

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800

Open access books available

122,000

International authors and editors

135M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.

For more information visit www.intechopen.com



The Sick Adipocyte Theory: The Forces of Clustering at Glance

Valmore Bermúdez et al.*

Endocrine and Metabolic Diseases Research Center, The University of Zulia, Maracaibo, Venezuela

1. Introduction

The concept and repercussions of Obesity have evolved alongside Humankind. First seen as an advantageous trait in the beginning of time, it's now a double edged sword definition that shows how slowly genometabolic traits are acquired and how quickly can environmental factors turn it around. Being obese is not only a matter of Body Mass Index (BMI) and adiposity, its influence stretches out to include type 2 Diabetes Mellitus (T2DM), Psychological disorders like depression, anxiety disorders, and other eating disorders, Osteoarticular problems, Metabolic Syndrome, Cardiovascular Diseases (CVD) like hypertension, stroke, and myocardial infarction, Neurological disorders, Cancer, and even Immunity-related issues, such as low grade inflammation (Must, 1999; Oster, 2000; Thompson, 2001; Marchesini, 2003; Adami, 2003; Niskanen, 2004; Panagiotakos, 2005).

Obesity has been rising slowly yet steadily ever since the Industrial revolution and its pace has increased since the dawn of the 20th Century. Even though nutritional disorders have plagued Man, it was common to see that undernutrition and malnourishment were the higher numbers around the globe. Yet, the tables were turned when Gardner & Halweil published in 2000 that the number of excess-weight patients surpassed the number of the underweight population, welcoming Humanity to the supersized phase of the *land of milk and honey* (O'Dea, 1992). In 2006, the World Health Organization reported that by 2005 1.6 billion above 15 years of age would be overweight and at least 400 million would be obese, while it is predicted to reach 2.3 billion of overweight and over 700 million of obese adults by the year 2015 (World Health Organization [WHO], 2006). The figures published by Kelly et al, 2008 darken the scope, predicting that by 2030 1.12 billion individuals will be obese and 2.16 million will be overweight.

There are many factors that have influenced the increasing prevalence of obesity worldwide, and have influenced the scientific community to coin the term *obesogenic* environment (Egger & Swinburn, 1997) as the external factors that act as "second hit" triggers in the

*Joselyn Rojas^{1,2}, Miguel Aguirre^{1,3}, Clímaco Cano¹, Nailet Arraiz¹, Carlos Silva Paredes¹, Marcos Lima³, Raquel Cano^{1,4}, Eneida Fonseca¹ and Manuel Velasco^{1,5}

1 *Endocrine and Metabolic Diseases Research Center, The University of Zulia, Maracaibo, Venezuela*

2 *Institute of Clinical Immunology, University of Los Andes, Mérida, Venezuela.*

3 *Endocrinology Service, I.A.H.U.L.A, Mérida, Venezuela*

4 *Endocrinology and Metabolic Diseases Unit, University Hospital of Caracas, Venezuela*

5 *Clinical Pharmacologic Unit, Vargas Medical School, Central University of Venezuela, Venezuela*

multifactorial theory of obesity (see Figure 1). Many factors have been nominated and proven key to the etiology of obesity, such as dietary energy intake, physical activity, intrauterine environment (fetal programming), and other comorbidities like alcohol intake, physical disabilities, endocrine disorders, drug treatments, among others (Pi-Sunyer, 2002; Caballero, 2007). Physical activity has become fundamental in the intervention strategies for primary (Pate et al., 1995) and secondary prevention (Thompson, 2003) in obese patients, since it has been portrayed as a major independent risk factor for coronary artery disease (Fletcher et al., 1992). It can be defined as any voluntary skeletal muscle movement that consumes energy, usually measured by at least 30 minutes of physical activity that consumes at least 4 METs (*i.e.* brisk walk) (Dunn et al., 1998). On the contrary, physical *inactivity* (sedentarism) is the lack of these ~ 30 minutes of energy consumption a day (Dunn et al., 1998), resulting in positive energy balance.

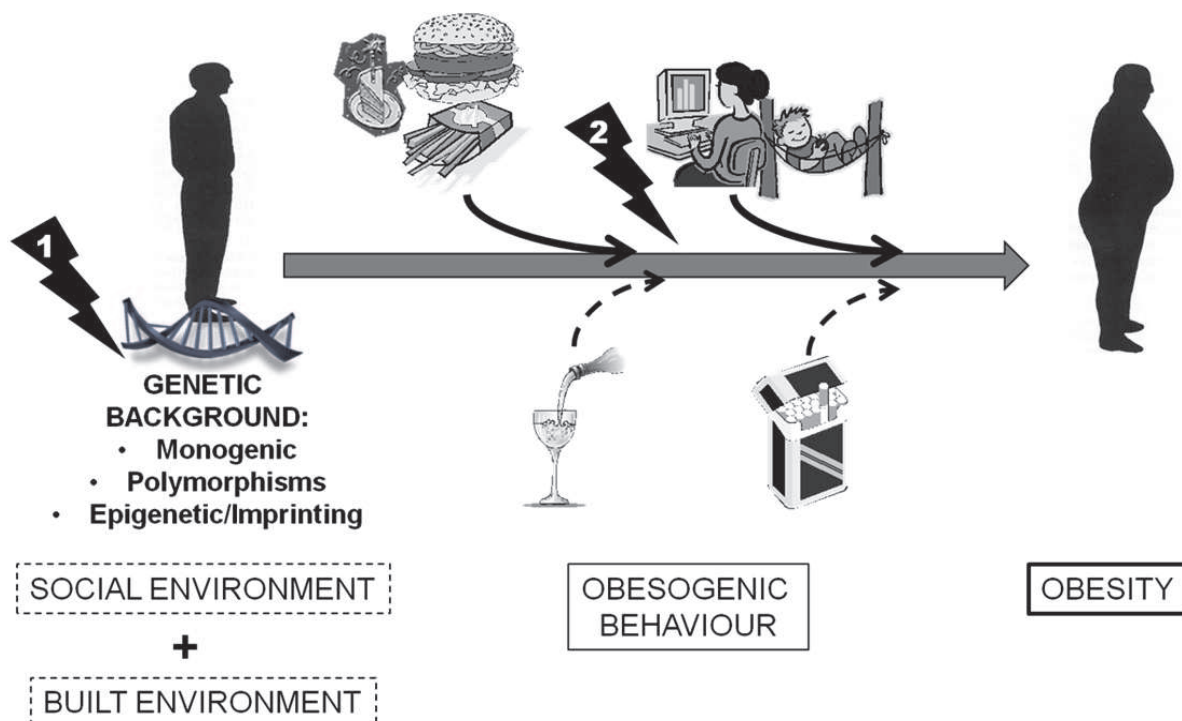


Fig. 1. The Two Hit proposal of obesity. A subject who is genetically-prone to obesity - either due to a monogenic syndrome, associated polymorphisms or imprinting (as seen *in utero*) have the first hit intrinsically. If he is subject to an obesogenic environment and subsequently develops an obesogenic behaviour (second hit), the end result will be progressive weight gain till obesity values are achieved. The obesogenic factors include high fat/carbohydrate diet, low physical activity, alcohol and smoking habits.

One of the interesting aspects about the term "physical activity" is that it's used as an interchangeable term between "cardiorespiratory fitness", but they aren't defined equally nor do they have the same impact on the patients. Physical activity relates to energy expenditure while cardiorespiratory fitness relates to oxygen supplition by the heart. However, both terms can relate to the same definition but they don't explain the same aspects. In a meta-analysis by Williams, 2001 concludes that these terms should be treated as different and independent risk factors, findings that are similar to those reported by Hein et

al., 1992 concerning 4,999 men who were followed for 17 years in the Copenhagen Male Study, using physical fitness and leisure time physical activity as risk factors for ischemic heart disease (IHD). This team reported that being very fit offers no protection to IHD when sedentary, and being unfit and sedentary offers higher risk for this disease. Other studies have examined the relationship between fitness and sedentarism [Fletcher et al., 1996; Rosengren et al., 1997; Pollock et al., 2000; Blair et al., 2001] demonstrating without a doubt that sedentarism has been underestimated for a long time (Saltin, 1992).

2. Set

A sedentary patient is a real conundrum, and each one is unique especially if overweight/obese. Adiposity varies in degree and distribution, being classified according to anatomical location as subcutaneous and visceral adipocytes, each with a different metabolic profiling.

2.1 Adipocytes

Classically, white adipose tissue – adipocytes are recognized as the lipid-storing professional cells, and we remark professional because other types of cells can accumulate lipids yet it is not their main objective, as can be seen with myocytes, β -cells and neurons. The key feature of the mature adipocyte is that it can store fat without compromising its integrity or anatomy. The ontogeny of the adipocytes is still poorly understood, yet the process is being researched relentlessly (Gregoire et al., 1998; Darlington et al., 1998; Godínez-Gutiérrez et al., 2002)]. Mesenchymal stem cells differentiate into adipoblasts, which subsequently express early transcription markers and enter the preadipocyte I phase; the markers for the preadipocytes are $\alpha 2$ Col6, Lipoprotein lipase, IGF-1 and Krox20. Once the cell's fate has been decided, mitosis and clonal expansion begins entering the pre-adipocyte II phase, characterized by active C/EBP β/γ , SREBP-1, PPAR $\gamma 2$ and KLF5. Maturity of the cell cannot begin until it leaves the cell cycle and starts differentiation in coordination with upregulation of late markers which induce cell arrest and begin lipid accumulation: C/EBP α , GLUT4, Perilipin, TNF- α , TGF- β , lipogenic and lipolytic enzymes. The mature adipocyte develops when the markers include the expression and adipocyte-related hormones, cytokines and enzymes related lipid storage and release towards blood circulation. Perhaps the most interesting aspect of adipocyte differentiation is how preadipocytes are driven towards adipocyte profile (Fu et al., 2004; Simons et al., 2005; Sethi et al., 2007), which is all a gameplay of members of the Peroxisome-Proliferator-Activated-Receptors and the CCAAT-enhancer-binding protein (C/EBP) families. The first step is the short-term expression of C/EBP β and C/EBP $\gamma 2$, followed closely by C/EBP α which activates PPAR $\gamma 2$, responsible for the adipogenesis genetic program. The sterol-response-element-binding-protein-1c (SREBP1c) activates the lipogenic program through PPAR γ , finalizing the accomplishment of the differentiated phenotype; see Figure 2.

The mature adipocyte (Gregoire, 2001; Kershaw et al., 2004; Halberg et al., 2008) is a very specialized cell which is the center of energy storage and provision mechanisms, which is under a very tight central and peripheral control. Besides the basic anatomical role, the adipocytes are also endocrine cells which secrete several factors including leptin, adiponectin, TNF- α , acylation stimulation protein, SPARC (secreted protein acidic and rich in cysteine), and PGAR/FIAF (PPAR γ , Angiopoietin related/fasting-

induced adipose tissue). This adipocyte secretome incorporates adipose tissue to immunologic processes with low grade inflammation phenomena and autoimmunity-related diseases, and angiogenesis due to synthesis of angiogenic factors, various effects from macrophagic-related substances, extracellular matrix deposition and metalloproteinase remodeling (Frünbeck et al., 2001; Kershaw, et al., 2004). Given these features is not unusual to find that adipose tissue is part of several axes such as the adipo-insular axis (Kieffer et al., 2000; Vickers et al., 2001) [36-37], the adipocyte-vessels-brain axis (Elmqvist et al., 2004; Guzik et al., 2007; Mietus-Snyder et al., 2008), and the adipocyte-myocyte axis (Sell et al., 2006; Taube et al., 2009).

