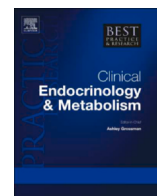




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Cardiometabolic outcomes of early onset hypogonadism in males

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Testosterone is an important vascular hormone, with multiple effects reported on the vasculature. As such, boys and men with early onset hypogonadism may have altered cardiovascular function, with the potential to result in adverse cardiometabolic outcomes in adulthood. Given the fact that cardiovascular changes in the young can affect future cardiovascular health, there is a need to better understand the influence of androgens on the vasculature in those with conditions such as 46, XY Disorders of Sex Development and Klinefelter Syndrome. This review summarises what is known about hypogonadism and the effects of testosterone supplementation in adults with hypogonadism, as well as what is currently understood in those with early onset hypogonadism specifically. A number of research gaps persist in this area and there is a need for international collaborative studies to address these for future generations of affected individuals.

Introduction

Over the last 25 years, studies investigating sex differences in the prevalence and outcomes of cardiovascular diseases (CVDs) have increased dramatically, with clear evidence that the pathophysiology of CVD is influenced by both sex and gender [1,2]. Indeed, CVD presents differently in men and women, with men more likely to develop macrovascular coronary disease whereas women are more likely to develop microvascular and specifically cerebrovascular disease as well as heart failure with preserved ejection fraction [3]. It seems therefore, that cardiovascular (CV) function, including blood pressure (BP) development and regulation, is influenced by the biological effects of the sex chromosomes and sex hormones.

Testosterone and its more potent metabolite 5 α -dihydrotestosterone (DHT) are the principal steroidal androgens and whilst their presence is critical for typical male sex development; their deficiency is important for typical female sex development. Androgens also exert significant influence on the vasculature via modulation of vascular function and atherosclerotic plaque formation through both genomic and non-genomic mechanisms [4]. Androgens can act through multiple signalling pathways within the same cells and their effects can be both vasoprotective and vaso-injurious, depending on factors including the heterogeneity of the vascular endothelium, differential expression of androgen and sex hormone receptors in endothelial and vascular smooth muscle cells (VSMCs), and the

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extent of androgen exposure [4]. Research indicates that both deficient and excessive levels of testosterone are associated with an increased risk of CVD [5], although to date, there is no clear evidence that timing of puberty affects long-term cardiovascular parameters [6]. Previously, the focus of CV research has been on the impact of hypogonadism on adult and elderly men. However, given our increasing understanding that premature evidence of vascular ageing can result in adverse cardiometabolic outcomes in adulthood, there is a need to consider the effects of hypogonadism in the young. As such, this review will focus on the effects of hypogonadism in males with congenital or genetic causes of early onset hypogonadism.

The burden of cardiovascular disease and early vascular aging (EVA)

The fact that CVD remains the leading cause of death worldwide is often reported and remains unchanged despite significant public health efforts and advances in treatment [7]. CVD incidence and mortality are particularly problematic in low and middle income countries, where CVD burden continues to increase [8]. Importantly, however most CVDs are preventable by addressing behavioural risk factors such as smoking, obesity and lack of physical activity, and as such it is important to identify those who are at risk of early CVD to ensure that appropriate risk stratification is optimised.

Cardiovascular risk factors such as obesity, hypertension and atherogenic lipid profiles are rising in young children, with this rise being attributed to maternal complications during pregnancy, genetic inheritance and environmental risk factors in early life [9]. The Foetal Origins of Disease hypothesis was first proposed by Barker and colleagues in the 1980s and suggested that CVDs originate through adaptations made by the foetus when it is compromised in some way in utero so that typical embryological development does not occur or there are imbalances in the nutrient supply to the foetus or impaired growth [10]. Barker's landmark studies focussed on the realisation that infants born low birth weight (LBW) had an increased risk of ischaemic heart disease later in life [11,12].

This theory has evolved into the Developmental Origins of Health and Disease Model and has been corroborated by multiple studies which have shown associations between adverse foetal conditions and CVD. For example, the children of mothers who were obese or who had gestational diabetes during pregnancy have increased carotid intima media thickness (CIMT) and increased adiposity compared to healthy controls [13]. It also appears that maternofetal stressors may result in epigenetic changes leading to alterations in the sympathetic nervous system, renin angiotensin system and hypothalamic pituitary axis, with consequent modifications to kidney, heart and blood vessel function [14].

