

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

5,500

Open access books available

136,000

International authors and editors

170M

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



Dyslipidemia Induced by Stress

Fernanda Klein Marcondes¹, Vander José das Neves¹,
Rafaela Costa¹, Andrea Sanches¹, Tatiana Sousa Cunha^{1,2},
Maria José Costa Sampaio Moura³, Ana Paula Tanno⁴
and Dulce Elena Casarini^{5*}

1. Introduction

The pioneering work of Hans Selye (1936) led to the use of the word “stress” in a biological context gaining popularity world-wide. Stress is as an organic response to stressors that can be aversive stimuli or unknown situations capable of compromising homeostasis. During the stress reaction, the sympathetic nervous system and hypothalamic-pituitary-adrenal axis are stimulated. Consequently, serum concentrations of classical stress hormones, namely catecholamines and glucocorticoids, are increased and act on cells and tissues inducing adaptive changes in order to protect the organism and allow its survival. In addition, the stress reaction can also modulate immune system activities and the secretion of other hormones (gonadotrophins, estrogen, testosterone, thyroid, angiotensins).

Considering that organic homeostatic systems are subject to frequent environmental and internal variations, Sterling and Eyer (1988) proposed the term allostasis to describe the adaptive processes that actively maintain stability through physiological changes.

The terms eustress and efficient allostasis describe facile adaptation, such as a quick peak stress response to mobilize energy to deal with an acute stressor, and a rapid return to baseline, when the stressor terminates. On the other hand, distress or allostatic load refers to an imbalance in systems that promote adaptation (Epel, 2009; Korte et al., 2005). This imbalance can simply be the result of too much repeated stress, but it can also be the result of adaptive systems that are out of balance and fail to shut-off or, alternatively, systems that fail to return to normal (Epel, 2009). Therefore the shut-off of the stress response is particularly important, because, when systems do not shut off in time, they can cause damage or promote pathology (McEwen, 1998).

The classical stress hormones, glucocorticoids (cortisol) and catecholamines (epinephrine and norepinephrine), are catabolic and modulate the breakdown of glycogen, triglycerides and proteins into molecules that can be rapidly metabolized in order to generate energy (Black, 2002). These responses enable energy substrates to be directed to organs and tissues

*¹Department of Physiological Sciences, Piracicaba Dental School, University of Campinas, Piracicaba, Brazil

²Science and Technology Institute, Federal University of São Paulo, São José dos Campos, Brazil

³Life Sciences Center, Pontifical Catholic University of Campinas, Campinas, Brazil

⁴Division of Pharmacy, Faculty of Americana, Americana, Brazil

⁵Department of Medicine, Federal University of São Paulo, São Paulo, Brazil

with the greatest demand during the stress reaction, and support the fight or flight reaction to a stressor.

During acute stress, there is a rapid and transient increase in blood concentrations of total cholesterol, low-density lipoprotein (LDL), apoprotein B, triglycerides, and free fatty acids (Stoney, 2007). This increase persists as long as the stressor is maintained (Black, 2002), and disappears in stress-free periods (Stoney et al., 1999). In chronic stress situations, it has been shown that dyslipidemia is maintained and may persist even after the stressor is no longer present (Neves et al., 2009).

2. Dyslipidemia induced by stress: Physiological mechanisms

Many studies have shown the effect of stress on lipid metabolism. Stress associated with a major disaster, such as an earthquake or loss of job and income is associated with increased total cholesterol, LDL, and triglycerides in the bloodstream (Stoney, 2007). The perception of increased stress during a period of high workload is associated with elevated cholesterol in the bloodstream and ingestion of foods that increase cholesterol (McCann et al., 1990). Acute psychological stress in healthy men and women reduces the clearance rate of exogenous fat (Stoney et al., 2002). Chronic psychological stress increased the plasma cholesterol level in medical students (O'Donnell et al., 1987). In a more recent study, Yoo et al., 2011, showed high prevalence of hypercholesterolemia in stressed female law enforcement officers in comparison with the general female population. Moreover, elevated basal cortisol concentrations and lower circadian cortisol variability can induce dyslipidemia in patients with depressive and anxiety disorders (Venn et al., 2009; Vogelzangs et al., 2007). These patients presented hypercortisolism, increased serum levels of total cholesterol, LDL, and triglycerides and decreased serum levels of HDL (Venn et al., 2009).

In animal studies, it has been shown that electric shock stress increases plasma cholesterol concentrations (Berger et al., 1980), and unpredictable immobilization stress decreases HDL, increases blood LDL, and very-low-density lipoprotein (VLDL) concentrations in rats (Bryant et al., 1988). Chronic mild unpredictable stress increases triglycerides, total cholesterol, VLDL, and LDL concentrations in the bloodstream of stressed rats compared with control rats and this effect was observed 15 days after the stress protocol had ended (Neves et al., 2009).

The stressful modern lifestyle exerts a strong influence on lipid metabolism (Black, 2002) and may transform adaptive responses to pathophysiological changes. Acute increases in blood lipids are necessary for the individual to survive and adapt to the stressor. However prolonged changes in lipid metabolism induced by chronic stress can result in cardiovascular diseases such as atherosclerosis, coronary heart disease, and stroke (Brindley et al., 1993).

The negative effects of sustained stress-induced dyslipidemia are related to a bidirectional relationship between stress hormones and insulin. Catecholamines directly stimulate free fatty acid and glycerol secretion in the bloodstream from fat depots, a process that may result from increased blood flow through adipose tissue or from adipose- β_2 adrenoceptor stimulation (Stoney, 2007). Stress-induced high glucocorticoid concentration exerts a permissive effect on these lipolytic actions of catecholamines (Brindley et al., 1993). Since insulin regulates triglyceride synthesis and hepatic VLDL production, insulin resistance results in unregulated triglyceride synthesis and VLDL production (Stoney, 2007) and

triglycerides are secreted by the liver in large quantities within the VLDL particles (Black, 2003). Therefore both catecholamines and glucocorticoids antagonize the actions of insulin, contributing to insulin resistance (Kyrou & Tsigos, 2009; Lafontan & Langin, 2009).

Moreover, hyperinsulinemia acts centrally to stimulate sympathetic nervous system activity, resulting in increased secretion of catecholamines (Black, 2003), and the absence of satisfactory insulin action facilitates the actions of cortisol and glucagon, which in turn stimulate phosphatidate phosphohydrolase activity to synthesize hepatic triglyceride (Brindley et al., 1993).

The cortisol also induces apoprotein B (apo B) secretion from the liver in the proportion of one apo B molecule per VLDL particle (Brindley et al., 1993), consequently increasing the VLDL concentrations in the bloodstream. As each VLDL particle is metabolized to intermediate-density lipoprotein (IDL) or LDL, the action of the cortisol that stimulates apo B secretion also results in increased LDL particles in the blood. Furthermore, in the presence of stress-induced insulin resistance, high levels of glucocorticoids suppress the hepatic LDL receptors, which delay LDL clearance (Stoney, 2007).

Contributing to all these processes, it has been shown that perilipin, which coats the surface of lipid droplets to restrict lipase access to the triglyceride core within the droplet, may suffer phosphorylation and/or down-regulation by glucocorticoid action, thereby facilitating the lipolysis of triglycerides in fatty acids and glycerol (Xu et al., 2001). This sets off a vicious cycle, leading to more and more triglycerides being produced by the liver and secreted in VLDL particles, as a result of the stimulation of glucocorticoids and fatty acids.

In addition, norepinephrine and cortisol inhibit lipoprotein lipase activity, leading to diminished triglyceride clearance, decrease in HDL concentration, and increase in VLDL, IDL, and LDL concentrations in the bloodstream (Stoney, 2007). Norepinephrine also diminishes hepatic triglyceride lipase activity, which in turn promotes high concentrations of lipoproteins rich in triglycerides in the blood (Stoney, 2007).

In the context of stress-induced dyslipidemia, changes in food ingestion must also be considered. During acute stress, transient dyslipidemia and food intake inhibition are mediated by β -adrenergic activation and increased hypothalamic corticotrophin releasing hormone (CRH) levels which act as catabolic signals. On the other hand, chronic activation of the hypothalamic-pituitary-adrenal axis has been associated with overeating and obesity (Dallman et al., 2004; Nishitani & Sakakibara, 2006). Many studies have supported this relationship. Lemieux & Coe, 1995, related that approximately 50% of women with posttraumatic stress disorder as a result of childhood sexual abuse were overweight, and also showed high concentrations of norepinephrine, epinephrine, and dopamine in urine. Changes in sleep-wake cycles associated with stress, resulting in sleep loss, induce decreased leptin levels, increased ghrelin levels, and increased hunger and appetite (Pejovic et al., 2010; Spiegel et al., 2004). In addition, the parent's lifestyle can influence metabolism, and individuals exposed to maternal stress during intrauterine life can exhibit deregulation of body weight control mechanisms and blood lipid profile (De Moura, 2008). The relationship between excessive glucocorticoids and visceral fat accumulation has also been discussed by Björntorp & Rosmond, 1999.

Thus, the typical response to chronic stress is not by way of avoiding food but by increasing the intake of sugar- and fat-rich comfort foods, which make people feel better

(Stoney, 2007; Torres & Nowson, 2007). Dallman et al., 2003, suggested that people or animals eat comfort food in an attempt to reduce activity in the 'chronic stress-response network' with its attendant anxiety. They suggested the following mechanism: first, in the periphery, glucocorticoids stimulate accretion of mesenteric energy stores; second, as the abdominal energy-generated (unidentified) signal increases, the negative input to catecholaminergic cells in the nucleus tractus solitarius reduces the synthesis of enzymes required for norepinephrine synthesis; third, the decreased noradrenergic signal to the hypothalamic paraventricular nucleus (PVN), in turn, decreases CRH synthesis and secretion. Thus, there is a powerful metabolic feedback control of CRH in the PVN, which may indirectly decrease glucocorticoid-action in the central nucleus of the amygdala; and thereby control anxiety (Korte et al., 2005). Consequently, all these mechanisms can lead to obesity and dyslipidemia due to overeating. In addition, it has been proposed that when chronic stress, to which animals and humans cannot easily adapt, is combined with high-fat high-sugar diets, it stimulates the sympathetic nerves to upregulate the expression of neuropeptide Y, an adrenergic cotransmitter and stress mediator. Stress and hypercaloric diets also increase glucocorticoid concentration in visceral fat, which in turn upregulates the expression of neuropeptide Y and its receptor Y2R, resulting in fat growth, hyperinsulinemia and hyperlipidemia (Bartolomucci et al., 2009; Kuo et al., 2008).

Some studies have also shown that glucocorticoid actions in the target tissues depend not only on circulating hormone levels, but also on intracellular glucocorticoid receptors and activities of both 11 β -Hydroxysteroid dehydrogenase type 1 (11 β -HSD1) and 2 (Bose et al., 2009). The effects of glucocorticoid are enhanced by the enzyme 11 β -HSD1 in the stromal cells of visceral fat, since this enzyme catalyzes the conversion of inactive cortisone to active glucocorticoid in local tissue. It has been shown that transgenic knockout mice, which overexpress 11 β -HSD1 in adipose tissue, present accumulation of visceral adipose tissue, hypertension, dyslipidemia and glucose intolerance (Masuzaki et al., 2001; Masuzaki & Flier, 2003). Therefore 11 β -HSD1 plays an important role in the development of metabolic disease associated with stress (Bose et al., 2009; Walker & Stewart, 2003).

In addition, cytokines such as interleukin 6 (IL-6), tumor necrosis factor (TNF)- α , and leptin released from fatty cells also contribute to dyslipidemia induced by stress. IL-6 increases the activity of 11 β -HSD1 with consequent expansion of visceral fat. TNF- α induces lipolysis in adipose tissue. Both IL-6 and TNF- α decrease lipoprotein lipase activity, contributing to the increase in triglyceride levels induced by stress (Black, 2003). Moreover, TNF- α induces insulin resistance because it depresses insulin receptor activity (Yudkin et al., 2000). TNF- α also induces IL-6 synthesis, and stimulates leptin synthesis, which acts centrally to decrease appetite and increase thermogenesis to decrease fat storage (Black, 2003). Leptin increases the activity of sympathetic nervous system centrally (Mohamed-Ali et al., 1998), which in turn stimulates increased release of TNF- α and IL-6 from adipocytes (Black, 2003). This sympathetic nervous system hyperactivity induced by high levels of leptin in the bloodstream would provide an additional effect of catecholamines on the genesis of insulin resistance and dyslipidemia associated with stress in obese individuals.

