ONLINE FIRST

REVIEW ARTICLE

A Systematic Review on the Role of Advanced Glycation End-products (AGEs) in the Development of PCOS

Yasmin Akhtar[1], Salma Malik[2], Muna Bhutta[3], Sara Muhammad Atta Almanan[3], Tahira Bashir Solehria[4], Muhammad Kashif Malik[5*]

[1]*Khyber Medical College, Peshawar, KPK-Pakistan*
[2]*Al-Hammadi Hospital, Riyadh, Saudi Arabia*
[3]*Al-Iman General Hospital Riyadh, Saudi Arabia*
[4]*Kingdom Hospital, consulting Clinics, Riyadh, Saudi Arabia*
[5]*Prince Sultan Military Medical City, Riyadh, Saudi Arabia*
Correspondence: *drkmalik71@gmail.com*
doi: 10.22442/jlumhs.2024.01101

ABSTRACT

This review was done to investigate the research done globally and in Pakistan about the role of AGEs in developing PCOS. Literature was searched at any time by using Google Scholar and PubMed. Keywords used were "PCOS", "polycystic ovarian syndrome", "Advanced glycation end-products", "AGEs", and "Pakistan". Inclusion criteria were original research on humans, animals, or cell culture, showing the effect of AGEs on ovarian tissue. No research was found in Pakistan, emphasizing the point that Pakistan does not take the issue of AGEs seriously. All that was found was the relationship of AGEs with cardiovascular diseases or the prevalence of PCOS in Pakistani women. The original research done elsewhere globally was included in this review. Eighteen research studies have been conducted since 2000, including the relationship of AGEs with PCOS. Five studies found higher levels of AGEs in the blood and ovaries of patients with PCOS compared to controls. Three studies showed that dietary AGEs were directly associated with PCOS. Five animal (rats/mice) studies showed the effect of a diet high in AGEs on the ovaries of mice. Three cell line studies also showed a relationship between AGEs and ovarian tissues. Almost all human, animal, or cell-line studies showed the relationship of AGEs on the morphology or functioning of ovarian tissue. An easier way to prevent PCOS might be to control the AGE content in the diet.

KEYWORDS: PCOS, polycystic ovarian syndrome, Advanced glycation end-products, AGEs, Pakistan.

INTRODUCTION

Globally, about 70% of females are infertile due to PCOS[1]. Pakistan has an infertility rate of 21.9%, of which 38.5% is attributable to PCOS.[2] Worldwide prevalence of PCOS ranges from 2.2 to 26%, and the estimated prevalence of PCOS in Pakistan is 17.6%.[3] However, the frequency of PCOS in Pakistani women was claimed to be 52% in some studies, which is more than double that in the white population[4–7]. The annual economic cost for the initial evaluation of PCOS is 93 million dollars, and the total assessment and treatment of PCOS women is 4.36 billion dollars in the USA[8].

Like many other non-communicable metabolic diseases, the prevalence of PCOS is increasing as a result of modern lifestyle factors[9]. Advanced glycation end products (AGEs) in food are produced by the thermal processing of food, a prevalent technique used for food production[10]. Thermal processing results in a "Maillard reaction", which forms glycated molecules, and further chemical changes produce irreversible AGEs. AGEs have also been implicated as a cause of PCOS, as their levels are raised in the blood and ovaries of women with PCOS[11].

The world, as well as Pakistan, holds a significant burden of infertility due to PCOS. This review investigated how much research was done globally and in Pakistan about the role of AGEs in developing PCOs and to which extent further studies were needed globally and in Pakistan.

METHODOLOGY & DISCUSSION

Literature has been searched for any time previously by using Google Scholar and PubMed. Original research articles were searched in the English language only. Keywords used were "PCOS", "polycystic ovarian syndrome", "Advanced glycation end-products", "AGEs", and "Pakistan". Inclusion criteria were original research on humans, animals, or cell culture, showing the effect of AGEs on ovarian tissue. No other types of research were added. The study was conducted from September to December 2023. Hence, the time taken for the composition of the review was about three months. AMSTAR 2 was used for the quality assessment of the review. (**Figure I**)

No research was found in Pakistan on the relationship of AGEs with PCOS. All that was found was the relationship of AGEs with cardiovascular diseases or the prevalence of PCOS in Pakistani women. To emphasize the effects of AGEs on PCOS, the original research done elsewhere globally was included in this review. The earliest research on this topic was a human study in Greece in 2005. **(Table I)**

A total of 84 articles were identified, of which three were duplicates. Twenty-eight review articles were excluded. Three studies showed the effects of different substances on AGE levels, and they were excluded. Similarly, 29 studies showing the effects of AGEs on conditions other than PCOs were also excluded from the review. Three studies were excluded as they provided information about the origin of AGEs alone. Hence, 18 studies were included in the review, out of which Nine were human studies, five were animal studies, and four were ovarian cell line studies. **(Table I)**

Eighteen research studies have been conducted since 2000, including the relationship of AGEs with PCOS. Five studies from Greece found higher levels of AGEs in the blood and ovaries of patients with PCOS compared to controls. A non-randomized interventional study from Greece showed that dietary AGE modifications were directly associated with changes in metabolic and hormonal profiles in women with PCOS. One retrospective case-control study from India showed higher chances of developing PCOS in women who consumed higher amounts of AGEs

in their diet. Similarly, a retrospective case-control study from Iran showed that healthy eating habits were associated with decreased odds of getting PCOS. However, one retrospective case-control study from Iran showed lesser food consumption and lower AGE levels in PCOS patients than in the control group because these patients were being treated for a long time.

