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Review Article

Dietary advanced glycation end products (AGE) and female infertility

Diyet ileri glikasyon son ürünleri (AGE) ve kadın infertilitesi

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Abstract

Advanced glycation end products (AGEs) are molecules formed by non-enzymatic reactions between reducing sugars and proteins, nucleic acids, or lipids. Advanced glycation end products may be formed endogenously under normal metabolic conditions or metabolic conditions such as diabetes and hyperglycemia, or exogenously during processing of foods at high temperatures and low humidity, including roasting, grilling, and frying. The accumulation of AGEs has a significant role in the development of disorders associated with infertility. Infertility is an increasingly common health problem in recent years. Dietary habits and nutrient intake are among the many factors affecting infertility in women. Receptor AGEs (RAGE) and AGEs have been observed in theca and granulosa cells of the ovaries. High levels of AGEs affect fertility through ovarian dysfunction, follicular growth, oocyte number, fertilization rate, embryo development, adverse effects on pregnancy rate, insulin resistance, apoptosis, endothelial dysfunction, increased inflammation, and reactive oxygen species (ROS). This review aims to investigate the pathophysiology of AGEs and their receptors, as well as their possible implications for female reproductive health.

Öz

İleri glikasyon son ürünleri (AGE), indirgen şekerler ile proteinler, nükleik asitler veya lipitler arasındaki enzimatik olmayan reaksiyonlar sonucu oluşan moleküllerdir. İleri glikasyon son ürünleri; normal metabolik koşullar veya diyabet, hiperglisemi gibi metabolik koşullarda endojen olarak oluşabildiği gibi, ızgara, kavurma ve kızartma dahil olmak üzere besinlerin yüksek sıcaklıklarda ve düşük nemde işlenmesi sırasında ekzojen olarak da oluşabilmektedir. İleri glikasyon son ürünlerinin birikimi infertilite ile ilişkili hastalıkların patogenezinde önemli bir rol oynamaktadır. İnfertilite, son yıllarda giderek yaygınlaşan bir sağlık sorundur. Kadınlarda infertiliteyi etkileyen birçok etmen arasında beslenme alışkanlıkları ve besin ögesi alımları da yer almaktadır. Reseptör AGE (RAGE) ve AGE'ler yumurtalıkların teka ve granülosa hücrelerinde gözlenmiştir. Yüksek AGE düzeyi; ovaryum disfonksiyonu, foliküler büyüme, oosit sayısı, fertilizasyon oranı, embriyo gelişimi, gebelik oranının olumsuz etkilenmesi, insülin direnci, apoptoz, endotel disfonksiyon, inflamasyon ve reaktif oksijen türlerinde (ROS) artış yollarıyla fertilite üzerinde etki göstermektedir. Bu derlemede, AGE'lerin ve reseptörlerinin patogenezi ve bunların kadın üreme sağlığı üzerindeki potansiyel etkileri incelenmiştir.

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INTRODUCTION

Advanced glycation end products (AGEs) are molecules formed as a result of the non-enzymatic reaction of proteins, lipids, or nucleic acids with reductive sugars (1, 2). The Maillard reaction between the amino groups of proteins and the carbonyl groups of reduced sugars results in the formation of Schiff bases. High reactive carbonyl compounds and AGEs are formed by dehydration and rearrangement of Amadori products. The formation of Schiff bases and Amadori products are reversible steps that also occur in acute hyperglycemia (3, 4). Advanced glycation end products are also formed by glycolysis, ketone bodies pathway, lipid peroxidation pathways, and polyol pathway (Figure 1) (5, 6). AGEs have different formation mechanisms and precursors. Therefore, AGEs exist in a wide variety of forms in foods, tissues, and human blood. The most well-known AGEs are carboxymethyl lysine (CML), carboxyethyl arginine (CEA), carboxyethyl lysine (CEL), carboxymethyl arginine (CMA), pyrraline, pentosidine, methylglyoxal lysine dimer (MOLD), and glyoxyl-derived lysine dimer (GOLD) (6).

AGEs have exogenous and endogenous sources. They occur endogenously, usually in high plasma glucose and diabetes. Fatty acid and glucose oxidation under conditions of oxidative stress may result in the production of reactive carbonyls which contribute to the formation of AGEs. In addition, aging and dietary fructose intake can also cause endogenous AGEs production (7). Exogenous AGE sources may be listed as smoking, sedentary lifestyle, Western diet, hypercaloric diets, high-fat diets, high refined and simple carbohydrate diets, high fructose intake, and consumption of foods cooked using high temperatures (8, 9). Food composition, cooking temperature and duration, pH, moisture, and the presence of trace metals are the key variables affecting the rate of AGE production in foods (10). Increased dietary intake of fatty meats, fats, processed foods, and full-fat dairy products and decreased intake of low-fat dairy products, fish, fruits, vegetables, legumes, and whole grains increase AGE intake. At the same time, processes such as broiling, frying, roasting, and grilling cause higher AGE formation in foods compared to poaching, boiling, steaming, and stewing. For example, 90 grams of chicken (roasted) contains 5418 kilounits (kU) of AGEs, while the same amount of chicken (boiled in water/1 hour) contains 1011 kU of AGEs (11). An increase in AGE levels is correlated with longer food storage times and higher food storage temperatures (12).

Dietary intake of AGEs varies according to age, gender, disease status, databases used, and the method of food consumption recording used. Therefore, it is not possible to provide precise values specific to a particular age group or disease. It was found that daily AGE intake in healthy individuals ranged between about 8500-23000 kU/day, and CML intakes were 2.2-4.4 mg/day in individuals with different diseases (13-18). Modern dietary intake is estimated to be 25 to 75 mg/day for AGEs, with milk and bakery products being the major contributors (7). In a review of data, they determined the daily dietary intake of AGEs to be around 9000-23000 kU/day for healthy individuals (19).