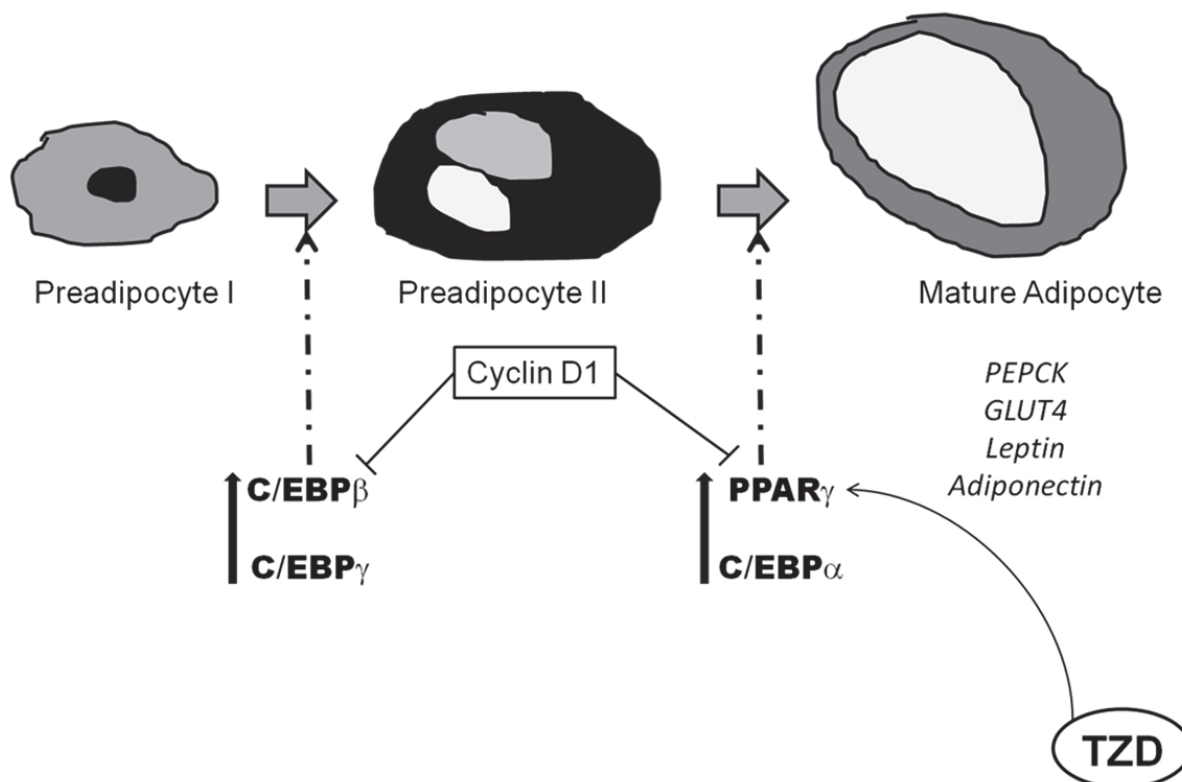


Fig. 2. Adipogenesis. The mature adipocyte goes through several stages of maturation until the professional lipid-storing profile is achieved. The interplay between CCAAT-enhancer binding protein (C/EBP) isoforms with Peroxisome-Proliferator-Activated Receptor- γ (PPAR γ) ensures the progression towards final differentiation once the preadipocyte II has left the cell cycle. As long as Cyclin D1 is active, progression to a G₀ phase will be difficult – almost impossible – since this factor inhibits the differentiation transcription factors. Thiazoliniliones (TZD) are known agonists of the PPAR γ enhancing the adipogenic program.

2.2 Myocytes

Sarcomeres are the functional elements of muscles cells. The contractile unit is composed of myosin fibers and actin, whose interaction allows the shortening of itself, displaying as a contracted myocyte. There are several classifications for muscle cells (Scott et al., 2001), yet the biochemical differentiation is discussed here. Muscle fibers are classified (Pette & Staron, 1997; Bassel-Budy & Olson, 2006) in Type I, Type IIa, Type IIc/x, and Type IIb, having

particular metabolic properties, a) fast-twitch glycolytic fibers (types IIx and IIb), b) fast-twitch oxidative fibers (type IIa), and c) the slow-twitch oxidative fibers (type I). Dynamically, muscle fibers are classified as slow-twitch and fast-twitch motor units, and the fast fibers are subdivided in fast-twitch fatigue-resistant, fast-twitch fatigue-intermediate, and fast-twitch fatigable. Humans have a mixture of these muscle fibers and the number changes as the weight/metabolic profile is modified throughout life. Obese subjects are known to have few type I fibers and more type IIb fibers compared to lean subjects (Hickey et al., 1995). Tanner et al., 2001 reported that obese African-American women had low levels of type I fibers, and lower levels compared to obese Caucasian women, which reflects that fiber content also varies according to ethnicity.

Skeletal muscle is more than just the motor unit which gives us the possibility of movement, it's also the most important tissue for glucose disposal, making it an essential part in energy metabolism (DeFronzo et al., 1985) and the primary target for insulin-resistance related disturbances (Lillioja et al., 1987). The disposal of glucose into skeletal muscle is fiber-specific, being greater in type I fibers compared with type IIa and IIb (Song et al., 1999) [50]. Type I/slow twitch oxidative myocytes are more efficient in regards of insulin binding, enhanced insulin receptor and post-receptor cascade activities, and higher GLUT4 translocation, compared to Type II/fast-twitch glycolytic myocytes; this suggests that insulin's actions are more *oxidative than glycolytic*. Type II muscle fibers are insulin resistant (Henriksen et al., 1990; Henriksen & Holloszy, 1991) giving a partial explanation to the insulin resistance observed in obesity, which is also associated with abnormal lipid partitioning and intramuscular lipid accumulation.

2.3 The sick and the dying

In obesity, myocytes are sick while adipocytes die slowly due to asphyxiation. The interaction of both is what makes the adipocyte-myocyte axis so important in obesity and related diseases including Type 2 Diabetes; see Figure 3.

Plasticity - the ability to non-reversibly adapt to external load/pressure - can be seen in adipocytes, expressed as hypertrophy and hyperplasia (Arner et al., 2010). In overfed states, adipose tissue's capacity to store excessive energy safely reaches its limit, causing a "spill-over" effect all over the body. This nutritional overload mechanism and subsequent damage can be seen in models for catch-up growth (Dulloo et al., 2009; Summhammer et al., 2009), where refeeding states are associated with hyperinsulinemia, lipogenesis, plasma membrane switching from polyunsaturated fatty acids to saturated fatty acids, increased triglyceride production, ending in adipocyte hypertrophy and glucose intolerance. How plasticity can be associated to insulin-resistance is a very complex scenario. Genetic background - *thriftness* - is a strong influential factor (Lindsay et al., 2001; Kadowaki et al., 2003; Prentice et al., 2005). Thrifty related genes and metabolic profiles ensure that all excess energy ingested will be "efficiently" stored, reminiscing those famine/feast days of the hunter-gatherers or the postnatal days of intrauterine-growth-restricted newborns. Thrifty traits have many targets (Prentice et al., 2005), yet 2 are essential: metabolic thrift, which is focused on mitochondrial electronic transport, protein turnover, fuel channeling, and substrate cycling, and adipogenic thrift, which relates to proneness of fat gain.

The physiological adaptation to overnutrition is not without intricacy, since 2 theories have been proposed. The *adipokine dysregulation* conveys the fact that overfed states triggers changes in the quantum and quality of the substances expressed in the adipocyte, for example, adiponectin secretion is lowered in obesity (Arita et al., 1999; Weyer et al., 2001),

while resistin's is enhanced (Steppan et al., 2002; Vendrell et al., 2004). The second theory is based on *ectopic fat accumulation* of lipids in myocytes, hepatocytes and β -cells, where intramyocellular lipids correlates to insulin resistance (Virkamäki et al., 2001; Moro et al., 2008).

The continued stimulus and lipid accumulation makes the adipocyte (140 - 180 μ m in diameter [Brook et al., 1972]) hypertrophy but the size of the cell is limited by the oxygen supply. Hypoxia (Hosogai et al., 2007) and increase synthesis of secretory proteins (Marciniak & Ron, 2006) are the main cause for adipocyte's endoplasmic reticulum (ER) stress via the unfolded protein response (UPR) pathway. The latter proposal is quite simple to grasp since never-ending signals for secretion goes awry when the unfolded protein in the ER lumen surpasses the folded proteins quota due to a) lack of necessary components for the synthesized molecule, b) frequency of the secretion signal, and 3) shortage of chaperone proteins due to "sequestration" within the abnormal proteins accumulated within the lumen. This traffic alteration has been linked to several diseases including Type 2 diabetes (Scheuner & Kaufman, 2008), Tumor hypoxia and prognosis (Koumenis & Wouters, 2006), Alzheimer's (Kudo et al., 2006) and Parkinson's Disease (Ryu et al., 2002).

In 2004, Trayhurn & Woods suggested for the first time that it was hypoxia the culprit for low-chronic inflammation of obesity, conveying that as the adipose tissue advances and the outer sectors become hypoxic, inflammatory cytokines and acute phase proteins are locally secreted to enhance angiogenesis and stop the vicious cycle. Hypoxia in adipose tissue is due to hypoperfusion, especially after the 100 μ m diameter phase of the hypertrophic adipocyte, suggesting that achieving 180 μ m is a hypoxic state (Ye et al., 2007). In adipose tissue, low oxygen levels can alter gene expression, being related to decreased adiponectin mRNA, which is controlled by C/EBP and is inhibited by UPR-induced CHOP (C/EBP homologous protein) (Hosogai et al., 2007). It also can modify adipocyte secretome (Wang et al., 2007), resulting in enhanced expression of Hypoxia Induced Factor-1 α (inducing GLUT1 mRNA), IL-6, leptin, Plasminogen activator inhibitor 1 (PAI-1), and Vascular Endothelial growth factor (VEGF), while haptoglobin and adiponectin are markedly decreased. Taking this one step further, hypoxia inhibit insulin post-receptor cascade through HIF-1 α and HIF-2, which is thought to be crucial for the insulin resistance state observed in obese patients (Regazzetti et al., 2009); this is mediated by lowered autophosphorylation of the insulin receptor by means yet to be understood, but apparently it involves the mTOR (mammalian target of rapamycin) (Dann et al., 2007), S6K pathway (Um et al., 2006) and subsequent activation of NF- κ B (Michiels et al., 2002). Almost 6 years later, hypoxia is now known to be a glucose metabolism modulator, which at first can induce glucose uptake - via GLUT1 synthesis and export - but can later decreased due to IRS-1 and insulin receptor phosphorylation, while at the same time, it can induce free fatty acid (FFA) release, leading to adipocyte dysfunction and worsening of peripheral insulin resistance (Yin et al., 2009; Copps et al., 2009).

To finally dissect adipocyte's cyanotic life, macrophages enter the picture. Adipose tissue is not a homogenous organ, in fact is very heterogeneous and is populated with adipocytes, fibroblasts, vascular endothelia and immunologic cells. One of these, are the macrophages, who contribute significantly to the inflammatory array of signals being sent from the adipocyte (Weisberg et al., 2003). Insulin resistance depends of the abdominal adipose tissue distribution and plasticity, rather than pre-adipocyte and small adipose cells (Hauner, 2010). Adipose tissue macrophages are responsible perpetuating pre-adipocyte state and

differentiation signal (Lacasa et al., 2007), by secreting $\text{TNF-}\alpha$ and IL-1 , known suppressors of the adipogenic program via $\text{NF-}\kappa\text{B}$ which quashes $\text{PPAR}\gamma$ dependent genes. Macrophage's secretome include VEGF, $\text{TNF-}\alpha$, IL-1b , IL-6 , reactive oxygen species (ROS), and prostaglandins. Monocyte recruitment towards the adipose tissue is regulated by many molecules, but C-C motif chemokine ligand 2 (CCL2) and its receptor (CCR2) are perhaps the most important ones (Bruun et al., 2005), so importantly that blocking macrophage infiltration surrounding dead/dying adipocytes is a proper therapeutic goal (Bruun et al., 2005).

