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Adipocytokines, Oxidative Stress and Impaired Cardiovascular Functions

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1. Introduction

In spite of the considerable progress in their diagnosis, prevention and treatment, cardiovascular diseases remain the number one cause of death worldwide. This is partially due to the rapidly growing incidence of obesity, which is a well-known independent risk factor for insulin resistance, diabetes, dyslipidaemia, high blood pressure and thrombosis (Lopaschuck et al., 2007).

The metabolic complications of obesity, often referred to as the metabolic syndrome, characterized by a heterogenic complex of symptoms and consist of glucose intolerance, central obesity, dyslipidemia (hypertriglyceridemia, elevated nonesterified fatty acids (NEFAs), and decreased high-density lipoprotein (HDL) cholesterol), and hypertension. These, often culminating in β-cell failure, impaired glucose tolerance and type 2 diabetes (T2D). In addition, dyslipidaemia, coronary heart disease (CHD), systemic hypertension and premature heart failure are pathologies related (Hubert et al., 1983). Abdominal obesity, ectopic lipid accumulation, hepatic steatosis, and sleep apnea can also be included in the metabolic complications of obesity (Parati et al., 2007).

On the other hand, obesity leads to an alteration in the profile of hormones secreted by adipose tissue (adipokines). Secretion of adipocytokines has been shown particularly for visceral fat (Dusserre et al., 2000; Fontana et al., 2007; Yang & Smith, 2007). It is evident that many of these adipokines have the ability to influence other tissues such as the liver, muscle and brain, e.g. the adipokine leptin affects appetite regulation, others have an important impact on the consequences of adipose tissue inflammation (e.g. interleukin 6 (IL), PAI-1, monocyte chemoattractant protein 1 [MCP-1]) and vascular biology (e.g. serum amyloid A [SAA]) (Bastard et al., 2002; Mutch et al., 2001; Sartipy et al., 2003; Stofkova, 2009; Yang et al., 2006). In addition, increased tumor necrosis factor (TNF) and IL-6 expression and

secretion from adipose tissue are involved in both whole-body and local insulin resistance at different tissue sites.

The principal purpose of this chapter is to describe how the adipocytokines and oxidative stress interact with insulin signaling in the context of low-grade inflammation related to obesity in order to promote cardiovascular complications.

2. Pathophysiology of cardiovascular morbidity

2.1 Introduction

The pathophysiology of cardiovascular morbidity is complex and multifactorial. Oxidative stress is an important contributory factor to the etiology of many cardiovascular diseases, including atherosclerosis, coronary heart disease (heart attack), cerebrovascular disease (stroke), cardiomyopathies, peripheral vascular disease, diabetes, heart failure, and hypertension (Dusting & Triggle, 2005). Ischemic heart disease and hypertension are the two most important causes of heart failure in the Western world. Other common causes include valvular heart disease (especially aortic stenosis and mitral regurgitation).

Arterial hypertension is the most prevalent cardiovascular risk factor and the leading cause of morbidity and mortality from cardiovascular disease (CVD) worldwide (Gómez-Marcos et al., 2009). Heart failure (HF) is a complex clinical syndrome caused by impaired ventricular performance. It is the final common pathway for a variety of cardiovascular disease processes, leading to potentially disabling symptoms and shortened life expectancy. Currently, 1% of the population aged 50–59 yr, and 10% of those over 80 yr, have HF; is the only major cardiovascular condition that is increasing in prevalence, because of an ageing population and improved survival from other CVD (Kotzé & Howell, 2008). Understanding these profound mechanisms of disease can help clinicians identify and treat CVD, as well as help patients prevent these potentially devastating complications.

2.2 Epidemiology

Cardiovascular diseases are the world's largest killers, claiming 17.1 million lives a year, CVD contributed to a third of global deaths. An estimated 79 400 000 American adults (1 in 3) have 1 or more types of CVD. Of these, 37 500 000 are estimated to be age 65 or older (Rosamond et al., 2007).

Extensive epidemiological research has established diabetes, hyperlipidemia, hypertension, and cigarette smoking, as independent risk factors for CHD. The risk increases 2–3 folds with tobacco smoking, with age and is greater for women than for men. In contrast, cardiac events fall 50% in people who stop smoking and the risk of CVDs, also decreases significantly over the first two years after stopping smoking (Khot, et al., 2003).

The health interview part of the National Health and Nutrition Examination Survey (NHANES) III was used to categorize adults over 50 years of age by presence of metabolic syndrome (National Cholesterol Education Program [NCEP] definition) with or without diabetes. The prevalence of CHD for each group was then determined. Metabolic syndrome (MetS) is very common, with ~44% of the U.S. population over 50 years of age meeting the NCEP criteria. In contrast, diabetes without MetS is uncommon (13% of those with

diabetes). Older Americans over 50 years of age without MetS regardless of diabetes status had the lowest CHD prevalence (8.7% without diabetes, 7.5% with diabetes). Those with MetS without diabetes had higher CHD prevalence (13.9%) and, those with both MetS and diabetes had the highest prevalence of CHD (19.2%) compared with those with neither (Alexander et al., 2003).

The Systematic Coronary Risk Evaluation (SCORE) data set comprises data from 12 European cohort studies. The SCORE population was also divided into gender and age strata: under 40, 40–49, 50–59, and over 60. The rate of CVD mortality in each body mass index (BMI) category was calculated, each 5-unit increase in BMI was associated with an increase in CVD mortality of 34% in men and 29% in women. This increases the public health importance of BMI as both a simple indicator and mediator of CVD risk (Dudina et al., 2011).

2.3 Pathologies associated to cardiovascular morbidity

Impaired myocardial diastolic relaxation (e.g., diastolic dysfunction) is the earliest myocardial contractility observed in metabolic conditions such as obesity, insulin resistance, and hypertension. Diastolic dysfunction manifests as a reduction in velocity of myocardial relaxation, as well as decreasing myocardial compliance. Mechanisms that contribute to this selective cardiac dysfunction include decreases in energy production due to reductions in mitochondrial respiration, increased oxidative stress, and defective contractile and intracellular “Ca2+” regulatory proteins. Abnormalities in “Ca2+” signaling/flux and myofilament function contribute to the cardiomyopathic alterations observed in the metabolic syndrome (Ren et al., 2010). Reductions in the oxidative capacity of the mitochondrial electron transport chain are manifested in obese, insulin-resistant persons as well as diabetic patients. Mitochondria in endothelial cells are thought to play an important role in cellular signaling as sensors for local oxygen concentration and regulations of nitric oxide (NO) production. Renin-angiotensin-aldosterone system (RAAS)-mediated increases in nicotinamide-adenine dinucleotide phosphate (NADPH) oxidase activity and generation of reactive oxygen species (ROS) may result in mitochondrial damage and associated decreases in oxidative phosphorylation, Adenosine triphosphate (ATP) production and bioavailable NO (Ren et al., 2010).

The mechanisms underlying ventricular dysfunction are dysfunction of cardiac myocytes and longstanding pressure or volume overload. As myocardial contractility decreases, the stroke volume drops and the end-diastolic volume and pressure increase. If sustained in the long-term, this volume increase leads to what is termed cardiac remodelling. This involves myocardial hypertrophy, chamber enlargement and an increase in ventricular wall stress, and increases oxygen demand. An increase in ventricular stiffness also occurs due to increased collagen deposition in the heart, which impairs filling and exacerbates the situation (Kotzé & Howell, 2008).

The new paradigm of atherosclerosis links oxidative stress, inflammation, thrombosis, and endothelial dysfunction. Growing evidence indicates that chronic and acute overproduction of ROS under pathophysiologic conditions is integral in the development of CVD (Madamanchi et al., 2005). Coronary artery disease (CAD) is one of the most frequent causes of death and disabling symptoms worldwide. Epidemiological studies have indicated the

rising prevalence of atherosclerosis globally (Tedgui & Mallat, 2006). Formation of atheromatous plaques in the arteries obstructs the supply of oxygen and nutrients to the myocardium, resulting in CHD (Woods et al., 2000).

2.3.1 Diabetes

Diabetes is a prime risk factor for CVD, the link between diabetes and CVD is complex and multifactorial. The presence of insulin resistance, impaired glucose tolerance, and overt diabetes, are associated with an increased risk of CVD, these conditions are also accompanied by the presence of oxidative stress (Woods et al., 2000). Vascular disorders include retinopathy and nephropathy, peripheral vascular disease (PVD), stroke, and CAD. Diabetes also affects the heart muscle, causing both systolic and diastolic heart failure.

