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# Dyslipidemia Induced by Stress

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## 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 alostasis to describe the adaptative 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 adaptative 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

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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 along 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 adaptative 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-$\beta_2$ 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 hypothalmic 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 11β-Hydroxysteroid dehydrogenase type 1 (11β-HSD1) and 2 (Bose et al., 2009). The effects of glucocorticoid are enhanced by the enzyme 11β-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 11β-HSD1 in adipose tissue, present accumulation of visceral adipose tissue, hypertension, dyslipidemia and glucose intolerance (Masuzaki et al., 2001; Masuzaki & Flier, 2003). Therefore 11β-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 11β-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.

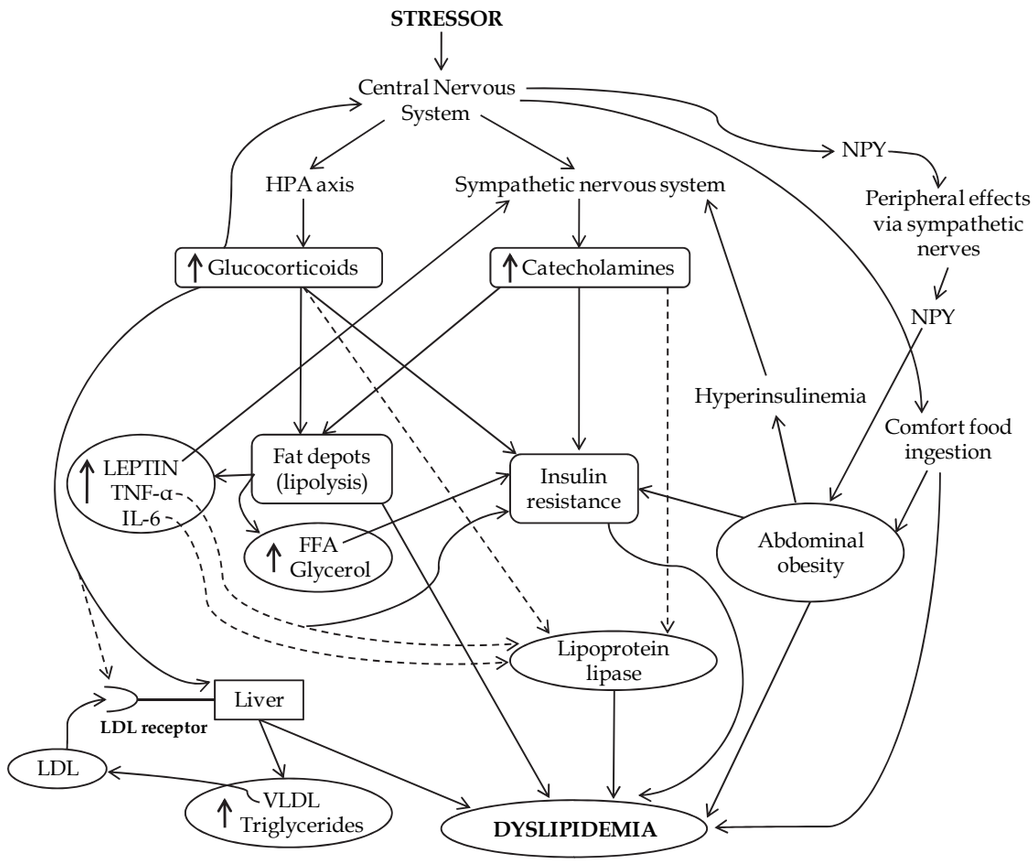


Fig. 1. Schematic representation of physiological mechanisms of dyslipidemia induced by stress. Hypothalamic-pituitary-adrenal axis (HPA), low-density lipoprotein (LDL), very-low-density lipoprotein (VLDL), free fatty acids (FFA), neuropeptide Y (NPY), tumor necrosis factor (TNF-α), interleukin 6 (IL-6). 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 ($BH_4$) synthesis, which stabilizes eNOS (Mitchell et al., 2004). If $BH_4$ 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 glucorticoids, 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 calveolin-eNOS complex, and reduce the interaction between $Ca^{2+}$-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 machrophage proliferation involving glucose-dependent oxidation of LDL in atherosclerotic lesions. Toll like receptors are expressed by machrophages 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 kB (NF-kB) 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-kB pathway leads to the synthesis of the following proinflammatory chemokines: interleukin 1-β, inteleukin 6, TNF-α, monocyte chemoattractant protein-1, intercellular adhesion molecule-1. Interleukin 1-β and inteleukin 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-kB, 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 ($AT_1R$) 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 $AT_1R$. 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 $AT_1R$ density and its functional responsiveness to vasoconstrictors, whereas the administration of statins reduces $AT_1R$ 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 $AT_1R$ antagonism improves hypercholesterolemia-associated endothelial dysfunction, resulting in an anti-atherosclerotic effect (Taguchi et al., 2011).

