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CARDIAC HEALTH IN PATIENTS OF POLYCYSTIC OVARY SYNDROME: A REVIEW

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ABSTRACT

There has been a tremendous rise in the Polycystic Ovary Syndrome (PCOS) cases in the past one decade and it can be attributed to our changing lifestyle and a highly stressed routine. PCOS not just leads to infertility, but the development of risk factors of Cardiovascular diseases (CVD) is a matter of concern and should be addressed at a larger scale both in our country and worldwide. Various biochemical and physiological parameters have been found to be altered in PCOS affected women. These factors may directly or indirectly lead to cardiovascular diseases and thus lead to a poor cardiac health in women of reproductive age group.

KEY WORDS

Cardiovascular diseases, PCOS cases, cardiac

1.1 INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is a heterogeneous, genetically complex, endocrine disorder of unclear etiology in women and its principal features include hyperandrogenism i.e. androgen excess [1], hirsutism [2], ovulatory dysfunction [3a] and numerous follicular cysts in enlarged ovaries [4]. It is considered as the most common endocrine disorder affecting 10-18% premenopausal women (12-45 years), with 6–7% prevalence worldwide [3b,5].

The syndrome was initially recognized by Stein and Leventhal in the 1930s [6]. But owing to the genetic heterogeneity and diverse clinical manifestation there is no consensus on the diagnostic criteria and definitions of PCOS. To date, three major criteria have been proposed to define PCOS: 1) The National Institute of Child Health and Human Development (NIHCD) suggested in 1990 that the presence of oligoovulation, androgen excess and exclusion of other causes for polycystic ovary as the diagnostic criteria [7] ; 2) The Rotterdam workshop in 2003 set a diagnostic criteria based on the presence of any two manifestations amongst oligoovulation/anovulation, excess androgen activity and polycystic ovaries [8]; 3) In 2006 the Androgen Excess PCOS Society suggested a defining/diagnostic criteria where a PCOS patient must show the presence of excess androgen activity, oligoovulation /anovulation and/or polycystic ovaries while excluding other causes of androgen excess [9].

The level of reproductive hormones as well as insulin varies significantly in PCOS patients as compared to unaffected females. The PCOS subjects exhibit disproportionately high secretion of luteinizing hormone (LH) with relatively low follicle stimulating hormone (FSH) secretion. There is a generalised dysregulation of ovarian androgen secretion which is further increased by the high insulin levels (hyperinsulinemia) seen in these patients.

Besides the reproductive abnormalities, a host of metabolic complications including insulin resistance, obesity, increased central adiposity, dyslipidemia, atherogenic lipid profile and hypertension are evident in women having PCOS. It is estimated that nearly 70% of women with PCOS have impaired glucose tolerance and 7-10% develop type 2 diabetes [10,11].

As compared to the normally cycling women, the PCOS patients are found to be at a greater risk to

cardiovascular diseases (CVD) which is suggested by the elevated levels of various risk factors involved with CVD [12]. Dyslipidaemia, diabetes, and obesity are all potent cardiovascular risk factors that tend to cluster in women with polycystic ovary syndrome and thus they represent a large group of women at risk for developing early onset cardiovascular diseases. In the past two decades, there has been an increasing concern regarding the susceptibility towards cardiovascular diseases in women suffering from Polycystic Ovary Syndrome. While there is a definite increase in the level of cardiovascular risk factors in these subjects, large scale prospective studies lack in ascertaining the prevalence of CVD events. Therefore, the occurrence of cardiovascular disease in these patients is not uniform and requires further study.

PCOS has a genetic basis as is suggested by the familial clustering and heredity that is implicated in the origin of the syndrome [13, 14]. It is considered as a polygenic trait wherein a variety of predisposing genes and protective genomic variants interact under the influence of environmental factors. Candidate genes for PCOS include the genes involved in ovarian and adrenal steroidogenesis, steroid hormone effects, gonadotropin action and regulation, insulin action and secretion, regulation of lipid metabolism etc. Gene expression studies on the genes found within or near these loci can help in finding a genetic basis between the metabolic disorders and PCOS. Both linkage and association studies would help in providing insights to this hypothesis and thus increase our understanding about Polycystic Ovary Syndrome (PCOS). The prevalence of metabolic disorders in these patients require genome wide association studies (GWAS) in order to ascertain a genetic basis/inclination towards the development of cardiovascular diseases, insulin resistance, type II diabetes as well as lipodystrophies [15, 16].

The elucidation of this genetic predisposition requires linkage as well as association studies. Certain genome wide association studies and candidate wide association studies (CWAS) have revealed of single nucleotide polymorphisms (SNP) with suggestive evidence of association with PCOS when compared to controls [15].

1.2 CARDIOVASCULAR RISK FACTORS IN PCOS

1.2.1 Biochemical and Clinical factors

The risk towards CVD includes both biochemical and clinical factors. Insulin resistance and dyslipidemia are major biochemical risk factors apart from other markers like C-reactive proteins, adiponectin, plasminogen activator I and other markers of oxidative stress.

