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POLYCYSTIC OVARIAN SYNDROME: ORDER AND DISORDER IN THE OXIDATIVE STEADY STATE

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ABSTRACT

Cellular redox steady state is the hallmark of a healthy body. Oxidative stress (OS) a signature of dysfunctional oxidation status in the body is related to the onset of various chronic diseases like diabetes, cardiovascular morbidities, neurological diseases, psychological ailments and recently with polycystic ovarian syndrome (PCOS). Oxidative stress is touted to be a factor contributing to the pathogenesis of PCOS. Being an endocrine disorder affecting approximately 10-15% women of reproductive age worldwide, PCOS has become a major concern which not only affects the fertility but also hampers the overall wellbeing of the women affected with it. Understanding the crosstalk between oxidative stress and PCOS with focus on hyperinsulinemia, hyperandrogenism and chronic inflammation the major manifestations of PCOS is the major objective of this review.

KEY WORDS

Oxidative stress (OS), PCOS

Introduction:

From the first article ever indicating any role of oxidative stress (OS) in human disease to the present scenario where Reactive oxygen species (ROS) is being implicated in various diseases of metabolic, physiological and even neurological morbidities there has been a tremendous rise in the study and scope of Reactive oxygen species with respect to human health.

ROS initially was being studied for its role in various physiological pathways, its action as a secondary messenger in signal transduction and protective role in fine tuning inflammation to maintain the healthy state of the body. But, with more progress in research on ROS, its role in various diseases also began to be highlighted such as glaucoma [1], inflammation, cancer [2], chronic kidney disorders [3], diabetes mellitus [4] and epileptic seizures [5] to name a few. The enormous literature available makes it very difficult for any article to encompass all the aspects of ROS in human diseases. Therefore, the scope of this review article is to understand the role of reactive oxygen species in the occurrence and severity of the most common endocrine disorder in females of reproductive age i.e. Poly cystic ovarian syndrome or PCOS. Oxidative stress is known to affect PCOS patients irrespective of their being obese or lean [6].

What is polycystic ovarian syndrome?

Polycystic ovary syndrome (PCOS), first described in mid19th century by A. Chereau is a common endocrine disorder reported in women of reproductive age and is one of the primary causes of anovulatory subfertility or infertility [7]. PCOS women generally manifest hyperandrogenism, amenorrhea, obesity along with enlarged fluid filled multiple sac like cysts in the ovaries. Patients suffering from PCOS are subfertile and have irregular or absent ovulation. The underlying major cause of PCOS is very difficult to demarcate as it is a disease with multifactorial origin [8]. Though there is not one fit all definition of PCOS, the central

feature of polycystic ovarian syndrome is increased insulin resistance irrespective of the body mass index (BMI) of the patients, being prevalent in both obese and lean women. Around 9.7% Indian females have been diagnosed with PCOS [9]. Hyperinsulinemia along with obesity and dyslipidemia is frequently encountered in PCOS patients and consists of metabolic dysregulation [10]. This metabolic syndrome increases the risk of developing Type II diabetes, cardiovascular diseases and ovarian cancers in women with PCOS and the jeopardy increases with age [11].

Diagnosis of PCOS:

Many a times, patients are diagnosed with polycystic ovaries only when they report with infertility in the gynaecology departments. Diagnosis of PCOS is based on either of the three well established criteria namely, 1) 1990 NIH criteria: according to which patients are diagnosed with PCOS if they present both a) Oligo-anovulation b) Clinical and/or biochemical manifestations of androgen excess [12].

2) 2003 Rotterdam criteria: Patients are diagnosed if they have any 2 of the three criteria a) Oligo-anovulation b) Clinical and/or biochemical manifestations of androgen excess. c) Polycystic ovarian morphology (PCOM) in a pelvic ultrasonography scan [13].

3) 2006 Androgen excess- PCOD society criteria: Patients are diagnosed if they present all the following a) clinical/biochemical signatures of androgen excess. b) ovarian dysfunction including oligo-anovulation and/or PCOM [14].

In India, the 2003 Rotterdam criteria is widely used for diagnosis of PCOS and might further increase the prevalence to 10% [10].

