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

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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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[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^{ε}-(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

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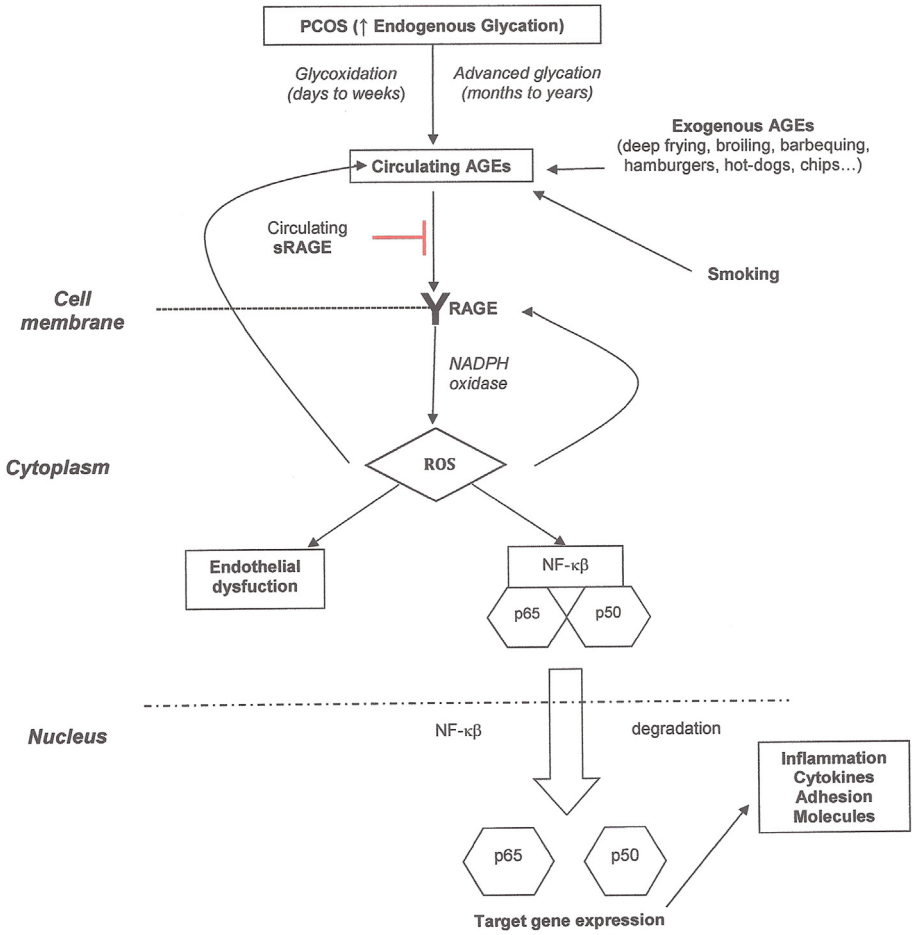

Fig. 1 – A schematic diagram of AGEs forming and AGE–RAGE signaling cascade in endothelial cells through translocation of NFκB into the nucleus.AGEs are formed either *endogenously* or *exogenously*. Intracellular effects are mediated through binding of AGEs to specific cellular receptors RAGE, leading to ROS production via activation of NADPH oxidase with subsequent nuclear translocation of NF-κB, which targets several genes involved in inflammation, immune response, and apoptosis. Additionally, increased superoxide production causes an increased formation of AGEs and over-expression of RAGE, acting as positive-feedback loop and thus worsening the inflammatory response. sRAGE acts as a decoy for ligands, thus competitively inhibiting AGE–RAGE interaction and its downstream pro-inflammatory signaling. *AGEs (advanced glycation end products), cellular receptor for AGEs (RAGE), soluble receptor for AGEs (sRAGE), NF- B (nuclear factor kappa-light-chain-enhancer of activated B cells), ROS (reactive oxygen species).*

anovulation, particularly when there is concomitant obesity [48–51].

