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Review

The role of low-grade inflammation in the polycystic ovary syndrome

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ABSTRACT

PCOS is not only the most frequent cause of oligomenorrhea in young women, but also a metabolic disorder characterized by insulin resistance, glucose intolerance, dyslipidemia, and obesity, especially the visceral phenotype. PCOS represents a broad spectrum of endocrine and metabolic alterations which change with age and with increasing adiposity. In fact, during adolescence and youth the predominant clinical manifestations of PCOS are menstrual abnormalities, hirsutism and acne, whereas in peri-menopausal and post-menopausal periods metabolic disorders and an increased risk for cardiovascular diseases prevail. The pathogenetic links between PCOS and metabolic or cardiovascular complications are still debated. However, recent evidence has been focused on a condition of low-grade chronic inflammation as a potential cause of the long-term consequence of the syndrome.

In this review we describe the state of low-grade inflammation observed in PCOS. In addition, we hypothesize the potential mechanisms responsible for the generation of this inflammatory state and the role played by low-grade inflammation in linking hyperandrogenism and insulin resistance with the metabolic and cardiovascular long-term complications of the syndrome.

Contents

Abbreviations: ADMA, asymmetric dimethylarginine; A-FABP, adipocyte fatty acid-binding protein; AGEs, advanced glycation endproducts; MA, molecular adhesions; Akt/PKB, Akt/protein kinase B; CRP, C reacting protein; ESR, erothrocyte sedimentation rate; ET-1, endothelin-1; FMD, flow-mediated dilatation; FFA, free fatty acids; GLUT-4, glucose transporter 4; GSK3, glycogen synthase kinase 3; HDL, high density lipoprotein; HIF-1α, hypoxia inducible factor-1α; HMG-CA, 3-hydroxy-3-methyl glutaryl-coenzyme A; HSL, hormone sensitive lipase; IMT, intima media thickness; IL-1, interleukin-1; IL-6, interleukin-6; IL-8, interleukin-8; IL-18, interleukin-18; iNOS, inducible Nitric Oxide Synthase; IP-10, interferon-inducible protein-10; IRS-1, insulin receptor substrate-1; LDL, low density lipoprotein; MCP-1, monocyte chemotactic protein-1; MIF1, macrophage migration inhibitory factor-1; MMP2, matrix metallopeptidase 2; MMP9, matrix metallopeptidase 9; MPV, platelet mean volume; NF-κB, nuclear factor-κB; NO, nitric oxide; PAF, platelet activating factor; PAI-1, plasminogen activator inhibitor-1; PCOS, polycystic ovary syndrome; PDGF, platelet-derived growth factor; PPAR-, peroxisome proliferator activated receptor-; RANTES, regulated on activation normal T expressed and secreted; RAS, renin–angiotensin system; sE-selectin, soluble E selectin; sICAM-1, soluble Intercellular Adhesion Molecule-1; sVCAM-1, soluble Vascular Cell Adhesion Molecule-1; SOCS3, suppressor of cytokine signaling 3; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α; TRL4, Toll like receptor 4; VEGF, vascular endothelial growth factor; vWF, von Willebrand Factor.

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1. Introduction

PCOS, one of the most common causes of female infertility, affects approximately 6–8% of reproductive-age women (Azziz et al., 2004). The diagnostic criteria of PCOS, which have changed over the years, are currently based on the presence of clinical/biochemical hyperandrogenism in association with chronic oligo-anovulation and/or polycystic ovaries at ultrasound, after the exclusion of other causes (PCOS Consensus Workshop Group, 2004). Insulin resistance has never been included in the diagnostic criteria of the syndrome, although it is present in 50–70% of PCOS women, regardless of coexistent obesity, and is a triggering factor in the pathogenesis of ovarian and adrenal hyperandrogenism, through different mechanisms described in detail elsewhere (Ehrmann, 2005). Hyperandrogenism, in turn, contributes to the generation of insulin resistance through the stimulation of lipolysis, and therefore the increased blood availability of FFA, and the modification of muscle skeletal structure by the increment of less insulin sensitive type 2 muscle fibers and the decreased density of capillaries and of glycogen content (Cortón et al., 2007). Androgens, in addition, promote the differentiation of pre-adipocytes into mature adipocytes, particularly at visceral level, thus facilitating the development of the abdominal obesity phenotype, a condition that has been described in approximately 60% of PCOS women and that has been associated with a worse clinical and biochemical phenotype (Pasquali et al., 2006).

The mechanisms by which hyperandrogenism, insulin resistance and abdominal obesity influence each other in PCOS have been sufficiently clarified over the years. However, it still remains unclear how and whether the three factors play a specific role in the development of metabolic (Legro et al., 2001, 1999; Gambineri et al., 2009; Ehrmann et al., 1999) or cardiovascular events (Dahlgren et al., 1992; Talbott et al., 1995) in PCOS. Some studies have associated insulin resistance and hyperinsulinemia with low levels of HDL-cholesterol, and through this factor with the metabolic syndrome (Gambineri et al., 2009), with impaired glucose tolerance and type 2 diabetes (Gambineri et al., 2004), or with ventricular diastolic dysfunction (Tiras et al., 1999) and vascular stiffness (Orio et al., 2004a; Kelly et al., 2002; Lakhani et al., 2000; Meyer et al., 2005). However, hyperandrogenemia has also been associated with glucose intolerance in PCOS (Gambineri et al., 2004), and with other aspects of the metabolic syndrome, such as hypertension (Chen et al., 2007). A state of low-grade chronic inflammation, which has recently been described in women with PCOS, is likely to represent one of the potential links between hyperandrogenism, insulin resistance or abdominal obesity and the long-term consequences of the syndrome.

