. In this way FFAs cover the energy needs of the periphery while peripheral insulin resistance spares glucose for non-insulin dependent uptake in the brain.

Whatever the underlying mechanism, there are two main consequences of dysfunctional adipose tissue: ectopic fat deposition and low-grade systemic inflammation, both of which contribute to the development of insulin resistance and the manifestations of the MS (Fig. 3).

3.2.1. Ectopic fat deposition and insulin resistance

In conditions of positive energy balance, visceral adiposity or limited “adipose tissue expandability”, may lead to dysfunctional adipose tissue, resulting in increased flux of FFAs into the circulation and uptake by the liver or muscle cells and

Fig. 1 – Effects of insulin signaling on insulin target tissues (Upper panel). Insulin binds to its receptor (IR) resulting in tyrosine phosphorylation cascades that generate downstream signals. IR phosphorylates IRS and Shc. Upon phosphorylation IRS activates PI3K. PI3K phosphorylates phosphoinositides on the plasma membrane, producing PtdIns(3,4,5)P₃ or PIP₃. PIP₃ recruits and activates PDK1 which together with PI3K activates major targets of insulin signaling such as AKT1 and atypical forms of protein kinase C (aPKC). AKT1 phosphorylates and deactivates GSK3, which leads to activation of glycogen synthase and stimulation of glycogen synthesis. AKT1 also results in mTOR activation and increased protein synthesis. Moreover, AKT1 phosphorylates and inhibits FOXO1 transcription factor, a key regulator of gluconeogenesis. Finally, Akt together with aPKCs and other factors promotes insulin-stimulated glucose uptake via GLUT4 vesicle translocation to the plasma membrane. aPKC and PI3K play an important role in the activation of the transcription factor SREBP-1c (not shown), a central mediator of lipid synthesis. On the other hand phosphorylation of Shc promotes binding to Grb2. Grb2 recruits SOS which activates Ras, leading to subsequent activation of the serine/threonine kinases Raf, MEK-1/2 and ERK responsible for cell growth and differentiation. These pathways act in a concerted fashion regulating glucose, lipid and protein metabolism in liver, adipose tissue and muscle. Inhibition of insulin signaling and peripheral insulin resistance (Lower panel). In most cases insulin signaling is inhibited at the level of IRS. Serine phosphorylation of the IRS by the serine/threonine kinases JNK, IKK and nPKCs terminates the signal while the MAP kinase pathway is normally engaged and sensitive to insulin. This state of insulin resistance inhibits the metabolic actions of insulin in liver, adipose tissue and muscle with resultant decreased glucose uptake and increased lipolysis and hepatic glucose production. IR, insulin receptor; IRS, insulin receptor substrate; PI3K, phosphatidylinositol 3-kinase; PIP₃, phosphoinositide-(3,4,5)-triphosphate; PDK1, phosphatidylinositol-dependent kinase 1; aPKC, atypical protein kinase C; AKT, protein kinase B; GSK3, glycogen synthase kinase 3; mTOR, mammalian target of rapamycin; FOXO1, forkhead box O1; GLUT4, glucose transporter 4; Shc, Src homology 2 domain containing transforming protein 1; Grb2, growth factor receptor-bound protein 2; SOS, son of sevenless homolog 1; Ras, G protein rat sarcoma viral oncogene homolog; Raf, serine/threonine kinase Raf; MEK-1/2, MAPK-kinase; ERK, extracellular receptor kinase; SREBP-1c, sterol responsive element binding protein 1c; JNK, c-Jun aminoterminal kinase; IKK, inhibitor of I κ B kinase; nPKC, novel protein kinase C; PIP₂, phosphoinositide-(4,5)-bisphosphate.