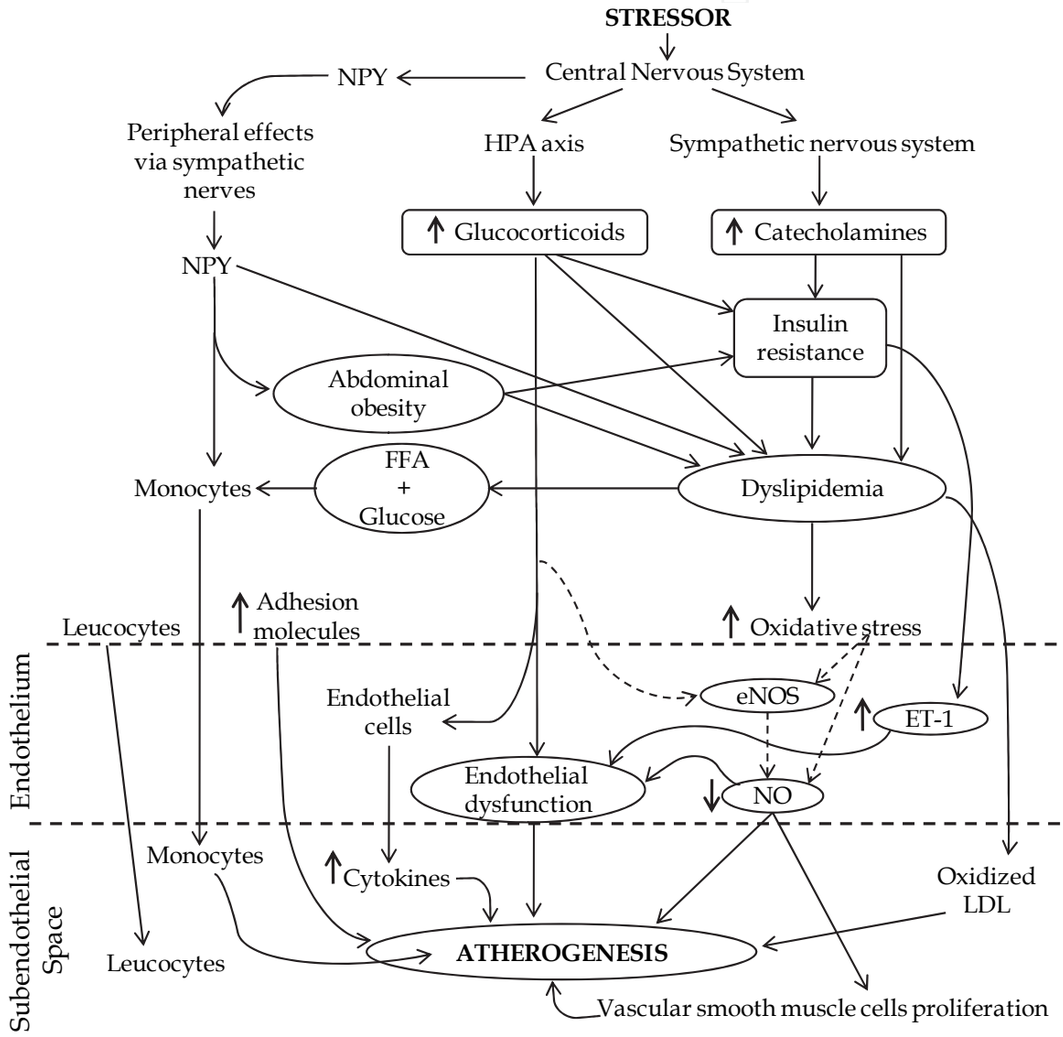


Fig. 2. Schematic representation of putative mechanisms involved in the relations between among stress, dyslipidemia, and atherosclerosis. Hypothalamic-pituitary-adrenal axis (HPA), neuropeptide Y (NPY), low-density lipoprotein (LDL), very-low-density lipoprotein (VLDL), free fatty acids (FFA), endothelial 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 maladaptative 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 glucorticoids 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.

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## 7. References

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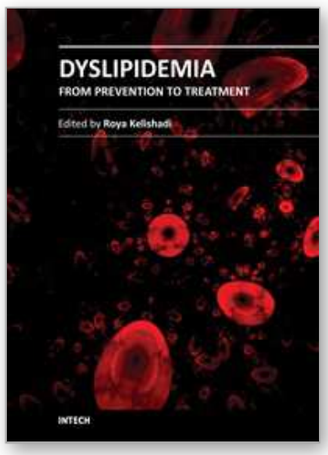


**Dyslipidemia - From Prevention to Treatment**
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Dyslipidemia has a complex pathophysiology consisting of various genetic, lifestyle, and environmental factors. It has many adverse health impacts, notably in the development of chronic non-communicable 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.

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