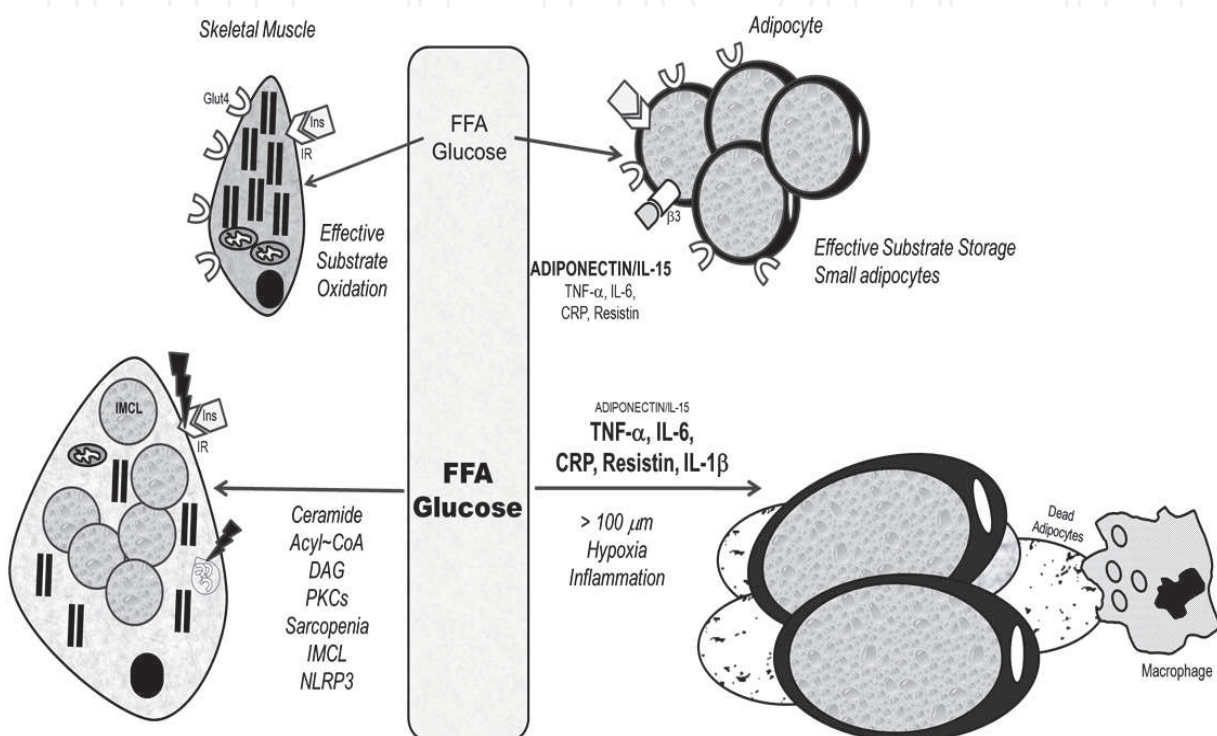


Fig. 3. The Sick and the Dying. This diagram depicts the effects of elevated free fatty acids (FFA) and hyperglycemia on adipocytes and myocytes, as it is observed in obese patients. Once the injury is fixed and has reach a point of no return, both cells begin plasticity to cope with the hostile environment. The sick myocyte loses sarcomeres at the expense of intramyocellular lipid droplets, which are source of acyl-CoAs, diacylglycerol (DAG) and ceramides, who in turn focus on serine/threonine phosphorylation of Insulin receptor and IRS-1, blunting the insulin pathways - becoming insulin resistant- Meanwhile, the growing adipocyte becomes hypoxic, releasing several cytokines who in turn affect myocyte's already weakened metabolism, perpetuating the metabolic disturbance. As the adipocytes die in the sidelines of the adipose tissue, macrophages are recruited, worsening the inflammatory microenvironment.

The progressive growth and demise of adipocytes have collateral damage - a very sick insulin resistant skeletal myocyte. The sick myocyte not only has impaired insulin signaling, but also decreased expression of myogenin (muscle-specific transcription factor involved in myogenesis), IL-6 , IL-8 and MCP-1 (monocyte chemotactic protein), with higher ceramides levels and lower mitochondrial capacity (Sell et al., 2008). How the muscle becomes insulin resistant is (still) a matter of debate, even though several mechanisms have been proposed.

Sir Phillip Randle (1963) was the first one to formulate a theory trying to explain how fuel substrates changed in muscle and how this would explain skeletal muscle insulin resistance (Randle et al., 1963). The Randle's Hypothesis (glucose-fatty acid cycle) proposes that FFA compete with glucose as fuel substrate for mitochondrial oxidation, increasing β -oxidation within the myocyte. The consumption of FFA would in turn inhibit pyruvate dehydrogenase and phosphofructokinase, acting as barriers in the glycolytic pathway and reduced glucose uptake and oxidation. Over 30 years later, Shulman, 2000 singlehandedly dethroned Randle's hypothesis, by stating that low FFA intramyocellular metabolism or enhanced lipid uptake leads to cytosolic accumulation of metabolites such as diacylglycerol, ceramides and acyl-CoA, which in turn activate serine/threonine kinase (PKC) cascade that end with the phosphorylation and inhibition of Insulin Receptor and IRS-1, blunting insulin post-receptor pathways, decreasing PI3-k activation and glucose uptake via GLUT4.

Beyond the glucose utilization blunting, others morphological changes occur within the sick myocyte. Skeletal muscle also shows plasticity traits, anatomical and functional. It can use glucose or lipids for fuel production; however, in obesity lipid oxidation is decreased due to diminished enzyme capacity and reduced carnitine-palmitoyl transferase 1 (CPT1) activity (Kelley et al., 1999). Triglyceride (TAG) accretion in muscle can be attributed to 2 causes: reduced fatty acid oxidation (Kim et al., 2000) or enhance TAG synthesis (Hulver et al., 2003). Intramyocellular lipids (IMCL) are a far better predictor of muscular insulin resistance than BMI or waist-hip ratio (Pan et al., 1997), and it inversely correlates to visceral visfatin levels (Varma et al., 2007). IMCL turnover determines the amount of accumulation inside the myocyte, which modulates the level of lipid metabolites that can alter the PI3K pathways, via activation of PKC isotypes. Breakdown of the IMCL results in acyl-CoAs which can be readily oxidized in mitochondria (Guo, 2007), but it has been reported that obese mitochondria are slow oxidizers (mitochondrial dysfunction [Rabøl et al., 2010; Pagel-Langenickel et al., 2010]) and are positioned in different parts of the cytosol, slowing oxidation and increasing the cytosolic lipid droplet, making this lipid handling alteration a metabolic risk for insulin resistance (Koonen et al., 2010). There is a paradox in this whole IMCL issue: highly trained athletes use IMCL as a source for energy during exercise (Klein et al., 1994), so it makes for quite a riddle. Since from a sports point of view IMCL is advantageous, then the harm is not whether the IMCL are formed or not, it's the availability of toxic lipid intermediates.

Now, how does a dying adipocyte, full of TAG and choking on ER stress, can make the susceptible myocyte sick? Since adipose tissue is considered an endocrine organ, then cross-talks with other organs is plausible. The first evidence of this dialogue was published by Dietze et al., 2002 using skeletal myocytes cultured in the same medium as adipocytes. They reported a profound disturbance in insulin signaling, characterized by nulled insulin-stimulated phosphorylation of IRS-1, reduced Akt activation, inducing an insulin resistant state. Several of the adipokines have been implicated in the process, including TNF- α (Hotamisligil, 1999), resistin (de Luis et al., 2009), IL-6 (Rotter et al., 2003), leptin (Shimomura et al., 1999), adiponectin (Yamauchi et al., 2001), MCP-1 (Sartipy et al., 2003) and RBP-4 (Graham et al., 2006), among others. One important feature between adipose-induced muscle insulin resistance is the role of the macrophages, which are slowly becoming pivotal for (adipose) and skeletal muscle insulin resistance. Macrophages cultured with palmitate serum medium secrete major proinflammatory cytokines that lower insulin action (Samokhvalov et al., 2009) via JNK mediated decreased phosphorylated Akt (Varma et al., 2009). SIRT1, a member of the Sirtuin family of NAD-dependent deacetylases, is able

to blunt macrophages capacity for inducing insulin resistance in Zucker fatty rats, shedding light to the complex axis (Yoshizaki et al., 2010). All in all, adipokine mediators are able to induce reversible (regeneration of myotubes and IL-6 secretion) and irreversible (IL-8 and MCP-1 secretion and myogenin expression) changes in the muscle proteome promoting insulin resistance in the myocyte (Sell et al., 2008; Kewalrami et al., 2010).

3. Go

3.1 Glycemic control

Physical activity and diet are the primary tools to intervene and modify lifestyle in the obese patient, yet it's not exclusive, since these strategies can also be applied to type 2 diabetics, hypertensive patients, and other insulin-disturbances related diseases. Physical activity can be defined as any daily activity undertaken for at least 30 minutes a day that ends in caloric consumption, and it's deficiency is considered an individual risk factor for cardiovascular disease (Carnethon, 2009). It has been proposed the basic etiology of complex diseases is associated with disturbances of oxygen metabolism (Koch & Britton, 2008), making cardiorespiratory fitness a fine predictor for health risk (Lee et al., 2005), metabolic syndrome (LaMonte et al., 2005) and type 2 diabetes (Sawada et al., 2010). Regular exercise improves glycemic control, weight reduction and manages metabolic risks associated with adiposity. The molecular basics for this improvement have been extensively reviewed somewhere else (Hayashi et al., 1997; Hamilton et al.; 2000, Rose et al., 2005) and are shown in Figure 4. The mechanisms that are at play to ensure glucose uptake and consumption seem redundant since it centers on the translocation of GLUT4 towards the membrane, enhanced by AMPK, Ca⁺⁺/Calmodulin dependent protein kinase, and Nitric Oxide, and act as insulin mediators during and after exercise mediating increases glucose and fatty acid oxidation (Turcotte & Fisher, 2008). The main destination of glucose uptake is to replenish the glycogen stores in the skeletal muscle, and it does not depend on insulin signaling, since there is no increase IRS-1, IRS-2 or PI3K activation.

Focusing on the muscle fibers, constant exercise is known to induce a switch of muscle fibers towards the type I ones. Fiber shifts are thought to be the end result of fast myosin chain induction, with concomitant reduction of slow type I myosine. This muscle functional plasticity can be induced by any type of exercise, endurance, sprint or heavy resistance (Andersen et al., 1994; Fitts, 2003). The basic changes of fibers is characterized by reduction of type IIb percentage with slow increase of type IIa and type I, turning muscle metabolism into an oxidant kind over time, and become resistant to fatigue since the myocyte recovers from "metabolic stunnedness" and efficiently synthesizes ATP during and after exercise. The mechanisms underlying these adaptations are still poorly understood, but it is possible that AMPK and calcineurin activate parallel pathways that control myocyte adaptation (Röckl et al., 2007).

AMP-activated protein kinase (AMPK) is a pivotal regulator of intracellular energy during stressful states like starvation, hypoxia, exercise, among others, and it is central in the hormonal control of metabolic processes that consume or produce ATP (Lim et al., 2010). AMPK is active when AMP/ATP ratio rises, inhibiting ATP consuming pathways and enhancing ATP producing processes like glucose and FFA oxidation. During exercise, AMPK is activated and immediately phosphorylates and inhibits acetyl~CoA carboxylase (ACC), the key enzyme that synthesizes malonyl~CoA - negative allosteric modulator of

CPT1. Once CPT1 is released from control, β -oxidation continues full force (Musi et al., 2001). AMPK also modulates glycogen synthesis by increasing glucose availability inside the cell via phosphorylation and inhibition of Akt-Substrate 160 (AS160), main break for translocation of GLUT4 vesicles, and, regulates IMCL breakdown via phosphorylation of Hormone sensitive lipase (Jørgensen et al., 2006). And on a final note, AMPK can modulate the expression of GLUT4 by regulating GLUT4 enhancer factor (GEF) and myocyte enhancer factor 2 (MEF2) (Holmes et al., 2005) guaranteeing an appropriate glucose-uptake phenotype. Calcineurin - cyclosporine-sensitive, calcium-regulated serine/threonine phosphatase - is an enzyme that controls the signaling pathway for myogenic processes by modulation of the MyoD and MEF2 transcription factors (Chin et al., 1998), considered fundamental for fiber remodeling (Schiaffino et al., 2002; Bassel-Duny et al., 2003) with PPAR δ as downstream effector (Wang et al., 2004).

