REVIEW

AGEs-related dysfunctions in PCOS: evidence from animal and clinical research

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Abstract

Polycystic ovary syndrome (PCOS) is the most common female endocrine disorder in women in their reproductive age. In recent years, the role of advanced glycation end products (AGEs) in PCOS has gained great attention. AGEs are highly reactive molecules that can be assumed by diet or endogenously synthesized as by-products of metabolic processes. AGE deposition increases with aging, hyperglycemia, insulin resistance, and glycotoxin-rich diet. Therefore, it has become imperative to understand the underlying mechanism of AGEs actions and its downstream effects in PCOS pathophysiology. By integrating evidence from human studies and experimental models, the present review points out that altered AGE deposition is a common feature in all PCOS phenotypes. Searching for possible mechanisms involved in the adaptive response against glycation injury in oocytes and ovaries, the role of SIRT1, the main member of the mammalian sirtuin family, has also recently emerged. Therefore, further studies based on anti-AGE interventions could be helpful in creating innovative strategies for counteracting PCOS and its effects on fertility.

Key Words

- polycystic ovary syndrome (PCOS)
- advanced glycation end products (AGE)
- receptor for AGE (RAGE)
- glycotoxin-rich diet
- ovary
- SIRT1

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Introduction

Polycystic ovary syndrome (PCOS) is the most common female endocrine disorder with an incidence rate of 5–10% in women in their reproductive age. Diagnosis is based on the observation of at least two features among anovulation or rare ovulation, hyperandrogenemia, and polycystic ovaries on ultrasound examination (PCOM) (The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group 2003). Women with PCOS have a higher risk of insulin resistance with compensatory hyperinsulinemia, type 2 diabetes mellitus, obesity, dyslipidemia, metabolic syndrome, and cardiovascular complications (reviewed by Carvalho *et al.* 2018). Insulin resistance is observed up to 47% in lean PCOS and up to 76% in obese PCOS (Diamanti-Kandarakis & Dunaif 2012, Cassar *et al.* 2016). The hyperinsulinemia is associated with increased steroidogenesis and dysregulation of follicle growth (Franks *et al.* 2000).

The etiology of PCOS is still under debate. There is emerging evidence suggesting that PCOS is a polygenic and multifactorial hormonal and metabolic dysfunction making relevant the hereditary influences, lifestyle, and nutritional habits (Livadas & Diamanti-Kandarakis 2013, Witchel *et al.* 2015, Bruni *et al.* 2021). In the last decade, a theoretical role of advanced glycation end products (AGEs) in PCOS has emerged. Indeed, accumulation of these toxic molecules is favored by hyperglycemia, insulin resistance, diet, and genetics. Thus, they deserve much attention as factors involved in PCOS pathophysiology.

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In this review we summarized the current knowledge on this topic by integrating biological and clinical evidence from PCOS women with mechanistic studies in PCOS animal models.

To this end we searched in the electronic database PubMed (MEDLINE), all the peer-reviewed journal articles published until March 2021 by using the search term 'advanced glycation and PCOS'. We considered all eligible research articles in English. Of the 64 found publications, 39 were research articles: 29 research papers on humans and 10 on animal models.

