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# Advanced glycation end products: A link between metabolic and endothelial dysfunction in polycystic ovary syndrome?

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ARTICLE INFO

*Article history:*
Received 26 April 2015
Accepted 17 August 2015

*Keywords:*
Polycystic ovary syndrome
Advanced glycation end products
RAGE
Inflammation
Endothelial dysfunction

ABSTRACT

Polycystic ovary syndrome (PCOS), a heterogeneous syndrome of reproductive and metabolic alterations, is associated with increased long-term risk of cardiovascular complications. This phenomenon has been linked to an increase in oxidative stress and inflammatory markers. Advanced glycation end products (AGEs) are pro-inflammatory molecules that trigger a state of intracellular oxidative stress and inflammation after binding to their cell membrane receptors RAGE. The activation of the AGE–RAGE axis has been well known to play a role in atherosclerosis in both men and women. Women with PCOS have systemic chronic inflammatory condition even at the ovarian level as represented by elevated levels of serum/ovarian AGEs and increased expression of the pro-inflammatory RAGE in ovarian tissue. Data also showed the presence of sRAGE in the follicular fluid and its potential protective role against the harmful effect of AGEs on ovarian function. Thus, whether AGE–RAGE axis constitutes a link between metabolic and endothelial dysfunction in women with PCOS is addressed in this review. Additionally, we discuss the role of hormonal changes observed in PCOS and how they are linked with the AGE–RAGE axis in order to better understand the nature of this complex syndrome whose consequences extend well beyond reproduction.



## 1. Introduction

Polycystic ovary syndrome (PCOS) is a heterogeneous syndrome that causes reproductive and metabolic alterations [1,2]. The reported prevalence of PCOS ranges between 2.2% to 26% in various countries, depending on the recruitment process of the study population, and the criteria used for its definition [3–7]. PCOS is associated with hyperandrogenemia

*Abbreviations:* AGE, advanced glycation end products; RAGE, cellular receptor for AGEs; sRAGE, soluble receptor for AGEs; CVD, cardiovascular disease; PCOS, polycystic ovary syndrome; MG, synthetic methylglyoxal; eNOS, endothelial nitric oxidase synthase NOS; NO, nitric oxidase; ROS, reactive oxygen species; AMH, anti-Mullerian hormone; IVF, in vitro fertilization; TF, tissue factor; TNF-α, tumor necrosis factor alpha; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone.

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http://dx.doi.org/10.1016/j.metabol.2015.08.010
0026-0495/

[4], insulin resistance (IR) [8,9], impaired glucose tolerance, type 2 diabetes [2], dyslipidemia [10–12], and cardiovascular disease (CVD) [13,14].

Moreover, evidence indicates that low-grade chronic inflammation in PCOS could represent a reason for the long-term metabolic and cardiovascular complications [15]. CVD is one of the leading causes of female morbidity and mortality in the United States [16]. Given its high prevalence, PCOS may potentially account for a significant proportion of atherosclerotic heart disease observed in women [17], independent of obesity or age [18–20]. These findings were reflected by increased coronary calcium, increased carotid intima- media thickness, and endothelial dysfunction [21,22].

One of the emerging pro-inflammatory molecules that are elevated in PCOS is advanced glycation end-products (AGEs). Women with PCOS have elevated serum AGEs and an upregulation of the membranous pro-inflammatory receptor RAGE (receptor for AGEs) was demonstrated in their ovaries [23]. With the increasing evidence for AGEs' role in PCOS-associated inflammation and their role in CVD, this review aims to present an update on the mechanisms by which AGEs act and how the AGE–RAGE axis could potentially play a pivotal role in the pathophysiology of CVD observed in women with PCOS.

## 2. How do AGEs Form?

AGEs can be formed either endogenously or exogenously [24–26]. Endogenously, advanced glycation takes place in all cell types and refers to a reaction, known as the Maillard reaction, between reducing sugars and amino residues present in proteins, lipids, and DNA. This is followed by rearrangements and final cross-linking to generate AGEs leading to loss of protein structure and function, followed by some instances with cellular apoptosis. Examples of AGEs include $N^{\varepsilon}$-(carboxymethyl) lysine (CML), pyrraline and pentosidine [26]. AGEs accumulate in the serum and tissues with aging and their formation is accelerated by hyperglycemia, IR, obesity, metabolic syndrome, hypoxia and oxidative stress [26].