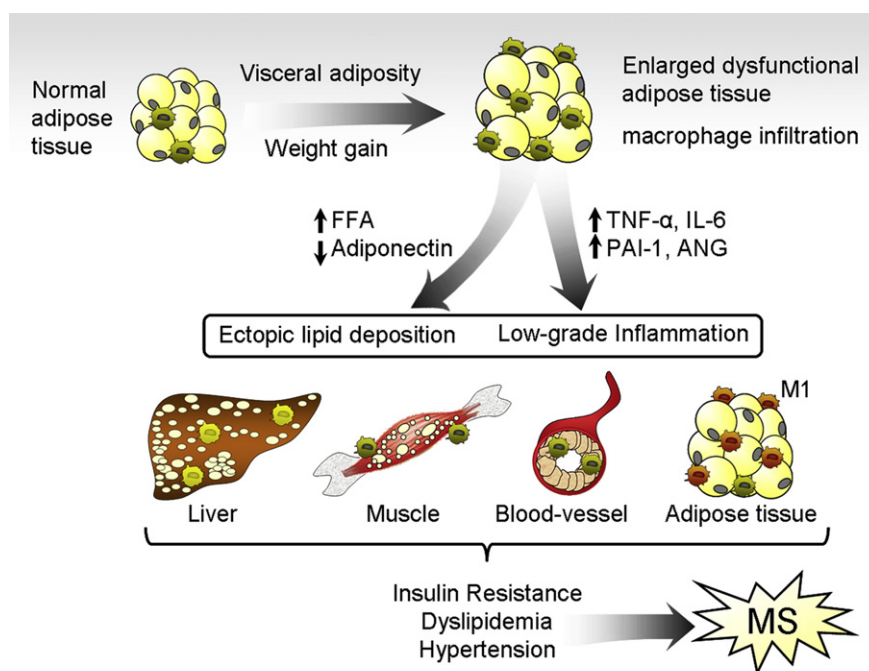


Fig. 3 – Adipose tissue expansion, insulin resistance and the metabolic syndrome. In conditions of positive energy balance, weight gain and increased visceral adiposity lead to hypertrophic and dysfunctional adipocytes. In this state FFAs are released in the circulation, adiponectin production is diminished and secretion of proinflammatory cytokines as well as PAI-1 and ANG is increased. Macrophages are recruited, infiltrate the hypertrophic adipose tissue and acquire the proinflammatory M1 phenotype contributing further to the proinflammatory state. High levels of FFAs and sustained levels of proinflammatory factors result in ectopic lipid deposition in non-adipose tissues and systemic low-grade inflammation, both activating the insulin resistance mechanism in insulin target tissues. In this state, systemic insulin resistance, dyslipidemia and hypertension result in the metabolic syndrome phenotype.

other organs. Activated fatty acids (i.e. fatty acyl-CoAs) are metabolized via one of two pathways, β -oxidation in the mitochondria and storage as TGs in lipid droplets.

The rate-limiting step for β -oxidation of long-chain fatty acids is their transport into the mitochondria via CPT-1 which, as alluded to above, is activated by adiponectin and leptin derived from adipocytes [66]. The synthesis of TGs from fatty acids entails the sequential addition of fatty acyl-CoA moieties to glycerol backbone and the formation of intermediary fatty acid metabolites, including lysophosphatidic acid (LPA), phosphatidic acid (PA) and diacylglycerol (DAG). When the availability of saturated fatty acids is high, ceramide is also formed [67].

When fatty acid flux exceeds the ability of the oxidation pathway to dispose of fatty acyl-CoAs, the latter follow, under the influence of insulin, the storage pathway, which is then saturated. As a result, fatty acids and intermediates of fatty acid metabolism (i.e. LPA, PA, DAG, ceramides) accumulate in peripheral cells. In turn, these lipid metabolites can activate a number of different serine kinases, including JNK, IKK and nPKC that can negatively regulate insulin action through serine phosphorylation of IRS proteins [22,68,69]. Ceramides can also impair insulin action through the ability to inhibit PKB/Akt [69].

Although ectopic fat deposition correlates with insulin resistance in skeletal muscles and liver [70,71], studies in

endurance-trained athletes found that increased intramyocellular lipid correlates with insulin sensitivity [72,73]. Transgenic mice with skeletal muscle overexpression of diacylglycerol acyltransferase-1 (DGAT-1), an enzyme that catalyzes the last step of TG synthesis, replicate the “athletes paradox”. These mice have comparable levels of intramuscular lipid content to mouse models with fat-induced insulin resistance; however, DGAT-1 mice are insulin sensitive, with reduced levels of DAG and ceramides, and increased mitochondrial fatty acid oxidation in a similar way to trained athletes [74]. These phenomena suggest that lipid accumulation in the form of TGs is neutral and that it is the accumulation of intermediate lipid metabolites that may act as lipotoxins disrupting insulin action [75].

Whereas, the lipid metabolite hypothesis has gained strong support, several other plausible theories to explain lipid induced insulin resistance have been proposed. Prominent among these are models centered on endoplasmic reticulum (ER) stress, mitochondrial stress and redox imbalance as well as inflammation (discussed below). Each of these cellular insults is thought to engage stress-sensitive serine kinases disrupting insulin signaling as above [76].

In summary, therefore, surplus FFA flux to skeletal muscles, exceeding the ability for mitochondrial β -oxidation, would lead to intracellular accumulation of fatty acid intermediates, and/or induction of ER or mitochondrial stress,

all of which can activate the mechanism of insulin resistance. In a way the activation of the insulin resistance mechanism would serve as a protective mechanism against intracellular lipid accumulation that if unabated could lead to cellular stress and apoptosis [8]. In a similar way, accumulation of lipid metabolites in the liver (hepatic steatosis) would lead to hepatic insulin resistance and consequent increase in hepatic glucose and TG production. Moreover, ectopic lipid deposition in the pancreatic islets would lead to β -cell dysfunction and apoptosis [8,77].

3.2.2. Low-grade inflammation and insulin resistance

It is increasingly recognized that hypertrophic adiposity is characterized by a state of chronic low-grade inflammation that, along with lipotoxicity, contributes to systemic insulin resistance and the manifestations of the metabolic syndrome. It is also recognized that the hypertrophic adipose tissue is highly infiltrated by macrophages and other immune cells that actively participate in the inflammatory process [78–80]. Notably, macrophage infiltration in adipose tissue precedes the development of insulin resistance and the ectopic lipid deposition in obese animals and humans [78,79].

Several mechanisms, including microhypoxia, ER stress, adipocyte necrosis and dysregulated chemokine and adipokine secretion have been proposed as initiators of macrophage infiltration in adipose tissue [3,77,81]. As a general model, hypertrophic and metabolically stressed adipocytes secrete chemokines, including MCP-1, leukotrienes B₄ (LTB₄) and others that attract monocytes into fat tissue where they become adipose tissue macrophages (ATMs) [79,82].