The formation of AGEs

AGEs are a heterogeneous class of molecules mainly formed by a multistage chemical transformation named Maillard reaction (Fig. 1). In the early step, non-enzymatic reactions involving a condensation/glycation process between the carbonyl group of reducing sugars, such as glucose and fructose, and the free amino group of proteins, lipids, and nucleic acids lead to the formation of respective Schiff bases, which are unstable and reversible. The subsequent rearrangement of the Schiff base produces Amadori products, which are more stable and form covalent adducts on molecules with negative effects on their biological function and metabolism (Ott *et al.* 2014). A common example of this process is glycated hemoglobin (HbA1c), an Amadori product used as a marker of hyperglycemia. In the final stage of glycation, Amadori products may be transformed to AGEs by irreversible oxidation or hydrolysis (Ott *et al.* 2014). The Maillard reaction also generates highly reactive dicarbonyls, also referred to as alpha-oxoaldehydes, including methylglyoxal (MG), glyoxal, and 3-deoxyglucosone that represent powerful glycating agents (Sibbersen & Johannsen 2020). These molecules can also be derived from glucose autoxidation, lipid peroxidation, and the polyol pathway (Sibbersen & Johannsen 2020). In addition to its activity as an AGE precursor, MG has deleterious effects on mitochondrial respiration, proliferation, survival, and redox balance (Kold-Christensen & Johannsen 2020). Reactive carbonyl groups are constantly being produced via normal metabolism and when production overrides detoxification, AGEs accumulate. AGE formation in the body may take several days or weeks to complete in the body with final AGE concentration depending on the half-life of the glycated proteins (Sibbersen & Johannsen 2020). To overcome a dicarbonyl overload, a condition referred to as carbonyl stress, cells rely on enzymatic defenses. The MG detoxification system includes two enzymes working in tandem, glyoxalase 1 (GLO1) and glyoxalase 2 (GLO2): GLO1 catalyzes the formation of S-D-lactoylglutathione from MG, with reduced GSH acting as a cofactor; GLO2 catalyzes the hydrolysis of S-D-lactoylglutathione to D-lactate and regenerates GSH (Tatone *et al.* 2014).

Some of the most commonly formed AGEs include carboxymethyl lysine (CML), carboxyethyl lysine (CEL), and the hydroimidazolones, the latter being mostly produced from the interaction of MG with arginine residues (MG-H1, Kuzan 2021). Less common AGEs such as argpyrimidine, a MG-AGE, pentosidine, pyrraline, and glucosepane also play a role in human diseases (Kuzan 2021).

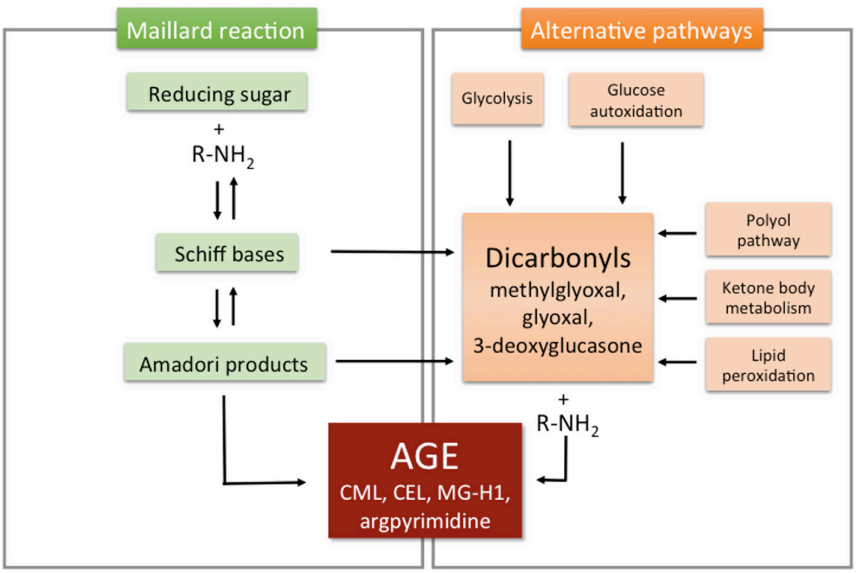

Figure 1
Schematic pathway of endogenous production of AGEs. Non-enzymatic reactions of reducing sugars with amino groups of proteins produce respective Schiff bases, which undergo Amadori rearrangement to raise Amadori products. Irreversible reactions can produce further chemical modifications leading to advanced glycation end products (AGEs), such as CML, CEL, MG-H1, and argpyrimidine. Reactive dicarbonyls including methylglyoxal, glyoxal, and 3-deoxyglucosone are formed through several pathways: the Maillard reaction, glycolysis, glucose autoxidation, the polyol pathway, ketone body metabolism, or lipid peroxidation. Dicarbonyl compounds react further to form irreversible products, the so-called AGEs. A full color version of this figure is available at https://doi.org/10.1530/JOE-21-0143.

