International Journal of Research and Review
Vol.7; Issue: 7; July 2020
Website: www.ijrrjournal.com
Review Article *E-ISSN: 2349-9788; P-ISSN: 2454-2237*

Effect of High Levels of Testosterone on Cardiovascular Risk in Polycystic Ovary Syndrome (PCOS)

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ABSTRACT

Polycystic ovary syndrome (PCOS) is a common endocrine disorder characterized by oligo ovulation, hyperandrogenism and the presence of polycystic ovaries. PCOS is closely related to the hyperandrogensim (HA). Postmenopausal hyperandrogenism is a condition of relative or absolute androgen excess originating from either the adrenals and/or the ovaries. Clinical manifestations of HA include hirsutism, acne, androgenic alopecia and virilisation. In PCOS women, HA has been associated with metabolic disturbances that increase the risk for cardiovascular disease (CVD). Many clinical studies have underlined the relationship between PCOS and cardiovascular risk is due to a lipid or glucose altered metabolism, hypertension, systemic inflammatory condition and vascular injuries. In this review article, we mainly focussed on PCOS related cardiovascular disease due to increased levels of testosterone. Management of hyperandrogenism along with life-style intervention has beneficial effects on cardiovascular risk factors in PCOS. We determined the etiology of relative and absolute androgen excess in postmenopausal women and this review provides extensive overview on the development of cardiovascular risk factors in PCOS females due to increased levels of testosterone.

Keywords: Polycystic ovary syndrome, oligo ovulation, hyperandrogenism, hirsutism, alopecia, virilisation, hypertension, vascular injuries and cardiovascular events

INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrine and reproductive disorder among adult women [1-3] and that effect 10-18% of women of reproductive age. [4] It is a heterogeneous medical condition of unknown etiology, but there is an extensive evidence of multiple interactions between genetic, environmental, and behavioral factors are known to cause this syndrome. [1] According to Stein and Leventhal, [5] PCOS is characterized by heterogeneous presentation of clinical and/or biochemical hyperandrogenism, oligoovulation or anovulation and the presence of polycystic ovaries, when other etiology's are excluded. [6,7] Apart from these clinical features, PCOS patients are often insulin resistant, obese and have metabolic syndrome, with arterial hypertension, dyslipidemia, impaired glucose tolerance or frank type 2 diabetes, low-grade inflammation and increased pro-thrombotic state. [8] Insulin resistance and low grade inflammation are to be associated with increased risk of development of cardiovascular disease in patients with polycystic ovary syndrome. [9] Coronary artery disease (CAD) is one of the major causes of death in postmenopausal women. Endogenous free testosterone levels in postmenopausal women has been consequently associated with the incidence of CAD independent of BMI and other risk factors, such as diabetes, hypertension, smoking, and hyperlipidemia. [10]

The leading cause of Hyperandrogenism (HA) in women of reproductive age is a polycystic ovary syndrome. HA in PCOS is described as a presence of hirsutism or an increase in

serum testosterone or the free androgen index (FAI). [11] HA (elevated androgen levels) is associated with an increased risk of cardiovascular diseases through complex and multidirectional pathways and exposure of Hyperandrogenism may influence body fat distribution, insulin resistance and other cardio metabolic risk factors. [8] An important quantification of this androgen excess and free androgen index are tends to be a better predictors of many health outcomes, especially cardiovascular disease as compared with testosterone alone. [10] However, the current review aimed to identify the PCOS related cardiovascular disease due to increased levels of testosterone.

CAUSES OF HYPERANDROGENISM:

Hyperandrogenism is described by either hirsutism and/or excess of blood testosterone levels and it plays key role in the diagnosis of polycystic ovary syndrome. [12] Along with the excess androgens, some rely on the development of true hirsutism, acne and androgenic alopecia to make the diagnosis of hyperandrogenism as part of the PCOS phenotype. [13] Androgens are produced by the adrenal glands as well as by the ovaries and are throughout the life. [11] Various studies described that testosterone levels rise during early puberty and adolescence and reach a peak adult level within a few years after menarche. Testosterone concentrations are majorly influenced by the stage of puberty and the menstrual cycle along with other factors. [14] Androgen secretion in pre- and postmenopausal women rely on the luteinizing hormone (LH) stimulation and the persistently increased gonadotropin levels maintains ovarian androgen secretion after menopause besides the substantial decline of estrogen levels. [15] The loss of ovarian function in postmenopausal women leads to a drastic fall of estrogen levels, whereas secretion of testosterone remains at the same levels, or may even increase. This rapid decrease of estrogen with menopause causes a period of relative androgen excess. [10] The hyperinsulinemia intrinsically considered as a possible cause of an increased ovarian androgen production and alters the process of gonadal steroidogenesis both directly and indirectly. [6] In both pre- and postmenopausal women, androgen secretion is aggravated by the presence of insulin resistance (IR) and hyperinsulinemia, mostly observed in obese women, with insulin acting as a co-gonadotropin. [15]

TRADITIONAL AND NEWER CARDIOVASCULAR RISK FACTORS IN PCOS:

Traditional cardiovascular disease risk factors in PCOS:

The traditional and modifiable cardiovascular risk factors are hypertension, dyslipidemia, obesity, smoking, diabetes and have 40% prevalence of polycystic ovaries in postmenopausal women, and this was associated with mild changes in cardiovascular risks with elevations in circulating triglycerides, but no difference in cholesterol levels compared with controls. Non modifiable risk factors include age, gender and family history of cardiovascular diseases. [13]

Coagulation and Fibrinolytic Disturbances:

PCOS associated with the disturbances in circulating markers of coagulation and fibrinolysis may contribute to cardiovascular disease risk. Thrombin activated fibrinolysis inhibitor levels were found to be higher in PCOS women than controls and that contributing to hypo fibrinolytic state and accelerated atherosclerosis. [8] Previous studies reported that dysregulation of the hemostatic system in women with PCOS, particularly hypo fibrinolysis, Hypercoagulability [16] and endothelial and platelet dysfunction. [17] The potential mechanisms of coagulation disturbances were observed in women with PCOS and have high circulating concentrations of PAI-1 and fibrinogen that correlated with low sex hormone binding

globulins (SHBG) and high insulin levels independent of age and BMI. [18] Several studies recognized a strong positive correlation between hyperandrogenism and hypo fibrinolysis in women with PCOS contributing to a prothrombotic state. [16]

Markers of Atherosclerosis:

The prevalence and extent of coronary artery calcification (CAC) were reported by several studies to be higher in both younger and older women with PCOS than in controls, independently of age and BMI. [19] It has been suggested that the reported increase in CAC among PCOS women is related to the increased LDL-C lower HDL-C and hyperinsulinemia. [20] Increased intima-media wall thickness (IMT) is an early marker of atherosclerosis. Increased carotid intima-media wall thickness (CIMT) is also a strong independent predictor of the occurrence of major cardiovascular events in later life. [21]

Vascular endothelial dysfunction:

Decreased brachial artery flow-mediated dilation (FMD) is a marker of endothelial function, in young normal weight, overweight, and obese women with PCOS compared to body mass matched controls. [22] It is recognized that elevated androgen levels in the PCOS women may contribute to the observed decline in endothelial function relative to controls. [23] Several variables involved in endothelial dysfunction have been related to the PCOS. A recent meta-analysis observed that homocysteine is a mediator of endothelial injury and its higher concentrations were seen in PCOS women than in controls of similar age and BMI. [24] Plasminogen activator inhibitor-1 (PAI-1) inhibits fibrinolysis and in higher levels predisposes to accelerate the development of atherosclerosis and has been shown to be elevated in normal weight young PCOS women relative to the controls. [16]

Cardiac dysfunction:

Several studies analysed that increased left ventricular mass index (LVMi) and decreased diastolic filling in young PCOS women compared to age- and BMI-matched controls. [25] LVMi is an early predictor of CVD morbidity and mortality. Both of these abnormalities occur independently of excess weight, particularly decreased left ventricular ejection fraction has been reported in young overweight and obese women with PCOS compared to controls. [25]

The risk of cardiovascular events in PCOS:

The age-specific incidence of cardiovascular events was significantly higher in PCOS patients over 45 compared with the local female population, with odds ratio as high as 12.88 in women over 65 with a premenopausal history of PCOS. [26] A recent meta-analysis demonstrated the risk of coronary heart disease (CHD) and stroke is doubled in PCOS women, despite adjusting for body mass index (BMI), there was a 55% increase in risk. [4] Previous studies indicated a 2-fold increased risk of CHD and stroke for patients with PCOS relative to women without PCOS. [27] The meta-analysis estimated 55% increase in the risk for CHD and stroke in PCOS women using only studies that adjusted for BMI, showing that BMI is not the only cause of increased risk of cardiovascular events in women with PCOS. [27]

ASSOCIATION BETWEEN INCREASED TESTOSTERONE LEVELS AND CARDIOVASCULAR EVENTS IN PCOS FEMALES:

High levels of testosterone are associated with an increased cardiovascular risk through complex and multidirectional pathways. [8] A study reported that total testosterone was an independent risk factor for aortic calcification (AC). In animal model study, testosterone increases atherosclerosis in female monkeys but conferred a protective effect in males. [20] A

similar study reported that men with the highest total testosterone levels had a reduced risk of aortic calcification, but, conversely, women with elevated testosterone levels had the highest risk for coronary artery calcification (CAC). [20] A study conducted by Paradisi et al suggested that elevated androgen levels play a key role in endothelial dysfunction. [28] A similar study compared women with reporting a history of regular menses and a history of very irregular menses among 82,439 women aged 20–35 years had a significantly higher risk of nonfatal and fatal cardiovascular disease, even after adjustment for BMI, age, menopausal status, and smoking. [29] High circulating androgen levels have been associated with an unfavorable cardiovascular risk profile and increased prevalence of subclinical atherosclerosis in postmenopausal women. [11] Increased carotid intima media wall thickness (CIMT) is a predictor of occurrence of major cardiovascular events in PCOS women. [21] The increase in CIMT is associated with high levels of testosterone, insulin, increased age and abdominal obesity in PCOS women. [30]

THE MECHANISMS INVOLVED IN HIGH LEVELS OF TESTOSTERONE AND RISK OF CARDIOVASCULAR EVENTS:

The relationship between CVD risk and reproductive endocrine disorders (early menopause and PCOS) supports the idea that endogenous sex steroids have a role in development of CVD. [31] Elevated levels of testosterone are likely to be found in women with PCOS even after menopause in relative to estradiol. A study conducted by Pinole et al revealed that androgen levels gradually increases after the age of 50 years and relative hyperandrogenemia exists in women with PCOS after menopause. [32] The pathological mechanisms underlying the syndrome are determined by the complex interaction between the functionality of the hypothalamic-pituitary-ovarian or hypothalamic-pituitary-adrenal axis and metabolic disorders, such as obesity, insulin resistance and compensatory hyperinsulinemia. [33] Several pathogenic hypotheses try to explain the increased peripheral availability of androgen hormones, which depend on excessive ovarian and adrenal production. [34] The hyperinsulinemia is solely considered as a possible cause of an increased ovarian androgen production, which alters gonadal steroidogenesis process ,both directly and indirectly. [6]

Various mechanisms involved in high levels of testosterone are:

Insulin resistance:

It is described as diminution in the biological responses to insulin levels. [35] Previous studies suggested that four independent risk factors for myocardial infarction in women with PCOS are increasing waist: hip ratio, raised serum triglyceride concentrations, diabetes and hypertension. [36] Earlier literature concerning the interrelationship of insulin resistance and hyperandrogenaemia. Some authors suggested that hyperinsulinemia results in raised ovarian androgens and it is associated with decreased levels of sex hormone binding globulins, thereby increasing the circulation of free testosterone. [35] Along with luteinising hormone, Hyperinsulinemia stimulates stimulate androgen biosynthesis through ovaries; insulin decreases Insulin Growth Factor binding globulin 1 (IGFBP-1) and increases free IGF and thus increases ovarian theca cell proliferation and androgenesis as well. [6] Furthermore, insulin stimulates thecal cells which in turn stimulate testosterone biosynthesis in women with PCOS by activating receptors and using inositol-glycan mediators as the signal transduction system. [37]

