FACULDADE DE MEDICINA
UNIVERSIDADE DO PORTO

MESTRADO INTEGRADO EM MEDICINA

2012/2013

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# Cortisol: the villain in Metabolic Syndrome?

**Março, 2013**

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# Cortisol: the villain in Metabolic Syndrome?

**Mestrado Integrado em Medicina**

**Área: Bioquímica**

**Trabalho efetuado sob a Orientação de:**

**Professor Doutora Laura Ribeiro**

**Trabalho organizado de acordo com as normas da revista:**

**Revista da Associação Médica Brasileira**

**Março, 2013**

U.PORTO
FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO
UNIDADE CURRICULAR
PROJETO DE OPÇÃO
DISSERTAÇÃO / MONOGRAFIA

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**Projeto de Opção do 6º ano – DECLARAÇÃO DE REPRODUÇÃO**

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**Título da ~~Dissertação~~/Monografia** (cortar o que não interessa):
Cortisol: the villain in Metabolic Syndrome?

**Orientador:**
Professora Doutora Laura Ribeiro

**Coorientador (se aplicável):**

**Ano de conclusão:** 6º

**Designação da área do projeto:**
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Assinatura: Silvia Paredes

## Dedicatória

Este trabalho é dedicado aqueles que eu mais amo e que de diversas formas marcaram a minha vida.

Aos meus pais, por todos os sacrifícios que fizeram por mim, por tudo aquilo que me ensinaram, pelo apoio na hora das decisões importantes e pelo suporte nos momentos menos afortunados.

Ao meu irmão Carlos, pelo suporte constante em todas as decisões da minha vida, boas ou más. À Carina, pelo exemplo de pessoa que é e ao Santiago, que é a luz da minha vida.

À minha restante família, especialmente à tia Isaura com quem sempre pude contar e à tia Nelly, que embora do outro lado do mundo, nunca deixou de demonstrar o seu carinho e apoio. E ao meu avô, que apesar da doença nunca se esqueceu de mim e que, com certeza, gostaria de estar presente neste momento.

Ao Miguel, por todo o carinho e pela extrema paciência e força que me deu quando me senti sem vontade de continuar.

Aos melhores amigos do mundo, por estarem sempre ao meu lado, em todas as ocasiões. À Bia, por me ensinar todos os dias a ver a vida de uma forma melhor. À Sara e ao Filipe, pela companhia e incentivo mesmo nos momentos de maior desânimo. Ao Tó, pela compreensão e bondade. Ao Vítor, por ter cuidado de mim como uma irmã. Ao António Augusto, à Joaninha, à Ana e ao Vitinha por estarem presentes sempre que precisei. À Anabela, pelo exemplo de persistência e tenacidade.

Ao Edipinho e ao Neco, pelo afeto e pelas longas horas de companhia durante todo o meu percurso académico.

# Cortisol: the villain in Metabolic Syndrome?

# Cortisol: o vilão na Síndrome Metabólica?

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**Conflits of interest:** none

**Summary**

**Background:** Stress is defined as a state of threat to homeostasis and stress response involves the activation of behavioral and physiological systems that promote survival. Indeed, stress response leads to the activation of the hypothalamic-pituitary-adrenal axis, which through the release of glucocorticoids, exerts determinant effects upon environment adaptation and energy metabolism. Prolongation of the stress response, as in chronic stress, can have detrimental effects, especially on whole body metabolism. The metabolic syndrome can be described as a cluster of metabolic abnormalities that increase the risk of heart disease and type 2 diabetes. Several studies suggest that intense and chronic reactivity to stress can be a predictor of metabolic syndrome.

**Objective:** This article reviews the state of the art regarding the association between glucocorticoid actions and both obesity and insulin resistance, two main features of the metabolic syndrome.

**Methods:** A methodological assessment of the literature on PubMed and SciELO databases was conducted by using the following terms: stress, metabolic syndrome, glucocorticoids, obesity, insulin resistance, hypothalamic-pituitary-adrenal-axis and 11β-hydroxysteroid dehydrogenase.

**Results:** Chronic stress, mainly through hypothalamic-pituitary-adrenal axis dysregulation, promotes the accumulation of visceral fat. Reciprocally, obesity promotes a systemic low-grade inflammation state, mediated by increased adipokine secretion, which can chronically stimulate and disturb stress system. 11β-hydroxysteroid dehydrogenase appears as a fascinating entity that multiplies the complexity of glucocorticoid system biology.

**Conclusions:** Given the strong evidences linking glucocorticoids release, obesity and type 2 diabetes, a better understanding of the mechanisms underlying this link might be useful for prevention and treatment of the metabolic syndrome.

**Keywords:**

Stress; Glucocorticoids; Obesity; Insulin resistance; Metabolic Syndrome; 11β-Hydroxysteroid Dehydrogenase.

**Resumo**

**Introdução:** O stresse pode ser definido como um estado de ameaça à homeostasia e a resposta ao stresse envolve a ativação de sistemas comportamentais e fisiológicos que visam a sobrevivência do indivíduo. A resposta ao stresse conduz à activação do eixo hipotálamo-hipófise-suprarrenal, que, através da libertação de glicocorticóides, exerce efeitos determinantes na adaptação ao ambiente e no metabolismo energético. O prolongamento da resposta ao stresse, como no stresse crónico, pode acarretar efeitos adversos, particularmente no metabolismo. A síndrome metabólica pode ser definida como uma agregação de alterações metabólicas que aumentam o risco de doença cardiovascular e diabetes tipo 2. Vários estudos sugerem que a reatividade intensa, e sustentada, ao stresse pode ser um preditor de risco para síndrome metabólica.

**Objetivo:** Este artigo revê o estado da arte relativamente à associação entre as ações dos glicocorticóides e a obesidade e a resistência à insulina, dois dos principais componentes da síndrome metabólica.

**Métodos:** Foi conduzida uma revisão da literatura nas bases de dados PubMed e SciELO usando as seguintes palavras-chave: stresse, síndrome metabólica, glicocorticóides, obesidade, resistência à insulina, eixo hipotálamo-hipófise-suprarrenal e 11β-hidroxiesteróide desidrogenase.

**Resultados:** O stresse crónico, principalmente através da desregulação do eixo hipotálamo-hipófise-suprarrenal, promove a acumulação de gordura visceral. Ao mesmo tempo, a obesidade promove um estado inflamatório sistémico de baixo grau, mediado por alterações na secreção de adipocinas, que cronicamente podem estimular e perturbar o sistema de stresse. A 11β-hidroxiesteróide desidrogenase é uma entidade fascinante que amplia a complexidade da biologia do sistema glicocorticóide.