PCOS and Oxidative stress:

A lot of reports have implicated a significant rise in oxidative stress in PCOS patients, by evaluation of various circulating stress markers like malondialdehyde (MDA), superoxide dismutase (SOD), glutathione peroxidase (GPx) [15], total antioxidant capacity (TAC) [16] and total glutathione (GSH) levels [17]. ROS level have been shown to be positively associated with obesity, hyperinsulinemia, androgen excess, acanthosis nigricans and chronic inflammation [18-21]. Although OS is a potential stimulus of PCOS [15], it is quiet uncertain to linearly correlate abnormal OS levels of PCOS patients as either a manifestation of PCOS itself or a presentation due to other imminent or potential metabolic and physiological dysregulations. Excessive ROS levels in tissues reflect disparity between production and elimination of reactive oxygen species (ROS) generated through the mitochondrial electron transport chain [22]. These excessive accumulated ROS *in vivo* induces cellular membrane [23], protein [24], and lipid peroxidation [25]. ROS encompasses both free and non-free radical oxygenated moieties, like peroxide (O_2^{2-}), superoxide ($O_2^{\cdot-}$), and hydroxyl radical (°OH). Reactive nitrogen and sulfur species also contribute towards OS [26]. In general, redox status is assessed by measurement of circulating redox markers however, not only is it hard to reveal redox status with identical biomarkers in several diseases, the results too would not hold substantial significance either. Because, ROS usually triggers different set of signal transduction pathways in different diseases, therefore biomarkers imployed to assess ROS mediated OS in a specific disease are partial and ought to be always zeroed on carefully.

Besides above mentioned complications, altered oxidative steady state has been shown to regulate carcinogenesis[27]. ROS have been proposed to cause genetic aberrations by targeting DNA, causing DNA strand breaks, point and/or deletion mutations, anomalous DNA-DNA, and DNA-protein cross-linking [28]. Therefore, when such mutations occur in the protooncogenes and/or tumor suppressor genes, cell proliferation jettisons out of control, due to faulty and disrupted DNA repair mechanism [29]. Alternatively, OS could bring about epigenetic changes through DNA methylation, DNA acetylation and silencing of tumor suppressor genes [30]. Therefore, OS accompanied by an increase ROS levels could be one of the major fundamental causes of increased gynecological cancer risks in PCOS patients.

ROS, obesity and PCOS:

Obese patients likely have more severe oxidative stress (OS) levels [31], and more significant correlations between OS markers and obesity indexes, such as BMI is observed [32]. Levels of ROS markers reflecting degrees of lipid peroxidation

(measured through MDA, low density lipoprotein and thiobarbituric reactive substance) and protein peroxidation (protein carbonylation and advanced oxidative protein products) are significantly elevated in the obese patients as compared with the normal controls. Chronic diseases associated with obesity have elevated ROS levels as their hallmark. A recent study undertaken by Khan et al. [33] reported that systemic redox dysfunction as manifested by elevated OS levels of obese females without smoking history, and any other obesity related conditions like hypertension, type 2 diabetes, dyslipidemia, liver and kidney dysfunction, and tumor history were still found to be significantly higher than non-obese control females, while their total GSH levels in erythrocytes were appreciably lower. Thus, obesity is directly linked and further contributes to the elevated OS levels in PCOS [34].

However, obesity alone is not the sole determining factor primarily causing more serious oxidative status in PCOS patients, a large number of other factors are thought to contribute as well. Non-obese/lean women with PCOS too have higher elevated OS levels as compared to those of without PCOS [15]. Even when, PCOS patients with abdominal obesity are not included in the study, while those with peripheral obesity are studied, the results do not alter [35]. Hence, obesity is a one of the overbearing factors which contribute to the elevated OS levels in PCOS but is not the only factor.

ROS, Insulin resistance and PCOS

Insulin resistance (IR) is a metabolic dysfunction wherein the insulin produced by the beta cells in pancreas at a given concentration is not sufficiently utilized and produces less-than-anticipated biological effect, due to the inability of cells to respond to the standard actions of the insulin hormone, leading to dysfunctions in transfer and utilization of available glucose [36]. Fasting insulin (FINS) and homeostasis model assessment of insulin resistance (HOMA-IR) are the currently employed investigations in clinical settings to diagnose insulin resistance [35]. IR is considered to the basal mechanistic undertone leading to polycystic ovary syndrome (PCOS) and its pathogenesis [13], where IR in PCOS patients ranges anywhere from 50% to 70% [37] as compared to non PCOS control.