Therefore, dyslipidemia induced by stress involves complex interactions among stress hormones, insulin, adipose tissue metabolism and cytokines. Figure 1 indicates the physiological mechanisms of dyslipidemia induced by stress.

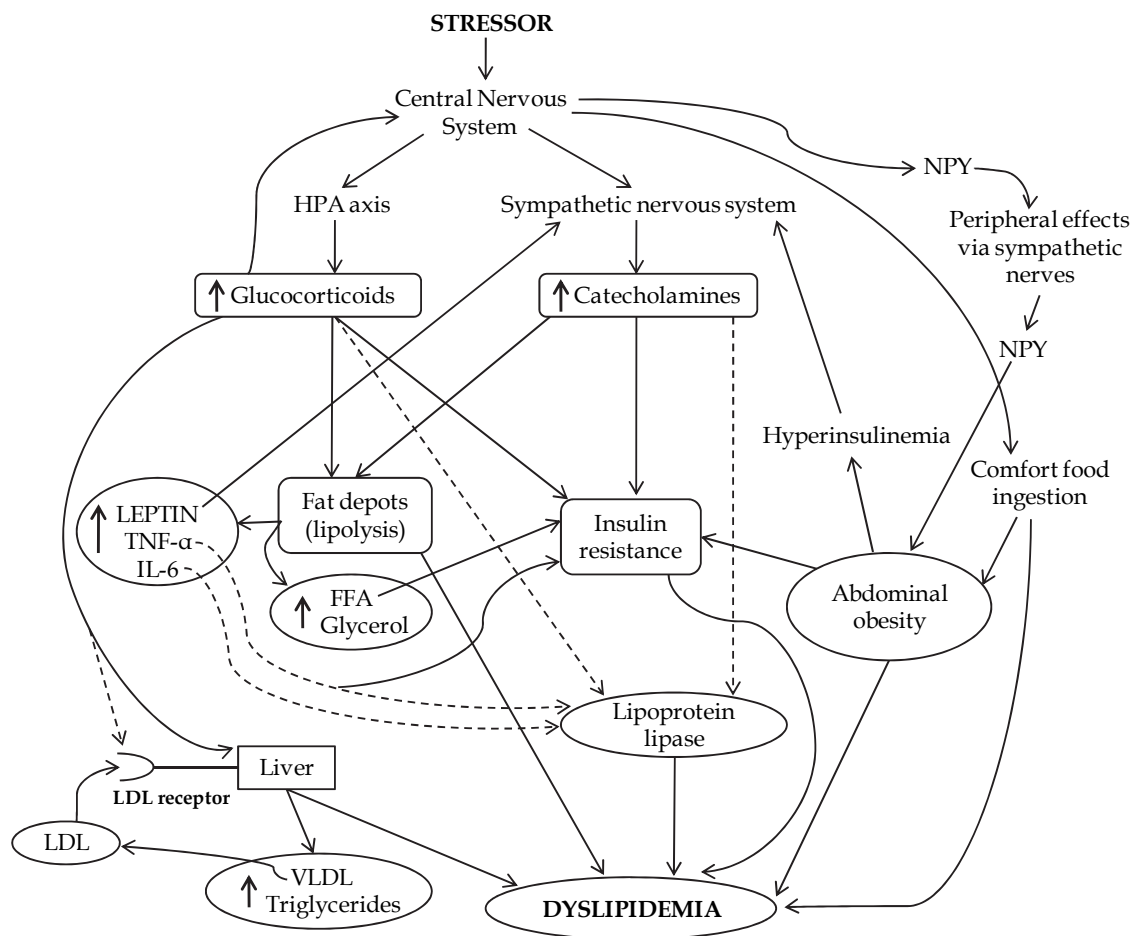


Fig. 1. Schematic representation of physiological mechanisms of dyslipidemia induced by stress. Hypothalamic-pituitary-adrenal axis (HPA), low-density lipoprotein (LDL), very-low-density lipoprotein (VLDL), free fatty acids (FFA), neuropeptide Y (NPY), tumor necrosis factor (TNF- α), interleukin 6 (IL-6). Solid arrows show stimulatory effects; dashed arrows indicate inhibitory effects.

3. Stress, dyslipidemia and atherosclerosis: Putative mechanisms

Atherogenic dyslipidemia is a major underlying cause of the development of atherosclerosis, which is an inflammatory disease (Mullick et al., 2006; Sheril et al., 2009). Since the stress-induced atherogenic lipid profile potentiates the effects of dietary and genetic factors in atherogenesis (Brindley et al., 1993), stress has been recognized as a risk factor for atherosclerosis (Kyrou & Tsigos, 2009; Shively et al., 2009). However, despite the association between dyslipidemia and atherosclerosis, many individuals develop severe atherosclerotic lesions associated with low serum lipid concentration, and others develop far more severe atherosclerosis than would be expected on the basis of a modest elevation of serum lipids (Kaplan et al., 1983). In this context, other effects of stress, not related specifically to dyslipidemia, are also involved in atherogenesis (Bierhaus et al., 2003; Gu et al., 2009) and approximately 40% of cases without known causal factor, have been attributed to stressful situations (Black, 2002).

The atherogenic effects of stress include changes in nitric oxide (NO) and cytokine production, vascular smooth muscle mitogenesis, occurrence of insulin resistance, neuropeptide Y (NPY) actions and modulation of the renin-angiotensin system activity. These effects are directly and indirectly related to stress-induced dyslipidemia, as will be pointed out below.

The healthy endothelium provides a smooth barrier that limits the activation of proinflammatory factors, blocks the transfer of Apo-B 100-containing atherogenic lipid particles into subendothelial space, inhibits the release of chemokines and cytokines, and prevents platelet and monocyte adhesion to the vascular wall (Cersosimo & DeFronzo, 2006). A high amount of NO is produced by endothelial nitric oxide synthase (eNOS). It is a vasodilator, has antithrombogenic properties, is an inhibitor of smooth muscle cell proliferation and of leukocyte- and monocyte-adhesion (Badimón & Martínez-González, 2002; Sudano et al., 2006). Decrease in NO bioavailability is a key feature of endothelial dysfunction resulting in lower responses to vasodilator agents (Codoñer-Franch et al., 2011), and represents an early stage of atherosclerosis (Badimón & Martínez-González, 2002). Endothelial dysfunction contributes to the development and progression of atherosclerosis by favoring coagulation, inflammatory cell adhesion, imbalance between vasoconstriction and vasodilation, and by enhancing transendothelial transport of atherogenic particles (Cersosimo & DeFronzo, 2006).

High stress-induced glucocorticoid levels reduce the expression of guanosine triphosphate cyclohydrolase 1 messenger ribonucleic acid (mRNA), necessary for tetrahydrobiopterin cofactor (BH₄) synthesis, which stabilizes eNOS (Mitchell et al., 2004). If BH₄ levels decrease, endothelial eNOS becomes uncoupled and transfers electrons to molecular oxygen generating superoxide anions (Rizzo et al., 2009), which react avidly with NO to form peroxynitrites (Förstermann & Münzel, 2006), resulting in diminished NO bioavailability, and favoring the traffic of oxidized lipids across the endothelium. Associated with this injurious effect of glucocorticoids, the high LDL levels induced by stress also decrease eNOS mRNA expression (Liao et al., 1995).

Considering dyslipidemia induced by stress, it has been reported that before structural changes appear, chronic elevations of cholesterol in the bloodstream are frequently associated with impaired endothelium-dependent NO production due to increased interaction between caveolin and eNOS (Feron et al., 1999). Caveolin proteins are expressed in the majority of the cell types that play a role in atherogenesis, including endothelial cells, macrophages, and smooth muscle cells (Frank & Lisanti, 2004). High levels of LDL-cholesterol increase the caveolin concentration in endothelial cells (Feron et al., 1999), strengthen the caveolin-eNOS complex, and reduce the interaction between Ca²⁺-calmodulin and eNOS. These effects decrease eNOS translocation from caveolae to the cytoplasm and considerably diminish NO production (Feron et al., 1999; Frank & Lisanti, 2004). In addition, lipid peroxidation induced by stress also impairs nitric oxide production (NO), stimulates inflammatory response, and increases the traffic of inflammatory molecules and oxidized LDL to sub-endothelial space, leading to vascular endothelial dysfunction (Black, 2002; Black, 2003; Black & Garbutt, 2002; Rizzo et al., 2009).

Insulin resistance is also involved in the atherogenic effects of stress. Insulin stimulates NO production by the endothelium (Muniyappa & Quon, 2007). During chronic stress cortisol-induced insulin resistance (Black, 2002; Kyrou & Tsigos, 2009) decreases this effect, and endothelial dysfunction may occur. In addition, insulin resistance is associated with inhibition of the phosphatidylinositol 3-kinase pathway and over-stimulation of the

mitogen-activated protein kinase pathway in endothelial cells. Impairment of the phosphatidylinositol 3-kinase pathway reduces eNOS activity, and accentuates free fatty acid-evoked oxidative stress. These effects decrease NO bioavailability and promote an imbalance between vasoconstriction and vasodilation (Cersosim & DeFronzo, 2006; Muniyappa & Quon, 2007) predisposing the individual to atherosclerosis and arterial hypertension. In addition insulin resistance increases the reactive oxygen species, reducing eNOS activity (Muniyappa et al., 2008).

Morphological changes in blood vessels are also associated with atherosclerosis. The increase in intima media thickness (IMT) in the carotid artery has been used as a marker of target organ damage in human hypertension (Sierra & de la Sierra, 2008). In experimental studies, the IMT of the aorta observed in stressed rats (Okruhlicová et al., 2008) was related to the atherogenic effects of stress. In healthy blood vessels, NO produced by the endothelium maintains the mitogenic quiescence of smooth muscle cells. Decreased NO bioavailability induced by stress-related glucocorticoid levels or -insulin resistance results in the loss of this effect and consequently vessel wall hypertrophy may occur (Costa & Assreuy, 2005). In fact, it has been observed that rats submitted to chronic mild unpredictable stress presented higher IMT and lower relaxation response to acetylcholine in the thoracic aorta, in comparison with non stressed animals. These effects were observed 15 days after the end of the stress protocol and were associated with insulin resistance and dyslipidemia. However, in this study, the dyslipidemia induced by the hypercaloric diet alone, did not promote morphological or functional changes in the thoracic aorta, or insulin resistance evidencing the role of stress in pro-atherogenic effects (Neves et al., 2011).

NPY, a hormone known as orexigenic peptide, may also be involved in the atherogenic effects of stress. Some stressors such as cold and aggression, increase the release of NPY from sympathetic nerves (Kuo et al., 2007). The peripheral actions of NPY are stimulatory, synergizing with glucocorticoids and catecholamines to potentiate the stress response. It causes prolonged vasoconstriction, potentiating the effect of norepinephrine, induces hyperlipidemia, and vascular remodeling via smooth muscle cell proliferation, in addition to stimulating monocyte migration and activation (Kuo et al., 2007). NPY upregulates its Y2 receptors in a glucocorticoid-dependent manner in abdominal fat, consequently leading to abdominal obesity, hyperinsulinemia and dyslipidemia (Kuo et al., 2008). In blood vessels, Y1 and Y5 receptor activation promotes pro-atherogenic responses (Zukowska, 2005).