PCOS and Hypertension:

According to WHO, Arterial hypertension (AH) is defined as a systolic (SBP) and (DBP) diastolic blood pressure of > 140 and > 90 mmHg respectively. [6] A

study conducted by Chen and Yang et al reported that high testosterone levels and no SHBG increases the risk of elevated SBP and DBP values even adjusted for age, body mass index, and other anthropometric, metabolic and hormonal variables. [38] Lecke et al [39] demonstrated the association between CYP19 gene expression, levels of aromatase and blood pressure; androgen excess may be involved in the high levels of CYP19, a gene encoding for the enzyme aromatase, expressed in abdominal tissue fat. A high expression of this gene, induces low estrogen and high androgen concentrations.

Obesity:

Obesity mainly associated with the greater disposition of femoral and truncal abdominal fat distribution. Hyperandrogenism is associated with a prevalence of truncal abdominal fat. Women with PCOS have a greater truncal abdominal fat distribution as it is described by the presence of an increased waist: hipratio. [35]

Dyslipidemia:

It is defined as abnormality of lipid metabolism. High density lipoproteins (HDL) play a key role in lipid metabolism and it is most important predictor of cardiovascular risk in PCOS women. [40] Several studies noticed that reduced HDL cholesterol and elevated serum triglycerides, along with elevated plasminogen activator inhibitor-I concentrations explains hyperandrogenism pathogenesis in PCOS. [6]

Ischaemic heart disease:

Several studies concluded that altered fat distribution is associated with androgen excess may be an indicator of a greater risk for ischaemic heart disease. [35] The incidence of coronary artery disease is correlated with carotid atherosclerosis. [35] Increased intima-media wall thickness (IMT) is an early marker of atherosclerosis. [21]

MANAGEMENT OF HYPERANDROGENISM IN PCOS WOMEN:

Treatment of Hyperandrogenism is depends on the underlying cause of obesity, PCOS, adrenal and ovarian tumors. [15] Administration of oestrogen containing oral contraceptive has beneficial effects on excess androgens. Pill containing the anti-androgenic progestogen cyproterone acetate is administered in cyclical doses, or drospirenone-containing combined oral contraceptives could be beneficial for hirsutism. [5] Metformin has been used for the treatment of polycystic ovary syndrome [4] and it can increases insulin sensitivity by decreasing gluconeogenesis, lipogenesis and enhancing glucose uptake in the liver, skeletal muscle, adipose tissue and ovaries. [8] Hyperandrogenism related to Ovarian hyperthecosis can be treated either by bilateral oophorectomy or GnRH analogs, which improve symptoms and may improve concomitant metabolic abnormalities. [15] Administration of liraglutide has been associated with a significant reduction in BMI and which is a more sensitive indicator of visceral obesity and metabolic outcomes. [4] The management of PCOS targets the anovulation, infertility, hirsutism, or acne being the most common complaints. [14] Spironolactone was able to improve insulin sensitivity and is also recommended in the treatment of hyperandrogenism- associated symptoms such as acne and hirsutism. [14] A recent meta-analysis observed that combination of life-style modifications such as exercise, duration of diet and behavioural change plus metformin for 6 months is associated with lower BMI and subcutaneous adipose tissue as compared to lifestyle plus placebo. [8]

CONCLUSION

In the present study, we concluded that high levels of testosterone increase the risk of cardiovascular events in PCOS females. Testosterone plays a major role in women and it is essential regulator of cardiovascular, bone and brain functions.

Persistent high levels of testosterone in women after menopause were associated with an increase in surrogate markers of CVD. Hyperandrogensim is mainly associated with the lack of estrogen production, increased insulin resistance that develops with weight increases, and possibly with aging. Excess concentration of testosterone levels after menopause is a serious condition and that needs careful evaluation in order to diagnose the underlying cause. The cardiovascular risk was predicted by baseline age and screening for the elements of the metabolic syndrome. The risk of cardiovascular events was also associated with the use of oral contraceptives.

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How to cite this article: Sneha S. Effect of high levels of testosterone on cardiovascular risk in polycystic ovary syndrome (PCOS). International Journal of Research and Review. 2020; 7(7): 285-292.

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