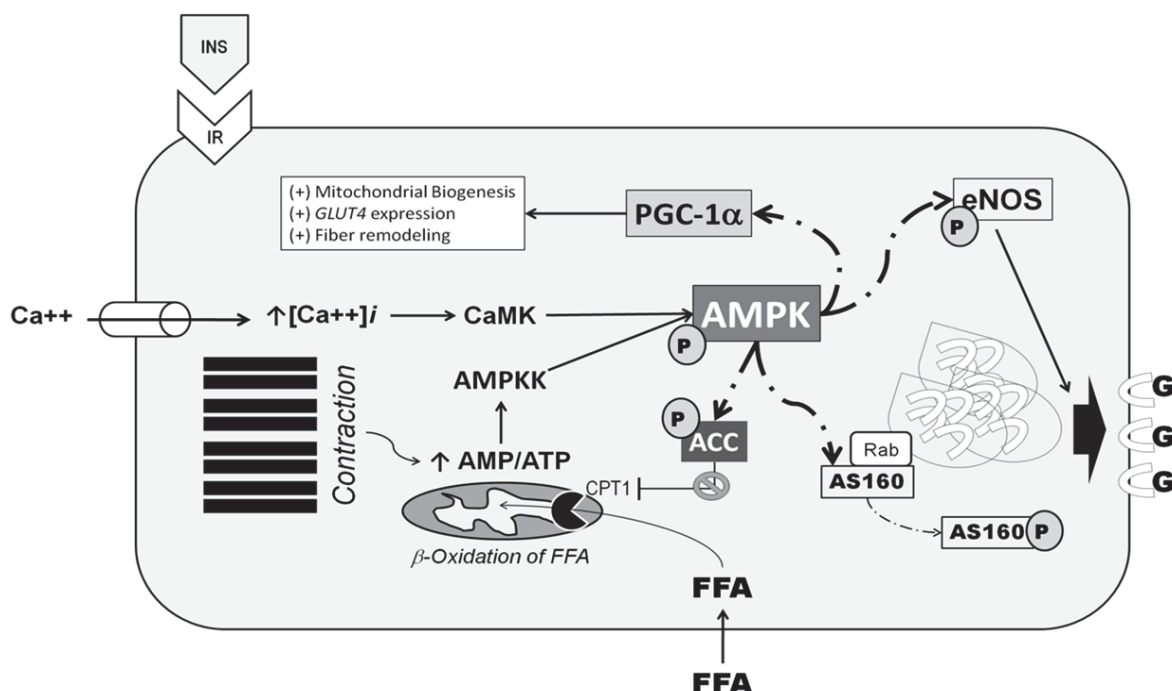


Fig. 4. Molecular basics of exercise. Once the AMP/ATP rises continuously according to muscle workout, AMPK kinase (AMPKK) is activated, alongside Ca^{++} /calmodulin dependent Kinase (CaMK), both known to phosphorylate the α -subunit of AMPK, activating it. AMPK then inhibits by phosphorylation Acetyl~CoA Carboxilase, enzyme known to synthesize malonyl~CoA, main negative modulator of carnitine-palmitoyl transferase 1 (CPT1); blocking malonyl~CoA synthesis, β -oxidation is enhanced, using free fatty acids (FFA) from circulation and from lipid storage inside the myocyte. Secondly, AMPK activates PPAR γ coactivator 1 α (PGC-1 α) which co-induces the PPAR γ adipogenic program. Next, AMPK phosphorylates and activates endothelial Nitric Oxide Synthetase, which generates nitric oxide which serves as a vasodilator (increasing and maintaining blood flow) and is also an enhancer of GLUT4 translocation. Finally, AMPK phosphorylates Akt Substrate 160 (AS160), who is blocking Rab-GTPase molecule from initiating the movements of the GLUT4 vesicles towards the membrane. Once AS160 is "neutralized", GLUT4 are exported to the plasma membrane, increasing glucose uptake.

Insulin sensitivity restoration is a bit more complicated. Muscle straightening activity has been known to enhance sensitivity among adults, serving as proper program to reduce insulin resistance (Cheng et al., 2007). Glucose uptake and IMCL turnover have been implicated, yet there is paradox lingering around, endurance athletes have higher intramuscular lipids but are highly insulin sensitive (Goodpaster et al., 2001; Meex et al., 2010). Now, this beneficial effect can be obtained whether acutely – daily muscle contraction inducer energy flux – and by chronic modifications – mitochondrial oxidative capacity and induced GLUT4 expression (Thyfaut, 2008; Jiang et al., 2010).

3.2 Thriftiness

As we have formerly mentioned, exercise is associated with modification of gene expression, specially affecting genes that control energy deposit and consumption, even in high training statuses. The Thrifty genotype theory published in 1962 (Neel, 1962) proposed that genes that favored energy saving during feast/famine cycles in the Late Paleolithic Era were incorporated into the human genome, because they were advantageous during famine phases. Exercise can modify gene expression according to the type of activity exerted, for example, aerobic exercise (endurance) is not associated with increased phosphorylated p70^{S6K}, but high resistance work-out is indeed related (Sherwood et al., 1999). Wendorf & Goldfine, 1991 proposed that during those hunter-gatherers years a selective insulin resistance in muscle had to be imposed, to avoid hypoglycemia during fasting and allow energy storage during feeding, traits that would turn disastrous in a sedentary individual, such as the obese patient. Evidence of this theory can be seen in different racial groups all around the world. The Arizona Pima Indians have the highest prevalence of diabetes in the world with increased sedentarism, compared to the Mexican Pimas (Valencia et al., 1999) and the scenario is similar with the Pacific Islanders in Asia (Zimmet et al., 1990). Needless to say, physical inactivity is then associated with insulin resistance and the genetic implications of exercise and its mediators are an important aspect of the whole concept, and in desperate need of continuous investigation (Abate et al., 2003; Chakravarthy et al., 2004).

3.3 Inflammation

Other metabolic changes are observed during physical training in obese patients, such as anti-inflammatory effects. In previous sections, the low-grade inflammation characteristically seen in obesity was discussed. Pedersen et al., 2007 reported that since the muscle was able to release cytokines under exercise conditions, these signaling molecules should be named *myokines* and the para/endocrine effects should be separated from their usual physiological profile.

Interleukin-6 is perhaps the most important of these myokines, yet the muscle is known to secrete IL-8, IL-15, IL-10 and IL-1ra, and very intense exercise can induce TNF- α secretion (see Table 1) (Petersen et al., 2005; Marini et al., 2010). The IL-6 expression and release pattern is astounding, with a 100-fold level in response to exercise. The dilemma lies in this: how does a known insulin resistance-mediating molecule can exert protective effects? The answer lies in the true inflammatory levels and profiles. It has been suggested that IL-6 plays a villain role in the metabolic syndrome, alongside TNF- α . Nevertheless, Kubaszek et al., 2003 reported that the risk genotypes for metabolic disturbances (including obesity and type 2 diabetes) are characterized by increased transcription of TNF- α with decreased expression of IL-6. Now, the reader needs to be reminded that TNF- α triggers the release of

IL-6, not the other way around, so it's logical to conclude that adipocyte derived TNF- α induces local expression of IL-6 in the adipose tissue (Pedersen et al., 2007), which correlates with the fact that IL-6 is not overtly elevated in diabetic patients and is not highly expressed in lean patients with insulin resistance (Carey et al., 2004). The insulin-sensitizing effects of IL-6 are still controversial, yet it has been reported that the myokine enhances glucose uptake and glycogen synthesis in the myocyte, via activation of AMPK while reducing TNF- α levels (Pedersen et al., 2007).

Myokine	Locus	Effect
IL-6	7p21	Anti-inflammatory when secreted before TNF- α (Carey et al., 2004; Pedersen et al., 2007).
IL-8	4q12-q13	Angiogenesis and neutrophil chemoattraction thru the CXCR2 (Freydelund et al., 2007).
IL-15	4q31	Reduction of body fat, especially visceral body fat (Carbó et al., 2001; Acharyya et al., 2004)
IL-10	1q31-q32	Downregulation of Proinflammatory cytokines and chemokines (de Vries, 1995; Acharyya et al., 2004)
IL-1ra	2q14.2	Restriction and modulation of the inflammatory response during exercise (Ostrowski et al., 1999; Opal et al., 2000; Suzuki et al., 2000)

Table 1. Myokines and their effects concerning Obesity and Metabolic Syndrome.

Parallel to IL-6 effects, IL-15 has progressively risen as a major modulator of fat metabolism and muscle accretion in skeletal muscle over the past 15 years, which have been discussed elsewhere (Carbó et al., 2000; Quinn et al., 2008; Argilés et al., 2009), yet the following aspects need to be discussed. IL-15 is a cytokine which is related to NK cell maturation, which actions are not reserved for the immunology universe. This protein is synthesized also by placenta, muscle and other tissues, supporting the idea of non-immune functions in such organs. Muscle hypertrophy at the expense of myotube accretion by inhibition of protein degradation is observed in animal models (Quinn et al., 2002), and this has been proposed as a therapeutic option for wasting syndromes such as cancer (Carbó et al., 2000). This effect is probably due to induction of PPAR- δ which mediates protein synthesis in such cells. As for adipose tissue, the cytokine has been related to reduce lipid accumulation in pre-adipocytes enhancing their differentiation, and inducing adiponectin secretion in matured adipocytes (Quinn et al., 2005). These findings were further confirmed, when it was proven that IL-15 effect also reached brown adipose tissue, with an acute induction of thermogenesis via upregulation of Uncoupling Proteins 1 and 3, PPAR- δ and - α and a final association with reduction of white adipose tissue mass (Almendo et al., 2008). The evidence pointed to a more multifaceted muscle-adipose axis with IL-15 as remote modulator (Quinn et al., 2009) when secreted from skeletal muscle, inducing GLUT4, enhancing glucose utilization, reducing adipose deposition and adipocyte size. Further studies have linked polymorphisms of IL-15 and metabolic syndrome propensity, including the following protein SNPs: rs1589241, rs1057972 (Pistilli et al., 2008), with a unique relation to metabolically obese normal weight patients (Di Renzo et al., 2006).

On a final note, a new twist in the *metainflammation phenomena* (Hotamisligil, 2006) observed in obesity has been described. The innate receptors members of the Pattern Recognition

Receptor Family, the NLRPs, are part of an ancestral detection system which recognizes danger associated molecules, resulting in the recruitment of Caspase-1 and the activation of IL-1 β and IL-18, known proinflammatory cytokines (Lamkanfi & Dixit, 2009). Receptor NLRP3 has been associated to lipotoxicity sensing by recognizing ceramides production in macrophages and adipocytes, contributing to obesity-related inflammation by synthesis of IL-1 β and blunted insulin signaling in liver and adipose tissue (Vandanmagsar et al., 2011). Moreover, IL-1 β has been proven to regulate adipogenesis towards a more insulin resistance phenotype (Stienstra et al., 2010), which renders fundamental in a proinflammatory and toxic environment which is seen around the hypoxic and pre-adipocyte rich areas of adipose tissue.

4. Conclusions

Obesity is a multifactorial disease, characterized by adiposity-related consequences and disease, such as type 2 diabetes, cardiovascular disease, obstructive sleeping apnea, osteoarthritis, and cancer. Understanding the molecular dialogue between the 2 principally affected cells – adipocyte and skeletal myocyte – serves as the underlying scientific platform to understand why physical activity is beneficial and mandatory in these patients. The very notion that glucose uptake is enhanced in skeletal muscle during and after exercise provides a great glycemic control strategy, lowering the effects of excessive glucose in circulating plasma, like glycosylated hemoglobin levels (Andrade-Rodríguez et al., 2007; Sigal et al., 2007), increases plasma glutamine and arginine levels for the production of NO and glutathione not only improving vasodilation properties but also increasing antioxidant defenses (Krause & de Bittencourt, 2008), and myocyte-derived IL-6 enhances glucose induced insulin secretion (Newsholme et al., 2010).

The application of a proper exercise program in obese patients, along with diet and lifestyle modification, ensures that the obese myocyte will get in shape, with a dynamic IMCL turnover, improved glucose and fat oxidation, genetic modulation of fiber remodeling, ending in progressive and sustained metabolic control. The dying myocytes will stop being so stressed with external stimuli and over-availability of substrates, decreasing in size and in oxygen requirements, modulating macrophage recruitment and inflammatory signals derived from them. The application of therapeutic drugs to improve the effects of exercise and act synergistically has been reported.

Thiazolidinediones (TZD) are a group of drugs that activate PPAR γ , modulating all the downstream genes regulated by the transcription factor, including acyl-CoA synthetase, phosphoenolpyruvate carboxykinase and lipoprotein lipase, inducing FFA capture and storage in de novo adipocytes, lowering FFA levels in plasma at the cost of fast redistribution (“Lipid-steal” phenomenon) (Bermúdez et al., 2010). In insulin resistant models, TZD correct impaired myocyte insulin action (Zierath et al., 1998), normalize muscular insulin sensitivity and GLUT4 synthesis in conjunction with exercise (Hayener et al., 2000), lower waist-hip ratio due to a selective increase in lower body fat (Shadid et al., 2003), improve exercise capacity in type 2 diabetic patients (Regensteiner et al., 2005), and increase adiponectin levels (Yang et al., 2002) just as exercise does (Kriketos et al., 2004; Højbjerg et al., 2007); which is why the combination of a TZD and exercise are self-complementary in the treatment of insulin resistance (Lessard et al., 2007). The world-famous biguanide, Metformin, is the other pharmacological candidate to enhance exercise effects on the insulin resistance milieu. Exercise has been known to improve metformin

effects (Tang et al., 2001), acting as co-adjuvants in the reduction of the incident of diabetes (Doggrell, 2002), increasing vascular function and lowering Ischemia Coronary Artery Disease patients (Jadhay et al., 2006), and finally, both can reduce the expression of the fat transporter FAT/CD36, blunting the progression of ceramides-mediated insulin resistance in myocyte (Smith et al., 2007). The insulin sensitizing effect of metformin are carried out via activation of AMPK (Hawley et al., 2002), simulating the very first effects on physical activity in skeletal muscle. Finally, Exercise is an ideal lifestyle intervention suitable and rightful to all obese patients, due to its counteracting measures against the molecular derangements observed in obesity, modulating local and systemic metabolic disturbances.