Insulin can also act indirectly to raise the serum concentration of free testosterone, the level of which does not seem to be tightly regulated in women, by inhibiting the hepatic production of sex-hormone–binding globulin (SHBG) [52]. Therefore, an improvement in insulin sensitivity in women with PCOS leads to a decrease in ovarian androgen biosynthesis, an increase in the concentration of SHBG, and a resultant decrease in free testosterone concentration [53]. Interestingly, serum levels of AGEs correlate with the hormonal abnormalities observed in women with PCOS [23,54]; for instance, we have shown a correlation between serum AGEs and serum testosterone [54].

Additionally, it has been reported that changes in dietary AGEs parallel changes in insulin sensitivity, oxidative stress and hormonal status in women with PCOS and therefore lowering the concentration of AGEs in food may improve these variables [55]. Serum levels of AGEs, testosterone, oxidative stress, insulin and HOMA-IR index were significantly increased on the isocaloric diet with high AGEs compared to the hypocaloric diet with ad-libitum AGEs content diet and subsequently decreased on the isocaloric diet with low AGEs diet (compared to high AGEs) ($p < 0.05$ for all parameters). BMI remained unaltered throughout the high AGEs and low AGEs periods compared to the hypocaloric diet period. Serum AGEs and dietary AGEs were strongly correlated with insulin during low AGEs period. Such findings may have important clinical implications for women with PCOS, as dietary habits seem to play a role in the pathophysiogy of the syndrome [56]. Additionally, dietary AGEs, regardless of BMI, may modify both metabolic and hormonal parameters of women with

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PCOS [55]. Moreover, the diet-induced elevation in AGEs' levels and the increased oxidative stress may directly induce insulin-signaling defects [57].

5. What Happens to Circulating sRAGE and Ovarian AGEs and RAGE in PCOS?

Serum AGEs are distinctly elevated in women with PCOS compared to women who only have the isolated characteristics of PCOS syndrome [23]. Diamanti-Kandarakis et al. demonstrated that women with PCOS exhibited statistically higher AGE levels (7.96 ± 1.87 U/ml, $p < 0.001$) compared to those with isolated hyperandrogenaemia (5.61 ± 0.61 U/ml), anovulation (5.53 ± 1.06 U/ml), women with PCO morphology only (rather than PCOS) on ultrasound (5.26 ± 0.25 U/ml) and controls (5.86 ± 0.89 U/ml) [23]. Moreover, compared to women without PCOS, insulin resistant women with PCOS (without overt hyperglycemia) have higher levels of serum AGEs (9.81 ± 0.16 *vs.* 5.11 ± 0.16, $p < 0.0001$), and up-regulation of RAGE expression in their monocytes (30.91 ± 10.11 *vs.* 7.97 ± 2.61, $p < 0.02$) [54]. Additionally, IR indices such as Quantitative Insulin Sensitivity Check Index (QUICKI) and Homeostasis Model Assessment (HOMA) showed a positive correlation with serum AGE levels [54].

Interestingly, phosphatidyl inositol-3 kinase (PI-3 K) mediates insulin signaling at the post-receptor level and it also mediates the clearance of AGEs via the macrophage scavenger receptor (MSR) pathway [58,59]. Therefore, the presence of IR in normoglycemic women with PCOS could alter the clearance of AGEs via decreased activity of PI-3 K, which has been demonstrated previously in women with PCOS [60,61]. Hence, one could conclude that PCOS is associated with elevated levels of AGEs that, in turn, can exacerbate manifestations of PCOS such as IR.