In addition to AGEs that form endogenously, AGEs are contained in different kinds of foods and are named as glycotoxins. Animal and human research demonstrated that dietary AGEs significantly contribute to the development of pathologies (Sergi *et al.* 2021, Song *et al.* 2021). They are commonly present in uncooked animal-derived foods and their formation is promoted by thermal processing, such as grilling, broiling, roasting, searing, and frying (Uribarri *et al.* 2010). This process is also known as non-enzymatic browning since it results in brown color appearance. Analysis of the browned food has revealed the presence of heterogeneous AGEs with high molecular weight named melanoidins. The content of AGEs in food has been extensively investigated by Goldberg *et al.* (2004) and Uribarri *et al.* (2010). A limited number of AGEs, such as hydroimidazolones, is derived exclusively from endogenous sources (Ravichandran *et al.* 2019). Due to their existence in different forms in foods, ongoing studies have been focusing on the development of reliable analytical methods for AGE identification in food matrices (Cheng *et al.* 2021).

Since AGEs formation occurs during normal metabolism, long-lived proteins such as collagen are more likely to be glycated and form AGEs, which have been initially proposed as a marker of aging.

A further mechanism underlying AGE effects is the formation of irreversible cross-linking with proteins, affecting their turnover and functionality. During aging, molecules of the extracellular matrix become damaged through many modifications including glycation, crosslinking, and accumulation, leading to matrix stiffness, which intensifies aging-associated alterations.

Moreover, AGEs are actively involved in a positive feedback loop leading to oxidative stress (Papachristoforou *et al.* 2020). Oxidative stress promotes the last step of advanced glycation, hence, accelerating AGE accumulation. AGEs, in turn, activate proinflammatory pathways and reactive oxygen species (ROS) generation (Fleming *et al.* 2011, Papachristoforou *et al.* 2020). This effect is mediated by engagement of specific cell-surface receptors, such as the receptor for AGEs (RAGE), a multiligand member of the immunoglobulin superfamily of cell surface (Erusalimsky *et al.* 2021). AGE–RAGE interaction activates intracellular multiple inflammatory signaling pathways including the transcription factor nuclear factor KB (NFKB) and its target genes, TNFa, interleukin1, interleukin 6, and VCAM1 (Fig. 2). AGE-bound RAGE triggers the activity of NADPH oxidase increasing the production of ROS. Two RAGE isoforms are present that are known as soluble RAGEs (sRAGEs): the cleaved form, known as cRAGE, is generated by proteolytic cleavage of membrane-bound RAGE by the metalloproteases ADAM-10 and MMP-9; the second form of sRAGE, called esRAGE (endogenous secretory RAGE) that results from alternative splicing of RAGE pre-mRNA (Erusalimsky *et al.* 2021). The expression of esRAGE may be influenced by impaired glucose metabolism. Together, sRAGEs act as decoy receptors by binding RAGE ligands and blocking their interaction with membrane-bound RAGE.

AGE accumulation could be implicated in different pathological conditions such as diabetes, atherosclerosis, chronic kidney disease, decline in memory with age, pathophysiology of eye diseases, cardiovascular complications, erectile dysfunction, polycystic ovary syndrome (PCOS), cancer, elevated cellular oxidative and inflammatory state, schizophrenia, and Alzheimer's disease (Prasad 2019).