5. References

- Abate N. & Chandalia M. (2003). The impact of ethnicity on type 2 diabetes. *Journal of Diabetes and its Complications* Vol. 17, No. 1 (January - February 2003), pp. 39-58.
- Acharyya S, Ladner K, Nelsen LL, Damrauer J, Reiser PJ, et al. (2004). Cancer cachexia is regulated by selective targeting of skeletal muscle gene products. *Journal of Clinical Investigation* Vol. 114, No. 3 (August 2004), pp. 370-78.
- Adami HO & Trichopoulos D. (2003). Obesity and mortality from cancer. *New England Journal of Medicine* Vol. 348, No.17 (April 2003), pp.1623-24.
- Almendo V, Fuster G, Busquets S, Ametller E, Figueras M, et al. (2008). Effects of IL-15 on rat brown adipose tissue: uncoupling proteins and PPARs. *Obesity* Vol. 16, No. 2 (February 2008), pp. 285-89.
- Andersen JL, Klitgaard H & Saltin B. (1994). "Myosin heavy chain isoforms in single fibers from m. vastus lateralis of sprinters: influence of training". *Acta Physiologica Scandinavica* Vol. 151, No. 2 (June 1994), pp. 135-42.
- Andrade-Rodríguez HJ, Valadez-Castillo FJ, Hernández-Sierra JF, Gordillo-Moscoso AA, Dávila-Esqueda ME, et al. (2007). Effectiveness of supervised aerobic exercised in alternating weekdays associated with glycosilated hemoglobin levels among type 2 sedentary diabetic patients. *Gaceta Medica de Mexico* Vol. 143, No. 1 (January-February 2007), pp. 11-5.
- Argilés JM, López-Soriano FJ & Busquets S. (2009). Therapeutic potential of interleukin-15: a myokine involved in muscle wasting and adiposity. *Drug Discovery Today* Vol. 14, No. 3-4 (February 2009), pp. 208-13.
- Arita Y, Kihara S, Ouchi N, Takahashi M, Maeda K, et al. (1999). Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. *Biochemical and Biophysical Research Communications* Vol. 257, No. 1 (April 1999), pp.79-83.
- Arner E, Westermark PO, Spalding KL, Britton T, Rydén M, et al. (2010). Adipocyte turnover: relevance to human adipose tissue morphology". *Diabetes* Vol. 59, No. 1 (January 2010), pp. 105-09.
- Bassel-Duby R & Olson E. (2006). Signaling pathways in skeletal remodeling. *Annual Review of Biochemistry* Vol. 75, pp. 19-37.
- Bassel-Duny R & Olson EN. (2003). Role of calcineurin in striated muscle: development, adaptation and disease. *Biochemical and Biophysical Research Communications* Vol. 311, No. 4 (November 2003), pp. 1133-1141.
- Bermúdez V, Finol F, Parra N, Parra M, Pérez A, et al. "PPAR- γ agonists and their role in type 2 diabetes mellitus management". *American Journal of Therapeutics* Vol. 17, No. 3 (May-June 2010), pp. 274-283.

- Blair SN, Cheng Y & Holder JS. (2001). Is physical activity or physical fitness more important in defining health benefits?. *Medicine Science in Sports and Exercise* Vol.33, No.6 (June 2001), pp.S379-S399.
- Brook CG, Lloyd JK & Wolf OH. Relation between age of onset of obesity and size and number of adipose cells. *British Medical Journal* Vol. 2, No. 5804 (April 1972), pp. 25-27.
- Bruun JM, Lihn AS, Pedersen SB, Richelsen B. (2005). Monocyte chemoattractant protein-1 release is higher in visceral than subcutaneous human adipose tissue (AT): implication of macrophage resident in the AT. *Journal of Clinical Endocrinology and Metabolism* Vol. 90, No. 4 (April 2005), pp. 2282-89.
- Caballero B (2007). The global epidemic of obesity: an overview. *Epidemiologic Reviews* Vol.29, (June 2007), pp.1-5.
- Carbó N, López-Soriano J, Costelli P, Alvarez B, Busquets S, et al. (2001). Interleukin-15 mediates reciprocal regulation of adipose and muscle mass: a potential role in body weight control. *Biochimica et Biophysica Acta* Vol. 1526, No. 1 (April 2001), pp. 17-24.
- Carbó N, López-Soriano J, Costelli P, Busquets S, Alvarez B, et al. (2000). Interleukin-15 antagonizes protein waste in tumour-bearing rats. *British Journal of Cancer* Vol. 83, No. 4 (August 2000), pp. 526-31.
- Carey AL, Bruce CR, Sacchetti M, Anderson MJ, Olsen DB, et al. (2004). Interleukin-6 and tumor necrosis factor-alpha are not increases in patients with type 2 diabetes: evidence that plasma IL-6 is related to fat mass and not insulin responsiveness. *Diabetologia* Vol. 47, No. 6 (June 2004), pp. 1029-37.
- Carnethon MR. (2009). Physical activity and cardiovascular disease: how much is enough?. *American Journal of Lifestyle Medicine* Vol. 3, No. 1 (July 2009), pp. 44S-49S.
- Chakravarthy M. &Booth FW. (2004). Eating, exercise and 'thrifty' genotypes: connecting the dots toward an evolutionary understanding of modern chronic disease. *Journal of Applied Physiology* Vol. 96, No. 1 (January 2004), pp. 3-10.
- Cheng YJ, Gregg E, De Rekeneire N, Williams DE, Imperatore G, et al. (2007). Muscle-strengthening activity and its association with insulin sensitivity. *Diabetes Care* Vol. 30, No. 9 (September 2007), pp. 2264-70.
- Chin E, Olson EN, Richardson JA, Yang Q, Humphries C, et al. (1998). A calcineurin - dependent transcriptional pathway controls skeletal muscle fiber type. *Genes & Development* Vol. 12, No. 16 (August 1998), pp. 2499-2509.
- Copps K &White M. (2009) Breathing room: the (un)natural history of adipose microhypoxia and insulin resistance. *Diabetes* Vol. 58, No. 1 (January 2009), pp.26-27.
- Dann SG, Selvaraj A & Thomas G. mTOR complex1-S6K1 signaling: at the crossroads of obesity, diabetes and cancer. *Trends in Molecular Medicine* Vol. 13, No. 6 (June 2007), pp. 252-59.
- Darlington G, Ross S & MacDougald O. (1998). The role of C/EBP genes in adipocyte differentiation. *Journal of Biological Chemistry* Vol.273, No.46 (November 1998), pp. 30057-060.
- de Luis DA, Gonzalez Sagrado M, Conde R, Aller R, Izaola O, et al. (2009). Relation of resistin levels with cardiovascular risk factors and insulin resistance in non-diabetes obese patients. *Diabetes Research and Clinical Practice* Vol. 84, No. 2 (May 2009), pp.174-8.

- de Vries J. (1995). Immunosuppressive and anti-inflammatory properties of interleukin 10. *Annals of Medicine* Vol. 25, No. 5 (October 1995), pp. 537-41.
- DeFronzo RA, Gunnarsson R, et al. (1985). Effect of insulin on peripheral and splanchnic glucose metabolism in noninsulin-dependent (type II) diabetes mellitus. *Journal of Clinical Investigation* Vol.76, No. 1 (July 1985), pp. 149-155.
- Di Renzo L, Bigioni M, Bottini FG, Del Gobbo V, Premrov MG, et al. (2006). Normal weight obese syndrome: role of single nucleotide polymorphism of IL-15Ralpha and MTHFR 677C–T genes in the relationship between body composition and resting metabolic rate. *European Review for Medical Pharmacological Sciences* Vol. 10, No. 5 (September-October 2006), pp. 235-45.
- Dietze D, Koenen M, Röhrig K, Horikoshi H, Hauner H, et al. (2002). Impairment of insulin signaling in human skeletal muscle cells by co-culture with human adipocytes. *Diabetes* Vol. 51, No. 8 (August 2002), pp. 2369-76.
- Doggrell S. (2002). Metformin & lifestyle intervention prevent type 2 diabetes: lifestyle intervention has the greater effect. *Expert Opinion on Pharmacotherapy* Vol. 3, No. 7 (July 2002), pp. 1011-13.
- Dulloo AG, Jacquet J, Seydoux J, Montani JP. (2006). The thrifty 'catch-up fat' phenotype: its impact on insulin sensitivity during growth trajectories to obesity and metabolic syndrome. *International Journal of Obesity (London)* Vol.30, No. S4 (December 2006), pp. S23-S35.
- Dunn A, Andersen R, Jakicic JM. (1998). Lifestyle physical activity interventions. History, short- and long-term effects, and recommendations. *American Journal of Preventive Medicine* Vol.15, No.4 (November 1998), pp.398-412.
- Egger G & Swinburn B (1997). An ecological approach to the obesity pandemic. *British Medical Journal* Vol.315, No.7106 (August 1997), pp.477-80.
- Elmqvist JK & Flier J. (2004). The fat-brain axis enters a new dimension. *Science* Vol. 304, No. 5667 (April 2004), pp. 63-64.
- Fitts R. (2003). Effects of regular exercise training on skeletal contractile function". *American Journal of Physical Medicine & Rehabilitation* Vol. 82, No. 4 (April 2003), pp. 320-31.
- Fletcher GF, Balady G, Blair SN, Blumenthal J, Caspersen C, et al. (1996). A statement for Health Professionals by the Committee on Exercise and Cardiac rehabilitation of the Council on Clinical Cardiology, American Heart Association.. *Circulation* Vol.94, No.4 (August 1996), pp.857-62.
- Fletcher GF, Blair SN, Blumenthal J, Caspersen C, Chaitman B, et al. (1992). Statement on exercise. Benefits and recommendations for the physical activity programs for all Americans. A statement for health professionals by the Committee on Exercise and Cardiac Rehabilitation of the Council on Clinical Cardiology, American Heart Association. *Circulation* Vol.86, No.1 (July 1992), pp.340-44.
- Frühbeck G, Gómez-Ambrosi J, Muruzábal FJ, Burrell MA. (2001). The adipocyte: a model for integration of endocrine and metabolic signaling in energy metabolism regulation. *American Journal of Physiology Endocrinology and Metabolism* Vol. 280, No. 6 (June 2001), pp. E827-E847.
- Frydelund-Larsen L, Penkowa M, Akerstrom T, Zankari A, Nielsen S, et al. (2007). Exercise induces interleukin-8 receptor (CXCR2) expression in human skeletal muscle. *Experimental Physiology* Vol. 92, No. 1 (January 2007), pp. 233-40.

