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PCOS, TYPE II DIBETES MELLITUS, OBESITY COEXISTENCE: AN METABOLIC DISASTER & A WAY THROUGH IT

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ABSTRACT

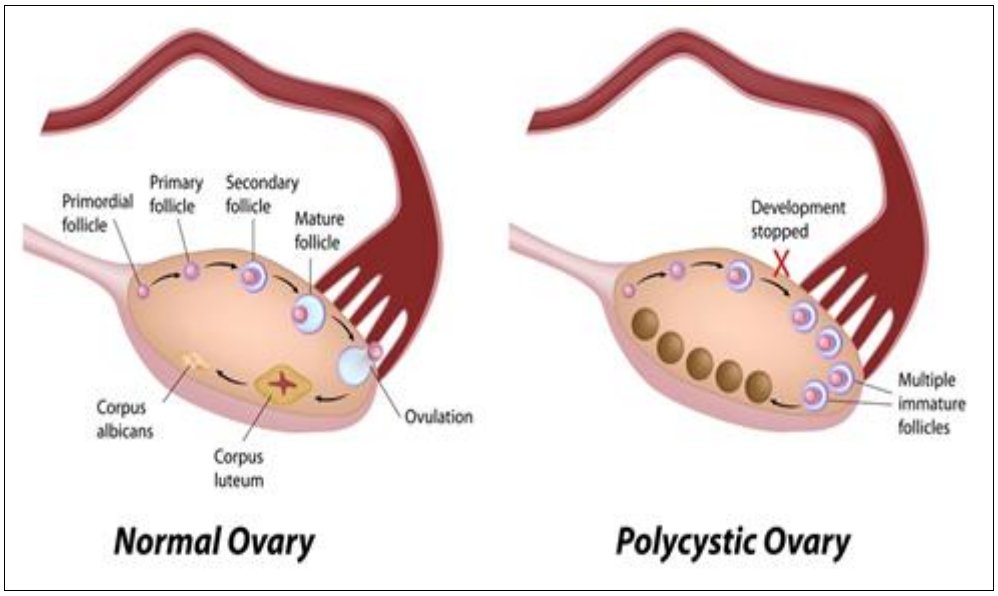
Polycystic ovary syndrome (PCOS) is one of the most frequently encountered endocrine disorder occurring in women of reproductive age. Primary clinical manifestations are menstrual irregularities, infertility, and hirsutism. However if not treated properly, a patient is at risk for type 2 diabetes, obesity, dyslipidemia and cardiovascular disease. The hallmarks of this metabolic disaster are hyperandrogenism and hyperinsulinemia. Great controversy exists as to which state precedes the other. Research consistently demonstrates that weight loss and dietary changes appear to affect all parameters of hormonal and metabolic fluctuation. In this review we have attempted to cover pathophysiology of this disaster in brief. Moreover we have discussed various old, new and future therapeutic ways to come out of these endocrine and metabolic complications.

KEYWORDS: PCOS, Type II Diabetes mellitus, Obesity, Dyslipidemia, treatments.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the commonest endocrine disorder in women of reproductive age and the most frequent cause of anovulating infertility in developed countries. Common clinical manifestations of PCOS include menstrual disorders, due to the anovulation, and androgen excess signs, such as hirsutism, oily skin, acne and androgenic alopecia.[1] A principal characteristic of PCOS is associated metabolic aberrations like insulin resistance (IR) and obesity. Indeed, 38–88% of patients with PCOS are overweight or obese.[1, 2] As we can see in "Fig. *1*", in PCOS ovarian follicles are chronically stimulated by

the low levels of FSH, but do not reach complete maturation. The elevated androgens prevent complete follicular development. Therefore the ovaries are filled with multiple small follicles of 2-10 mm in size and with a prolonged life span which leads to cyst formation. In fact the number of primordial follicles is similar to that of normal ovary, but the numbers of primary and secondary follicles are twice than those observed in the normal ovary.[3]