The etiology of this excess cardiovascular morbidity and mortality is not completely clear (Dokken, 2008). Evidence suggests that although hyperglycemia, the hallmark of diabetes, contributes to myocardial damage after ischemic events, it is clearly not the only factor, because both pre-diabetes and the presence of the MetS, even in normoglycemic patients, increase the risk of most types of CVD (Alexander, 2003; Dokken, 2008). In diabetes, where CVD is of particular concern, there are multiple sources of ROS including the auto-oxidation of glucose, increased substrate flux, and decreased levels of NADPH through the polyol pathway. Formation of advanced glycation end products (AGEs) and their interaction with cellular targets, such as endothelial cells, may lead to oxidative stress and promote formation of oxidized LDL (ox-LDL) (Ceriello & Motz, 2004).

The recent explosion of the worldwide epidemic of MetS combining disturbances in glucose and insulin metabolism, excess predominantly abdominally distributed weight, mild dyslipidemia, and hypertension, with the subsequent development of obesity, T2D and CVD, compromises progress made in reducing the morbidity and mortality of CVD in recent years. Cardiovascular risk increases in parallel to insulin resistance (as estimated by the homeostasis model assessment index (HOMA) both patients with diabetes and nondiabetic (Saely et al., 2005).

2.3.2 Metabolic syndrome

The incidence of CVD, coronary heart disease, and T2D has not been well defined in persons with the MetS. Conclusions were that MetS is common and is associated with an increased risk for CVD and T2D in both sexes, according to metabolic syndrome traits. MetS accounts for up to one third of CVD in men and approximately half of new T2D over 8 years of follow-up (Wilson et al., 2005).

A large family study of T2D in Finland and Sweden (the Botnia study) were included in the analysis of cardiovascular risk associated with the MetS. The aim of the study was to assess the prevalence of cardiovascular morbidity and mortality associated with the MetS by applying the WHO definition. In women and men, respectively, the MetS was seen in 10 and 15% of subjects with normal glucose tolerance, 42 and 64% of those with impaired fasting glucose (IFG)/impaired glucose tolerance (IGT), and 78 and 84% of those with T2D. Cardiovascular mortality was markedly increased in subjects with the MetS (12.0 vs. 2.2%, $p< 0.001$). Of the individual components of the MetS, microalbuminuria conferred the strongest risk of cardiovascular death (RR 2.80; $p< 0.002$) (Isomaa et al., 2001).

2.3.3 Obesity

Obesity has been increasing in epidemic proportions in both adults and children. In adults, overweight is defined as a BMI 25 to 29.9 Kg/m^2 and obesity as BMI ≥30 Kg/m^2. Other indexes that have been used less commonly but possibly with more predictive power include body fatness, waist circumference (WC), waist-to-hip ratio (WHR), and weight-to-height ratio. A recent study of nearly 360,000 participants from 9 European countries showed that both general obesity and abdominal adiposity are associated with risk of death and support the importance of WC or WHR in addition to BMI for assessing mortality risk. Obesity has many adverse effects on hemodynamics and CV structure and function (Lavie et al., 2009).

Elevated BMI predisposes to congestive heart failure (CHF) by promoting increased blood pressure, diabetes, and CHD. Factors related to obesity and hypertension, include: endothelial dysfunction, insulin resistance, sympathetic nervous system, substances released from adipocytes (IL-6, TNF-α, etc.), and sleep apnea (Poirier et al., 2006).

The role of obesity in the initiation and acceleration of tissue inflammation has been well studied. Excess adipose tissue can contribute to inflammation in two ways: (a) ectopic fat storage induces lipotoxicity, promoting an intracellular inflammatory response and (b) altered adipokine production in obesity contributes to the inflammatory response. It is now recognized that adiponectin has a role in both of these processes. Related to demonstrated association between hypo-adiponectinaemia and metabolic dysfunction (Cnop et al., 2003) the proposal provides that a replacement of adiponectin may function as pharmacological therapy (Chandran et al., 2003).

2.3.4 Endothelial dysfunction

Healthy endothelium regulates blood vessel tone, platelet activation, leukocyte adhesion, thrombogenesis, and inflammation. The net effect of healthy endothelium is vasodilatory, anti-atherogenic, and anti-inflammatory (Dokken, 2008). Endothelial dysfunction has been observed in patients with established coronary artery disease or coronary risk factors, both in the coronary and peripheral vasculature (Heitzer et al., 2001).

As shown in figure 1, endothelial dysfunction a key factor in atherogenesis, is associated with an increased risk of cardiovascular events and highest risk for vascular morbidity and mortality. A major risk for atherosclerotic plaque rupture is aging. One possible mechanism is that aging is associated with endothelial cell senescence, which is a risk factor for endothelial apoptosis and endothelial denudation, rendering the atherosclerotic plaque prone to rupture (Hulsmans et al., 2011).

A primary event in atherogenesis is the infiltration of activated inflammatory cells into the arterial wall. ROS can be produced from both endogenous and exogenous substances. Potential endogenous sources include mitochondria, cytochrome P450 metabolism, peroxisomes, and inflammatory cell activation. In the vascular wall, ROS are generated by several mechanisms, including NADPH oxidases, xanthine oxidase, the mitochondrial respiratory chain, lipoxygenases, and nitric oxide synthases. ROS formation can be stimulated by mechanical forces (e.g., stretch, pressure, shear stress), environmental factors (such as hypoxia), secreted factors coupled to tyrosine kinase receptors (e.g., platelet derived

growth factor, PDGF), and secreted factors coupled to G protein-coupled receptors such as angiotensin II (Lehoux et al., 2006; Dokken, 2008; Hulsmans et al., 2011).

The general process of lipid peroxidation consists of three stages: initiation, propagation, and termination (Catalá, 2006). The initiation phase of lipid peroxidation includes hydrogen atom abstraction. Several species can abstract the first hydrogen atom and include the radicals: hydroxyl (−OH), alkoxyl (RO−), peroxyl (ROO−), and possibly HO_2− but not H_2O_2 or O_2−. The membrane lipids, mainly phospholipids, containing polyunsaturated fatty acids are predominantly susceptible to peroxidation because abstraction from a methylene (CH2-) group of a hydrogen atom, which contains only one electron, leaves at the back an unpaired electron on the carbon, CH-. The presence of a double bond in the fatty acid weakens the C–H bonds on the carbon atom nearby to the double bond and thus facilitates H- subtraction. The initial reaction of -OH with polyunsaturated fatty acids produces a lipid radical (L-), which in turn reacts with molecular oxygen to form a lipid peroxyl radical (LOO−).There they secrete ROS and oxidize lipoproteins, inducing foam cell formation and endothelial cell apoptosis, which in turn lead to plaque growth, erosion, and rupture (Hulsmans et al., 2011).

It is now widely recognized that chronic low-grade inflammation and oxidative stress play a key role in the initiation, propagation, and development of metabolic disorders. The aim of Hulsmans et al., (2011), was to review the functional roles of various microRNAs (miRs) in regulating oxidative stress and inflammation in adipose and vascular tissues leading to obesity and atherosclerosis, in order to analyze how these processes can be linked through communication between cells even at a remarkable distance, thus highlighting the communication between inflammatory and endothelial cells. The work of Targonski et al., was performed to evaluate the magnitude of the association between coronary endothelial dysfunction (CED) and cerebrovascular events. Kaplan-Meier analysis indicated that patients with CED had a significantly higher cumulative cerebrovascular event rate than those without CED (P=0.04). Presence of CED in patients without obstructive CAD is independently associated with an increased risk of cerebrovascular events (Targonski et al., 2003).

2.3.5 Dyslipidemia

The major threat to the macrovasculature for patients with and without diabetes is atherosclerosis, and dyslipidemia is highly correlated with atherosclerosis, up to 97% of patients with diabetes are dyslipidemic (Dokken, 2008). Insulin deficiency and insulin resistance promote dyslipidemia accompanied by increased oxidation, glycosylation, and triglyceride enrichment of lipoproteins.

Nonenzymatic glycosylation of HDL shortens its half-life and renders it less protective against atherosclerosis (Duell, 1991). The study of Marsuki et al., was undertaken to evaluate the effect, on macrophage cholesterol efflux, of functional modification of HDL by its glycation. They also investigated the effects of the glycation-inhibitors, metformin (MF) and aminoguanidine (AG), on glycated HDL-mediated cholesterol efflux. The conclusion was that glycated HDL particles are ineffective as acceptors of ATP-binding cassette transporter (ABCG1) mediated cholesterol efflux; and this may explain, at least in part, accelerated atherosclerosis in diabetic patients. Metformin serves as a possible candidate to restore impaired cholesterol efflux and reverse cholesterol transport (Matsuki et al., 2009).