- Fu M, Wang C, Li Z, Sakamaki T, Pestell RG. (2004). Cyclin D1: normal and abnormal functions. *Endocrinology* Vol.145, No. 12 (December 2004), pp.5439-47.
- Gardner G & Halweil B (2000). "Hunger, escaping excess". *World Watch* Vol.13, No.4 (July 2000), pp.25-35.
- Godínez-Gutiérrez S, Marmolejo-Orozco G, Marquez-Rodríguez E, Siordia-Vázquez JJ & Baeza-Camacho R. (2002). La grasa visceral y su importancia en obesidad. *Revista de Endocrinología y Nutrición* Vol. 10, No. 3 (July-September 2002), pp.121-27.
- Goodpaster B, He J, Watkins S, Kelley D. (2001). Skeletal muscle lipid content and insulin resistance: evidence for a paradox in endurance-trained athletes. *Journal of Clinical Endocrinology and Metabolism* Vol. 86, No. 1 (December 2001), pp. 5755-5761.
- Graham T, Yang Q, Blüher M, Hammarstedt A, Ciaraldi TP, et al. (2006). Retinol-binding protein 4 and insulin resistance in lean, obese, and diabetic subjects. *New England Journal of Medicine* Vol.354, No. 24 (June 2006), pp.2552-63.
- Gregoire F, Smas C & Sul HS (1998). Understanding adipocyte differentiation. *Physiological Reviews* Vol.78, No.3 (July 1998), pp.783-809.
- Gregoire F. (2001). Adipocyte differentiation: from fibroblast to endocrine cell. *Experimental Biology and Medicine* Vol.226, No. 11 (December 2001), pp.997-1002.
- Guo Z. (2007). Intramyocellular lipid kinetics and insulin resistance. *Lipids in Health and Disease* Vol. 6 (July 2007), pp.18-25.
- Guzik TJ, Marvar PJ, Czesnikiewicz-Guzik M, Korbut R. (2007). Perivascular adipose tissue as a Messenger of the brain-vessel axis: role in vascular inflammation and dysfunction". *Journal of Physiological Pharmacology* Vol.58, No. 4 (December 2007), pp.591-610.
- Halberg N, Wernstedt-Asterholm I, & Scherer PE. (2008). The adipocyte as an endocrine cell. *Endocrinology and Metabolism Clinics of North America* Vol. 37, No. 3 (September 2008), pp. 753-68.
- Hamilton M & Booth F. (2000). Skeletal muscle adaptation to exercise: a century of progress. *Journal of Applied Physiology* Vol. 88, No. 1 (January 2000), pp. 327-331.
- Hauer H. (2010). Adipose tissue inflammation: are small or large fat cells to blame?. *Diabetologia* Vol. 53, No. 2 (February 2010), pp. 223-225.
- Havener A, Reichart D & Olefsky J. (2000). Exercise and thiazolidinedione therapy normalize insulin action in the obese Zucker fatty rat. *Diabetes* Vol. 49, No. 12 (December 2000), pp. 2154-59.
- Hawley S, Gadalla AE, Olsen GS, Hardie DG. (2002). The antidiabetic drug metformin activates the AMP-activated protein kinase cascade via an Adenine Nucleotide-independent mechanism. *Diabetes* Vol. 51, No. 8 (August 2002), pp. 2420-25.
- Hayashi T, Wojtaszeski J & Goodyear L. (1997). Exercise regulation of glucose in skeletal muscle. *American Journal of Physiology Endocrinology and Metabolism* Vol. 273, No. 6 pt1 (December 1997), pp. E1039-E1051.
- Hein HO, Suadicani P, Gyntelberg F. (1992). Physical fitness or physical activity as predictor of ischemic heart disease? A 17-year follow-up in the Copenhagen Male Study. *Journal of Internal Medicine* Vol.232, No.6 (December 1992), pp.471-79.
- Henriksen EJ & Holloszy JO. Effect of diffusion distance on measurement of rat skeletal muscle glucose transport in vitro. *Acta Physiologica Scandinavica* Vol.143, No. 4 (December 1991), pp. 381-86.

- Henriksen EJ, Bourey RE, Rodnick KJ, Koranyi L, Permutt MA, Holloszy JO. (1990). Glucose transport protein content and glucose transport capacity in rat skeletal muscle: *American Journal of Physiology Endocrinology and Metabolism* Vol. 259, No. 4(pt 1) (October 1990), pp. E593-E598.
- Hickey MS, Carey JO, Azevedo JL, Houmard JA, Pories WJ, Israel RG, Dohm GL. (1995). Skeletal muscle fiber composition is related to adiposity and in vitro glucose transport rate in humans. *American Journal of Physiology Endocrinology and Metabolism* Vol. 268, No. 3(pt 1) (March 1995), pp. E453-E457.
- Højbjerg L, Rosenzweig M, Dela F, Bruun JM, Stallknecht B. (2007). Acute exercise increases adipose tissue interstitial adiponectin concentration in healthy overweight and lean subjects. *European Journal of Endocrinology* Vol. 157, No. 5 (November 2007), pp. 613-23.
- Holmes B, Sparling DP, Olson AL, Winder WW, Dohm GL. (2005). Regulation of muscle GLUT4 enhancer factor and myocyte enhancer factor 2 by AMP-activated protein kinase. *American Journal of Physiology Endocrinology and Metabolism* Vol. 289, No. 6 (December 2005), pp. E1071-E1076.
- Hosogai N, Fukuhara A, Oshima K, Miyata Y, Tanaka S, et al. (2007). Adipose tissue hypoxia in obesity and its impact on adipocytokine dysregulation. *Diabetes* Vol. 56, No. 4 (April 2007), pp. 901-11.
- Hotamisligil GS. (1999). Mechanism of TNF-alpha induced insulin resistance. *Experimental and Clinical Endocrinology & Diabetes* Vol. 107, No. 2, pp.119-125.
- Hotamisligil GS. (2006). Inflammation and metabolic disorders. *Nature* Vol. 444, No. 7121 (December 2006), pp. 860-67.
- Hulver MW, Berggren JR, Cortright RN, Dudek RW, Thompson RP, et al. (2003). Skeletal muscle lipid metabolism with obesity. *American Journal of Physiology Endocrinology and Metabolism* Vol. 284, No. 4 (April 2003), pp. E741-E747.
- Jadhav S, Ferrel W, Greer I, Petrie JR, Cobbe SM, et al. (2006). Effects of metformin on microvascular function and exercise tolerance in women with angina and normal coronary arteries. *Journal of the American College of Cardiology* Vol. 48, No. 5 (September 2006), pp. 956-96.
- Jiang LQ, Garcia-Roves PM, de Castro Barbosa T, Zierath JR. (2010). Constitutively active calcineurin in skeletal muscle increases endurance performance and mitochondrial respiratory capacity. *American Journal of Physiology Endocrinology and Metabolism* Vol. 298, No. 1 (January 2010), pp. E8-E16.
- Jørgensen S, Richter EA & Wojtaszewski J. (2006). Role of AMPK in skeletal muscle metabolic regulation and adaptation in relation to exercise. *Physiology* Vol. 574, No. pt 1 (July 2006), pp. 17-31.
- Kadowaki T, Hara K, Yamauchi T, Terauchi Y, Tobe K, et al. (2003). Molecular mechanism of insulin resistance and obesity. *Experimental Biology and Medicine* Vol.228, No. 10 (November 2003), pp. 1111-1117.
- Kelley DE, Goodpaster B, Wing RR, Simoneau JA. (1999). Skeletal muscle fatty acid metabolism in association with insulin resistance, obesity and weight loss. *American Journal of Physiology Endocrinology and Metabolism* Vol. 277, No.6 pt 1(December 1999), pp. E1130-E1141.

- Kelly T, Yang W, Chen CS, Reynolds K, He J. (2008). Global burden of obesity in 2005 and projections to 2030. *International Journal of Obesity (London)* Vol.32, No.9 (September 2008), pp.1431-37.
- Kershaw E & Flier J. (2004). Adipose tissue as an endocrine organ. *Journal of Clinical Endocrinology & Metabolism* Vol 89, No. 6 (June 2004), pp. 2548-56.
- Kewalrami G, Bilan OJ & Klip A. (2010). Muscle insulin resistance: assault by lipids, cytokines and local macrophages". *Current Opinion in Clinical Nutrition and Metabolic Care* Vol. 13, No. 4 (July 2010), pp.382-90.
- Kieffer TJ & Habener JF. (2000). The adipoinsular axis: effects of leptin on pancreatic β -cells. *American Journal of Physiology Endocrinology and Metabolism* Vol. 278, No. 1 (January 2000), pp.E1-E14.
- Kim JY, Hickner RC, Cortright RL, Dohm GL, Houmard JA. (2000). Lipid oxidation is reduced in obese human skeletal muscle. *American Journal of Physiology Endocrinology and Metabolism* Vol. 279, No. 5 (November 2000), pp. E1039-E1044.
- Klein S, Coyle EF & Wolfe RR. (1994). Fat metabolism during low-intensity exercise in endurance-trained and untrained men. *American Journal of Physiology Endocrinology and Metabolism* Vol. 267, No. 6 pt 1 (December 1994), pp. E934-E940.
- Koch LG & Britton SL. (2008). Aerobic metabolism underlies complexity and capacity. *Journal of Physiology* Vol. 586, No. 1 (January 2008), pp. 83-95.
- Koonen D, Sung M, Kao C, Dolinsky VW, Koves TR, et al. (2010). Alterations in skeletal muscle fatty acid handling predisposes middle-aged mice to diet-induced insulin resistance. *Diabetes* Vol. 59, No. 6 (June 2010), pp. 1366-75.
- Koumenis C & Wouters B. (2006). Translating tumor hypoxia: unfolded protein response (UPR)–dependent and UPR–independent pathways. *Molecular Cancer Research* Vol.4, No. 7 (July 2006), pp. 423-36.
- Krause Mda S & de Bittencourt PI. (2008). Type 2 diabetes: can exercise impair autoimmune event? The L-arginine/glutamine coupling hypothesis. *Cell Biochemistry and Function* Vol. 26, No. 4 (June 2008), pp. 406-33.
- Kriketos A, Gan SK, Poynten AM, et al. (2004). Exercise increases adiponectin levels and insulin sensitivity in humans. *Diabetes Care* Vol. 27, No. 2 (February 2004), pp. 629-30.
- Kubaszek A, Pihlajamaki J, Komarovski V, Lindi V, Lindström J, et al. (2003). Promoter polymorphism of the TNF-alpha (G-308A) and IL-6 (C-174G) genes predict the conversion from impaired glucose tolerance to type 2 diabetes: the Finnish Diabetes Prevention Study. *Diabetes* Vol. 52, No. 7 (July 2003), pp. 1872-76.
- Kudo T, Katayama T, Imaizumi K, Yasuda Y, Yatera M, et al. (2002). The unfolded protein response is involved in the pathology of Alzheimer's disease. *Annals of the New York Academy of Sciences* Vol. 977, pp.349-55.
- Lacasa D, Taleb S, Keophiphath M, Miranville A, Clement K. (2007). Macrophage-secreted factors impair human adipogenesis: involvement of proinflammatory state in preadipocytes. *Endocrinology* Vol. 148, No. 2 (February 1007), pp. 868-77.
- Lamkanfi M & Dixit VM. (2009). Inflammasomes: guardians of cytosolic sanctity. *Immunological Reviews* Vol. 227, No. 1 (January 2009), pp. 95-105.
- LaMonte M, Barlow C, Jurca R, Kampert JB, Church TS, et al. (2005). Cardiorespiratory fitness is inversely associated with incident of metabolic syndrome. A prospective study of men and women. *Circulation* Vol. 112, No. 4 (July 2005), pp. 505-12.

- Lee SJ, Kuk J, Katzmarzyk PT, Blair SN, Church TS, et al. (2005). Cardiorespiratory fitness attenuates metabolic risk independent of abdominal subcutaneous and visceral fat in mean. *Diabetes Care* Vol. 28, No. 4 (April 2005), pp. 895-901.
- Lessard S, Rivas D, Chen ZP, Bonen A, Febbraio MA, et al. (2007). Tissue-specific effects of rosiglitazone and exercise in the treatment of lipid-induced insulin resistance. *Diabetes* Vol. 56, No. 7 (July 2007), pp. 1856-64.
- Lillioja S, Young A, Culter C, Ivy JL, Abbott WG, et al. (1987). "Skeletal muscle capillary density and fiber type are possible determinants of in vivo insulin resistance in man. *Journal of Clinical Investigation* Vol. 80, No.2 (August 1987), pp. 415-24.
- Lim CT, Kola B & Korbonits M. (2010). "AMPK as a mediator of hormonal signaling. *Journal of Molecular Endocrinology* Vol. 44, No. 2 (February 2010), pp. 87-97.
- Lindsay RS & Bennett PH. (2001). Type 2 diabetes, the thrifty phenotype - an overview. *British Medicine Bulletin* Vol. 60, pp. 21-32.
- Marchesini G, Natale S, Tiraferri F, Tartaglia A, Moscatiello S, et al (2003). The burden of obesity on everyday life: a role for osteoarticular and respiratory diseases. *Diabetes Nutrition and Metabolism* Vol.16, No.5-6 (October-December 2003), pp.284-90.
- Marciniak SJ & Ron D. (2006). Endoplasmic reticulum stress signaling in disease. *Physiological Reviews* Vol. 86, No. 4 (October 2006), pp. 1133-1149.
- Marini M & Veicsteinas A. (2010). The exercised skeletal muscle: a review". *European Journal of Translational Myology - Myology Reviews* Vol. 10, No. 3, pp. 105-120.
- Meex R, Schrauwen-Hinderling V, Moonen-Kornips E, Schaart G, Mensink M, et al. (2010). Restoration of muscle mitochondrial function and metabolic flexibility in type 2 diabetes by exercise training is paralleled by increased myocellular fat storage and improved insulin sensitivity. *Diabetes* Vol. 59, No. 3 (March 2010), pp. 572-79.
- Michiels C, Minet E, Mottet D, Raes M. (2002). Regulation of gene expression by oxygen: NF-kappaB and HIF-1, two extremes. *Free Radical Biology and Medicine* Vol. 33, No. 9 (November 2002), pp.1231-42.
- Mietus-Snyder M & Lustig RH. (2008). Childhood obesity: adrift in the limbic triangle. *Annual Review Medicine* Vol. 59, pp.147-62.
- Moro C, Bajpeyi S & Smith SR. (2008). Determinants of intramyocellular triglyceride turnover: implications for insulin sensitivity. *American Journal of Physiology Endocrinology and Metabolism* Vol. 294, No. 2 (February 2008), pp.E203-E213.
- Musi N, Fujii N, Hirshman M, Ekberg I, Fröberg S, et al. (2001). AMP-activated protein kinase (AMPK) is activated in muscle of subjects with type 2 diabetes during exercise. *Diabetes* Vol. 50, No. 5 (May 2001), pp. 921-27.
- Must A, Spadano J, Coakley E, Field AE, Colditz G, Dietz WH. (1999). The disease burden associated with overweight and obesity. *Journal of the American Medical Association* Vol. 282, No.16 (October 1999), pp.1523-29.
- Neel JV. (1962). Diabetes mellitus: a 'thrifty' genotype rendered detrimental by 'progress'?. *American Journal of Human Genetics* Vol. 14 (December 1962), pp. 353-62.
- Newsholme P, Homem de Bittencourt P, O'Hagan C, De Vito G, Murphy C, et al. (2010). Exercise and possible molecular mechanism of protection from vascular disease and diabetes: the central role of ROS and nitric oxide. *Clinical Science* Vol. 118, No. 5 (November 2010), pp. 341-49.
- Niskanen L, Laaksonen D, Nyysönen K, et al. "Inflammation, abdominal obesity, and smoking as predictors of hypertension". *Hypertension* 2004;44:859-65