Five animal (rats/mice) studies have been conducted since 2012. One of these studies showed an accumulation of AGEs in the ovaries of PCOS mice compared to those of controls. Four (4) of these studies showed the effect of a high-age diet on these animals. All these studies showed impairment of ovarian morphology and functions. **(Table I)**

One Human ovarian cell study from Japan showed higher amounts of AGEs in tissues from PCOS patients than controls. Two cell line studies showed cyst formation due to the effects of AGEs on these tissues. One such study also showed impairment of insulin signaling due to AGEs and concluded that this impairment could contribute to PCOS. **(Table I)**

Almost all the global studies included in this systematic review showed a positive relationship between AGEs and PCOS. No studies were found in Pakistan about the relationship of AGEs with PCOS; however, studies on the relationship of AGEs with cardiovascular and other conditions in Pakistan. Other studies found in Pakistan were the prevalence studies of PCOS in Pakistani women. Only one human study was found from India, and two from Iran. Japan and Taiwan were the other Asian countries where cell culture and animal studies were conducted. Amongst European countries, most human studies were from Greece. Only one animal study was found in Italy. No study was found from any other continent, although PCOS has been found in almost every part of the world and ethnicity[28]. **(Table I)**

PCOS might result from modern sedentary urban environments defined by diet changes, low physical activity levels, and increased exposure to environmental pollutants in urban areas[29]. Studies from Pakistan and India also showed a higher prevalence of PCOS in the urban population compared to the rural population[30,31]. Rapid economic changes have led developing countries like India and Pakistan to adopt an energy-rich diet and a sedentary lifestyle. A study in Pakistan observed that the probability of developing PCOS was most significant at adolescence and younger ages compared to older age groups[32]. A growing prevalence of PCOS was found even in the pre-adolescent age group. The youth indulge in junk food as it is cheaper and due to the 'Westernization' of lifestyles[33,34]. Although about three-fourths of PCOS patients are overweight and/or obese[35], interestingly, obesity is not included in the definition of PCOS. According to the definition, PCOS is characterized by menstrual abnormalities, acne, hirsutism, high androgen levels, and changes in ovarian morphology. The International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome stresses the importance of diet and physical activity to prevent complications of PCOS[36].

Rapid changes in economies have led to busier lifestyles and families with both working parents and have resulted in quick meal solutions[37]. These factors led to adopting an energy-rich diet and a sedentary lifestyle. Many new dietary components, food preservation techniques, cooking methods, new environmental chemicals, and toxins have surfaced and diffused through human culture[9]. Food processing prolongs shelf-life, increases the convenient availability of ready-to-eat and semi-prepared foods, and decreases the cost of food[38]. Heat treatment of food is a widespread technique used to produce food. High temperature produces flavor and gives desired color to food products, like coffee and cereals roasting, cakes and bread baking, and meat grilling. The underlying mechanism for their formation is the "Maillard reaction" [10].

The Maillard reaction produces glycated molecules, which on further chemical changes of these products, result in the formation of irreversible AGEs. AGEs are heterogeneous substances

produced by reactions between reducing sugars or oxidized lipids and free amino acids, phospholipids, or nucleic acids (**Figure II**). The reaction of primary amines with carbonyl compounds produces Schiff bases[39]. AGEs formed by sugar-derived carbonyls include CEL and MG-H1. AGEs formed by lipid peroxidation and oxidative stress include CML, a ligand for the receptor for AGEs (RAGE) (**Figure II**)[40]. AGEs adversely affect several processes either directly by linking with proteins or indirectly by binding to receptors on the surface of different cells. When bound to receptors, AGEs activate various pathways that regulate protein transcription within living cells. Hence, AGEs can affect tissue activities like cell development/cell death. AGEs are found in people with diabetes due to glucose substrates and in aging patients due to oxidative damage. AGEs are believed to participate in the pathophysiology of many chronic diseases. AGE levels are raised in the blood and ovaries of patients with PCOS and might contribute to the metabolic changes happening in polycystic ovarian syndrome. In vitro and animal studies advocate that AGEs might be related to abnormal steroid production and follicle formation. AGEs could alter insulin intracellular signaling for glucose transporters, hence leading to insulin resistance[41].

