Cushing syndrome, metabolic syndrome and inflammation: a suggested way out

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Summary

Endogenous hypercortisolism is associated with an increased cardiovascular risk. Cushing Syndrome (CS) shares many clinical features with metabolic syndrome, including abdominal obesity, systemic arterial hypertension, insulin resistance, dyslipidemia, and thrombotic diatesis. Moreover, CS represents an interesting pattern of an endocrine disorder associated with chronic low-grade inflammation which is not blunted by the resolution of hypercortisolism. The proinflammatory state that accompanies the metabolic syndrome may provide a connection between CS, inflammation and metabolic processes, which is highly deleterious for vascular functions. There is evidence that dietary patterns similar to those of the Mediterranean-style diet exert positive effects on almost all components of the metabolic syndrome and other conditions associated with, including inflammation, insulin resistance, and endothelial dysfunction. Therefore, an intervention strategy based on lifestyle changes may play a role in patients with resolution of hypercortisolism in which the anti-inflammatory effects of cortisol are lost and cytokines levels are increased. In this setting, the Mediterranean healthy dietary pattern may represent an innovative approach in order to improve the disease course and to reduce in the long term the cardiovascular risk of people affected by CS.

KEY WORDS: Cushing syndrome, metabolic syndrome, chronic low-grade inflammation, mediterranean diet.

Introduction

Glucocorticoids are considered essential hormones for life (1). Their levels raise up to ten times the normal values in stressing contexts, in order to provide more blood and energy supply to cells and tissues (2, 3). Glucocorticoids also act as potent anti-inflammatory agents stabilizing lysosomal membranes, inhibiting prostaglandins and leukotrienes synthesis, blocking the inflammatory response mediators and reducing vascular permeability, chemotactic activity and leukocycte diapedesis (4, 5). They also show immunosuppressor activity modulating lymphocyte, monocyte and eosinophil biological action and inhibiting antibodies production by B lymphocytes (6).
Cushing syndrome (CS) represents a clinical condition produced by the chronic exposure to glucocorticoids excess. The endogenous CS is caused by increased cortisol secretion by adrenocortical tumors or hyperplasia whereas the Cushing disease is usually sustained by excessive ACTH release from a pituitary corticotrope adenoma (and less frequently by ectopic ACTH or CRH production) (7, 8).
Endogenous hypercortisolism is associated with an increased cardiovascular risk. Untreated patients affected by CS undergo a fourfold mortality increase compared with general population (9). Clinical features linked to cardiovascular risk are visceral obesity, insulin-resistance, impaired glucose tolerance (IGT) and diabetes, hypertension, hyperlipidemia and pro-thrombotic state (10).
Adipose tissue is an endocrine organ producing different cytokines involved in vascular inflammation, endothelial dysfunction, insulin-resistance, hypertension, atherosclerosis, and bone remodeling (11). Each clinical condition accompanied by visceral adiposity, including CS, is characterized by an increased release of pro-inflammatory cytokines which are consid-

ered as biomarkers of future cardiovascular disease. In CS, the most important changes in cytokine milieu refer to adiponectin, as well as TNF α, IL-6 and PAI-1 (12, 13).

Adiponectin is an adipocyte-derived plasma protein with insulin sensitising, anti-inflammatory and anti-atherogenic properties. In human studies, plasma adiponectin levels are negatively correlated with obesity, anthropometric indices and insulin resistance, diabetic dyslipidaemia and cardiovascular disease (14, 15). Moreover, low plasma adiponectin levels are an independent risk factor for future development of type 2 diabetes (16). The findings of an inverse correlation between adiponectin increase and TNF- α decrease after weight loss in obese women (17), seem to give some credit to the hypothesis that raised TNF-a circulating levels in obesity are causally linked to reduced adiponectin concentrations.

The role of adiponectin in CS is still unclear. Some evidence suggests the dominant role of visceral adiposity instead of hypercortisolism in reducing adiponectin levels (12); on the other hand, low adiponectin levels have been found in non obese patients with CS, suggesting that hypercortisolism may impact adiponectin levels, independent of body weight (18).

IL-6 is generally increased in patients with CS, although its level may be influenced by the anti inflammatory effects of glucocorticoids. During the course of the disease, fluctuations in IL-6 levels are observed, as they are elevated in subclinical CS, decreased in overt CS, increased during post-operatory hypocortisolism (19) and diminished in the course of replacement therapy with corticosteroids (20).

