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Review

Oxidative stress and cardiovascular complications in polycystic ovarian syndrome

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ABSTRACT

Polycystic ovarian syndrome (PCOS) is a complex endocrine condition which is associated with metabolic and cardiovascular complications. It is elevated to a metabolic disorder with significant long term health ramification due to the high prevalence of insulin resistance (IR), impaired glucose tolerance, type 2 diabetes (T2D), dyslipidemia and numerous cardiovascular risk factors in PCOS women. This article concentrates on the recent developments in the regulation of oxidative stress (OS) in PCOS and on the association between PCOS and CVD outcomes.

The prognostic events that define the severity of PCOS and involvement of cardiovascular risk in PCOS include endothelial dysfunction (ED) and impaired cardiac structure. Fact is that, in PCOS women, the circulating biomarkers of OS are in abnormal levels that are independent of overweight, which depicts the participation of OS in the pathophysiology of this common derangement. In addition, hyperglycemia (HG) *per se*, promotes reactive oxygen species (ROS) generation in PCOS. When the destructive ROS outbalances the concentration of physiological antioxidants, OS occurs. The resultant OS, directly stimulates hyperandrogenism and causes extensive cellular injury, DNA damage and/or cell apoptosis. To further the burden, the total serum antioxidant level in PCOS women is compromised, which diminishes the body's defense against an oxidative milieu. Thus, it is evident that OS regulates several cellular mechanisms in PCOS. Improving our understanding about the regulation of OS, critical role of ROS and protein biomarkers in PCOS should lead to novel therapeutic strategies in addressing PCOS-induced CVD. Besides, it is possible that the beneficial effects of dietary or therapeutic antioxidants have significant clinical relevance in PCOS.

Contents

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Introduction

PCOS is one of the most common endocrine and metabolic disorders affecting 6–14% of women of child-bearing age [1]. Hyperinsulinemia and hyperandrogenemia are the two principal characteristic features of PCOS [2]. While PCOS, being a polygenic trait, is caused by a number of underlying genetic interactions and predispositions, the environmental factors including diet, exercise, pollution and stress significantly contribute to the disease development [3]. Analysis of cardiovascular risk factors such as hyperinsulinemia and abnormal plasma lipids in PCOS women suggest that they are at a greater risk for developing CVD. These findings emphasize that the significance of PCOS for women's health extends far beyond the implications for reproductive function [4]. Due to the multi-etiologic nature of PCOS which has combinations of clinical complications including impaired glucose tolerance, prevalence of T2D, increased risk of hypertension, dyslipidemia, and elevated ED, broader clinical diagnostic criteria is required for its diagnosis. Of the said complications in PCOS, ED is a crucial factor in the development of CVD. ED is caused by an imbalance between the production and bioavailability of endothelium-dependent relaxing factors and endothelium-dependent constricting factors, characterized as OS, which is associated with increased ROS generation and decreased antioxidant concentration. ED contributes to the increased risk of atherosclerosis and CVD in insulin-resistant subjects with PCOS [5]. In affected women, HG, independent of obesity, is known to promote ROS production that leads to ED. The presence of OS in PCOS women is well documented in infertile women [6], hence, the purpose of this review is to bring together the current information on the (i) role of OS in the development of PCOS and (ii) association between PCOS and CVD outcomes. Specific emphasis is placed on the mechanisms by which OS contributes to cardiovascular pathophysiologies in PCOS setting. Here we, discuss the potential circulating protein levels as biomarkers of vascular disease in PCOS.

ROS generation in the endothelium

The endothelial lining of blood vessels in the heart is an active tissue that plays a crucial role in maintaining the cardiovascular homeostasis, including important functions such as the regulation of vascular tone, tissue perfusion, myocardial function, vascular permeability, blood fluidity, anticoagulant activity and inflammatory responses [7]. Nitric oxide (NO), a critical regulator of vascular homeostasis, is generated by the endothelial cells (EC). It is formed from its precursor L-arginine *via* the enzymatic action of endothelial NO synthase (eNOS) in the plasma membrane caveolae, in the presence of co-factors such as tetrahydrobiopterin, flavin-adenine-dinucleotide, flavin-mononucleotide, heat shock protein-90 and nicotinamide-adenine-dinucleotide-phosphate that are necessary for optimal eNOS activity and NO production. Decreased bioavailability of the substrate L-arginine or the co-factors results in eNOS uncoupling and leads to increase in intracellular superoxide (SO) generation [8].