Exogenous sources of AGEs are cooked foods, like fried, baked, microwave-heated food, and especially caramelized food[42]. AGEs naturally occur in raw animal-origin foods because they are high in protein and/or fat (**Table II**). Dry heating results in the formation of ten to a hundred times new AGEs as compared to uncooked food[39]. Within the meat group, items made by related methods showed that the highest levels of AGEs were present in beef and cheeses (**Table II**), and chicken, fish, and eggs followed these[39,43]. Over the past decades, the consumption of broiler chicken has increased in the Pakistani population because broiler chicken is the most economical and accessible source of animal protein in developing countries like Pakistan[44]. Lean red meats and chicken also contain high levels of AGEs when cooked with dry heat because lean muscle has highly reactive amino-lipids, along with reducing sugars, like fructose or glucose-6-phosphate[43]. Storage also affects the AGE contents of meat due to the oxidation and Maillard reaction that occurs continuously during storage[45]. During freeze-thaw cycles, AGEs increase significantly in meats because these cycles accelerate the oxidation of lipids and proteins, which can generate large amounts of free radicals, promoting the Maillard reaction and formation of AGEs[46].

High-fat cheeses, like American cheese and Parmesan, contain more AGEs than lower-fat cheeses, like low-fat mozzarella, cheddar, and cottage cheese[43]. Like cheeses, uncooked food items obtained from animals contain large amounts of AGEs (**Table II**); this probably occurs due to pasteurization, or keeping these items for a long time at room temperature, like in preservation by smoking, salting, and drying, or like in the aging process. Followed by oils and nuts, high-fat spreads like butter, margarine, cream cheese, and mayonnaise are also very high in AGEs. Various extraction and cleansing processes, demanding heat, and air and dry conditions make certain cheeses, oils, and butter AGE-rich, even uncooked[43].

An average human diet consists of approximately 75 mg of AGEs each day[42]. Glycated proteins, huge ones, are resistant to proteases. Hence, it is difficult to remove them from the organisms' systems. It is roughly calculated that approximately 30% of AGEs are removed in the urine through a healthy kidney; otherwise, the excreted amount is lower[47]. A list of AGE content in food samples was prepared from 2003 to 2008 in New York, USA. Foods were cooked using standard cooking techniques like boiling, broiling, deep-frying, oven-frying, and roasting[43]. The primary AGE analyzed in this list was CML. Raw beef and chicken have higher AGE content than milk and carbohydrates.

Higher fat content was found to increase AGE content, for example, higher fat percentage in beef as compared to lean beef, and skin in chicken as compared to skinless chicken (**Table II**). Microwave has lesser AGE content than grilled or fried meat, but much higher than raw, steamed, or boiled meat. Grilled beef has a higher AGE content than pan-fried or deep-fried meat. Similarly, like commercially fried chicken, breaded and deep-fried chicken has much higher AGE content, especially if cooked with skin. The fried egg has a very high AGE content compared to the poached one (**Table II**). Cheese has a very high AGE content even when uncooked, and even higher AGE content with higher fat content than low-fat ones (**Table II**). All nut butter, butter, oils, mayonnaise, and margarine have very high AGE content. Milk and fruit juices have shallow AGE content. Amongst carbohydrate foods, boiled rice and potatoes have low AGE content. AGE content is very high in potato French fries, especially commercially cooked. Pasta has a somewhat higher AGE content than bread and rice because it has a higher protein content in its structure, and it is also processed before cooking (**Table II**).

About 70% of females are infertile due to PCOS[1], and Pakistan has 38.5% of infertility attributable to PCOS.[2] Although the global prevalence of PCOS ranges from 2.2 to 26% and the estimated prevalence of PCOS in Pakistan is 17.6% [3], the prevalence of PCOS in South Asian women, especially in Pakistani women, was claimed to be 52% in some studies, which is more than double that in the UK population.[4–7,44] The annual economic cost for the initial evaluation of PCOS is 93 million dollars and is even more significant to the total assessment and treatment of PCOS women, i.e., 4.36 billion dollars in the USA[8] the need for control of this AGE intake cannot be overemphasized.

Diminished intake of AGEs can be attained by decreasing high AGE items, including cheeses, meats, and highly treated foods. AGE levels of AGEs are lower in cooked carbohydrate foods like fruits, vegetables, whole grains, and milk (**Table II**) [39]. Hence, consuming fish, grains, fruits, vegetables, and low-fat milk should be encouraged. Consumers should be instructed about low-AGE-producing cooking techniques for meats like boiling, poaching, and stewing[10]. Food should be prepared at low temperatures, for shorter periods, and with high moisture, and acidic marinades like lemon juice and vinegar should be used. Vitamin D supplementation elevates serum RAGE levels (which prevent deposition of AGEs) in women with PCOS. At the same time, Metformin can downregulate RAGE in osteoblast-like cells and inhibit AGE deposition[48].

