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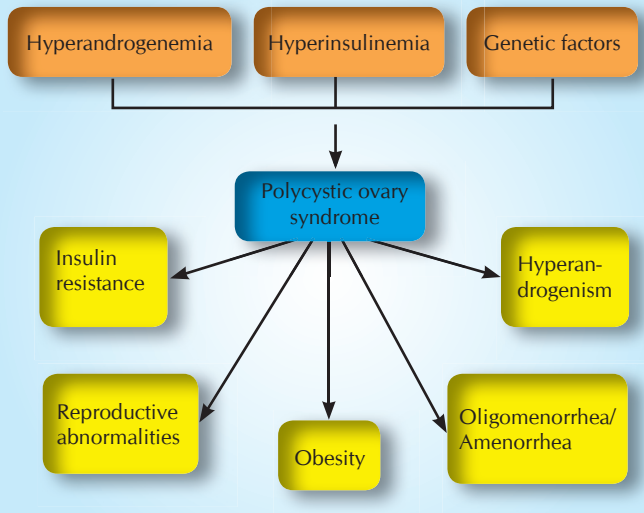
Oxidative stress in polycystic ovarian syndrome

Introduction

Polycystic ovary syndrome (PCOS) is a widely prevalent endocrine disorder afflicting women during their reproductive age. According to the European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine criteria, the prevalence of PCOS has been established to be 15%-20% globally.[1] The pathophysiology of this disorder is complex and elusive to most investigators. PCOS includes a wide spectrum of clinical signs and symptoms characterized by reproductive (infertility, irregular menses, hyperandrogenism, hirsutism, polycystic ovaries), metabolic (insulin resistance, impaired glucose tolerance, type 2 diabetes mellitus, cardiovascular diseases, obesity) and psychological features (increased anxiety, depression and worsened quality of life) (figure 1).[2,3] Oxidative stress (OS, an imbalance between oxidants and antioxidants) has been found to be present in women with PCOS regardless of their body mass index (BMI). The reproductive cells and tissues remain stable only when a balance between the oxidant and antioxidant mechanism is maintained.[4] Obesity influences certain features of PCOS such as hyperandrogenism, hirsutism, infertility and pregnancy complications. Furthermore, obesity also impairs insulin resistance and exacerbates reproductive and metabolic features of PCOS.[2] The interventions targeting PCOS should address the present needs of the patient and provide prophylaxis against any future complications.[5]

Figure 1: Pathogenesis of polycystic ovary syndrome



Source: Bates GW Jr, Propst AM. Polycystic ovarian syndrome management options. *Obstet Gynecol Clin North Am.* 2012 Dec;39(4):495-506.

Oxidative stress in polycystic ovary syndrome

Oxidative stress is the result of an imbalance between oxidant and antioxidant mechanisms. When the imbalance favors oxidants, generation of excessive amounts of reactive oxygen species (ROS) results in detrimental consequences. When the ROS are formed in excess and outnumber antioxidants, there is extensive DNA damage and/or cell apoptosis.[6] Furthermore, reactive nitrogen species (RNS), such as nitrogen oxide (NO) with an unpaired electron are also highly reactive and toxic and may contribute to OS in the body. OS has been reported to be present in women with PCOS irrespective of whether they are lean or have metabolic abnormalities.[7] Several *in vivo* studies performed to ascertain the role of OS in the pathogenesis of PCOS have demonstrated increased presence of OS biomarkers

validating the role of OS in the disease development. OS biomarkers investigated include malondialdehyde (MDA), protein carbonyl, total antioxidant capacity (TAC), superoxide dismutase (SOD), glutathione peroxidase (GPx), and glutathione (GSH).[4] Kuscu *et al* demonstrated that levels of biomarkers MDA and SOD were significantly higher in a PCOS group compared with a control group (MDA level: 0.12±0.03 vs. 0.10±0.03; SOD level: 8.0±0.7 vs. 7.28±0.8). Furthermore, the levels of these oxidants in the PCOS group were found to be high in both obese patients and their non-obese counterparts. These findings suggested that concentration of plasma oxidative stress markers such as MDA is raised in PCOS subjects and the increase in them was independent of obesity.[8]