Tissue macrophages responding to changes in the local environment are polarized to the highly proinflammatory M1-like phenotype to secrete proinflammatory cytokines such as TNF- α , IL-1 β , IL-6 and IL-8. Similarly, a shift of adipose tissue T cell population with a decrease in T regulatory cells and increase in CD4 Th1 and CD8 T effector cells also contributes to the proinflammatory process [63,83]. In addition, dysregulated secretion of adipokines from dysfunctional adipose tissue with increase in leptin and decrease in adiponectin secretion may also contribute to the proinflammatory switch of resident macrophages and immune T cells [84].

Further evidence suggests a cross-talk between infiltrating macrophages and adipocytes underlying the chronic inflammation in hypertrophic adipose tissue. Indeed, macrophage-derived proinflammatory cytokines acting via a paracrine way activate intracellular inflammatory pathways (e.g. JNK, IKK) in neighboring adipocytes to induce insulin resistance, further exacerbating lipolysis and FFA release in the circulation. In turn, saturated fatty acids released from adipocytes activate toll-like receptor-4 (TLR4) signaling in macrophages inducing the production of inflammatory cytokines in a feed-forward cycle [85].

As in adipose tissue, in the liver, activation of proinflammatory pathways in Kupffer cells, the resident hepatic macrophages, and probably recruited macrophages from circulating monocytes, would lead to the local release of inflammatory cytokines. In turn these cytokines can activate proinflammatory pathways in hepatocytes, causing hepatic insulin resistance [79,86]. In a similar way, intramuscular

adipose tissue depots are present between muscle fibers, and macrophages are recruited to these fat depots. It is possible, although not yet proven, that cytokines produced locally could contribute to muscle insulin resistance [87].

In summary, activation of proinflammatory pathways within insulin target cells, such as adipocytes, hepatocytes and myocytes, provides a mechanism for the inflammation-related component of insulin resistance. In addition, systemic low-grade inflammation contributes to classical lipid changes associated with the MS – increased TGs and decreased high density lipoprotein-C (HDL-C) – as well as to vascular endothelial and pancreatic β -cell dysfunction [13,88].

From a teleologic perspective, tissue inflammatory responses and macrophage recruitment serve a normal physiologic purpose, such as host defense or restoration of tissue homeostasis in response to cellular stress. However in hypertrophic obesity, tissue inflammation becomes chronic or remains unresolved and progresses to a pathophysiologic condition contributing to insulin resistance and the manifestations of the MS [69] (Fig. 3).

4. Role of chronic stress in central obesity and insulin resistance

When under threat, the human body elicits a set of neuroendocrine responses including activation of the hypothalamic–pituitary–adrenal (HPA) axis and the sympathoadrenal system (SNS) with resultant increase in the secretion of glucocorticoids and catecholamines, respectively. The concerted effect of these stress responses is mobilization of FFAs from adipose tissue and glucose from the hepatic glycogen stores which, together with the development of a state of insulin resistance, will ensure energy supply for a “fight or flight” response that is crucial for the survival of the individual [10,89,90].

In today’s society, stress is more likely to be psychological (emotional, social, professional) rather than physical. The stress response for a psychological stressor is similar to the response to a physical challenge, i.e. activation of the HPA axis and the SNS. However, psychological stress is different, in that it is not tied to an increased metabolic demand, and thus the energy mobilized is not used but is simply restored in the body as fat [89]. Moreover, in psychological stress, there is no clear beginning and end, and it is likely to be protracted.

Chronic stress tends to alter the anabolic/catabolic hormonal balance. It shifts the hormonal balance toward low levels of the anabolic hormones that promote growth of lean and skeletal muscle and prevent adiposity, such as growth hormone (GH) and sex hormones. In parallel, chronic stress promotes greater cortisol levels, or cortisol levels that are not well counter-regulated by anabolic hormones. Cortisol in turn, increases insulin levels through insulin resistance, and the co-elevation of both hormones preferentially increases abdominal adiposity [91,92]. In addition, chronic cortisol excess induces a state of “leptin resistance” associated with increased appetite or “stress-eating” [93,94]. In this way, chronic stress contributes to the development of central obesity and its consequences, as discussed earlier.

5. Insulin resistance, β -cell dysfunction and type 2 diabetes

In the presence of insulin resistance, the normal response of the pancreatic islet to a chronically excessive fuel load is enhanced insulin secretion by both β -cell expansion and augmented function. The compensatory hyperinsulinemia maintains blood glucose levels within normal range until the β -cells can no longer produce sufficient insulin, resulting initially in glucose intolerance and eventually in DM2 [95].

The functional adaptation of the β -cell, in the face of insulin resistance, places it at risk because it necessitates high rates of β -cell metabolism with risk of β -cell damage from mitochondrial and ER stress [96,97]. As mentioned earlier, the β -cell is also vulnerable to the lipotoxic effects of excess lipid flux to pancreatic islets, as well as to the damaging effects of the proinflammatory cytokines deriving from visceral obesity [98]. The concerted actions of these metabolic stressors contribute to progressive β -cell dysfunction.

However the β -cell is particularly prone to damage from the above stressors in individuals with genetic factors that increase β -cell susceptibility. Interestingly, the recent search for DM2 genes has identified more polymorphisms in genes involved in β -cell growth and function, than in genes related to insulin action [99]. Thus, a number of genes associated with β -cell dysfunction in type 2 diabetic individuals have been described. Of these genes, the transcription factor 7-like 2 (TCF7L2) is best established [100,101]. Studies have shown that a single nucleotide polymorphism of the TCF7L2 gene is associated with impaired insulin secretion and can predict DM2 in multiple ethnic groups [94]. TCF7L2 encodes for a transcription factor involved in Wnt signaling, which plays a central role in the regulation of β -cell proliferation and insulin secretion [102,103].