In addition to all the above-mentioned mechanisms, the inflammatory process also forms part of the stress response (Black, 2003), and is pathophysiologically linked to atherosclerosis (van Oostrom et al., 2004). In the atherogenic process, the high level of catecholamines induced by stress stimulates endothelial permeability to the traffic of oxidized LDL. Once trapped in the endothelium of an artery, LDL can undergo progressive oxidation, cross the endothelial barrier, and be internalized by macrophages expressing scavenger receptors, leading to lipid peroxide formation and accumulation of cholesterol esters, culminating in foam cells formation (Ross, 1999; Singh & Mehta, 2003). Oxidized LDL upregulates the expression of adhesion molecules and secretion of chemokines, which contributes to the recruitment of circulating monocytes and leukocytes (Cersosimo & DeFronzo, 2006; Steinberg, 2002). One of the initial steps in the formation of atherosclerosis is the adhesion of monocytes to the endothelium, their entry into sub-endothelial space, followed by their differentiation into macrophages (Lamharzi et al., 2004). These cells are then responsible for taking up LDL and other particles, thereby starting the atherogenesis process (Lamharzi et al., 2004). In foam cell formation, the macrophages in the endothelial

space also have VLDL receptors, which bind the apolipoprotein (apo) E-containing lipoproteins, including VLDL, intermediate density lipoprotein, and β -migrating VLDL. The LDL-receptor-related protein in macrophages is also capable of binding apo E-containing lipoproteins, lipoprotein lipase, and lipoprotein lipase-triglyceride-rich lipoprotein complex (Nakazato, 1996), leading to a sequence in the development of atherosclerosis.

In addition, high levels of free fatty acids also may amplify monocyte inflammation via toll-like receptors in the presence of high glucose levels (Dasu & Jialal, 2011). Lamharzi et al., 2004, showed that free fatty acids in concert with glucose stimulate macrophage proliferation involving glucose-dependent oxidation of LDL in atherosclerotic lesions. Toll like receptors are expressed by macrophages in murine and human lipid-rich atherosclerotic plaques and upregulated by oxidized LDL (Xu et al., 2001). Recently Gu et al., 2009, showed the importance of toll-like receptor 4 in atherosclerosis induced by chronic mild stress in aortas from apolipoprotein-E-knockout-mice. Toll-like receptor 4 is present in T cells, monocytes, and macrophages, and is a key signaling receptor of innate immunity. Toll-like receptor 4 plays an important role in atherogenesis because it recognizes pathogen-associated molecular patterns and activates inflammatory cells via the nuclear factor κ B (NF- κ B) pathway (Bierhaus et al., 2003; Gu et al., 2009). During the stress reaction, glucocorticoids and catecholamines can induce cytokine production by endothelial cells and macrophages (Black, 2003; Chae et al., 2001) and activation of the NF- κ B pathway leads to the synthesis of the following proinflammatory chemokines: interleukin 1- β , interleukin 6, TNF- α , monocyte chemoattractant protein-1, intercellular adhesion molecule-1. Interleukin 1- β and interleukin 6 influences smooth muscle cell proliferation and/or migration (Gu et al., 2009), and inhibits eNOS activity (Muniyappa et al., 2008). TNF- α increases endothelin-1 secretion, decreases NO production in endothelial cells, inducing vasoconstriction (Muniyappa & Quon, 2007), and can induce interleukin 6 production (Black, 2003). Monocyte chemoattractant protein-1 is correlated with neointimal proliferation and plays a role in the transition from the stable state of lesion to the more complex state of atherosclerosis (Tellez et al., 2011). Intercellular adhesion molecule-1 may contribute to accelerating atherosclerosis in insulin-resistant states (Muniyappa et al., 2008). Hypertriglyceridemia associated with stress may also increase NF- κ B, consequently activating proinflammatory molecules (Fitch et al., 2011).

In addition, the accumulation of macrophages may also be associated with increased plasma concentration of C-reactive protein (CRP) (Ross, 1999). CRP is the principal down-stream mediator of inflammatory acute phase response, which is primarily derived via interleukin 6-dependent hepatic biosynthesis (Pradhan et al., 2001). CRP interacts with oxidized LDL to form proatherogenic oxidized LDL/CRP complexes, perpetuating vascular inflammation, triggering an autoimmune response, and accelerating atherogenesis (Matsuura et al., 2009; Sitia et al., 2010).

Activation of the renin-angiotensin system (RAS) by stress also plays a role in the pathogenesis of endothelial dysfunction, hypertension and atherosclerosis. Lipid accumulation in blood vessels enhances the expression of RAS components, which in turn stimulates accumulation of oxidized LDL in blood vessels (Singh & Mehta, 2003). Activation of the angiotensin II-type 1 receptor (AT₁R) leads to vasoconstriction and neurohumoral activation, and is associated with reduced NO bioavailability, vascular cell apoptosis, increased oxidized LDL receptor expression, and proinflammatory cytokine production (Sitia et al., 2010). According Nickening et al., 1999, LDL-cholesterol can accumulate in vascular smooth muscle cells, and this effect is mediated via AT₁R. Angiotensin II increases LDL uptake

by arterial wall macrophages (Keidar et al., 1994). Angiotensin II binds LDL and the angiotensin II-modified LDL is taken up by macrophages via scavenger receptors, leading to cellular cholesterol accumulation (Keidar et al., 1996). In atherogenic dyslipidemia, hypercholesterolemia increases AT₁R density and its functional responsiveness to vasoconstrictors, whereas the administration of statins reduces AT₁R expression and deregulates its functions. Moreover, the localization of angiotensin-converting enzyme in atherosclerotic lesions suggests a capacity for local generation of angiotensin II and proinflammatory substances (Sitia et al., 2010). There is also evidence that hypercholesterolemia increases plasma angiotensinogen and angiotensin peptide production (Sitia et al., 2010), and that AT₁R antagonism improves hypercholesterolemia-associated endothelial dysfunction, resulting in an anti-atherosclerotic effect (Taguchi et al., 2011).

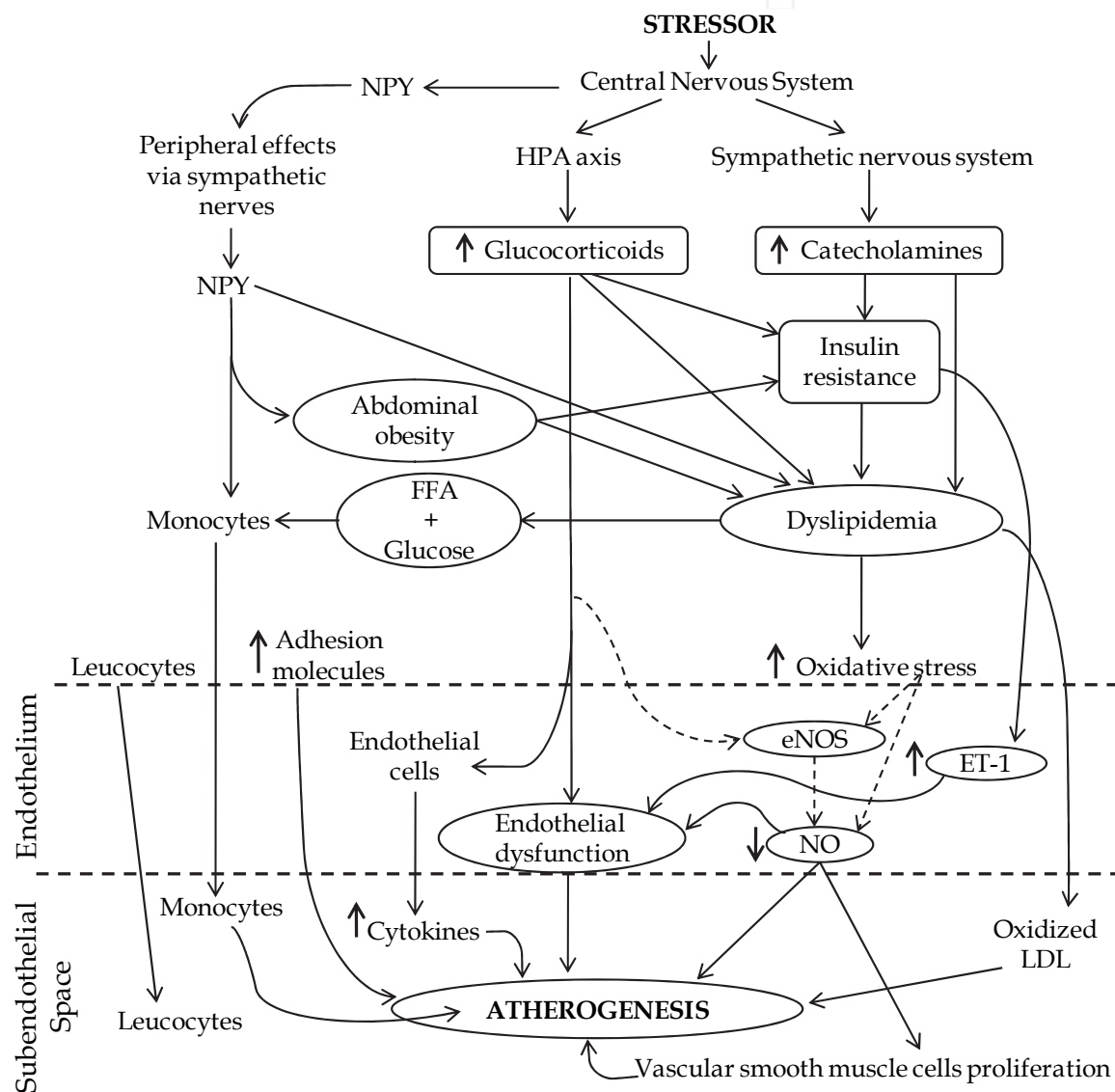


Fig. 2. Schematic representation of putative mechanisms involved in the relations between among stress, dyslipidemia, and atherosclerosis. Hypothalamic-pituitary-adrenal axis (HPA), neuropeptide Y (NPY), low-density lipoprotein (LDL), very-low-density lipoprotein (VLDL), free fatty acids (FFA), endothelial nitric oxide synthase (eNOS), nitric oxide (NO), endothelin 1 (ET-1). Solid arrows show stimulatory effects; dashed arrows indicate inhibitory effects.

Atherosclerosis is an inflammatory disease and stress contributes to its development. Therefore, if we can block or minimize the stress components that directly or indirectly induce atherogenesis, it will be possible to preserve the protective components of vascular function and structure, thereby developing new preventive and therapeutic possibilities. Figure 2 illustrates the putative mechanisms of the relations between stress, dyslipidemia, and atherosclerosis.

4. Reduction of dyslipidemia induced by stress: Physical exercise and nutritional intervention

The role of stress in the etiology of chronic degenerative diseases is increasingly recognized (Gerber & Pühse, 2009; Holmes et al., 2010; Tsatsoulis & Fountoulakis, 2006; Yin et al., 2005). Moreover, it has been reported that obese people have an exaggerated response to stress, which may further increase the risk of weight gain, leading to the development of insulin resistance, hyperlipidemia, diabetes mellitus, hypertension and atherosclerosis in both men and women. This burden of chronic degenerative diseases is strongly influenced by several lifestyle factors, including the way an individual perceives a stressful situation, i.e., “mental fitness” and also his/her general physical condition or “physical fitness” (McEwen, 1998). Tsatsoulis & Fountoulakis, 2006, demonstrated that stress-mediated allostatic load, in the presence of physical inactivity, is associated with an increased risk of mental and physical illness, and direct evidence for this notion has been provided by several studies. A strong inverse association between physical activity and the metabolic syndrome has been demonstrated, and several years ago this association was shown to be much steeper in unfit individuals (Kriska et al., 1993; Lindgärde & Saltin, 1981). Evidence for this view was also provided by the MacArthur studies of successful aging based on a large cohort of elderly men and women (Seeman et al., 1997), showing that subjects with low levels of physical and mental fitness had higher prevalence of cardiometabolic disease when compared with those with high fitness levels. Moreover, a strong association between physical inactivity, excessive food consumption, high-fat diet and increasing incidence of insulin resistance, Type 2 diabetes, (Hawley, 2004; Steanovv et al., 2011), development of obesity (Venables & Jeukendrup, 2009; Vessby, 2000) and depression (Win et al., 2011) has also been described in the literature. Considering that stress, physical inactivity, and aging (associated with declining physical activity and metabolic rate, coupled with an energy intake not matched to the declining need), in addition to a high-fat diet, are the very features of our current lifestyle, the incidence of this “stress-induced/exercise deficient” phenotype is becoming increasingly prevalent in modern society (Davy et al., 1996, Hawley, 2004, Poehlman et al., 1995, Schiut et al., 1998, Tsatsoulis & Fountoulakis, 2006).