- O'Dea K (1992). Obesity and diabetes in "the land of milk and honey. *Diabetes Metabolism Review* Vol.8, No.4 (December 1992), pp. 373-88.
- Opal SM & DePalo VA. (2000). Anti-inflammatory cytokines. *Chest* Vol. 117, No. 4 (April 2000), pp. 1162-72.
- Oster G, Edelsberg J, O'Sullivan AK, Thompson D. (2000) The clinical and economic burden of obesity in a managed care setting. *American Journal of Managing Care* Vol. 6, No.6, (June 2000), pp. 681-89.
- Ostrowski K, Rohde T, Asp S, Schjerling P, Pedersen BK. (1999). Pro- and anti-inflammatory cytokine balance in strenuous exercise in humans. *Journal of Physiology* Vol. 515 (February 1999), pp. 287-91.
- Pagel-Langenickel I, Bao J, Pang L, Sack M. (2010). The role of mitochondria in the pathology of skeletal muscle insulin resistance. *Endocrine Reviews* Vol. 31, No. 1 (February 2010), pp. 25-51.
- Pan DA, Lillioja S, Kriketos AD, Milner MR, Baur LA, et al. (1997). Skeletal muscle triglycerides levels are inversely related to insulin action. *Diabetes* Vol. 46, No. 6 (June 1997), pp. 983-88.
- Panagiotakos DB, Pitsavos C, Yannakoulia M, Chrysohoou C, Stefanadis C. (2005). The implication of obesity and central fat on markers of chronic inflammation: the ATTICA study. *Atherosclerosis* Vol.183, No.2 (December 2005), pp.308-15.
- Pate RR, Pratt M, Blair SN, Haskell WL, Macera CA, et al. (1995). Physical activity and public health - A recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. *Journal of the American Medical Association* Vol.273, No.5 (February 1995), pp.402-07.
- Pedersen BK, Åkerström TC, Nielsen AR, Fischer CP. (2007). Role of myokines in exercise and metabolism. *Journal of Applied Physiology* Vol. 103, No. 3 (September 2007), pp. 1093-98.
- Pedersen BK, Febbraio M & Mooney R. (2007). Interleukin-6 does/does not have a beneficial role in insulin sensitivity and glucose homeostasis. *Journal of Applied Physiology* Vol. 102, No. 2 (February 2007), pp. 814-16.
- Petersen AM & Pedersen BK. (2005). The anti-inflammatory effect of exercise. *Journal of Applied Physiology* Vol. 98, No. 4 (April 2005), pp.1154-62.
- Pette D & Staron RS. (1997). Mammalian skeletal muscle fiber type transitions. *International Review of Cytology* Vol. 170, pp.143-223.
- Pistilli EE, Devaney JM, Gordish-Dressman H, Bradbury MK, Seip RL, et al. (2008). Interleukin-15 and Interleukin-15Ra SNPs and association with muscle, bone and predictors of metabolic syndrome. *Cytokine* Vol. 43, No. 1 (July 2008), pp. 45-53.
- Pi-Sunyer FX. (2000). The obesity pandemic: pathophysiology and consequences of obesity. *Obesity Research* Vol.10, No.10, pp.97S-104S.
- Pollock M, Franklin B, Balady G, Chaitman BL, Fleq JL, et al. (2000). AHA Science Advisory. Resistance exercise in individuals with and without cardiovascular disease. *Circulation* Vol.101, No.7 (February 2000), pp.28-33.
- Prentice A, Rayco-Solon P & Moore S. (2005). Insights from the developing world: thrifty genotypes and thrifty phenotypes. *Proceedings of the Nutrition Society* Vol.64, No. 2 (May 2005), pp.153-161.
- Quinn LS, Anderson BG, Drivdahl RH, Alvarez B, Argilés JM. (2002). Overexpression of interleukin-15 induces skeletal muscle hypertrophy in vitro: implications for

- treatment of muscle wasting disorders. *Experimental Cell Research* Vol. 280, No. 1 (October 2002), pp. 55-63.
- Quinn LS, Anderson BG, Strait-Bodey L, Stroud AM, Argilés JM. (2009). Oversecretion of interleukin-15 from skeletal muscle reduces adiposity. *American Journal of Physiology Endocrinology and Metabolism* Vol. 296, No. 1 (January 2009), pp. E191-E202.
- Quinn LS, Strait-Bodey L, Andersen BG, Argilés JM, Havel PJ. (2005). Interleukin-15 stimulates adiponectin secretion by 3T3-L1 adipocytes: evidence for a skeletal muscle-to-fat- signaling pathway. *Cell Biology International* Vol. 29, No. 6 (June 2005), pp. 449-57.
- Quinn LS. (2008). Interleukin-15: a muscle-derived cytokine regulating fat-to-lean body composition. *Journal of Animal Science* Vol. 86, No. 14 Suppl (April 2008), pp. E75-E83.
- Rabøl R, Larsen S, Højberg PM, Almdal T, Boushel R, et al. (2010). Regional anatomic differences in skeletal muscle mitochondrial respiration in type 2 diabetes and obesity. *Journal of Clinical Endocrinology and Metabolism* Vol.95, No. 2 (February 2010), pp.857-63.
- Randle PJ, Garland PB, Hales CN, Newsholme EA. (1963). The glucose fatty acid cycle: its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus". *Lancet* Vol.13, No.1 (April 1963), pp.7285-89.
- Regazzetti C, Peraldi P, Grémeaux T, Najem-Lendom R, Ben-Sahra I, et al. (2009). Hypoxia decreases insulin signaling pathways in adipocytes. *Diabetes* Vol.58, No.1 (January 2009), pp. 95-103.
- Regensteiner J, Bauer T & Reusch J. (2005). Rosiglitazone improves exercise capacity in individuals with type 2 diabetes. *Diabetes Care* Vol. 28, No. 12 (December 2005), pp. 2877-83.
- Röckl K, Hirshman MF, Brandauer J, Fujii N, Witters LA, et al. (2007). Skeletal muscle adaptation to exercise training. AMP-activated protein kinase mediates muscle fiber type shift. *Diabetes* Vol. 56, No. 8 (August 2007), pp. 2062-69.
- Rose AJ & Richter EA. "Skeletal muscle glucose uptake during exercise: how is it regulated?". *Physiology* (Bethesda) Vol. 20 (August 2005), pp. 260-70.
- Rosengren A &Wilhelmsen L. (1997). Physical activity protects against coronary death and deaths from all causes in middle-aged men. Evidence from a 20-year follow-up of the primary prevention study in Göteborg. *Annals of Epidemiology* Vol.7, No.1 (January 1997), pp.69-75.
- Rotter V, Nagaev I & Smith U. (2003). Interleukin-6 (IL-6) induces insulin resistance in 3T3-L1 adipocytes and is, like IL-8 and Tumor Necrosis Factor- α , overexpressed in human fat cells from insulin-resistant subjects. *Journal of Biological Chemistry* Vol. 278, No. 46 (November 2003), pp. 45777-784.
- Ryu E, Harding H, Angelastro JM, Vitolo OV, Ron D, et al. (2002). Endoplasmic reticulum stress and the unfolded protein response in cellular models of Parkinson's disease. *Journal of Neuroscience* Vol. 22, No. 24 (December 2002), pp. 10690-698.
- Saltin B (1992). Sedentary lifestyle: an underestimated health risk. *Journal of Internal Medicine* Vol.232, No.6 (December 1992), pp. 467-69.
- Samokhvalov V, Bilan P, Schertzer JD, Antonescu CN, Klip A. (2009). Palmitate-and lipopolysaccharide-activated macrophage evoke contrasting insulin responses in

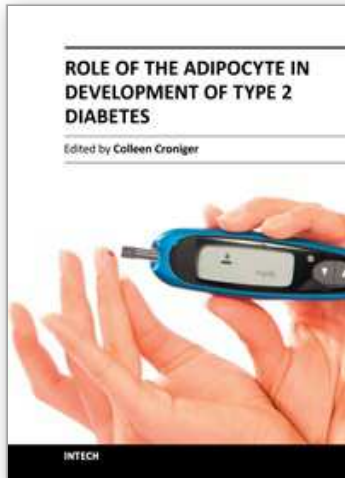
- muscle cells. *American Journal of Physiology Endocrinology and Metabolism* Vol. 296, No. 1 (January 2009), pp.E37-E46.
- Sartipy P & Loskutoff D. (2003). Monocyte chemoattractant protein 1 in obesity and insulin resistance. *Proceedings of the National Academy of Sciences of the United States of America* Vol. 100, No. 12 (June 2003), pp.7265-70.
- Sawada S, Lee IM, Naito H, Noguchi J, Tsukamoto K, et al. (2003). Long-term trends in cardiorespiratory fitness and the incidence of type 2 diabetes. *Diabetes Care* Vol. 33, No. 6 (June 2010), pp. 1353-57.
- Scheuner D & Kaufman R. (2008). The unfolded protein response: a pathway that links insulin demand with β -cell failure and diabetes. *Endocrine Reviews* Vol. 29, No. 3 (may 2008), pp.317-33.
- Schiaffino S & Serrano AL. (2002). Calcineurin signaling and neural control of skeletal muscle fiber type and size. *Trends in Pharmacological Sciences* Vol. 23, No. 12 (December 2002), pp. 569-75.
- Scott W, Stevens J & Binder-Macleod SA. (2001). Human skeletal muscle fiber type classifications. *Physical Therapy* Vol. 81, No. 11 (November 2001), pp. 1810-16.
- Sell H, Dietze-Schroeder D & Eckel J. (2006). The adipocyte-myocyte axis in insulin resistance. *Trends in Endocrinology and Metabolism* Vol. 17, No. 10 (December 2006), pp. 416-22.
- Sell H, Eckardt K, Taube A, Tews D, Gurqui M, et al. (2008). Skeletal muscle insulin resistance induced by adipocyte-conditioned medium: underlying mechanisms and reversibility. *American Journal of Physiology Endocrinology and Metabolism* Vol. 294, No. 6 (June 2008), pp. E1070-E1077.
- Sethi JK & Vidal-Puig AJ. (2007). Adipose tissue function and plasticity orchestrate nutritional adaptation. *Journal of Lipid Research* Vol. 48, No. 6 (June 2007), pp.1253-62.
- Shadid S & Jensen M. (2003). Effects of pioglitazone versus diet and exercise on metabolic health and fat distribution in upper body obesity. *Diabetes Care* Vol. 26, No. 11 (November 2003), pp. 3148-52.
- Sherwood DJ, Dufresne SD, Markuns JF, Cheatham B, Moller DE, et al. (1999). Differential regulation of MAP kinase, p70(S6k) and Akt by contraction and insulin in rat skeletal muscle. *American Journal of Physiology* Vol. 276, No. 5 pt 1 (May 1999), pp. E870-E878.
- Shimomura I, Hammer R, Ikemoto S, Brown MS, Goldstein JL. (1999). Leptin reverses insulin resistance and diabetes mellitus in mice with congenital lipodystrophy. *Nature* Vol. 401, No. 6748 (September 1999), pp.73-76.
- Shulman G. (2000). Cellular mechanisms of insulin resistance. *Journal of Clinical Investigation* Vol.106, No2 (July 2000), pp.171-76.
- Sigal RK, Kenny GP, Boulé NG, Wells GA, Prud'homme D, et al. (2007). Effects of aerobic training, resistance training, or both on glycemic control in type 2 diabetes: a randomized trial. *Annals of Internal Medicine* Vol. 147, No. 6 (September 2007), pp. 357-69.
- Simons PJ, van de Pangaart P, van Roomen CP, Aerts JM, Boon L. (2005). Cytokine-mediated modulation of leptin and adiponectin secretion during in vitro adipogenesis: evidence that tumor necrosis factor- α - and interleukin-1 β treated

