4 Environmental Factors Responsible for Obesity and Insulin Resistance in Polycystic Ovary Syndrome

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Polycystic ovary syndrome (PCOS) is an important public health concern with reproductive, metabolic, and psychological features. PCOS is one of the most common endocrine disorders in reproductive-aged women affecting 8–13% of them [1]. Except meeting the diagnostic criteria, women with PCOS present with metabolic disturbances including insulin resistance (IR), metabolic syndrome, prediabetes, type 2 diabetes (DM2), and cardiovascular risk factors [1]. The prevalence of insulin resistance ranges from 50 to 70% [2].

Obesity is associated with deterioration of reproductive and metabolic status in women with PCOS. Hence, it is necessary to address any factor that increase the risk of obesity in PCOS. Among environmental factors endocrine-disrupting chemicals (EDCs), advanced glycated end products (AGEs), and vitamin D are proposed to have an impact on obesity and insulin resistance in polycystic ovary syndrome.

Exposure to environmental toxins, EDCs and AGEs, may lead to endocrine, metabolic, and reproductive disruption resulting in development of different PCOS phenotypes and adverse health effects. Metabolic disorders include increase in insulin resistance, oxidative stress, and inflammation that result in increased adipogenesis and finally leads to obesity [3]. Vitamin D deficiency has been postulated to play a role in the pathogenesis of insulin resistance and to be related to metabolic risk factors in PCOS [4, 5].

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4.1 Endocrine-Disrupting Chemicals

A 2000 report documented 2300 pesticide exposures in American schools from 1993 to 1996.

In 2004, levels of polybrominated diphenyl ethers (PBDEs) were about 40 higher in North American women than in Swedish women, based on samples of breast milk. A 2001 study showed that 96% of the pregnant women surveyed tested positive for bisphenol A (BPA).

As of October 2013, there are nearly 1000 endocrine-disrupting chemicals on The Endocrine Disruption Exchange's (TEDX) list. A 2008 study showed that 19 out of 20 children tested had PBDE levels an average of 3.2 times higher than their mothers [6].

Most of the 2000 chemicals that come on the market each year don't go through even simple tests to determine toxicity [6].

An endocrine-disrupting chemical (EDC) is an exogenous chemical, or mixture of chemicals, than can interfere with any aspect of hormone action. It is suggested that EDCs influence hormone action in different ways. EDCs or their metabolites can influence hormone metabolism in tissues-specific manner, and may directly interfere with hormone action only in those tissues where they are generated. EDCs or their metabolites may also interact with hormone receptors in a tissue-specific manner and exert direct agonist or antagonist effects, either because some tissues exhibit greater receptor density or because different receptor isoforms are expressed in different tissues [7].

4.1.1 Bisphenol A

One of EDCs, bisphenol A is considered to interfere with the endocrine system and play a role in the development of insulin resistance and obesity with major contributors being modern human diet and genomic composition.

Bisphenol A (BPA) is one of the most common plasticizers; it was first synthesized in 1891 and was discovered to be estrogenic in 1936. The xenoestrogen PBA is especially prevalent as a component used in rigid plastic products such as compact discs, dental materials, cosmetics, food and beverage containers, food and formula can linings, and glossy paper receipts. The BPA from food containers can leach into foods when they are heated or scratched and then be ingested [8]. More BPA is produced annually that any other chemicals (EDCs) with 15 billion pounds produced in 2013.

In the human urine, BPA was detected in 52 up to 100% of participants [9]. These findings indicate broad human exposure to BPA. The Environmental Protection Agency (EPA) in the USA has established the tolerable daily intake (TDI) for BPA at 50 mg per kg (body weight) per day in 1988 [10]. In January 2015, European Food Safety Authority has reduced TDI for BPA from 50 to 4 mg per kg (body weight) per day [10].