Thus, in the presence of insulin resistance, associated with central obesity, β -cell decompensation and failure and the clinical expression of DM 2 occur earlier in those individuals with a genetic predisposition for β -cell susceptibility defect.

6. Concluding remarks

Primitive humans had to undertake considerable physical activity to gain food and had to adapt to prolonged periods of famine. When food was available they would store energy as fat in order to use it during periods of low nutrient availability, thus ensuring survival and reproduction. Perhaps human evolution also favored truncal fat deposition for men as it provided an easy energy reserve during periods of food scarcity with minimum hindrance in movement. In women, peripheral fat deposition was favored for the increased energy demands of pregnancy and lactation [104].

Modern man has inherited the same trait for fat storage but lives in a different environment characterized by uninterrupted high energy food intake and low physical activity. Modern lifestyle favors positive energy balance that, in the long term, creates the need for surplus fat storage. When the capacity for safe lipid storage in adipose tissue is exceeded,

then lipid overflow to non-adipose tissues occurs. This is more likely to occur in individuals with dysfunctional adipose tissue associated with central obesity. In this case, the lipid overload to peripheral insulin-target cells exceeds their capacity to fully metabolize the fatty acids. This can lead to cellular accumulation of fatty acid intermediates (e.g. DAG, ceramide) with ultimate activation of a number of serine kinases, including JNK, IKK and nPKC. The activation of these serine kinases represents a convergence point for the induction of insulin resistance [30].

Primitive man also had to fight off infection in order to survive. To this end, activation of the innate immunity together with a strong proinflammatory response was the adaptive mechanism. In order to meet the energy needs against infection, ready energy substrates, mainly in the form of glucose and FFAs, were made available through temporary induction of insulin resistance by the proinflammatory cytokines. In modern lifestyle, overnutrition promotes adipose tissue inflammation and a state of chronic low-grade inflammation [105]. In this context, activation of proinflammatory pathways within insulin target cells, such as the adipocyte, hepatocyte and myocyte, leads to cell autonomous insulin resistance in these cells. This provides a mechanism for the inflammation-related component of insulin resistance in adipose tissue, liver and skeletal muscle that characterizes the MS phenotype [64].

Finally, in primitive man, the stress response mechanism was acutely activated by physical stressors and led to insulin resistance and mobilization of energy to be used for an adaptive response. In today's society, chronic activation of the stress system by psychosocial stress leads to inappropriate induction of insulin resistance. However, in this case the energy mobilized is not used but is restored as fat in visceral depots, contributing to central obesity and the manifestations of the MS [91].

In summary, therefore, the adaptive mechanisms of fat storage, and temporary insulin resistance helped primitive man survive famine, infection and physical stressors by ensuring energy storage and mobilization, as required. In the current environment, lifestyle-induced central obesity with associated ectopic lipid deposition and low-grade inflammation together with chronic stress activates the same mechanism of insulin resistance, favoring the development of the MS. Thus, the manifestation of the MS in modern man could present a maladaptive phenotype in the current environment. In a way, the mechanism of insulin resistance may be viewed as the biologic equivalent of the "sword of Damocles". It could be protective or damaging depending on the environment in which humans live their lives [106].

7. Clinical implications and future perspectives

Evidence provided in this review suggests that the mechanisms that modulate insulin action may have helped human survival in times of famine, infection or trauma and stress. These mechanisms may become pathogenic in the modern environment of nutrient excess. Thus, for the modern man,

when facing a chronic energy surplus, the inability of subcutaneous adipose tissue to expand through hyperplasia may lead to hypertrophic and inflamed adipose tissue. The resulting systemic low-grade inflammation and lipid spillover with ectopic fat deposition may be at the root cause of insulin resistance in liver and muscle and consequent increase in cardiovascular risk.

At a clinical level, strategies aiming at relieving lipid storage pressure in adipose tissue may have an impact on ectopic lipid deposition and inflammation and may represent the most efficient therapeutic target for the prevention and treatment of insulin resistance and its comorbidities. This can be achieved by decreasing caloric intake and/or increasing energy expenditure by regular physical exercise. This notion is supported by a recent study in newly diagnosed patients with DM2 who were put on an 8-week hypocaloric (600 kcal/day) diet. This dietary intervention led to normalization of both hepatic insulin sensitivity and β -cell function and was associated with decreased hepatic and pancreatic lipid stores [107]. Thus, the abnormalities underlying DM2 may be reversible by effectively relieving ectopic lipid deposition with a reduction in dietary energy intake.

On the other hand, chronic exercise training has been shown to protect from lipotoxicity and attenuate lipid-induced insulin resistance in human subjects [108]. Relevant to this effect of exercise training may be the recent identification of a novel peptide, named irisin after the Greek messenger goddess Iris [109]. Irisin is a myokine that is released into the circulation during exercise and triggers the transformation of white fat cells into brown-in-white cells and, by increasing total energy expenditure, mitigates diet-induced insulin resistance in animal models [109]. Thus, irisin could serve as an injectable treatment for metabolic disease and other disorders that are improved by exercise.