Lifestyle changes (increased physical activity, body weight loss, dietary intake of polyphenolic and anti-inflammatory compounds (curcumin, resveratrol, etc.), and dietary modifications) are important to reduce AGEs (20). A decrease in dietary AGEs is associated with reducing saturated fats, processed foods, and refined carbohydrates, increasing fruits, vegetables, whole grains, and low-fat dairy products, and reducing the use of dry heat and high-temperature cooking methods such as frying, roasting, grilling, and baking (21, 22). Microwave cooking did not elevate dietary AGE content in the same way as other dry heat cooking methods by reason of it has a relatively short time of cooking (6 minutes or less). A low or acidic pH is preferable for marinating as it reduces AGE formation. Similarly, the use of olive oil has also been associated with lower AGE formation (11). In addition, metal ion chelators (citric acid, etc.), dietary energy restriction, low glycemic index diet, and a Mediterranean diet may also contribute to the reduction of AGEs (23). Reducing dietary AGEs, better glycemic control, smoking cessation, regular physical activity, and lifestyle changes have been reported to reduce AGEs (24). Pharmacotherapeutics, dietary components, endogenous scavengers, and enzymes are involved in the reduction of endogenous AGEs (25). Antioxidant agents, antiglycolytics, antihypertensives, vitamins, and chelators have been shown to reduce AGEs. In addition, AGE-RAGE signaling blockers, AGE inhibitors, AGE crosslink breakers, and phytochemicals may also be effective in reducing

AGEs. None of the AGE-modifying drugs have been approved. However, clinical trials and tests are underway (24, 26).

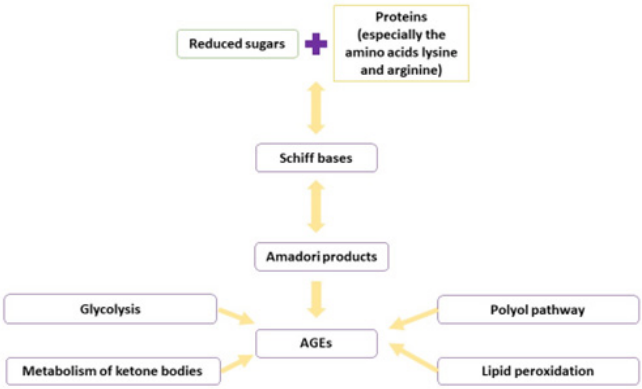

Figure 1. Schematic formation of AGEs (3-6)

AGE: Advanced Glycation End Products

Consumed AGEs can be absorbed by 10-30%. It is reported that 60-80% of dietary pyrraline and pentosidine can be absorbed. While 2/3 of the absorbed AGEs are found in the circulation. While it has been found that 30% of AGEs in the blood of healthy individuals are excreted in the urine, this rate has decreased to <5% in people with diabetic nephropathy (19, 27, 28). AGEs can be free or protein-bound. Protein-bound AGEs need to be hydrolyzed. Both types of AGEs can be degraded by microbiota, but the degradation products are not known (29). AGEs that do not interact with the microbiota and are not absorbed are excreted in feces (19, 29). Some enzyme systems are involved in the removal of dicarbonyl precursors of AGEs by the body. Glyoxalase 1 and 2 (GLO 1 and 2) convert glyoxal and methylglyoxal to lactic acid and glycolic acid, respectively. The glyoxalase detoxification system is involved in maintaining dicarbonyl homeostasis and preventing AGE formation (30).

AGEs may exert their effects on the body through their receptors. RAGE is a cell surface receptor with several ligands for pattern recognition that is a member of the immunoglobulin superfamily (31). RAGEs have been identified in many different tissues (monocytes/macrophages, endothelial cells, neuronal cells, dendritic cells, etc.) and cause activation of different signaling pathways (32). Endogenous and exogenous AGEs activate RAGE. Reactive oxygen species (ROS) and oxidative stress increase as a result of RAGE activating NADPH oxidase (10). RAGEs may affect Janus kinase/signal transduction and activator of transcription (JAK-STAT), extracellular signal regulatory kinase (ERK), Jun-N-terminal kinase (JNK), the mitogen-activated protein kinase (MAPK) p38 signaling pathways through different mechanisms. These signal transduction pathways may also lead to the activation of transcription factors such as nuclear factor kappa B (NF-kB), which results in the production of proinflammatory cytokines such as interleukins (IL) 1, IL-6, IL-17, tumor necrosis factor-alpha (TNF-a), vascular cell adhesion molecule-1 (VCAM-1), transforming growth factor-beta (TGF-β), and endothelin. AGEs have a connection to disease through these pathways (33).

Additionally to the membrane-bound form of the RAGE, there is also a soluble RAGE (sRAGE) isoform present in circulation and body fluids. It is generally believed that sRAGE plays a protective anti-inflammatory role by acting as a trap receptor, binding RAGE ligands, and preventing their communication with RAGE which is membrane-bound (31, 34). Although individual AGEs and sRAGE levels vary in diseases, it has been reported that a high AGE/sRAGE ratio may be a risk factor for diseases (35).

Another receptor is AGE receptor 1 (AGE-R1). The AGE-R1 receptor has been identified as a macrophage scavenger receptor involved in the uptake, degradation, and removal of AGEs. AGE-R1 negatively affects AGE-RAGE interacting signaling pathways and reduces RAGE-induced oxidative stress and inflammation. In this way, it contributes to the defense against AGE toxicity (25).

High dietary AGE intake has been associated with aging, dementia, bone and muscle dysfunction, altered gut microbiota, diabetes, cancer, and obesity. It has also been suggested that high dietary AGE intake may cause ovular and testicular dysfunction and infertility (36).

WOMAN INFERTILITY

Infertility is defined as the failure to achieve pregnancy after at least 12 months of unprotected sexual intercourse. It can occur in either the male or female reproductive system (37, 38).

The World Health Organization (WHO) estimated that 186 million people worldwide and 48 million couples live with infertility and their prevalence was reported as 15% (39). The Centers for Disease Control and Prevention (CDC) reports that about 19% of women between the ages of 15 and 49 say they were unable to conceive after trying for a year (38). Infertility may be caused by ovulatory dysfunction, tubal obstruction, endometriosis, decreased ovarium reserve, and uterine factors in women (40). On infertile couples, it was reported that 48.8 % of infertility cases were only of female origin, and 52.1% of them were caused by ovular problems (41). Genetic, environmental, lifestyle, and metabolic factors are associated with infertility in women (42-46). Many factors such as environmental pollution, heavy metals, chemicals and pesticides, extreme heat, smoking, alcohol, caffeine, some drugs, stress, socioeconomic factors, radiation, disruption of circadian rhythm, obesity, microbiota, thyroid problems, insulin resistance, and eating disorders have been associated with infertility in women (42, 43, 47). Nutrition has an important place among the factors affecting female infertility. Dietary AGEs are one of the factors that may affect fertility in women's nutrition (48). The objective of this review was to evaluate the effect of dietary AGEs on PCOS-related symptoms, ovarian function, and embryo quality.