Endothelial cells are involved in the generation of ROS and reactive nitrogen species (RNS) such as SO, hydrogen peroxide (H_2O_2), NO, peroxynitrite ($ONOO^{\bullet-}$), hydroxyl radicals, and other free radicals [9]. Most ROS are generated from mitochondria, due to leakage of electrons from electron transport chain whereas other sources include NAPDH oxidase (Nox), xanthine oxidase (xox), cytochrome P450 and uncoupled eNOS. Superoxide production generally involves one-electron reduction of molecular O_2 which rapidly gets converted into H_2O_2. Superoxide then reacts with NO at a significantly faster rate than with superoxide dismutase (SOD), in which NO may outcompete SOD and react with SO to form $ONOO^{\bullet-}$ that exacerbates cytotoxicity. Of the enzymatic antioxidants, SOD degrades SO to H_2O_2 while, catalase and glutathione peroxidase (GPx) degrade H_2O_2 into water. Thus, evidence demonstrate that redox signaling, in response to highly regulated ROS production by specific enzymes and ROS-dependent inactivation of NO, is a critical mechanism in the pathogenesis of several cardiovascular disorders [10].

It is established that PCOS is associated with OS in which production of free radicals is followed by decreased serum total antioxidant levels. The potential sources of free radicals in PCOS include adipose tissue, fatty acid oxidation, hyperglycemia and enzymatic sources (Nox) from mononuclear cells. Besides Nox of MNCs, the major enzymatic source of free radicals, different isoforms of Nox found in the endothelium, fibroblasts, vascular smooth muscle cells and myocardial cells contribute to the ROS generation in PCOS. These cardiovascular forms of enzyme are the major intrinsic sources of ROS and are strongly associated with atherosclerosis and hypertension [132]. Recently, an increased activity of another ROS-producing enzyme, xox has been shown in PCOS women [133]. Hence, upregulated endothelial xanthine oxidase is another important source of free radicals in PCOS.

Oxidative stress in PCOS

Preservation of physiological cellular functions depends on the homeostatic balance between oxidants and antioxidants. This ratio is altered by an increase in the levels of ROS and/or RNS and/or a decrease in the antioxidant defense mechanisms [11]. Excessive ROS overpowers the body's natural antioxidant defense system, creating an environment unsuitable for female physiological reactions. In other words, reproductive cells and tissues will remain stable only when the antioxidant:oxidant status is in balance. Oxidative stress generally known to be present in PCOS women regardless of whether they are lean or have metabolic abnormalities, has been documented in infertile PCOS women [12]. Despite the fact that OS influences female reproductive system, it also regulates cardiovascular system [13]. The profound factors in PCOS that increases OS are IR and HG, however, non-obese PCOS patients without IR were also reported to have elevated oxidant status [14]. Although no difference in cardiovascular risk is reported in some studies [15], ED that precedes evident CVD [16] is reported in even young women with PCOS [17]. The presence of high inflammatory and endothelial markers in PCOS setting causes ED [18]. In fact, subclinical CVD is reported in the obese PCOS group [19].

Lipid peroxidation process revealing malonyldialdehyde (MDA) is accepted to reflect OS [20], while SOD, an antioxidant enzyme, serves as a defensive mechanism of the body. Intracellular and cell wall damage due to increased ROS leads to an increase in MDA levels. While SOD defends the body against free oxygen radicals and balances the increased oxidative load levels [21]. It has been shown that lipid peroxidation and ROS formation causes oxidative stress and damage. Detoxification of these products occurs through transformation of the reduced form of glutathione (GSH) to oxidized form (GSSG) by the enzyme, glutathione peroxidase. The oxidized glutathione is converted back to the reduced form by the enzyme glutathione reductase. When cells are exposed to excessive amounts of oxidants, due to the formation of oxidized dimer form of glutathione (GSSG) that exceeds the metabolic limit, there will be oxidative stress [22]. Indeed, a reduction in the GSH/GSSG ratio and GSH levels occurs due to the increase in ROS production and a decrease in oxygen consumption which results in impaired mitochondrial function in PCOS women [23,24].

IR is highly prevalent in PCOS women than in the control [25–27]. A compensatory increase in pancreatic β-cell insulin secretion occurs in the presence of IR to maintain glucose homeostasis [28]. In PCOS, this compensatory insulin hyper-secretion is independent