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SHORT REVIEW

Cardiovascular risk factors and events in women with androgen excess

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Abstract Androgen excess (AE) was approximated to be present in 7 % of the adult population of women. Polycystic ovary syndrome (PCOS) is the most prevalent among them, followed by idiopathic hirsutism (IH), congenital adrenal hyperplasia (CAH), hyperandrogenic insulin-resistant acanthosis nigricans (HAIRAN) syndrome, and androgen-secreting neoplasms (ASNs). Increased cardiovascular risk was implicated in women with AE. Serum testosterone independently increases risk for cardiovascular disease (CVD), and correlates even with indices of subclinical atherosclerosis in various populations of postmenopausal women. Hyperandrogenism in PCOS is closely related to the aggravation of abdominal obesity, and together with insulin resistance forming the metabolic core for the development of CVD. However, phenotypic variability of PCOS generates significant influence on the cardiometabolic risks. Numerous risk factors in PCOS lead to 5–7 times higher risk for CVD and over 2-fold higher risk for coronary heart disease and stroke. However, issue on the cardiometabolic risk in postmenopausal women with hyperandrogenic history is still challenging. There is a significant overlapping in the CVD characteristics of women with PCOS and variants of CAH. Relevant clinical data on the prevalence and cardiometabolic risk and events in women with IH, HAIRAN syndrome or ASNs are scarce. The effects of various oral contraceptives (OCs) and antiandrogenic compounds on metabolic profile are varying, and could be related to the selected populations and different therapy regiments mainly conducted in women with PCOS. It is assumed relation of OCs containing antiandrogenic progestins to the increased risk of cardiovascular and thromboembolic events.

Keywords Cardiovascular risk · Hyperandrogenism · Insulin resistance · Lipids · Atherosclerosis · Polycystic ovary syndrome

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Introduction

Androgen excess (AE) is among the most common endocrine disorders in women of the reproductive age, although it could be expressed even in the earlier or later periods of life. The primary source of endogenous AE is the ovary or the adrenal gland. AE results in the development of hirsutism, androgenic alopecia, acne, or menstrual irregularity, while severe and prolonged hyperandrogenism could lead to virilization.

Considering that increased cardiovascular risk was implicated in women with AE, the aim of this review is to analyze presence of specific cardiovascular risk factors, surrogate markers for cardiovascular diseases and cardiovascular events in the most common AE disorders.

Classification and the prevalence of androgen excess disorders

The corpus of AE disorders could be separated between more specific ones that have explicit clinical characteristics,

and the less specific ones diagnosed after exclusion of other hyperandrogenic states. Group of specific AE disorders includes congenital and non-classical adrenal hyperplasia (CAH and NCAH, respectively), hyperandrogenic insulin-resistant acanthosis nigricans (HAIRAN) syndrome, and androgen-secreting neoplasms (ASNs). Group of AE disorders diagnosed by exclusion includes polycystic ovary syndrome (PCOS), idiopathic hyperandrogenism, and idiopathic hirsutism (IH) [1, 2].

AE in the general population of the reproductive aged women was earlier approximated on 7 % [3, 4]. The assessment of the functional AE was available for PCOS only, with the prevalence 4–25 % [3–5], while the prevalence of other AE disorders was largely unknown. Recent study on the Mediterranean premenopausal women showed that 14.7 % had AE. Besides the confirmed prevalence of PCOS for the observed region, IH (5.2 %) was almost equally prevalent as PCOS [5].

In the population of women with AE, only a few larger clinical studies analyzed the prevalence of the specific disorders. The most frequent was PCOS with the prevalence between 60 and 80 % [1, 2]. The wide range in the prevalence could be attributed to the analyzed populations mainly in the studies originating from the North America or the definition used for the diagnosis of PCOS. Frequency of other specific disorders was smaller, being 0.2 % for ASNs, 3.7 % for HAIRAN syndrome, 5–7.6 % for IH, and 1.5–4.3 % for NCAH, respectively [1, 2].