Based on the above mentioned findings, it is reasonable to assume that physical inactivity may potentiate the stress-related allostatic load and comorbidities, since the energy substrate that is mobilized during stress is not oxidized but is stored in visceral fat depots. This adaptation creates a vicious cycle, in which perceived stress is also associated with decreased participation in several health behaviors including exercise, social behaviors, stress management/rest, and safety/environmental behaviors, as shown by Padden et al., 2011, in the study on health behavior of military spouses during deployment separation. In this context, physical exercise practiced as a non-pharmacological alternative, either with or without the association of pharmacological therapies, is very important, and a great deal of attention should be given to the barriers imposed, especially by mood disorders, including depression. Individuals in this

condition are at disadvantage, since most of the time they lack the energy and motivation to exercise, and this overwhelming feeling of lethargy seems very difficult to shift (Chaput et al., 2011). In this situation, when psychological stress is not accompanied by physical activity (such as the fight or flight reaction) and by effective use and fast clearance of free fatty acids, triggered by stimulation of the sympathetic nervous system, these are converted into triglycerides by the liver and then circulate in the blood within the VLDL (Howard et al., 1993). In fact, this maladaptive situation can lead to the development of dyslipidemia, reflected by elevated plasma triglyceride and reduced HDL concentration, overproduction of VLDL-apolipoprotein (apo) B-100, decreased catabolism of apoB containing particles, and increased catabolism of HDL apoA-I particles (Watts et al., 2008; Watts et al., 2009).

While physical inactivity may potentiate the stress-induced allostatic load, there is accumulating evidence suggesting that the adoption of an active lifestyle, including exercise training, may play a protective role in stress system dysregulation, reducing vulnerability to stress, and possibly delaying or preventing the future development of comorbidities, such as dyslipidemia, hypertension and insulin resistance (Roberts & Barnard, 2005; Tsatsoulis & Fountoulakis, 2006). In addition, physical activity may induce favorable changes in traditional and emerging coronary heart disease biomarkers among individuals with, or at high risk of coronary heart disease (Chainani-Wu et al., 2011). Assuming that the stress response is a neuroendocrine mechanism that occurs in anticipation of physical action, it is reasonable to assume that physical activity should provide the vehicle to prevent or combat the somatic and emotional consequences of stress. Thus, physical activity may promote physical and psychological benefits that are involved in both the indirect action of exercise in reducing stress, and a direct effect on various metabolic functions of the body (McMurray & Hanckney, 2005).

The first rationale for using exercise as a stress reduction strategy was based on the cross-stressor adaptation, a promising hypothesis first presented in the 1990s (Sothmann et al., 1996), which has not received strong support since the publication of recent meta-analyses (Forcier et al., 2006; Hamer et al., 2006; Jackson & Dishman, 2006). According to Chaput et al., 2011, the key question now is whether physical activity, which seems to modulate the level of stress, may interact in the relationship between stress and obesity. Different possible mechanisms have been proposed, suggesting that exercise training might protect against stress induced obesity. Regular exercise has been demonstrated to have positive effects on plasma lipid and lipoprotein profiles (Durstine et al., 2002) and these results may have a significant independent effect on HDL cholesterol (Thompson et al., 1988). During physical activity, exercise increases lipid oxidation and lipolysis to ensure an adequate oxygen supply (McMurray & Hanckney, 2005), increases the ability of muscle tissue to take up and oxidize nonesterified fatty acids, and increases muscle lipoprotein lipase activity (Eriksson et al., 1997). Although studies indicate that exercise training changes gene expression in adipose tissue in different ways, affecting some types of adipose tissue more than others (Company et al., 2010), the lowering of plasma triglycerides proves the effects of exercise on VLDL kinetics. Moreover, it is important to highlight that a single 90-min bout of whole body resistance exercise (Tsekouras et al., 2009) or 2h of cycling (Magkos et al., 2006) was proven to be enough to decrease fasting plasma VLDL-triglyceride concentrations by increasing VLDL-triglyceride removal from plasma. These results may be due to the increase in blood flow and hepatic insulin sensitivity associated with an increase in lipoprotein lipase activity.

In addition to its possible direct effect modulating the stress response, exercise training improves insulin sensitivity, which might counteract the insulin resistance state produced

by chronic hypercortisolemia (Tsatsoulis & Fountoulakis, 2006). Insulin secretion could then be reduced, and thereby, its deleterious impact on energy intake may be diminished. Moreover, exercise training improves glucose tolerance among non-diabetic, non-obese subjects with hypertriglyceridemia (Lampman & Schteingart, 1991) and enhances the oxidative capacity of skeletal muscle (Tsatsoulis & Fountoulakis, 2006). Together, these beneficial adaptations could prevent stress-induced fat deposition by routing the energy mobilized in response to the stressor toward oxidation rather than storage.

Apart from the protective effects of exercise on the physical and metabolic aspects related to stress, a number of psychological and cognitive benefits have also been reported in the literature. These include improvements in depression and anxiety scores and general improvement in mood, cognitive functioning (Callaghan, 2004; Tsatsoulis & Fountoulakis, 2006), well-being and self esteem, leading to a decrease in body fat, triglycerides, LDL/HDL cholesterol ratio in stressed patients (De Geus & Stubbe, 2007). Physical activity can improve mental health by reducing depressive symptoms in young men (McGale et al., 2011) and in patients with metabolic syndrome (Rubenfire et al., 2011). Moreover exercise induces the elevation of circulating brain derived neurotrophic factor, which is known to improve the health and survival of nerve cells, suggesting that exercise influences brain health (Yarrow et al., 2010). Using animal models, exercise has also been shown to induce antidepressant responses (Greenwood et al., 2003). In rats, swimming exercise induces a remission of anhedonic symptoms suggesting that exercise training might induce biological alterations similar to those provided by antidepressant drugs. In addition, exercise plays an important role in hippocampal protection from damage caused by exposure to glucocorticoids (Sigwalt et al., 2011). In this context, physical activity was able to stimulate the proliferation of hippocampal cells (Ehninger & Kempermann, 2003), promote alterations in synaptic plasticity, neurogenesis and synaptogenesis (Castrén, 2005), and may also be linked to increased levels of brain testosterone (Mukai et al., 2006).

Another beneficial effect of exercise is related to feeding behavior. Stressful situations have been shown to affect feeding behavior (Wallis & Hetherington, 2009) that result in increased energy intake through the stimulation provided by ingesting palatable foods that may serve as feedback signals that reduce the perception and discomfort of stress, thereby contributing to the development of dyslipidemia and obesity (Dallman et al., 2005). Moreover glucocorticoids are associated with high neuropeptide Y secretion, which has an orexigenic activity and increases the intake of sugar- and fat-rich- comfort foods (Kuo et al., 2008) and can lead to a state of leptin resistance and elevated levels of this hormone (Zakrzewska et al., 1997). In this context, it has been demonstrated that physical activity has the potential to modulate appetite control by improving the sensitivity of the physiological satiety signalling system, by adjusting macronutrient preferences or food choices and by altering the hedonic response to food (Blundell et al., 2003). Indeed, dietary modification, associated with physical activity has been shown to exert significantly favorable effects on the treatment and prevention of stress-induced comorbidities, improving glycemia, blood pressure, body weight, fat distribution, and lipid profile, which in turn suggest that chronic degenerative diseases are largely preventable (Dagogo et al., 2010). Although exercise cannot change total cholesterol and LDL-cholesterol unless dietary fat intake is reduced, this result may be dependent on the amount of energy expenditure during exercise (Durstine et al., 2002). Furthermore, depending on the time that the exercise is performed (before or after ingestion of fatty foods), its acute responses related to improvement in lipoprotein metabolism may be different (Hashimoto et al., 2011). In a review of several studies realized by Leon & Sanchez

2001, one of proposals evaluated was the effects of aerobic exercise training on blood lipids and the relationship between these effects and diet. The results showed that majority of physically active individuals had an increase in HDL cholesterol, but this could be changed if there was a concomitant reduction in fat intake. The association between low-fat diet and exercise reduces LDL and HDL-cholesterol levels. Furthermore, reductions in total cholesterol, LDL-cholesterol and triglyceride levels were less frequently observed. As regards body weight loss, there was considerable variability between the groups, ranging from 7.2 Kg in the group that was not exposed to dietary intervention to 17.9 Kg in the group that underwent dietary intervention. In addition, Rubenfire et al., 2011, demonstrated that the association between changes in diet and exercise was effective in reducing cardiovascular risk in patients with metabolic syndrome. In this study, the nutritional component was based on a Mediterranean food pattern, and all the participants were provided with the information needed to optimize their nutritional choices in order to improve blood lipid and glucose levels, decrease body weight and blood pressure, and decrease insulin resistance (Rubenfire et al., 2011). It has also been proposed that high-fiber diets protect against obesity and cardiovascular disease by lowering insulin levels (Ludwig et al., 1999). In obese men, the implementation of a high-fiber and low-fat diet associated with regular physical activity resulted in significant reductions in inflammation and dyslipidemia by reducing serum lipids, insulin, oxidative stress, leukocyte-endothelial interactions (Roberts & Barnard, 2005).

Dietary fat influences glucose and lipid metabolism by altering cell membrane function, enzyme activity, insulin signaling, and gene expression (Risérus et al., 2009; Yamazaki et al., 2011) and dietary fructose consumption appears to induce dyslipidemia, obesity (Stanhope et al., 2009) and hypertension (Cunha et al., 2007; Farah et al., 2006). A combination of social stress and high-fat diet resulted in a significant imbalance in lipid regulation associated with changes in the expression of hepatic genes, responsible for its regulation (Chuang et al., 2010). Therefore, clinical strategies based on low fat and sugar intake associated with increase in physical exercise have been used, and have contributed to reducing the risks of developing coronary and metabolic diseases.

5. Conclusion

Dyslipidemia induced by stress is part of the body's response to cope with stressors. The mobilization of lipids, glucose and proteins, allows the organs and tissues to maintain homeostasis and adapt to the stressor. Any deficiency in the activation of this mobilization of energetic fuels can compromise the survival of the individual. Therefore, the increase in blood lipids induced by stress is adaptive and it should return to normal levels when the stressor ends. However, when the stressor is maintained over a long period, the dyslipidemia induced by stress persists and may have deleterious effects, contributing to the occurrence of insulin resistance, obesity, hypertension and atherosclerosis. Considering that physical inactivity may potentiate these effects, the association of physical exercise and control of hypercaloric food consumption have been used in the treatment of dyslipidemia. Knowledge about the physiological mechanisms involved in the adaptive role of transient dyslipidemia induced by acute stress, and in the deleterious effects of sustained dyslipidemia induced by chronic stress is very important in the improvement and development of preventive and therapeutic approaches because in modern society we are continuously exposed to stressors.

6. Acknowledgment

The authors thank Margery Galbraith for English editing.