BPA exert diabetogenic and obesogenic effects. BPA contributes to insulin action in several mechanisms. It has an impact on insulin synthesis and release by b-pancreatic cells, and insulin signaling within liver, muscle, adipose tissues [11].

BPA has been shown to act through variety of receptors, such as the estrogen receptors alpha and beta, ERa and ERb, membrane receptor G-protein-coupled receptor 30 (GPR30), and the estrogen-related receptor gamma ERRγ [12].

It was reported that BPA between 1 and 10 nmol/l concentrations interferes with adipocyte metabolism by increasing oxidative stress and contributing to inflammation due to inhibition of adiponectin release and stimulation of interleukin 6 and tumor necrosis factor release [13]. Additionally, Wells et al. suggested a relation between BPA exposure and central obesity. They observed higher BPA concentrations in individuals with higher waist-to-hip ratio [14].

BPA acts as a xenoestrogen, thus binding to estrogen receptors. However, the interaction of BPA with ER receptors is relatively weak, ranging 2–3 orders of magnitude lower compared to estrogens [10].

It has been well described that all three estrogen receptors (ERa, ERb, and the G protein coupled ER (GPER)) are present on rodent and human b cells [10]. It has been reported that BPA mimics the action of estradiol and exerts effects on energy balance and glucose homoeostasis [15]. In vitro, BPA increased the frequency of glucose-induced ionized calcium oscillations in pancreatic beta cells and enhanced insulin secretion. In vivo, male mice taking daily doses of BPA presented higher insulin concentration in pancreatic beta cells and enhanced insulin secretion in comparison with control mice [15]. These changes result in hyperinsulinemia.

It is also known that BPA binds estrogen receptors in both adipocytes and pancreatic beta cells, and BPA-exposed cells develop lipid accumulation [15].

BPA acts in human tissues through ER receptors alpha, beta, and gamma resulting in gene expression. Additionally, BPA binds to membrane receptors resulting in non-genomic effects. Gene transcription depends on ER confirmation induced by BPA. Conformation alterations are responsible for recruitment of transcriptional co-regulators [10].

Other than the proposed ER-activation mechanism that involves binding to nuclear receptors, it has been suggested that BPA may exert its effects through rapid non-genomic pathways [10]. Binding to membrane ER receptor promotes rapid influx of calcium ion [10]. BPA causes membrane depolarization followed by alteration of conformation of voltage-dependent calcium channels. These changes do not require high BPA concentration; they occur at picomolar and at nanomolar concentrations [10].

In the animal study of Jayashree et al. [16], it has been demonstrated that after BPA administration glucose oxidation and glycogen content in the liver were decreased [11]. Another factor promoting hepatic insulin resistance – decreased Akt phosphorylation – was also reported. Additionally, decreased phosphorylation of Akt and GSK3b in skeletal muscle was found. It may explain how BPA contributes to insulin resistance in the muscle. Menale et al. [17] showed that BPA decrease the expression of PCSK1 gene in human pancreatic cell line [11]. PCSK1 contributes to insulin synthesis. The BPA action on adipose tissue was also investigated [11]. BPA

administration caused increase in circulating inflammatory factors and local inflammation in the white adipose tissue. In addition higher plasma leptin levels were detected.

Decreased glucose utilization and phosphorylation of insulin receptor contributes to impaired insulin action in 3T3-L1 cells [11]. It has been demonstrated that BPA induced adipogenesis in 3T3-L1 preadipocytes [8]. Its actions comprise enhanced mRNA expression and increased enzymatic activity of 11β-hydroxysteroid dehydrogenase type 1 (11-βHSD type 1). 11-βHSD type 1 induces adipogenesis in human adipose tissue [8]. It suggests that BPA contributes to obesity susceptibility [8].