1.2.1.1 Insulin Resistance:

Insulin resistance is thought to play a role in the pathogenesis of PCOS, and is usually aggravated by co-existent obesity. Both lean and obese women with PCOS have increased rates of insulin resistance and type 2 diabetes mellitus compared with body mass index (BMI) matched controls [17]. Insulin resistance has been associated with endothelial dysfunction and increased cardiovascular risk. Although insulin resistance is often seen as the cause of increased risk for CVD among PCOS patients, not all PCOS patients have insulin resistance and thus indicate the presence of CVD independent of insulin resistance [18].

1.2.1.2 Dyslipidemia

Dyslipidemia is very common in PCOS patients and may exhibit different patterns, including low levels of high-density lipoprotein (HDL)-cholesterol (HDL-C), increased values of triglycerides and total and low-density lipoprotein (LDL)-cholesterol (LDL-C), as well as altered LDL quality [19, 20].

A comparison between PCOS- IR (insulin resistant) patients and PCOS non-IR or PCOS-IS (insulin sensitive) patients on the basis of their lipid profile indicated higher CV risk factors in case of insulin resistant patients, wherein a significant decrease was found in HDL of PCOS-IR patients (P value=0.0075). Also the highly significant decrease was observed in the level of triglyrides (P value=0.005) in case of PCOS-IR patients as compared to PCOS-IS patients [17].

Meta-analysis reports have found that women afflicted with PCOS had higher level of triglycerides, amounting to 26 mg/dL (95% confidence interval [CI] 17–35) and lower levels of HDL-cholesterol concentrations 6 mg/dL (95% CI 4–9) as compared to non-PCOS subjects. Also, LDL-cholesterol and nonHDL- cholesterol concentrations were higher in PCOS: by 12 mg/dL (95% CI 10–16) and 19 mg/dL (95% CI 16–22), respectively. In Women with similar Body Mass Index (BMI), LDL-cholesterol and

nonHDL-cholesterol were still higher in PCOS: by 9 mg/dL (95% CI 6–12) and 16 mg/dL (95% CI 14–19), respectively [21].

Besides the biochemical risk factors various clinical parameters can attribute to CVD. Women with PCOS are generally more obese than age matched controls and have an elevation of both Body Mass Index (BMI) as well as waist/hip ratio [22]. Obesity is associated with risk factors for atherosclerosis, such as hypertension, insulin resistance and dyslipidemia. Central pattern of obesity as suggestive by the increased waist/hip ratio is a significant and independent cardiovascular risk factor. This association between central adiposity and CVD in PCOS might be related to low plasma adiponectin level which requires further study [23].

1.2.2 Physiological parameters

Various functional and morphological studies provide an association between PCOS patients and cardiovascular diseases.

1.2.2.1 Functional Studies

Left ventricular diastolic dysfunction is an early manifestation of diabetic cardiomyopathy. In a case-control, echocardiographic study, women with PCOS were found to have an increased isovolumetric relaxation time (IVRT), an index of early LV diastolic dysfunction, and lower ejection fraction compared with weight matched controls [24].

Arterial stiffness of the peripheral circulation is associated with increased systolic blood pressure, pulse pressure and ventricular load. Lakhani et al. demonstrated increased stiffness of both internal and external carotid arteries in woman with both PCOS and PCO (ultrasonographic polycystic ovaries alone) compared with controls.

Endothelial dysfunction is an early event in the evolution of atherosclerosis. It is the most widely studied surrogate cardiovascular endpoint in PCOS. Endothelial dysfunction signifies not only impaired arterial vasodilation but also increased arterial stiffness, hypertension and increased vascular oxidative stress.

1.2.2.2 Morphological Studies

Carotid wall thickness is shown to predict cardiovascular events and is associated with an elevated age-adjusted cardiovascular risk. Guzick et al. [25] assessed women with PCOS and controls using carotid ultrasonography and found increased carotid mean intimal medial thickness (CIMT) in the PCOS group. It was found that with increase in age, the CIMT became significanty higher in the PCOS group as compared to the non-PCOS patients from the same age group [18].

Coronary arterial calcification reflects the underlying degree of atherosclerosis and helps in the prediction of clinical events. In the coronary circulation, electron beam computer tomography has been employed to demonstrate increased arterial calcification in PCOS women compared with controls [26].

A summary of the biochemical, clinical and functional parameters for assessing risk factors is provided in Fig.1.

CONCLUSION

Polycystic Ovary Syndrome (PCOS) is an endocrinopathy whose genetic basis is yet to be established for a wide range of metabolic disturbances associated with this disease. Majority of the evidences available indicate a definite genetic link between PCOS and Insulin Resistance (IR) and in the past decade association and linkage studies have provided insights into the genes and loci responsible for IR and subsequent Type II diabetes in PCOS patients [27]. It has been proposed that women with PCOS are prone towards developing cardiovascular diseases (CVD) and the same has been observed in clinical studies where an increased level of CVD risk factors are present in PCOS patients [17]. Genome wide association studies (GWAS) and candidate wide association studies (CWAS) have tried to find a genetic basis towards the development of CVD in these subjects and helped in the elucidation of certain loci which can be candidates for further analyses studies [15,16].