2. The concept of low-grade inflammation

The term low-grade inflammation identifies a condition characterized by the increase in the circulation of several mediators of inflammation in response to a noxious stimulus. They include classic molecules, such as TNF-α, IL-1, IL-6, CRP, as well as molecules originated from hyperneutrophilia or lymph monocytosis, such as ESR and white cell count.

3. Low-grade inflammation in obesity, type 2 diabetes, and cardiovascular diseases

Obesity, particularly the visceral phenotype, is frequently associated with insulin resistance, dyslipidemia, type 2 diabetes and cardiovascular disorders (Fujioka et al., 1987; Kanai et al., 1990) and the link between these conditions has been assumed to be chronic inflammation. Recently, in fact, visceral obesity has been defined as a state of low-grade inflammation because visceral adipose tissue is able to produce cytokines (TNF-α, IL-6, and IL-1), chemokines (IP-10, IL-8, IL-18, MCP-1, and RANTES), and other adipokines (FFA, PAI-1, leptin, resistin, visfatin, and adiponectin) that act, directly or indirectly, as mediators of systemic inflammation. The hinge mechanism of the inflammatory process in general and of that observed in the adipose tissue has been related to hypoxia caused by a reduced tissutal vascularization. In obesity, in fact, a decrease of 30–40% of blood flow per unit of adipose tissue has been observed, mainly related to two factors (Summers et al., 1996; Jansson et al., 1998; Karpe et al., 2002): (i) the reduction in capillary vasodilatation and the increment in capillary vasoconstriction, due to the increased release of angiotensin II and increased activity of the sympathetic system (Goossens et al., 2004); and (ii) the compression of stroma blood vessels by hypertrophic adipocytes, a phenomenon particularly evident in peripheral adipocytes (Bell et al., 2008; Brahimi-Horn and Pouyssegur, 2007; Hosogai et al., 2007). In turn, hypoxia may increase the availability of several factors involved in the process of inflammation. One of the most important is HIF-1 (Semenza, 2002; Papandreou et al., 2006; Cancello et al., 2005), whose amounts are significantly increased through the inhibition of the ubiquitin–proteasome complex which is involved in the degradation of HIF-1 (Semenza, 2002; Papandreou et al., 2006; Cancello et al., 2005; Minet et al., 2001). Once activated, HIF-1α moves into the nucleus where it dimerizes with HIF-1β and the derived complex then binds to the promoter of several target genes involved in the process of inflammation, such as VEGF (Semenza, 2002; Papandreou et al., 2006; Cancello et al., 2005; Minet et al., 2001), TNF-α, IL-1, IL-6, MCP-1, PAI-1, MIF1 (Koong et al., 2000; Calandra et al., 1995), iNOS, MMP9, and MMP2 (Semenza et al., 2000). Another factor induced by hypoxia is NF-κB which migrates into the nucleus where it activates the transcription of several inflammatory genes (TNF-α, IL-1, IL-6, iNOS, and MA) (Michiels et al., 2002; Baeuerle and Henkel, 1994). The release of these cytokines and chemokines, in association with the abundance of necrotic adipocytes induced by tissue hypoxia, in turn determines a marked recruitment of macrophages into the adipose tissue, especially in the visceral adipose tissue (Cinti et al., 2005; Zeyda et al., 2007). These 'recruited macrophages', predominantly of the M1 subclass, (Lumeng et al., 2007) seem to be responsible for the maintenance of the adipose tissue inflammation, by the activation of Th1 (Gordon, 2003), and for the progressive adipocyte dysfunction and, ultimately, adipocyte necrosis, which maintains the mechanism through a vicious circle (Fig. 1). An additional mechanism involved in the maintenance of adipose tissue inflammation is represented by the angiogenesis hypoxia induced by the release of several angiogenetic factors like VEGF, PDGF, TNF-α, MIF, IL-6, IL-8, TGF-β, angiopoietin, leptin, and adiponectin from adipocytes and macrophages (Sierra-Honigmann et al., 1998; Shibata et al., 2004; Ferrara and Kerbel, 2005; Pang et al., 2008).

Interestingly, the chronic inflammatory state associated with obesity is also related to the insulin resistance state (Sell and Eckel, 2009), and endothelian dysfunctions (Yudkin et al., 1999).

Hypertrophic adipocytes release FFA as a result of increased activity of HSL. In turn, mimicking lipopolysaccharides, these FFA act in a paracrine manner on resident macrophages and on adipocytes by binding to the TRL4 (Song et al., 2006), which results in a stimulation of the release of cytokines and chemokines by both cells, together with an alteration of the insulin signaling pathways through the decrease in the phosphorylation of serine/threonine protein kinase Akt/PKB and of GSK3 (Song et al., 2006). In synergy with FFA, the release of TNF-α by macrophages and adipocytes determines a stimulation of lipolysis, with a consequent further increase of FFA, a reduction of adiponectin and of PPAR- expression, and an increase in serine phosphorylation of the insulin receptor and its substrate 1 (IRS-1). All these mechanisms con-