Polycystic ovary syndrome (PCOS)

Polycystic ovarian syndrome (PCOS) is a prevalent reproductive and endocrine condition that mostly impacts women throughout their reproductive years (49). Some metabolic problems (hyperandrogenism, insulin resistance, oxidative stress, inflammation, and obesity) may associated in women with PCOS. In addition, epigenetic factors, environmental toxins, physical/emotional stress, and diet may have an impact on PCOS development (50). AGE and receptors may also be associated with PCOS and PCOS-related symptoms (51-55).

Immunoreactivity of AGEs and RAGE was found in the ovarium theca, granulosa, and endothelial cells of women with PCOS. AGE staining in healthy ovarian granulosa cells was found to be slightly lower than in PCOS women (56). In another study, it was shown that the levels of RAGE immunoreactivity, RAGE mRNA expression, RAGE protein, and AGE accumulation were elevated in the granulosa cells of individuals diagnosed with PCOS in contrast to the control group (57).

In a meta-analysis, AGEs were among the increased serum cardiovascular disease risk markers in PCOS women (58). Women with PCOS were shown to have higher serum AGE levels than the control group (51, 52). RAGE expression was also higher in PCOS women's monocytes than in healthy women, and it was positively linked with serum AGEs (52). In addition, follicular fluid sRAGE levels were found to be significantly lower in PCOS women (53, 54), and a positive significant correlation between follicular fluid sRAGE concentration and 25 OH vitamin D level (54). Vitamin D supplementation increased sRAGE levels (59). Wang et al (53) found that the levels of sRAGE (follicular fluid) were elevated in pregnant women, including those with PCOS, as well as healthy women, in comparison to non-pregnant women. The total number of retrieved oocytes and the levels of sRAGE in the follicular fluid were positively correlated in the control group (53).

In the case of PCOS, obesity status was also associated with sRAGE concentrations. Serum sRAGE levels in PCOS women with normal body weight were found to be significantly higher than in other overweight and obese women and serum AGE levels of obese women were found to be higher than those of the other two groups. Additionally, the study observed that serum levels of AGEs were greater in obese women compared to both the normal-weight PCOS group and the overweight group (60). In recent research, regarding sRAGE concentrations in the serum and follicular fluid, there was no statistically significant difference between PCOS and non-PCOS women; nevertheless, there was a positive correlation between PCOS women's body mass index (BMI) and follicular fluid sRAGE levels (61). When these studies are evaluated, it can be thought that sRAGE levels may be negatively related to the pregnancy status and the oocyte numbers in PCOS women.

Hyperandrogenism and insulin resistance:

Hyperandrogenism and insulin resistance are two typical PCOS symptoms (62). AGEs may affect insulin and testosterone hormones (55, 63). Serum AGEs, testosterone, insulin, and glucose levels increased in rats given a diet rich in AGE, and a positive relationship was found between serum AGE levels and fasting glucose, fasting insulin, and testosterone levels (55, 63).

There was a positive relationship between serum AGE levels and testosterone, free androgen index (FAI), insulin, homeostasis model assessment of insulin resistance (HOMA-IR), glucose/insulin ratio, and fasting glucose level, and a positive correlation with quantitative insulin sensitivity calculation index (QUICKI) in PCOS (52, 64). In addition, a negative relationship was found between serum sRAGE and FAI, and HOMA-IR (50). A low AGE diet (poaching, stewing, steaming, boiling under 180°C) significantly decreased serum AGEs, oxidative stress, HOMA-IR, insulin, and testosterone levels compared to a diet high in AGEs in PCOS women (65).

As studies evaluating the effect of dietary AGEs on PCOS are relatively few in the literature, and the connection with insulin resistance, obesity, and diabetes has generally been examined. In subjects with metabolic syndrome, low AGE dietary intake was associated with lower serum CML and HOMA-IR levels (66). Similarly, low AGE dietary intake was associated with increased insulin sensitivity, decreased urinary AGEs excretion, HOMA-IR levels, and fasting insulin levels (67, 68). In comparison to a diet high in AGEs, a low AGEs diet was found to be linked with lower levels of total cholesterol, insulin resistance, low-density lipoprotein (LDL) cholesterol, fasting insulin, leptin levels, and BMI as well as higher levels of adiponectin in the meta-analysis and systematic review (69, 70). In another systematic review evaluating the restriction of dietary AGEs in different studies of type 2 diabetes, the effect of AGEs on glycemic control, inflammation, and oxidative stress is controversial. However, at least one glycation marker's serum levels were observed to be declining in several trials. The results of AGEs-restricted diets (6 weeks 10,000 kU/day or 300 mg AGEs/day habitual consumption) showed a reduction in serum insulin, HbA1C, and HOMA-IR values (71). In another study conducted on individuals with type 2 diabetes, fasting blood glucose, HbA1c, triglyceride, and C-reactive protein (CRP) values were substantially lower, and the Mediterranean diet score was significantly higher in the first quartile of dietary AGE intake (Dietary AGE: <6612 kU/day) compared to the other quartiles. Dietary AGE consumption is negatively and statistically significantly impacted by the scores for the Mediterranean diet (72). A significant decrease in serum CML, total cholesterol, and triglyceride levels also occurred as a result of energy-restricted Mediterranean diet intervention (73). RAGE mRNA expression and serum CML levels decreased when Mediterranean diet eating habits and scores results improved (74).

AGEs may reduce insulin sensitivity by disrupting insulin receptor signaling pathways in different cells. In human granulosa cells, AGEs affected insulin resistance by significantly reducing insulin-induced phosphorylation of the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) signaling pathway and inhibiting membrane translocation of glucose transporter (GLUT)-4 (75, 76) (Figure 2). In addition to the effect of AGEs on insulin and glucose, hyperandrogenism occurring in PCOS may also affect AGE expression. In human PCOS granulosa cells, testosterone increased RAGE mRNA expression through UPR transcription factor C/EBP homologous protein (CHOP), androgen receptor (AR), and estrogen receptor (ESR)-mediated pathways activated during endoplasmic reticulum (ER) stress (57). In line with all these studies, an increase in AGE/RAGEs may be one of the parameters affecting hyperandrogenism and insulin resistance associated with PCOS.