Hypertriglyceridemia can lead to increased production of the small, dense form of LDL and to decrease HDL transport of cholesterol back to the liver (Poirier et al., 2006). In addition to the characteristic pattern of increased triglycerides and decreased HDL cholesterol found in the plasma of patients with diabetes, abnormalities are seen in the structure of the lipoprotein particles, where the predominant form of LDL cholesterol is the small, dense form. Small LDL particles are more atherogenic than large LDL particles because they can more easily penetrate and form stronger attachments to the arterial wall, and they are more susceptible to oxidation (Stocker & Keaney, 2004). In diabetic patients, LDL particles can also become glycated, in a process similar to the glycation of hemoglobin. Glycation of LDL lengthens its half-life and therefore increases the ability of the LDL to promote atherogenesis (Dokken, 2008).

2.3.6 Atherosclerosis

Atherosclerosis is no longer considered a pure lipid disorder. It has become increasingly clear that inflammation is at the root of atherosclerosis and its complications. In addition to playing a causal role in lesion formation, inflammation can yield predictive and prognostic information of considerable clinical utility. In addition to serving as biomarkers of atherosclerotic events, inflammatory mediators directly participate in lesion formation, propagation, and eventual rupture and in this fashion may represent a powerful tool to assess endothelial cell activation. Clearly, understanding the mechanisms and mediators of endothelial dysregulation and inflammation may yield new targets to predict, prevent, and treat cardiovascular disease (Szmitko, 2003).

Many common conditions predisposing to atherosclerosis, such as hypercholesterolemia, hypertension, diabetes, and smoking, are associated with a reduced vascular availability of NO, a free radical that not only produces vasodilation but also has potent antiatherogenic properties, such as inhibition of platelet aggregation, prevention of smooth muscle cell proliferation, reduction of lipid peroxidation, and inhibition of adhesion molecule expression (Landmesser & Harrison, 2001). Impaired endothelium-dependent vasodilation, a surrogate for NO bioavailability, may predict cardiovascular events. Thus, the loss of NO not only alters vascular tone but also may explaining in part why these conditions are risk factors for atherosclerosis.

3. Reactive oxygen species and oxidative stress in cardiovascular diseases

Oxidative stress (OS) is an imbalance between production and degradation of ROS in cells, leading eventually to enhanced oxidative modification of biomolecules. Therefore, is a phenomenon associated with pathogenetic mechanisms of several diseases including atherosclerosis, cancer, diabetes mellitus, heart failure, hypertension, inflammatory diseases, as well as psychological diseases or aging processes (Naito et al., 2010). An increase in ROS and/or a weakening in the antioxidant defense mechanisms can cause OS. Accumulating evidence suggests that OS increases with age, and that therapeutic and life style approaches that reduce oxidative stress likely slow the development of atherosclerotic cardiovascular disease. Increased cellular ROS is an important contributor to the pathophysiology of vascular diseases, including atherosclerosis, restenosis, myocardial infarction and stroke. Additionally, some ROS act as intracellular messengers, and ROS accumulation activates

proinflammatory signaling pathways with an increased propensity for the formation of atherosclerotic lesions within the vessel wall (Runge et al., 2010).

The antioxidant enzymes superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) serve as primary line of defense in destroying free radicals. However, there are several human antioxidant genes, classified according to genes whose products are defined as "antioxidant enzymes" the first two groups, and genes whose products are not enzymes, but also deal directly with reactive species. Also, are subclassified into 3 functional groups: peroxidases: catalase, ceruloplasmin (ferroxidase), glutathione peroxidase 1-7, lactoperoxidase, myeloperoxidase, peroxiredoxin 1-6; superoxide dismutases: copper chaperone for superoxide dismutase, superoxide dismutase 1, soluble (amyotrophic lateral sclerosis 1 (adult), superoxide dismutase 2, mitochondrial, superoxide dismutase 3, extracellular and thiol redox proteins: glutaredoxin (thioltransferase), glutaredoxin 2,3,5, glutathione reductase,methionine sulfoxide reductase A, metallothionein 1A, 1B, 1E,1F,1G,1H,1M,1X,2A, protein disulfide isomerase family A, member 6, selenoprotein P, plasma, 1, sulfiredoxin 1 homolog (S. cerevisiae), thioredoxin, thioredoxin 2, thioredoxin domain containing 1,2,3,4,5,6,8,9,10,11,12,13,14,17, thioredoxin interacting protein, thioredoxin-like 1, 4A, 4B, thioredoxin reductase 1,2,3 (Dusting & Triggle, 2005).

An elevation of ROS may cause CVD due the overproduction of superoxide anion (O_2•-). This overproduction is detrimental, because of the rapid interaction of O_2•- with NO, which leads to the loss of NO bioavailability and increase in the production of peroxynitrite (ONOO−). A subsequent reduction in the vascular effects of NO, as well as a reduction in the antiatherogenic effects of NO, as a consequence will compromise cardiovascular function. An elevation of O_2•- will also lead to the oxidation of the important co-factor in the regulation of nitric oxide synthase, tetrahydrobiopterin (BH_4), and this will lead to an "uncoupled eNOS", which will then synthesize O_2•- rather than NO (Dusting & Triggle, 2005).

The term ROS refers to a subset of molecules called "free radicals", however there are some ROS which are not free radicals, such as hydrogen peroxide. This term refers to any molecule that contains an unpaired electron in the outer orbital. This unpaired electron makes the molecule highly reactive that leads to the formation of bonds between the ROS and other compounds (Dokken, 2008). Unpaired electron makes the molecule highly reactive, seeking to either donate an electron to another compound or take up protons from another compound to obtain a stable electron pair. These free radicals include superoxide anion (O_2•-), hydroxyl radical (•OH), and the free radical form of nitric oxide (•NO). Other members of the ROS family include hydrogen peroxide (H_2O_2) and peroxynitrite ($ONOO^-$) (Dusting & Triggle, 2005). On the other hand, several enzyme systems are known to be sources of ROS including the mitochondrial respiratory chain, xanthine oxidase, NADPH oxidase, cyclooxygenase, cytochrome P450, and uncoupled eNOS. Mitochondria are the source of ROS. There is also growing evidence that NADPH-oxidase is a major source of vascular superoxide production.

The high reactivity of free radicals leads to the formation of bonds between the ROS and other compounds, altering the structure and function of the tissue. Because of the reactive propensity of these molecules, ROS can directly damage a number of cell components, such as plasma membranes and organelles (Dokken, 2008). In diabetes, where cardiovascular disease is of particular concern, there are multiple sources of ROS including the auto-

oxidation of glucose, increased substrate flux, and decreased levels of NADPH through the polyol pathway. Formation of AGEs products and their interaction with cellular targets, such as endothelial cells, may lead to oxidative stress and promote formation of oxidized LDL (Ceriello & Motz, 2004).

Increased production of oxygen-derived free radicals such as the superoxide anion has been linked to impaired endothelial vasomotor function in experimental models of atherosclerosis. Accordingly, treatment with antioxidants has been shown to improve coronary and peripheral endothelial function in patients with CAD or coronary risk factors (Heitzer et al., 2001). Mechanisms that contribute to this selective cardiac dysfunction include decreases in energy production due to reductions in mitochondrial respiration, increased oxidative stress, and defective contractile and intracellular "Ca^{2+}" regulatory proteins. Changes in mitochondrial biogenesis and function have been documented in the metabolic syndrome and diabetes. Alterations in mitochondrial biogenesis as well as mitochondrial content and function provoke a heterogeneous group of CVD risk factors that constitute the metabolic syndrome. (Ren et al., 2010). It is increasingly recognized that important aspects of mitochondrial dysfunction that contribute to CVDs are induction of apoptosis and changes in mitochondrial morphology under the influence of oxidative stress. Finally, inefficient mitochondrial oxidative phosphorylation/biogenesis and increases in oxidative stress appear to be overarching abnormalities contributing to cardiac diastolic function, the hallmark of metabolic cardiomyopathy (Ren et al., 2010).

4. Adipocytokines and the metabolic complications of obesity

4.1 Fat depots, adipocitokines and their relation to the human metabolic syndrome

Adipose tissue is composed of adipocytes embedded in a loose connective tissue meshwork containing adipocyte precursors, fibroblasts, immune cells, and various other cell types. Adipose tissue was traditionally considered an energy storage depot with few interesting attributes. However, adipocytes express and secrete a variety of products known as 'adipokines', including leptin, adiponectin, resistin and visfatin, as well as cytokines and chemokines such as TNF-α, IL-6 and monocyte chemoattractant protein (Antuna-Puente et al., 2008) and due to the dramatic rise in obesity and its metabolic sequelae during the past decades, adipose tissue gained tremendous scientific interest. It is now regarded as an active endocrine organ that, in addition to regulating fat mass and nutrient homeostasis, releases a large number of bioactive mediators (adipokines) modulating hemostasis, blood pressure, lipid and glucose metabolism, inflammation, and atherosclerosis (see figure 1).