**Conclusões:** Dadas as fortes evidências que ligam a libertação de glicocorticóides, a obesidade e a diabetes tipo 2, um conhecimento mais aprofundado sobre os mecanismos envolvidos nesta associação pode ser útil na prevenção e tratamento da síndrome metabólica.

**Palavras chave:** Stresse; Glicocorticóides; Obesidade; Resistência à insulina; Síndrome Metabólica; 11β-hidroxiesteróide desidrogenase.

# Index

**Abbreviations**

11β-HSD1 - 11β-Hydroxysteroid Dehydrogenase Type 1

11β-HSD2 - 11β-Hydroxysteroid Dehydrogenase Type 2

ACTH – Adrenocorticotropic hormone

AMPK – 5-adenosine monophosphate-activated protein kinase

AVP – Vasopressin

BMI – Body mass index

CBG - Corticosteroid-binding globulin

CRH – Corticotropin-releasing hormone

G6Pase - Glucose-6-phosphatase

GC - Glucocorticoids

GR – Glucocorticoid receptor

H6PDH - Hexose-6-phosphate dehydrogenase

HPA - Hypothalamic-pituitary-adrenal

IL-1 – Interleukin-1

IL-6 - Interleukin-6

MS –Metabolic Syndrome

MR - Mineralocorticoid receptor

NADPH - Nicotinamide adenine dinucleotide phosphate

NPY - Neuropeptide Y

PEPCK – phosphoenolpyruvate carboxykinase

PPAR - Peroxisome proliferator-activated receptor

TAG - Triglycerides

TNFα – Tumor necrosis factor α

## Introduction

Stress is defined as a state of threatened homeostasis [1, 2], and comprises a complex repertoire of physiologic and behavioral responses that aim to restore the challenged body equilibrium [3]. The hypothalamic-pituitary-adrenal (HPA) axis and the central and peripheral components of the autonomic nervous system are responsible for crucial functions of the stress system [4]. Acute activation of stress reaction leads to a cluster of time-limited, behavioral and physical changes that are normally adaptive and aim to improve the chances of individuals to survive [4, 5]. Inadequate, excessive, and/or prolonged reactions to stress may lead to disease [5]. Chronic stress, a prolonged threat to homeostasis by persistent or frequently repeated stressors, is an important aspect of daily life leading to the development of a wide range of diseases and syndromes [4]. In fact, long exposure to stress can disrupt the pathways involved in metabolism, growth, reproduction, immunity, personality and behavior development [1].

The metabolic syndrome (MS) can be described as a cluster of metabolic abnormalities, in which fat accumulation appears to play a central role and has a thigh relationship with type 2 diabetes [6]. Obesity has become recognized as one of the major health problems threatening the world today with a strong and deleterious impact on health status and health-care costs [7-10]. To allow humans to cope with periods of starvation, they were genetically programed to accumulate high amounts of energy. However, nowadays modern lifestyles offer open access to food and promote sedentary habits, leading to a progressive cycle of overeating and weight gain [11]. The prevalence of type 2 diabetes mellitus is expected to get worse in the next decades [11] and is an important cause of mortality and morbidity worldwide [12]. It has been raised the hypothesis that an adverse psychosocial environment contributes to development of obesity and type 2 diabetes [13, 14]. In fact, intense stress reactivity and an abnormal recovery after stress predict MS development [15]. Long exposure to psychological stress may impair the capacity of the organism to maintain a biological balance and thus disrupt homeostasis [16], causing adverse metabolic effects. Several studies have shown a significant association between glucocorticoids (GC), visceral fat, type 2 diabetes and MS [3, 17, 18].

## Methods

This review will discuss the link between GC metabolic effects and the development of obesity, insulin resistance and the MS. A methodological assessment of the literature on PubMed and SciELO databases was conducted without setting limits for year publication but selecting both English and Portuguese papers with full text availability. The following terms were used for this review: stress, metabolic syndrome, glucocorticoids, obesity, insulin resistance, hypothalamic-pituitary-adrenal-axis and 11β-hydroxysteroid dehydrogenase.

**Stress and mediators of stress response - HPA axis**

The HPA axis is important in maintaining a dynamic equilibrium or homeostasis in a constantly changing environment [4, 19]. The paraventricular nucleus of the hypothalamus contains neuroendocrine neurons that synthesize and secrete vasopressin (AVP) and corticotropin-releasing hormone (CRH). CRH and AVP are released from neurosecretory nerve terminals at the median eminence. CRH is transported to the anterior pituitary through the portal blood vessel system of the hypophyseal stalk and AVP is transported by axonal transport to the posterior pituitary. There, CRH and AVP act synergistically to stimulate the secretion of stored adrenocorticotropic hormone (ACTH) from corticotrope cells. ACTH is transported by blood to the adrenal gland, where it rapidly stimulates the biosynthesis of GC [4, 20, 21]. GC, in turn, inhibit CRH at the hypothalamic level, and interfere with ACTH-secretion in the anterior pituitary, thereby establishing a regulatory feedback loop [22]. The activity of this endocrine system is characterized by a robust circadian rhythm with cortisol levels peaking in the early morning hours around the time of awakening and being lowest around midnight [23]. Diurnal variations are modulated by changes in lighting, feeding schedules, and physical activity, and are disrupted in face of a stressor [4]. Inflammatory mediators can also be secreted in response to different stressors and can activate the HPA axis [24]. For instance, tumor necrosis factor-α (TNFα), interleukin-1 (IL-1) and interleukin-6 (IL-6) are mainly present in states of chronic inflammatory stress and can activate HPA axis [24]. GC are present in the systemic circulation mainly bound to corticosteroid-binding globulin (CBG) (approximately 90%) and also, to albumin (4–5%) [23]. Only 5–6% of the total circulating GC remain in an unbound state and, thus, biologically active [25]. CBG may have, either a buffer function blunting elevations of free cortisol during a secretory peak or a reservoir role maintaining cortisol pool during times of reduced secretion [26]. GC exert an inhibitory feedback action in the stress response system, which is fundamental in limiting the duration of the total GC tissue exposure, thus minimizing their catabolic, adipogenic, antireproductive, and immunosuppressive effects [4]. GC exert their actions by binding to two types of intracellular receptors: the glucocorticoid receptor (GR) which responds to high levels of GC and the mineralocorticoid receptor (MR) responding to low levels of GC [22, 27]. GC modulate the expression of a wide-range of genes in a DNA-dependent and independent manner [4, 22, 23, 28]. It is of note that

numerous genes encoding important proteins that are directly or indirectly implicated in several metabolic pathways are rigorously regulated by GC (Table 1) [4, 23].