Of the therapies currently available for the treatment of DM2 very few specifically target ectopic lipid deposition [110]. In this regard, the hypoglycemic effect of peroxisome proliferator-activated receptor- γ (PPAR- γ) agonists is mediated by their action in promoting the production of new subcutaneous adipocytes and, in this way, protecting against ectopic fat deposition [111]. However the clinical use of these compounds has been compromised by undesirable side effects. Recently, it was found that vascular endothelial growth factor-B (VEGF-B) controls endothelial uptake and transport of fatty acids in heart and skeletal muscle [112]. Further studies by the same investigators have shown that both genetic and pharmacological inhibition of VEGF-B signaling in rodent models with DM2 can limit ectopic lipid accumulation, restore peripheral insulin sensitivity, and preserve islet functionality. Thus inhibition of VEGF-B signaling may be another novel and promising treatment option to target the underlying pathophysiology of DM2 [113].

In closing, evidence is accumulating that the development of insulin resistance and its metabolic outcomes in the current environment may be a consequence of the exhaustion of adipose tissue to handle a chronic exposure to energy overload. This evidence favors a need for a conceptual shift from adipose tissue mass (defined as obesity) to adipose tissue function. This could also explain why not all obese people are

insulin resistant and why many insulin resistant individuals are not obese.

Understanding the molecular mechanisms underlying adipose tissue remodeling and function may lead to novel therapeutic strategies to prevent the development of metabolic disease in the current environment. An outstanding question to answer is whether increased visceral adiposity is a primary phenomenon or simply a marker of the inability of subcutaneous adipose tissue to expand through hyperplasia, in a metabolically safe way. In the meantime we should not lose sight of Hippocrates' observation: walking is man's best medicine.

Conflict of interest

The authors declare no conflict of interest.

REFERENCES

- [1] Despres JP, Lemieux I, Bergeron J, et al. Abdominal obesity and the metabolic syndrome: contribution to global cardiometabolic risk. *Arterioscler Thromb Vasc Biol* 2008;28(6):1039–49.
- [2] Reaven GM. The metabolic syndrome: time to get off the merry-go-round? *J Intern Med* 2011;269(2):127–36.
- [3] Mandavia CH, Pulakat L, Demarco V, et al. Over-nutrition and metabolic cardiomyopathy. *Metabolism* 2012;61(9):1205–10.
- [4] Gale EA. The myth of the metabolic syndrome. *Diabetologia* 2005;48(9):1679–83.
- [5] Kahn R, Buse J, Ferrannini E, et al. The metabolic syndrome: time for a critical appraisal: joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2005;28(9):2289–304.
- [6] Simmons RK, Alberti KG, Gale EA, et al. The metabolic syndrome: useful concept or clinical tool? Report of a WHO Expert Consultation. *Diabetologia* 2010;53(4):600–5.
- [7] Grundy SM. Metabolic syndrome: connecting and reconciling cardiovascular and diabetes worlds. *J Am Coll Cardiol* 2006;47(6):1093–100.
- [8] Unger RH, Scherer PE. Gluttony, sloth and the metabolic syndrome: a roadmap to lipotoxicity. *Trends Endocrinol Metab* 2010;21(6):345–52.
- [9] Despres JP, Lemieux I. Abdominal obesity and metabolic syndrome. *Nature* 2006;444(7121):881–7.
- [10] McEwen BS. Protective and damaging effects of stress mediators. *N Engl J Med* 1998;338(3):171–9.
- [11] Cahill Jr GF, Owen OE. Starvation and survival. *Trans Am Clin Climatol Assoc* 1968;79(13–20).
- [12] Levin BR, Lipsitch M, Bonhoeffer S. Population biology, evolution, and infectious disease: convergence and synthesis. *Science* 1999;283(5403):806–9.
- [13] Esteve E, Ricart W, Fernandez-Real JM. Dyslipidemia and inflammation: an evolutionary conserved mechanism. *Clin Nutr* 2005;24(1):16–31.
- [14] Ziegler MG, Elayan H, Milic M, et al. Epinephrine and the metabolic syndrome. *Curr Hypertens Rep* 2012;14(1):1–7.
- [15] Barth E, Albuszies G, Baumgart K, et al. Glucose metabolism and catecholamines. *Crit Care Med* 2007;35(Suppl. 9):S508–18.