Table I: Studies included in the systematic review

First author, Year	Country	Subjects, animals, or cell lines	Findings
[12] Diamanti-Kandarakis, 2005	Greece	29 women with PCOS/ 22 non-PCOS women	AGEs* were higher in the serum of PCOS** patients as compared to non-PCOS patients.
[13]Diamanti-Kandarakis, 2007	Greece	6 women with PCOS/ 6 non-PCOS women	AGEs were higher in the ovaries of PCOS patients as compared to non-PCOS patients.
[14]Diamanti-Kandarakis, 2008	Greece	100 women with PCOS/ 25 non-PCOS women	AGEs were higher in the serum of PCOS patients as compared to non-PCOS patients.
[15]Diamanti-Kandarakis, 2009	Greece	37 women with PCOS (anovulatory)/ 23 women with PCOS (regularly ovulating)/ 11 non-PCOS anovulatory women/ 25 normal women.	AGEs were higher in the serum of PCOS patients as compared to non-PCOS patients.
[16]Charikleia, 2011	Greece	75 women with PCOS/ 25 non-PCOS women	AGEs were higher in the serum of PCOS patients as compared to non-PCOS patients.
[17]Tantalaki, 2014	Greece	23 PCOS women	Dietary AGEs modifications are associated with parallel changes in metabolic and hormonal changes in PCOS patients.
[18]Mohan, 2019	India	52 PCOS women/ 104 non-PCOS women	Women who consume high AGE in diet have four times higher chances of developing PCOS.
[19]Hosseini, 2017	Iran	99 PCOS patients/198 non-PCOS patients	Healthy eating is inversely associated with the risk of PCOS in adult women.
[20]Emami, 2023	Iran	19 PCOS patients/ 26 non-PCOS patients	Low diet intake and low AGEs levels were found in PCOS patients.
[21]Azhary, 2020	Japan	Granulosa cells from 11 PCOS/ 10 controls	AGEs levels are higher in granulosa cells of PCOS patients than in controls

[21]Azhary, 2020	Japan	10 mice with PCOS/ 10 controls	AGE levels are higher in granulosa cells of mice with PCOS
[22]Kandaraki, 2012	Greece	23 female Wistar rats fed chow high in AGE/ 24 rats fed with chow low in AGE.	Better ovarian activity was observed in the low-AGE diet group
[23]Chatzigeorgiou, 2013	Greece	10 female Wistar rats fed with chow high in AGE/ 10 rats fed with chow low in AGE.	Ovarian activity was affected by high-AGE diet
[24]Di Emidio, 2019	Italy	9 female CD-1 mice fed with chow high in AGE/ 9 rats fed with water	Mice fed with AGE diet showed ovarian functional alterations
[25]Lin, 2019	Taiwan	12 rats fed with AGE/ 12 rats not fed with AGE	Ovarian morphology was affected by the AGE diet
[25]Lin, 2019	Taiwan	Human ovarian granulosa cell line (KGN) treated with AGEs	AGEs have deleterious effects on ovarian cells, and a raised number of follicle cysts were found
[26]Papachroni, 2010	Greece	Ovarian tissues from PCOS women/controls	AGEs promote cyst formation in ovaries
[27]Diamanti-Kandarakis, 2016	Greece	Human ovarian granulosa cell line (KGN) treated with AGEs	Intraovarian AGEs affect insulin function and might contribute to PCOS.

*Advanced glycation end-products, **Polycystic ovarian syndrome

Table II: Advanced glycation end-product content in various foods

Food item with cooking method/preparation:	AGE*(kilounits):	Serving size:
Beef:		
Beef, raw	707	100 grams
Beef, steak, microwaved, 6 min	2,687	100 grams
Beef, ground, pan browned, marinated 10 min with lemon juice	3,833	100 grams
Beef, ground, 20% fat, pan browned	4,928	100 grams
Beef, roast	6,071	100 grams
Beef, steak, grilled 4 min	7,416	100 grams
Beef, steak, pan-fried w/olive oil	10,058	100 grams
Chicken:		
Chicken, breast, skinless, raw	769	100 grams
Chicken, breast, steamed in foil, 15 min	1,058	100 grams
Chicken, breast, boiled in water	1,210	100 grams
Chicken, breast, skinless, microwave, 5 min	1,524	100 grams
Chicken, breast, skinless, roasted	4,768	100 grams
Chicken, breast, breaded/pan fried	7,430	100 grams
Chicken, breast, breaded, deep fried, 20 min	9,722	100 grams
Chicken, breast, breaded, oven-fried, with skin	9,961	100 grams
Egg:		
Egg, poached, below simmer, 5 min	90	100 grams
Egg, fried, one large	2,749	100 grams
Cheese:		
Cheese, cottage, 1% fat	1,453	100 grams
Cheese, mozzarella, reduced fat	1,677	100 grams
Cheese, cheddar, aged, 2% fat	2,457	100 grams
Cheese, cheddar	5,523	100 grams
Cheese, American, white, processed	8,677	100 grams
Cream cheese, Philadelphia original (Kraft)	8,720	100 grams
Fast food:		
Macaroni and cheese	2,728	100 grams
Beef, hamburger (McDonald's)	5,418	100 grams
Pizza, thin-crust	6,825	100 grams
Fats:		
Peanut butter, smooth	7, 517	100 grams
Oil, canola	9,020	100 ml
Mayonnaise	9,400	100 grams
Oil, olive	11, 900	100 ml
Margarine	17,500	100 grams
Butter	26, 480	100 grams
Milk:		