11β-Hydroxysteroid Dehydrogenase (11β-HSD) catalyzes the interconversion of inactive cortisone to active cortisol, or vice-versa [23, 29]. 11β-Hydroxysteroid Dehydrogenase type 2 (11β-HSD2) predominates in renal tubules protecting the MR from excessive stimulation by cortisol. It has also been identified in the colon, salivary glands and placenta [25]. Apparent mineralocorticoid excess syndrome results from defective 11β-HSD2. Its deficiency allows cortisol to bind to MR inducing sodium retention, hypokalemia and hypertension [30, 31]. 11β-Hydroxysteroid Dehydrogenase type 1 (11β-HSD1) which is mostly expressed in liver, fat, gonadal tissue and central nervous system, is believed to function as a reductase generating active cortisol at a prereceptor level, thus enhancing GC receptor activation [32]. The co-localization of 11β-HSD1 with Hexose-6-phosphate dehydrogenase (H6PDH) has an important role in providing nicotinamide adenine dinucleotide phosphate (NADPH) as cofactor to drive the direction to 11β-HSD1 reductase [25].

**Physiological effects of glucocorticoids**

GC are the final mediators of HPA axis activation, playing a key role in modulating immunological and inflammatory responses, energy metabolism and cardiovascular homeostasis and general body responses to stress [25]. In order to face threats imposed by stressors, generalized responses are activated towards the restoration of homeostasis. Behavioral adaptation includes increased arousal, euphoria and cognition, enhanced analgesia, and sleep inhibition. Physical adaptation includes increases in cardiovascular tone, respiratory rate, and metabolism. The activation of HPA axis promotes a redirection of energy, in order to deliver oxygen and nutrients to organs and tissues involved in the functional system of adaptation. In the meantime, other non-emergent functions, such as digestion, reproduction, growth, and overall immunity, are temporarily suppressed [4, 32, 33] . All these acute effects increase the capacity for generation of energy over a limited period of time improving the ability to 'fight or flight' [32]. GC induce lipolysis, even though they favor abdominal and dorsocervical fat accumulation [28]. Given that GC promote delivery of fuel to skeletal muscle, the increase

in triglycerides (TAG) stores in adipose tissue in clinical conditions with GC excess appears paradoxical. This paradox probably reflects the combination of elevated GC levels concomitantly with elevated insulin levels in individuals who are able to ingest unrestricted energy without consuming it – for instance, through physical exercise. In these circumstances, fatty acid esterification predominates over lipolysis and, combined with stimulation of pre-adipocyte differentiation, promotes fat accumulation [32, 34].

GC increase hepatic gluconeogenesis and decrease glucose uptake and insulin sensitivity, thus favoring hyperglycemia. In order to provide amino acids as an additional substrate for oxidative pathways, GC cause protein degradation at multiple tissues such as muscle, bone, and skin. GC also antagonize the anabolic actions of growth and thyroid hormones, insulin, and sex steroids on their target tissues [4, 33]. Globally, stress response is responsible for a shift of normal metabolism, favoring a catabolic state which returns to normal after stress removal. Chronic exposure to stress, however, can be potentially damaging, as long exposure to GC can dysregulate multiple metabolic pathways leading to a progressively increase in visceral adiposity, hyperglycemia, dyslipidemia, hypertension and insulin resistance [4, 33]. Elevated circulating GC levels also result in myopathy, osteopenia or osteoporosis, osteonecrosis, mental disturbances, increased susceptibility to infections and infertility [32, 33, 35]. GC actions in the central nervous system are complex [33]. GC affect the capacity to apprehend sensations and establish suitable reactions to stimuli [36], modulate behavior and humor and interfere with memory retention [5]. Short-term changes in immunological function may be valuable, preventing the damage caused by sustained exposure to various cytokines [4, 5, 37].

## Metabolic Syndrome

The MS is a cluster of metabolic abnormalities that increase the risk for type 2 diabetes mellitus and cardiovascular disease. It can be defined as a state of disturbed metabolic homeostasis characterized by the combination of central obesity, insulin resistance, dyslipidemia, and hypertension [20, 28, 38-40]. The worldwide incidence of both obesity and MS has been significantly rising in the last decades, threatening to become the new epidemic of this century. In fact, currently MS affects ¼ of the adult Portuguese population [41]. It is noteworthy to mention that these clinical conditions often show a relationship with indices of stress [42]. Although obesity per se is not a required feature for the diagnosis of MS, several evidences suggest that both visceral obesity and insulin resistance have a key role in the pathogenic mechanisms underlying the MS [13, 35, 43]. The distribution of fat seems to be a powerful predictor of cardiometabolic disease [44]. Many prospective studies have shown that central obesity is more often correlated to the features of MS [9, 43, 45]. This pathophysiologic relationship is consistent with the emphasis on waist measurement for MS criteria rather than body mass index (BMI), as an indicator of obesity-related cardiovascular risk [43]. In fact, even in normal-weight subjects, increased abdominal circumference is associated with increased risk of cardiovascular disease [46].

## Clinical association between hypercortisolism and the metabolic syndrome

The similarities between the clinical features of Cushing syndrome and those of MS raised the hypothesis that MS is associated with GC excess [15, 23, 33, 47]. Cortisol excess has been implicated in the development of diabetes and obesity, highlighting the role of psychological stress on both conditions (Figure 1) [48-50]. Indeed, human studies have documented that abdominal obesity and its metabolic comorbidities are significantly correlated with stress-related conditions such as adverse life events, psychological disturbances, and psychosocial problems [3]. In fact, the individual inability to cope with long-term environmental adverse stressful events has been related to HPA axis hyperactivation in obesity, particularly the visceral phenotype [15]. Chronic work stress also seems to predict general and central obesity during midlife [1]. Prolonged and nonremitting stress may result in chronic hyperactivation of the HPA axis with resulting sustained GC release [42, 51], which can progressively cause visceral fat accumulation and insulin resistance [48, 49]. In line with this, patients with MS seem to have HPA axis hyperactivity and a functional hypercortisolism [23, 52]. On the contrary, in obese individuals, the circulating GC levels have been reported as normal or even low [2, 53-57]. Several hypotheses can explain an abnormal secretion of cortisol in obesity. Firstly, the presence of a primary neuroendocrine abnormality can cause an irregular central drive to CRH, ACTH and cortisol. Second, an altered peripheral metabolism of cortisol due to dysregulation of 11β-HSD1 can also explain normal or low cortisol concentrations in obesity [58]. On the other hand, it has been suggested that cortisol production rate may increase as the amount of visceral fat enlarges [59], however as said before in most cases its plasma concentrations are normal or even lower. This might be partly explained by enhanced metabolic clearance of cortisol [28, 55], due to a combination of enhanced 5α-redutase activity and impaired regeneration of cortisol from cortisone by 11β-HSD1 in liver, which results in the increase of cortisol urinary metabolites excretion [58]. In accordance with this, it has been shown that patients with obesity and MS show increased urinary excretion of free cortisol and its metabolites [28]. Interestingly, the excretion of urinary free cortisol correlates with anthropometric parameters of visceral fat distribution [58]. Overall, there appears to be a hyperactivity of the HPA axis in response to stress in patients with visceral obesity [3, 28, 55], which is in accordance with results that show a higher release of cortisol after stimulation with ACTH and greater