During positive caloric balance there are two factors important for the development of metabolic disease. First one is a type of the fat accumulation, i.e., due to increase in size (hypertrophy) or in number (hyperplasia) of fat cells. The next factor is a place of fat storage, i.e. subcutaneous (SC) or visceral (Vis) fat (Wajchenberg, 2000; Bays et al., 2008). In humans, white adipose tissue (WAT) produces over 50 'adipokines', including TNF-α which contributes to the low-grade inflammation found in obesity, leptin which has effects on food intake, and a host of other agents with a variety of effects (Lago et al., 2007). In parallel with these proinflammatory events, WAT also produces anti-inflammatory cytokines such as adiponectin (which, paradoxically, tends to be lower in obese individuals) and IL-10 and IL1R1 (IL-1Rα; production of which is proportional to body weight).

4.2 Leptin

Hyperleptinaemia is common in obesity and reflects increased adiposity and leptin resistance. Nevertheless, leptin resistance may not be complete as several actions of leptin, such as cardiovascular sympatho-activation, might be preserved in obese subjects known to be resistant to the metabolic effects of leptin (i.e. selective leptin resistance). Notably, the renal and sympathetic actions of leptin may play an important role in the pathogenesis of hypertension related to obesity and metabolic syndrome. Furthermore, the lipotoxic effect of leptin resistance may cause insulin resistance and β cell dysfunction, increasing the risk of T2D. Leptin has also been shown to possess proliferative, pro-inflammatory, pro-thrombotic, and pro-oxidative actions (Buettner et al., 2006).

4.3 Adiponectin

Adiponectin, referred to as adipocyte complement-related protein of 30 kDa (ACRP30), is a protein secreted from adipocytes (Correia & Rahmouni, 2006), that is abundantly present in plasma (Scherer et al., 1995; Berg et al., 2001). It is now well established that adiponectin has potent salutary actions on peripheral insulin sensitivity, and circulating adiponectin levels are reduced in obesity, insulin resistance and T2D (Scherer et al., 1995; Kern et al., 2003). Mice lacking adiponectin have reduced insulin sensitivity (Weyer et al., 2001; Kubota et al., 2002; Maeda et al., 2002); in contrast, adiponectin overexpression in ob/ob mice, confers dramatic metabolic improvements, e.g., in various mouse models, Holland et al. (2011) show that the insulin-sensitizing and antiapoptotic actions of adiponectin are partly related to its effects on sphingolipid metabolism, providing a new unifying mechanism for the pleiotropic beneficial actions of adiponectin. Adiponectin stimulates the cellular activity of ceramidase, which removes the fatty acyl chain from ceramides. This liberates sphingosine, which can subsequently be phosphorylated by sphingosine kinases to generate the antiapoptotic metabolite sphingosine-1-phosphate (S1P). Furthermore, liver-specific overexpression of the adiponectin receptors, AdipoR1 and AdipoR2, increased hepatic ceramidase activity and, concomitantly, reduced hepatic ceramide content. These *in vivo* models of varying adiponectin expression and AdipoR1 and R2 overexpression demonstrate a strong association between adiponectin levels, hepatic ceramide content and insulin sensitivity (Holland et al., 2011).

In the beta cell model of apoptosis, adiponectin protected against the development of hyperglycemia-a key feature of pancreatic insufficiency-by partially preserving beta cell mass and insulin content. Using mouse primary cardiomyocytes and a pancreatic beta cell line, Holland et al. (2011) showed that adiponectin prevents cell death induced by the saturated fatty acid palmitate and a short chain ceramide analog, C2-ceramide. Mechanistically, the insulin-sensitizing actions of adiponectin, which include enhanced glucose use and fatty acid oxidation (Yamauchi et al., 2003), inhibition of serine kinases that antagonize insulin signaling and enhanced mitochondrial biogenesis, are believed to occur via receptor-dependent activation of the 5′-AMP–activated protein kinase (AMPK). Intriguingly, it is known that adiponectin also exerts potent antiapoptotic effects and prevents myocardial apoptosis in response to ischemia-reperfusion injury (Shibata et al., 2005) and lipid-induced pancreatic beta cell apoptosis (Rakatzi et al., 2004).

Several studies have linked hypoadiponectinemia to diabetes (Kern et al., 2003), hypertension (Kim et al., 2007), atherosclerosis, and endothelial dysfunction (Chow et al., 2007). More recent studies have shown that the high-molecular weight (HMW) oligomer is inversely associated with the risk for diabetes independent of total adiponectin (Kadowaki et al., 2007), and the HMW oligomer is responsible for the association of adiponectin with traits of metabolic syndrome (Heidemann et al., 2008; Lara-Castro et al., 2006). On the other hand, adiponectin improves insulin sensitivity by increasing energy expenditure and fatty acid oxidation through activation of AMPK, and by increasing the expression of PPARα target genes such as CD36, acyl-coenzyme oxidase, and uncoupling protein-2 (Kadowaki et al., 2007). Alternatively, adiponectin may lead to an improved metabolic profile by the expansion of SC adipose tissue with decreased levels of macrophage infiltration (Nawrocki et al., 2006), similar to the actions of peroxisome proliferator-activated receptor (PPAR)-γ agonists; reduction of lipotoxicity and inflammation associated with obesity (Wang et al., 2007), and adiponectin has also had vasculoprotective effects mediated via an increase in endothelial nitric oxide production, or modulation of expression of adhesion molecules and scavenger receptors (Chow et al., 2007; Zhu et al., 2008).

In addition, work in experimental models has shown that adiponectin mediates beneficial actions in cardiovascular and metabolic-associated diseases (Sam & Walsh, 2010). For example, in mouse models, adiponectin modulates hypertrophic signals in the heart and exhibits direct anti-hypertrophic properties; in addition to improving vascular function and pathological remodeling (Antuna-Puente et al., 2008); the hypoadiponectinemia might be observed in subjects with hypertension and other cardiovascular diseases and could be a useful pharmacologic tool to improve membrane microviscosity in hypertension, via the NO dependent mechanisms (Tsuda, 2011).

It has been demonstrated that plasma adiponectin levels increased during weight reduction or blockade of the rennin angiotensin system indicating that adiponectin might be beneficial for preventing the development of atherosclerotic changes. The results of Kurata et al. indicate that blockade of Angiotensin II receptor ameliorates adipocytokine dysregulation and that such action is mediated, at least in part, by targeting oxidative stress in obese adipose tissue.

4.4 Resistin

Resistin is a 12-kDa peptide that was originally discovered as a result of examining differential gene expression of mouse adipose tissue after thiazolidinediones (TZD) treatment (Steppan et al., 2001). The thiazolidinediones a class of drugs that work through PPARγ agonism, are insulin sensitizers and have been shown to improve cardiac risk factors and decrease cardiovascular events; may potentially correct the inflammatory disarray, endothelial dysfunction, dyslipidemia, and plaque vulnerability associated with diabetic cardiovascular disease through their effects on insulin resistance and fat metabolism. Resistin was decreased by TZD treatment of mice and was increased in insulin-resistant mice. Furthermore, treatment with antiresistin antibody improved insulin sensitivity and glucose transport in mice and mouse adipocytes, respectively (Steppan et al., 2001). Additional studies in mice suggest that an important site of action of resistin is on hepatic glucose production (Rajala et al., 2003). Therefore, resistin is clearly an important adipokine that likely plays a role in the development of insulin resistance; however, it appears to be quantitatively less important in humans than other adipokines.

4.5 Visfatin

Visfatin is expressed in many cells and tissues, and was previously identified as a protein involved in B-cell maturation (pre-B colony enhancing factor) (Kitani et al., 2003; Samal et al., 1994). More recently, visfatin was described to be a highly expressed protein with insulin-like functions, and was predominantly found in visceral adipose tissue, from which the name visfatin was derived (Fukuhara et al., 2005). Injection of visfatin in mice lowered blood glucose, and mice with a mutation in visfatin, and nicotinamide adenine dinucleotide (NAD) biosynthetic activity ionotropy, which is essential for β-cell function (Revollo et al., 2007). In human studies, a positive correlation between visceral adipose tissue visfatin gene expression and BMI was noted, along with a negative correlation between BMI and SC fat visfatin (Berndt et al., 2005; Varma et al., 2007), suggesting that visfatin regulation in these different depots is different, and adipose depot ratios are highly dependent on the obesity of the subjects. Variable results were obtained regarding the relationship between visfatin and diabetes or insulin resistance (Varma et al., 2007; Chen et al., 2006; Hammarstedt et al., 2005; Haider et al., 2006). Therefore, there are a number of inconsistencies among the different studies of visfatin, and the role of this adipokine in obesity and insulin resistance is not clear.