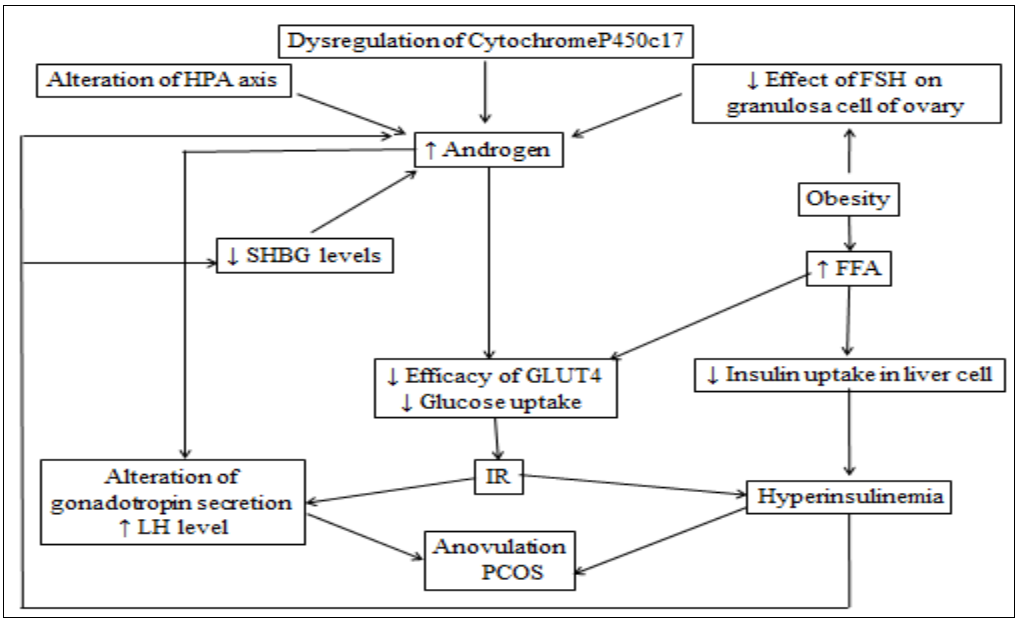
"Fig.1": Cyst formation in polycystic ovary

Pathophysiology ("Fig.*2*")

The etiology of polycystic ovaries remains unknown; however, there is growing consensus that the key features are androgen excess, IR, abnormal gonadotropin dynamics and obesity.

The ovaries and the adrenal glands contribute equally to testosterone production in women[4] however; in PCOS the main source of androgens is thought to come from the ovaries. Dysregulation of cytochrome p450c17, is the androgen-forming enzyme in both the adrenals and the ovaries, maybe the central pathogenic mechanism underlying hyperandrogenism in PCOS. Normally less than 3% of testosterone circulates freely in the serum.Most circulating androgens are bound, primarily to sex hormone-binding globulin (SHBG).When bound to SHBG, the hormone is considered as biologically inactive. Any condition that decreases the levels of SHBG or other binding proteins can lead to a relative excess of circulating androgens.[5] Androgens may both directly and indirectly result in alterations in glucose metabolism, ultimately causing a hyperinsulinemic state. Additionally androgens may also directly inhibit peripheral and hepatic insulin action. One study suggested that testosterone could induce IR in women with PCOS by reducing the number and efficacy of glucose

transport proteins, specifically the type-4 glucose transporter (GLUT-4). GLUT-4 appears to be responsible for the insulin-related uptake of glucose in muscle and fat. Other key factor which play important role in PCOS is central obesity. It's observed that women with central obesity have higher free androgen levels and exhibit significantly higher levels of insulin insensitivity compared to weight matched controls.[6] Androgens and increased free fatty acids (FFAs) inhibit hepatic insulin extraction, resulting in hyperinsulinemia and IR.[7] Testosterone facilitate lipolysis, provides increased FFA concentrations.[8] Even more important to this mechanismis the fact that elevated FFA levels inhibits insulin mediated glucose uptake in skeletal muscle, a condition that defines IR.[9] IR and compensatory hyperinsulinemia are characteristic metabolic disturbances of many, but not all, women with PCOS. However, the order of events remains unclear and is not known whether hyperandrogenism results from the hyperinsulinemia and IR or vice versa.[10]