Milk, whole (4% fat)	5	250 ml
Milk, fat-free, with A and D (microwaved, 2 min)	8	250 ml
Milk, fat-free, with A and D (microwaved, 3 min)	34	250 ml
Bread:		
Bread, white, slice	83	100 grams
Bread, white, slice, toasted	107	100 grams
Rice, white, quick cooking, 35 min	9	100 grams
Pasta, cooked 12 min	242	100 grams
Potato, white, boiled for 25 min	17	100 grams
Potato, white, roasted 45 min, with 5 ml oil	218	100 grams
Potato, white, French fries, homemade	694	100 grams
Potato, white, French fries (McDonald's)	1,522	100 grams
Fruit juice:		
Juice, orange, from fresh fruit	0	250 ml
Juice, apple	2	250 ml
Juice, orange	6	250 ml

*Advanced glycation end-products

Figure I: Flow diagram of systematic review

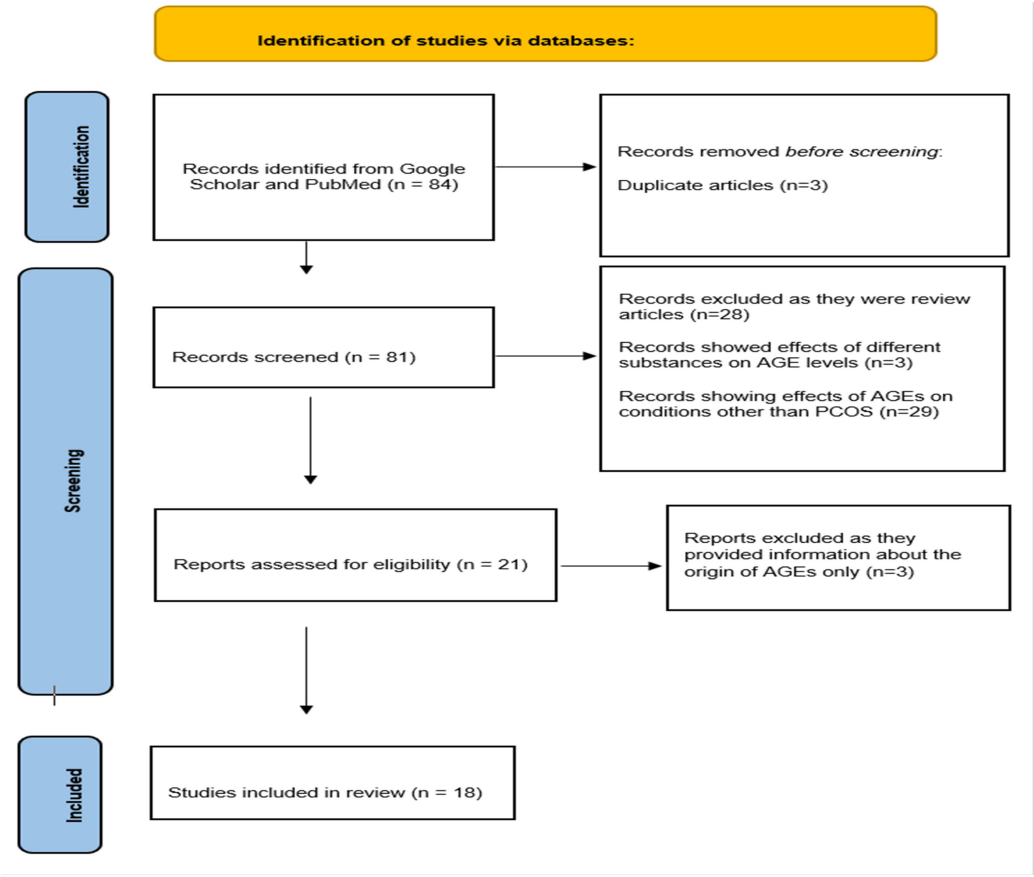
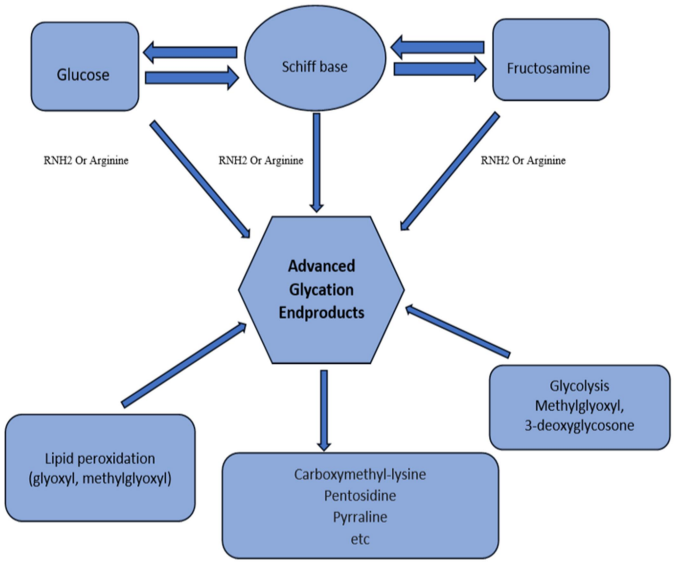


Figure II: Formation of AGE's in vivo (Adopted version)[49]



CONCLUSION

Almost all human, animal, or cell-line studies showed the relationship of AGEs on the morphology or functioning of ovarian tissue. An easier way to prevent PCOS might be to control the AGE content in the diet.