As mentioned earlier, data to date demonstrated that women with PCOS have ovarian chronic inflammatory condition represented by elevated levels of serum/ovarian AGEs and up-regulation of ovarian RAGE [23,33]. Diamanti-Kandarakis et al. demonstrated that in PCOS ovaries, granulosa cells displayed stronger RAGE expression then theca interna cells when compared to controls [33]. The authors also showed that NF-κB (p50/p65) was expressed in the cytoplasm of theca interna and granulosa cells of both normal and PCOS ovaries; whereas the NF-κB p65 subunit was only observed in granulosa cells nuclei of PCOS tissue [33]. Interestingly, it was suggested that accumulation of AGEs' products at the level of the ovarian follicle might trigger early ovarian aging [62] or could be responsible for reduced glucose uptake by granulosa cells, potentially altering follicular growth [26]. Additionally, very recently Diamanti-Kandarakis et al. demonstrated that AGEs interfere with insulin signaling in granulosa cells and prevent glucose transporter (Glut-4) membrane translocation. These data suggest that intra-ovarian AGEs accumulation may contribute to the pathophysiology of conditions associated with anovulation and insulin resistance such as PCOS [63]. Presently, there are no data comparing levels of sRAGE between women with or without PCOS. Anti-Mullerian hormone (AMH) is considered one of the best markers of ovarian reserve. Interestingly, Merhi et al. showed a positive correlation between follicular fluid sRAGE and follicular fluid AMH protein levels [64]. Moreover, it was demonstrated that follicular fluid sRAGE protein concentration, similar to AMH, could predict the number of oocytes retrieved for in vitro fertilization. The authors concluded that sRAGE may relate to the reproductive environment and therefore to reproductive potential. Specifically this may indicate a functionality role for sRAGE in the follicular fluid and the activity of the AGE–RAGE system in ovarian follicles [64] implying a protective role for sRAGE from the harmful effect of AGEs on ovarian folliculogenesis [65].

6. Do AGEs Exacerbate Insulin Resistance in PCOS?

It is well established that almost two thirds of women with PCOS are predisposed to developing IR [66] and ultimately diabetes [67–69], both of which are typically exacerbated by obesity [70,71]. AGEs have been implicated in the development of IR in PCOS (Fig. 2) [72]. This aspect has been discussed in details in our previous paper [65]. Additionally, restriction of AGEs, without altering caloric or nutrient intake, has been shown to ameliorate IR and extend mice life span [73]. Moreover, in patients with type 2 diabetes, AGE-restricted diet improved IR [74]. A reduced demand on beta cells for insulin release appears to be directly related to AGE restriction [74]. A study in overweight women demonstrated that consumption of a low-AGE diet over 4 weeks improved IR [75].

An interesting observation was made in that by the fifth generation, methylglyoxal-fed F5-mice developed insulin resistance followed by diabetes mellitus at 16–18 months of age, whereas AGE-restricted F5-mice did not develop these changes until the age of 36 months or more [76]. The changes represented the effect of a known AGE (methylglyoxal) added to food that otherwise had a low AGE content [76]. Metformin therapy is known to improve the metabolic and hormonal profiles in PCOS [77,78]. In one study [77], women with PCOS received a dose of 1700 mg of metformin daily for a 6-month period. Serum levels of AGEs were reduced after metformin administration in 22 women with PCOS (9.98 ± 0.13 [before metformin] *vs.* 9.86 ± 0.11 [after metformin], $p < 0.05$). In a subgroup analysis of 16 women with PCOS and normal glucose tolerance, the drop in serum AGEs was potentiated (9.98 ± 0.19 [before] *vs.* 9.81 ± 0.15 [after], $p < 0.02$). Body mass index remained unchanged after metformin therapy but there was a drop in testosterone levels ($p = 0.01$) and free androgen index ($p = 0.009$) [77]. That study indicated that metformin therapy reduces the levels of the atherogenic AGE molecules in the serum of women with PCOS. Besides metformin, a 6-month treatment with a combination of N-acetylcysteine (1200 mg) plus L-arginine (ARG) (1600 mg) showed a potential to restore gonadal function and to improve insulin sensitivity in women PCOS [79].

7. Are AGEs Associated With Adiposity in PCOS?

Approximately 30% to 75% of women with PCOS are obese [80]. Jia et al. demonstrated a direct link between AGEs and adiposity where MG directly stimulated adipogenesis in a cell line model derived from adipose tissue [81]. We have previously