AGEs in PCOS women

The role of serum AGEs

About 15 years ago, Diamanti–Kandarakis' research group observed increased levels of AGEs in the serum of women affected by PCOS. Moreover, a positive correlation was disclosed between serum AGEs and testosterone levels and a negative correlation was found between AGE protein and glucose/insulin ratio (Diamanti-Kandarakis *et al.* 2005). Among different metabolic parameters, testosterone was the only independent predictor of AGEs. The hypothesis of the role of advanced glycation in PCOS was further supported by Kaya *et al.* (2009), who correlated advanced oxidation protein products (AOPP) with cardiovascular disease (CVD) in PCOS (Kaya *et al.* 2009). A metanalysis has confirmed that AGEs are listed among serum CVD risk markers that are increased in women with PCOS compared with controls (Toulis *et al.* 2011). As already mentioned, AGEs activate NFKB, the transcription factor which upregulates gene expression of molecules involved in vascular injury and endothelial dysfunction, including adhesion molecules and endothelin 1 (ET1). This is an endothelial-derived vasoconstrictor peptide and is considered as a major biochemical marker of endothelial dysfunction. By limiting the investigation to young, lean, and non-insulin resistant women with PCOS, ET1 levels were found to be positively associated with AGEs suggesting that the detrimental effect of AGEs on endothelial cells may involve increased ET1 production (Christakou *et al.* 2011).

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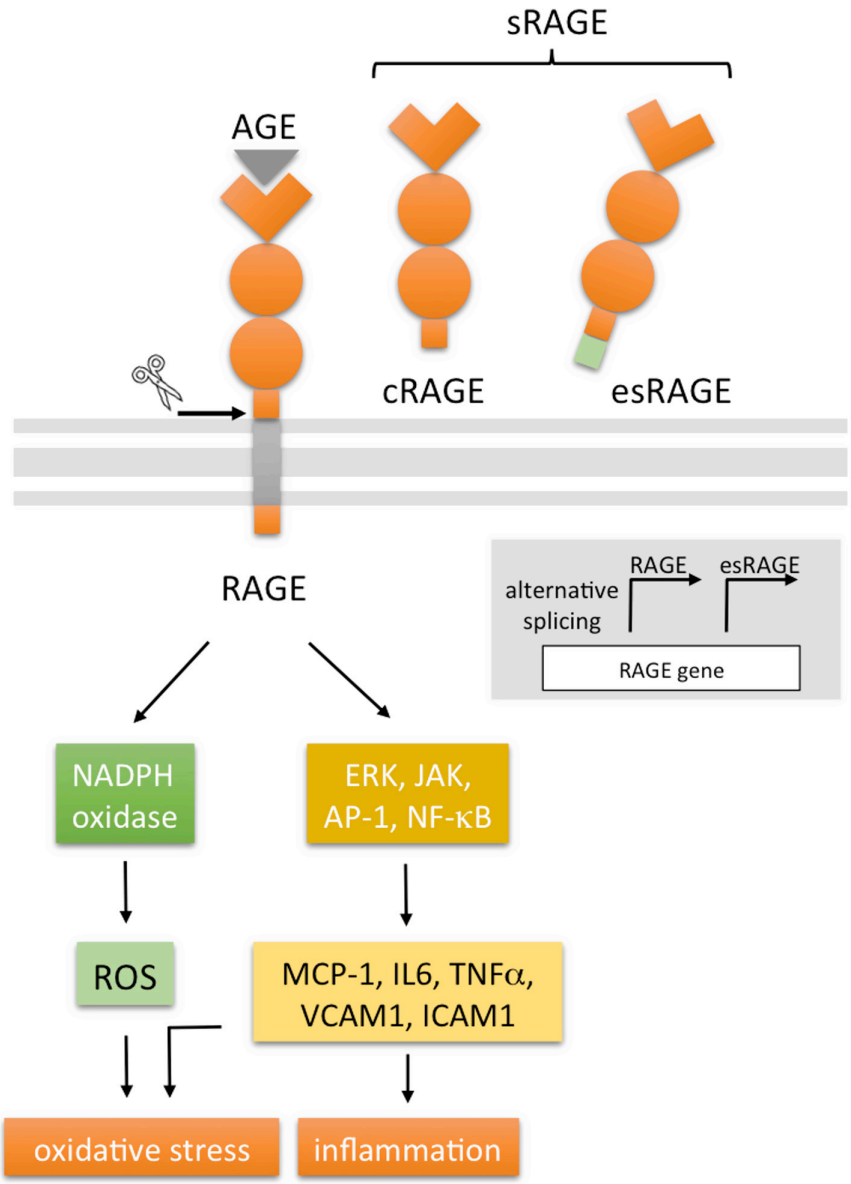