Endotel dysfunction:

In PCOS, the lysyl oxidase (LOX) (collagen synthesis) enzyme was high, which is involved in endothelial dysfunction and extracellular matrix formation (77-79). The presence of endothelial dysfunction in individuals with PCOS has been found to potentially elevate the likelihood of developing cardiovascular disease. Furthermore, this dysfunction has been seen to be linked with hyperandrogenism (80, 81). Insulin resistance, hyperandrogenism, and obesity are considered as potential mediators of endothelial function in PCOS (82). Serum endothelin-1 (ET-1) and AGE levels were increased in PCOS women and serum AGE levels were positively correlated with ET-1 (51). Endogenous and exogenous AGEs increase circulating AGEs, which may lead to increased insulin resistance, obesity, inflammation, and oxidative stress. This may be effective in the formation of endothelial dysfunction (83, 84). Reducing dietary AGE levels decreased endothelial dysfunction (VCAM-1), insulin resistance, and inflammatory cytokines (85). AGEs increased ET-1 and LOX expression by activating activator protein-1 (AP-1) and NF-kB in endothelial cells (86). A positive relationship was found between LOX staining and AGEs immunoreactivity and NF-kB p65 staining in granulosa cells (87). Inhibition of LOX improved the estrous cycle, luteinizing hormone (LH)/ follicle-stimulating hormone (FSH) ratio, and total number of oocytes (79). This may indicate that increased

AGEs in patients with PCOS may cause endothelial dysfunction by affecting inflammatory pathways, oxidative stress, and markers of endothelial function (Figure 2).

Oxidative stress and inflammation:

PCOS is associated with increased inflammation and oxidative stress. Oxidative stress may increase due to environmental and genetic factors. Oxidative stress can trigger and worsen symptoms associated with PCOS, such as hyperandrogenism, insulin resistance, obesity, infertility, and follicular apoptosis (88). In addition, insulin resistance, hyperandrogenism, and obesity may increase oxidative stress (89). The increase in AGEs may cause oxidative stress by increasing ROS through NADPH oxidase activation (90, 91) (Figure 2). Since PCOS is considered a disease accompanied by low-grade chronic inflammation, an increase in inflammatory cytokines (TNF-α, CRP, IL-8, IL-6, IL-18) may occur (92). In cultivated granulosa-lutein cells, AGE treatment elevated the activating transcription factor 4 (ATF4) mRNA expression, IL-6, and IL-8 (93). In granulosa cells from PCOS women, intervention with sRAGE decreased TNF-α, IL-6, CRP, RAGE, fosfo-ERK, AP-1, fosfo-AKT levels, vascular endothelial growth factor (VEGF), and specificity protein (SP) 1 transcription factor mRNA and protein levels (53, 94). A low AGEs diet or Mediterranean diet may have positive effects on ROS and inflammation by reducing oxidative stress, TNF-α, malondialdehyde (MDA), AGEs, and RAGE levels (65, 66, 95).

AGEs and RAGEs, signaling mediator NF-kB have been observed in the ovarian theca and granulosa cells of PCOS women (56, 87). The ERK and NF-kB pathways are activated when increased AGE levels (96). Activation of AP-1, NF-kB, MAPK pathways, increased phosphorylation of inhibitor of kappa B kinase (IKK)α/β and Ikappa Balfa (IκBα), activation of p38, ERK 1/2, STAT3 signaling pathways increased inflammation through increased level of IL-6, VEGF-A, intracellular adhesion molecule-1 (ICAM-1), ROS (97-99), VEGF, cycloxygenase 2 (COX-2), prostaglandin E2 (PGE2), metalloproteinase-13 (MMP-13) (99), interferon-gamma (IFN-γ), TNF-α (100, 101), IL-1β mRNA expression (102), and IL-17 (103) (Figure 2). In addition, rats fed with high AGEs showed a decrease in GLO-1 activity (104). All these conditions affect follicular development and ovular processes.

Ovarium function

AGEs may affect ovarian function, especially steroidogenesis, and folliculogenesis (105, 106). In luteinized granulosa cells, AGEs significantly increased steroidogenic acute regulatory protein (StAR), CYP11A1 (p450 side-chain cleaving enzyme), CYP17A1 (17α hydroxylase/17,20 lyase), 3β hydroxysteroid dehydrogenase (3β-HSD) mRNA gene expression, luteinized hormone receptor (LHR) and increased estradiol levels in cell culture media (105). Perinatal exposure to a high AGE diet altered ovarian folliculogenesis and gene expression. High AGE consumption caused arrested folliculogenesis, decreased serum anti-mullerian hormone (AMH) levels, ovarian AMH, AMH receptor type 2 (AMHr2), and CYP19A1 (aromatase) mRNA gene expression, and impaired estrous cycles (106). Furthermore, AGEs affect the LH-induced MAPK/ERK signaling pathway and decrease ERK ½ activation in human granulosa cells. In addition, a decrease in FSH-induced ERK ½ phosphorylation may occur. Since ERK 1/2 is involved in cell proliferation, differentiation, and oocyte maturation, it may be effective in folliculogenesis (107). It has been revealed that AGEs may upregulate AMHR-2 gene expression and increase AMH-induced SMAD 1/5/8 phosphorylation in granulosa cells. Therefore, AGEs have the potential to affect folliculogenesis by altering AMH signaling pathways (108) (Figure 2).

In contrast to mice fed a control or low AGE diet, those on a high AGE diet had increased ovarian weight, high AGE expression and RAGE staining in ovarian tissues, and high theca interna AGE expression (63, 104). Human studies have assessed how AGEs and their receptors affect the quantity and quality of oocytes. sRAGE levels of follicular fluid were positively associated with high-quality embryos, number of retrieved oocytes, and fertilized oocytes (109, 110), while a negative correlation was found between AGE in follicular fluid, and the fertilization rate, number of retrieved oocytes, fertilized oocytes, antral follicle count, metaphase II (MII) oocytes, total embryos, and high-quality embryos (111, 112). According to Yao et al. (111), women with less than seven oocytes had significantly higher follicular fluid AGE levels (19.6±4.5 μg/ml) than women with seven to fifteen or more oocytes (15.8±5.7 μg/ml). The cut-off value of follicular fluid AGE concentration for ovarian stimulation was 15.3 μg/ml (111).