7. References

- Badimón, L. & Martínez-González J. (2002). Endothelium and vascular protection: an update. *Revista española de cardiología*, Vol.55, No.1 (January 2002), pp. 17-26, ISSN 0300-8932.
- Bartolomucci, A.; Cabassi, A.; Govoni, P.; Ceresini, G.; Cero, C.; Berra, D.; Dadomo, H.; Franceschini, P.; Dell'Omo, G.; Parmigiani, S. & Palanza, P. (2009). Metabolic consequences and vulnerability to diet-induced obesity in male mice under chronic social stress. *PloS one [electronic resource]*. Vol.4, No.1, (January 2009), pii. e4331, ISSN 1932-6203 online.
- Berger, D.F.; Starzec, J.J.; Mason, E.B. & DeVito, W. (1980). The effects of differential psychological stress on plasma cholesterol levels in rats. *Psychosomatic medicine*, Vol.42, No.5, (September 1980), pp.481-492, ISSN 0033-3174.
- Bierhaus, A.; Wolf, J.; Andrassy, M.; Rohleder, N.; Humpert, P.M.; Petrov, D.; Ferstl, R.; von Eynatten, M.; Wendt, T.; Rudofsky, G.; Joswig, M.; Morcos, M.; Schwaninger, M.; McEwen, B.; Kirschbaum, C. & Nawroth, P.P. (2002). A mechanism converting psychosocial stress into mononuclear cell activation. *Proceedings of the National Academy of Sciences of the United States of America*, Vol.100, No.4, (February 2003), pp. 1920-1925, ISSN 0027-8424.
- Björntorp, P. & Rosmond, R. (1999). Hypothalamic origin of the metabolic syndrome X. *Annals of the New York Academy of Sciences*, Vol.892, (November 1999), pp. 297-307, ISSN 0077-8923.
- Black, P.H. (2002). Stress and the inflammatory response: a review of neurogenic inflammation. *Brain, behavior, and immunity*, Vol.16, No.6, (December 2002), pp. 622-653, ISSN 0889-1591.
- Black, P.H. (2003). The inflammatory response is an integral part of the stress response: Implications for atherosclerosis, insulin resistance, type II diabetes and metabolic syndrome X. *Brain, behavior, and immunity*, Vol.17, No.5, (October 2003), pp. 350-364, ISSN 0889-1591.
- Black, P.H. & Garbutt, L.D. (2002). Stress, inflammation and cardiovascular disease. *Journal of psychosomatic research*, Vol.52, No.1, (January 2002), pp. 1-23, ISSN 0022-3999.
- Blundell, J.E.; Stubbs, R.J.; Hughes, D.A.; Whybrow, S. & King, N.A. (2003). Cross talk between physical activity and appetite control: does physical activity stimulate appetite? *The Proceedings of the Nutrition Society*, Vol.62, No.3, (August 2003), pp. 651-661, ISSN 0029-6651.
- Bose, M.; Oliván, B. & Laferrère, B. (2009). Stress and obesity: the role of the hypothalamic-pituitary-adrenal axis in metabolic disease. *Current opinion in endocrinology, diabetes, and obesity*, Vol.16, No.5, (October 2009), pp. 340-346, ISSN 1752-296X.
- Brindley, D.N.; McCann, B.S.; Niaura, R.; Stoney, C.M. & Suarez, E.C. (1993). Stress and lipoprotein metabolism: modulators and mechanisms. *Metabolism: clinical and experimental*, Vol.42, No.9 Suppl 1, (September 1993), pp. 3-15, ISSN 0026-0495.
- Bryant, H.U; Story, J.A. & Yim G.K. (1988). Assessment of endogenous opioid mediation in stress-induced hypercholesterolemia in the rat. *Psychosomatic medicine*, Vol.50, No.6, (November-December 1988), pp. 576-585, ISSN 0033-3174.

- Callaghan, P. (2004). Exercise: a neglected intervention in mental health care? *Journal of psychiatric and mental health nursing*, Vol.11, No.4, (August 2004), pp. 476-483, ISSN 1351-0126.
- Castrén, E. (2005). Is mood chemistry? *Nature reviews. Neuroscience*, Vol.6, No.3, (March 2005), pp. 241-246, ISSN 1471-003X.
- Cersosimo, E. & DeFronzo, R.A. (2006). Insulin resistance and endothelial dysfunction: the road map to cardiovascular diseases. 2006. *Diabetes/metabolism research and reviews*, Vol.22, No.6, (November/December 2006), pp. 423-436, ISSN 1520-7552.
- Chae, C.U.; Lee, R.T.; Rifai, N. & Ridker, P.M. (2001). Blood pressure and inflammation in apparently healthy men. *Hypertension*, Vol.38, No.3, (September 2001), pp. 399-403, ISSN 0194-911X.
- Chainani-Wu, N.; Weidner, G.; Purnell, D.M.; Frenda, S.; Merritt-Worden, T.; Pischke, C.; Campo, R.; Kemp, C.; Kersh E.S. & Ornish, D. (2011). Changes in Emerging Cardiac Biomarkers After an Intensive Lifestyle Intervention. *The American journal of cardiology*, Epub ahead of print, doi:10.1016/j.amjcard.2011.03.077, ISSN 1879-1913.
- Chaput, J.P.; Klingenberg, L.; Rosenkilde, M.; Gilbert, J.A.; Tremblay, A. & Sjödén, A. (2010). Physical activity plays an important role in body weight regulation. *Journal of obesity [electronic resource]*, Vol.2011 (2011), pii. 360257, ISSN 2090-0716 on line, ISSN 2090-0708 print.
- Chuang, J.C.; Cui, H.; Mason, B.L.; Mahgoub, M.; Bookout, A.L.; Yu, H.G.; Perello, M.; Elmquist, J.K.; Repa, J.J.; Zigman, J.M. & Lutter, M. (2010). Chronic social defeat stress disrupts regulation of lipid synthesis. *Journal of lipid research*, Vol.51, No.6, (June 2010), pp. 1344-1353, ISSN 0022-2275.
- Codoñer-Franch, P.; Tavárez-Alonso, S.; Murria-Estal, R.; Megías-Vericat, J.; Tortajada-Girbés, M. & Alonso-Iglesias, E. (2011). Nitric oxide production is increased in severely obese children and related to markers of oxidative stress and inflammation. *Atherosclerosis*, Vol.215, No.2, (April 2011), pp. 475-480, ISSN 0021-9150.
- Company, J.M.; Booth, F.W.; Laughlin, M.H.; Arce-Esquivel, A.A.; Sacks, H.S.; Bahouth, S.W. & Fain, J.N. (2010). Epicardial fat gene expression after aerobic exercise training in pigs with coronary atherosclerosis: relationship to visceral and subcutaneous fat. *Journal of applied physiology*, Vol.109, No.6, (December 2010), pp. 1904-1912, ISSN 8750-7587.
- Costa, R.S. & Assreuy J. (2005). Multiple potassium channels mediate nitric oxide-induced inhibition of rat vascular smooth muscle cell proliferation. *Nitric oxide: biology and chemistry/official journal of the Nitric Oxide Society*, Vol.13, No.2, (September 2005), pp. 145-51, ISSN 1089-8603.
- Cunha, T.S.; Farah, V.; Paulini, J.; Pazzine, M.; Elased, K.M.; Marcondes, F.K.; Irigoyen, M.C.; De Angelis, K.; Mirkin, L.D. & Morris, M. (2007). Relationship between renal and cardiovascular changes in a murine model of glucose intolerance. *Regulatory peptides*, Vol.139, No.1-3, (March 2007), pp. 1-4, ISSN 0167-0115.
- Dagogo-Jack, S.; Egbunu, N. & Edeoga, C. (2010). Principles and practice of nonpharmacological interventions to reduce cardiometabolic risk. *Medical principles and practice: international journal of the Kuwait University, Health Science Centre*, Vol.19, No.3, (March 2010), pp. 167-175, ISSN 1011-7571.
- Dallman, M.F.; La Fleur, S.E.; Pecoraro, N.; Gomez, F.; Houshyar, H. & Akana, S.F. (2004). Minireview: Glucocorticoids - food intake, abdominal obesity, and wealthy nations in 2004. *Endocrinology*, Vol.145, No.6, (June 2004), pp. 2633-2638, ISSN 0013-7227.

- Dallman, M.F.; Pecoraro, N.; Akana, S.F.; La Fleur, S.E.; Gomez, F.; Houshyar, H.; Bell, M.E.; Bhatnagar, S.; Laugero, K.D. & Manalo, S. (2003). Chronic stress and obesity: a new view of "comfort food". *Proceedings of the National Academy of Sciences of the United States of America*, Vol.100, No.20, (September 2003), pp. 11696-11701, ISSN 0027-8424.
- Dallman, M.F.; Pecoraro, N.C. & la Fleur, S.E. (2005). Chronic stress and comfort foods: self-medication and abdominal obesity. *Brain, behavior, and immunity*, Vo.19, No.4 (July 2005), pp. 275-280. ISSN 0889-1591.
- Dasu, M.R. & Jialal, I. (2010). Free fatty acids in the presence of high glucose amplify monocyte inflammation via Toll-like receptors. *American journal of physiology. Endocrinology and metabolism*, Vol. 300, No.1, (January 2011), pp. E145-154, ISSN 1522-1555 online, ISSN 0193-1849 print.
- Davy, K.P.; Evans, S.L.; Stevenson, E.T. & Seals, D.R. (1996). Adiposity and regional body fat distribution in physically active young and middle age women. *International journal of obesity and related metabolic disorders: journal of the International Association for the Study of Obesity*, Vol.20, No.8, (August 1996), pp. 777-783, ISSN 0307-0565.
- De Geus, E.J.C. & Stubbe, J.H. (2007). Aerobic exercise and stress reduction, In: *Encyclopedia of Stress*, pp. 73-78, George Fink (editor), ELSEVIER, ISBN 978-0-12-088503-9, San Diego, CA – USA.
- De Moura, E.G.; Lisboa, P.C. & Passos, M.C. (2008). Neonatal programming of neuroimmunomodulation-role of adipocytokines and neuropeptides. *Neuroimmunomodulation*, Vol.15, No.3, (October 2008), pp.176-188, ISSN 1021-7401.
- Durstine, J.L.; Grandjean, P.W.; Cox, C.A. & Thompson, P.D. (2002). Lipids, lipoproteins, and exercise. *Journal of cardiopulmonary rehabilitation*, Vol.22, No.6, (November/December 2002), pp. 385-398, ISSN 0883-9212.
- Dzubur Kulenović, A.; Kucukalić, A. & Malec, D. (2008). Changes in plasma lipid concentrations and risk of coronary artery disease in army veterans suffering from chronic posttraumatic stress disorder. *Croatian medical journal*, Vol.49, No.4, (August 2008), pp. 506-514, ISSN 0353-9504.
- Ehninger, D. & Kempermann, G. (2003). Regional effects of wheel running and environmental enrichment on cell genesis and microglia proliferation in the adult murine neocortex. *Cerebral Cortex*, Vol.13, No.8, (August 2003), pp. 845-851, ISSN 1047-3211.
- Epel E.S. (2009). Psychological and metabolic stress: a recipe for accelerated cellular aging? *Hormones (Athens)*, Vol.8, No.1, (January-March 2009), pp. 7-22, ISSN 1109-3099.
- Eriksson, J.; Taimela, S. & Koivisto, V.A. (1997). Exercise and the metabolic syndrome. *Diabetologia*, Vol.40, No.2, (February 1997), pp. 125-135, ISSN 0012-186X.
- Farah, V.; Elased, K.M.; Chen, Y.; Key, M.P.; Cunha, T.S.; Irigoyen, M.C. & Morris, M. (2006). Nocturnal hypertension in mice consuming a high fructose diet. *Autonomic neuroscience: basic & clinical*. Vol.130, No.1-2, (December 2006), pp. 41-50, ISSN 1566-0702.
- Feron, O.; Dessy, C.; Moniotte, S.; Desager, J.P. & Balligand, J.L. (1999). Hypercholesterolemia decreases nitric oxide production by promoting the interaction of caveolin and endothelial nitric oxide synthase. *The Journal of clinical investigation*, Vol.103, No.6, (March 1999), pp. 897-905, ISSN 0021-9738.
- Fitch, K.V.; Stavrou, E.; Looby, S.E.; Hemphill, L.; Jaff, M.R. & Grinspoon, S.K. (2011). Associations of cardiovascular risk factors with two surrogate markers of subclinical atherosclerosis: Endothelial function and carotid intima media thickness. *Atherosclerosis*, Epub ahead of print, doi: 10.1016/j.atherosclerosis.2011.04.009, (April 2011), ISSN 0021-9150.