Conflict of Interest: No conflicts of interest, as stated by authors.
Financial Disclosure / Grant Approval: No funding agency was involved in this research.
Data Sharing Statement: The corresponding author can provide the data proving the findings of this study on request. Privacy or ethical restrictions bound us from sharing the data publically. The questionnaire used in this is given in the Annexure.

AUTHOR CONTRIBUTION

Akhtar Y:	Concept of study, critical review, final approval
Malik S:	Concept of study, drafting, final approval
Bhutta M:	Data analysis, drafting, final approval
Almanan SMA:	Data analysis, critical review, final approval
Solehria TB:	Interpretation of data, drafting, final approval
Malik MK:	Data analysis, drafting, final approval

REFERENCES

1. Ajmal N, Khan SZ, Shaikh R. Polycystic ovary syndrome (PCOS) and genetic predisposition: A review article. EJOG: X. 2019;3:100060. doi:10.1016/j.eurox.2019.100060
2. Rizvi M, Islam MdA, Aftab MT, Naqvi AA, Jahangir A, Ishaqui AA et al. Knowledge, attitude, and perceptions about polycystic ovarian syndrome, and its determinants among Pakistani undergraduate students. Mallhi TH, ed. PLoS ONE. 2023;18(5):e0285284. doi:10.1371/journal.pone.0285284
3. Lone, Munawar N, Babar S, Sultan S, Malik S, Nazeer K, Riaz S. Association of the CYP17 and CYP19 gene polymorphisms in women with polycystic ovary syndrome from Punjab, Pakistan. Gynecol. Endocrinol. 2021;37(5):456-461. doi:10.1080/09513590.2020.1822803
4. Azhar A, Abid F, Rehman R. Polycystic Ovary Syndrome, Subfertility and Vitamin D Deficiency. J Coll Physicians Surg Pak. 2020;30(05):545-546. doi:10.29271/jcpsp.2020.05.545
5. Sidra S, Tariq MH, Farrukh MJ, Mohsin M. Evaluation of clinical manifestations, health risks, and quality of life among women with polycystic ovary syndrome. Garzon S, ed. PLoS ONE. 2019;14(10):e0223329. doi:10.1371/journal.pone.0223329
6. Zulfiqar S, Noor S, Rafique S, Rehman B, Babar A, Shahid T et al. Investigation of Prevalence and Awareness of Polycystic Ovary Syndrome among Pakistani Females: Polycystic Ovary Syndrome in Pakistani Women. PPASB. 2022;59(1):77-83. doi:10.53560/PPASB(59-1)703
7. Shakeel M, Ashraf F, Wajid A. Sexual functioning as predictor of depressive symptoms and life satisfaction in females with Polycystic Ovary Syndrome (PCOS). Pak J Med Sci. 2020;36(7). doi:10.12669/pjms.36.7.2562
8. Malik M, Latif F, Hussain A. Health Related Quality of Life and Depression among Women with Poly Cystic Ovary Syndrome (PCOS) in Pakistan. BJMHR. 2020;7(12):28-43. doi:10.46624/bjmhr.2020.v7.i12.003
9. Rodgers RJ, Suturina L, Lizneva D, Davies MJ, Hummitzsch K, Irving-Rodgers HF et al. Is polycystic ovary syndrome a 20th-century phenomenon? Med. Hypotheses. 2019;124:31-34. doi:10.1016/j.mehy.2019.01.019
10. Nowotny K, Schröter D, Schreiner M, Grune T. Dietary advanced glycation end products and their relevance for human health. ARR. 2018;47:55-66. doi:10.1016/j.arr.2018.06.005
11. Mouanness M, Nava H, Dagher C, Merhi Z. Contribution of Advanced Glycation End Products to PCOS Key Elements: A Narrative Review. Nutrients. 2022;14(17):3578. doi:10.3390/nu14173578
12. Diamanti-Kandarakis E, Piperi C, Kalofoutis A, Creatsas G. Increased levels of serum advanced glycation end-products in women with polycystic ovary syndrome. Clin. Endocrinol. 2005;62(1):37-43. doi:10.1111/j.1365-2265.2004.02170.x
13. Diamanti-Kandarakis E, Alexandraki K, Piperi C, Aessopos A, Paterakis T, Katsikis I et al. Effect of metformin administration on plasma advanced glycation end product levels in women with polycystic ovary syndrome. Metab. 2007;56(1):129-134. doi:10.1016/j.metabol.2006.09.006
14. Diamanti-Kandarakis E, Katsikis I, Piperi C, Kandaraki E, Piouka A, Papavassiliou AG et al. Increased serum advanced glycation end-products is a distinct finding in lean women with polycystic ovary syndrome (PCOS). Clin. Endocrinol. 2008;69(4):634-641. doi:10.1111/j.1365-2265.2008.03247.x

15. Diamanti-Kandarakis E, Piouka A, Livadas S, Piperi C, Katsikis I, Papavassiliou AG et al. Anti-mullerian hormone is associated with advanced glycosylated end products in lean women with polycystic ovary syndrome. Eur. J. Endocrinol. 2009;160(5):847-853. doi:10.1530/EJE-08-0510
16. Charikleia C, Frangiskos E, Sarantis L, Christina P, Christos A, Evangelos M et al. Strong and positive association of Endothelin-1 with AGEs in PCOS: A causal relationship or a bystander? Hormones. 2011;10(4):292-297. doi:10.14310/horm.2002.1320
17. Tantalaki E, Piperi C, Livadas S, Kollias A, Adamopoulos C, Koulouri A et al. Impact of dietary modification of advanced glycation end products (AGEs) on the hormonal and metabolic profile of women with polycystic ovary syndrome (PCOS). Hormones. 2014;13(1):65-73. doi:10.1007/BF03401321
18. Mohan S, Db S. Relation between dietary advanced glycation end (AGE) products and polycystic ovary syndrome (PCOS) – evidence from a case-control study. RNJPH. 2019;4(4).
19. Hosseini MS, Dizavi A, Rostami H, Parastouei K, Esfandiari S. Clinical Research Development Unit, Baqiyatallah University of Medical Sciences, Tehran, Iran., Dizavi A, et al. Healthy eating index in women with polycystic ovary syndrome: A case-control study. IJRM. 2017;15(9):575-582. doi:10.29252/ijrm.15.9.575
20. Emami N, Alizadeh A, Maleki-Hajiagha A, Dizavi A, Vesali S, Moini A. Serum and follicular fluid levels of soluble receptor for advanced glycation end-products in women with and without polycystic ovary syndrome. J Ovarian Res. 2023;16(1):127. doi:10.1186/s13048-023-01224-z
21. Azhary JMK, Harada M, Kunitomi C, Kusamoto A, Takahashi N, Nose E et al. Androgens Increase Accumulation of Advanced Glycation End Products in Granulosa Cells by Activating ER Stress in PCOS. Endocrinology. 2020;161(2):bqaa015. doi:10.1210/endocr/bqaa015
22. Kandaraki E, Chatzigeorgiou A, Piperi C, Palioura E, Palimeri S, Korkolopoulou P et al. Reduced Ovarian Glyoxalase-I Activity by Dietary Glycotoxins and Androgen Excess: A Causative Link to Polycystic Ovarian Syndrome. Mol Med. 2012;18(8):1183-1189. doi:10.2119/molmed.2012.00293
23. Chatzigeorgiou A, Kandaraki E, Piperi C, Livadas S, Papavassiliou AG, Koutsilieris M et al. Dietary glycotoxins affect scavenger receptor expression and the hormonal profile of female rats. J. Endocrinol. 2013;218(3):331-337. doi:10.1530/JOE-13-0175
24. Di Emidio G, Santini SJ, D'Alessandro AM, Vetuschi A, Sferra R, Artini PG et al. SIRT1 participates in the response to methylglyoxal-dependent glycative stress in mouse oocytes and ovary. Biochim Biophys Acta Mol Basis Dis. 2019;1865(6):1389-1401. doi:10.1016/j.bbadis.2019.02.011
25. Lin P, Chang C, Wu K, Shih C, Chiang W, Chen H et al. Dietary Glycotoxins, Advanced Glycation End Products, Inhibit Cell Proliferation and Progesterone Secretion in Ovarian Granulosa Cells and Mimic PCOS-like Symptoms. Biomolecules. 2019;9(8):327. doi:10.3390/biom9080327
26. Papachroni KK, Piperi C, Levidou G, Korkolopoulou P, Pawelczyk L, Diamanti-Kandarakis E et al. Lysyl oxidase interacts with AGE signalling to modulate collagen synthesis in polycystic ovarian tissue. J Cellular Molecular Medi. 2010;14(10):2460-2469. doi:10.1111/j.1582-4934.2009.00841.x

27. Diamanti-Kandarakis E, Chatzigeorgiou A, Papageorgiou E, Koundouras D, Koutsilieris M. Advanced glycation end-products and insulin signaling in granulosa cells. Exp Biol Med (Maywood). 2016;241(13):1438-1445. doi:10.1177/1535370215584937
28. Safiri S, Noori M, Nejadghaderi SA, Karamzad N, Carson-Chahhoud K, Sullman MJM et al. Burden of female breast cancer in the Middle East and North Africa region, 1990–2019. Arch Public Health. 2022;80(1):168. doi:10.1186/s13690-022-00918-y
29. Charifson MA, Trumble BC. Evolutionary origins of polycystic ovary syndrome: An environmental mismatch disorder. Evol. Med. Public Health. 2019;2019(1):50-63. doi:10.1093/emph/eoz011
30. Deswal R, Nanda S, Ghalaut VS, Roy PS, Dang AS. Cross-sectional study of the prevalence of polycystic ovary syndrome in rural and urban populations. Intl J Gynecology & Obste. 2019;146(3):370-379. doi:10.1002/ijgo.12893
31. Mushtaq A, Bibi A, Kausar N. Increased Risk of Infertility, Marital Maladjustment and Psychological Morbidity in PCOS Patients of Southern Punjab, Pakistan. PJZ. 2023;55(4). doi:10.17582/journal.pjz/20210919130943
32. Rizvi M, Abbas A, Tanwir S, Sabah A, Ali ZM, Sundrani MM et al. Perception and Attitude of Patients regarding Polycystic Ovarian Syndrome (PCOS) in Tertiary Care Hospitals of Pakistan - A Survey Based Study. IJPT. 2014; 5(3):147-152
33. Munir M, Oubaid M, Baig AA, Azam A, Khalil H. Recent facts of eating habits and obesity among adolescent; a case of Pakistan. IJNMS. 2023; 2(2):49-57
34. Mistri S. Relations between Dietary Habits, Lifestyle and Leading Obesity. In: Takada A, Himmerich H, eds. Psychology and Pathophysiological Outcomes of Eating. IntechOpen; 2021; 1-26. doi:10.5772/intechopen.98307
35. Cincione RI, Losavio F, Ciolli F, Valenzano A, Cibelli G, Messina G et al. Effects of Mixed of a Ketogenic Diet in Overweight and Obese Women with Polycystic Ovary Syndrome. IJERPH. 2021;18(23):12490. doi:10.3390/ijerph182312490
36. Mizgier M, Jarząbek-Bielecka G, Formanowicz D, Jodlowska-Siewert E, Mruczyk K, Cisek-Wozniak A et al. Dietary and Physical Activity Habits in Adolescent Girls with Polycystic Ovary Syndrome (PCOS)-HAstudy. JCM. 2021;10(16):3469. doi:10.3390/jcm10163469
37. Rabotata S, Malatji TL. Factors influencing fast food consumption: a case study of University of Venda Students, Limpopo, South Africa. TSSJ. 2021;26:888-899. doi:10.47577/tssj.v26i1.5176
38. Van Boekel M, Fogliano V, Pellegrini N, Stanton C, Scholz G, Lalljie S et al. A review on the beneficial aspects of food processing. Mol. Nutr. Food Res. 2010;54(9):1215-1247. doi:10.1002/mnfr.200900608
39. Chen JH, Lin X, Bu C, Zhang X. Role of advanced glycation end products in mobility and considerations in possible dietary and nutritional intervention strategies. Nutr Metab (Lond). 2018;15(1):72. doi:10.1186/s12986-018-0306-7
40. Scheijen JJLJM. The Analysis of Advanced Glycation End-products: A Mass Spectrometry-Based Approach & Its Applications. Maastricht university; 2017. doi:10.26481/dis.20170621js
41. Merhi Z, Kandaraki EA, Diamanti-Kandarakis E. Implications and Future Perspectives of AGEs in PCOS Pathophysiology. TEM. 2019;30(3):150-162. doi:10.1016/j.tem.2019.01.005
42. Waqas K, Chen J, Van Der Eerden BCJ, Ikram MA, Uitterlinden AG, Voortman T et al. Dietary Advanced Glycation End-Products (dAGEs) Intake and Bone Health: A Cross-

Sectional Analysis in the Rotterdam Study. Nutrients. 2020;12(8):2377. doi:10.3390/nu12082377
43. Uribarri J, Woodruff S, Goodman S, CAI W, Chen X, Pyzik R et al. Advanced Glycation End Products in Foods and a Practical Guide to Their Reduction in the Diet. J. Am. Diet. Assoc. 2010;110(6):911-916.e12. doi:10.1016/j.jada.2010.03.018
44. Gul R, Iqbal S, Anwar Z, Ahdi SG, Ali SH, Pirzada S. Pre-pregnancy maternal BMI as predictor of neonatal birth weight. Petry CJ, ed. PLoS ONE. 2020;15:e0240748. doi:10.1371/journal.pone.0240748
45. Huang S, Dong X, Zhang Y, Chen Y, Yu Y, Huang M et al. Formation of advanced glycation end products in raw and subsequently boiled broiler muscle: biological variation and effects of postmortem ageing and storage. Food Sci. Hum. Wellness. 2022;11(2):255-262. doi:10.1016/j.fshw.2021.11.012
46. Wu X, Zhang Z, He Z, Wang Z, Qin F, Zeng Met al. Effect of Freeze-Thaw Cycles on the Oxidation of Protein and Fat and Its Relationship with the Formation of Heterocyclic Aromatic Amines and Advanced Glycation End Products in Raw Meat. Molecules. 2021;26(5):1264. doi:10.3390/molecules26051264
47. Kuzan A. Toxicity of advanced glycation end products (Review). Biomed Rep. 2021;14(5):46. doi:10.3892/br.2021.1422
48. Garg D, Merhi Z. Advanced Glycation End Products: Link between Diet and Ovulatory Dysfunction in PCOS? Nutrients. 2015;7(12):10129-10144. doi:10.3390/nu7125524
49. Gugliucci A, Menini T. The Axis AGE-RAGE-Soluble RAGE and Oxidative Stress in Chronic Kidney Disease. In: Camps J, ed. Oxidative Stress and Inflammation in Non-Communicable Diseases - Molecular Mechanisms and Perspectives in Therapeutics. Vol 824. Adv. Exp. Med. Biol. Springer International Publishing; 2014:191-208. doi:10.1007/978-3-319-07320-0_14