IR causes hyperglycemia which in turn leads to higher free fatty acid levels causing an upsurge in ROS production [38]. Excess simple sugars like glucose and free fatty acid when absorbed in the cell, leads to the transfer of reducing metabolites, like pyruvic acid and acetyl coenzyme A, into the mitochondrial membrane for oxidation, leading to augmented the electron transport chain (ETC), subsequently increasing ROS production. Failure of simultaneous significant elevation and clearance of oxidative species by action of superoxide dismutase and catalase along with peroxidases further leads to the accumulation of ROS in the cells and tissues [39]. In high glucose IR animal models, ROS levels are positively correlated with dysregulated levels of ROS biomarkers like (MDA, GSH, protein carbonylation etc.) [40].

In a recent study, 11% reduction in the body weight lead to enhanced insulin sensitivity by as high as 71% and the FINS levels dropped down significantly by 33% [41].

Though the complete intricate details of the oxidative stress induced insulin resistance remains elusive, it has been OS has been verified to play decisive part in IR pathogenesis [42].

Thus, ROS is closely related to IR and is likely to be a major cause of IR in PCOS through post-insulin receptor defect. Furthermore, studies with antioxidants like vitamin C, Vitamin E, Vitamin D and α-lipoic acid indicate a favorable effect on insulin sensitivity and suggest an opportunity towards new therapeutic approaches to IR [43].

ROS, inflammation and PCOS:

Interplay between chronic low-grade inflammation and PCOS has been established and inflammation is one of the major manifestations of PCOS and is presumed to reinforce the pathogenesis and severity of PCOS [44]. Levels of inflammatory markers like interferon-γ (INF-γ), C-reactive protein (CRP), tumor necrosis factor (TNF), interleukin-6 (IL-6), interleukin-18 (IL-18), monocyte chemotactic protein-1 (MCP-1), and acute phase serum amyloid A (APSAA), have been reported to be elevated in women with PCOS compared to non- PCOS control [45-47]. Relation between enhances ROS levels and inflammation had been established time and again

by various researchers. It is difficult to differentiate between inflammation and ROS clearly; they are generally co-accompanied [48]. Reactive oxygen species (ROS) induces release of inflammatory factors causing the setting up of inflammatory response, via activating nuclear factor-κB (NF-κB), activated protein-1 (AP-1), and hypoxia-inducible factor-1 (HIF-1) associated pathways[49].

Inflammation along with IR has also been shown to aggravate PCOS [50]. It has been reported that when elevated levels of adipose-derived TNF-α were neutralised in mice, insulin sensitivity was improved [51].

This increase in continuing inflammation also aggravates the symptoms of hyperandogenemia due to availability of free Insulin like growth factor (IGF-1) along with decreased sex hormone binding globin (SHBG) which causes excess androgen production [52].

Conclusion:

Systematically, the anomalous redox dysregulation and ensuing oxidative stress in polycystic ovary syndrome (PCOS) patients not only causes genetic instability but also raise the risk of cancers. OS has been shown to be clearly associated with obesity, dyslipidemia, insulin resistance (IR), chronic inflammation, and androgen excess, which are the common manifestations and possible aggravators of PCOS and endometrial and ovarian cancer and could lead to the precipitation of a complex interconnected heterogeneous disease physiology. ROS and several proinflammatory factors, produced as a result of extreme OS, induce IR primarly through IRS-PI3K-Akt axis through activation of several downstream associated signaling pathways, such as NF-κB, TNF-β and JNK among several others. Hyperinsulinemia, compensates for IR, and underwrites propensity to develop cancer pathogenesis by mutations in proto-oncogenes and activating various p53 dependent cell proliferation signaling pathways and ultimately causes malignancies. In addition, hyperandrogenemia can induce ROS, IR, and chronic inflammation *in vivo* and plays a role in development of obesity too. Thus, it remains to be ascertained and decipher new or other existing pathways which might cross and interlink together and render us a yet not studied insight into the pathogenesis of PCOS and related morbidities.