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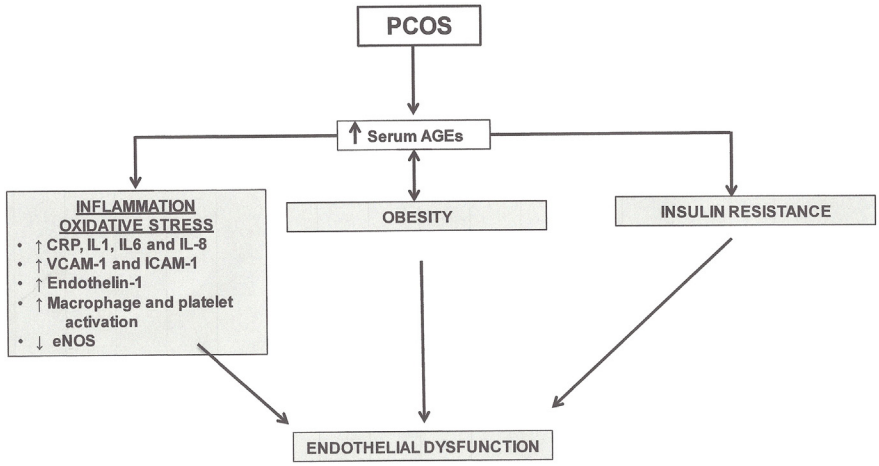

Fig. 2 – Increased serum levels of AGEs could represent a trigger for endothelial cell dysfunction in women with PCOS.Serum levels of AGEs are elevated in PCOS. Elevation in serum AGEs is associated with obesity, insulin resistance, and inflammation; all of which are triggers for endothelial cell dysfunction. *IL (interleukin), ICAM-1 (intercellular adhesion molecule 1), VCAM-1 (vascular cell adhesion molecule 1), eNOS (endothelial nitric oxide synthases).*

discussed that aspect, as well as sRAGE correlation with adiponectin, in details in a previous paper [65]. Very recently, more data demonstrated that high AGEs may represent a risk factor for metabolic syndrome, type 2 diabetes, and cardiovascular disease [82]. In a study that aimed to assess the association of endogenous and exogenous AGEs with metabolic syndrome criteria, AGEs ($^{\epsilon}$N-carboxymethyllysine, methylglyoxal) were markedly elevated in obese persons with more than one other metabolic syndrome criteria but not in obese without metabolic syndrome criteria. Therefore, high dietary AGE consumption and serum AGEs' levels may link healthy obesity to at-risk obesity [82].

Dietary AGEs may modify both metabolic and hormonal parameters of affected women, without changes in BMI [55]. Moreover, diet-induced elevation of AGEs' levels and the increased oxidative stress may directly induce insulin-signaling defects, as suggested by previous studies [55,57]. Short- and long-term food restriction has been shown to reduce the accumulation of AGEs [83,84]. Additionally, Gaen et al. showed that RAGE-mediated CML (one of the AGEs) accumulation in human adipose tissue and the activation of the CML-RAGE axis caused dysregulation of adipokines in obesity [85]. Further, RAGE deficiency was associated with decreased fat mass and smaller adipocyte size, less body weight, and less epidermal fat weight [86,87]. Several studies demonstrated that plasma sRAGE level is inversely correlated with obesity [88,89]. Interestingly, sRAGE levels rise significantly after surgical weight loss [90], further suggesting an association between AGEs and adiposity (Fig. 2). Diet modification has been shown to alter PCOS phenotypes; for instance, polyunsaturated fatty acids (PUFAs) modulated hormonal and lipid profiles and supplementation with long-chain (LC) n-3 (omega-3) PUFAs improved androgenic profiles in women with PCOS where LC n-3 PUFA supplementation reduced plasma bioavailable testosterone concentrations [91]. Additionally, Omega-3 fatty acids have been shown to improve insulin sensitivity in PCOS patients [92].

8. Do AGEs Cause Endothelial and Vascular Dysfunction in Women With PCOS?

Women with PCOS have a higher prevalence of subclinical atherosclerosis, as reflected in dysregulation of endothelial function assessed by decreased flow mediated dilation, increased carotid intimal–medial thickness (CIMT), and presence of coronary artery calcification [93–96]. However, in the study population that consisted of 85 Taiwanese–Chinese women (aged 17–35 years), there were no significant differences in CIMT between the PCOS and the controls groups [97]. Whether the disagreement between these studies was due to ethnic difference in the population studied remains to be determined.

Moreover, it has been shown that endothelial function is compromised even in young and nonobese women with PCOS [98,99]. Interestingly, a recent study demonstrated that women with PCOS have increased sympathetic drive and impaired endothelial function independent of obesity and metabolic disturbances [100]. That was demonstrated by an elevated multiunit muscle sympathetic nervous system activity and elevated firing rate of the vasoconstrictor neurons in women with PCOS [100].