Also from an epidemiologic point of view, there are several studies to investigate positive correlation between exposure to PBA and obesity. In 3390 Chinese adults aged 40 year or older BPA were was positively associated with generalized obesity, abdominal obesity, and insulin resistance [18]. Another study provided evidence for a positive association between urinary BPA concentrations and waist circumference in the group of 1030 Korean adults [19]. In the National Health and Nutritional Examination Survey (NHANES) 2003–2008, the association between urinary BPA levels and obesity in the US population was reported [20]. Moreover, Hong et al. found that higher urinary BPA levels are associated with obesity and insulin resistance in Korean reproductive-aged women [15].

It is known that BPA promotes hyperandrogenism state, impairs oocyte development and folliculogenesis, and has a negative impact on metabolic parameters such as insulin resistance, obesity, oxidative stress, and inflammation [4]. Additionally, another studies have been conducted to investigate relationship between metabolic disturbances in PCOS and BPA. That is, a case control study of 71 women with PCOS and 100 women without PCOS showed positive association between BPA and insulin resistance. Moreover, higher serum BPA concentration was found in PCOS women [21].

Authors of meta-analysis have also demonstrated that BPA levels in PCOS women were significantly higher than controls. They found that high BPA levels were significantly associated with high BMI and high HOMA-IR [22]. Several mechanisms have been proposed to explain BPA action on insulin resistance. Findings from different studies pointed to changes of the structures and metabolism of pancreas leading to impaired insulin secretion. They also showed changes of insulin signaling in liver and muscles [22]. Studies in women with PCOS did not reveal the exact mechanisms for impact of BPA on insulin resistance [22], but there are numerous studies conducted in animals or cell culture elucidating these mechanisms (as described before).

4.2 Advanced Glycation End Products

Advanced glycation end products (AGEs) are derivatives of nonenzymatic glucose–protein, glucose–lipids, and glucose–nucleic acids reactions [23]. They are the end products of a chemical procedure called Maillard reaction [23]. These

processes are irreversible. Aging, hyperglycemia, obesity, oxidative stress, and hypoxia accelerate the generation of their precursors [24]. AGEs are formed exogenously from thermally processed foods that are rich in proteins and reducing sugars. It is known that 10% of ingested AGEs are absorbed [25]. It has been reported that AGEs play a role in the pathogenesis of different diseases by causing oxidative stress, altering enzymatic activities, affecting cytotoxic pathways, or damaging nucleic acids.

It has been shown that serum AGEs are elevated in women with PCOS [26]. In another study increased serum levels of AGEs and upregulation in advanced glycation end products receptor (RAGE) expression in circulating monocytes in women with PCOS with insulin resistance without hyperglycemia had been found [26]. AGEs have also been reported to correlate with insulin, HOMA, and waist-to-hip ratio in these women [27]. Elevated serum AGEs levels were also found in lean women with PCOS without insulin resistance [27].

AGEs group includes over 20 heterogeneous compounds [11]. They bind to receptor or form crosslinks with extracellular matrix [24]. The AGE receptor (RAGE) binds also other molecules/ligands (i.e., amyloid b peptide) [24]. When ligands bind to RAGE, they activate signaling pathways (the PI3K/AKT pathways or the mitogen-activated protein kinase (MAPK) signaling pathways), and finally, genes associated with inflammation and apoptosis are transcripted [24]. The AGE–RAGE binding activates also JAK-2/STAT-1, another signaling pathway that contributes to inflammation and cytokine production. This signaling pathway is associated with the composition and activity of proteasomal subunits [24].

Physiological role of RAGE is yet not well understood, but it displays a role in immune or inflammatory response. Cytokines (IL-1, IL-6, IL-8) and chemokines are formed after AGE binding to RAGE which leads to the activation of inflammatory processes. Then through NADPH oxidase, as well as activation of the transcription factor NF-kB, excess oxidative stress is generated [24]. The excessive reactive oxygen species (ROS) production leads to upregulation in RAGE expression [24].