- Forcier, K.; Stroud, L.R.; Papandonatos, G.D.; Hitsman, B.; Reiches, M.; Krishnamoorthy, J. & Niaura, R. (2006). Links between physical fitness and cardiovascular reactivity and recovery to psychological stressors: a meta-analysis. *Health psychology: official journal of the Division of Health Psychology, American Psychological Association*, Vol.25, No.6, (November 2006), pp. 723-739, ISSN 0278-6133.
- Förstermann, U. & Münzel, T. (2006). Endothelial nitric oxide synthase in vascular disease: from marvel to menace. *Circulation*, Vol.113, No.13, (April 2006), pp. 1708-1714, ISSN 0009-7322.
- Frank, P.G. & Lisanti, M.P. (2004). Caveolin-1 and caveolae in atherosclerosis: differential roles in fatty streak formation and neointimal hyperplasia. *Current opinion in lipidology*, Vol.15, No.5, (October 2004), pp. 523-529, ISSN 0957-9672.
- Gerber, M. & Pühse, U. (2009). Review article: do exercise and fitness protect against stress-induced health complaints? A review of the literature. *Scandinavian journal of public health*, Vol.37, No.8, (November 2009), pp. 801-819, ISSN 1403-4948.
- Greenwood, B.N.; Foley, T.E.; Day, H.E.; Campisi, J.; Hammack, S.H.; Campeau, S.; Maier, S.F. & Fleshner, M. (2003) Freewheel running prevents learned helplessness/behavioral depression: role of dorsal raphe serotonergic neurons. *The Journal of neuroscience: the official journal of the Society for Neuroscience*, Vol.23, No.7, (April 2003), pp. 2889-2898, ISSN 0270-6474.
- Gu, H.; Tang, C.; Peng, K.; Sun, H. & Yang, Y. (2009). Effects of chronic mild stress on the development of atherosclerosis and expression of toll-like receptor 4 signaling pathway in adolescent apolipoprotein E knockout mice. *Journal of biomedicine & biotechnology*, Vol.2009, (August 2009), pp. 1-13, ISSN 1110-7243.
- Hamer, M.; Taylor, A. & Steptoe, A. (2005). The effect of acute aerobic exercise on stress related blood pressure responses: a systematic review and meta-analysis. *Biological psychology*, Vol.71, No.2, (2006), pp. 183-190, ISSN 1873-6246 online, ISSN 0301-0511 print.
- Hawley, J.A. (2004). Exercise as a therapeutic intervention for the prevention and treatment of insulin resistance. *Diabetes/metabolism research and reviews*, Vol.20, No.5, (September/October 2004), pp. 383-393, ISSN 1520-7552.
- Hashimoto, S.; Ootani, K.; Hayashi, S. & Naito, M. (2011). Acute Effects of Shortly Pre-Versus Postprandial Aerobic Exercise on Postprandial Lipoprotein Metabolism in Healthy but Sedentary Young Women. *Journal of atherosclerosis and thrombosis*, Epub ahead of print, doi: 10.5551/jat.8482 (June 2011), ISSN 1880-3873.
- Holmes, M.E.; Ekkekakis, P. & Eisenmann, J.C. (2009). The physical activity, stress and metabolic syndrome triangle: a guide to unfamiliar territory for the obesity researcher. *Obesity reviews: an official journal of the International Association for the Study of Obesity*, Vol.11, No.7, (July 2010), pp. 492-507, ISSN 1467-789X online, 1467-7881 print.
- Howard, B.V. (1993). Insulin, insulin resistance, and dyslipidemia. *Annals of the New York Academy of Sciences*, Vol.683, (June 1993), pp. 1-8, ISSN 1749-6632.
- Jackson, E.M. & Dishman, R.K. (2006). Cardiorespiratory fitness and laboratory stress: a meta-regression analysis. *Psychophysiology*, Vol.43, No.1, (January 2006), pp. 57-72, ISSN 0048-5772.
- Kaplan, J.R.; Manuck, S.B.; Clarkson, T.F.; Lusso, F.M.; Taub, D.M. & Miller, E.W. (1983). Social stress and atherosclerosis in normocholesterolemic monkeys. *Science*, Vol.220, No.4598, (May 1983), pp. 733-735, ISSN 0036-8075.

- Keidar, S.; Kaplan, M.; Shapira, C.; Brook, J.G. & Aviran, M. (1994). Low density lipoprotein isolated from patients with essential hypertension exhibits increased propensity for oxidation and enhanced uptake by macrophages: a possible role for angiotensin II. *Atherosclerosis*, Vol.107, No.71, (May 1994), pp. 71-84, ISSN 0021-9150.
- Keidar, S.; Kaplan, M. & Aviram, M. (1996). Angiotensin II-modified LDL is taken up by macrophages via the scavenger receptor, leading to cellular cholesterol accumulation. *Arteriosclerosis, thrombosis, and vascular biology*, Vol.16, No.1, (January 1996), pp.97-105, ISSN 1079-5642.
- Korte, S.M.; Koolhaas, J.M.; Wingfield, J.C. & McEwen, B.S. (2004). The Darwinian concept of stress: benefits of allostasis and costs of allostatic load and the trade-offs in health and disease. *Neuroscience and behavioral reviews*, Vol.29, No.1, (February 2005), pp. 3-38, ISSN 1873-7528 online, ISSN 0149-7634 print.
- Kriska, A.M.; LaPorte, R.E.; Pettitt, D.J.; Charles, M.A.; Nelson, R.G.; Kuller, L.H.; Bennett, P.H. & Knowler, W.C. (1993). The association of physical activity with obesity, fat distribution and glucose intolerance in Pima Indians. *Diabetologia*, Vol.36, No.9, (September 1993), pp. 863-869, ISSN 0012-186X.
- Kuo, L.E.; Abe, K. & Zukowska, Z. (2007). Stress, NPY and vascular remodeling: Implications for stress-related diseases. *Peptides*, Vol.28, No.2 (February 2007), pp. 435-440, ISSN 0196-9781.
- Kuo, L.E.; Czarnecka, M.; Kitlinska, J.B.; Tilan, J.U.; Kvetnanský, R. & Zukowska, Z. (2008). Chronic stress, combined with a high-fat/high-sugar diet, shifts sympathetic signaling toward neuropeptide Y and leads to obesity and the metabolic syndrome. *Annals of the New York Academy of Sciences*, Vol.1148, (December 2008), pp. 232-237. ISSN 0077-8923.
- Kyrou, I & Tsigos, C. (2009). Stress hormones: physiological stress and regulation of metabolism. *Current opinion in pharmacology*, Vol.9, No.6, (December 2009), pp. 787-793, ISSN 1471-4892.
- Lafontan, M. & Langin, D. (2009). Lipolysis and lipid mobilization in human adipose tissue. *Progress in lipid research*, Vol.48, No.5, (September 2009), pp. 275-297, ISSN 0163-7827.
- Lamharzi, N.; Renard, C.B.; Kramer, F.; Pennathur, S.; Heinecke, J.W.; Chait, A. & Bornfeldt, K.E. (2004). Hyperlipidemia in concert with hyperglycemia stimulates the proliferation of macrophages in atherosclerotic lesions: potential role of glucose-oxidized LDL. *Diabetes*, Vol.53, No.12, (December 2004), pp. 3217-3225, ISSN 0012-1797.
- Lampman, R.M. & Schteingart, D.E. (1991). Effects of exercise training on glucose control, lipid metabolism, and insulin sensitivity in hypertriglyceridemia and non-insulin dependent diabetes mellitus. *Medicine and science in sports and exercise*, Vol.23, No.6, (June 1991), pp. 703-712, ISSN: 0195-9131.
- Lemieux, A.M. & Coe, C.L. (1995). Abuse-related posttraumatic stress disorders: evidence for chronic neuroendocrine activation in women. *Psychosomatic medicine*, Vol. 57, No.2, (March/April 1995), pp.105-115, ISSN 0033-3174.
- Leon, A.S. & Sanchez, O.A. (2001). Response of blood lipids to exercise training alone or combined with dietary intervention. *Medicine and science in sports and exercise*, Vol.33, No.6, (June 2001), pp. S502-S515, ISSN 0195-9131.
- Liao, J.K.; Shin, W.S.; Lee, W.Y. & Clark, S.L. (1995). Oxidized low-density lipoprotein decreases the expression of endothelial nitric oxide synthase. *The Journal of biological chemistry*, Vol.270, No.1, (January 1995), pp. 319-324, ISSN 0021-9258.

- Lindgärde, F. & Saltin, B. (1981). Daily physical activity, work capacity and glucose tolerance in lean and obese normoglycaemic middle-aged men. *Diabetologia*, Vol.20, No.2, (February 1981), pp. 134-138, ISSN 0012-186X.
- Ludwig, D.S.; Pereira, M.A.; Kroenke, C.H.; Hilner, J.E.; Van Horn, L.; Slattery, M.L. & Jacobs, D.R. Jr. (1999). Dietary fiber, weight gain, and cardiovascular disease risk factors in young adults. *JAMA*, Vol.282, No.16, (October 1999), pp. 1539-1546, ISSN 0098-7484.
- Magkos, F.; Wright, D.C.; Patterson, B.W.; Mohammed, B.S. & Mittendorfer, B. (2005). Lipid metabolism response to a single, prolonged bout of endurance exercise in healthy young men. *American journal of physiology. Endocrinology and metabolism*, Vol.290, No.2, (February 2006), pp. E355-E362. ISSN 1522-1555 online, 0193-1849 print.
- Masuzaki, H. & Flier JS. (2003). Tissue-specific glucocorticoid reactivating enzyme, 11 beta-hydroxysteroid dehydrogenase type 1 (11 beta-HSD1)--a promising drug target for the treatment of metabolic syndrome. *Current drug targets. Immune, endocrine and metabolic disorders*, Vol.3, No.4, (December 2003), pp. 255-262, ISSN 1568-0088.
- Masuzaki, H.; Paterson, J.; Shinyama, H.; Morton, N.M.; Mullins, J.J.; Seckl, J.R. & Flier, J.S. (2001). A transgenic model of visceral obesity and the metabolic syndrome. *Science*, Vol.294, No.5549, (December 2001), pp. 2166-2170, ISSN 0036-8075.
- Matsuura, E.; Kobayashi, K.; Matsunami, Y.; Shen, L.; Quan, N.; Makarova, M.; Suchkov, S.V.; Ayada, K.; Oguma, K. & Lopez, L.R. (2009). Autoimmunity, infectious immunity, and atherosclerosis. *Journal of clinical immunology*, Vol.29, No.6, (November 2009), pp. 714-721, ISSN 0271-9142.
- McEwen, B.S. (1998). Protective and damaging effects of stress mediators: central role of the brain. *Dialogues in clinical neuroscience*, Vol.8, No.4, (2006), pp. 367-381, ISSN 1294-8322.
- McCann, B.S.; Warnick, G.R. & Knopp, R.H. (1990). Changes in plasma lipids and dietary intake accompanying shifts in perceived workload and stress. *Psychosomatic medicine*, Vol.52, No.1, (January/February 1990), pp. 97-108, ISSN 0033-3174.
- McGale, N.; McArdle, S. & Gaffney, P. (2011). Exploring the effectiveness of an integrated exercise/CBT intervention for young men's mental health. *British journal of health psychology*, Vol.16, No.3, (September 2011), pp.457-471, ISSN 1359-107X.
- McMurray, R.G. & Hackney, A.C. (2005). Interactions of metabolic hormones, adipose tissue and exercise. *Sports medicine*, Vol.35, No.5, (2005), pp. 393-412, ISSN 0112-1642.
- Mitchell, B.M.; Dorrance, A.M.; Mack, E.A. & Webb, R.C. (2004). Glucocorticoids decrease GTP cyclohydrolase and tetrahydro-biopterin-dependent vasorelaxation through glucocorticoid receptors. *Journal of cardiovascular pharmacology*, Vol.43, No.1, (January 2004), pp. 8-13, ISSN 0160-2446.
- Mohamed-Ali, V.; Pinkney, J.H. & Coppack, S.W. (1998). Adipose tissue as an endocrine and paracrine organ. *International journal of obesity and related metabolic disorders: journal of the International Association for the Study of Obesity*, Vol.22, No.12, (December 1998), pp. 1145-1158, ISSN 0307-0565.
- Mukai, H.; Tsurugizawa, T.; Ogiue-Ikeda, M.; Murakami, G.; Hojo, Y.; Ishii, H.; Kimoto, T. & Kawato, S. (2006). Local neurosteroid production in the hippocampus: influence on synaptic plasticity of memory. *Neuroendocrinology*, Vol.84, No.4, (2006), pp. 255-263, ISSN: 0028-3835.
- Mullick, A.E.; Tobias, P.S. & Curtiss, L.K. (2006). Toll-like receptors and atherosclerosis: key contributors in disease and health? *Immunologic research*, Vol.34, No.3, (2006), pp. 193-209, ISSN 0257-277X.