Early vascular ageing (EVA) describes the process, via which the structure and function of blood vessels are altered in a young person prematurely, to mimic those seen in an aged population. Initially structural and mechanical changes develop with evidence of vascular remodelling, increased collagen cross linking and VSMC proliferation leading to a thickened arterial media. This causes shear stress resulting in arterial stiffness. The next stage is where, because of this arterial stiffness, and in combination with epigenetic changes, inflammation and oxidative stress develop in combination with altered secretion of growth factors and vasoactive agents resulting in arterial calcification and arteriosclerosis. Finally, plaque formation occurs resulting in early atherosclerosis, predisposing the individual to CVDs [15]. Modifiable risk factors for EVA include obesity, smoking, lack of physical activity and high blood pressure, and addressing these factors can reverse this process, although there is a window of opportunity, as the plasticity of blood vessels reduces over the lifespan (Fig. 1.). As such, there is a need to identify people with EVA early in the life course, while blood vessels still demonstrate plasticity, so that any detrimental factors in the lifestyle can be addressed early in infancy, childhood or adolescence [15]. Indeed, there is some suggestion that by the time adults start to have regular BP monitoring and screening, it may be too late to reduce the risk and that interventions for adults who are already affected cannot significantly alter disease trajectory [16].

Role of androgens on the vasculature

Androgens are vasoactive hormones and have a number of often contrasting actions within the vasculature, as has been extensively reviewed elsewhere [4]. The Androgen Receptor (AR) is widely expressed in various cardiovascular cells, including cardiomyocytes [17], endothelial cells [18], and VSMCs [19]. The genomic effects of testosterone occur over a period ranging from several hours to days and involve it binding to a cytosolic AR [20,21]. This interaction leads to modifications in gene expression, promoting an increase in hydrogen sulfide (H_2S) production, which subsequently induces vasodilation through the activation of transient receptor potential vanilloid 4 (TRPV4) channels and large-conductance calcium-activated potassium (BKCa) channels [22,23]. Furthermore, studies on the thoracic aorta of male Wistar rats demonstrate that testosterone stimulation results in a concurrent increase in H_2S production and associated vasodilation, a process that is AR-dependent [24–26]. AR activity is inversely proportional to the number of CAG repeats, with the normal sequence ranging from 11 to 31 triplets [27]. This variation may contribute to the differing vascular effects of testosterone seen in different individuals.

Androgens can also exert effects through a non-DNA-binding-dependent (non-genomic) mechanism, rapidly inducing secondary messengers to initiate cellular processes [28,29]. Androgens can exert vascular effects through the G protein-coupled receptor family C group 6-member A (GPC6A) and the zinc-regulated transporter [Zrt]-protein 9 (ZIP9) [30–33]. GPC6A is a non-classical receptor through which androgens mediate extracellular signal-regulated kinase (ERK) activation [34]. It has been demonstrated that GPC6A functions not only as a target of androgens but also as a regulator of androgen activity. ZIP9 also serves as both a membrane AR and a zinc transporter. Notably, ZIP9 has been shown to influence apoptosis, with a reduction in apoptotic activity observed in cells transfected with ZIP9 [32].

In vascular smooth muscle, testosterone's nongenomic actions include the rapid release of Ca^{2+} from intracellular stores such as the endoplasmic reticulum, modulation of ion channels, and interactions with cell surface receptors, including G protein-coupled receptors (GPCRs). Testosterone can also inhibit extracellular Ca^{2+} influx through L-type Ca^{2+} channels while activating K^+ channels, leading to membrane hyperpolarisation and subsequent closure of calcium channels, ultimately resulting in vasodilation [35–38]