Iyer et al. (112) also found that women with <7 MII oocytes had significantly higher AGE (follicular fluid) levels (22.7±11.3 µg/ml) compared to ≥7 MII oocyte numbers (17.2±7.53 µg/ml). In this study, 16.5 µg/ml was set as the cut-off point for follicular fluid AGE level to predict oocyte number and clinical pregnancy. Follicular fluid AGEs above this value may result in lower clinical pregnancy and oocyte response (112). In women aged 37 years and older receiving in-vitro fertilization (IVF) treatment, an increase of 500 pg/mL in follicular fluid sRAGE levels was reported to increase the chance of clinical pregnancy by 64.9% (110). According to another study, the level of AGE in the follicular fluid was found to be greater in the suboptimal group (4-9 oocytes) (6.8 ± 2.20 µg/ml) compared to the optimal group (10-15 oocytes) (5.3 ± 2.01 µg/ml), based on the number of oocytes retrieved (113).

AGEs have effects on hormones as well as ovarian function. Numerous hormones, including leptin, insulin, adiponectin, testosterone, estrogen, progesterone, and AMH, have been linked to higher levels of endogenous and exogenous AGEs in the body. It is thought that AGEs can mimic hormones and bind to or block hormone receptors. In this way, they may affect the action of hormones in the target tissue. In addition, they may act as antagonists and bind to the cell surface or nuclear receptors, thereby inhibiting endogenous hormone signaling (27, 114). Serum sRAGE levels were positively associated with 25 OH vitamin D, follicular fluid AMH, and sex hormone-binding globülin (SHBG) in women undergoing IVF treatment and negatively correlated with glucose and insulin (105, 109). High dietary and serum AGEs were associated with low progesterone and estradiol (E2) levels. Additionally, it was discovered that the expression of granulosa AGE was adversely associated with progesterone and E2 (55, 104). Table 1 shows some studies examining the metabolic and hormonal effects of dietary and nutrition-related AGEs. Figure 2 summarizes the effect of AGEs on female infertility using the research and review articles included in the review (48, 51, 75, 76, 83-87, 90, 91, 93, 96-103, 105-108, 115).

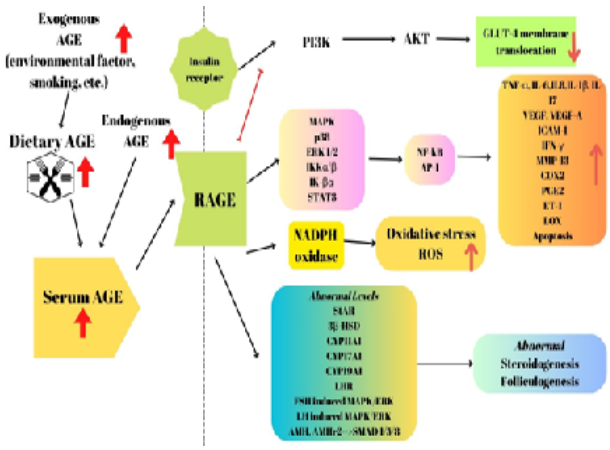

Figure 2. Association of AGEs with Female Fertility

Abbrev AGE: Advanced Glycation End Products, ROS: Reactive oxygen species, RAGE: Receptor AGE, AP-1: Activator protein-1, MAPK: Mitogen-activated protein kinase, NF-kB: Nuclear factor kappa B, PI3K: Phosphatidylinositol 3-kinase, AKT: Protein kinase B, AMH: Anti-Mullerian hormone, AMHr: Anti-Mullerian hormone receptor, StAR: Steroidogenic acute regulatory protein, ERK: Extracellular signal-regulated kinase, CYP11A1: p450 side-chain cleaving enzyme, CYP17A1: 17α hydroxylase/17,20 lyase, 3β-HSD: 3β hydroxysteroid dehydrogenase, CYP19A1: Aromatase, FSH: Follicle stimulating hormone, LHR: Luteinizing hormone receptor, IL: Interleukin, VEGF: Vascular endothelial growth factor, ET-1: Endothelin-1, LOX: Lysyl oxidase, COX-2: Cyclooxygenase 2, PGE2: Prostaglandin, MMP-13: Metalloproteinase-13, TNF-α: Tumor necrosis factor alpha, IFN-γ: Interferon-gamma, GLUT-4: Glucose transporter-4, ICAM-1: Intracellular adhesion molecule-1, IKK: Inhibitor of kappa B kinase, AMHr2: AMH receptor type.