4.6 Apelin

Apelin is another short peptide released from adipocytes upon stimulation by e.g. insulin and the endogenous ligand of the human orphan G-protein-coupled APJ receptor. In line with this, plasma apelin levels are increased in obesity associated with insulin resistance and hyperinsulinemia (Beltowski, 2006). In the cardiovascular system, apelin elicits endothelium-dependent, nitric oxide-mediated vasorelaxation and in rodents, apelin also increases cardiac contractility *in vivo* (Ashley et al., 2005; Atluri et al., 2007) and causes a rapid fall in both arterial blood pressure and systemic venous tone (Tatemoto et al., 2001; Lee, 2005) with corresponding reductions in left ventricular afterload and preload (Ashley et al., 2005; Tatemoto et al., 2001).

Apelin-APJ system, expressed in the central nervous system and in a variety of peripheral tissues, is involved in the regulation of the immune response, brain signaling, hemodynamic homeostasis, vasodilatation, inotropy, angiogenesis and glucose metabolism (Sorli et al., 2006; Zhang et al., 2009). In the cardiovascular system, high expression of APJ mRNA has been observed in the heart (Zhang et al., 2009). Apelin expression is restricted to endothelial cells and negligible in cardiomyocytes in normal myocardium, but detectable in failing hearts (Földes et al., 2003). Of all the active fragments identified to date, apelin-13 may represent the most potent biological ligand (Kawamata et al., 2001). Current studies suggest that apelin expression is at least maintained and possibly augmented in mild, compensated chronic heart failure but declines in severe disease (Japp & Newby, 2008). Exogenous apelin administration during myocardial injury can preserve cardiac function (Chandrasekaran, 2008). Some researchers suggested that apelin reduces infarct size and protects myocardial cells against ischemia-reperfusion (I/R) injury by activating the reperfusion injury salvage kinase (RISK) pathway. The RISK pathway incorporates phosphatidylinositol 3-OH kinase (PI3K)/Akt, p44/42 mitogen-activated protein kinase (MAPK) and extracellular signal-regulated MAPK (ERK1/2) (Simpkin, 2007).

5. Inflammatory pathway activation and interactions with endothelial cells

5.1 Endothelial cells

The vascular endothelium, located at the interface of blood and tissue, is able to sense changes in hemodynamic forces and blood borne signals and react by synthesizing and releasing vasoactive substances. Vascular homeostasis is maintained by a balance between endothelium-derived relaxing and contracting factors. With disruption of this balance, mediated by inflammatory and traditional cardiovascular risk factors, the vasculature becomes susceptible to atheroma formation. Inflammatory mediators appear to play a fundamental role in the initiation, progression, and eventual rupture of atherosclerotic plaques.

5.1.1 Endothelial dysfunction

Endothelial dysfunction implies diminished production or availability of NO and/or an imbalance in the relative contribution of endothelium-derived relaxing and contracting factors, those included endothelin-1 (ET-1), angiotensin, and several oxidants. However, endothelial dysfunction, as assessed in terms of vasomotor dysfunction, can occur well before the structural manifestation of atherosclerosis and thus can serve as an independent predictor of future cardiovascular events (Behrendt & Ganz, 2002).

Hypercholesterolemia, traditional cardiovascular risk factor, promotes attachment of blood leukocytes to the endothelium. Oxidized low-density lipoprotein causes endothelial activation and changes its biological characteristics in part by reducing the intracellular concentration of NO (Cominacini, 2001).

On the other hand, angiotensin II can induce the production of ROS, increase the expression of the proinflammatory cytokines as IL-6 and monocyte chemoattractant protein-1 (MCP-1), and upregulate VCAM-1 on ECs. High levels of CRP can also promote endothelial dysfunction by quenching the production of NO and diminishing its bioactivity (Verma, 2002). These endothelial modifications promote inflammation within the vessel wall, setting the stage for the initiation and progression of an atherosclerotic lesion.

5.2 Adiponectin and inflammatory activation

Recent research has focused on the origin of the inflammatory markers in obesity and the extent to which adipose tissue has a direct effect. The production of adipokines by visceral adipose tissue is of particular interest since their local secretion by visceral fat depots may provide a novel mechanistic link between obesity and the associated vascular complications. Under conditions of inflammation associated with cardiovascular disease, as well as an increase in mobilization of fatty acids from adipose tissue, there is increased secretion of pro-atherogenic, pro-inflammatory adipocytokines and chemokines.

The cardiometabolic benefits of adiponectin may be driven largely through improvements in vascular homeostasis, especially through improving endothelial function. Some studies have demonstrated impaired endothelial function in adiponectin-deficient mice (Teoh et al., 2008) demonstrated that adiponectin plays an important role to limit endothelial activation

and inflammation in experimental sepsis. On the contrary, in adiponectin-deficient mice exhibit profound reduction in survival following cecal ligation and puncture.

5.3 Mediators of inflammation

The inflammatory processes are mediated by several factors secreted by adipocytes collectively called adipocytokines (adiponectin, leptin, ghrelin, visfatin and resistin) some of which seem to play an important role in obesity-associated insulin resistance and cardiovascular complications. Tissue levels of TNF-α, IL-6, leptin and visfatin were significantly higher in patients with CAD relative to control subjects. Significantly higher tissue levels of these four cytokines from abdominal fat depots were found compared to those from epicardial fat in CAD patients.

IL-6 is secreted by a wide variety of cells such as endothelial cells, adipocytes, β pancreatic cells, monocytes, and macrophages. This cytokine is essential in reducing the inflammatory process by promoting the synthesis of anti-inflammatory cytokines and by negatively regulating inflammatory targets. In humans, higher circulating IL-6 levels have been associated with obesity and visceral fat deposition, increased risk of impaired glucose tolerance, T2D and high blood pressure. IL-6 is a central mediator of the acute-phase response and a primary determinant of hepatic production of CRP. Visceral adipose tissue secretes about two to three times more IL-6 than subcutaneous tissue, secreting also other molecules that stimulate further IL-6 expression (Curti, 2011).

In obesity, the pro-inflammatory effects of cytokines through intracellular signaling pathways involve the NF-κB and JNK systems. Thus, it can be considered that obesity corresponds to a sub-clinical inflammatory condition that promotes the production of pro-inflammatory factors involved in the pathogenesis of insulin resistance (Bastard et al., 2002).

5.4 Vasculature as part of the immune system

Blood vessels are integral components of the immune system; they are important part in lymphocyte circulation and act as portals between tissue and blood compartments. Endothelial cells express toll-like receptors, (Kunjathoor, 2002) whose ligation induces expression of leukocyte adhesion molecules, inducible NO synthase 2, endothelin, IL-1, and other inflammatory molecules. These cells also express the scavenger receptors CD36 and LOX-1, and can internalize ligands such as modified LDL particles. ECs are located at the interface of blood and tissues, and play a pivotal role in the inflammatory response. Their activation causes leukocyte recruitment, increased permeability, edema, and other characteristic features of inflammation. Furthermore, ECs can activate adaptive immunity by presenting foreign antigens to specific T cells.

5.5 Mammalian Target Of Rapamycin (mTOR) signaling pathway

The mammalian target of rapamycin (mTOR) signaling pathway integrates both intracellular and extracellular signals and serves as a central regulator of cell metabolism, growth, proliferation and survival. Discoveries that have been made over the last decade show that the mTOR pathway is activated during various cellular processes (e.g. tumor

formation and angiogenesis, insulin resistance, adipogenesis and T-lymphocyte activation) and is deregulated in human diseases such as cancer and T2D (Laplante & Sabatini, 2009). *In vivo* stimulators of adipogenesis have not been clearly identified, but may include insulin, IGF-1, as well as certain fatty acids and/or their metabolites. Insulin/IGF-1 acts on cell surface receptors, activating key intracellular signaling proteins. One of these signaling pathways, mTOR that is binds to, and inhibited by, rapamycin, an immunosuppressant that blocks T cell proliferation. The mTOR protein is a 289-kDa serine-threonine kinase that belongs to the phosphoinositide 3-kinase (PI3K)-related kinase family and is conserved throughout evolution (Laplante & Sabatini, 2009). The role of mTORC1 in regulating lipid synthesis, which is required for cell growth and proliferation, is beginning to be appreciated. It has been demonstrated that mTORC1 positively regulates the activity of sterol regulatory element binding protein 1 (SREBP1) (Porstmann et al., 2008) and of PPAR-γ (Kim & Chen, 2004), two transcription factors that control the expression of genes encoding proteins involved in lipid and cholesterol homeostasis.