Polycystic ovary syndrome in lean and obese women

BMI influences the susceptibility to develop PCOS, with obese women showing higher risk of its development compared to the non-obese women. Obesity plays a pivotal role in the pathogenesis of PCOS. Several epidemiological surveys have shown that 50% of women with PCOS are obese and overweight.[9] The prevalence of clinical manifestations and health risks in obese and lean PCOS women are summarized in table 1 and table 2.[10] While both insulin and metabolic indices are similar in lean women with and without PCOS, obese women with PCOS are more insulin-resistant compared to their counterparts without PCOS.[11] Obesity may be responsible for insulin resistance and associated hyperinsulinemia in women with PCOS, which may in turn be responsible for hyperandrogenism in these women. Obese women with PCOS have greater severity of hyperandrogenism associated clinical features (such as hirsutism, menstrual abnormalities and anovulation) than normal-weight PCOS women.[9] Additionally, obesity and insulin resistance also increases risk of type 2 diabetes mellitus and cardiovascular diseases in these women.[2]

Table 1: Prevalence of various clinical features in obese vs. lean women with polycystic ovary syndrome

Clinical features	Obese (%)	Lean (%)
Menstrual cycles:		
Abnormal	79.2	44
Withdrawal bleed	42	9.4
Delayed	26	14
Early	7.6	18
Normal	20.8	56
Oligo-ovulation	6	14.6
Normal ovulation	14.8	41.4
Clinical hyperandrogenism:		
Clinical hyperandrogenism present	74.2	50.6
Hirsutism	33.6	28
Acne and oily skin	40.6	22.6
Hirsutism, acne and oily skin	18.6	16.6
Clinical hyperandrogenism absent	25.8	49.4

Source: Majumdar A, Singh TA. Comparison of clinical features and health manifestations in lean vs.. obese Indian women with polycystic ovarian syndrome. *J Hum Reprod Sci.* 2009 Jan-Jun;2(1):12–17.

Table 2: Prevalence of various manifestations in obese vs. lean women with polycystic ovary syndrome

Health manifestations	Obese (%)	Lean (%)
Hypertension		
Normotensive	59	64.8
Prehypertensive	23	29.2
Hypertensive	18	6
Diabetes		
No diabetes	63.2	84
Impaired glucose tolerance (IGT)	25	10
Diabetes	11.8	6
IGT + diabetes	36.8	16
Endometrium		
Day 2 Endometrial thickness <4mm on ultrasonography	75.4	89.2
Day 2 Endometrial thickness >4mm on ultrasonography	24.6	10.6
No endometrial hyperplasia	19	8.6
Endometrial hyperplasia	5.6	2

Source: Majumdar A, Singh TA. Comparison of clinical features and health manifestations in lean vs.. obese Indian women with polycystic ovarian syndrome. *J Hum Reprod Sci.* 2009 Jan-Jun; 2(1):12–17.

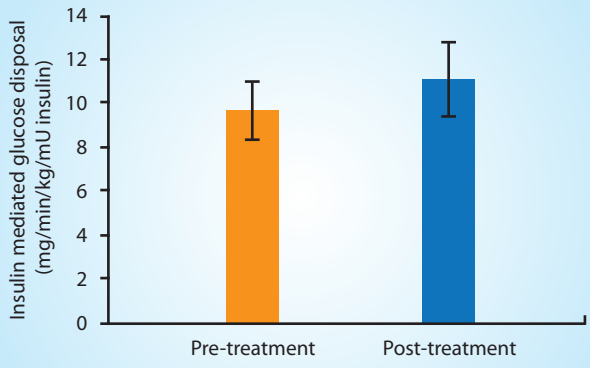
BMI is also known to have an influence on OS in PCOS. Blair *et al*[12] conducted a study to demonstrate the effect of obesity on OS in women with PCOS. It was revealed that oxidant status was increased in obese and lean PCOS subjects compared to their weight-matched controls without PCOS [total oxidant status (TOS), obese PCOS patients vs. obese controls: 42.42±4.49 vs. 32.57±1.97 micromol H2O2 Equiv/L and lean PCOS patients vs. lean controls:

33.69±1.59 vs. 28.69±1.18 micromol H2O2 Equiv/L]. Moreover, TAC was lower in the lean PCOS group relative to their weight-matched controls without PCOS (TAC: lean PCOS patients vs. lean controls, 1.10±0.09 vs. 1.49±0.03 nmol Trolox Equiv/L). Thus, it can be inferred that obese females are more likely to manifest PCOS relative to lean or normal weight females.