Table 1. Metabolic and Hormonal Effects of AGEs

Authors, year	Sample (Human, Animal, or Cell) and Method	Results	Conclusions
In-vitro studies			
Diamanti-Kandarakis et. al. 2016 (75)	Human granulosa-like tumor cell line (KGN); Group 1: Control Group Group 2: Insulin Group (100 ng/ml) Group 3: Human Glycation Albumin (HGA) Group (50,150,200 µL/ml) Group 4: Insulin (100 ng/ml)+HGA (200 µg/ml)	-Phosphorylated AKT was found to be increased in KGN cells as a result of insulin treatment compared to control and HGA groups. -HGA was demonstrated to reduce the phosphorylation of AKT caused by insulin. -The AKT phosphorylation levels in all treatment groups were reduced to values below basal levels when the KGN cells were subjected to pretreatment with the particular PI3K inhibitor. -Administration of HGA alone and in combination with insulin reduced GLUT-4 membrane translocation.	-AGEs inhibited insulin signaling and reduced membrane translocation of GLUT-4 in granulosa cells. -There is support for the hypothesis that AGE accumulation in the ovaries as a result of endogenous and exogenous AGE sources may influence the pathophysiology of conditions characterized by anovulation and insulin resistance, such as PCOS, by affecting insulin signaling. -An AGE-restricted diet could one day be a new PCOS treatment option.
Merhi et. al. 2018 (105)	In vitro fertilization (IVF) between the ages of 26-42; 71 Follicular Fluid 12 Cumulus Granulosa Cells Group 1: Control (n = 4) Group 2: 0.4 mg/ml HGA intervention (n = 4) Group 3: 0.4 mg/ml HGA+ 100 Nm Vitamin D intervention (n = 4)	-Positive correlations were found between follicular fluid sRAGE levels and 25 OH vitamin D, pentosidine, CML, and sex hormone binding globulin (SHBG), while negative correlations were seen between insulin and glucose levels. -Vitamin D3 reduced the expression of RAGE mRNA and its protein levels. In-vitro HGA intervention bound and activated membrane RAGE. Intervention with HGA; StAR, 3 -HSD, CYP11A1, CYP17A1, and LHR mRNA levels increased, but FSHR mRNA levels and CYP19A1 did not change. -HGA+ vitamin D inhibited the increase in CYP17A1, CYP11A1, StAR, and LHR mRNA levels and decreased CYP19A1 mRNA levels. - Higher estradiol (E2) levels were found in HGA and HGA+Vitamin D groups after 48 hours compared to the control group.	-This study presented evidence that vitamin D supplementation may be useful in preventing some ovarian dysfunctions and that this supplementation may be a strategy to enhance ovarian function. -The discovery of newer therapeutic medicines, such as AGE blockers, may offer a promising strategy for the treatment and prevention of ovarian dysfunction.
Kandaraki et. al. 2018 (107)	Human granulosa KGN cells 100 ng/ml FSH or 200 ng/ml LH Intervention to all cells with 0.2 mg/ml HGA	-It was found that ERK ½ phosphorylation increased in response to LH. - ERK ½ phosphorylation was found to decrease as a result of LH+HGA. -FSH intervention was found to increase ERK ½ phosphorylation and MAPK/ERK kinase (MEK) ½. -FSH+HGA resulted in decreased phosphorylation of MEK ½ and ERK ½.	- AGEs have been found to inhibit the activity of steroidogenic enzymes. -Inappropriate induction of ERK ½ by AGEs may affect follicular response to hormones and differentiation pathways. -The accumulation of AGEs from exogenous or endogenous sources in the intra-ovarium interferes with the effects of LH and FSH hormones. The pathophysiology of diseases like PCOS, which are characterized by anovulation and insulin resistance, may be affected by this, according to certain theories. -Limitations of this study; Use of KGN cells and not primary granulosa cells Use of HGA instead of CML or methylglyoxal for AGEs
Takahashi et. al. 2019 (93)	Cultured human granulosa-lutein cells (GLCs); AGE (µg/mL): 0-50-100-200-500	-AGEs intervention dose-dependently increased IL-8, and IL-6, activating transcription factor 4 (ATF4) mRNA expression. -IL-8 and IL-6 mRNA expression and protein release are elevated by AGE and mediated by ATF4.	-In human granulosa cells, AGEs have been shown to affect inflammatory cytokines.

Table 1. Metabolic and Hormonal Effects of AGEs (continuation of the table)

Authors, year	Sample (Human, Animal, or Cell) and Method	Results	Conclusions
In-vitro studies			
Merhi, 2019 (108)	IVF treatment of 26-42 years of age 6 women's luteinized granulosa cells; Group 1: Control Group Group 2: HGA Group (0.4 mg/ml) Group 3: HGA (0.4 mg/ml)+vitamin D (100 nm) KGN cells; Group 1: Control Group Group 2: Recombinant AMH (rAMH) (50 ng/ml) Group 3: rAMH (50 ng/ml)+ HGA Group (0.4 mg/ml) Group 4: rAMH (50 ng/ml)+HGA (0.4 mg/ml)+vitamin D (100 nm)	Granulosa cells in comparison to the control group; HGA increased AMHR-2 mRNA expression, and AMH mRNA expression was unchanged. HGA+Vitamin D decreased the HGA-induced increase in AMHr2 mRNA expression, and AMH mRNA expression was unchanged. KGN cells in comparison to the control group; rAMH increased the phosphorylation of SMAD 1/5/8. rAMH+HGA treatment increased the SMAD 1/5/8 phosphorylation compared to the other groups. Vitamin D decreased the SMAD 1/5/8 phosphorylation induced by HGA.	Proinflammatory AGEs can affect the level of AMH in granulosa cells. Vitamin D3 can reduce this effect of AGEs, thus acting as an anti-inflammatory agent. Recognizing the AGE-RAGE signaling pathway in PCOS-affected women who experience ovarian dysfunction; o High levels of AGEs, o Abnormally elevated levels of AMH, oLow vitamin D levels, may help to understand the cause
Wang et. al. 2020 (94)	Granulosa cells obtained from follicular fluid from PCOS under the age of 35 years of IVF treatment Group 1: Control 0 µL/ml Sraw Group 2: 0.6 µL/ml sRAGE Group 3: 1.2 µL/ml sRAGE	Intervention with sRAGE compared to the control group; TNF-a , CRP, IL-6, RAGE, AP-1, and p-ERK levels decreased.	In PCOS patients, sRAGE reduced the level of inflammation factors.
In-vivo studies			
Diamanti-Kandarakis et. al. 2007 (63)	60 Winstar Rat (6 Months Intervention) Group 1: Control Group (Standard rat diet) Group 2: Diet Low in AGE Group 3: Diet High in AGE	The group that consumed high AGE feed exhibited higher ovarian weight, fasting glucose, insulin, testosterone, and serum AGE levels in comparison to the other two groups. AGEs was negatively correlated with body weight and significantly positively correlated with ovarian weight, fasting glucose, and serum testosterone levels. It was determined that AGEs expression increased in the ovarian tissues of mice fed high AGE-containing feed compared to control/low AGE-containing feed-fed mice. AGE immunoreactivity was discovered to be present in the ovarian stroma, theca, and luteinized cells. The high AGE group had increased AGE expression in theca interna cells. RAGE expression was significantly higher in granulosa and theca cell layers. RAGE immunoreactivity and staining were higher in high-AGE ovarian tissue AGEs and RAGE staining were observed in uterine tubes in all groups.	Excess dietary glycolytics accumulate in ovarian tissues in experimental animals. Further research into how dietary glycotoxins affect structural and functional changes in the female reproductive system is advised in order to generalize these findings to humans.