Exogenous AGEs could be introduced into the circulation together with nutrients processed by common methods such as dry heat or other food processing methods for example ionization [27]. Human and animal studies demonstrated that about 10% of AGEs contained in a meal could be absorbed into the circulation, of which two-thirds remain in the body for 72 h [28,29]; a period of time long enough to promote oxidative stress and cause tissue injury [28]. Diamanti-Kandarakis et al. demonstrated that in female rats, a high-AGE diet for 6 months increased serum AGEs' levels and caused higher deposition of their pro-inflammatory RAGE in the ovarian tissue and caused an increase in ovarian weight (usually observed in women with PCOS) compared to animals fed a low-AGE diet [30]. These data provide evidence for the impact of dietary AGEs on reproductive dysfunction, causing a pattern observed in PCOS.

Another exogenous source of AGEs is smoking [31]. Both the aqueous extracts of tobacco and cigarette smoke contain glycotoxins—highly reactive glycation products that can rapidly induce AGE formation on proteins. Smoking has been shown to worsen the already elevated risk for metabolic syndrome in women with PCOS [32]. Whether this phenomenon is partly induced by AGEs remains to be determined [31].

## 3. Different Types of AGEs' Receptors

AGEs could cause tissue injury via cross-linking with extracellular matrix of tissues throughout the body or by binding to RAGE on the surface of various cells such as endothelial cells and mononuclear phagocytes [33]. RAGE, a member of the immunoglobulin superfamily, has transmembrane, cytosolic and extracellular domains. RAGE is expressed in many tissues including the vascular system [34]. The binding of AGEs to RAGE causes intracellular signaling that leads to reactive oxygen species (ROS) production mainly via activation of the pro-inflammatory transcription factor (NF-κB) and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (Fig. 1). Subsequently, there is an increase in the production of pro-inflammatory cytokines (such as IL-1, IL-6 and IL-8), chemokines, apoptosis regulators such as bcl-2, Fas, adhesion molecules (such as VCAM-1 and ICAM-1), as well as macrophage and platelet activation [35,36]. Interestingly, ROS production caused by RAGE activation causes a positive feedback loop therefore up-regulating RAGE expression [37,38], thus leading to exacerbation of the inflammatory processes. Induction of RAGE has been documented in inflammatory processes, atherosclerosis and recently PCOS [34,39].

The soluble form of RAGE (sRAGE) is a product of both splicing of *RAGE* gene and/or cleavage of membrane-bound RAGE by proteases belonging to the zinc-dependent metzincin family of metalloproteases [40]. Following its formation, sRAGE receptors circulate and act as decoy for AGEs by binding them and thus competitively inhibiting AGE–RAGE interaction and its downstream pro-inflammatory signaling [41]. In many instances, sRAGE is often considered an anti-inflammatory receptor.

## 4. The Role of Hormonal Change Observed in PCOS

The metabolic–hormonal complexity observed in PCOS represents a biological model illustrating the relationship between hormonal pattern and cardiovascular risk profile [42,43]. The key endocrine abnormalities of the reproductive axis include accelerated GnRH pulsatile activity, increased secretion of pituitary LH, theca-stromal cell hyperactivity and hypofunction of the FSH-granulosa cell axis [44,45]. Increased LH pulse frequency and amplitude leading to persistently increased LH levels may directly enhance theca androgen synthesis. On the other hand, it has been suggested that elevated LH levels result from an impaired negative feedback on LH secretion, due to excessive androgen action on the hypothalamic–pituitary axis [46]. Insulin may play a part in the development of the typical increased amplitude and frequency of GnRH and LH pulse secretion seen in PCOS since, elevation of LH and GnRH secretion in response to insulin infusion have been observed in vitro, both in dose-dependent and in time-dependent fashions [45,47]. The compensatory hyperinsulinemia is considered to be a promoter of the hyperandrogenism and chronic oligo- or