Insulin resistance and hyperinsulinemia are found in approximately 50 up to 70% of women with PCOS. Oxidative stress and inflammation contribute to hyperinsulinemia and insulin resistance [24]. It is suggested that excessive oxidative stress is one of the features of PCOS and it cannot be compensated by the antioxidant mechanisms [24].

Increased AGEs level is associated with inflammatory markers such as high-sensitivity C-reactive protein (CRP), fibrinogen, 8-isoprostanes (a marker of lipid peroxidation), TNF-a, and vascular adhesion molecule-1 (VAM-1) [28].

There is a system of glyoxalases that protects cells from damage caused by cytotoxic metabolites such as AGEs [24]. This is the glyoxalase detoxification system. It comprises two glyoxalases GLO-I and GLO-II [24]. Significant reduction of ovarian GLO activity has been reported in PCOS animal study. Animals fed a high-AGE diet had lower ovarian GLO activity than animals fed a low-AGE diet [24].

AGEs change insulin cell signaling and modify glucose transporters and glucose metabolism in insulin-sensitive cells, also in ovarian cells. That is, RAGE overexpression led to a decrease in GLUT-4 gene expression and attenuation of insulin

signaling in adipocytes and caused morphological changes of adipocytes [24]. Women with PCOS presented impaired action of GLUT-4 [24]. Insulin resistance (IR) in PCOS has complex molecular pathophysiology. It includes different mechanisms: a post-binding receptor defect, low levels of IRS-1 expression, impaired IRS-1 phosphorylation, reduced activity of the serine/threonine kinase AKT2, and altered glucose transporter GLUT-4 translocation to the plasma membrane [24]. Hence, it is suggested that AGEs impair insulin signaling and glucose metabolism through several mechanisms.

Thera are different studies presenting the effect of AGEs on glucose metabolism. In one study the effect of human glycated albumin (HGA) on glucose transport in the human granulosa KGN cell in the presence of insulin was investigated [24]. Inhibition of insulin-mediated AKT phosphorylation was found in these cells. HGA also inhibited insulin-induced GLUT-4 translocation from the cytoplasm to the membrane compartments of KGN cells [24]. In skeletal muscle cells the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (PKB) pathway (part of insulin signaling cascade) was suppressed by HGA [24]. HGA activated PKCa that caused an increase in serine/threonine phosphorylation of IRS and ultimately altered insulin metabolic signals [24]. In addition, it has been reported that AGEs cause b cell malfunction in animals [24].

Obesity is also commonly observed in women with PCOS, in 30–75% of cases [23]. Recent studies have shown how AGEs contribute to the development of obesity [27]. For example, in animal studies, weight gain in mice fed with high-AGE diet and low-AGE diet was compared. Animals on H-AGE diet had a significant weight gain in comparison to control group [27].

The effect of high-AGE diet on hormonal and metabolic parameters in human was also investigated. Low-AGE diet in comparison with high-AGE diet resulted in lower testosterone levels, HOMA-IR, and improved oxidative stress status in women with PCOS [25]. Results suggest a novel treatment strategy for ovarian dysfunction by decreasing AGEs in diet to attenuate AGEs effects.

In another study association between AGEs/soluble receptor of advanced glycation end products (AGEs/sRAGE) and anthropometric parameters in reproductive-aged PCOS patients was investigated. Positive correlation between serum levels of AGEs and BMI was found. On the contrary serum levels of sRAGE were decreased along with increased BMI [23].

There is evidence that AGEs induced the production of inflammatory mediators in adipocytes and macrophages via RAGE activation [29]. It has been found that MG stimulated adipogenesis by the upregulation of Akt signaling (increased the phosphorylation of Akt1) [30]. MG treatment increased also the phosphorylation of p21 and p27. P21 and p27 are the major regulators of the cell cycle. The increased phosphorylation of p21 and p27 activates their degradation and leads to the entry of cells to S phase that enhance cell proliferation [30].