The binding of insulin to its cell-surface receptor promotes the tyrosine kinase activity of the insulin receptor, the recruitment of insulin receptor substrate 1 (IRS1), the production of phosphatidylinositol (3,4,5)-triphosphate [PtdIns(3,4,5)P_3] through the activation of PI3K, and the recruitment and activation of AKT at the plasma membrane. In many cell types, activation of mTORC1 strongly represses the PI3K-AKT axis upstream of PI3K. Activation of S6 kinase 1 (S6K1) by mTORC1 promotes the phosphorylation of insulin receptor substrate 1 (IRS-1) and reduces its stability (Harrington et al., 2005). This auto-regulatory pathway, characterized as the S6K1-dependent negative feedback loop, has been shown to have profound implications for both metabolic diseases and tumorigenesis (Manning, 2004) and pro-inflammatory cytokines, such as TNFα, activate IkB kinase-β (IKKβ), which physically interacts with and inactivates tuberous sclerosis complex 1 (TSC1), leading to mTORC1 activation (Lee et al., 2007). This positive relationship between inflammation and mTORC1 activation is thought to be important in tumor angiogenesis and in the development of insulin resistance.

5.6 Adiponectin as anti-inflammatory action

Adiponectin exerts potent anti-inflammatory effects, as documented in experimental studies where authors demonstrate that reduces TNF-α production in response to various stresses in plasma, adipose tissue, vascular wall, heart, and liver (Kojima et al., 2003; Ujiie et al., 2006). In addition, antagonizes several of the inflammatory effects of TNF-α (Ouchi et al., 2003); can facilitate the removal of early apoptotic cells by macrophages and modulate the processes of inflammation and autoimmunity. This activity was mediated by calreticulin expressed on the phagocytic cell surface and not by any of the previously identified adiponectin receptors. Because the accumulation of cell corpses can cause inflammation and immune system dysfunction, these authors suggest a mechanism by which hypoadiponectinemia can contribute to the development of diabetes, atherosclerosis, and other complex diseases in which chronic inflammation is a contributing factor (Takemura et al., 2007). Thus, while AdipoR1 and AdipoR2 may mediate the metabolic properties of adiponectin (Yamauchi et al., 2003), calreticulin controls aspects of adiponectin's antiinflammatory actions (Hug et al., 2004). *In vitro* studies demonstrate that adiponectin adheres to injured vascular endothelium

(Okamoto et al., 2000) and inhibits TNF-α-induced monocyte adhesion to endothelial cells. It also decreases the expression of endothelial cell adhesion molecules (Ouchi et al., 1999) and TNF-α-induced NFkB activation (Ouchi N et al., 2000).

Adiponectin has been shown to have a role in hepatic inflammation and steatosis. Hypo-adiponectinaemia is associated with nonalcoholic steatohepatitis (Targher et al., 2004) and adiponectin has been shown to have beneficial anti-inflammatory effects in liver, reducing steatosis, hepatomegaly and inflammation in mouse models of alcoholic and non-alcoholic fatty liver disease (Xu et al., 2003).

5.7 New mediators of inflammation and endothelial cell activation

5.7.1 Oxidized low-density lipoprotein receptor-1 and LOX-1

Oxidatively modified Ox-LDL and lectin-like oxidized LDL receptor-1 (LOX-1) are contributing factors of endothelial dysfunction, an early cellular event during atherogenesis. The primary receptor for Ox-LDL in endothelial cells is LOX-1. Under physiological conditions, LOX-1 may play a role in host defense (is expressed at low levels), whereas pathological states such as atherosclerosis, diabetes, dyslipedemia, hypertension dramatically and disease states that promote vascular injury, LOX-1 is highly expressed in blood vessels increase (Mattaliano et al., 2010), and may be involved in binding pro-atherogenic materials, such as ox-LDL, that activate the endothelium. With its ability to bind products that induce inflammation and endothelial activation, elevated LOX-1 expression was observed in both initial and advanced atherosclerotic lesions (Li et al., 2002). Induction of LOX-1 expression is mediated by angiotensin II and endothelin-1, both antagonists of NO (Chen et al., 2006). LOX-1 is a type II transmembrane glycoprotein that is known to recognize a wide array of structurally distinct ligands besides Ox-LDL. These include activated platelets, AGEs, apoptotic bodies, bacteria, and CRP. LOX-1 plays a critical role in the development of atherosclerosis. This may suggest that increased LOX-1 transcriptional promoter activity may equal increased LOX-1 gene expression and elevated risk of atherosclerosis. Accordingly, decreased LOX-1 promoter activation may reduce the incidence of atherosclerosis and related diseases (Chen et al., 2006).

5.7.2 Protease-Activated Receptors (PARs)

Protease-Activated Receptors (PARs) are a family of 7-transmembrane–domain, G-protein–coupled receptors that function to link tissue injury to appropriate cellular responses, such as inflammation and tissue repair, which may contribute to disease. Under the influence of the traditional cardiovascular risk factors, the endogenous defenses of the vascular endothelium begin to break down, resulting in endothelial dysfunction and injury (see figure 1). PAR activation is also linked to the secretion of IL–6, the cytokine that promotes CRP synthesis, which itself triggers many of the steps in the inflammatory process. Overall, PAR activation appears to promote the inflammatory response within the intimal tissue, enhancing the initiation and progression of atherosclerotic plaques. Rosiglitazone, a selective PPARγ agonist, exerts anti-inflammatory effects in both obese and T2D individuals by decreasing plasma concentrations of CRP, serum amyloid-A, and matrix metalloproteinase (Stienstra, 2007).

5.7.3 Lipocalin-2

A member of the lipocalin family, lipocalin-2, also known as neutrophil gelatinase–associated lipocalin, modulates inflammation and is another adipokine that is elevated in the adipose tissue of obese mouse models and in the plasma of obese and insulin-resistant humans. *In vitro* studies suggest that lipocalin-2 induces insulin resistance in adipocytes and hepatocytes. The plasma level of another member of the lipocalin family, lipocalin-type prostaglandin D synthase, serves as a biomarker of coronary atherosclerosis (Yan, 2007).

6. Oxidative Stress in conditions and comorbidities that aggregate with cardiovascular disease

Obesity, is associated with inflammation and ROS production, while advanced glycation end-products (AGEs), through their receptor (AGER or RAGE), play an important role on these processes. This is a multiligand receptor of the immunoglobulin superfamily that binds advanced glycation end-products. Thus, increased epicardial, pericardial (EAT), or subcutaneous adipose tissue (SAT) is associated with the presence and severity of coronary artery calcium. The AGE–RAGE engagement is widely related with CVD and ROS generation, mainly mediated by NADPH-oxidase. This enzyme consists in two membrane-bound subunits, the gp91-PHOX protein (NOX2) or some of its homologs (named NOX from 1 to 5) and p22-PHOX protein. Once activated, NADPH-oxidase produces superoxide anions from oxygen and NADPH or NADH. Enhanced ROS production is an important factor associated with some CVD such as CAD. Furthermore, Rodino-Janeiro et al. (2010, 2011) have previously observed that EAT may undergone higher oxidative stress than SAT in patients with CAD because of lower expression of some antioxidant enzymes, like catalase, and higher expression of RAGE in EAT than in SAT. Oxidation of phospholipids in LDL, which infiltrates into the injured vessel wall, results in the formation and accumulation of ox-LDL. These, is pro-atherogenic, produces several abnormal biological responses, such as attracting leukocytes to the intimal of the vessel, improving the ability of the leukocytes to ingest lipids and differentiate into foam cells, and stimulating the proliferation of leukocytes, endothelial cells, and smooth muscle cells, all of which are steps in the formation of atherosclerotic plaque. Furthermore, activated macrophages express scavenger receptors that internalize ox-LDL. However, unregulated uptake of ox-LDL leads to production of lipid-loaded foam cells (Hulsmans et al., 2011).

6.1 Oxidative stress and the beta-cell

Glucotoxicity, lipotoxicity, and glucolipotoxicity are secondary phenomena that are proposed to play a role in all forms of T2D. They are implicated in the pathogenesis of β–cell dysfunction (Poitout & Robertson, 2008). Hyperglycemia and hyperlipidemia follow the primary pathogenesis of diabetes and exert additional toxic effects on β-cells. The concept of toxicity derived because physiologically, it presents a continuous overstimulation of the β-cell by glucose could eventually lead to depletion of insulin stores, worsening of hyperglycemia, and finally deterioration of β-cell function. So, a prolonged *in vitro* exposure of isolated islets or insulin-secreting cells to elevated levels of fatty acids is associated with

inhibited glucose-induced insulin secretion, impaired insulin gene expression, and induction of cell death by apoptosis.