Table 1. Metabolic and Hormonal Effects of AGEs (continuation of the table)

Authors, year	Sample (Human, Animal, or Cell) and Method	Results	Conclusions
In--vivo studies			
Kandaraki et. al. 2012 (104)	47 Female Winstar Rat (3 months) Group A (non -androgenized): A1: Diet high in AGE (n: 9) A2: Diet low in AGE (n: 9) Group B (androgenized) B1: Diet high in AGE (n: 14) B2: Diet low in AGE (n: 15)	Group A: A diet with high AGE diet increased ovarian weight, fasting glucose, insulin, testosterone, serum AGE, AGE immunostaining granulosa, and decreased E2, progesterone, and GLO-1 activity. Group B: High AGE diet increased the ovarian weight, fasting insulin, testosterone, serum AGEs, AGEs immunostaining granulosa, decreased E2, and progesterone. When fed the matching meal type, the activity of GLO-I was decreased in androgenized rats compared to non-androgenized animals. (A1>B1, A2>B2) Ovarian GLO-I activity was positively correlated with estradiol, and progesterone levels and negatively correlated with the AGE expression of ovarium granulosa cells. Serum AGE levels were inversely correlated to estradiol and progesterone levels and positively correlated with testosterone, insulin, ovarian weight, and AGE expression in ovarian granulosa cells. In the granulosa cells, the high AGE group showed higher levels of AGE expression.	Dietary AGEs and androgens decreased GLO-1 activity. Increased dietary AGE intake leads to increased ROS. In hyperandrogenic conditions, increased accumulation of AGEs and a concomitant increase in ROS can lead to worsening of already impaired ovarian function. Low dietary AGE intake improved GLO-1 activity. Due to the negative effect of androgens and dietary AGE intake on GLO-1 activity, the use of anti-androgens and consumption of low AGE diets may potentially have a positive effect. Further studies should be conducted in this regard.
Chatzigeorgiou et. al. 2013 (55)	Female Winstar Rat (N: 20) Group 1: Diet Low in AGE Group 2: Diet High in AGE	The group with high dietary AGE intake had increased testosterone, insulin, and glucose levels and decreased E2 and progesterone levels compared to the low group. Positive correlations were found between serum AGE levels and insulin and testosterone, and negative correlations with E2 and progesterone.	It has been reported that the amount of dietary AGEs may affect hormone levels (increase in testosterone level and decrease in E2, and progesterone levels).
Merhi et. al. 2020 (106)	7-week CD1 female mice 2 weeks before mating and 6 weeks after mating during pregnancy and a lactation diet containing a low AGE or High AGE was applied. Group 1: Low Age Diet (n:10) Group 2: High Age Diet (n:13)	Perinatal high AGE diet exposure; Delayed vaginal opening and lower birth weight were observed. The intervention results in a delay in the beginning of puberty, a reduction in the duration of the proestrus phase, and an increase in the duration of the metoestrus phase. Serum AMH, leptin, and adiponectin levels were found to decrease. Although ovarian sizes were similar, they exhibited fewer corpora lutea. Folliculogenesis was interrupted in most follicles at the secondary follicle stage. Ovarian CYP19a1, AMH, and AMHr2 mRNA gene expression were found to be reduced. Similar ovarian mRNA expression of FSHr and LHcgr was observed between the two groups.	Perinatal exposure to a diet high in AGEs; This may lead to impairments in perinatal growth, pubertal onset, and the development of reproductive organs. Decreased ovarian follicular development and ovulation. According to some reports, elevated AGEs may disrupt hypothalamus function, which in turn may affect female reproductive function. As a result, further research on the neuroendocrine axis should be expanded.

Table 1. Metabolic and Hormonal Effects of AGEs (continuation of the table)

Authors, year	Sample (Human, Animal, or Cell) and Method	Results	Conclusions
Human studies			
Iranı et. al. 2014 (59)	Women in PCOS and control groups with vitamin D deficiency; PCOS Group: 22/16 women Control group: 45/35 women Supplementation: 50000 IU Vitamin D3 once a week for 8 weeks	Serum sRAGE and baseline BMI were found to be negatively correlated. Serum AGE was negatively correlated with serum AMH. It was found that AMH level decreased and sRAGE level increased as a result of vitamin D supplementation in the PCOS group.	In vitamin D-deficient PCOS patients, supplementation was linked to normalized serum AMH levels and follicular development. Understanding the function of the AGE-RAGE signaling pathway in the ovaries may present novel therapeutic prospects for the treatment of PCOS-related ovulatory dysfunction.
Tantalaki et. al. 2014 (65)	23 women with PCOS Group A: Baseline (Dietary AGE: 10.9±4.3 x106 U/day Group B: Hypocaloric diet (Dietary AGE: 9.6±4.3 x106 U/day Group C: Isocaloric high AGE diet (Dietary AGE: 16.1±1 x106 U/day Group D: Isocaloric low AGE diet (Dietary AGE: 5.7±0.3 x106 U/day	HOMA-IR, insulin, serum AGE, testosterone, SHBG, oxidative stress, and free androgen index (FAI) increased in the group consuming a high AGE diet compared to baseline. HOMA-IR, insulin, serum AGEs, testosterone, and oxidative stress were decreased in the group consuming a low AGE diet compared to the group consuming a high AGE diet. Serum AGE levels (IU/mL) group A, B, C, and D respectively: 9.1±1.4, 8.9±1.6, 10.4±1.4, 8.2±1.6 IU/mL.	Exogenous AGEs, which are known to be powerful endocrine disruptors and are frequently found in Western diets, may be a contributing factor in PCOS by aggravating the metabolic, hormonal, and oxidative stress.
Merhi et. al. 2014 (109)	31 women to evaluate serum levels 33 women receiving IVF treatment for follicular fluid assessment The evaluation was made according to BMI groups.	BMI and serum sRAGE were found to be negatively correlated. It was found that serum sRAGE level was higher in subjects with BMI <25 kg/m^2 compared to subjects with BMI ≥25 kg/m^2. The number of oocytes retrieved correlated positively with follicular fluid sRAGE level. Follicular fluid sRAGE level was positively correlated with AMH protein level.	The levels of sRAGE and AMH in follicular fluid were related. This suggests that sRAGE is associated with the reproductive system. It has been suggested that the function of sRAGE in follicular fluid has not been conclusively proven but may reflect the activity of the AGE-RAGE axis in ovarian follicles. sRAGE has been implicated in the pathophysiology of ovarian health
Liao et. al. 2017 (60)	18-44 ages 148 women diagnosed with PCOS; Group 1: Normal body weight <24 kg/m^2 (n: 53) Group 2: Overweight ≥24- <28 kg/m^2 (n: 50) Group 3: Obese ≥ 28 kg/m^2 (n: 45)	Obese women had elevated levels of serum AGEs in comparison to the other two groups. Women with a normal body weight had a greater level of serum sRAGE in comparison to the other two groups. The serum sRAGE level of women with abdominal obesity (waist circumference >85 cm) was found to be lower compared to women without abdominal obesity. When HOMA-IR and FAI were divided into quartiles, the sRAGE level in the fourth quartile was found to be lower compared to the first quartile.	sRAGE has been related to FAI and insulin resistance in PCOS. The AGE/sRAGE system, in especially for obese women with PCOS, may represent a feasible therapeutic target, although further study is required to properly comprehend and describe the role of sRAGE.