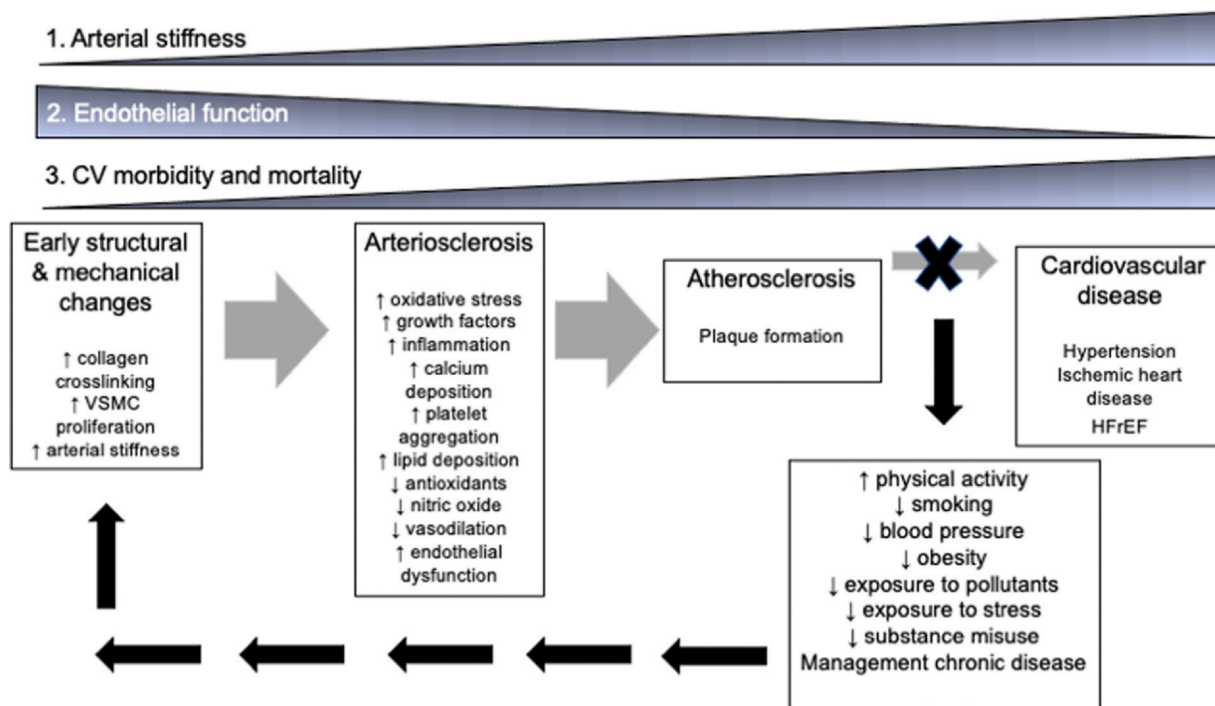


Fig. 1. Pathogenesis of early vascular ageing and cardiovascular disease. Stepwise progression from early structural and mechanical changes to the development of arteriosclerosis and atherosclerosis, resulting in gradual increases in arterial stiffness, reductions in endothelial function and overall increased risk of cardiovascular morbidity and mortality. These changes are reversible, and the development of cardiovascular disease can be preventable with the introduction of appropriate lifestyle modifications, such as increasing physical activity. Abbreviations: HFrEF: heart failure with reduced ejection fraction; VSMC: vascular smooth muscle cell.

At physiological concentrations, testosterone inhibits PGF2 α -induced Ca²⁺ fluxes in VSMCs potentially contributing to testosterone-induced vasodilation [39]. A recent study demonstrated that transdermal testosterone administration in men with hypogonadism and severe hypotestosteronemia induces acute vasodilation and improves arterial stiffness via non-genomic mechanisms. Notably, these effects persist beyond 96 hours of treatment, indicating the involvement of both genomic and nongenomic pathways in the vascular response [40].

Testosterone has been associated with increased reactive oxygen species (ROS) generation and apoptosis in VSMCs, which may contribute to cardiovascular dysfunction and oxidative stress [19]. It increases key ROS sources, such as NADPH oxidase, and reduces the expression of antioxidant enzymes [41]. Testosterone induces ROS production in VSMCs from both normotensive and hypertensive rats, leading to elevated mRNA levels of Nox1 and Nox4, as well as increased p47phox protein expression and VSMC migration [42]. Additionally, testosterone increases mitochondrial ROS generation, activates procaspase-8 and -3, reduces oxygen consumption, and promotes apoptosis through the expression of death receptors [19].