Endothelial dysfunction is promoted by high levels of IL-6 and TNF-α and low expression/activity of endothelial nitric oxide synthase (eNOS), which lead to decreased nitric oxide (NO) synthesis and reduced vasodilation [101]. An attenuation of NO-based signaling in platelets and blood vessels has been found in women with PCOS and these changes were present from early adult life, contributing to premature atherogenesis [102]. Additionally, several studies have shown that PCOS is associated with high levels of adhesion molecules, such as soluble intercellular adhesion molecule 1, soluble vascular adhesion molecule 1; endothelin-1, and sE-selectin—all of which are known markers of endothelial dysfunction [103,104]. Endothelin-1 (ET-1) (a peptide which causes endothelial dysfunction) levels were found to be

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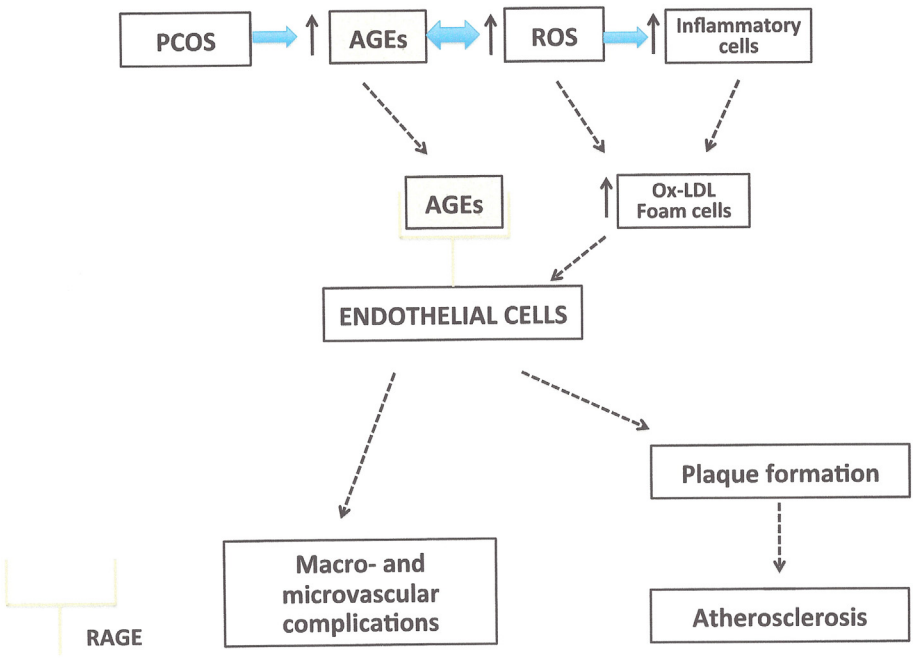

Fig. 3 – AGEs and RAGE play a central role in the development of macro- and microvascular complications in women with PCOS.AGE–RAGE binding elicits reactive oxygen species (ROS) generation that leads to the formation of foam cells causing atherosclerosis, macro- and microvascular complications.Ox-LDL (oxidized low-density lipoprotein).

positively and strongly associated with AGEs in both women with PCOS and controls, suggesting that the detrimental effect of AGEs on endothelial cells may involve increased ET-1 production. Since ET-1 has been shown to enhance oxidative stress, it could possibly be creating a vicious cycle between ET-1 and AGEs in PCOS (Fig. 2) [105]. Interestingly, in a study where women with PCOS had elevated levels of ET-1 and lower levels of NO compared to controls of similar age and BMI, metformin administration reduced ET-1 and increased NO levels in PCOS [106].

Several authors have demonstrated that sRAGE levels were lower in subjects with atheromatous plaques than those without a plaque, whereas serum AGEs levels were significantly higher [107–109]. Interestingly, AGEs, TNF-α, and estradiol (E_2) all up-regulate RAGE mRNA and protein levels in human vascular endothelial cells, and this process was mediated by two distinct nuclear complexes: p65/p50 NF-κB and Sp-1/ERα [110]. Therefore, continuous exposure to AGE, TNF-α, and/or E_2 and sustained enhancement of RAGE expression may cause a further accumulation of AGE in the vasculature, resulting in an exacerbation of AGE–RAGE mediated vascular dysfunction (Fig. 3).