Androgen excess and the development of cardiovascular risk in women

An existence of the increased cardiovascular risk (CVR) was implicated in women with AE [6]. Serum testosterone and cardiovascular diseases (CVD) could form an *U* shaped relationship in which women with either low or high testosterone levels have an increased risk for CVD independently of age, adiposity, ovarian function, and smoking [6]. Even more, a positive correlation between testosterone levels and indices of subclinical atherosclerosis was confirmed in a large population of postmenopausal women of different ethnicities [7]. At the level of vascular endothelium androgens induce inflammation and oxidative stress (OS) and increase renal reabsorption of sodium and water, thus proving their role in progression of atherosclerosis and development of hypertension [8, 9]. Indirectly, androgens act by increasing visceral adiposity and decreasing lipolysis in subcutaneous fat, insulin sensitivity, circulating high-density-lipoprotein cholesterol (HDL-C) levels, and low-density-lipoprotein cholesterol (LDL-C) clearance [10]. Obesity is a known independent risk factor for the metabolic syndrome (MetS), type 2 diabetes (T2D) and CVD, and closely related to hyperandrogenism, which favor development of abdominal obesity and insulin resistance (IR), particularly in women [10, 11]. Androgens stimulate activity of lipoprotein lipase (LPL) thus leading to accumulation of both subcutaneous and visceral fat [10]. Atherogenic lipid profile due to the AE is mainly characterized by lower HDL-C and increased LDL-C levels as a consequence of blunted LDL-receptor activity or by enhanced LPL activity [12].

Although the majority of relevant studies have proposed an association between AE and CVR in women, some of them have provided inconsistent data showing negative or neutral association of androgens with the prevalence rates of CVD or CVD surrogate markers. These discrepancies could be attributed to the heterogeneity of the study populations, and more importantly, to the limitations of commonly used androgen assays [13].

Surrogate and non-traditional markers of cardiovascular disease

Surrogate markers for CVD can be divided into functional and structural. While functional studies include measurement of brachial flow mediated dilatation (FMD), pulse wave velocity and heart rate recovery, structural changes are developing after atherosclerosis progression, and could be assessed by the measurement of carotid intima-media thickness (CIMT), coronary artery calcification (CAC), cardiac ultrasonography and anteroposterior diameter of the infrarenal abdominal aorta. Additionally, there is a continuously enlarging pool of non-traditional markers of endothelial dysfunction. Being more convenient for detection using biochemical probes, these markers could facilitate an early detection of subclinical atherosclerosis in young and relatively low-risk populations, including subgroups with AE. Nowadays, recognized non-traditional markers include increased C-reactive protein (CRP), serum uric acid (UA), homocysteine, adhesion molecules, endothelin-1, advanced glycation end products (AGEs), asymmetric dimethylarginine (ADMA), ischemia-modified albumin (IMA), and the presence of prothrombotic state [14].

Cardiovascular risk and events in specific androgen excess disorders

Polycystic ovary syndrome

Derangement in various metabolic indices, specific cell products and prothrombotic state characterize PCOS. However, phenotypic variability mirrored by ovulatory dysfunction and hyperandrogenism, seems to generate significant influence on CVR spectrum in this population [15].

It was confirmed that cardiometabolic risks are mostly prevalent in hyperandrogenic PCOS phenotypes [16], and that multivessel CVD correlates with level of circulating testosterone [17]. Approximately 60–80 % of PCOS women have hyperandrogenemia, while 50–70 % have IR [10]. IR appears to play the main role in the development of CVR. Both lean and obese women with anovulatory and hyperandrogenic PCOS phenotype showed more severe IR in comparison to control women of similar age and body mass index (BMI) [10]. At the level of arterial endothelium IR has a direct hypertrophic effect, reduces production and enhances inactivation of nitric-oxide, and consequently increases synthesis of vasoconstricting agents, like endothelin-1 [18, 19].

Dyslipidemia characterized about 70 % of PCOS women [20]. It is most often presenting by hypertriglyceridemia, lower HDL-C and elevated levels of small dense LDL-C, forming atherogenic dyslipidemic profile typical for the state of IR [21]. While those classical lipid components of MetS are considered to be consequent to the IR, LDL-C seems to be more androgen dependent [22]. This is in line with recent findings in Mediterranean PCOS women with MetS and elevated LDL-C that represent two distinct entities in the pathways toward increased CVR [23]. Through mechanisms mediated by androgen receptors or influencing the LPL activity, AE could modify LDL early in life, thus giving a prolonged period for oxidative transformation of those particles into ones with more atherogenic potential [12, 24].

Hypertension occurs in 10–40 % of the PCOS women. However, while some studies confirm its association with hyperandrogenism, other point on that obesity is *sine qua non* feature of hypertensive PCOS women [25].