Figure 2
Signaling pathways activated by AGE–RAGE interaction. Plasma membrane-bound RAGE consist of three main regions: an intracellular tail, a transmembrane helix, and an extracellular domain formed by immunoglobulin-like subdomains V, C1, and C2. The interaction between AGEs and RAGE activates NADPH oxidase which increases the reactive oxygen species (ROS) content contributing to the establishment of oxidative stress. The AGE–RAGE interaction also causes the activation of signaling pathways resulting in inflammation and oxidative stress. Cleavage of membrane-bound RAGE causes the release of its extracellular portion (cRAGE). Alternative splicing of the RAGE gene results in the generation of esRAGE, which contributes to the sRAGE pool. Taken together, sRAGEs act as decoy receptor binding RAGE ligands and block interaction with membrane-bound RAGE. A full color version of this figure is available at https://doi.org/10.1530/JOE-21-0143.

Based on the potential role of AGEs in the pathogenesis of PCOS, some attempts have been in order to discover the effects of strategies aimed to lower serum AGEs on PCOS phenotype. To this end, Diamanti–Kandarakis and Kalofoutis' group (Diamanti-Kandarakis *et al.* 2006) investigated the beneficial effects of orlistat, a lipase inhibitor (Hauptman *et al.* 1992) based on the knowledge that fat enriched foods favor AGE production during cooking (Goldberg *et al.* 2004). The study reported that orlistat administration decreased AGE absorption following an AGE-rich meal in normal as well as in women with PCOS. Accordingly, low AGE dietary content reduced serum level of AGEs together with metabolic, hormonal, and oxidative stress biomarkers in PCOS women, so highlighting the relevance of low AGE intake as part of lifestyle changes recommended for alleviating PCOS symptoms (Tantalaki *et al.* 2014). AGE levels were reduced after metformin administration in women with PCOS, although body mass index (BMI) as well as the other parameters studied remained unchanged apart from a drop of androgens (Diamanti-Kandarakis 2007).

By comparing the effects of oral contraceptives and metformin on CVD risk markers in PCOS patients, Christakou & Diamanti-Kandarakis (2014) found that, although both of them had beneficial effects, metformin administration displayed greater efficacy in lowering serum AGEs. This may be helpful for tailoring therapy in order to modulate side-effects of drug intervention.

Potential targets for anti-AGE therapeutical strategies include sRAGEs, the physiological defense against

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circulating AGEs (see above). In obese PCOS patients, serum AGEs increased with the body fat accumulation, whereas the serum sRAGEs decreased (Liao *et al.* 2017). In women with PCOS, vitamin D3, known to positively affect serum anti-Mullerian hormone (AMH), increased circulating sRAGEs, thereby exerting a protective effect against the inflammatory action of AGEs (Irani & Merhi 2014).

The role of intraovarian AGEs

Increased AGE deposition has been detected in the PCOS ovarian tissue (Kandaraki *et al.* 2012). A causative link between AGE signaling and deposition of excess collagen in PCOS tissue has been established and taken as an evidence of AGE implication in PCOS symptoms related to extracellular matrix perturbation (Hassani *et al.* 2019). Accumulation of AGEs has been demonstrated in granulosa cells of PCOS patients. A recent study on *in vitro* human granulosa cells has demonstrated that exposure to testosterone increases the expression of the RAGEs and the accumulation of AGEs supporting the hypothesis of a prominent role of hyperandrogenism in this process (Azhary *et al.* 2020). The authors also disclosed the efficacy of a RAGE inhibitor in preventing AGE increase. Based on the finding that endoplasmic reticulum (ER) stress participates in AGE accumulation related to hyperandrogenism, the use of a RAGE inhibitor or an ER stress inhibitor may represent novel strategies in PCOS therapy. Recently, it has been reported that exposure to five different types of AGEs inhibited the proliferation of primary human granulosa cells and KGN cells in association with luteinizing hormone receptor (LHR) down regulation and reduced secretion of progesterone (Lin *et al.* 2019). Silber *et al.* (2020) proposed an *in vitro* PCOS model of granulosa cells based on prolonged incubation of KGN granulosa cells with insulin/AGEs. By using this model, it was demonstrated that VEGF, IL6/8, and PEDF mRNA correlated with hyperangiogenesis and chronic inflammation. Exposure to rPEDF reduced AGE-induced elevation of VEGF and IL6/8 (Silber *et al.* 2020).