Studies have also shown that women with PCOS have increased serum CML (carboxymethyl-lysine, one of the AGEs) in comparison to the control group, independently of obesity and insulin resistance [25].

4.2.1 Vitamin D

Vitamin D receptors are expressed in 2776 genomic positions and modulate the expression of 229 genes in more than 30 different tissues, such as skeleton, brain, breast, pancreas, parathyroid glands, immune cells, cardiomyocytes, and ovaries [2].

Women with PCOS are likely to have an increased risk of vitamin D deficiency (VDD). The prevalence of vitamin D deficiency among the general adult population is estimated about 20–48% [2], while among women with PCOS approximately 67–85% [31].

Vitamin D affects glucose metabolism. It contributes to increased insulin secretion, increased insulin sensitivity, increased glucose uptake, and expression of insulin receptor [32]. Multiple cellular and molecular mechanisms have been proposed to explain this. 1,25-dihydroxyvitamin D enhance insulin release from β-cells, transcriptional activation of the human insulin receptor gene, and suppression of the release of proinflammatory cytokines that are involved in insulin resistance [33]. Vitamin D may also exert effect on insulin action due to the regulation of extracellular calcium concentration and normal calcium influx across cell membranes [34].

Vitamin D deficiency was observed in obese individuals. In a large study comprising 42,024 persons, 10% increase of BMI was associated with 4% decrease of serum vitamin D [35]. The National Health and Nutrition Examination Survey (2001–2004) showed that abdominal obesity was associated with vitamin D deficiency [36]. Drincic et al. recommend 2–3 times higher daily dose of vitamin D supplementation in obese persons in comparison to normal (2.5 IU/kg) [37].

In Tsakova et al.'s study, higher prevalence of vitamin D deficiency in obese women with PCOS than in lean women with PCOS (70% vs. 60%) was found [38].

In obese individuals, a higher proportion of vitamin D, which is fat soluble, is sequestered in adipose tissues; and hence, bioavailability of the vitamin is lowered [5].

There is an evidence that vitamin D level plays an important role in insulin sensitivity and glucose metabolism.

Negative correlation between serum vitamin D levels and waist circumference, triglycerides, fasting glucose, and HOMA-IR were found [39]. It has been reported that PCOS patients with vitamin D deficiency were more likely to have increased levels of fasting glucose and HOMA-IR compared to those without vitamin D deficiency [2].

Inverse association between vitamin D concentration and HOMA-IR, glucose, CRP, and triglycerides have been found in many studies [2]. These studies have also shown positive correlation between vitamin D concentration and HDL-C or QUICKI.

It has been demonstrated that both intrinsic and extrinsic factors contribute to insulin resistance in PCOS women [40]. Impaired serine phosphorylation of the insulin receptor-1 is the intrinsic factor [40]. Ngo et al. investigated the potential role of vitamin D and NO responsiveness (defined as platelet response to NO donor) as extrinsic factors [40]. They found on multivariate analysis that NO responsiveness and 25(OH)D3 levels were significantly associated with QUICKI. Low

vitamin D levels and low platelet response to NO donor correlated with low QUICKI in the whole study group.

Another prospective study investigated effects of calcium and vitamin supplementation on serum insulin level, HOMA-IR, and QUICKI [41]. The 8 weeks supplementation in PCOS women with vitamin D deficiency led to a significant reduction in serum insulin levels, HOMA-IR score, and a significant elevation in QUICKI index.

Li et al. reported that severe vitamin D deficiency correlated with insulin resistance and was independent of BMI and waist-to-hip ratio in women with PCOS. They also showed higher insulin levels in women without PCOS but with severe vitamin D deficiency [5].

It was proposed by Irani et al. that vitamin D attenuates the effects of the AGE–RAGE system in vitamin D-deficient women with PCOS due to increase of serum sRAGE levels. sRAGE acts as an anti-inflammatory factor. It binds circulating AGEs and blocks the intracellular events following the AGE–RAGE binding [42]. It has been demonstrated that vitamin D3 supplementation significantly increased serum sRAGE levels [42]. It was also observed that serum sRAGE was inversely correlated with BMI.