"Fig.2": Pathophysiology of PCOS

Consequences and complications

Studies have demonstrated both *in vivo* and *in vitro,* that hyperinsulinemia stimulates ovarian androgen production and decreases the synthesis of SHBG by the liver.[11] In this manner, Insulin resistance and hyperinsulinemia may insult ovarian function contributing to excessive androgen production and disruption of the ovulatory process.[12] It has also been shown that chronic hyperandrogenism and hyperinsulinemia affect the hypothalamus pituitary ovary axis (HPA axis) and thus secretion of gonadotropins, in favor of increased luteinizing hormone (LH), which again contributes to the mechanism of anovulation.[13]

Insulin resistance is a known key factor in the development of type 2 diabetes. Several studies have demonstrated that type 2 diabetes occurs with increased frequency in women with PCOS[14,15], hence PCOS recently has been identified as a significantnon modifiable risk factor associated with type 2diabetes by the International Diabetes Federation and by the American Diabetes Association.[16] Some long term prospective clinical trials were performed to check impact of PCOS on prevalence of type II DM, which confirm that the incidence of type 2 diabetes in Italian women with PCOS is 2.6 times higher than that of the general female population.[17, 18] In another clinical trial with participation of 91 women having PCOS, level of proinsulin was measured. Data suggest rise in proinsulin concentration which again alarms for risk of insulin resistance in future.[19] Then again in one study it was found that insulin action is reduced in adipocytes of women with PCOS, which results into decreased glucose transport, with a reduction in autophosphorylation of fibroblast insulin receptors and leads to a doubling the risk of type II diabetes mellitus and obesity.[20]

Dyslipidemia is also a common aberration in PCOS and includes high levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and triglycerides (TGs) and decreased high-density lipoprotein cholesterol (HDL-C) levels. Lipid abnormalities are present in 65-81% of PCOS and much higher levels are observed in those with higher insulin resistance.[21] In women with PCOS, especially in the presence of obesity and IR, increased markers of cardiovascular disease including C-reactive protein, endothelin 1,adiponectin, homocystein, plasminogen activator inhibitor-1 (PAI-1)[22-24] and oxidative stress markers have also been reported.[25]

THE OLD THERAPEUTIC TOOLS

Life style modification

Weight loss through exercise and diet has been proven effective in restoring ovulatory cycles and achieving pregnancy for many patients.[26] In obese anovulatory women with PCOS, weight loss of even 5%to 10%of body weight often restores ovulatory cycles.[27] In support of this some studies were carried out where a high carbohydrate (55%), low protein (15%) hypocaloric diet and low carbohydrate (40%), high protein (30%) hypocaloric diet showed significant weight loss and decrease in circulating androgen and insulin levels.[28]

Routine exercise plays important role in maintaining reproductive health of women with PCOS. Exercise increases insulin sensitivity and helps to achieve and maintain weight loss. Other lifestyle factors such as excessive caffeine intake, alcohol consumption, and smoking

should also be taken in to consideration.[29] Long-term lifestyle modifications can decrease the complication during pregnancy such as abortion, high BP and gestational diabetes mellitus. It also reduces risk of predisposition to health conditions such as type 2 diabetes mellitus and cardiovascular disease.[29, 30]

Clomiphene citrate (CC)

It's a first-line ovulation induction agent. It's a selective estrogen receptor modulator that stimulates endogenous FSH production and secretion by interrupting estrogen feedback to the hypothalamus and pituitary.