- human preadipocytes are potent leptin producers. *Cytokine* Vol. 32, No. 2 (October 2005), pp.94-103.
- Smith AC, Mullen KL, Junkin KA, Nickerson J, Chabowski A, et al. (2007). Metformin and exercise reduce muscle FAT/CD36 and lipid accumulation and blunt the progression of high-fat diet-induced hyperglycemia. *American Journal of Physiology Endocrinology and Metabolism* Vol. 293, No. 1 (July 2007), pp. E172-E181.
- Song, XM, Ryder JW, Kawano Y, et al. (1999). Muscle fiber type specificity in insulin signal transduction. *American Journal of Physiology Regulatory Integrative Comparative Physiology* Vol. 277, No. 6 (December 1999), pp. R1690-R1696.
- Steppan C & Lazar MA. (2002). Resistin and obesity-associated insulin resistance". *Trends in Endocrinology and Metabolism* Vol. 13, No. 1 (January-February 2002), pp. 18-23.
- Stienstra R, Joosten LA, Koenen T, van Tits B, van Diepen, et al. (2010). The inflammasome-mediated caspase-1 activation controls adipocyte differentiation and insulin Sensitivity. *Cell Metabolism* Vol. 12, No. 6 (December 2010), pp. 593-605.
- Summermatter S, Marcelino H, Arsenijevic D, Buchala A, Aprikian O, et al. (2009). Adipose tissue plasticity during catch-up growth fat driven by thrifty metabolism. *Diabetes* Vol. 58, No. 10 (October 2009), pp. 2228-37.
- Suzuki K, Yamada M, Kurakake S, Okamura N, Yamaya K, et al. (2000). Circulating cytokines and hormones with immunosuppressive but neutrophil-priming potentials rise after endurance exercise in humans. *European Journal of Applied Physiology* Vol. 81, No. 4 (March 2000), pp. 281-87.
- Tang T & Reed MJ. (2001). Exercise adds to metformin and acarbose efficacy in db/db mice. *Metabolism* Vol. 50, No. 9 (September 2001), pp. 1049-53.
- Tanner CJ, Bakarar H, Dohm L, Pories WJ, MacDonald KG, Cunnigham PR, et al. (2001). Muscle fiber type is associated with obesity and weight loss. *American Journal of Physiology Endocrinology and Metabolism* Vol. 282, No. 6 (June 2001), pp.E1191-E1196.
- Taube A, Eckardt K & Eckel J. (2009). Role of lipid-derived mediators in skeletal muscle resistance. *American Journal of Physiology Endocrinology and Metabolism* Vol. 297, No. 5 (November 2009), pp. E1004-E1012.
- Thompson D, Wolf A. (2001) The medical-care cost burden of obesity. *Obesity Reviews* Vol.2 No.3 (August 2001), pp. 189-97.
- Thompson P. (2003). "Exercise and. physical activity in the prevention and treatment of atherosclerotic cardiovascular disease. *Arteriosclerosis Thrombosis and Vascular Biology* Vol.23, No.8 (August 2003), pp.1319-21.
- Thyfault JP. (2008). Setting the stage: possible mechanisms by which acute contraction restores insulin sensitivity in muscle. *American Journal of Physiology Regulatory Integrative and Comparative Physiology* Vol. 294, No. 4 (April 2008), pp. R1103-R1110.
- Trayhurn P & Woods IS. (2004). Adipokines: inflammation and the pleiotropic role of white adipose tissue. *British Journal of Nutrition* Vol. 92, No. 3 (September 2004), pp. 347-55.
- Turcotte L & Fisher J. (2008). Skeletal muscle insulin resistance: roles of fatty acid metabolism and exercise. *Physical Therapy* Vol. 88, No. 11 (November), pp. 1279-96.
- Um SH, D'Alessio D & Thomas G. Nutrition overload, insulin resistance and ribosomal protein S6 kinase 1, S6K1. *Cell Metabolism* Vol. 3, No. 6 (June 2006), pp.393-402.
- Valencia ME, Bennett PH, Ravussin E, Esparza J, Fox C, et al. (1999). The Pima Indians in Sonora, Mexico. *Nutrition Reviews* Vol. 57, No. 5 pt 2 (May 1999), pp. S55-S57.

- Vandanmagsar B, Youm YH, Ravussin A, Galgani JE, Stadler K, et al. (2011). The NLRP3 inflammasome instigates obesity-induced inflammation and insulin resistance. *Nature Medicine* Vol. 17, No. 2 (February 2011), pp. 179-88.
- Varma V, Yao-Borengasser A, Rasouli N, Nolen GT, Phanavanh B, et al. (2009). Muscle inflammatory response and insulin resistance: synergistic interaction between macrophages and fatty acid leads to impaired insulin action. *American Journal of Physiology Endocrinology and Metabolism* Vol. 296, No. 6 (June 2009), pp. E1300-E1310.
- Varma V, Yao-Borengasser A, Rasouli N, Bodles AM, Phanavahn B, et al. (2007). Human visfatin expression: relationship to insulin sensitivity, intramyocellular lipids, and inflammation. *Journal of Clinical Endocrinology and Metabolism* Vol. 92, No. 2 (February 2007), pp.666-72.
- Vendrell J, Broch M, Vilarrasa N, Molina A, Gómez JM, et al. (2004). Resistin, adiponectin, ghrelin, leptin, and proinflammatory cytokines: relationships in obesity. *Obesity Research* Vol. 12, No. 6 (June 2004), pp.962-71.
- Vickers MH, Reddy S, Ikenasio BA, Breier BH. (2001). Dysregulation of the adipoinular axis - a mechanism for the pathogenesis of hyperleptinemia and adipogenic diabetes induced by fetal programming. *Journal of Endocrinology* Vol. 170, No. 2 (August 2001), pp. 323-332.
- Virkamäki A, Korshennikova E, Seppälä-Lindroos A, Vehkavaara S, Goto T, et al. (2001). Intramyocellular lipid is associated with resistance to in vivo insulin actions on glucose uptake, antilipolysis, and early insulin signaling pathways in human skeletal muscle. *Diabetes* Vol. 50, No. 10 (October 2001), pp.2337-43.
- Wang B, Wood IS & Tryhurn P. (2007). Dysregulation of the expression and secretion of inflammation related adipokines by hypoxia in human adipocytes. *European Journal of Physiology* Vol.455, No. 3 (December 2007), pp. 479-92.
- Wang YX, Zhang CL, Yu RT, Cho HK, Nelson MC, et al. (2004). Regulation of muscle fiber type and running endurance by PPAR δ . *PLoS Biology* Vol. 2, No. 10 (October 2004), pp. 1532-39.
- Weisberg S, Hunter D, Huber R, Lemieux J, Slaymaker S, et al. (2006). CCR2 modulates inflammatory and metabolic effects of high-fat feeding. *Journal of Clinical Investigation* Vol. 116, No. 1 (January 2006), pp.115-124.
- Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, et al. (2003). Obesity is associated with macrophage accumulation in adipose tissue. *Journal of Clinical Investigation* Vol. 112, No. 12 (December 2003), pp. 1796-1808.
- Wendorf M & Goldfine ID. (1991). Archaeology of NIDDM. Excavation of the 'thrifty' genotype. *Diabetes* Vol. 40, No. 2 (February 1991), pp. 161-65.
- Weyer C, Funahashi T, Tanaka S, Hotta K, Matsuzawa, et al. (2001). Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. *Journal of Clinical Endocrinology and Metabolism* Vol. 86, No. 5 (May 2001), pp. 1930-35.
- Williams PT. (2001). Physical fitness and activity as separate heart disease risk factors: a meta-analysis. *Medicine and Science in Sports and Exercise* Vol.33, No. 5 (May 2001), pp.754-61.
- World Health Organization (September 2006). Obesity and Overweight. In: WHO, January 2011, available from

- <http://www.who.int/mediacentre/factsheets/fs311/en/print.html>
- Yamauchi T, Kamon J, Waki H, Terauchi Y, Kubota N, et al. (2001). The fat-derived hormone adiponectin reverses insulin resistance associated with both lipodystrophy and obesity. *Nature Medicine* Vol. 7, No. 8 (August 2001), pp.941-46.
- Yang WS, Jeng CY, Wu TJ, Tanaka S, Funahashi T, et al. (2002). Synthetic peroxisome proliferator-activated receptor-gamma agonist, rosiglitazone, increases plasma levels of adiponectin in type 2 diabetes patients. *Diabetes Care* Vol. 25, No. 2 (February 2002), pp. 376-80.
- Ye J, Gao Z, Yin J, He Q. (2007). Hypoxia is a potential risk factor for chronic inflammation and adiponectin reduction in adipose tissue of ob/ob and dietary obese mice. *American Journal of Physiology Endocrinology and Metabolism* Vol. 293, No. 4 (October 2007), pp. E1118-E1128.
- Yin J, Gao Z, He Q, Zhou D, Guo Z, Ye J. (2009). Role of hypoxia in obesity-induced disorders of glucose and lipid metabolism in adipose tissue. *American Journal of Physiology Endocrinology and Metabolism* Vol. 296, No. 2 (February 2009), pp. E333-E342.
- Yoshizaki T, Schenk S, Imamura T, Babendure JL, Sonoda N, et al. (2010). SIRT1 inhibits inflammatory pathways in macrophages and modulates insulin sensitivity. *American Journal of Physiology Endocrinology and Metabolism* Vol. 298, No. 3 (March 2010), pp. E419-E428.
- Zierath J, Ryder J, Doebber T, Woods J, Wu M, et al. (1998). Role of skeletal muscle in thiazolidinedione insulin sensitizer (PPAR γ agonist) action. *Endocrinology* Vol. 139, No. 12 (December 1998), pp. 5034-41.
- Zimmet P, Dowse G, Finch C, Serjeantson S, King H. (1990). The epidemiology and natural history of NIDDM - lessons from the South Pacific. *Diabetes/Metabolism Reviews* Vol. 6, No. 2 (March 1990), pp. 91-124.

IntechOpen



Role of the Adipocyte in Development of Type 2 Diabetes

Edited by Dr. Colleen Croniger

ISBN 978-953-307-598-3

Hard cover, 372 pages

Publisher InTech

Published online 22, September, 2011

Published in print edition September, 2011

Adipocytes are important in the body for maintaining proper energy balance by storing excess energy as triglycerides. However, efforts of the last decade have identified several molecules that are secreted from adipocytes, such as leptin, which are involved in signaling between tissues and organs. These adipokines are important in overall regulation of energy metabolism and can regulate body composition as well as glucose homeostasis. Excess lipid storage in tissues other than adipose can result in development of diabetes and nonalcoholic fatty liver disease (NAFLD). In this book we review the role of adipocytes in development of insulin resistance, type 2 diabetes and NAFLD. Because type 2 diabetes has been suggested to be a disease of inflammation we included several chapters on the mechanism of inflammation modulating organ injury. Finally, we conclude with a review on exercise and nutrient regulation for the treatment of type 2 diabetes and its co-morbidities.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Valmore Bermúdez, Joselyn Rojas, Miguel Aguirre, Címaco Cano, Naillet Arraiz, Carlos Silva Paredes, Marcos Lima, Raquel Cano, Eneida Fonseca and Manuel Velasco (2011). The Sick Adipocyte Theory: The Forces of Clustering at Glance, Role of the Adipocyte in Development of Type 2 Diabetes, Dr. Colleen Croniger (Ed.), ISBN: 978-953-307-598-3, InTech, Available from: <http://www.intechopen.com/books/role-of-the-adipocyte-in-development-of-type-2-diabetes/the-sick-adipocyte-theory-the-forces-of-clustering-at-glance>

INTECH
open science | open minds

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2011 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the [Creative Commons Attribution-NonCommercial-ShareAlike-3.0 License](#), which permits use, distribution and reproduction for non-commercial purposes, provided the original is properly cited and derivative works building on this content are distributed under the same license.

IntechOpen

IntechOpen