ACTH release after CRH infusion [2, 59]. Moreover, chronically active HPA axis has an inadequate suppression by dexamethasone [60]. Several studies have shown that in obesity different stimulus such as neuropeptides, psychological stress and mixed meal tests induced an hyperactivation of HPA axis [15]. Individuals that show elevated levels of cortisol in response to perceived stress show a higher association with central fat mass and signs of MS [55, 61]. Animal studies demonstrated that cynomolgus monkeys subjected to high stress levels comparably to controls secreted higher amounts of GC and were less sensitive to their negative feedback [51]. Another study reported that these animals undergoing physical and psychological stress presented higher basal cortisol levels and increased cortisol release after ACTH stimulation, which was associated with greater visceral fat accumulation [42]. In the adipose tissue, lipids are stored as TAG. GC increase lipolysis in adipocytes as a result of increased transcription and expression of the lypolytic proteins adipose triglyceride lipase and hormone-sensitive lipase, increasing the amount of fatty acids in circulation, which, in turn, contribute to triglyceride accumulation in other tissues [62]. In liver, GC increase the expression of fatty acid synthase increasing lipid production, thus favoring hepatic steatosis. GC also promote the secretion of lipoproteins [23]. TAG in circulation, as components of both very low-density lipoproteins and chylomicrons, when hydrolyzed release fatty acids that can be taken up by the surrounding tissues for use or storage, mainly in liver, muscle and central adipocytes [19]. GC promote the differentiation of adipose stromal cells to mature adipocytes, increasing visceral fat accumulation [19, 63] and redistributing adipose tissue from peripheral to central depots, and increasing the size and number of fat cells [28, 56].

Adenosine monophosphate activated protein kinase (AMPK) is a sensor of cellular energy status and is activated in response to a decrease of this state. When activated, AMPK stimulates appetite in the hypothalamus and switches anabolic into catabolic pathways, such as glycolysis and fatty acid oxidation. GC inhibit the AMPK system thus contributing to central fat deposition [64]. GC increase caloric and dietary fat intake [19] and suppress thermogenesis [15].

Growing evidence suggests that there is a relationship between type 2 diabetes and chronic stress disorders [1]. In fact, circulating cortisol concentrations are higher in people with glucose intolerance and type 2 diabetes [65]. GC raise blood glucose levels through several mechanisms [62]. GC impair the insulin-dependent glucose uptake in peripheral

tissues [66], enhance glucose production in the liver and inhibit insulin secretion from pancreatic β-cells [51]. Thus, cortisol excess can be correlated with diabetes mellitus in clinical settings [62]. Insulin stimulates translocation of the GLUT4 glucose transporters from intracellular compartments to plasma membrane, increasing the rate of glucose utilization [66], however this action is inhibited by high levels of GC [23]. In insulin sensitive tissues, such as liver and skeletal muscle, GC also impair pathways involved in insulin receptor activation [3, 62, 67]. GC promote gluconeogenesis by stimulating the expression of phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase), the rate-limiting enzymes of this pathway, resulting in increased hepatic glucose output and hyperglycemia [23, 62]. GC decrease GLUT2 expression in pancreatic β-cells and impair calcium disposal on insulin secretory process, thus affecting its secretion [23, 68].

Obesity seems to be implicated in the development of insulin resistance [43, 46]. In fact, pathophysiological accumulation of lipids in liver has been identified as an independent risk factor for insulin resistance and MS [22]. Free fatty acids inhibit insulin secretion by pancreas and decrease glucose uptake [69]. GC release increases lipolysis generating free fatty acids into the circulation, which in turn impair insulin signaling pathways downstream of its receptor, thus promoting insulin resistance [46, 70]. In humans, the administration of dexamethasone decreases glucose oxidation, which can be due to an increase of free fatty acids plasmatic levels [66]. Thus, insulin resistance can result from an excess of visceral fat [46, 71]. On the other hand, insulin resistance impairs lypogenesis, thus increasing the plasmatic levels of free fatty acids, creating a vicious circle [70]. Adipokines play an important role on fat accumulation and insulin resistance [46, 70]. Adiponectin modulates a number of metabolic processes, including glucose homeostasis and fatty acid oxidation. It promotes insulin sensitivity and is negatively regulated by GC [28]. Hypoadiponectinemia is an independent risk factor for developing MS and type 2 diabetes mellitus [72]. Leptin plays a key role in regulating both energy intake and metabolism, and its circulating levels are directly proportional to body fat. Activation of hypothalamic leptin receptors suppresses appetite, induces satiety and increases energy expenditure [73]. High sustained concentrations of leptin released from adipose tissue result in desensitization of leptin receptor leading to leptin resistance [70, 74]. Unusually high circulating leptin levels and low adiponectin levels are generally exhibited by

patients with obesity, insulin resistance and MS [46]. Visfatin is a recently discovered adipokine with insulin-mimetic properties [43]. ACTH reduces the expression of both visfatin and adiponectin, thus promoting a temporary state of insulin resistance. Neuropeptide Y (NPY) release in response to HPA axis activation seems to promote abdominal fat storage. GC stimulate NPY hypothalamic secretion and up-regulate the NPY Y2 receptor in visceral fat. NPY increases food intake and storage of energy as fat and NPY Y2 receptor activation stimulate fat angiogenesis, proliferation and differentiation of new adipocytes [74].