The general belief is that CVD risk factors are elevated in PCOS patients because of the presence of insulin resistance [17, 28]. But it has been seen that women with both insulin resistance and non-insulin resistance are susceptible towards the development of cardiovascular problems. Therefore, the susceptibility towards cardiovascular disease in PCOS patients can be attributed to factors other than those which are derived as a consequence of insulin resistance. These patients have an intrinsic inclination towards

development of cardiovascular diseases which provides a genetic basis for the development of CVD in them. Cardiovascular diseases are characterized by an abnormal lipid profile and evidently, the dyslipidemia found in patients of PCOS, indicate towards the greater risk of these women for CVD. Genetic factors leading to a predisposition of cardiac diseases in PCOS women remains an area of scarce studies. Various genes related to cardiovascular disease may be studied in women with or without PCOS to ascertain if women with PCOS are genetically predisposed for CVD.

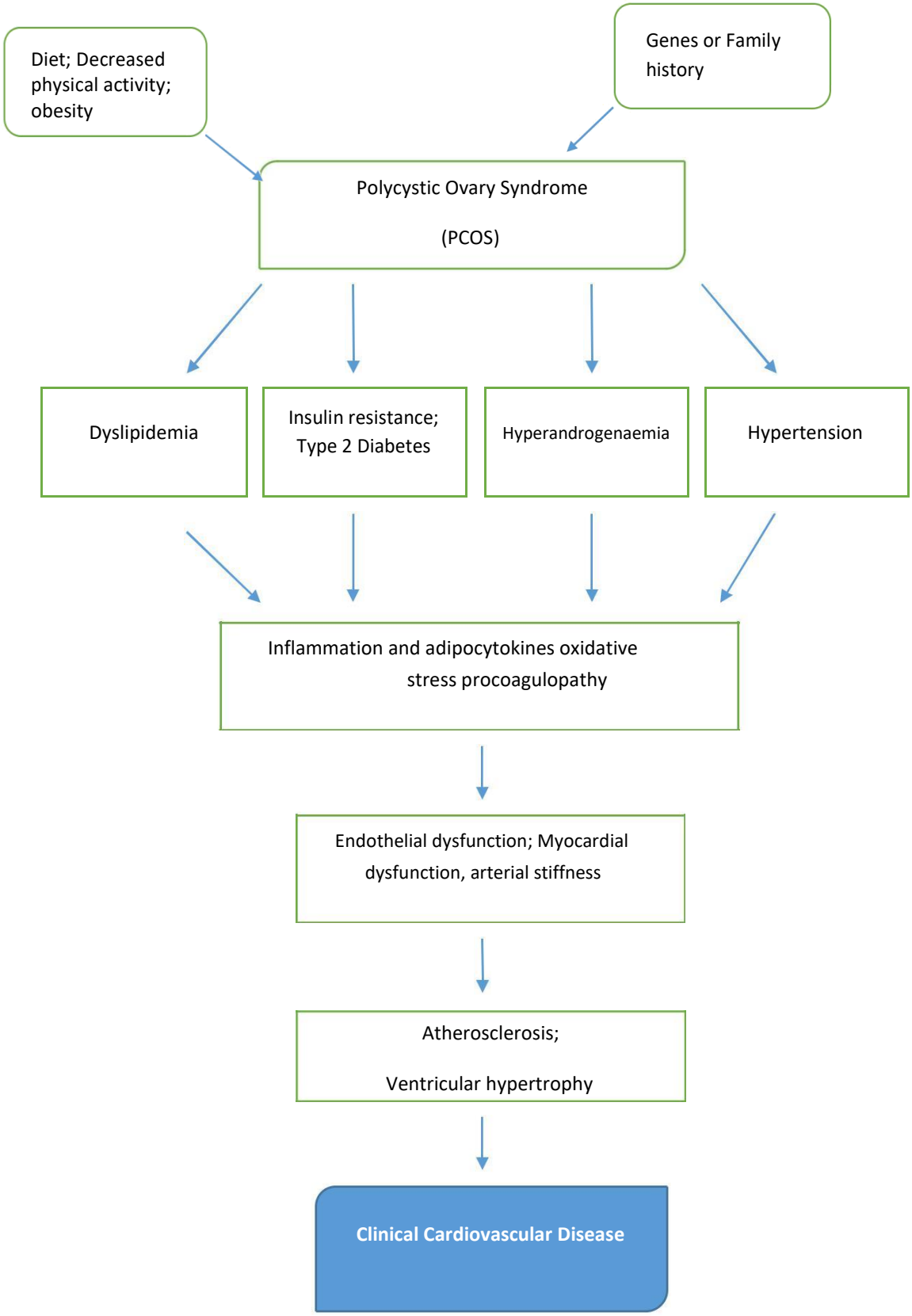

Fig.1. Hypothetical scheme for the pathogenesis of cardiovascular disease in PCOS (adopted from Cussons et al., [12])

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