Although C-reactive protein (PCR) is not an adipokine, its circulating concentrations are under the control of adipokines and its role in inflammation is well defined. Cross-sectional analyses have shown strong and independent associations of CRP levels with measures of body fat (21, 22). High levels of CRP in obesity also predict later development of diabetes (23).

CS represents an interesting pattern of an endocrine disorder associated with metabolic abnormalities and chronic low-grade inflammation which is not blunted by the resolution of hypercortisolism. Paradoxically, in the active phase of the disease, characterized by the onset of the several associated comorbidities, such as metabolic syndrome, diabetes and visceral obesity, the increase in adipokines levels is partly hidden by the potent anti-inflammatory effect played by cortisol. Long term studies in patients who have suffered from CS show a persistent increased cardiovascular risk in these individuals. Indeed, the accumulation of visceral fat does not recede after treatment, with persistently elevated levels of pro-inflammatory cytokines (12). It has been suggested that the persistence of the trunk fat is an effect of cortisol excess on the omental adipose tissue, stimulating the conversion of pre-adipocytes in adipocytes, thus contributing to increase of their number. Adipocyte hyperplasia also tends to remain constant even after the resolution of hypercortisolism (12, 24-26).

CS shares many clinical features with metabolic syndrome, including abdominal obesity, systemic arterial hypertension, insulin resistance, dyslipidemia, and thrombotic diatesis (10). The Adult Treatment Panel III (ATP-III) guideline suggests a working definition of the metabolic syndrome that includes the presence of at least 3 of the following characteristics: waist circumference > 102 cm in men and > 88 cm in women; triglycerides >150 mg/dL; HDL < 40 mg/dL in men and < 50 mg/dL in women; blood pressure > 130/85 mmHg; fasting glucose > 100 mg/dL (27). Insulin-resistance is thought to be a key feature of the syndrome, that is highly prognostic of cardiovascular events. Chronic inflammation may represent a triggering factor in the origin of the metabolic syndrome: stimuli such as overnutrition, physical inactivity, and ageing would result in cytokine hypersecretion and eventually lead to insulin resistance and diabetes in genetically or metabolically predisposed individuals. All the parameters included in the diagnosis of the metabolic syndrome are associated with a low-grade inflammation state (22, 28), which in turn is associated with an increased cardiovascular risk. The proinflammatory state that accompanies the metabolic syndrome may provide a connection between CS, inflammation and metabolic processes, which is highly deleterious for vascular functions.

Diet and inflammation

Lifestyle interventions are the initial therapies recommended for treatment of the metabolic syndrome (27). Whereas each risk factor of the metabolic syndrome (visceral obesity, atherogenetic dyslipidemia, elevated blood pressure, and hyperglycemia) can be dealt individually, the initial therapeutic approach to the metabolic syndrome should focus on reversing its root causes (29). In theory, the ideal diet should target many, if not all, the dietary components thought to influence the cardiometabolic risk, including all types of fat (saturated, polyunsaturated, monounsaturated, and *trans* fats), fiber, fish, carbohydrates, and proteins. There is evidence that dietary patterns similar to those of the Mediterranean-style diet exert positive effects on almost all components of the metabolic syndrome and other conditions associated with, including inflammation, insulin resistance, and endothelial dysfunction (30, 13).

Observational studies have examined the association of the Mediterranean diet with inflammatory markers in healthy persons (31-34), and they generally report inverse correlations. In a subsample of the Nurses' Health Study (33), a Mediterranean diet index score was inversely associated with markers of inflammation (circulating IL-6 and CRP) as well as markers of endothelial dysfunction (the adhesion molecules Intercellular Adhesion Molecule 1 [ICAM-1], Vascular Cell Adhesion Molecule 1 [VCAM-1] and soluble E-selectin [sE-selectin]). Similar findings were reported in the ATTICA study (32), involving 1514 men and 1528 women: subjects with greater adherence to the Mediterranean diet (those in the highest tertile) had

17% lower IL-6 and 20% lower CRP concentrations, compared with those in the lowest tertile in analyses that adjusted for other cardiovascular risk factors. In another observational study (34) made of obese subjects (625 men and 712 women with abdominal adiposity), adoption of the Mediterranean diet in conjunction with moderate physical activity was associated with a reduced likelihood of having high CRP levels by 72%.