6.2 Oxidative stress and diabetic vascular complications

Cardiovascular risk factors promote the production of ROS, excessive generation of ROS and has expression of eNOS been implicated in a variety of pathological events such as diabetes, hypertension, atherosclerosis, ischemia-reperfusion injury, CVD and neurodegenerative disease (Halliwell & Gutteridge, 2007). Results from several studies showed that the increase in ROS levels precedes the hyperglycemia and insulin resistance, suggesting a causal role of ROS in the disease process. Atherosclerosis is considered as the underlying pathology of cardiovascular diseases such as peripheral vascular disease, stroke, and coronary heart disease. The pathology of atherosclerosis is complex and involves structural elements of the arterial wall, platelets, leukocytes, and inflammatory cells such as monocytes and macrophages (Libby et al., 2002; Weber et al., 2008). The endothelium is a dynamic interface between the arterial wall and the circulating cells. Therefore, endothelial dysfunction accounts for one of the primary causes of atherosclerosis. Since the endothelium is the major source of NO in the vasculature, loss of normal cellular function can result in altered NO synthesis. The endothelium provides a constitutive supply of NO from eNOS, and under certain conditions (e.g. inflammation) it can produce excessive NO from the inducible isoform of NOS (iNOS). Therefore, regulation of NOS is central in the development and progression of atherosclerosis.

In particular, increased glucose leads to increased mitochondrial formation of ROS. Superoxide is a ROS that produces peroxynitrite when reacting with NO. Peroxynitrite induces cellular damage through depletion of the co-factor of the eNOS, tetrahydrobiopterin (BH4). Also, it activates the denominated classic pathways of diabetic complications, including: a) the polyol pathway, b) the AGE pathway, c) the protein kinase C (PKC) pathway, and d) the hexosamine pathway. Several studies suggested that intermittent low and high glucose conditions are even more deleterious to endothelial cell function than a steady, constant increase of glucose. These conditions also induce endothelial cells to enter into a proinflammatory state, and this state is associated with the upregulation of various adhesion molecules and proinflammatory cytokines (Piconi et al., 2004).

iNOS is very relevant to diabetic pathophysiology. Recent reports reveal that decreased expression of eNOS accompanies increased expression of iNOS and nitrotyrosine during the progression of diabetes in rats (Nagareddy et al., 2005). This finding suggests that induction of iNOS in cardiovascular tissues is dependent on the duration of diabetes and contributes significantly to depressed responses to vasoactive agents. *In vivo* studies revealed that oxidative stress due to hyperglycemia, occurring before late complications, become clinically evident (Pitocco et al., 2009). This finding suggests that oxidative stress plays a crucial role in the pathogenesis of late diabetic complications. It has also been described in human studies that endothelial cells in diabetes fail to produce sufficient amount of NO and fail to relax in response to endothelium-dependent vasorelaxants e.g. acetylcholine, bradykinin, shear stress, etc (Avogaro et al., 2006).

Further clinical data have demonstrated that rapid glycemic swings are associated with an exacerbated degree of oxidant production in human diabetes (Monnier et al., 2006), and are

deleterious to the endothelial function of T2D patients (Ceriello et al., 2008). Overall, these data outline the importance of steady glucose control and the potential involvement of oxidative and nitrosative stress in the pathogenesis of complications due to poorly controlled diabetes. Diabetic subjects have reduced antioxidant capacity which could favor oxidative stress. A decline in important cellular antioxidant defense mechanisms, including the glutathione redox system and vitamin C-vitamin E cycle, significantly increases the susceptibility to oxidative stress. Thus, attempts have been made to reduce oxidative stress-dependent cellular changes in patients with diabetes by supplementation with naturally occurring antioxidants, especially vitamins E and C, lipoic acid levels are reduced in diabetic patients.

It has now been established that measurement of F2-isoprostanes is the most reliable approach to assess oxidative stress status *in vivo*, providing an important tool to explore the role of oxidative stress in the pathogenesis of human disease. In addition, products of the isoprostane (IsoP) pathway have been found to exert potent biological actions and therefore may be pathophysiologic mediators of disease. IsoPs, 8-iso-PGF2α and 8-iso-PGE2 possess potent biological effects in various systems and they also serve as mediators of oxidant stress through their vasoconstrictive and inflammatory properties (Kaviarasan et al., 2009). There exists a significant correlation between blood glucose and urinary IsoPs levels, suggesting that peroxidation is related to glycemic control. In vascular smooth muscle cells, F2-IsoPs formation was found to be induced *in vitro* by high glucose concentrations.

6.3 Cardiovascular disease

The diverse responses of the microvasculature to CVD risk factors include oxidative stress, enhanced leukocyte and platelet-endothelial cell adhesion, impaired endothelial barrier function, altered capillary proliferation, enhanced thrombosis, and vasomotor dysfunction (Granger et al., 2010).

As shown in figure 1, an imbalance between the production and detoxification of ROS in vascular endothelial cells can result in the oxidative modification of cell components, impair cell function and/or can enhance cell death via apoptosis or necrosis. The oxidative activation of enzymes (phospholipase A2) and transcription factors (nuclear factor kB, NFkB) that accompanies excess ROS production can also result in an enhanced biosynthesis of lipids (platelet activating factor, leukotrienes) and proteins (adhesion molecules, cytokines) that promote inflammation. Superoxide, by virtue of its ability to inactivate nitric oxide (an anti-inflammatory molecule), is another link between oxidative stress and the induction of a pro-inflammatory phenotype in the vasculature. This oxidative stress in the vessel wall is often accompanied by an increased production of superoxide anion by circulating immune cells, and there is evidence for a causal link between these two sources of ROS: circulating cells and vessel wall.

Different enzymatic sources have been implicated in the enhanced ROS production, including NADPH oxidase, xanthine oxidase, mitochondrial enzymes, and uncoupled nitric oxide synthase. It remains to clarify whether the pro-hypertensive effects of the superoxide anion relate to its ability to inactivate NO or to indirectly promote the production of endogenous vasoconstrictors, such as endothelin. NADPH-oxidase has received the most

attention as a potential source of ROS in hypertension (HTN), followed by xanthine oxidase. Both endothelial cell- and leukocyte-associated NADPH-oxidase have been implicated in HTN-induced superoxide production, and there is evidence linking both cellular sources of the enzyme to activation of the angiotensin II type 1 receptor (AT1r) and to cytokines (TNF-α) derived from circulating immune cells (Crimi et al., 2007; Harrison & Gongora, 2009).

While some adipokines as leptin and adiponectin have been shown to promote the expression of endothelial cell adhesion molecules (CAMs) and leukocyte-endothelial cell adhesion (LECA) are known to exert an inhibitory effect on these responses. The absence of LECA in the microcirculation of obese mice under basal conditions suggests either that the pro- and anti-adhesive adipokines are in balance or that the systemic plasma levels achieved by these mediators do not cause overt inflammation in tissues distant from their source (adipose tissue). The latter possibility is supported by evidence of an increased sensitivity (priming) of endothelial cells and leukocytes in obese animals to inflammatory stimuli.

However, within the microvasculature of adipose tissue, a robust inflammatory response is noted under basal conditions, as reflected by an increased expression of the endothelial cell adhesion molecules ICAM-1 and E- and P-select in, with an accompanying recruitment of rolling and firmly adherent leukocytes, and the formation of platelet-leukocyte aggregates. The reduced LECA may be linked to adiponectin deficiency since the adipokine is a potent inhibitor of LECA and its production/release is diminished during adipogenesis (Singer & Granger, 2007).

6.4 Oxidative stress in aortic valves

Superoxide levels also are increased in stenotic aortic valves from humans. Heistad et al., (2009) found, in stenotic valves removed during surgical replacement of the aortic valve, that superoxide is increased greatly near calcified regions of the valve. Others authors (Miller et al., 2008) also found, in valves obtained at surgery or autopsy, that oxidative stress is increased in stenotic aortic valves. Thus, in calcified stenotic aortic valves as well as in atherosclerotic lesions, oxidative stress is increased. But, there are important differences in mechanisms that account for oxidative stress in aortic valves and in atherosclerotic arteries. In calcific aortic stenosis, increased production of superoxide may be mediated by "uncoupling" of NOS, as NOS primarily produces superoxide instead of nitric oxide NAD(P)H expression and activity do not appear to be increased in aortic valves (Miller et al., 2008). In striking contrast, increased expression and activity of NADPH-oxidase appears to be a major mechanism for oxidative stress in atherosclerotic lesions. Oxidative stress, in addition to contributing to fibrosis, may activate matrix metalloproteinases (MMPs) in the aortic valve and arteries. In the valve, MMPs may play a permissive role in expansion of calcification of the valve, and degraded fragments of collagen and elastin also may increase pro-calcific signaling in valvular interstitial cells. Activation of MMPs in arteries probably is harmful in a different way, by contributing to plaque rupture.