There is evidence suggesting that androgens, contrary to their previously discussed negative effects, can also have beneficial impacts on the vascular endothelium. Testosterone plays a role in repairing and preventing endothelial injury, such as in atherosclerosis, by promoting endothelial proliferation and recruiting endothelial progenitor cells (EPCs) crucial for neovascularisation [43,44]. The AR is present in EPCs and circulating EPC levels are lower in patients with hypogonadotropic hypogonadism [45,46]. Testosterone therapy in individuals with low testosterone levels can reverse endothelial dysfunction [47,48]. Chronic androgen stimulation (24 hours) appears to have a direct effect on endothelial cells, with DHT increasing vascular endothelial growth factor levels and enhancing the proliferative, migratory, and adhesive abilities of EPCs, processes regulated by the rho kinase pathway [49].

In addition, studies have suggested that testosterone may act as an anti-calcification agent. Growth arrest-specific gene 6 (*Gas6*) is a key molecule involved in regulating VSMC calcification [50]. *Gas6* is considered a pro-survival factor that reduces apoptosis, a crucial process in VSMC calcification [51]. In VSMCs, the AR was found to directly bind to the androgen response element in the *Gas6* promoter region, leading to the transactivation of *Gas6*. This interaction resulted in the inhibition of inorganic phosphate (Pi)-induced calcification in vascular cells. It has also been suggested that testosterone has a protective effect on vascular ageing by regulating vascular smooth muscle senescence via *Gas6* activation [52].

Effects of hypogonadism on the vasculature in adults and effects of testosterone replacement therapy

Given the known effects of androgens on the vasculature, it is no surprise that there has been significant interest over the years regarding testosterone replacement therapy (TRT) and cardiovascular health in adult men with hypogonadism, although this relationship has been subject to significant debate. Although limited by heterogeneity, a meta-analysis of community-based studies has

reported that lower endogenous testosterone levels are associated with increased risks of both all-cause and cardiovascular mortality [53]. More recently, a Danish population-based cohort of 18,238 men demonstrated that those with low total testosterone had significantly higher 5-year risks of stroke (2.4 % vs. 1.5 %), myocardial infarction (1.5 % vs. 1.2 %), venous thromboembolism (1.4 % vs. 0.9 %), and all-cause mortality (17.8 % vs. 6.8 %) than those with normal levels. However, after propensity score weighting, only the association with all-cause mortality remained significant, suggesting that hypogonadism may act more as a biomarker of underlying ill health than a direct cause of cardiovascular events, while retaining prognostic relevance [54]. Consistent with this, the Swedish MrOS (Osteoporotic Fractures in Men) study of 2416 men found that those in the highest testosterone quartile (≥ 550 ng/dL; 19.1 nmol/L) had a lower 5-year risk of cardiovascular events compared with those in the lower quartiles [55].

The potential pathophysiological link between hypogonadism and cardiovascular risk is multifactorial, with evidence supporting a bidirectional relationship between low testosterone and adverse cardiometabolic features. In a meta-analysis of individual participant data, low concentrations of total testosterone, sex hormone-binding globulin (SHBG), and free testosterone were associated with a more adverse cardiometabolic phenotype compared to individuals with higher sex hormone concentrations [56]. This was driven in large part by increased visceral adiposity, hypertriglyceridaemia, and impaired glucose regulation, all of which are established risk factors for CVD [56].

However, these associations are not universally observed. In the MrOS Sleep Study, a prospective cohort of 552 older men followed over 7.4 years, baseline levels of testosterone, estradiol, and SHBG were not associated with incident coronary, cerebrovascular, or peripheral arterial events, even after multivariable adjustment [55]. Similarly, in a UK Biobank cohort of 149,436 men, lower serum testosterone and calculated free testosterone were independently associated with all-cause and cancer-specific mortality, but not with cardiovascular mortality [57]. Conversely, higher SHBG levels were linked to increased all-cause, cardiovascular, and cancer-related mortality, suggesting distinct and potentially divergent roles for sex steroids and their binding proteins in long-term health outcomes.

In the context of prostate cancer, androgen deprivation therapy (ADT), particularly involving GnRH agonists or combined androgen blockade, has consistently been associated with increased cardiovascular risk in observational studies. Meta-analyses have reported elevated risks of cardiovascular death (HR 1.36, 95 % CI 1.10–1.68), myocardial infarction (HR 1.20, 95 % CI 1.05–1.38), and stroke with GnRH agonists [58]. In contrast, randomised controlled trials have not consistently corroborated these associations. Abiraterone, however, appears to confer a distinct cardiovascular toxicity profile, with pooled data showing increased risks of cardiac events (RR 1.41, 95 % CI 1.21–1.64) and grade ≥ 3 hypertension (RR 2.19, 95 % CI 1.73–2.78) across both observational and randomised studies.

Our understanding of the cardiovascular effects of exogenous testosterone has been substantially improved through recent large-scale trials. The TestES meta-analysis of 35 randomised controlled trials ($n = 5601$, mean age 65 years), including individual participant data from 17 trials ($n = 3431$), reported no significant difference in cardiovascular event rates between testosterone and placebo groups (7.5 % vs. 7.2 %; OR 1.07, 95 % CI 0.81–1.42), with similarly low and non-significant differences in mortality (0.4 % vs. 0.8 %; OR 0.46, 95 % CI 0.17–1.24) [59].

Nonetheless, interpretation of these findings is constrained by methodological limitations. The median follow-up duration was short (9.5 months), limiting inferences regarding long-term safety. Furthermore, nearly 50 % of included trials did not provide individual participant data, thereby reducing the statistical power for subgroup analyses. Persistent heterogeneity in study design, baseline cardiovascular risk, testosterone formulation, and treatment duration further complicates interpretation, despite efforts to account for these factors in sensitivity analyses.

The TRAVERSE trial represents the most rigorous assessment to date of testosterone's cardiovascular safety in a high-risk population. This large, randomised, placebo-controlled trial enrolled 5246 men aged 45–80 years with hypogonadism and either established cardiovascular disease or elevated cardiovascular risk [60]. Over a mean follow-up of 33 months, transdermal testosterone was noninferior to placebo for the primary composite outcome of major adverse cardiovascular events (MACE) (7.0 % vs. 7.3 %, HR 0.96, 95 % CI 0.78–1.17), with consistent findings across sensitivity and subgroup analyses.

Although the results provide reassurance regarding atherothrombotic risk, certain adverse events were more frequent in the testosterone group, including atrial fibrillation (3.5 % vs. 2.4 %), arrhythmias requiring intervention (5.2 % vs. 3.3 %), and pulmonary embolism (0.9 % vs. 0.5 %) [60]. While not primary endpoints, these findings highlight the importance of monitoring for non-atherosclerotic cardiovascular complications in men receiving testosterone therapy.

Interpretation of the TRAVERSE findings is limited by several factors. Over 60 % of participants discontinued treatment prior to trial completion, resulting in a median exposure of less than 22 months. Additionally, outcome data were only available for approximately 80 % of the potential follow-up period. The trial's exclusive use of transdermal testosterone also limits generalisability to other formulations, particularly intramuscular injections, which may have differing cardiovascular profiles. These caveats necessitate cautious interpretation, though TRAVERSE remains the most definitive trial to date assessing cardiovascular safety in this population.

Taken together, the current evidence suggests that while low endogenous testosterone is associated with adverse cardiometabolic profiles and increased all-cause mortality, its direct role in cardiovascular disease remains uncertain. Exogenous testosterone therapy, particularly when administered transdermally in men with established or elevated cardiovascular risk, does not appear to increase the risk of major adverse cardiovascular events in the short to medium term. However, observed increases in non-atherothrombotic events such as arrhythmias and thromboembolism underscore the need for careful patient selection, ongoing surveillance, and further investigation into formulation-specific effects and long-term outcomes.

Table 1

Types of hypogonadism diagnosed in early life. Abbreviations: AMH: anti-Müllerian Hormone; FSH: follicle stimulating hormone; FSH-R: FSH-receptor; LH: luteinising hormone; LH-R: LH-receptor; T: testosterone.

Type of early onset hypogonadism	Typical biochemistry	Examples of congenital/genetic cause
Primary (gonadal)	Low T Normal-high FSH and LH Low AMH and inhibin B	Disorders of Sex Development <ul style="list-style-type: none"> • <i>Gonadal dysgenesis</i> • <i>Leydig cell hypoplasia</i> • <i>Steroidogenic defects</i> • <i>FSH-R defects</i> • <i>AMHR defects</i> • <i>Testicular regression syndromes</i> • <i>Partial androgen insensitivity syndrome</i> • <i>5α-reductase deficiency</i> • <i>Non specific disorders of undermasculinisation</i> Klinefelter Syndrome Higher grade sex chromosome aneuploidies Myotonic dystrophy type 1 Congenital hypogonadotrophic hypogonadism Kallmann syndrome Multiple pituitary hormone deficiency (<i>PROPI, LHX3, LHX4</i>) Septo-optic dysplasia Isolated central hypogonadism
Secondary (central)	Low T Low FSH and LH	Prader Willi Syndrome Bardet-Biedl Congenital hypogonadotrophic hypogonadism with concomitant testicular dysfunction (may include individuals with <i>PROKR2, FGFR2, CHD7</i> polymorphisms)
Mixed	Low T Low/normal/high FSH and LH Low/normal/high AMH and inhibin B	

Early onset hypogonadism

Early onset hypogonadism refers to any condition which is characterised by inadequate testosterone production in infancy or early childhood. Hypogonadism can be a transient physiological phenomenon during adolescence, but it is also one of the commonest permanent endocrine conditions in childhood that requires active management throughout adulthood [61]. Hypogonadism can present in early life for a number of reasons (Table 1). Primary hypogonadism is generally caused by gonadal dysfunction and secondary hypogonadism is due to pituitary pathology but a mixed pattern of both central and gonadal hypogonadism may be present in some conditions such as hypogonadotrophic hypogonadism with testicular dysfunction due to a lack of timely descent of the testes.

Differences and Disorders of Sex Development (DSD) represent the commonest cause of early onset hypogonadism and encompass a group of conditions with diverse pathophysiology, which usually present in the newborn or adolescent age groups. In boys, most affected cases will have a karyotype of 46,XY and 46,XY DSD can be considered in three groups: disorders of gonadal (testicular) development; disorders of androgen synthesis or action; and other causes including hypogonadotrophic hypogonadism, cryptorchidism and isolated hypospadias. Data from the I-DSD Registry on the sdmregistries.org platform show that there is a trend towards raising more severely affected newborns with an XY karyotype as boys and it is likely that these individuals are at greater risk of severe hypogonadism in adulthood [62]. Thus, the prevalence of men with early onset hypogonadism is likely to increase over the next few years across the world and there is therefore a need to consider the impact of this early onset hypogonadism on their future cardiovascular status. In particular, data from the dsdlife cohort study [63] demonstrated that men with a range of XY DSD conditions had increased rates of CVD and hypertension compared to controls. In addition 20 % of individuals with XY DSD have been reported to have co-existing CV anomalies elsewhere [64], with children with hypospadias being 6 times more likely than children without hypospadias to be born with a significant congenital heart defect [65]. Raised BP has also been reported in 20 % of children and young people with 46,XY DSD, compared to the estimated global prevalence of 5 % [66].

46,XY DSD represents a heterogeneous group of conditions, where the phenotype is consistent with reduced male sex hormone action, likely secondary to dysregulation of a critical period in foetal development called the Masculinisation Programming Window (MPW) [67]. The clinical phenotype is useful to determine the timing of interruption to the MPW with earlier disruption resulting in more significant undervirilisation whereas later disruption may present with isolated cryptorchidism or micropenis [68]. The extent of disruption to the MPW and resultant lack of in utero androgen exposure may be demonstrated via the anogenital distance (AGD), which was first shown to alter in response to anti-androgen exposure during gestational days 15.5–19.5 in rats, which is equivalent to weeks 8–14 gestation in humans [67]. Reduced AGD has been associated with cryptorchidism and hypospadias in children [69] and hypogonadism, prostate cancer and subfertility in adults [70–72].

Overall, there are limited data available regarding specific 46,XY DSD conditions and CVD risk. For example, although it is known that the enzyme 5 α -reductase regulates insulin sensitivity in men [73] and modulates VSMC proliferation [74], little is documented regarding the long-term cardiovascular outcomes of individuals with *SRD5A2* variants and resultant 5 α -reductase deficiency. With regard to AR variants, women with complete androgen insensitivity syndrome (CAIS) are reported to have increased rates of obesity and altered cholesterol profiles [75] consistent with reports of hormone replacement therapy improving biochemical and ultrasound markers of vascular endothelial function in a cohort of 20 women with XY DSD [76]. Of note, however, a multicentre randomised

crossover trial demonstrated that treatment with transdermal oestradiol or testosterone worsened lipid profiles in women with CAIS [77]. In addition, one international study investigating the long-term outcomes of men with partial androgen insensitivity syndrome (PAIS) found that no cases had recorded investigations in relation to their cardiometabolic health although nearly 10% of the individuals were obese [78]. Overall, our knowledge regarding the effects of an AR variant on the vasculature in terms of long-term cardiometabolic implications is lacking and further research into the vascular implications of XY DSD continue to be required.

Hypospadias

Hypospadias is a common presenting feature in those with 46,XY DSD and may be present in approximately 1 in 300 newborns [79]. Subcutaneous penile resistance arteries from young boys with hypospadias with no known congenital heart disease (median age 2 years) had increased U46619 induced vasoconstriction, reduced acetylcholine induced endothelium-dependent and sodium nitroprusside induced endothelium-independent vasorelaxation, consistent with a pathological CV phenotype compared to penile arteries from age-matched controls undergoing routine religious circumcision. In addition, VSMCs harvested from these arteries demonstrated evidence of increased reactive oxygen species production and oxidative stress, and incubation of the arteries with N-acetylcysteine, a broad anti-oxidant, reversed the impaired CV phenotype seen in arteries from boys with hypospadias, suggesting that oxidative stress may be a key mechanism for this effect. Given that testosterone mediates ROS production in the vasculature, this may be related to the lack of in utero androgen exposure experienced in hypospadias [80]. When the arteries were incubated with testosterone, the contractile phenotype also improved, as did vasodilation, although interestingly DHT had limited effect [81].

From a clinical perspective, adolescents born with hypospadias (median age 14 years) had increased systolic blood pressure, pulse pressure and CIMT standard deviation score (SDS) compared to healthy age-matched control boys ($p < 0.05$), with no differences in metabolic parameters including body mass index (BMI) or cholesterol levels [80]. None of these individuals had received prior androgen therapy. In addition, men born in Scotland with hypospadias were at increased risk of arrhythmia, hypertension and heart failure [80]. A further registry based study in Sweden also demonstrated that men born with hypospadias were more likely to be diagnosed with adult onset hypogonadism, delayed puberty, type 2 diabetes and CVD [82]. As such, it is clear that young men with 46, XY DSD and in particular hypospadias are at risk of premature CVD, although the mechanisms surrounding this association require further analysis.

Congenital hypogonadotrophic hypogonadism (CHH)

CHH is another condition in which affected individuals are likely to have had deficient androgen exposure during critical periods of foetal programming and is often diagnosed either secondary to delayed puberty, or at birth secondary to cryptorchidism or hypospadias. There is an increased risk of congenital cardiac defects, most often reported in those with conditions such as CHARGE syndrome [83]. Early onset coronary artery disease has also been demonstrated [84] along with reports of hypertension [85], although limited studies exist to date. One study identified higher arterial BP, waist circumference, triglyceride, fasting glucose, fasting insulin, homeostatic model assessment of insulin resistance (HOMA-IR) and lower high density lipoprotein in young men (mean age 21.68 years) with CHH compared to controls [86]. Of note, this group also reported that supplementation with testosterone increased blood pressure and triglyceride levels, suggesting the need for close monitoring in those receiving testosterone treatment.

Recently, kisspeptin, a protein encoded by the *KISS1* gene, which is critical for the initiation of puberty, was found to be connected to genes within the genetic obesity network including proopiomelanocortin (POMC), glucagon and leptin (LEP), all of which are implicated in obesity disorders [87], demonstrating an interaction between the central control of puberty and obesity. The luteinising hormone/choriogonadotropin receptor (*LHCGR*) is also involved in the kisspeptin-mediated network, suggesting that individuals with Leydig cell hypoplasia may therefore be more susceptible to obesity. Indeed, women with polycystic ovarian syndrome and polymorphisms within *LCHGR* are more likely to be obese and develop early metabolic complications as a consequence [88].

Klinefelter Syndrome (KS)

Boys and men with KS most commonly have a 47, XXY karyotype and CVD risk is often reported in affected individuals. In men with KS, mortality secondary to cardiometabolic diseases (SMR (standardised mortality ratio) 1.3; 95% CI 1.1–1.5) and diabetes is increased [89]. Metabolic complications appear to be evident from childhood with overall rates of metabolic syndrome in the paediatric KS population ranging from 36 [90] - 80% [91]. In addition, hospital admission data from Denmark have demonstrated that men with KS have up to a six-fold increased risk of thromboembolic events compared to controls [92]. Clinically significant echocardiographic changes as well as increased CIMT have also been reported, although studies in this area are scarce [93] and increased office BP has been documented in children with KS. Of note, lifestyle factors may exacerbate CV risk in men with KS, with a recent study of 132 men with KS demonstrating reduced physical activity, income and social support compared to controls in addition to increased daily smoking, all of which are likely to contribute to cardiometabolic risk [94].

Prader Willi Syndrome

PWS is a condition associated with early onset hypogonadism in which cardiovascular dysfunction is well documented in long-term cohort studies [95]. Three types of hypogonadism have been identified in cases with PWS: central (21%), primary (21%) and a

combination (55 %) [96]. In addition, obesity may exacerbate both the hypogonadal and cardiovascular phenotypes. Although boys with PWS frequently require sex steroid supplementation, there are safety concerns in those with significant BMI levels, particularly due to the known associations between PWS and thromboembolism [97]. Given that mortality in patients with PWS is 3 % per year and that in nearly half of these cases, the cause of death is cardiopulmonary in origin, there is a need to further investigate the timing of CV dysfunction and its association with hypogonadism.

Summary

Testosterone is an important vasoactive hormone and has a number of actions within the vasculature. Adult hypogonadism is associated with significant increases in CV morbidity and mortality, and testosterone supplementation may improve these. Adverse CV function can present early in life resulting in poor CV outcomes in adulthood if preventative measures are not implemented and risk stratification undertaken. Many studies have demonstrated associations between early onset hypogonadism and altered CV function including in individuals with hypospadias, congenital hypogonadotrophic hypogonadism and Klinefelter Syndrome, consistent with our understanding that cardiovascular status is influenced by exposure to sex steroids as well as sex chromosomes. What remains unclear is why CV dysfunction develops in children with early onset hypogonadism and whether a lack of androgen exposure is solely responsible. In addition, there is no current consensus on a need to monitor CV status in young people born with conditions associated with early onset hypogonadism or how best to manage CV dysfunction once identified. Of course, individuals may also develop hypogonadism during early childhood secondary to tumours, late effects of oncology treatment, trauma or other chronic conditions, and although these are out with the scope of the current review, it is likely these will also lead to consequences on the vasculature and as such the need for screening and monitoring of CV function in these conditions should also be considered. Overall, there is a need for research to be undertaken to investigate these issues in all those at risk of early onset hypogonadism, ideally with international collaboration particularly given the low prevalence of some of the congenital and genetic causes. Through early identification and management, it is hoped that the CV burden of disease can therefore be reduced for affected individuals.

Research agenda

- Why does premature cardiovascular dysfunction develop in children with early onset hypogonadism?
- When does cardiovascular dysfunction develop in children with early onset hypogonadism?
- How can this cardiovascular dysfunction best be managed and indeed prevented?

Practice points

- Hypogonadism in adults is associated with significant increases in cardiovascular morbidity and mortality.
- Individuals with early onset hypogonadism, including 46, XY Disorders of Sex Development have been demonstrated to have altered vascular function.
- Adverse cardiovascular function in early life will result in poor cardiovascular outcomes in adulthood if preventative measures are not implemented.

CRediT authorship contributions statement

AKLH conceptualised the review. MP, PC and AKLH wrote the article. All authors approved the final manuscript prior to submission.

Ethics approval, consent for publication and availability of data and materials

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Declaration of Competing Interest

The authors have no conflicts of interest.

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