Therefore, supplementation of antioxidants, along with lifestyle modifications should be the method of choice to target and manage PCOS along with symptomatic treatment in women till newer insights emerge.

References:

[1] A. Izzotti, A. Bagnis, S.C. Saccà, The role of oxidative stress in glaucoma, Mutation Research/Reviews in Mutation Research, 612 (2006) 105-114.

[2] S. Reuter, S.C. Gupta, M.M. Chaturvedi, B.B. Aggarwal, Oxidative stress, inflammation, and cancer: How are they linked? Free radical biology & medicine, 49 (2010) 1603-1616.

[3] A. Modaresi, M. Nafar, Z. Sahraei, Oxidative stress in chronic kidney disease, Iranian journal of kidney diseases, 9 (2015) 165-179.

[4] F. Giacco, M. Brownlee, Oxidative stress and diabetic complications, Circulation research, 107 (2010) 1058-1070.

[5] E.J. Shin, J.H. Jeong, Y.H. Chung, W.K. Kim, K.H. Ko, J.H. Bach, J.S. Hong, Y. Yoneda, H.C. Kim, Role of oxidative stress in epileptic seizures, Neurochemistry international, 59 (2011) 122-137.

[6] T. Sabuncu, H. Vural, M. Harma, M. Harma, Oxidative stress in polycystic ovary syndrome and its contribution to the risk of cardiovascular disease, Clinical biochemistry, 34 (2001) 407-413.

[7] A.E. Joham, H.J. Teede, S. Ranasinha, S. Zoungas, J. Boyle, Prevalence of infertility and use of fertility treatment in women with polycystic ovary syndrome: data from a large community-based cohort study, Journal of women's health (2002), 24 (2015) 299-307.

[8] R.J. Norman, D. Dewailly, R.S. Legro, T.E. Hickey, Polycystic ovary syndrome, Lancet (London, England), 370 (2007) 685-697.

[9] R. Nidhi, V. Padmalatha, R. Nagarathna, R. Amritanshu, Prevalence of polycystic ovarian syndrome in Indian adolescents, Journal of pediatric and adolescent gynecology, 24 (2011) 223-227.

[10] S.J. Ramanand, B.B. Ghongane, J.B. Ramanand, M.H. Patwardhan, R.R. Ghanghas, S.S. Jain, Clinical characteristics of polycystic ovary syndrome in Indian women, Indian Journal of Endocrinology and Metabolism, 17 (2013) 138-145.

[11] T. Zuo, M. Zhu, W. Xu, Roles of Oxidative Stress in Polycystic Ovary Syndrome and Cancers, Oxidative Medicine and Cellular Longevity, 2016 (2016).

[12] S. Franks, Diagnosis of polycystic ovarian syndrome: in defense of the Rotterdam criteria, The Journal of

Clinical Endocrinology & Metabolism, 91 (2006) 786-789.

[13] T.R. ESHRE, A.-S.P.C.W. Group, revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome, Fertility and sterility, 81 (2004) 19-25.

[14] N.F. Goodman, R.H. Cobin, W. Futterweit, J.S. Glueck, R.S. Legro, E. Carmina, American Association of Clinical Endocrinologists, American College of Endocrinology, and Androgen Excess and PCOS society disease state clinical review: guide to the best practices in the evaluation and treatment of polycystic ovary syndrome-part 1, Endocrine Practice, 21 (2015) 1291-1300.

[15] M. Murri, M. Luque-Ramirez, M. Insenser, M. Ojeda-Ojeda, H.F. Escobar-Morreale, Circulating markers of oxidative stress and polycystic ovary syndrome (PCOS): a systematic review and meta-analysis, Human reproduction update, 19 (2013) 268-288.

[16] F.F. Verit, O. Erel, Oxidative stress in nonobese women with polycystic ovary syndrome: correlations with endocrine and screening parameters, Gynecologic and obstetric investigation, 65 (2008) 233-239.

[17] Y. Dinger, T. Akcay, T. Erdem, E. Ilker Saygili, S. Gundogdu, DNA damage, DNA susceptibility to oxidation and glutathione level in women with polycystic ovary syndrome, Scandinavian journal of clinical and laboratory investigation, 65 (2005) 721-728.