- [16] Saltiel AR, Kahn CR. Insulin signalling and the regulation of glucose and lipid metabolism. *Nature* 2001;414(6865):799–806.
- [17] Taborsky Jr GJ. The physiology of glucagon. *J Diabetes Sci Technol* 2010;4(6):1338–44.
- [18] Fernandez-Real JM, Pickup JC. Innate immunity, insulin resistance and type 2 diabetes. *Diabetologia* 2012;55(2):273–8.
- [19] Saltiel AR, Pessin JE. Insulin signaling pathways in time and space. *Trends Cell Biol* 2002;12(2):65–71.
- [20] Taniguchi CM, Emanuelli B, Kahn CR. Critical nodes in signalling pathways: insights into insulin action. *Nat Rev Mol Cell Biol* 2006;7(2):85–96.
- [21] Aronis KN, Mantzoros CS. A brief history of insulin resistance: from the first insulin radioimmunoassay to selectively targeting protein kinase C pathways. *Metabolism* 2012;61(4):445–9.
- [22] Schenk S, Saberi M, Olefsky JM. Insulin sensitivity: modulation by nutrients and inflammation. *J Clin Invest* 2008;118(9):2992–3002.
- [23] Medema RH, de Vries-Smits AM, van der Zon GC, et al. Ras activation by insulin and epidermal growth factor through enhanced exchange of guanine nucleotides on p21ras. *Mol Cell Biol* 1993;13(1):155–62.
- [24] Goalstone M, Carel K, Leitner JW, et al. Insulin stimulates the phosphorylation and activity of farnesyltransferase via the Ras-mitogen-activated protein kinase pathway. *Endocrinology* 1997;138(12):5119–24.
- [25] Vendelbo MH, Clasen BF, Treebak JT, et al. Insulin resistance after a 72-h fast is associated with impaired AS160 phosphorylation and accumulation of lipid and glycogen in human skeletal muscle. *Am J Physiol Endocrinol Metab* 2012;302(2):E190–200.
- [26] Mulder AH, Tack CJ, Olthaar AJ, et al. Adrenergic receptor stimulation attenuates insulin-stimulated glucose uptake in 3T3-L1 adipocytes by inhibiting GLUT4 translocation. *Am J Physiol Endocrinol Metab* 2005;289(4):E627–33.
- [27] Haig D. Genetic conflicts in human pregnancy. *Q Rev Biol* 1993;68(4):495–532.
- [28] Saltiel AR. Putting the brakes on insulin signaling. *N Engl J Med* 2003;349(26):2560–2.
- [29] Gual P, Le Marchand-Brustel Y, Tanti JF. Positive and negative regulation of insulin signaling through IRS-1 phosphorylation. *Biochimie* 2005;87(1):99–109.
- [30] Gregor MF, Hotamisligil GS. Inflammatory mechanisms in obesity. *Annu Rev Immunol* 2011;29:415–45.
- [31] Pirola L, Johnston AM, Van Obberghen E. Modulation of insulin action. *Diabetologia* 2004;47(2):170–84.
- [32] Zick Y. Ser/Thr phosphorylation of IRS proteins: a molecular basis for insulin resistance. *Sci STKE* 2005(268):e4.
- [33] Cornier MA, Bessesen DH, Gurevich I, et al. Nutritional upregulation of p85alpha expression is an early molecular manifestation of insulin resistance. *Diabetologia* 2006;49(4):748–54.
- [34] Draznin B. Mitogenic action of insulin: friend, foe or 'frenemy'? *Diabetologia* 2010;53(2):229–33.
- [35] Armstrong E. Relative brain size and metabolism in mammals. *Science* 1983;220(4603):1302–4.
- [36] Peters A, Schweiger U, Pellerin L, et al. The selfish brain: competition for energy resources. *Neurosci Biobehav Rev* 2004;28(2):143–80.
- [37] Madsen PL, Hasselbalch SG, Hagemann LP, et al. Persistent resetting of the cerebral oxygen/glucose uptake ratio by brain activation: evidence obtained with the Kety–Schmidt technique. *J Cereb Blood Flow Metab* 1995;15(3):485–91.
- [38] Peters A. The selfish brain: competition for energy resources. *Am J Hum Biol* 2011;23(1):29–34.
- [39] Thorens B, Mueckler M. Glucose transporters in the 21st Century. *Am J Physiol Endocrinol Metab* 2010;298(2):E141–5.
- [40] Leonard WR, Robertson ML, Snodgrass JJ, et al. Metabolic correlates of hominid brain evolution. *Comp Biochem Physiol A Mol Integr Physiol* 2003;136(1):5–15.
- [41] Peters A, Kubera B, Hubold C, et al. The selfish brain: stress and eating behavior. *Front Neurosci* 2011;5:74.
- [42] Thorens B. Brain glucose sensing and neural regulation of insulin and glucagon secretion. *Diabetes Obes Metab* 2011;13(Suppl 1):82–8.
- [43] Neel JV. The "thrifty genotype" in 1998. *Nutr Rev* 1999;57(5 Pt 2):S2–9.
- [44] Trayhurn P. Endocrine and signalling role of adipose tissue: new perspectives on fat. *Acta Physiol Scand* 2005;184(4):285–93.
- [45] Frayn KN, Karpe F, Fielding BA, et al. Integrative physiology of human adipose tissue. *Int J Obes Relat Metab Disord* 2003;27(8):875–88.
- [46] Ahima RS, Flier JS. Adipose tissue as an endocrine organ. *Trends Endocrinol Metab* 2000;11(8):327–32.
- [47] Havel PJ. Update on adipocyte hormones: regulation of energy balance and carbohydrate/lipid metabolism. *Diabetes* 2004;53(Suppl 1):S143–51.
- [48] Lee YH, Magkos F, Mantzoros CS, et al. Effects of leptin and adiponectin on pancreatic beta-cell function. *Metabolism* 2011;60(12):1664–72.
- [49] Gautron L, Elmquist JK. Sixteen years and counting: an update on leptin in energy balance. *J Clin Invest* 2011;121(6):2087–93.
- [50] Schaffer JE. Lipotoxicity: when tissues overeat. *Curr Opin Lipidol* 2003;14(3):281–7.
- [51] Sims EA, Danforth Jr E, Horton ES, et al. Endocrine and metabolic effects of experimental obesity in man. *Recent Prog Horm Res* 1973;29:457–96.
- [52] Garg A, Misra A. Lipodystrophies: rare disorders causing metabolic syndrome. *Endocrinol Metab Clin North Am* 2004;33(2):305–31.
- [53] Moller DE, Kaufman KD. Metabolic syndrome: a clinical and molecular perspective. *Annu Rev Med* 2005;56:45–62.
- [54] Heilbronn LK, Gan SK, Turner N, et al. Markers of mitochondrial biogenesis and metabolism are lower in overweight and obese insulin-resistant subjects. *J Clin Endocrinol Metab* 2007;92(4):1467–73.
- [55] Kaess BM, Pedley A, Massaro JM, et al. The ratio of visceral to subcutaneous fat, a metric of body fat distribution, is a unique correlate of cardiometabolic risk. *Diabetologia* 2012;55(10):2622–30.
- [56] Wajchenberg BL, Nery M, Cunha MR, et al. Adipose tissue at the crossroads in the development of the metabolic syndrome, inflammation and atherosclerosis. *Arq Bras Endocrinol Metab* 2009;53(2):145–50.
- [57] Goss AM, Gower BA. Insulin sensitivity is associated with thigh adipose tissue distribution in healthy postmenopausal women. *Metabolism* 2012, <http://dx.doi.org/10.1016/j.metabol.2012.05.016>.
- [58] Tchernof A. Sex differences in energy balance, body composition and body fat distribution. In: Tsatsoulis A, Wyckoff J, Brown FM, editors. *Diabetes in women: pathophysiology and therapy*. New York: Human Press; 2009. p. 1–24.
- [59] Montague CT, O'Rahilly S. The perils of portliness: causes and consequences of visceral adiposity. *Diabetes* 2000;49(6):883–8.
- [60] Mauriege P, Brochu M, Prud'homme D, et al. Is visceral adiposity a significant correlate of subcutaneous adipose cell lipolysis in men? *J Clin Endocrinol Metab* 1999;84(2):736–42.
- [61] Bluher M. Adipose tissue dysfunction in obesity. *Exp Clin Endocrinol Diabetes* 2009;117(6):241–50.
- [62] Skurk T, Alberti-Huber C, Herder C, et al. Relationship between adipocyte size and adipokine expression and secretion. *J Clin Endocrinol Metab* 2007;92(3):1023–33.