The starting dose of clomiphene citrate is 50 mg per day for5 days, commencing between day 2 and 6 of menses. Further dose adjustment can be done as per requirement.[31] Although 60% to 85% of patients will ovulate on treatment, only50% of them will conceive. Amongst that approximately 50% of conceptions will occur on 50 mg dose, with another 20%- 25% and 10% occurring on 100 mg and 150 mg doses, respectively.[32] Lack of conception despite the evidence of ovulation may be the impact of anti-estrogenic effects of drug on the endometrium (thinning of endometrium).[33] Alternatives for ovulation induction should be considered if the periovulatory endometrium is becoming persistently thin on treatment with drug. In similar way, if pregnancy does not occur within 6 ovulatory cycles, another ovulation induction technique should be taken into consideration. Other limitations of drug treatment includes increased rate of twin (7% to 9%) and triplet (0.3%) pregnancy, and side effects such as vasomotor hot flashes, blurring of vision(due to anti estrogenic effect of drug on visual cortex). Additionally some evidences showed increased risk of borderline ovarian tumors on long term treatment thus its used should be limited to not more than 12 ovarian cycles.[34-36]

Oral contraceptives (OCs)

From many years the oral contraceptive pill (OC) has been considered as core therapy for PCOS. The combined oral contraceptives (COCs) are more frequently used for this purpose. The effects of OC on the PCOS are multifactorial and complex. It credited to the remarked reduction of LH secretion, inhibition of ovarian and adrenal androgen production and reduction of free testosterone due to increased production of SHBG in the liver.[37, 38] However, the effect of OCs on the metabolic profile in PCOS is remains less well-understood. Early studies in the general population have showed that use of OCs, containing high ethynyl-oestradiol (EE) doses, can induce insulin resistance (IR) and hyperglycaemia

and changes the lipid profile on detrimental side.[39,40] However, follow-up studies revealed a limited effect on metabolic risk with no clinical significant consequences when low doses of COCs were used.[41]

Studies on the effect of OC on insulin resistance also gave conflicting results with some showing no change[41] and others showed an increased insulin resistance.[43] In one meta-analysis the effect of OCs and metformin in PCOS was examined. No significant difference between the two treatments was found with regards to fasting glucose levels or diabetes development but metformin was superior to OCs in reducing fasting insulin levels. Due to the limitations of the current studies, further and longer studies are needed to establish the effect of OCs on glucose metabolism.

The available data stipulates that OCs may increase LDL-cholesterol and total cholesterol and increase HDL-cholesterol[42, 44, 45] and significantly increase TG or may have no effect at all.[42, 46, 47] Contrary to this, administration of the progestogen-only pill in PCOS women does not seem to interfere with lipid parameters.[48, 49] Increased TG, mostly together with increased total cholesterol levels, appear to be the commonest unfavorable effect of OC treatment in women with PCOS as specified in studies both in adults and adolescents obese and lean women with PCOS.[42, 45-49] The prospective effect of OC on TG levels is considered as the impact of the oestrogen component in the liver and resulting in reduction of triglyceride clearance. Thus OC with lower EE have adverse effect on TG level [50]. Moreover in women with PCOS different OCs are found to result in increased HDL cholesterol levels. An effect is appear to be mediated by the effect of the estrogen component on apolipoprotein A-I gene expression in the liver cells.[51]

To abridge, OC may have a negative effect on the metabolic aberrations of women with PCOS and the long-term benefits are unclear, especially in those with IGT, T2DM and dyslipidemia. Decision for their administration in women with PCOS should be based on the patient's phenotype and history and should always be combined with lifestyle modifications in order to neutralize some of their inauspicious effects. Although there are some data suggesting the OCs with low dose of EE (< 50μg) are associated with lower metabolic risk, it is not yet proven whether very low doses of EE (<20-15μg) have additional advantages on the metabolic profile or no.

Anti-androgens

Hyperadrogenaemia may be one of the initiating factors of metabolic aberrations in women with PCOS. Androgens exert this effect via the androgen receptor, which is expressed in the visceral fat. Up-regulation of lipolysis in visceral adipose tissue may reflect an androgen-induced metabolic defect of PCOS. Besides, androgens, by their direct action on the insulin signaling pathway, have like hood to contribute to peripheral insulin resistance in PCOS.[25] Anti-androgens are the drugs which act by competitive inhibition of androgen-binding receptors or by decreasing androgen production.[52] In PCOS, the observed favorable effects on some metabolic complications with anti-androgen treatment may be ascribed to the blockade of androgen receptor and reduction of androgen excess. Some examples of anti-androgens are cyproterone acetate, spironolactone and flutamide.