In 2016, Wang *et al.* by means of a prospective analysis, discovered that sRAGE concentrations in follicular fluid were reduced in PCOS patients when compared with control. Based on the inverse correlation with inflammation markers in follicular fluid, the data provided evidence for the protective role of sRAGE in the compromised follicular microenvironment of PCOS women (Wang *et al.* 2016).

Recent reports state that AGEs are involved in excessive androgen production in PCOS, because they modulate the activities of crucial steroidogenesis enzymes, such as: CYP type 11A, CYP type 17A1, and 3BHSD (Merhi *et al.* 2018, Lin *et al.* 2019). AGEs may interfere with intracellular insulin signaling and glucose transport in human granulosa cells, potentially affecting ovarian function and follicular growth (Diamanti-Kandarakis *et al.* 2016). Finally, AGEs also affect LH receptor and AMH receptor expression, and their signaling pathways in granulosa cells (Diamanti-Kandarakis 2009), hence, contributing to anovulation.

AGEs in PCOS animal models

Animal models have been useful to evaluate the effects of a possible AGE overload with PCOS on oocyte competence (Chang & Chan 2010, Tatone *et al.* 2011, Liu *et al.* 2013). Although the expression of glyoxalases makes female germ cells competent to deal with AGEs (Tatone *et al.* 2011, 2014, Tatone & Amicarelli 2013), *in vivo* and *in vitro* experiments have shown that MG reduced oocyte maturation, fertilization, and embryonic development. Moreover, it impaired the mitochondrial redox balance with damage to spindle, chromatin, and DNA structure (Chang & Chan 2010, Tatone *et al.* 2011, Liu *et al.* 2013).

Although PCOS in not present in rodents, different experimental protocols have been developed to recapitulate main PCOS features in rats and mice in order to understand the pathophysiological mechanisms and to provide pre-clinical evidence for therapeutic strategies (Osuka *et al.* 2019).

A valuable model to investigate the role of AGEs in PCOS is represented by the d-gal-model commonly used as an aging model (Park & Choi 2012). However, these mice were characterized by high AMH and testosterone serum levels in association with ovarian cysts and irregular estrous cycles. Administration of aminoguanidine, a well-known AGE reducer reverted these PCOS phenotypes (Park & Choi 2012).

In 2012, Diamanti-Kandarakis' group relied on a rat model induced by pre-pubertal administration of androgens (Diamandi-Kandarakis & Dunaif 2012). In this study, the excess of circulating androgens was demonstrated to increase AGE accumulation and induce deregulation of glyoxalase I at ovarian level. In addition, increased AGE intake by diet under hyperandrogenic condition caused an exacerbation of PCOS ovarian phenotype and alteration of hepatic functionality (Kandaraki *et al.* 2012, Palioura & Diamanti-Kandarakis 2015). The key role of diets enriched with AGEs or AGE precursors in the establishment of a PCOS-like syndrome was explored by different groups. Indeed, Chatzigeorgiou *et al.* (2013) observed that rats