- [63] Lumeng CN, Bodzin JL, Saltiel AR. Obesity induces a phenotypic switch in adipose tissue macrophage polarization. *J Clin Invest* 2007;117(1):175–84.
- [64] Trayhurn P. Adipose tissue in obesity—an inflammatory issue. *Endocrinology* 2005;146(3):1003–5.
- [65] Virtue S, Vidal-Puig A. It's not how fat you are, it's what you do with it that counts. *PLoS Biol* 2008;6(9):E237.
- [66] Hardie DG, Pan DA. Regulation of fatty acid synthesis and oxidation by the AMP-activated protein kinase. *Biochem Soc Trans* 2002;30(Pt 6):1064–70.
- [67] Chavez JA, Summers SA. Lipid oversupply, selective insulin resistance, and lipotoxicity: molecular mechanisms. *Biochim Biophys Acta* 2010;1801(3):252–65.
- [68] Itani SI, Ruderman NB, Schmieder F, et al. Lipid-induced insulin resistance in human muscle is associated with changes in diacylglycerol, protein kinase C, and IkkappaB-alpha. *Diabetes* 2002;51(7):2005–11.
- [69] Savage DB, Petersen KF, Shulman GI. Disordered lipid metabolism and the pathogenesis of insulin resistance. *Physiol Rev* 2007;87(2):507–20.
- [70] Unger RH, Clark GO, Scherer PE, et al. Lipid homeostasis, lipotoxicity and the metabolic syndrome. *Biochim Biophys Acta* 2010;1801(3):209–14.
- [71] Szendroedi J, Roden M. Ectopic lipids and organ function. *Curr Opin Lipidol* 2009;20(1):50–6.
- [72] Machann J, Haring H, Schick F, et al. Intramyocellular lipids and insulin resistance. *Diabetes Obes Metab* 2004;6(4):239–48.
- [73] Russell AP. Lipotoxicity: the obese and endurance-trained paradox. *Int J Obes Relat Metab Disord* 2004;28(Suppl 4):S66–71.
- [74] Liu L, Zhang Y, Chen N, et al. Upregulation of myocellular DGAT1 augments triglyceride synthesis in skeletal muscle and protects against fat-induced insulin resistance. *J Clin Invest* 2007;117(6):1679–89.
- [75] Muoio DM. Revisiting the connection between intramyocellular lipids and insulin resistance: a long and winding road. *Diabetologia* 2012;55(10):2551–4.
- [76] Muoio DM, Newgard CB. Mechanisms of disease: molecular and metabolic mechanisms of insulin resistance and beta-cell failure in type 2 diabetes. *Nat Rev Mol Cell Biol* 2008;9(3):193–205.
- [77] Heilbronn L, Smith SR, Ravussin E. Failure of fat cell proliferation, mitochondrial function and fat oxidation results in ectopic fat storage, insulin resistance and type II diabetes mellitus. *Int J Obes Relat Metab Disord* 2004;28(Suppl 4):S12–21.
- [78] Weisberg SP, McCann D, Desai M, et al. Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest* 2003;112(12):1796–808.
- [79] Xu H, Barnes GT, Yang Q, et al. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *J Clin Invest* 2003;112(12):1821–30.
- [80] Olefsky JM, Glass CK. Macrophages, inflammation, and insulin resistance. *Annu Rev Physiol* 2010;72:219–46.
- [81] Hosogai N, Fukuhara A, Oshima K, et al. Adipose tissue hypoxia in obesity and its impact on adipocytokine dysregulation. *Diabetes* 2007;56(4):901–11.
- [82] Christiansen T, Richelsen B, Bruun JM. Monocyte chemoattractant protein-1 is produced in isolated adipocytes, associated with adiposity and reduced after weight loss in morbid obese subjects. *Int J Obes (Lond)* 2005;29(1):146–50.
- [83] Chatzigeorgiou A, Karalis KP, Bornstein SR, et al. Lymphocytes in obesity-related adipose tissue inflammation. *Diabetologia* 2012;55(10):2583–92.
- [84] Trayhurn P, Wood IS. Adipokines: inflammation and the pleiotropic role of white adipose tissue. *Br J Nutr* 2004;92(3):347–55.
- [85] 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(10):2062–8.
- [86] Cai D, Yuan M, Frantz DF, et al. Local and systemic insulin resistance resulting from hepatic activation of IKK-beta and NF-kappaB. *Nat Med* 2005;11(2):183–90.
- [87] Osborn O, Olefsky JM. The cellular and signaling networks linking the immune system and metabolism in disease. *Nat Med* 2012;18(3):363–74.