6.5 Atrial fibrillation

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in clinical practice and contributes to impaired quality of life, and increased morbidity and mortality. The

mechanisms underlying both the initiation and perpetuation of AF are not well established but are thought to involve inflammation and oxidative stress. Furthermore, a number of studies have shown that concentrations of inflammatory mediators or markers, such as IL-6 and high-sensitivity CRP (hs-CRP), are increased in patients with AF. One mechanism that may mediate the effects of inflammation in AF is oxidative stress. Elevated inflammatory biomarkers are strongly associated with AF. Inflammation has important prognostic implications in AF; large prospective studies have shown that elevated hs-CRP levels correlated with risk factors for stroke and overall prognosis. The positive correlation between elevated levels of TNF-α and N-terminal pro-brain natriuretic peptide (NTpBNP) and severity of AF suggests that these biomarkers could be prognostic markers for AF in clinical practice (Li et al., 2010).

6.6 Insulin resistance

A large number of studies have evidenced the pivotal role of oxidative stress in insulin resistance states such as metabolic syndrome, obesity, and T2D (Atabek et al., 2004; Block et al., 2002). Decreased antioxidant capacity, increased production of ROS with oxidation products of lipids, DNA, and proteins have been reported in plasma, urine, and various tissues, suggesting systemic and organ-specific oxidative stress. Recent evidence for systemic oxidative stress includes the detection of increased circulating and urinary levels of the lipid peroxidation product F2-isoprostane (8-epi-prostaglandin F2α) in both T1D and T2D patients (Davi et al., 2003). As described above, ROS and reactive nitrogen species (RNS) are able to directly modify the expression of adiponectin. Secreted almost exclusively from adipocytes, it is inversely correlated with fat mass in obesity and with its associated cardiovascular risk. It should be considered that, plasma and urinary lipid peroxidation markers indicative of systemic OS correlated with lower circulating adiponectin levels.

7. Conclusion

Figure 1 summarizes much of the content of this chapter, because it shows most of the cellular elements and signaling pathways in which highlights the participation of adipocytokines involved in the immune response and oxidative stress on the vascular endothelium. These alterations lead to development of atherosclerosis. And finally this endothelial damage, together with the increase in free radicals can cause multiorgan damage.

In conclusion, abnormal adipocytokine expression with consequent inflammation, oxidative stress itself may result from the inflammatory changes that occur in obesity. Therefore, a vicious cycle that provokes increased oxidative stress in obesity may exist. Reactive oxygen species that lead to increased oxidative stress can be generated in adipocytes and in other cell types such as leukocytes, all of which can be a source of increased oxidative stress in obese humans. Increased oxidative stress is independently associated with obesity measures including body mass index and waist-hip ratio. It is also associated with several CVD risk factors including smoking, blood glucose, and hyperlipidemia. Oxidative stress and increased adipocytokines may also promote endothelial dysfunction, atherogenesis, and coronary heart disease independent of traditional risk factors.

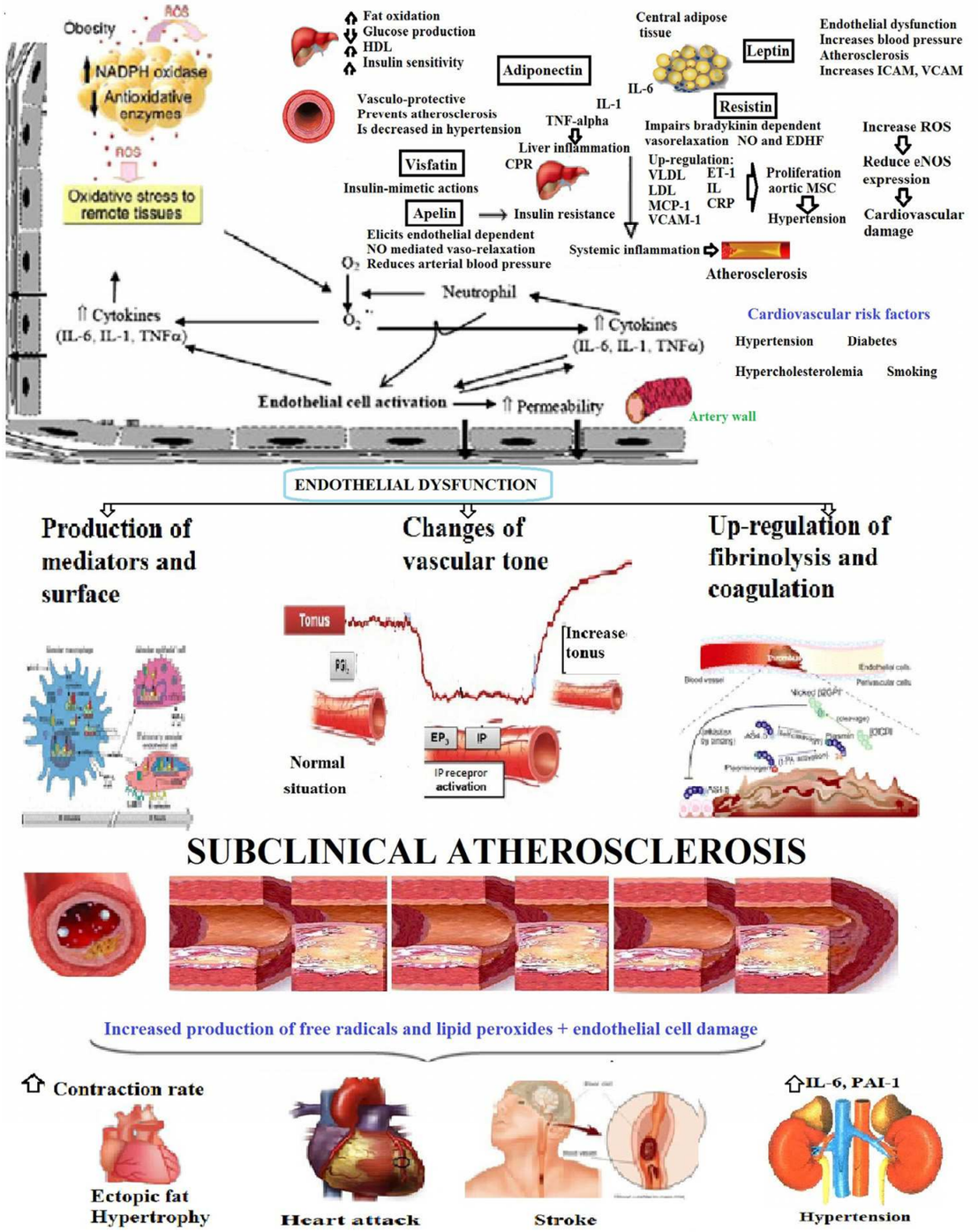

Fig. 1. Impaired cardiovascular functions and adipocytokines actions on oxidative stress. This figure shows the majority of cellular elements and signaling pathways in which highlights the participation of adipocytokines (framed) involved in the immune response and oxidative stress on the vascular endothelium. These alterations lead to development of atherosclerosis. And finally, this endothelial dysfunction can generate harmful free radicals and cause tissue and multiorgan damage.

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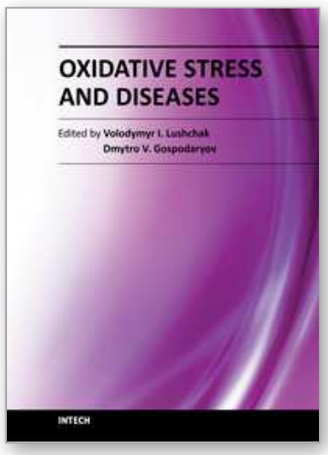

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The development of hypothesis of oxidative stress in the 1980s stimulated the interest of biological and biomedical sciences that extends to this day. The contributions in this book provide the reader with the knowledge accumulated to date on the involvement of reactive oxygen species in different pathologies in humans and animals. The chapters are organized into sections based on specific groups of pathologies such as cardiovascular diseases, diabetes, cancer, neuronal, hormonal, and systemic ones. A special section highlights potential of antioxidants to protect organisms against deleterious effects of reactive species. This book should appeal to many researchers, who should find its information useful for advancing their fields.

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