Table 1. Metabolic and Hormonal Effects of AGEs (continuation of the table)

Authors, year	Sample (Human, Animal, or Cell) and Method	Results	Conclusions
Human studies			
Emami et. al. 2023 (61)	PCOS women: 26 Non-PCOS women: 19	Compared to PCOS women, women without PCOS consumed considerably more dietary AGE. The levels of serum/follicular fluid sRAGE were found to be similar in both women with PCOS and those without PCOS. There was a significant positive correlation between BMI and a negative correlation between age with follicular fluid sRAGE levels in the PCOS group. A negative significant correlation was found between dietary AGE intake and follicular fluid sRAGE levels. A significant positive relationship was observed between the levels of sRAGE in serum and follicular fluid across all groups. PCOS and non-PCOS group follicular fluid sRAGE levels respectively: 3.6±1.33 and 3.5±1.04 ng/mL PCOS and non-PCOS group serum sRAGE levels respectively: 2.8±1.45 and 2,9±1.33 ng/mL PCOS and non-PCOS group dietary AGE intake respectively: 7490±3782.91 and 12698±7141.41 kU/100 g	This study found no significant difference in sRAGE (serum and follicular fluid levels) between women with PCOS and women without PCOS. Dietary AGE intake and BMI are parameters associated with sRAGE. There is a need for research with larger sample sizes in order to adequately monitor and evaluate the long-term effects of consuming a high dietary intake of AGEs.

Abbreviations: AGE: Advanced Glycation End Products, sRAGE: Soluble receptor AGE, RAGE: Receptor AGE, ROS: Reactive oxygen species, NF-kB: Nuclear factor kappa B, AP-1: Activator protein-1, MAPK: Mitogen-activated protein kinase, PI3K: Phosphotidylinositol 3-kinase, LHR: Lutehinizing hormone receptor, AMH: Anti Mullerian hormone, AMHr: Anti Mullerian hormone receptor, AMHr2: AMH receptor type 2, rAMH: Recombinant AMH, ERK: Extracellular signal-regulated kinase, StAR: Steroidogenic acute regulatory protein, CYP11A1: p450 side chain cleaving enzyme, CYP17A1: 17 hydroxylase/17,20 lyase, 3 -HSD: 3 hydroxysteroid dehydrogenase, CYP19A1: Aromatase, FSH: Follicle stimulating hormone, IL: Interleukin, VEGF: Vascular endothelial growth factor, ET-1: Endothelin-1, LOX: lysyl oxidase, COX-2: Cyclooxygenase 2, PGE2: Prostoglandin, MMP-13: Metalloproteinase-13, BMI: Body mass index, TNF-a : Tumor necrosis factor alpha, ICAM-1: Intracellular adhesion molecule-1, IFN-a : Interferon gamma, GLUT-4: Glucose transporter-4, HGA: Human glycation albumin, KGN: Human granulosa-like tumor cells, CML: Carboxy methyl lysine, GLO-1: Glyoxalase-1, IVF: In vitro fertilization, PCOS: Polycystic ovary syndrome, AKT: Protein kinase B, E2: Estradiol, ATF4: Activating transcription factor 4, FAI: Free androgen index, GLCs: Cultured human granulosa-lutein cells, HOMA-IR: Homeostasis Model Assessment of Insulin Resistance, MEK: MAPK/ERK kinase, CRP: C-reactive protein, LH: Luteinizing hormone, LHcgr: Luteinizing hormone/choriogonadotropin receptor

CONCLUSION AND RECOMMENDATIONS

Higher dietary intake of AGEs has been linked to elevated levels of AGEs and RAGE in theca and granulosa cells. This results in altered potential oocyte function, fertilization, and embryo development. Increased AGEs affect the increase of RAGE, which in turn increases inflammation and reactive oxygen species. In addition, increased dietary AGE intake decreases GLUT-4 expression, reducing glucose entry into the ovarium cells. This has been shown to impair follicular development and lead to abnormal ovular processes. Advanced glycation end products were negatively associated with follicular growth, oocyte number, fertilization rate, embryo development, and pregnancy rate, while sRAGE was positively associated with oocyte number, pregnancy rate, and follicular fluid AMH level. Reducing dietary AGE intake was associated with a decrease in serum AGE and receptors and may have positive effects on reproductive functions. It is important to make lifestyle changes to reduce dietary AGE intake. Increased physical activity, body weight loss, and healthy dietary modifications are recommended. Effective strategies for reducing dietary AGEs include decreasing the intake of saturated fats, processed foods, and refined carbohydrates while increasing the consumption of whole grains, vegetables, fruits, and low-fat dairy products. Additionally, minimizing the use of dry heat and high-temperature cooking methods such as roasting, frying, grilling, and baking can also contribute to the reduction of dietary AGEs. In particular, the Mediterranean diet is one of the nutrition models that may have a positive effect on the reduction of dietary AGE intake.

Although there are studies to evaluate the effect of dietary AGE and AGE-RAGE signaling pathways on ovular function, it is important to increase the number of these studies. Especially in the case of female fertility, it is necessary to evaluate the effect of different dietary intervention studies on diet, serum, follicular fluid AGE/Receptors, and disease-related parameters. The realization of these studies will be instructive in explaining the effect of nutrition on the AGE/RAGE axis and the female reproductive system.

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