GR signaling plays a significant role in metabolic regulation, and defects in this signaling pathway have been implicated in the development of several phenotypes of MS [75]. In fact, insulin resistance is associated with increased GR expression in skeletal muscle [62, 76, 77]. Several polymorphisms related to the HPA axis have been associated with HPA abnormal function and the development of MS [34, 57, 74, 78]. Chronic stress disorders are commonly associated with behavioral changes which lead to weight gain and metabolic abnormalities. Chronic stress seems to promote unhealthy behaviors such as a sedentary lifestyle, alcohol consumption, smoking and overeating [1]. Stress system affects the hypothalamic appetite-satiety centers therefore disturbing food intake [4]. The relationship between stress and food ingestion has been extensively investigated but has led to conflicting results [79, 80]. Increasing food intake during stress diminishes HPA axis response to stressors [81], which might explain why various individuals overeat when exposed to stress. Food ingestion to relieve anxiety is a harmful coping strategy and can lead to undesirable weight gain and obesity [61]. On the other hand, acute stress may be accompanied by a decrease on food consumption. Indeed, acute elevations of CRH can cause anorexia and stimulate energy expenditure. As mentioned before, NPY increases food intake and storage of energy as fat, and acute stress inhibits NPY release [4]. On the contrary, chronic stressful situations have the opposite effect and people experiencing a high stress reactivity tend to have a greater caloric intake, preferably dense calories [61]. In fact, long-term exposure to circulating GC seems to enhance consumption of high fat and highly palatable foods [74, 79-81] . GC also decrease energy expenditure [4] and diminish signs of satiety [61]. A high caloric intake is a mechanism that seems natural in response to fasting. However, this is not the case of psychological stress conditions, in which food is used rather to relief anxiety than to overcome fasting [19, 81, 82].

**11β-HSD1 role**

Tissue-specific dysregulation of cortisol metabolism is involved in the complex pathophysiology of obesity and the MS [56, 83]. In fact, 11β-HSD1 expression positively correlates with obesity and insulin resistance [56]. As mentioned before, circulating GC concentrations are occasionally abnormal in human obesity, however locally enhanced responsiveness to GC has also been implicated in MS development [1, 28, 62, 77, 78, 84].

Obese individuals have a tissue-specific 11β-HSD1 dysregulation [58, 65] in which 11β-HSD1 activity is found selectively increased in visceral fat depots and decreased in liver [32, 52, 85]. The relationship between the 11β-HSD1 function and metabolic disorders has been well established by studies using genetically modified rodent models. In fact, upregulation of 11β-HSD1 expression selectively in adipose tissue leads to a model of MS in mice [62, 78]. Mice with a similar degree of 11β-HSD1 overexpression in liver show an attenuated MS profile without visceral obesity [52]. On the contrary, knockout mice lacking 11β-HSD1 exhibit protection for MS features [31, 46, 52, 53, 65]. Peroxisome proliferator-activated receptors (PPAR) are a group of nuclear receptor proteins [86, 87] involved in adipocyte differentiation and fat redistribution to the periphery [53]. 11β-HSD1 knockout mice show higher expression of PPAR-ϒ receptor in all adipose tissue depots [77].

## Obesity as a chronic inflammatory state

In recent years, it has become clear that obesity is a state of chronic low-grade inflammation. The association between insulin resistance and the other components of the MS can be a consequence of their common outcomes as low-grade inflammation states [45, 46]. Adipose tissue releases cytokines that initiate a state of low-grade inflammation resulting in the metabolic, hemodynamic and vascular consequences of this state [45, 71]. The uninterrupted release of these pro-inflammatory adipokines is a chronic stimulus for HPA axis activation, creating a vicious cycle, in which hypercortisolemia promotes adipocyte growth and vice versa [4]. The pro-inflammatory cytokines, TNFα, IL-1 and IL-6 act synergistically activating HPA axis and increasing 11β-HSD1 expression in adipose tissue [23, 28, 53]. IL-6 concentrations have a strong correlation with visceral obesity [88] and are associated with insulin resistant [71, 89]. There is a positive association between TNFα concentrations and BMI, and this cytokine seems to be implicated in insulin resistance development [46, 59, 71, 73, 90].

**Glucocorticoids inhibitors as potential therapeutic targets**

To date, no single agent can ameliorate the underlying causes of MS [46]. Additional research is needed for novel agents to effectively treat the multiple abnormalities of this syndrome [40]. Antagonizing GC action has been taken as an approach to treat some of the MS features [23], leading to decreases in adiposity, glucose intolerance and insulin resistance [67], lowering fasting blood glucose and normalizing its postprandial levels [32, 76]. However, long- term systemic treatment with a GR antagonist may not be a viable option, since it can excessively activate the HPA axis causing adrenal hyperplasia and undesirable increase in cortisol, androgens and mineralocorticoids [62, 77, 78]. On the other hand, selective 11β-HSD1 inhibitors have shown considerable potential for MS treatment [28, 91]. Over the past years, clinical studies have been conducted for several 11β-HSD1 inhibitors [52, 62, 83, 92-94]. The ability to decrease intracellular cortisol levels in liver and adipose tissue, without altering circulating cortisol concentrations or responses to stress, is an exciting therapeutic strategy for obesity, type 2 diabetes mellitus and MS treatment. In fact, these drugs have been shown to ameliorate metabolic abnormalities, by improving lipid profile, insulin sensitivity, promoting glucose tolerance and blocking adipogenesis [28, 67, 68, 83, 85, 91-93, 95]. However, there are some concerns regarding the use of these drugs. 11β-HSD1 inhibition on hippocampus might decrease central feedback inhibition, which may cause HPA axis activation with increased GC release and enhancement of its effects in peripheral tissues. Moreover, non-selective compounds can potently inhibit 11β-HSD2 causing an apparent mineralocorticoid excessive release with sodium retention, hypertension and hypokalemia [77]. Nevertheless, PPARα and PPARϒ agonists are able to downregulate 11β-HSD1 activity in liver and adipose tissue, respectively [46, 96], which can be a promising approach. Emerging data suggest that dietary habits have a role on 11β-HSD1 modulation. Growing evidence suggest a variety of potential mechanisms of action trough which polyphenols prevent disease [97]. Naturally occurring 11β-HSD1 inhibitors include polyphenols, such as flavones and quercetin [52, 98]. Coffee has been reported to have anti-diabetic effects due to its ability to impair hepatic gluconeogenesis and inhibit 11β-HSD1 function [52, 99]. Dietary trans and saturated fatty acids appear to be involved in the development of MS, since they are able to increase local amplification of GC action in adipose tissue by upregulating 11β-HSD1 [52, 100]. Sucrose promotes simultaneously a decrease in hepatic 11β-HSD1 and an

increase in 11β-HSD1 in adipose tissue. Dietary sucrose increases H6PDH, which in turn, probably increases 11β-HSD1 activity and intracellular GC. These observations support the notion that increased activity of 11β-HSD1 in response to sucrose ingestion is able to cause obesity [52, 101]. The anti-obesity effect of vitamin A supplementation might be, in part, due to its ability to decrease 11β-HSD1 activity [102]. MS seems to be associated with vitamin D deficiency and accordingly vitamin D status optimization seems to improve MS features [103, 104]. A low-calcium diet alters GC metabolism leading to hepatic upregulation of 11β-HSD1 [105]; instead, a high intake of calcium, is associated with a low prevalence of MS [106].