Few intervention studies have been conducted to examine the effect of consuming the Mediterranean diet on markers of low-grade inflammation. In a randomized controlled study with 120 pre-menopausal obese women, the effects of a multidisciplinary approach (aiming at 10% weight reduction with a combination of a low-energy, Mediterranean-style diet and increased physical activity) were evaluated compared with a control group (17). Significant reduction in several markers of inflammation (CRP, IL-6 and IL-18) and an increase in adiponectin concentration were noted in the Mediterranean diet group compared with the control group. In another randomized controlled trial lasting 2 years (35), 180 subjects with the metabolic syndrome were assigned either to a Mediterranean-style diet or to a control group. After 2 years, inflammatory markers (CRP, IL-6, IL-7 and IL-18) decreased and endothelial function improved, compared with the control group. Interestingly, even after controlling for weight loss, the inflammatory markers declined more in subjects following the Mediterranean- style diet. In other related studies involving individuals with the metabolic syndrome, a consistent reduction in CRP concentration in the intervention group receiving the Mediterranean diet has been shown (36, 37). In the Prevención con Dieta Mediterránea (predimed) study, 772 asymptomatic subjects at high cardiovascular risk (diabetes or more than three CHD risk factors) were randomly assigned to a low-fat diet or one of two Mediterranean diets (38). Those allocated to the Mediterranean diets received nutritional education and either free virgin olive oil, or free nuts for 3 months. Both Mediterranean diets were beneficial in terms of significant reductions in serum IL-6, sICAM-1 and sVCAM-1 concentrations, while CRP concentration was reduced only in the Mediterranean diet supplemented with olive oil.

Interestingly, a recent meta-analysis (39) of epidemiological studies and randomized controlled trials considering a total of 534.906 participants showed that Mediterranean diet was associated with reduced risk or progression of metabolic syndrome.

Taken together, the results from these studies suggest that Mediterranean diets can lead to reduction in chronic low-grade inflammation and improvement in endothelial function.

Working hypothesis

CS is often associated with metabolic syndrome, visceral obesity and systemic low-grade inflammation, presenting elevated circulating concentrations of many inflammatory markers that are believed to play a role in causing both insulin resistance and other metabolic disturbances. Several studies indicate that metabolic syndrome generally persists after normalization of cortisolemia in CS patient. Thus, treatment of CS is not always sufficient to remove metabolic syndrome and specific approach for metabolic disturbances (high BP, dyslipidemia, IGT and diabetes, obesity) has to be addressed. Blood concentrations of inflammatory markers are lowered following weight loss, whether this is induced by diet or surgery, which most probably reflects the decrease in adipose tissue mass. A complementary role in reducing low-grade inflammation may be obtained with physical exercise (17, 32). In addition to the direct effect of foods and their constituents on postprandial inflammation, diet has an impact on chronic low-grade inflammation, manifested as the basal (i.e. fasting state) concentrations of inflammatory markers in the bloodstream, including cytokines, chemokines, acute-phase proteins, soluble adhesion molecules and cytokine receptors, etc. A healthy diet is associated with decreased low grade inflammation; in particular, protective components of a healthy dietary pattern are considered whole grains, fiber, vegetables, fruits, fish, Polyunsaturated Fatty Acids (PUFA), vitamin C, vitamin E and carotenoids (40). A meta-analysis comprising more than 1.5 million healthy subjects followed for a time ranging from 3-18 years and 40,000 fatal and nonfatal events, shows that greater adherence to Mediterranean diet is significantly associated with a reduced risk of both overall and cardiovascular mortality (41). Therefore, a healthy dietary pattern, as Mediterranean diet is thought to be, may be an important adjuvant treatment in improving the low-grade inflammation in overt CS. An intervention strategy based on lifestyle changes may also play a role in patients with resolution of hypercortisolism in which the anti-inflammatory effects of cortisol are lost and cytokines levels are increased. In this setting, the Mediterranean healthy dietary pattern may represent an innovative approach in order to improve the disease course and to reduce in the long term the cardiovascular risk of people affected by CS. Future research should focus on the long-term efficacy of this diet in people who suffer from CS, associated or not with metabolic syndrome, even after the resolution of hypercortisolism.

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