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fed with a high AGE diet exhibited increased levels of testosterone. Moreover, peripheral blood mononuclear cells from this PCOS rat model presented a decrease in the expression of AGE scavenger receptors, such as RAGE, that could contribute to AGE accumulation in tissues (Chatzigeorgiou *et al.* 2013). Alterations to the hormonal androgenic balance, together with a deregulation of the glyoxalase system and RAGE expression, have been observed also in ovaries from mice fed with an excess of MG, the most powerful AGE precursor (Di Emidio *et al.* 2019). Similarly, administration of MG-BSA induced alterations in terms of insulin resistance, hepatic lesions, ovarian morphology, and estrous cycle similar to those observed in dehydroepiandrosterone (DHEA)-induced PCOS mice (Lin *et al.* 2019). Ovaries from DHEA mice were characterized by extensive glycative stress, demonstrated by increased MG-AGE levels, altered collagen deposition, enhanced RAGE expression, and deregulation of the glyoxalase system (Di Emidio *et al.* 2020*a*,*b*). Searching for possible mechanisms involved in the adaptive response against glycation injury in ovaries from PCOS models, the role of SIRT1, one of the seven members of the mammalian sirtuin family, has recently emerged. SIRT1 is known to regulate oocyte and somatic cell physiology during almost all stages of folliculogenesis (Tatone *et al.* 2015, 2018). Recently, our research group found out that inhibition of SIRT1 activity reduces glyoxalase response to MG overload in mouse oocytes (Fig. 3) (Di Emidio *et al.* 2019). Upon MG exposure, mouse oocytes increased the expression of GLO1 and GLO2. Inhibition of SIRT1 activity by EX527 or Sirtinol prevented upexpression of both glyoxalases and also has detrimental effects on oocyte competence for meiosis resumption. On the other hand, activation of SIRT1 activity by resveratrol during MG exposure improved oocyte maturation rate, with high levels of glyoxalases (Di Emidio *et al.* 2019). Ovaries from DHEA induced-PCOS mice presented high levels of SIRT1 in association with upexpression of products involved in the antioxidant response at mitochondrial level, such as SIRT3 and superoxide dismutase 2 (SOD2), and a reduction of mitochondrial number and functionality. Moreover, SIRT1 also seemed to be involved in the activation of the autophagic pathway, in cooperation with AMP-activated protein kinase (AMPK) (Di Emidio *et al.* 2020*a*). The use of DHEA model has allowed discovering that acyl-L-carnitines alleviate ovarian dysfunctions and exert powerful anti-AGE activity as demonstrated by decreased AGE deposition, RAGE expression, and recovery of basal level. SIRT1 was also positively modulated under these conditions (Di Emidio *et al.* 2020*b*).

In a mouse model obtained by prenatal exposure to dihydrotestosterone (DHT) and post-natal high-fat diet, it was demonstrated that a therapy based on metformin in association with rPEDF was effective in controlling weight gain and reducing ovarian follicle RAGE and inflammatory status (Silber *et al.* 2020).

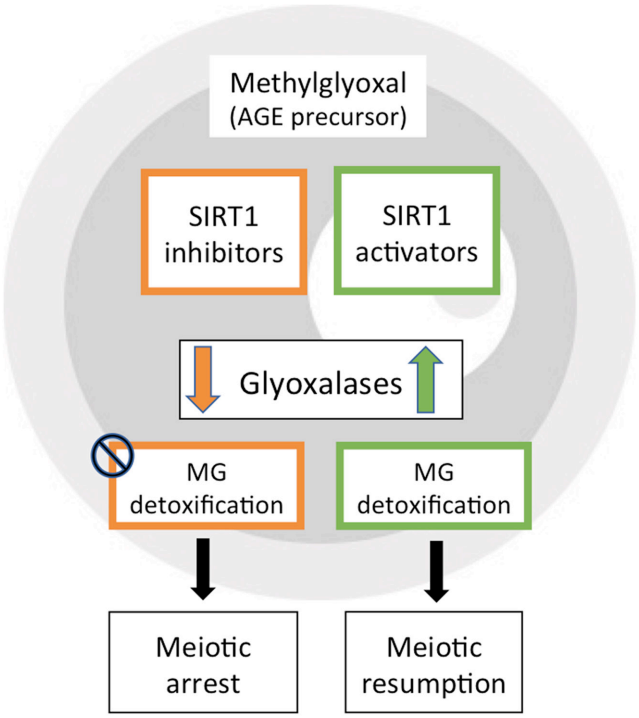

Figure 3
SIRT1 activity is required for glyoxalase functioning and oocyte competence for meiotic maturation. According to this working model, upon MG overload, GLO1 and GLO2 expression are increased in mouse oocytes. Inhibition of SIRT1 activity prevents the upexpression of both glyoxalases and reduced oocyte maturation rate. Activation of SIRT1 sustains glyoxalase activity with consequent improvement of oocyte competence for meiosis completion. A full color version of this figure is available at https://doi.org/10.1530/JOE-21-0143.