Interestingly, data reported an association between polymorphism in the TNF-α gene promoter and PCOS [111]. Analysis demonstrated that the –308A variant in the promoter of the TNFα gene clearly influenced the phenotype, resulting in increased basal and leuprolide-stimulated androgen concentrations in the group of carriers of this variant [111]. Additionally, data showed that in a Korean population, the –1031(T/C) polymorphism in the promoter region of TNF-α gene was associated with PCOS [112].

Osteoprotegerin is a cytokine receptor and a member of the TNF receptor superfamily, with anti-inflammatory and antiapoptotic effects [113]. In PCOS, osteoprotegerin has been negatively related with the amount of circulating androgens, while it is simultaneously associated with endothelial dysfunction and IR, independent of adiposity and androgen excess [113,114].

Asymmetrical dimethylarginine (ADMA), a guanidino-substituted analog of L-arginine, is a potent endogenous competitive inhibitor of the endothelial NO synthase [115]. Serum levels of ADMA have been shown to be elevated in different pathological conditions such as hypertension, diabetes, renal disease, and dyslipidemia [116–119]. Increased levels of ADMA reduce NO formation and are associated with endothelial dysfunction, thus ADMA has been regarded as a novel cardiovascular risk factor [115,120,121]. Insulin resistance may be the underlying mechanism of endothelial dysfunction through NO pathway in PCOS [122]. One study demonstrated that women with PCOS have elevated ADMA levels suggesting an increased risk for an early onset CVD [123]. In that study, women with PCOS (n = 83) were compared with a control group of healthy women (n = 39). The results showed that ADMA levels were significantly higher (0.56 ± 0.15 *vs.* 0.50 ± 0.10; p = 0.024; remained statistically significant after adjustment for BMI) and the arginine to ADMA ratio was lower (159.9 ± 43.6 *vs.* 195.1 ± 74.7; p = 0.028) in women with PCOS as compared to the control group [123]. In women with PCOS, ADMA plasma concentrations were positively correlated with BMI (r = 0.353; p = 0.001), fasting insulin (r = 0.405; p < 0.001), and fasting C peptide (r = 0.348; p = 0.001) [123]. Interestingly, ADMA levels decreased significantly after 6 months treatment with metformin (0.53 ± 0.06 *vs.* 0.46 ± 0.09; p = 0.013; n = 21) [123]. This well-designed study supports the hypothesis that ADMA could represent an important link between impaired insulin action and endothelial dysfunction in women with PCOS.

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9. Conclusion

PCOS, one of the most common endocrine disorders in women, increases the risk of CVD. Interestingly, the proatherogenic inflammatory molecules AGEs are elevated in the serum of women with PCOS. AGEs have been linked to the metabolic and reproductive disturbances observed in PCOS and there are data suggesting that blockade of the pro-inflammatory cellular receptors RAGE might be beneficial in IR states and oxidative stress conditions.

Recognizing the impact of AGEs on atherosclerosis, pharmacological strategies targeting reduction in the pathophysiological mechanisms caused by AGEs are being developed: 1) the blockade of AGEs' formation, 2) the prevention of AGE–RAGE interaction, and 3) the suppression of the RAGE downstream pathway, represent promising therapeutic strategies for CVD. The application of these promising therapies in women with PCOS has the potential to alleviate the long-term cardiovascular complications observed in this patient population. This review reinforces the need for more research pertaining to slowing down the AGE–RAGE axis in women with PCOS in order to alleviate the metabolic and endothelial dysfunctions that cause serious health consequences in this patient population.

Authors' Contribution

M.P-M proposed the idea and wrote the first draft of the manuscript.

M.P-M and Z.M. did literature review and wrote the outline and the first draft of the manuscript.

J.Z. drafted Figs. 2 and 3 along with their legends, and edited sections of the manuscript.

E.D-K edited the manuscript and provided critical revisions to the manuscript.

We do not have any potential conflict of interest to disclose.

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