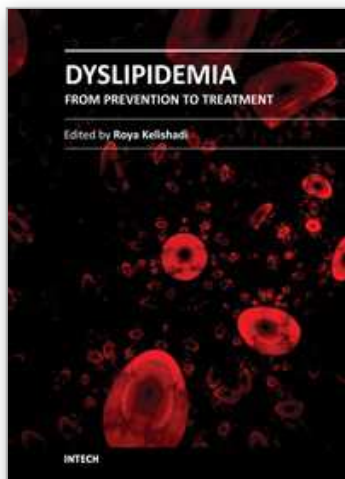
- Muniyappa, R. & Quon, M.J. (2007). Insulin action and insulin resistance in vascular endothelium. *Current opinion in clinical nutrition and metabolic care*, Vol.10, No.4, (July 2007), pp. 523-530, ISSN 1363-1950.
- Muniyappa, R.; Iantorno, M. & Quon, M.J. (2008). An integrated view of insulin resistance and endothelial dysfunction. *Endocrinology and metabolism clinics of North America*, Vol.37, No.3, (September 2008), pp. 685-711, ISSN 0889-8529.
- Nakazato, K.; Ishibashi, T.; Shindo, J.; Shiomi, M. & Maruyama, Y. (1996). Expression of very low density lipoprotein receptor mRNA in rabbit atherosclerotic lesions. *The American journal of pathology*, Vol.149, No.6, (December 1996), pp. 1831-1838, ISSN 0002-9440.
- Neves, V.J.; Moura, M.J.C.S.; Almeida, B.S.; Costa, R.; Sanches, A.; Ferreira, R.; Tamascia, M.L.; Romani, E.A.O.; Novaes, P.D. & Marcondes, F.K. (2011). Chronic stress, but not hypercaloric diet, impairs vascular function in rats. *Stress: the international journal on the biology of stress*, (2011), Epub ahead of print, doi:10.3109/10253890.2011.601369, ISSN 1025-3890.
- Neves, V.J.; Moura, M.J.C.S.; Tamascia, M.L.; Ferreira, R.; Silva, N.S.; Costa, R.; Montemor, P.L.; Narvaes, E.A.O.; Bernardes, C.F.; Novaes, P.D. & Marcondes, F.K. (2009). Proatherosclerotic effects of chronic stress in male rats: Altered phenylephrine sensitivity and nitric oxide synthase activity of aorta and circulating lipids. *Stress: the international journal on the biology of stress*, Vol.12, No.4, (July 2009), pp. 320-327, ISSN 1025-3890.
- Nickenig, G.; Bäumer, A.T.; Temur, Y.; Kebben, D.; Jockenhövel, F. & Böhm, M. (1999). Statin-sensitive dysregulated AT1 receptor function and density in hypercholesterolemic men. *Circulation*, Vol.100, No.21, (November 1999), pp. 2131-2134, ISSN 0009-7322.
- Nishitani, N. & Sakakibara, H. (2005). Relationship of obesity to job stress and eating behavior in male Japanese workers. *International journal of obesity : journal of the International Association for the Study of Obesity*, Vol.30, No.3, (March 2006), pp. 528-533, ISSN 1476-5497 online, ISSN 0307-0565 print.
- O'Donnell, L.; O'Meara, N.; Owens, D.; Johnson, A.; Collins, P. & Tomkin, G. (1987). Plasma catecholamines and lipoproteins in chronic psychological stress. *Journal of the Royal Society of Medicine*, Vol.80, No.6, (June 1987), pp. 339-342, ISSN 0141-0768.
- Okruhlicová, L.; Dlugosová, K.; Mitasíková, M. & Bernátová, I. (2008). Ultrastructural characteristics of aortic endothelial cells in borderline hypertensive rats exposed to chronic social stress. *Physiological research/Academia Scientiarum Bohemoslovaca*, Vol.57, Suppl.2, (March 2008), pp. S31-37, ISSN 0862-8408.
- Padden, D.L.; Connors, R.A. & Agazio, J.G. (2011). Determinants of health-promoting behaviors in military spouses during deployment separation. *Military medicine*, Vol.176, No.1, (January 2011), pp.26-34, ISSN: 0026-4075.
- Pejovic, S.; Vgontzas, A.N.; Basta, M.; Tsaousoglou, M.; Zoumakis, E.; Vgontzas, A.; Bixler, E.O. & Chrousos, G.P. (2010). Leptin and hunger levels in young healthy adults after one night of sleep loss. *Journal of sleep research*, Vol.19, No.4, (December 2010), pp. 552-558, ISSN 0962-1105.
- Poehlman, E.T.; Toth, M.J.; Bunyard, L.B.; Gardner, A.W.; Donaldson, K.E.; Colman, E.; Fonong, T. & Ades, P.A. (1995). Physiological predictors of increasing total and central adiposity in aging men and women. *Archives of internal medicine*, Vol.155, No.22, (December 1995), pp. 2443-2448, ISSN 0003-9926.

- Pradhan, A.D.; Manson, J.E.; Rifai, N.; Buring, J.E. & Ridker, P.M. (2001). C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA*, Vol.286, No.3, (July 2001), pp. 327-334, ISSN 0098-7484.
- Risérus, U.; Willett, W.C. & Hu, F.B. (2008). Dietary fats and prevention of type 2 diabetes. *Progress in lipid research*, Vol.48, No.1, (January 2009), pp. 44-51, ISSN 1873-2194 online, 0163-7827 print.
- Rizzo, M.; Kotur-Stevuljevic, J.; Berneis, K.; Spinas, G.; Rini, G.B.; Jelic-Ivanovic, Z.; Spasojevic-Kalimanovska, V. & Vekic, J. (2009). Atherogenic dyslipidemia and oxidative stress: a new look. *Translational research: the journal of laboratory and clinical medicine*, Vol.153, No.5, (May 2009), pp. 217-223. ISSN 1931-5244.
- Roberts, C.K. & Barnard, R.J. (2005). Effects of exercise and diet on chronic disease. *Journal of applied physiology*, Vol.98, No.1, (January 2005), pp. 3-30, ISSN: 8750-7587.
- Ross, R. (1999). Atherosclerosis--an inflammatory disease. *The New England journal of medicine*, Vol.340, No.2, (January 1999), pp. 115-126, ISSN. 0028-4793.
- Rubens, M.; Mollo, L.; Krishnan, S.; Finkel, S.; Weintraub, M.; Gracik, T.; Kohn, D. & Oral, E.A. (2011). The Metabolic Fitness Program: Lifestyle modification for the metabolic syndrome using the resources of cardiac rehabilitation. *Journal of cardiopulmonary rehabilitation and prevention*, Epub ahead of print doi: 10.1097/HCR.0b013e318220a7eb, (July 2011), ISSN 1932-751X.
- Schuit, A.J.; Schouten, E.G.; Miles, T.P.; Evans, W.J.; Saris, W.H.M. & Kok, F.J. (1998). The effect of six months training on weight, body fatness and serum lipids in apparently healthy elderly Dutch men and women International. *International journal of obesity and related metabolic disorders: journal of the International Association for the Study of Obesity*, Vol.22, No.9, (September 1998), pp. 847-853, ISSN 0307-0565.
- Seeman, T.E.; Singer, B.H.; Rowe, J.W.; Horwitz, R.I. & McEwen, B.S. (1997). Price of adaptation--allostatic load and its health consequences. *MacArthur studies of successful aging. Archives of internal medicine*, Vol.157, No.19, (October 1997), pp. 2259-2268, ISSN 0003-9926.
- Selye, H. (1936). A syndrome produced by diverse nocuous agents. *Nature*, Vol.138, (July 1936), p.32, ISSN 1476-4687.
- Sheril, A.; Jeyakumar, S.M.; Jayashree, T.; Giridharan, N.V. & Vajreswari A. (2008). Impact of feeding polyunsaturated fatty acids on cholesterol metabolism of dyslipidemic obese rats of WNIN/GR-Ob strain. *Atherosclerosis*, Vol.204, No.1, (May 2009), pp.136-140, ISSN 1879-1484 online, ISSN 0021-9150 print.
- Shively, C.A.; Register, T.C. & Clarkson, T.B. (2009). Social stress, visceral obesity, and coronary artery atherosclerosis: product of a primate adaptation. *American journal of primatology*, Vol.71, No.9, (September 2009), pp. 742-751, ISSN 0275-2565.
- Sierra, C. & de la Sierra, A. (2008). Early detection and management of the high-risk patient with elevated blood pressure. *Vascular health and risk management*, Vol.4, No.2, (April 2008), pp. 289-296, ISSN 1176-6344.
- Sigwalt, A.R.; Budde, H.; Helmich, I.; Glaser, V.; Ghisoni, K.; Lanza, S.; Cadore, E.L.; Lhullier, F.L.; F de Bem A.; Hohl, A.; J de Matos, F.; de Oliveira, P.A.; S Prediger, R.D.; A Guglielmo, L.G. & Latini, A. (2011). Molecular aspects involved in swimming exercise training reducing anhedonia in a rat model of depression. *Neuroscience*, Epub ahead of print, doi:10.1016/j.physletb.2003.10.071, (June 2011), ISSN 1873-7544.

- Singh, B.M. & Mehta, J.L. (2003). Interactions between the renin-angiotensin system and dyslipidemia: relevance in the therapy of hypertension and coronary heart disease. *Archives of internal medicine*, Vol.163, No.11, (June 2003), pp. 1296-1304, ISSN 0003-992
- Sitia, S.; Tomasoni, L.; Atzeni, F.; Ambrosio, G.; Cordiano, C.; Catapano, A.; Tramontana, S.; Perticone, F.; Naccarato, P.; Camici, P.; Picano, E.; Cortigiani, L.; Bevilacqua, M.; Milazzo, L.; Cusi, D.; Barlassina, C.; Sarzi-Puttini, P. & Turiel, M. (2010). From endothelial dysfunction to atherosclerosis. *Autoimmunity reviews*, Vol.9, No.12, (October 2010), pp. 830-834, ISSN 1568-9972.
- Sothmann, M.S.; Buckworth, J.; Claytor, R.P.; Cox, R.H.; White-Welkley, J.E. & Dishman, R.K. (1996). Exercise training and the cross-stressor adaptation hypothesis. *Exercise and sport science reviews*, Vol.24, (1996), pp. 267-287, ISSN 0091-6331.
- Spiegel, K.; Tasali, E.; Penev, P. & Van Cauter E. (2004). Brief communication: Sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. *Annals of internal medicine*, Vol. 141, No.11, (December 2004), pp. 846-850, ISSN 0003-4819.
- Stanhope, K.L.; Schwarz, J.M.; Keim, N.L.; Griffen, S.C.; Bremer, A.A.; Graham, J.L.; Hatcher, B.; Cox, C.L.; Dyachenko, A.; Zhang, W.; McGahan, J.P.; Seibert, A.; Krauss, R.M.; Chiu, S.; Schaefer, E.J.; Ai, M.; Otokozaawa, S.; Nakajima, K.; Nakano, T.; Beysen, C.; Hellerstein, M.K.; Berglund, L. & Havel, P.J. (2009). Consuming fructose-sweetened, not glucose-sweetened, beverages increases visceral adiposity and lipids and decreases insulin sensitivity in overweight/obese humans. *The journal of Clinical Investigation*, Vol.119, No.5, (May 2009), pp. 1322-1334, ISSN 0021-9738.
- Steanovv, T.S.; Vekova, A.M.; Kurktschiev, D.P. & Temelkova-Kurktschiev, T.S. (2011). Relationship of physical activity and eating behaviour with obesity and type 2 diabetes mellitus: Sofia Lifestyle (SLS) study. *Folia Medica*, Vol.53, No.1, (January/March 2011), pp. 11-18, ISSN 0204-8043.
- Steinberg, D. (2002). Atherogenesis in perspective: hypercholesterolemia and inflammation as partners in crime. *Nature medicine*, Vol.8, No.11, (November 2002), pp. 1211-1217, ISSN 1078-8956.
- Sterling, P. & Eyer, J. (1988). Allostasis: a new paradigm to explain arousal pathology. In: *Handbook of Life Stress, Cognition and Health*, Fisher, S. & Reason, J (editors), pp. 629-649, JOHN WILEY & SONS, ISBN-10: 0471912697/ISBN-13: 978-0471912699, New York - USA.
- Stoney, C.M. (2007). Cholesterol and Lipoproteins, In: *Encyclopedia of Stress*, George Fink (editor), pp. 478-483, ELSEVIER, ISBN 978-0-12-088503-9, San Diego, CA - USA.
- Stoney, C.M.; Niaura, R.; Bausserman, L. & Matacin, M. (1999). Lipid reactivity to stress: I. Comparison of chronic and acute stress responses in middle-aged airline pilots. *Health psychology : official journal of the Division of Health Psychology, American Psychological Association*, Vol.18, No.3, (May 1999), pp. 241-250, ISSN 0278-6133.
- Stoney, C.M.; West, S.G.; Hughes, J.W.; Lentino, L.M.; Finney, M.L.; Falko, J. & Bausserman, L. (2002). Acute psychological stress reduces plasma triglyceride clearance. *Psychophysiology*, Vol.39, No.1, (January 2002), pp. 80-85, ISSN 0048-5772.
- Sudano, I.; Spieker, L.E.; Hermann, F.; Flammer, A.; Corti, R.; Noll, G. & Lüscher, T.F. (2006). Protection of endothelial function: targets for nutritional and pharmacological interventions. *Journal of cardiovascular pharmacology*, Vol.47, No.2, (June 2006), pp. S136-S150, ISSN 0160-2446.