Concluding remarks

In the last decade, the role of AGEs in PCOS has gained a great deal of attention from clinicians and researchers who are involved in female reproductive dysfunctions. Overall, from current literature emerges that altered AGE deposition represents a common feature in all PCOS phenotypes revealing the pleiotropic effects of these compounds. The interaction of AGEs with their membrane receptors activates signaling pathways leading to increase of oxidative stress, inflammation, hyperandrogenism insulin resistance, and ovulatory dysfunction (Fig. 4). Effects on

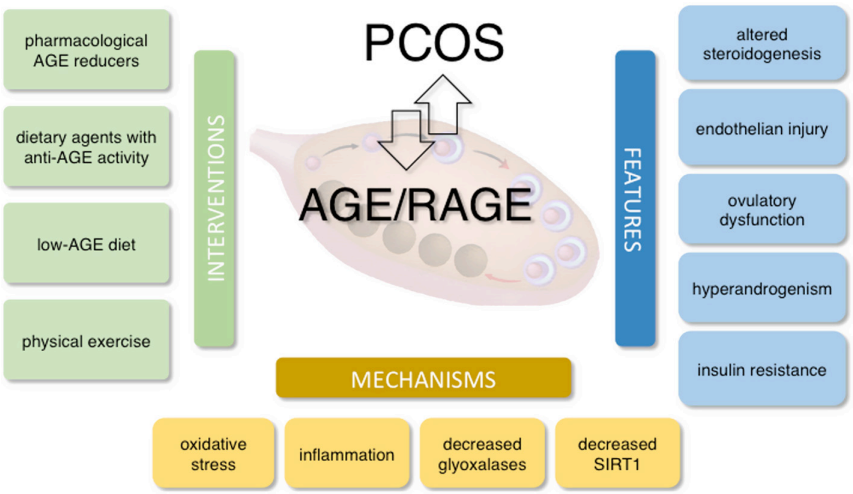

Figure 4
Altered deposition of AGE represents a common feature in all PCOS phenotypes. AGEs interaction with their receptors (RAGE) leads to the establishment of oxidative stress, inflammation, and decreased activity of glyoxalases and SIRT1. This condition contributes to altered steroidogenesis, endothelial injury, ovulatory dysfunction, hyperandrogenism, and insulin resistance. Pharmacological AGE reducers, dietary agents with anti-AGE activity, low-AGE diet, and physical exercise are considered possible beneficial interventions that aim to reduce AGE accumulation in order to ameliorate PCOS symptoms. A full color version of this figure is available at https://doi.org/10.1530/JOE-21-0143.

endothelium make AGEs important risk factors for CVD in PCOS women. Searching for involved mechanisms underlying AGE deposition in PCOS ovaries, animal models have recently provided evidence for deregulation of the glyoxalases, the main AGE detoxification system, and for the role of SIRT1.

Numerous molecules, including aminoguanidine, metformin, benfotiamine, and pyridoxamine, are under investigation for preventing AGE-related dysfunctions (Peyroux & Sternberg 2006, Reddy & Beyaz 2006, Takeuchi *et al.* 2010). Dietary agents with anti-AGE activity include medicinal plants (Peng *et al.* 2011, Elosta *et al.* 2012) such as green tea polyphenol compounds, which are more powerful than aminoguanidine (Sang *et al.* 2007). Further strategies to be taken into account as anti-AGE measures are reduced intake of glycotoxin and physical exercise (Falone *et al.* 2012*a*,*b*). Based on these concepts, we encourage investigation about the potential of synthetic anti-AGE molecules, dietary components, modification of diet AGE content, and exercise to control AGE accumulation during PCOS. Better understanding of these issues could be helpful in creating innovative strategies for counteracting PCOS and its effects on female fertility.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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