It has been shown that environmental factors play a role in the development of obesity and insulin resistance in PCOS women. There is a bulk of evidence that endocrine-disrupting chemicals, advanced glycated end products, and vitamin D deficiency contribute to these disorders. The results of in vitro and in vivo studies have demonstrated different mechanisms involved in the development of these conditions. They suggest new ways of treatment. In addition, they point to the importance of avoidance of exposure to deleterious environmental factors.

References

1. International evidence based guideline for the assessment and management of polycystic ovary syndrome. Copyright Monash University, Melbourne Australia; 2018.
2. He C, Lin Z, Robb SW, Ezeamama AE. Serum vitamin D levels and polycystic ovary syndrome: a systematic review and meta-analysis. Nutrients. 2015;7(6):4555–77. https://doi.org/10.3390/nu7064555.
3. Rutkowska AZ, Diamanti-Kandarakis E. Polycystic ovary syndrome and environmental toxins. Fertil Steril. 2016;106(4):948–58. https://doi.org/10.1016/j.fertnstert.2016.08.031.
4. Patra SK, Nasrat H, Goswami B, Jain A. Vitamin D as a predictor of insulin resistance in polycystic ovarian syndrome. Diabetes Metab Syndr. 2012;6(3):146–9. https://doi.org/10.1016/j.dsx.2012.09.006.
5. Li HW, Brereton RE, Anderson RA, Wallace AM, Ho CK. Vitamin D deficiency is common and associated with metabolic risk factors in patients with polycystic ovary syndrome. Metabolism. 2011;60(10):1475–81. https://doi.org/10.1016/j.metabol.2011.03.002.
6. Endo News April 2015.
7. Gore AC. Endocrine-disrupting chemicals. JAMA Intern Med. 2016;176(11):1705–6. https://doi.org/10.1001/jamainternmed.2016.5766.
8. Gore AC, Chappell VA, Fenton SE, et al. EDC-2: the Endocrine Society's second scientific statement on endocrine-disrupting chemicals. Endocr Rev. 2015;36(6):E1–E150. https://doi.org/10.1210/er.2015-1010.