## Conclusion

The major aim of this thesis was to review the literature concerning the involvement of glucocorticoids in the development of MS.

Epidemiological and clinical studies have documented that visceral obesity and other comorbidities of the MS are significantly correlated with stress-related conditions such as adverse life events and psychosocial problems. GC, crucial mediators involved in stress response, are required for proper metabolic and cardiovascular control, however when excessively released are implicated in a variety of chronic diseases. Indeed, chronic stress through dysregulation of the HPA axis response, leads to hypercortisolemia which in turn has an important role on promoting visceral obesity, one of the primary mechanisms in the pathogenesis of MS. Given the continuous and/or repetitive exposure to emotional, professional and social stressors, subjacent to the modern Western lifestyle, humans are chronically under stress. The more and more sustained link between psychological stress and the development of MS, highlights the importance of coping strategies to prevent or ameliorate high levels of stress in modern society. Physicians might have an important role, not only on the identification of patients under high levels of stress, but also through counseling and support concerning coping strategies to handle with daily challenges. To accomplish this, it would be crucial to include validated tools to measure psychosocial stress levels in anamnesis.

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| Upregulated genes — Pathway affected | Downregulated genes — Pathway affected |
|---|---|
| Leptin — Energy homeostasis | CRH — HPA axis regulation |
| GLUT4 — Glucose trasnport | POMC — HPA axis and appetite control |
| Glucose-6-phosphatase — Gluconeogenesis | TNF-α — Proinflammatory response |
| Hepatic PEPCK — Gluconeogenesis | Interleukin-6 — Proinflammatory response |
| Lipoprotein lipase — Lipid metabolism | Interleukin-8 — Proinflammatory response |
| Hormone sensitive lipase — Lipolysis | Adiponectin — Insulin signaling, Atherogenesis |
| VLDL receptor — Lipoprotein metabolism | Prolactin — Reproduction |
| Tyrosine aminotransferase — Amino acid catabolism | Osteocalcin — Bone metabolism |
| Tryptophan oxygenase — Amino acid catabolism | |

GLUT4: Glucose transporter 4; PEPCK: Phoshpoenolpyruvate carboxykinase; VLDL: Very low-density lipoprotein; CRH: Corticotropin-releasing hormone; HPA: Hypothalamic-pituitary-adrenal; POMC: Proopiomelanocortin; TNF-α: Tumor necrosis factor-α.

**Table 1**. Examples of glucocorticoid-sensitive genes involved in several important metabolic pathways.

(Adapted from Kyrou & Tsigos [1])

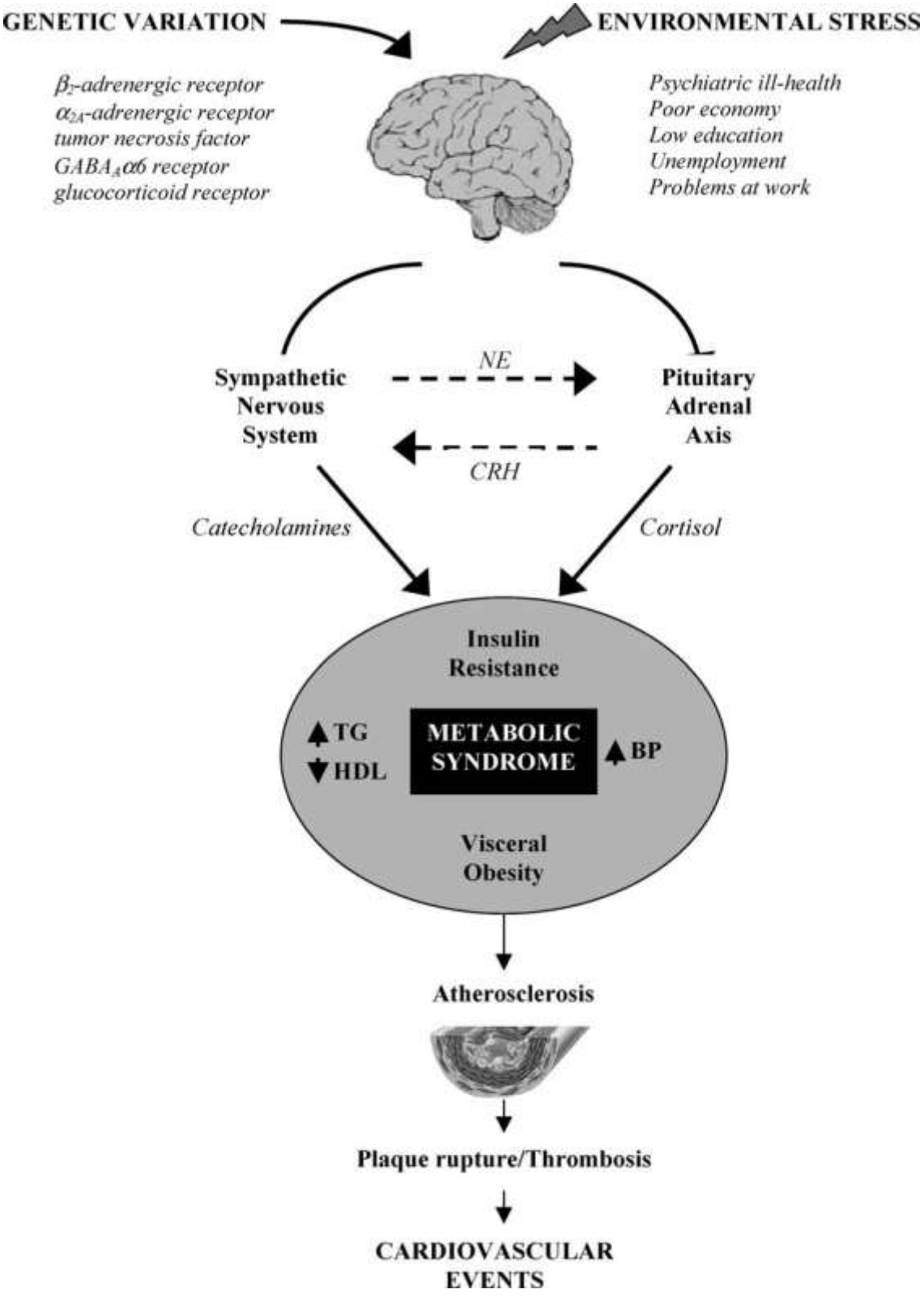


**Figure 1.** The stress response leads to activation of two major neurohumoral systems, the hypothalamic-pituitary-adrenal axis and the sympathetic-nervous-system which,

through the release of cortisol and catecholamines respectively, exert crucial roles upon energy metabolism, ultimately leading to the development of the features of the metabolic syndrome.