Considering cardiovascular events, there is inconsistency in data mainly due to the different approach used for the retrospective diagnosis of PCOS. Numerous risk factors in the PCOS populations could explain 5–7 times higher risk for CVD, as well as over 2-fold higher risk for coronary heart disease and stroke in comparison to the general healthy female population [26, 27]. In the fourth decade of life and older, PCOS women carry on higher risk for impaired glucose tolerance, T2D, MetS, and consequent early CVD [28]. Additionally, the youngest PCOS population, in transition from an adolescent into adult period, has a tendency toward worsening glycoregulation and dyslipidemia, thus shifting the time limits of atherosclerosis to the early periods of life [29]. Moreover, as metabolic disturbances are possible complication of the commonly used oral contraceptives, individual CVR should be assessed in all PCOS women before the therapy introduction [30].

PCOS has been associated with OS and chronic low-grade inflammation that irrespectively of BMI may generate hyperandrogenism, anovulation, and CVD [18, 31]. Moreover, IR concomitantly with hyperandrogenism stimulates low-grade inflammation independently of obesity [32]. This is in line with the existence of the number of data on the increased levels of non-traditional markers of CVR such as CRP, markers of OS, endothelin-1, prothrombotic factors, adhesion molecules, proinflammatory interleukins, homocysteine, IMA, ADMA, and advanced glycated end products (AGEs) [15, 19, 31, 33, 34]. Besides an established relation of the majority of these non-traditional markers with hyperinsulinemia, IR and obesity, some results indicate the relation of increased serum UA, endothelin-1, AGEs, IMA, and adhesion molecules with androgen levels [19, 33, 34].

PCOS is independently associated with an increased CIMT and CAC even after adjustment for age and BMI [35, 36]. PCOS women have lower FMD independently of age and BMI, and both IR and testosterone levels are independent predictors of FMD [37]. The enlargement of the anteroposterior diameter of the abdominal aorta in comparison to CIMT could represent even earlier indicator of premature atherosclerosis in PCOS [38]. Heart ultrasound performed on PCOS women usually shows increased left ventricular mass and atrial diameter [39], and higher epicardial fat thickness (EFT) that correlates with metabolic indices and testosterone levels [40].

Congenital adrenal hyperplasia

CAH is an autosomal recessive disorder of steroid synthesis in adrenal glands, most commonly caused by mutations in the CYP21A2 gene. Variable deficiency of the enzyme 21-hydroxylase (P450c21) is clinically manifested as salt-wasting type, simple virilizing type and nonclassic type (NCAH). AE in CAH is a consequence of decreased cortisol secretion, which by stimulating adrenocorticotrophic hormone secretion, leads to adrenal hyperplasia and increased androgen production. Hyperleptinemia and hyperinsulinemia proved in CAH patients could further aggravate androgen production, thereby inducing PCOS-like presentation with MetS [41].

CAH is characterized with the development of several CVRs as hypertension, obesity, IR, AE, and probably dyslipidemia [42]. A number of CVRs are overlapping between CAH and PCOS patients, while iatrogenic Cushing syndrome developed after supraphysiologic doses of glucocorticoid needed for the androgen suppression, could further aggravate an existing CVR factors [43].

Hypertension is prevalent among CAH patients either as a consequence of the disease or the therapy, and is the main reason of cardiovascular morbidity in young patients with CAH [44]. Obesity and IR are prevalent in patients with CAH [41, 42, 44, 45]. Although dyslipidemia was rarely

proved in patients with CAH [46, 47], obesity and IR are shown to be associated with dyslipidemia and androgen levels, respectively [45, 48].

From the surrogate markers of CVD, CIMT was found to be increased in different age subgroups of CAH and independently of either androgen or insulin levels or glucocorticoid treatment [45]. Recently, a significant vascular endothelial and smooth muscle dysfunction measured by FMD was found in adolescents with CAH [49].

Idiopathic hirsutism

IH, the second most common cause of hirsutism after PCOS, is associated with increased peripheral 5-alpha-reductase activity and/or polymorphism of androgen receptor gene and/or increased androgen sensitivity of hair follicles [50]. CVR factors in women with IH have been rarely studied, and with the heterogeneous results obtained. While some authors proved an existence of increased IR in this population [51], others did not [52]. Similarly to PCOS, women with IH have increased CRP, triglycerides, CIMT, and EFT that correlate with metabolic parameters and hyperandrogenism [40].