9. Vandenberg LN, Hauser R, Marcus M, Olea N, Welshons WV. Human exposure to bisphenol a (BPA). Reprod Toxicol. 2007;24(2):139–77. https://doi.org/10.1016/j.reprotox.2007.07.010.
10. Pjanic M. The role of polycarbonate monomer bisphenol-a in insulin resistance. PeerJ. 2017;5:e3809. https://doi.org/10.7717/peerj.3809.
11. Le Magueresse-Battistoni B, Multigner L, Beausoleil C, Rousselle C. Effects of bisphenol a on metabolism and evidences of a mode of action mediated through endocrine disruption. Mol Cell Endocrinol. 2018;475:74–91. https://doi.org/10.1016/j.mce.2018.02.009.
12. Le Magueresse-Battistoni B, Labaronne E, Vidal H, Naville D. Endocrine disrupting chemicals in mixture and obesity, diabetes and related metabolic disorders. World J Biol Chem. 2017;8(2):108–19. https://doi.org/10.4331/wjbc.v8.i2.108.
13. Ben-Jonathan N, Hugo ER, Brandebourg TD. Effects of bisphenol a on adipokine release from human adipose tissue: implications for the metabolic syndrome. Mol Cell Endocrinol. 2009;304(1–2):49–54. https://doi.org/10.1016/j.mce.2009.02.022.
14. Wells EM, Jackson LW, Koontz MB. Association between bisphenol a and waist-to-height ratio among children: National Health and nutrition examination survey, 2003-2010. Ann Epidemiol. 2014;24(2):165–7. https://doi.org/10.1016/j.annepidem.2013.06.002.
15. Hong SH, Sung YA, Hong YS, et al. Urinary bisphenol a is associated with insulin resistance and obesity in reproductive-aged women. Clin Endocrinol. 2017;86(4):506–12. https://doi.org/10.1111/cen.13270.
16. Jayashree S, Indumathi D, Akilavalli N, Sathish S, Selvaraj J, Balasubramanian K. Effect of Bisphenol-A on insulin signal transduction and glucose oxidation in liver of adult male albino rat. Environ Toxicol Pharmacol. 2013;35(2):300–10. https://doi.org/10.1016/j.etap.2012.12.016.
17. Menale C, Piccolo MT, Cirillo G, Calogero RA, Papparella A, Mita L, Del Giudice EM, Diano N, Crispi S, Mita DG. Bisphenol A effects on gene expression in adipocytes from children: association with metabolic disorders. J Mol Endocrinol. 2015;54(3):289–303. https://doi.org/10.1530/JME-14-0282.
18. Wang T, Li M, Chen B, et al. Urinary bisphenol a (BPA) concentration associates with obesity and insulin resistance. J Clin Endocrinol Metab. 2012;97(2):E223–7. https://doi.org/10.1210/jc.2011-1989.
19. Ko A, Hwang MS, Park JH, Kang HS, Lee HS, Hong JH. Association between urinary bisphenol a and waist circumference in Korean adults. Toxicol Res. 2014;30(1):39–44. https://doi.org/10.5487/TR.2014.30.1.039.
20. Teppala S, Madhavan S, Shankar A. Bisphenol a and metabolic syndrome: results from NHANES. Int J Endocrinol. 2012;2012:598180. https://doi.org/10.1155/2012/598180.
21. Kandaraki E, Chatzigeorgiou A, Livadas S, et al. Endocrine disruptors and polycystic ovary syndrome (PCOS): elevated serum levels of bisphenol a in women with PCOS. J Clin Endocrinol Metab. 2011;96(3):E480–4. https://doi.org/10.1210/jc.2010-1658.
22. Hu Y, Wen S, Yuan D, et al. The association between the environmental endocrine disruptor bisphenol a and polycystic ovary syndrome: a systematic review and meta-analysis. Gynecol Endocrinol. 2018;34(5):370–7. https://doi.org/10.1080/09513590.2017.1405931.
23. Liao Y, Huang R, Sun Y, et al. An inverse association between serum soluble receptor of advanced glycation end products and hyperandrogenism and potential implication in polycystic ovary syndrome patients. Reprod Biol Endocrinol. 2017;15(1):9. https://doi.org/10.1186/s12958-017-0227-8.
24. Merhi Z, Kandaraki EA, Diamanti-Kandarakis E. Implications and future perspectives of AGEs in PCOS pathophysiology. Trends Endocrinol Metab. 2019;30(3):150–62. https://doi.org/10.1016/j.tem.2019.01.005.
25. Tantalaki E, Piperi C, Livadas S, 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 (Athens). 2014;13(1):65–73. https://doi.org/10.1007/BF03401321.