- [88] Hotamisligil GS. Inflammation and metabolic disorders. *Nature* 2006;444(7121):860–7.
- [89] Charmandari E, Tsigos C, Chrousos G. Endocrinology of the stress response. *Annu Rev Physiol* 2005;67:259–84.
- [90] Peckett AJ, Wright DC, Riddell MC. The effects of glucocorticoids on adipose tissue lipid metabolism. *Metabolism* 2011;60(11):1500–10.
- [91] Bjorntorp P. Visceral fat accumulation: the missing link between psychosocial factors and cardiovascular disease? *J Intern Med* 1991;230(3):195–201.
- [92] Strack AM, Sebastian RJ, Schwartz MW, et al. Glucocorticoids and insulin: reciprocal signals for energy balance. *Am J Physiol* 1995;268(1 Pt 2):R142–9.
- [93] Zakrzewska KE, Cusin I, Sainsbury A, et al. Glucocorticoids as counterregulatory hormones of leptin: toward an understanding of leptin resistance. *Diabetes* 1997;46(4):717–9.
- [94] Tataranni PA, Larson DE, Snitker S, et al. Effects of glucocorticoids on energy metabolism and food intake in humans. *Am J Physiol* 1996;271(2 Pt 1):E317–25.
- [95] Leahy JL. Pathogenesis of type 2 diabetes mellitus. *Arch Med Res* 2005;36(3):197–209.
- [96] Scheuner D, Kaufman RJ. The unfolded protein response: a pathway that links insulin demand with beta-cell failure and diabetes. *Endocr Rev* 2008;29(3):317–33.
- [97] Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature* 2006;444(7121):840–6.
- [98] Wellen KE, Hotamisligil GS. Inflammation, stress, and diabetes. *J Clin Invest* 2005;115(5):1111–9.
- [99] Perry JR, Frayling TM. New gene variants alter type 2 diabetes risk predominantly through reduced beta-cell function. *Curr Opin Clin Nutr Metab Care* 2008;11(4):371–7.
- [100] Grant SF, Thorleifsson G, Reynisdottir I, et al. Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes. *Nat Genet* 2006;38(3):320–3.
- [101] Florez JC. The new type 2 diabetes gene TCF7L2. *Curr Opin Clin Nutr Metab Care* 2007;10(4):391–6.
- [102] Lyssenko V, Lupi R, Marchetti P, et al. Mechanisms by which common variants in the TCF7L2 gene increase risk of type 2 diabetes. *J Clin Invest* 2007;117(8):2155–63.
- [103] Welters HJ, Kulkarni RN. Wnt signaling: relevance to beta-cell biology and diabetes. *Trends Endocrinol Metab* 2008;19(10):349–55.
- [104] Lev-Ran A. Human obesity: an evolutionary approach to understanding our bulging waistline. *Diabetes Metab Res Rev* 2001;17(5):347–62.
- [105] Kolb H, Mandrup-Poulsen T. The global diabetes epidemic as a consequence of lifestyle-induced low-grade inflammation. *Diabetologia* 2010;53(1):10–20.
- [106] Nunn AV, Bell JD, Guy GW. Lifestyle-induced metabolic inflexibility and accelerated ageing syndrome: insulin resistance, friend or foe? *Nutr Metab (Lond)* 2009;6:16.
- [107] Lim EL, Hollingsworth KG, Aribisala BS, et al. Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. *Diabetologia* 2011;54(10):2506–14.
- [108] Phielix E, Meex R, Ouwens DM, et al. High oxidative capacity due to chronic exercise training attenuates lipid-induced insulin resistance. *Diabetes* 2012;61(10):2472–8.

- [109] Bostrom P, Wu J, Jedrychowski MP, et al. A PGC1- α -dependent myokine that drives brown-fat-like development of white fat and thermogenesis. *Nature* 2012;481(7382):463–8.
- [110] Stumvoll M, Goldstein BJ, van Haeften TW. Type 2 diabetes: principles of pathogenesis and therapy. *Lancet* 2005;365(9467):1333–46.
- [111] Yang X, Smith U. Adipose tissue distribution and risk of metabolic disease: does thiazolidinedione-induced adipose tissue redistribution provide a clue to the answer? *Diabetologia* 2007;50(6):1127–39.
- [112] Hagberg CE, Falkevall A, Wang X, et al. Vascular endothelial growth factor B controls endothelial fatty acid uptake. *Nature* 2010;464(7290):917–21.
- [113] Hagberg CE, Mehlem A, Falkevall A, et al. Targeting VEGF-B as a novel treatment for insulin resistance and type 2 diabetes. *Nature* 2012;490(7420):426–30.