TG – Triglycerides; HDL - High-density lipoprotein; BP – Blood pressure

(Adapted from Rosmond R [34])

## Agradecimentos

A minha gratidão à Professora Doutora Laura Ribeiro, pela atenção, pelo espírito científico, estímulo, disponibilidade e carinho com que conduziu a orientação deste trabalho.

O meu agradecimento à Engenheira Beatriz Gonçalves pela revisão linguística.

**Annex 1**

**Instructions to authors for publication in Revista da Associação Médica Brasileira**

## Objectives and editorial policy

**Revista da Associação Médica Brasileira** (RAMB) is a bimonthly publication of the Brazilian Medical Association. It has been published continuously since 1954. journal's aim is to publish articles that contribute to the advancement of medical knowledge. RAMB is indexed by major biomedical and scientific indices, including SciELO, Scopus, Science Citation Index Expanded (SCIE), Web of Science, Institute for Scientific Information (ISI), Index Copernicus, LILACS, MEDLINE, and CAPES - QUALIS B3.Currently, RAMB publishes six issues per year and also offers a free version online (www.ramb.org.br). The print edition contains the articles in the original language (the journal accepts manuscripts in Portuguese, English or Spanish). All full-text content, in English, is simultaneously published online. The online edition of RAMB is made freely available upon publication (www.ramb.org.br).

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### Manuscript submission

All articles and letters should be sent only via website: http://ees.elsevier.com/ramb/

The journal accepts manuscripts in Portuguese, Spanish or English. All submitted manuscripts must contain the manuscript title, authors' full names, institution with which the work is associated, and the section for which the article is intended, in addition to an accompanying cover letter.

All material submitted for publication in RAMB cannot be in the evaluation process,

have already been published, or be submitted later to publication in other journals. All submissions are reviewed by the Editorial Board. In preparing the manuscript, authors should indicate which areas are related to the editorial article in order to be sent to a specific editorial review. The Editorial Board strongly recommends that the authors do a search for articles related to the theme and previously published in this journal or other journals indexed in SciELO, using the same keywords of the proposed article. These items should be considered by the authors in preparing the manuscript in order to stimulate the scientific exchange between the SciELO journals.

**What happens after submission**

Due to the large number of manuscripts received, the Editorial Board has adopted selection criteria for the peer-review process. On receipt, the manuscript is appraised by a RAMB editor for its conformity to the guidelines and preferences of the journal. As occurred with other journals, most submitted manuscripts do not pass this initial screening and are not sent out for peer review. Manuscripts are initially evaluated according to the following criteria: subjects fall within the scope of the journal and are relevant to our readership, the main topic has general medical interest, title and abstract are appropriate, writing is clear, study methods are well defined and appropriate (including, in the case of clinical trials, sample size, statistical analysis and Ethics Committee approval), results are clearly presented, and conclusions are reasonable and supported by the data. This procedure aims to reduce the time between date of submission and editorial acceptance or rejection, without hindering the submission process. Only manuscripts that have passed this initial screening by the editors will undergo complete peer review.

If a manuscript is deemed unsuitable for publication by the editors, the authors will be notified of this decision within 2 weeks (starting after the review for proper formatting). Peer-review reports with the reviewers' recommendations about acceptance or rejection will be sent to the authors as soon as possible. Although there are strict time limits on the peer-review process, most journals count on the remarkable collaborative spirit of the scientific community, which, due to their numerous duties, cannot always meet deadlines. Authors who are advised that their manuscript must be revised are required to provide a document detailing their response to each reviewer's

comment upon resubmission. In addition, revised manuscripts should clearly indicate changes made to the text using red font, and the original text should be kept and marked as underlined text.

Papers are published on a first-come, first-served basis, but the Editorial Board reserves the right to make case-by-case exceptions. After acceptance for publication, the authors will receive page proofs for checking, but corrections should be limited to typesetting errors. Proofs should be returned within two days. After final approval by the authors, no changes can be made to the paper.

## EDITORIAL BOARD

The Editorial Board consists of an Editor-in-Chief, Associate Editors, Assistant Editors, and an Advisory Board in the following areas: Clinical Medicine, Clinical Surgery, Public Health, Pediatrics, Obstetrics and Gynecology, Bioethics, Oncology, Emergency and Intensive Care Medicine, Pharmaceutical Medicine, and Evidence-based Medicine. The Editorial Board is responsible for the initial appraisal and acceptance or rejection of manuscripts submitted for publication.

## Journal style and manuscript preparation

Manuscript pages should be typed in font size 12pt, using 1.5 spacing. Leave a 3-cm margin on all sides. Manuscripts should not exceed 15 pages (30 lines each) in length. All pages should be numbered consecutively, except for the title page.

### Title page

The title page should contain the following information:

a) Title of the paper, concise and not exceeding 75 characters or one line.

b) First and last names of each author, with their current affiliation.

c) Name and address of the institution with which the work is associated.

d) Cover letter signed by all authors listed on the manuscript, who must have approved the submitted manuscript and be responsible for reported research. Only one author

should be indicated as the corresponding author. Provide full contact details for the corresponding author, including full mailing address, telephone and fax numbers, and e-mail.

e) Ethical aspects. The cover letter should disclose any potential conflicts of interest associated with the publication of the article (e.g., professional or financial conflicts and/or direct or indirect benefits) that might be perceived to influence the results or discussion reported in the paper. The cover letter should also include, if applicable, the date of approval from the Research Ethics Committee of the institution to which the authors are affiliated.

**Manuscript components**

Original articles must contain the following sections: Introduction, Methods, Results, Discussion, Conclusions, and References.

**Footnotes**

Footnotes should be kept to the minimum necessary, being marked in the text and listed on a separate paper after the abstract, under a subheading "Footnotes".

## ACKNOWLEDGMENTS

All those who contributed significantly to the manuscript, but do not meet the criteria for authorship, should be listed in this section. This section should appear at the end of the text, prior to the References.