26. 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. https://doi.org/10.1111/j.1365-2265.2004.02170.x.
27. Garg D, Merhi Z. Relationship between advanced glycation end products and steroidogenesis in PCOS. Reprod Biol Endocrinol. 2016;14(1):71. https://doi.org/10.1186/s12958-016-0205-6.
28. Uribarri J, Cai W, Peppa M, et al. Circulating glycotoxins and dietary advanced glycation endproducts: two links to inflammatory response, oxidative stress, and aging. J Gerontol A Biol Sci Med Sci. 2007;62(4):427–33. https://doi.org/10.1093/gerona/62.4.427.
29. Gaens KH, Stehouwer CD, Schalkwijk CG. Advanced glycation endproducts and its receptor for advanced glycation endproducts in obesity. Curr Opin Lipidol. 2013;24(1):4–11. https://doi.org/10.1097/MOL.0b013e32835aea13.
30. Jia X, Chang T, Wilson TW, Wu L. Methylglyoxal mediates adipocyte proliferation by increasing phosphorylation of Akt1. PLoS One. 2012;7(5):e36610. https://doi.org/10.1371/journal.pone.0036610.
31. Thomson RL, Spedding S, Buckley JD. Vitamin D in the aetiology and management of polycystic ovary syndrome. Clin Endocrinol. 2012;77(3):343–50. https://doi.org/10.1111/j.1365-2265.2012.04434.x.
32. Rojas-Rivera J, De La Piedra C, Ramos A, Ortiz A, Egido J. The expanding spectrum of biological actions of vitamin D. Nephrol Dial Transplant. 2010;25(9):2850–65. https://doi.org/10.1093/ndt/gfq313.
33. Teegarden D, Donkin SS. Vitamin D: emerging new roles in insulin sensitivity. Nutr Res Rev. 2009;22(1):82–92. https://doi.org/10.1017/S0954422409389301.
34. Pittas AG, Lau J, Hu FB, Dawson-Hughes B. The role of vitamin D and calcium in type 2 diabetes. A systematic review and meta-analysis. J Clin Endocrinol Metab. 2007;92(6):2017–29. https://doi.org/10.1210/jc.2007-0298.
35. Vimaleswaran KS, Berry DJ, Lu C, et al. Causal relationship between obesity and vitamin D status: bi-directional Mendelian randomization analysis of multiple cohorts. PLoS Med. 2013;10(2):e1001383. https://doi.org/10.1371/journal.pmed.1001383.
36. Scragg R, Sowers M. Bell C; third National Health and nutrition examination survey. Serum 25-hydroxyvitamin D, diabetes, and ethnicity in the third National Health and nutrition examination survey. Diabetes Care. 2004;27(12):2813–8. https://doi.org/10.2337/diacare.27.12.2813.
37. Drincic A, Fuller E, Heaney RP, Armas LA. 25-Hydroxyvitamin D response to graded vitamin D_3 supplementation among obese adults. J Clin Endocrinol Metab. 2013;98(12):4845–51. https://doi.org/10.1210/jc.2012-4103.
38. Tsakova AD, Gateva AT, Kamenov ZA. 25(OH) vitamin D levels in premenopausal women with polycystic ovary syndrome and/or obesity. Int J Vitam Nutr Res. 2012;82(6):399–404. https://doi.org/10.1024/0300-9831/a000137.
39. Forouhi NG, Luan J, Cooper A, Boucher BJ, Wareham NJ. Baseline serum 25-hydroxy vitamin d is predictive of future glycemic status and insulin resistance: the Medical Research Council Ely prospective study 1990-2000. Diabetes. 2008;57(10):2619–25. https://doi.org/10.2337/db08-0593.
40. Ngo DT, Chan WP, Rajendran S, et al. Determinants of insulin responsiveness in young women: impact of polycystic ovarian syndrome, nitric oxide, and vitamin D. Nitric Oxide. 2011;25(3):326–30. https://doi.org/10.1016/j.niox.2011.06.005.
41. Asemi Z, Foroozanfard F, Hashemi T, Bahmani F, Jamilian M, Esmaillzadeh A. Calcium plus vitamin D supplementation affects glucose metabolism and lipid concentrations in overweight and obese vitamin D deficient women with polycystic ovary syndrome. Clin Nutr. 2015;34(4):586–92. https://doi.org/10.1016/j.clnu.2014.09.015.
42. Irani M, Minkoff H, Seifer DB, Merhi Z. Vitamin D increases serum levels of the soluble receptor for advanced glycation end products in women with PCOS. J Clin Endocrinol Metab. 2014;99(5):E886–90. https://doi.org/10.1210/jc.2013-4374.