Cyproterone acetate has been the most often used as an effective anti-androgen with pro-gesterone-like properties.[53] It can induce ovulation when it is used in combination with clomiphene citrate but may also have unfavorable consequences for women with PCOS as it can increase body weight and IR.[24, 54]

Spironolactone is an aldosterone antagonist and a competitive inhibitor of the androgen receptor, which results in inhibition of androgen production and can also inhibit 5α-reductase activity. Literature on metabolic effects of spironolactone in women with PCOs is limited and conflicting. Administration of spironolactone in lean PCOS women caused increased HDL cholesterol levels.

Flutamide, a nonsteroidal selective androgen receptor inhibitor without progestogenic activity, decreases the conversion of testosterone to its more active metabolite, dihydrotestosterone, in target tissues.[55] Its administration in women with PCOS results in noteworthy amelioration of the clinical and biochemical androgenic manifestations but with minimal or no effect on insulin sensitivity factor and insulin-stimulated glucose utilization rate.[56] Nevertheless, flutamide treatment in women with PCOS significantly decreased total cholesterol, LDL cholesterol and TG.[55] Addition of metformin to the treatment of flutamide and OC reflected metabolic benefits with further reduction of LDL cholesterol levels and an increase in HDL cholesterol levels.[57] Moreover, in obese women with PCOS, flutamide treatment had an added benefit on lipid profile when it was added to their hypocaloric diet.[25, 58]

Aromatase inhibitors

They block the conversion of testosterone and androstenedione to estradiol and estrone, respectively, and hence inhibit the estrogen-negative feedback on the hypothalamic–pituitary-axis. This leads to increased gonadotropin secretion, which in turn leads to ovarian follicular growth and development.[59, 60] Ovulation and pregnancy rates with aromatase inhibitors such as letrozole and anastrozole are appears to be promising, but the evidence on endometrial effects is conflicting, and most studies show equivalence with clomiphene citrate; an ovulation inducing agent.[60-62] Sign of embryotoxicity, fetotoxicity, and teratogenicity found in rats limit the use of these agents.[63]

THE NEW THERAPEUTIC TOOLS

Insulin sensitizers

The strong pathophysiological relationship of insulin resistance with PCOS and related aberrations supports the therapeutic use of insulin sensitizers in the management of PCOS. The extensive literature has shown that reduction in insulin levels pharmacologically ameliorates the sequelae of hyperinsulinemia and hyperandrogenemia. Insulin sensitizers, mainly metformin and thiazolinediones, can effectively handle the established metabolic derangements in PCOS; however their prophylactic role is unclear.

Metformin

Metformin, a biguanide, is an insulin sensitizer that has been used widely in the treatment of Type II DM. Its mechanism of action is complex and pleiotropic and is exerted on several tissues. Its principal action is in the liver with suppression of gluconeogenesis and hepatic glucose output, but it also enhances peripheral insulin action in the skeletal muscle and reduces glucose absorption from the digestive tract, with no significant direct effect on pancreatic insulin production.[64, 65] Metformin also ameliorates lipid profile via various mechanisms[55, 66], and directly inhibits thecal androgen production.[67] In women with PCOS, treatment with metformin appears to improve cardiometabolic parameters by improving insulin sensitivity, lowering blood glucose and androgen levels and possibly by its effects on body weight. These effects of metformin are more potent when it is combined with lifestyle intervention. Increased body weight and central obesity are associated with increased cardiometabolic risk in women with PCOS. Obesity is common in women with PCOs and weight loss in these women is of major importance. Recent data suggest that metformin may normalize appetite in obese women with PCOS by restoring neuropeptide Y secretion, which