## ABSTRACT

The abstract should not exceed 250 words and must include the following headings: Objective, Methods, Results, and Conclusion. After the abstract, the authors should provide a maximum of six key words in accordance with the Medical Subject Headings (MeSH) elaborated by the National Library of Medicine. Keywords in Portuguese and Spanish should be in accordance with the Health Science Descriptors (DeCS) elaborated by the Latin American and Caribbean Center on Health Sciences

Information (BIREME).

The abstract and keywords in Portuguese should be followed by an abstract and keywords in English. Articles written in Spanish should have an abstract in Spanish and in English. Articles written in English should have only an abstract in English.

**REFERENCES**

References should be numbered sequentially in the order in which they are cited in the text.

The names of all the authors up to six should be included, but when authors number seven or more, list the first six authors followed by "et al." Abbreviations of journal names should conform to those in Index Medicus, available at http://www.nlm.nih.gov/tsd/serials/lji.html or http://www.nlm.nih.gov/citingmedicine. If this is not possible, journal abbreviation should comply with the Brazilian Technical Standards Association (Associação Brasileira de Normas Técnicas, ABNT).

Examples are given below:

1. Parkin DM, Clayton D, Black RJ, Masuyer E, Friedl HP, Ivanov E, et al. Childhood leukaemia in Europe after Chernobyl: 5 year follow-up. Br J Cancer 1996;73:1006-12.

2. Vega KJ, Pina I, Krevsky B. Heart transplantation is associated with an increased risk for pancreatobiliary disease. Ann Intern Med 1996;124:980-3.

3. The Cardiac Society of Australia and New Zealand. Clinical exercise stress testing. Safety and performance guidelines. Med J Aust 1996; 164-282-4.

4. Cancer in South Africa [editorial]. S Afr Med J 1994;84:15.

5. Phillips SJ, Whisnant JP. Hypertension and stroke. In: Laragh JH, Brener BM, editors. Hypertension: pathophysiology, diagnosis and management. 2nd ed. New York: Raven Press; 1995.p.465-78.

6. Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis [serial on line] 1995 Jan-Mar [cited 1996 Jun 5];1(1):[24 screens]. Available from: URL: http://www.cdc.gov/ncidod/EID/eid.htm.

7. Leite DP. Padrão de prescrição para pacientes pediátricos hospitalizados: uma abordagem farmacoepidemiológica [dissertação]. Campinas: Faculdade de Ciências Médicas, Universidade Estadual de Campinas, 1998.

References to "unpublished data" and "personal communications" should be set in parentheses immediately after mention of the individual(s) name(s) in the text. For example: Oliveira AC, Silva PA and Garden LC (unpublished data). The author must obtain permission to use a "personal communication".

**REFERENCES IN THE TEXT**

Citations in the text are indicated by superscript Arabic numbers in the order in which they appear in the text. For example: In situations where normoglycemia is maintained,[6].

**FIGURES, TABLES, GRAPHS, SUPPLEMENTAL MATERIAL**

All tables, photographs, graphs, figures or supplemental material should be embedded within the manuscript. All material should provide clear and concise data that enhance, not duplicate, information in the text and should not exceed the TOTAL NUMBER OF THREE.

a) Submit only black-and-white, good-quality original figures (do not submit photocopies). Letters and symbols should be defined in the legend.

b) Figure and table legends must be self-explanatory and intelligible without reference to the text.

c) Each table, with title and legend, should be on a separate page.

d) Figures and tables, on separate pages, should have a title, show the first author's name, and be numbered separately using Arabic numbers in the order in which they appear in the text.

**ABBREVIATIONS**

The use of abbreviations should be kept to a minimum. When abbreviations are used, give the full term followed by the abbreviation in parentheses the first it is mentioned in the text. The abbreviation may appear in the text thereafter. Abbreviations used in tables and figures should be explained in the legend.

Use only generic names of drugs in the text.

## TERMINOLOGY

In order to employ official terms in our publications, RAMB adopts the Terminologia Anatomica: International Anatomical Terminology, approved by the International Federation of Associations of Anatomists (IFAA). For further information, consult the following references: FCAT - IFAA (1998) - International Anatomical Terminology - Stuttgart- Alemanha - Georg Thieme Verlag ou CTA-SBA (2001)- Terminologia Anatômica . S. Paulo . Editora Manole.

**Annex 2**

**Permission from the author Ioannis Kyrou to use table 1**

de: Sílvia Paredes <silvia.sparedes@gmail.com>
para: I.Kyrou@warwick.ac.uk
data: 6 de Fevereiro de 2013 às 00:04
assunto: Ask permission paper

Dear Professor Kyrou

My name is Sílvia Paredes and I am a medical student from the 6th year from the Faculty of Medicine of the University of Porto, Portugal.

To conclude my degree in medicine, I am preparing a master thesis about stress, obesity and diabetes and I would like to use one figure (table 1) from your paper entitled "Stress hormones: physiological stress and regulation of metabolism" (2009). Thus, I would like to ask your permission to use the referred figure in my thesis.

With my best regards,

Sílvia P.

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Dear Dr Paredes,

Thank you for your interest in our paper.

You have my permission to use the mentioned figure (table 1) from our paper entitled "Stress hormones: physiological stress and regulation of metabolism" in your thesis, provided of course that it is for academic - noncommercial - use only, and that you cite the related reference.

I hope that you find our paper helpful.

All the best with your thesis.

Best regards

Dr Ioannis Kyrou

**Annex 3**

**Permission from the author Roland Rosmond to use figure 1**

From: Laura Ribeiro <lribeiro@med.up.pt>

Date: 2013/3/15

Subject: MasterThesis

To: rolandrosmond@hotmail.com

Dear Prof. Rosmond,

My name is Laura Ribeiro and I work as Assistant Professor of Biochemistry at the Faculty of Medicine of the University of Porto in Portugal.

I am the supervisor of the master thesis of the student Silvia Paredes, a medical student from the 6th year.

To conclude the degree in medicine, she is preparing a master thesis about stress, obesity and diabetes and she would like to use one figure (fig 1) from your paper entitled "Role of stress in the pathogenesis of the metabolic syndrome" (2005).

Thus, we would like to ask your permission to use the referred figure in the master thesis.

Thanks in advance.

With my best regards,

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Dear Dr Ribeiro,

Please feel free to use any figure from the paper entitled "Role of stress in the pathogenesis of the metabolic syndrome" in the uppcoming Master Thesis.

Sincerely,

Roland Rosmond