Hyperandrogenic insulin-resistant acanthosis nigricans (HAIRAN) syndrome

HAIRAN syndrome is a rare disorder, thought to be a subset of PCOS [50]. Women with HAIRAN are more obese and insulin resistant than women with PCOS [1]. Although HAIRAN syndrome is characterized by overt IR that could exhibit various metabolic and cardiovascular consequences, long-term studies are lacking. As the distinction between PCOS and HAIRAN syndrome is less clear, it is possible that some findings on the cardiovascular outcomes in PCOS population could be extrapolated to HAIRAN population as well.

Androgen-secreting neoplasms

ASNs of adrenal or ovarian origin are rare type of endocrine tumors that could develop slowly until diagnosis. Except virilisation that is a rare phenomenon in PCOS, other clinical features can resemble PCOS. Therefore, small, slowly evolving ASNs, secreting low androgen concentrations, can be clinically indistinguishable from PCOS. Hence their diagnosis could be prolonged giving time for the development of possible metabolic and cardiovascular consequences. Ovarian androgen-secreting tumors (OAST) (<0.5 % of all ovarian tumors) usually secrete testosterone and/or other weak androgens with or without estrogens [53]. Cardiovascular consequences in OAST population have not been extensively studied. The only study that estimated long-term metabolic consequences in five women with OAST showed that although hyperandrogenism has been associated with IR and hyperlipidemia, there have been no changes in BMI, insulin sensitivity and lipid levels after the surgical treatment of OAST and confirmed decrease of androgen levels [54]. Possible explanation could be that high androgen levels may have caused down-regulation of androgen receptors. Adrenal ASNs are usually malignant tumors that produce testosterone with or without co-secretion of cortisol [50]. Studies on their metabolic and cardiovascular potential are lacking, as their high secretory activity and fast development require prompt treatment.

Effects of antiandrogen therapy on cardiovascular risk and events

Studies on the effects of antiandrogen therapy on CVR in women with AE provided inconsistent data which could be related mostly to the heterogeneous study populations and different therapy regiments. Relevant data are mainly related to women with PCOS. Regarding positive effects, it has been proved that pure antiandrogen receptor blocker, flutamide, improves lipid levels in women with PCOS [55]. Also, it has been shown that spironolactone, as one of the most prescribed antiandrogens in treatment of PCOS, normalizes endothelial function [56]. This could be attributed to both antiandrogen and antimineralocorticoid effects of the drug. The same positive action on endothelium was proved for antiandrogenic drug containing cyproterone acetate (CPA) in one study [57] but not for drospirenone (DRSP) used in the other study [58]. Moreover, the addition of spironolactone to OC conferred no CVR advantages in women with PCOS [59]. Additionally, administration of OCs containing DRSP, desogestrel and CPA as antiandrogenic progestogens results in worsening of lipid and CRP levels [58, 60], with the later effect that could be attributed to the influence of estrogen component on hepatic protein synthesis [58]. Combination of insulin sensitizer metformin with the OC therapy containing DRSP improved only indices of body composition and insulin sensitivity but without effect on the other traditional CVR factors in women with PCOS [61]. It is assumed that even low dose OCs containing antiandrogenic progestins may contribute to metabolic alterations and are linked to an increased risk of cardiovascular [62] and venous thromboembolic [63] events in general population as well in women with PCOS. Further randomized and long-term studies are needed to elucidate the effect of different antiandrogenic compounds on CVR and outcomes in women with AE.

Conclusion

AE disorders are frequent among women with specific phenotypic characteristics including age, race, ethnicity, as well as endocrine and metabolic profile, and possible genetic variations that are still unexplored. Besides PCOS that has an established high prevalence among AE disorders, recent findings on the greater prevalence of other rare hyperandrogenic conditions such as idiopathic hirsutism, raised a question on the real frequency of the AE in women. However, rare endocrine diseases like ASNs still remain underestimated with undefined long-term cardiometabolic consequences. Traditional and non-traditional CVR markers as well as their functional and mophological effects recognized throughout the surrogate indices, clearly imply on the existence of increased CVR and subclinical CVD in various types and age subgroups of women with AE. Several studies showed an increased frequency of cardiovascular events in specific subpopulations of women with AE like PCOS. However, the data on the CVR and events, as well on the effects of specific antiandrogen therapies should be challenged through the studies and clinical trials with specific etiopathogenic categories of women with AE, and related to their specified phenotypes including age, sociocultural, and metabolic characteristics.

Conflict of interest The authors of the manuscript declare that they have no conflict of interest.

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