[18] A. Savic-Radojevic, I. Bozic Antic, V. Coric, J. Bjekic-Macut, T. Radic, M. Zarkovic, T. Djukic, M. Pljesa-Ercegovac, D. Panidis, I. Katsikis, T. Simic, D. Macut, Effect of hyperglycemia and hyperinsulinemia on glutathione peroxidase activity in non-obese women with polycystic ovary syndrome, Hormones (Athens, Greece), 14 (2015) 101-108.

[19] F. Gonzalez, K.S. Nair, J.K. Daniels, E. Basal, J.M. Schimke, Hyperandrogenism sensitizes mononuclear cells to promote glucose-induced inflammation in lean reproductive-age women, American journal of physiology. Endocrinology and metabolism, 302 (2012) E297-306.

[20] A. Federico, F. Morgillo, C. Tuccillo, F. Ciardiello, C. Loguercio, Chronic inflammation and oxidative stress in human carcinogenesis, International journal of cancer, 121 (2007) 2381-2386.

[21] M. Matsuda, I. Shimomura, Increased oxidative stress in obesity: implications for metabolic syndrome, diabetes, hypertension, dyslipidemia, atherosclerosis, and cancer, Obesity research & clinical practice, 7 (2013) e330-341.

[22] A.M. Pisoschi, A. Pop, The role of antioxidants in the chemistry of oxidative stress: A review, European journal of medicinal chemistry, 97 (2015) 55-74.

[23] Y. Hiraku, S. Kawanishi, Immunohistochemical analysis of 8-nitroguanine, a nitrative DNA lesion, in relation to inflammation-associated carcinogenesis, Methods in molecular biology (Clifton, N.J.), 512 (2009) 3-13.

[24] I. Dalle-Donne, R. Rossi, D. Giustarini, A. Milzani, R. Colombo, Protein carbonyl groups as biomarkers of oxidative stress, Clinica chimica acta; international journal of clinical chemistry, 329 (2003) 23-38.

[25] G.O. Latunde-Dada, Ferroptosis: Role of lipid peroxidation, iron and ferritinophagy, Biochimica et biophysica acta, (2017).

[26] B. Halliwell, J.M. Gutteridge, C.E. Cross, Free radicals, antioxidants, and human disease: where are we now? The Journal of laboratory and clinical medicine, 119 (1992) 598-620.

[27] B. Halliwell, Oxidative stress and cancer: have we moved forward?, The Biochemical journal, 401 (2007) 1-11.

[28] D. Ziech, R. Franco, A. Pappa, M.I. Panayiotidis, Reactive oxygen species (ROS)--induced genetic and epigenetic alterations in human carcinogenesis, Mutation research, 711 (2011) 167-173.

[29] M.A. Lebedeva, J.S. Eaton, G.S. Shadel, Loss of p53 causes mitochondrial DNA depletion and altered mitochondrial reactive oxygen species homeostasis, Biochimica et biophysica acta, 1787 (2009) 328-334.

[30] K.V. Donkena, C.Y. Young, D.J. Tindall, Oxidative stress and DNA methylation in prostate cancer, Obstetrics and gynecology international, 2010 (2010) 302051.

[31] Y.S. Prakash, C.M. Pabelick, G.C. Sieck, Mitochondrial Dysfunction in Airway Disease, Chest, (2017).

[32] A.D. Dobrian, M.J. Davies, S.D. Schriver, T.J. Lauterio, R.L. Prewitt, Oxidative stress in a rat model of obesity-induced hypertension, Hypertension (Dallas, Tex.: 1979), 37 (2001) 554-560.

[33] N.I. Khan, L. Naz, G. Yasmeen, Obesity: an independent risk factor for systemic oxidative stress, Pakistan journal of pharmaceutical sciences, 19 (2006) 62-65.

[34] S.K. Kumanyika, The obesity epidemic: looking in the mirror, American journal of epidemiology, 166 (2007) 243-245.

[35] L. Chen, W.M. Xu, D. Zhang, Association of abdominal obesity, insulin resistance, and oxidative stress in adipose tissue in women with polycystic ovary syndrome, Fertil Steril, 102 (2014) 1167-1174.e1164.

[36] M.M. Lasram, I.B. Dhouib, A. Annabi, S. El Fazaa, N. Gharbi, A review on the molecular mechanisms involved in insulin resistance induced by organophosphorus pesticides, Toxicology, 322 (2014) 1-13.

[37] R.S. Legro, D. Finegood, A. Dunaif, A fasting glucose to insulin ratio is a useful measure of insulin sensitivity in women with polycystic ovary syndrome, The Journal of clinical endocrinology and metabolism, 83 (1998) 2694-2698.

[38] A. Bloch-Damti, N. Bashan, Proposed mechanisms for the induction of insulin resistance by oxidative stress, Antioxidants & redox signaling, 7 (2005) 1553-1567.

[39] I.R. Sweet, M. Gilbert, E. Maloney, D.M. Hockenbery, M.W. Schwartz, F. Kim, Endothelial inflammation induced by excess glucose is associated with cytosolic glucose-6-phosphate but not increased mitochondrial respiration, Diabetologia, 52 (2009) 921-931.

[40] J.P. Dias, S. Talbot, J. Senecal, P. Carayon, R. Couture, Kinin B1 receptor enhances the oxidative stress in a rat model of insulin resistance: outcome in hypertension, allodynia and metabolic complications, PloS one, 5 (2010) e12622.

[41] M.M. Huber-Buchholz, D.G. Carey, R.J. Norman, Restoration of reproductive potential by lifestyle modification in obese polycystic ovary syndrome: role of insulin sensitivity and luteinizing hormone, The Journal of clinical endocrinology and metabolism, 84 (1999) 1470-1474.

[42] S. Lim, M.J. Quon, K.K. Koh, Modulation of adiponectin as a potential therapeutic strategy, Atherosclerosis, 233 (2014) 721-728.

[43] J.L. Evans, B.A. Maddux, I.D. Goldfine, the molecular basis for oxidative stress-induced insulin resistance, Antioxidants & redox signaling, 7 (2005) 1040-1052.

[44] I. Alanbay, C.M. Ercan, M. Sakinci, H. Coksuer, M. Ozturk, S. Tapan, A macrophage activation marker chitotriosidase in women with PCOS: does low-grade chronic inflammation in PCOS relate to PCOS itself or obesity? Archives of gynecology and obstetrics, 286 (2012) 1065-1071.

[45] S. Mahalingaiah, E. Diamanti-Kandarakis, Targets to treat metabolic syndrome in polycystic ovary syndrome, Expert opinion on therapeutic targets, 19 (2015) 1561-1574.

[46] E. Diamanti-Kandarakis, T. Paterakis, K. Alexandraki, C. Piperi, A. Aessopos, I. Katsikis, N. Katsilambros, G. Kreatsas, D. Panidis, Indices of low-grade chronic inflammation in polycystic ovary syndrome and the beneficial effect of metformin, Human reproduction (Oxford, England), 21 (2006) 1426-1431.

[47] F. Gonzalez, K.S. Nair, J.K. Daniels, E. Basal, J.M. Schimke, H.E. Blair, Hyperandrogenism sensitizes leukocytes to hyperglycemia to promote oxidative stress in lean reproductive-age women, The Journal of clinical endocrinology and metabolism, 97 (2012) 2836-2843.

[48] H.N. Siti, Y. Kamisah, J. Kamsiah, The role of oxidative stress, antioxidants and vascular inflammation in cardiovascular disease (a review), Vascular pharmacology, 71 (2015) 40-56.

[49] R.M. Touyz, Molecular and cellular mechanisms in vascular injury in hypertension: role of angiotensin II, Current opinion in nephrology and hypertension, 14 (2005) 125-131.

[50] F. Gonzalez, N.S. Rote, J. Minium, J.P. Kirwan, Increased activation of nuclear factor kappaB triggers inflammation and insulin resistance in polycystic ovary syndrome, The Journal of clinical endocrinology and metabolism, 91 (2006) 1508-1512.

[51] G.S. Hotamisligil, N.S. Shargill, B.M. Spiegelman, Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance, Science (New York, N.Y.), 259 (1993) 87-91.

[52] D. LeRoith, C.T. Roberts, Insulin-like Growth Factors, Annals of the New York Academy of Sciences, 692 (1993) 1-9.

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