Management of oxidative stress in polycystic ovary syndrome: Role of alpha lipoic acid

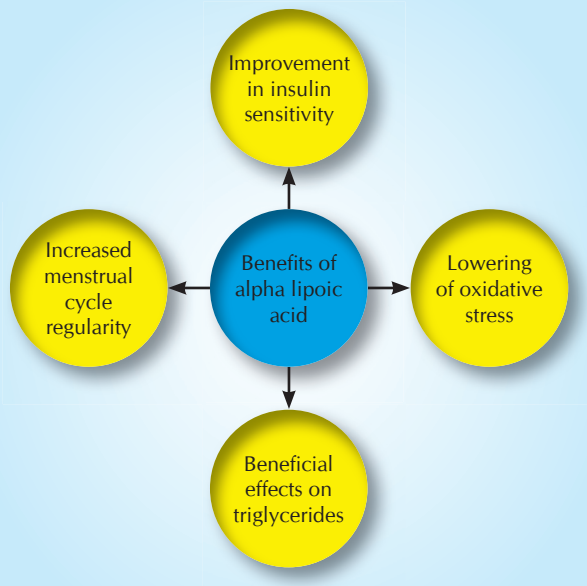
Evidence suggests that there is increased OS in patients with PCOS, which in turn could lead to insulin resistance. Therefore, PCOS women could gain from inhibitors of OS. Alpha lipoic acid (ALA), a well established antioxidant used in the management of OS in PCOS, is synthesized in the liver and other tissues and is a key component of several mitochondrial enzyme complexes responsible for oxidative glucose metabolism and cellular energy production. ALA functions as a safe and effective antioxidant, recycles vitamins C and E, elevates glutathione levels, and lowers ROS.[13,14] Masharani *et al*[14] conducted a clinical trial to evaluate the impact of ALA on women with PCOS. It was established that ALA improved insulin sensitivity and triglyceride levels, decreased OS and increased menstrual cycle regularity. Six non-obese, nondiabetic patients with PCOS were administered 600 mg of ALA twice a day for 4 months. There was an average improvement of 13.5% in insulin sensitivity with ALA therapy. The mean insulin mediated glucose disposal increased from 9.7±1.3 mg/min/kg/mU insulin to 11.1±1.7 mg/min/kg/mU insulin (figure 2). There was a significant decline in triglyceride levels of non-obese subjects with ALA therapy, 80±29 vs. 58±10, pre and post-treatment, respectively. Reduction in the level of OS markers among non-obese subjects was also observed. However, as ALA is a potent antioxidant, a future research is required to obtain a wider perspective to establish its role in PCOS especially among obese patients. Women with abnormal menstrual periods who were not on oral contraceptives during the treatment reported an increase in regularity and frequency of their periods. The supplement was well tolerated with no adverse reactions. These results showed that treating PCOS patients with ALA leads to improvement in insulin sensitivity, lowering of OS, beneficial effects on triglycerides and increased menstrual cycle regularity (figure 3).

Figure 2: Impact of alpha lipoic acid on insulin resistance in non-obese women with polycystic ovary syndrome



Source: Masharani U, Gjerde C, Evans JL, Youngren JF, Goldfine ID. Effects of Controlled-Release Alpha Lipoic Acid In Lean, Nondiabetic Patients with Polycystic Ovary Syndrome. *J Diabetes Sci Technol.* Mar 2010;4(2):359–364.

Figure 3: Advantages of alpha lipoic acid in women with polycystic ovary syndrome



Source: Masharani U, Gjerde C, Evans JL, Youngren JF, Goldfine ID. Effects of Controlled-Release Alpha Lipoic Acid In Lean, Nondiabetic Patients with Polycystic Ovary Syndrome. *J Diabetes Sci Technol.* Mar 2010;4(2):359–364.

Conclusion

PCOS is one of the most common female endocrinal abnormality. Obesity has been shown to play a crucial role in the pathogenesis of PCOS. Nevertheless, there are emerging evidences to substantiate the relationship between PCOS and OS and in turn its impact on insulin sensitivity. ALA

has been demonstrated to play a key role as a therapeutic agent for PCOS patients by improving insulin sensitivity, triglyceride levels, regularizing menstrual cycle abnormality and reducing oxidative stress. It appears to be a promising treatment option worth a consideration in PCOS patients.

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