is impaired in these women.[68] A meta-analysis of 13 controlled trials in women with PCOS concluded that metformin is potent in the reduction of fasting insulin levels.[69] Metformin reduces insulin resistance, increases insulin-stimulated glucose disposal[55] and thus may prevent the development of Type II DM. In a small retrospective study, the use of metformin in women with PCOS for 43 months showed a much lower conversion rate from normal glucose tolerance to impaired glucose tolerance (IGT) than previously observed (1.4% versus 16-19%) and none of the women, even those with IGT at the base line, developed diabetes.[70] Metformin has been shown to improve lipid abnormalities in PCOS. These effects of metformin seems to be multifactorial but may mainly rely upon its effect on its main metabolic tissues.[66] Metformin in the liver, via inhibition of acetyl-CoA carboxylase activity, decreases free fatty acid (FA) synthesis and increases mitochondrial FA oxidation and thus reduces plasma triglycerides.[71] Furthermore, metformin suppresses the expression of the lipogenic gene in the liver. The effect of metformin on insulin resistance and body weight reduction also contributes to the refinement of lipid profile in these women.[55] Androgen excess has been linked with atherogenic lipid profile in PCOS, particularly with reduced HDL cholesterol levels.[72] In this way, Metformin appears to have multiple favorable results on the metabolic aberrations in women with PCOS. It should be used in these women as an adjuvant to lifestyle intervention as their effect on improving cardiometabolic parameters is additive.

Thiazolinediones

The insulin sensitizer thiazolinediones (TZDs), also known as glitazones, and their action is mediated by binding and activating the nuclear receptor peroxisome proliferator-activated receptor gamma (PPARγ). They improve insulin sensitivity by regulating genes involved to adipose tissue metabolism. Activation of PPARγ by TZDs increases insulin sensitivity mainly in adipocytes and muscle cells[73] and also stimulates differentiation of adipose cells.[74] TZDs can also stimulate glucose transporter expression and other proteins in the insulin pathway. All these modifications are associated with a decrease in plasma FFA and TG concentrations.[73] Practically, pioglitazone is the only TZD that can be used today. Troglitazone, the first representative of this class of medications, was withdrawn from the worldwide market in 2000 because of its hepatotoxicity. Rosiglitazone was also suspended recently from the European market due to its association to increased cardiovascular mortality[75] and the FDA in USA has decide that rosiglitazone could be obtained only under a very stringent restricted program.When pioglitazone was administered to thirteen women

with a suboptimal response to metformin monotherapy an increase in HDL cholesterol levels was observed.[65] More and longer-term data are needed to establish the effect of TZDs on the metabolic aberrations of women with PCOS.

Antiobesity agents

Lifestyle changes are ineffective because obese patients who lose weight by lifestyle modifications are unable to maintain compliance with dietary restriction and exercise for longer period mostly, thus regain of lost bodyweight during following 2–5 years is very common. Therefore, supplementary pharmacological treatment for the management of obesity is frequently necessary.

Pharmacological treatment of obesity is recommended in obese patients with a body mass index (BMI) >30 or >27 with concomitant metabolic diseases, includingT2DM, which might coexist with dyslipidemia or hypertension. The treatment goal is moderate weight loss, approximately 5–10% of initial body weight, as this has been shown to substantially improve fertility and the metabolic risk factors associated with obesity. The antiobesity agents, depending on their mechanism of action, are divided into two categories. The first includes centrally acting agents, which reduce food intake by decreasing appetite and inducing satiety or by increasing energy expenditure. Sibutramine, a centrally acting agent which reduces body weight in patients with PCOS by 4.3% more than diet alone and improves insulin sensitivity and reduces circulating androgen levels that was recently withdrawn from the market because of adverse cardiovascular effects,[76, 77] The second category includes agents with peripheral action, which decrease fat absorption. The main representative of this class is orlistat, which was shown to reduce body weight and also to reduce IR and hyperandrogenemia in patients with PCOS.[78]

EMERGING THERAPEUTIC TOOLS

Statins

Statins are an emerging and promising new therapeutic option for women with PCOS. They act by a selective inhibition of 3-hydroxy- 3-methylglutaryl-coenzyme A (HMG-CoA), the rate-limiting enzyme in the cholesterol biosynthesis pathway [79].In women with PCOS statins appear to have diverse actions and in addition to lipid reduction, mainly LDL cholesterol levels, they target the underlying stimulation of thecal androgen production, steroidogenesis. Moreover they also adversely affect insulin resistance and hyperinsulinemia associated with the pathophysiology of PCOS. They also exhibit anti-oxidant, antiflammatory

and antiprolifarative effects.[80] In a randomized double blind placebo of atorvastatin versusplacebo in women with PCOS, atorvastatin improved lipid profile and reduced C-reactive protein (CRP), marker of inflammation in the body and serum insulin levels.[81] PCOS is associated with hyperlipidemia and endothelial dysfunction with low-grade inflammation and thus the improvement of lipid profile and the reduction of CRP and pro-inflammatory adhesion molecules with statins is of particular importance in this group.[82] The use of statins in the medical treatment of women with PCOS appears to have pleotropic benefits, but further studies of longer duration are needed to confirm the whole spectrum of their clinical implications in these groups. Based on the available data anddue to their potential teratogenicity, statins currently are not recommended to be used in women with PCOS and dyslipidemia who are planning pregnancy.

Acupuncture

Recently, a few studies have emerged on the use of acupuncture in women with PCOS. Acupuncture uses needles for manual or electrical sensory stimulation of somatic afferent nerves innervating the skin and muscles. Thus acupuncture may modulate somatic and autonomic activity and metabolic and endocrine functions. Its therapeutic effect depends on the needling 'dose', that is the intensity, the frequency, the type of stimulation and the intervals between stimulations[83] and psychological factors.[84] Evidence suggests that electrical stimulation of needles, electro-acupuncture (EA), may offer some benefits in women with PCOS such as improvement in hyperandrogenism and menstrual frequency.[85] Clinical evidence on the effect of acupuncture on the metabolic parameters of PCOS is lacking. Experimental evidence from animal studies though suggests a possible benefit of EA with repetitive muscle contraction on metabolic variables as it may activate a physiological processes similar to those resulting from physical exercise. In particular, in the periphery viaactivation of muscle fibers EA may modulate autonomic nervous system activity[86], increase blood flow, and improve peripheral insulin sensitivity in a dose-dependent manner[87] and in skeletal muscle increase glucose uptake and GLUT-4 expression[88]. As these parameters are involved in the pathophysiology of the PCOS their improvement may have beneficial effects on the metabolic profile of PCOS. Moreover, acupuncture stimulates neuropeptide release in the central nervous system, such as β-endorphin secretion, and may result in blood pressure and sympathetic nerve activity reduction.[89] Decreased sympathetic nerve activity is thought to be related to the decreased circulating testosterone levels and improvement of menstrual irregularities in women with PCOS. Additionally, in women with

PCOS, low-frequency acupuncture can reduce high circulating β-endorphin levels in the peripheral blood resulting in reduction of hyperinsulinemia and increasing insulin sensitivity.[90] Accordingly, although clinical trials are lacking, experimental animal data indicate that acupuncture with electrical stimulation may be of potential benefit on the metabolic aberrations of PCOS. Clinical randomized control studies though are needed to confirm this potential effect.

Dietary products and nutrients and herbal medicines

Recently attention has been paid to the emerging role of dietary products and nutrients, such as vitamins D, B_{12} and folate, and herbal supplements in the treatment of PCOS. Existing data, derived mainly from small and uncontrolled trials, indicate that various dietary supplements might be of some benefit in women with PCOS.

Vitamin D

Clinical studies have largely but not consistently indicate a role of vitamin D deficiency in the pathogenesis of insulin resistance and Type II DM.[91] The gene encoding the vitamin D receptor regulates about 3% of the human genome and affects genes that are important for glucose and lipid metabolism and blood pressure regulation.[92] In women with PCOS low levels of vitamin D are associated with obesity and insulin resistance, impaired β-cell function, IGT and metabolic syndrome, indicating a possible role of Vitamin D in the pathogenesis of PCOS.[93] Administration of vitamin D in women with PCOS improved insulin resistance and lipid profile, but the conducted studies were small and uncontrolled.[94] Some evidence also indicates a possible effect of Vitamin D on ovulation.[95] Further studies are warranted to establish the role of Vitamin D in PCOS treatment.