- Taguchi, I.; Inoue, T.; Kikuchi, M.; Toyoda, S.; Arikawa, T.; Abe, S. & Node, K. (2011). Pleiotropic effects of ARB on dyslipidemia. *Current vascular pharmacology*, Vol.9, No.2, (March 2011), pp. 129-135, ISSN 1570-1611.
- Tellez, A.; Schuster, D.S.; Alviar, C.; López-Berenstein, G.; Sanguino, A.; Ballantyne, C.; Perrard, X.Y.; Schulz, D.G.; Rousselle, S.; Kaluza, G.L. & Granada, J.F. (2011). Intramural coronary lipid injection induces atheromatous lesions expressing proinflammatory chemokines: implications for the development of a porcine model of atherosclerosis. *Cardiovascular revascularization medicine: including molecular interventions*, Epub ahead of print, doi:10.1016/j.carrev.2011.03.007, (May 2011), ISSN 1878-0938.
- Thompson, P.D.; Cullinane, E.M.; Sady, S.P.; Flynn, M.M.; Bernier, D.N.; Kantor, M.A.; Saritelli, A.L. & Herbert, P.N. (1988). Modest changes in high-density lipoprotein concentration and metabolism with prolonged exercise training. *Circulation*, Vol.78, No.1, (July 1988), pp. 25-34, ISSN 0009-7322.
- Torres, S.J. & Nowson, C.A. (2007). Relationship between stress, eating behavior, and obesity. *Nutrition*, Vol.23, No.11-12, (November/December 2007), pp. 887-894, ISSN 0899-9007.
- Tsatsoulis, A. & Fountoulakis, S. (2006). The protective role of exercise on stress system dysregulation and comorbidities. *Annals of the New York Academy of Sciences*, Vol.1083 (November 2006), pp. 196-213, ISSN 0077-8923.
- Tsekouras, Y.E.; Magkos, F.; Prentzas, K.I.; Basioukas, K.N.; Matsama, S.G.; Yanni, A.E.; Kavouras, S.A. & Sidossis, L.S. (2009). A single bout of whole-body resistance exercise augments basal VLDL-triacylglycerol removal from plasma in healthy untrained men. *Clinical science*, Vol.116, No.2, (January 2009), pp. 147-156, ISSN 0143-5221.
- van Oostrom, A.J.; van Wijk, J. & Cabezas, M.C. (2004). Lipaemia, inflammation and atherosclerosis: novel opportunities in the understanding and treatment of atherosclerosis. *Drugs*, Vol.64, No.2 (2004), pp. 19-41, 0012-6667.
- Veen, G.; Giltay, E.J.; DeRijk, R.H.; van Vliet, I.M.; van Pelt, J. & Zitman, F.G. (2009). Salivary cortisol, serum lipids, and adiposity in patients with depressive and anxiety disorders. *Metabolism: clinical and experimental*, Vol.58, No.6, (June 2009), pp. 821-827, ISSN 0026-0495.
- Venables, M.C. & Jeukendrup, A.E. (2009). Physical inactivity and obesity: links with insulin resistance and type 2 diabetes mellitus. *Diabetes/metabolism research and reviews*, Vol.25, No.1, (September 2009), pp. S18-S23, ISSN 1520-7552.
- Vessby, B. (2000). Dietary fat and insulin action in humans. *The British journal of nutrition*, Vol.83, No.1, (March 2000), pp. S91-S96, ISSN 0007-1145.
- Vogelzangs, N.; Suthers, K.; Ferrucci, L.; Simonsick, E.M.; Ble, A.; Schragger, M.; Bandinelli, S.; Lauretani, F.; Giannelli, S.V. & Penninx, B.W. (2007). Hypercortisolemic depression is associated with the metabolic syndrome in late-life. *Psychoneuroendocrinology*, Vol.32, No.2, (February 2007), pp.151-159, ISSN 0306-4530.
- Walker, E.A. & Stewart, P.M. (2003). 11beta-hydroxysteroid dehydrogenase: unexpected connections. *Trends in endocrinology and metabolism: TEM*, Vol.14, No.7, (September 2003), pp.334-339, ISSN 1043-2760.
- Wallis, D.J. & Hetherington M.M. (2008). Emotions and eating: Self-reported and experimentally induced changes in food intake under stress. *Appetite*, Vol.52, No.2, (April 2009), pp. 355-362, ISSN 1095-8304 online, 0195-6663 print.

- Watts, G.F.; Barrett, P.H.R. & Chan, D.C. (2008). HDL metabolism in context: looking on the bright side. *Current opinion in lipidology*, Vol.19, No.4, (August 2008), pp. 395-404, ISSN 0957-9672.
- Watts, G.F.; Ooi, E.M.M. & Chan, D.C. (2009). Therapeutic regulation of apoB100 metabolism in insulin resistance in vivo. *Pharmacology & therapeutics*, Vol.123, No.3, (September 2009), pp. 281-291, ISSN: 0163-7258.
- Win, S.; Parakh, K.; Eze-Nliam, C.M.; Gottdiener, J.S.; Kop, W.J. & Ziegelstein, R.C. (2011). Depressive symptoms, physical inactivity and risk of cardiovascular mortality in older adults: the Cardiovascular Health Study. *Heart: official journal of the British Cardiac Society*, Vol.97, No.6, (March 2011), pp. 500-505, ISSN 1355-6037.
- Xu, C.; He, J.; Jiang, H.; Zu, L.; Zhai, W.; Pu, S. & Xu, G. (2009). Direct effect of glucocorticoids on lipolysis in adipocytes. *Molecular endocrinology*, Vol.23, No.8, (May 2009), pp. 1161-1170, ISSN 0888-8809.
- Xu, X.H.; Shah, P.K.; Faure, E.; Equils, O.; Thomas, L.; Fishbein, M.C.; Luthringer, D.; Xu, X.P.; Rajavashisth, T.B.; Yano, J.; Kaul, S. & Arditi, M. (2001). Toll-like receptor-4 is expressed by macrophages in murine and human lipid-rich atherosclerotic plaques and upregulated by oxidized LDL. *Circulation*, Vol.104, No.25 (December 2001), pp. 3103-3108, ISSN 0009-7322.
- Yamazaki, Y.; Hashizume, T.; Morioka, H.; Sadamitsu, S.; Ikari, A.; Miwa, M. & Sugatani, J. (2011). Diet-induced lipid accumulation in liver enhances ATP-binding cassette transporter g5/g8 expression at bile canaliculi. *Drug metabolism and pharmacokinetics*, Epub ahead of print, doi:10.2133/dmpk.DMPK-11-RG-025, (May 2011), ISSN 1880-0920.
- Yarrow, J.F.; White, L.J.; McCoy, S.C. & Borst, S.E. (2010). Training augments resistance exercise induced elevation of circulating brain derived neurotrophic factor (BDNF). *Neuroscience letters*, Vol.479, No.2, (July 2010), pp. 161-165, ISSN 0304-3940.
- Yin, Z.; Davis, C.L.; Moore, J.B. & Treiber, F.A. (2005). Physical activity buffers the effects of chronic stress on adiposity in youth. *Annals of behavioral medicine: a publication of the Society of Behavioral Medicine*, Vol.29, No.1, (February 2005), pp. 29-36, ISSN 0883-6612.
- Yoo, H. & Franke, W.D. (2010). Stress and cardiovascular disease risk in female law enforcement officers. *International archives of occupational and environmental health*, Vol.84, No.3, (March 2011), pp. 279-286, ISSN 1432-1246 online, ISSN 0340-0131 print.
- Yudkin, J.S.; Kumari, M.; Humphries, S.E. & Mohamed-Ali, V. (2000). Inflammation, obesity, stress and coronary heart disease: is interleukin-6 the link? *Atherosclerosis*, Vol.148, No.2, (February 2000), pp. 209-214, ISSN 0021-9150.
- Zakrzewska, K.E.; Cusin, I.; Sainsbury, A.; Rohner-Jeanrenaud, F. & Jeanrenaud, B. (1997). Glucocorticoids as counterregulatory hormones of leptin: toward an understanding of leptin resistance. *Diabetes*, Vol.46, No.4, (April 1997), pp. 717-719, ISSN 0012-1797.
- Zukowska, Z. (2005). Atherosclerosis and angiogenesis: what do nerves have to do with it? *Pharmacological reports: PR*. Vol.57, Supplement, (June 2005), pp. 229-234, ISSN 1734-1140.



Dyslipidemia - From Prevention to Treatment

Edited by Prof. Roya Kelishadi

ISBN 978-953-307-904-2

Hard cover, 468 pages

Publisher InTech

Published online 03, February, 2012

Published in print edition February, 2012

Dyslipidemia has a complex pathophysiology consisting of various genetic, lifestyle, and environmental factors. It has many adverse health impacts, notably in the development of chronic non-communicable diseases. Significant ethnic differences exist due to the prevalence and types of lipid disorders. While elevated serum total- and LDL-cholesterol are the main concern in Western populations, in other countries hypertriglyceridemia and low HDL-cholesterol are more prevalent. The latter types of lipid disorders are considered as components of the metabolic syndrome. The escalating trend of obesity, as well as changes in lifestyle and environmental factors will make dyslipidemia a global medical and public health threat, not only for adults but for the pediatric age group as well. Several experimental and clinical studies are still being conducted regarding the underlying mechanisms and treatment of dyslipidemia. The current book is providing a general overview of dyslipidemia from diverse aspects of pathophysiology, ethnic differences, prevention, health hazards, and treatment.

How to reference

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

Fernanda Klein Marcondes, Vander José das Neves, Rafaela Costa, Andrea Sanches, Tatiana Sousa Cunha, Maria José Costa Sampaio Moura, Ana Paula Tanno and Dulce Elena Casarini (2012). Dyslipidemia Induced by Stress, *Dyslipidemia - From Prevention to Treatment*, Prof. Roya Kelishadi (Ed.), ISBN: 978-953-307-904-2, InTech, Available from: <http://www.intechopen.com/books/dyslipidemia-from-prevention-to-treatment/dyslipidemia-induced-by-stress>

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

© 2012 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the [Creative Commons Attribution 3.0 License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen