The Correlation Between Polycystic Ovary Syndrome and Cardiovascular Disease Risk
Polikistik Over Sendromu ve Kardiyovasküler Hastalık Risk İlişkisi

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Abstract
Polycystic ovary syndrome (PCOS) is a common endocrine disorder affecting at least 5%-10% of women of reproductive age. PCOS is characterized by hyperandrogenism, menstrual disturbance, anovulation, infertility and obesity and, also associated with an increased number of cardiovascular risk factors and early atherosclerosis. Hyperinsulinemia is a frequent finding in PCOS patients and has a cause-and-effect relationship with low-grade chronic inflammation and increased risk of cardiovascular disease. Turk Jem 2013; 17: 33-7

Key words: Polycystic ovary syndrome, insulin resistance, hyperandrogenemia, cardiovascular disease risk

Özet
Polikistik over sendromu (PKOS) üreme çağındaki kadınların %5-%10 unu etkileyen sık görülen endokrin bozukluktur. PKOS, hiperandrojenizm, menstrual bozukluk, anovulasyon, infertilite ve obezite ile karakterizedir ve kardiyovasküler risk faktörleri ve erken aterosklerozla ilişkilidir. Hiperinsülinemi PKOS'lu hastalarda sık görülen bir bulgudur ve düşük dereceli kronik inflamasyon ve artmış kardiyovasküler hastalık riski ile sebep-sonuç ilişkisi vardır. Turk Jem 2013; 17: 33-7

Anahtar kelimeler: Polikistik over sendromu, insülin direnci, hiperandrojenemi, kardiyovasküler hastalık riski

Introduction
Definition of the Polycystic Ovary Syndrome
Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of childbearing age and also, it is the most common cause of the oligo-anovulation and hyperandrogenism. Its prevalence has been reported as 5%-10% (1). PCOS has been defined for the first time in 1935 by Stein and Leventhal (2,3).

Today, a complete consensus on diagnostic criteria of PCOS has not been achieved yet. Attempts to set universal criteria for the diagnosis of PCOS first emerged in 1990 in a meeting sponsored by the U.S. National Institutes of Health (NIH). Based on the opinions of experienced people on the subject, criteria required for diagnosis were explained at the end of the meeting as the following:

1- Hyperandrogenism (hirsutism, acne, male pattern baldness) and / or hyperandrogenemia (elevated serum androgen concentration),
2- Menstrual irregularities due to chronic oligo-anovulation,
3- Elimination of secondary reasonable causes (such as hyperprolactinemia, late-onset adrenal hyperplasia, androgen-secreting tumors and Cushing's syndrome).

Polycystic ovary syndrome image on ultrasound examination has been noted as a possible criterion. According to this conference recommendations, the most important diagnostic criteria of PCOS are considered as hyperandrogenism and / or hyperandrogenemia. Under this definition, however, in some PCOS cases with hyperandrogenemia may not present findings of hyperandrogenism (e.g. presence of hirsutism), or hyperandrogenemia may not be seen while signs of hyperandrogenism are present(4).

Universal criteria for diagnosis announced in a meeting held in the city of Rotterdam in the Netherlands in 2003 sponsored by the ESHRE (European Society for Human Reproduction and Embryology) and ASRM (American Society for Reproductive Medicine):
1- Chronic oligo-anovulation,
2. Clinical or laboratory-confirmed Hyperandrogenism,
3. Polycystic ovary image on ultrasound examination

Again, together with the elimination of other possible diseases, at least two of these criteria should be present for the diagnosis of PCOS.

At the same meeting diagnostic criteria for polycystic ovary image was determined as follows,
- The presence of 12 or more follicles in each ovary with 2-9 mm in diameter and / or
- Increased ovarian volume (> 10 mL).

It has been suggested that polycystic ovary image on ultrasound examination should not be evaluated as PCOS if oligoamenorrheic or hyperandrogenism is absent (5).

As a result of the ongoing debate on the definition of PCOS, Androgen Excess Society rearranged the diagnostic criteria in 2009. They are:
1. Androgen excess (clinical and/or biochemical hyperandrogenism)
2. Over dysfunction (oligo-anovulation and / or polycystic ovarian morphology)
3. The elimination of other androgen excess and ovulatory disorders.

Androgen Excess Society suggests that these three criteria must coexist for the diagnosis of PCOS. This last criterion added a new phenotype, that is a female with normal ovulation, who has polycystic ovaries on ultrasound examination and hyperandrogenism (clinical or biochemical). Contrary to the Rotterdam criteria, Androgen Excess Society argues that diagnosis of PCOS based on ovulatory dysfunction and polycystic ovary image without hyperandrogenism is not acceptable (6).

Today common features of PCOS include skin symptoms of hyperandrogenism (hirsutism, alopecia, acne, hair loss, hyperhidrosis), menstrual irregularity, findings of insulin resistance (acanthosis nigricans) and obesity. An increase in insulin and insulin resistance are frequent findings in patients with PCOS. Low levels of chronic inflammation (7) and increased cardiovascular risk (CVs) have also been associated with this condition (8).

Clinical Characteristics

a. Hirsutism

It refers to a male pattern of body hair characterized by excessive sexual hair growth on women (9). In women with hirsutism excessive terminal hair growth is seen in areas sensitive to androgen (upper lip, chin, chest, back, waist, upper abdomen, lower abdomen, upper arm, thighs). The Ferriman-Gallwey method is a quantitative scoring system to evaluate the density of hair in androgen-sensitive areas (10). It is used for evaluating and rating this condition. For a mature female patient, this method use 9 body parts; the upper lip, chin, chest, lower back, upper back, lower and upper abdomen, upper arms and upper parts of legs, to evaluate hirsutism. The hair growth is rated from 0 to 4 in each of the 9 locations and the total score determines the classification of hirsutism: normal: <8; mild hirsutism: 8-15; and mid-advanced hirsutism: > 15

b. Menstrual Irregularities

It is characterized by oligomenorrhea, amenorrhea, a decrease in the ovulation frequency and anovulation. In patients with PCOS, menstrual irregularities begin in peripubertal period. Normal or slightly delayed menarche is followed by irregular menstrual cycles.

c. Metabolic Disorders

1. Obesity

Causes of PCOS accompanying obesity are still unknown but its presence is reported in varying rates from 10 to 75% in different series (11-13). Typically, it is centrally located. In adult women, waist circumference over 88 centimeters is evaluated as abdominal obesity (14). Even in PCOS patients with normal body weight, the body fat content is 50% more than that of normal subjects (15). Increased fat ratio, visceral adiposity in particular, coexists with hyperandrogenism, insulin resistance, glucose intolerance, and dyslipidemia (16). However, not all obese patients have insulin resistance and patients with insulin resistance are not necessarily obese. Nevertheless hyperinsulinemic case caused by insulin resistance and its anabolic effects on lipid metabolism (increased glucose uptake into adipocytes, triglyceride production and hormone-sensitive lipase inhibition) can be effective in the presence of obesity (17).

2. Insulin Resistance

Insulin binds to receptors on the cell membrane and it facilitates glucose uptake into cells by increasing the expression of glucose transporter in many tissues (18). In the events of failure of the insulin binding to its’ receptors, or of the transport mechanism, insulin sensitivity decreases and insulin resistance can be revealed. Studies show that insulin-mediated receptor autophosphorylation is significantly inoperative in about 50% of women with PCOS (19). In addition to these, decrease in insulin sensitivity and secretion disorders in pancreatic beta cells have been reported as well (20,21). Altogether, clinical results show that 30 to 40% of obese women with PCOS have impaired glucose tolerance and about 10% of them are becoming diabetic in their 40s (22,23).

3. Dyslipidemia

Whether or not women with PCOS have a characteristic dyslipidemia is a controversial topic. Yet studies generally report that these women have low HDL cholesterol and high triglyceride levels (24-28). Studies have often shown that they have high TG and LDL coexisting with low HDL levels, which is called atherogenic lipid profile. This condition is associated with insulin resistance and hyperandrogenism observed in these patients. Insulin increases glucose and triglyceride input and stimulates lipogenesis by increasing the production of acetyl-CoA in both arterial and adipose tissue (29).

4. Metabolic Syndrome:

It is a specific symptoms group characterized by insulin resistance, hyperglycemia, hypertension, hyperlipidemia, abdominal obesity and associated with increased cardiovascular risk (30). Metabolic syndrome is observed in 25% of patients with PCOS (31).

d. Cardiovascular Disease Risk

In patients with PCOS, the presence of obesity, insulin resistance, hyperinsulinemia, impaired glucose tolerance, dyslipidemia and increased visceral adiposity predispose cardiovascular diseases (CVD) (32-34). The increased risk of CVD observed in women with PCOS is not fully demonstrable but data shows an increased incidence of cardiovascular disease (35,36).
The evidence for increased cardiac morbidity and mortality is also insufficient. Various results are reported in epidemiological studies done in this matter. In early studies among women with PCOS, no significant increase has been observed in nonfatal and fatal CVD frequency (37,38), while an increase has been identified in the incidence of nonfatal cerebrovascular disease (38). In another study, however, a history of menstrual irregularities was found to be associated with an increase in nonfatal and fatal coronary heart disease (39).

In contrast to earlier studies, a recent sub-group study called Women's Ischemia Evaluation Study (WISE) reported a higher number of cardiovascular events seen in patients with PCOS (40). Moreover, the same study observed a higher incidence of multivessel coronary disease in women with PCOS and a correlation with increased serum testosterone levels. Again, in the same study, an increase was reported in frequency of diabetes, obesity and metabolic diseases in patients with PCOS. The frequency of not having a cardiovascular disease in five-year period was 78.9% in patients with PCOS, while this ratio rises up to 88.7% in patients without PCOS characteristics. In this study, the researchers have argued that in postmenopausal women, the recognition of characteristics of PCOS may create an opportunity for the prevention of coronary artery disease and cardiovascular events.

The study by Azeyedo and his colleagues showed that signs of PCOS in the reproductive period were associated with an increase in cardiovascular disease risk (41). In another study, PCOS was associated with premature carotid atherosclerosis and CRP, a marker of inflammation; and the presence of PCOS was found to be related with an increase in carotid intima-media thickness, independent from insulin levels and visceral adipose tissue (42).

Young adult women with PCOS have multiple risk factors for cardiovascular disease such as hyperinsulinemia, dyslipidemia and abdominal obesity, which are results of metabolic syndrome and insulin resistance (36,43,44). In addition, among PCOS patients, higher visceral adiposity was observed even in women of normal weight and higher levels of inflammatory adipocytokines production was monitored as well (45,46).

In the study by Cascella et al., visceral adipose tissue was found to be associated with insulin resistance and it appeared significantly higher in PCOS patients. In linear regression analysis of patients with PCOS, visceral adipose tissue and CRP levels were observed to have positive effects on carotid intima-media thickness (47).

In a research done by Krentz et al. involving 713 non-diabetic female patients with postmenopausal intact ovaries, a gradual correlation has been observed between cardiovascular disease and the presence of PCOS symptoms in patients' medical history (such as premenopausal menstrual irregularity, hirsutism or existing hyperandrogenism) (48).

1. **Endothelial Dysfunction**

Endothelial dysfunction is thought to be contributed to the development of atherosclerosis. The presence of endothelial dysfunction in women with PCOS is still controversial. Although some studies (49-52) demonstrate the presence of endothelial dysfunction, there are studies that suggest the opposite (53).

Insulin resistance (49,50), hyperandrogenism (50), high levels of CRP (49), and high total cholesterol (50) were found to be associated with endothelial dysfunction.

2. **Subclinical Atherosclerosis**

In most of the studies in literature, subclinical atherosclerosis process was shown to be increased in women with PCOS.

a: Evaluation of Coronary Artery Disease by angiography

Angiographic coronary artery disease was observed to be more common in patients with PCOS than normal individuals. In a study angiographically assessing 143 patients under 60 years old, who were followed up due to chest pain or valvular heart disease, ultrasonographic polycystic ovarian morphology has been observed in 42% of patients. In that study, polycystic ovarian morphology was found to be correlated with hirsutism, a decrease in high-density lipoprotein cholesterol (HDL-C) levels, hyperandrogenism and hypertriglyceridemia. Coronary artery disease was observed to be more common in women with polycystic ovarian morphology. In this study, however, no differentiated diagnosis was made between polycystic ovarian morphology and the presence of PCOS. Therefore, it was stated that further studies are needed to determine conclusive results (54).

b: **Carotid Intima Media Thickness**

In the majority of studies in literature an increased carotid intima-media thickness has been shown in women with PCOS (8,55,56). This condition is a finding in favor of increased atherosclerosis in PCOS.

c: **Coronary artery calcium identified by electron-beam computed tomography**

This is a non-invasive method of assessing coronary artery calcium as a risk factor for atherosclerosis. 36 premenopausal women of an average age of 38 having PCOS were compared to healthy individuals having similar features in terms of age and weight. Increased coronary artery calcium levels were more commonly observed in women with PCOS (57).

In another study involving 85 healthy subjects and 61 female patients ranging in age from 40 to 61, coronary artery disease and aortic calcification were found to be significantly higher in PCOS group. It is observed that independent from obesity, components of metabolic syndrome (low HDL-C and the presence of insulin resistance) mediates the correlation between PCOS and coronary artery calcification (58).

Coronary artery calcium was assessed in 8 (33%) out of 24 PCOS female patients in the average age of 31, while this number appeared as 2 (8%) out of 24 individuals in healthy control group with similar age and weight criteria (59).

In conclusion, current epidemiological data shows that the frequency of cardiovascular disease is increasing in PCOS, and this increase is thought to be mainly based on increasing overall and abdominal obesity, hyperinsulinemia and hyperandrogenemia. Yet, the identification of PCOS features while still in reproductive period and the determination of possible cardiovascular risk and then screening of patients in this respect can provide an opportunity in the prevention of cardiovascular events.
References

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