Herbal medicines

Herbal medicines have also been considered for the treatment of PCOS. Studies conducted using Chinese herbal medicine (CHM) and green tea and spearmint tea. CHM has been used for the treatment of IGT, Type II DM and PCOS but the evidence for benefit for all three conditions is weak. The exact pathophysiological mechanism for efficacy of CHM remains unknown and different mechanism might be implicated for the different preparations. In PCOS in rats some preparations seem to induce favorable alterations in glucose metabolism and insulin resistance and thus may have a favorable effect on hyperandrogenism.[96] CHM has been given as adjuvant therapy toother medications such as clomiphene. Thus forCHM

further studies are needed to establishsafety and efficacy before they can be recommendedfor use in women with PCOS.

Tea, which is widely consumed, has been shown in animal and human studies to have some beneficial effects on glucose and lipid metabolism[97] on hormonal profile[98] and on body weight reduction and induction of ovulation.[99] Improvement of all these parameters could be of importance in women with PCOS.Further studies are needed to examine the effect of tea on the metabolic parameters of PCOS.

Some herbs have also proved their effectiveness in PCOS and related complexities at preclinical and/ or clinical level such as *Liquorice:* (Botanical Name: *Glycyrrhiza glabra*, Family: Leguminosae), *Ginseng saponin:* (Botanical Name: *Panax ginseng*, Family: Araliaceae), *Flaxseed:* (Botanical Name: *Linum usitatissimum*, Family: Linaceae), *Aloe-vera:* (Botanical Name: *Aloe barbadensis*, Family: Liliaceae), *Cinnamon:* (Botanical Name: *Cinnamomum zeylanicum*, Family: Lauraceae) and *Chamomile:* (Botanical Name: *Matricaria chamomilla, Family*: Asteraceae).[100] However more studies are required to establish their role effectively.

Vitamin B_{12} and folate

It has been demonstrated that Vitamin B_{12} administration improves insulin resistance. In PCOS patients, insulin resistance, obesity and elevated homocystein levels are associated with lower serum vitamin B_{12} concentrations.[101] In another study supplementation of folate increased the effect of metformin on the vascular endothelium in women with PCOS, but the mechanism remains unknown.[102] Thus these preliminary data suggest a possible role of the above supplements in women with PCOS but further studies are needed.

Advanced glycation end product (AGE)-low diet

Women with PCOS are at increased atherogenic risk and endogenous AGEs seem to play a significant role.[103] Serum and tissue AGE levels seem to depend on endogenous and exogenous sources.[104] Diet has been shown to be a significant source of AGE, and contemporary methods of cooking (precooked fast-food meals heated in high temperatures) dramatically increase AGE concentration. Studies indicate that they may be implicated in direct and indirect insulin resistance mechanisms. Studies demonstrated that AGEs and their receptor RAGE are expressed in human ovarian tissue and a stronger localization of both was observed in the granulosa cell layer of PCOS ovaries. Data from studies in rats indicated that

a high-AGE diet for prolonged periods is associated with increased deposition of AGEs in ovarian tissue, suggesting an impact of environmental factors on ovarian tissues. Thus reduction in dietary AGEs might be of benefit in women with PCOs. Low AGE diet adminis-trationeffectively reduced serum AGE concentration in diabetes.[72] In women with PCOS orlistat seem to be potent to reduce serum AGE concentration by decreasing their absorption.[24]

CONCLUSIONS

Polycystic ovary syndrome is characterized by multiple metabolic aberrations, which are of great importance due to their potential lifelong consequences. The therapeutic management of these metabolic complications has evolved to incorporate new treatments resulting from the better understanding of the pathophysiology of the syndrome. Although treatment should be individualized, it should not target only isolated symptoms. Unfortunately the medications currently available for the treatment of PCOS are not fully able to deal with all the metabolic consequences and might have negative effects on different parameters. Longer, randomized controlled trials, needed to establish the benefit and safety of the available treatments on the metabolic aberrations of the PCOS. Therapies that might be addressing the multifaceted disturbances of individual subgroups might emerge as the preferable treatment.

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