HHS Public Access

Author manuscript

*Mayo Clin Proc*. Author manuscript; available in PMC 2020 March 01.

Published in final edited form as:

*Mayo Clin Proc*. 2019 March ; 94(3): 536–543. doi:10.1016/j.mayocp.2018.11.016.

# Androgens and blood pressure control: Sex Differences and mechanisms

**Reckelhoff Jane F., Ph.D.**

Department of Cell and Molecular Biology, Mississippi Center of Excellence in Perinatal Research, and Women's Health Research Center, University of Mississippi Medical Center, Jackson, MS

## Abstract

The role that androgens play in mediating elevated blood pressure is unclear. Low levels of androgens in men and increased levels of androgens in women, as occurs with polycystic ovary syndrome (PCOS), are both associated with increased risk for cardiovascular disease and elevated blood pressure. We have used animal models to evaluate the potential mechanisms by which males and females have differential responses to androgens that impact blood pressure regulation, and the implications these may have for the health of men and women.

### Keywords

transgender; hypertension; obesity; metabolic syndrome

## Introduction

The role that androgens play in mediating elevated blood pressure is unclear. Low levels of androgens in men are associated with obesity and cardiovascular disease.[1,2] In contrast, in women elevated levels of androgens cause polycystic ovary syndrome (PCOS) that is also characterized by increased body weight and characteristics of cardiovascular disease.[3,4] We have used animal models to evaluate the potential mechanisms by which males and females have differential responses to androgens that impact blood pressure regulation, and the implications these may have for the health of men and women.

### Androgens in men

Reductions in androgens are a common finding in men who are overweight or obese.[1,2,5,6] In fact, all chronic diseases, such as chronic kidney disease, cancers, atherosclerosclerosis, are associated with reductions in serum androgens in men. Whether the reduction in androgens is a cause or a consequence of chronic disease states, such as obesity and

**Contact information:** Jane F. Reckelhoff, Ph.D., Chair, Department of Cell and Molecular Biology, Director, Women's Health Research Center, University of Mississippi Medical center, Jackson, MS 39216-4505, jreckelhoff@umc.edu, Phone: 507-261-5462.

metabolic syndrome, is not known since there have been no serial studies in men to determine if reductions in androgens predated the development of a chronic disease. However, favoring the “consequence” concept, one could imagine that teleologically, the presence of a chronic disease in men may cause a reduction in androgen levels to prevent procreation and thus protect the species (“survival of the fittest”). Alternatively, a reduction in androgens could be a risk factor for development of chronic disease, and in fact, reductions in androgens are associated with reduced longevity, risk of fatal cardiovascular events, sarcopenia, osteoporosis, frailty, cognitive impairment, depression, sleep apnea, and atrial fibrillation.[7] In any case androgen supplements are becoming commonplace in obese men.

## Androgens and Male Obese Zucker Rats (OZR)

Male OZR (fa/fa) are a model of leptin receptor deficiency that is characterized by massive obesity. The control rats are the lean litter mates (LZR) (FA/FA). Male OZR are non-reproductive, and we showed several years ago that OZR have serum total testosterone levels that are approximately 30% of the levels found in male LZR.[8] We tested the hypothesis that if testosterone was increased in OZR to levels similar to or higher than LZR, that would cause renal injury and subsequent hypertension. Thus at 22 weeks of age, a time when blood pressure was not elevated, rats were implanted with testosterone-containing silastic pellets that increased serum total testosterone by 10-fold in both OZR and LZR.[8] Rats were treated for 10 weeks. In OZR, testosterone levels were approximately 4-fold higher than in control LZR.

We were very surprised by the outcome of these studies. Ten-fold increases in testosterone in the LZR was associated with increased albuminuria and proteinuria, increased glomerular sclerosis, but no changes in body weight, plasma cholesterol, leptin or insulin.[8] Testosterone supplements also had no effect on blood pressure in the LZR.

In contrast, in the OZR, testosterone supplements caused a > 200g reduction in body weight that was caused in part by increased activity.[8] In addition, plasma insulin, cholesterol, and leptin were reduced along with the area under the curve for oral glucose tolerance test (OGTT), thus attenuating the symptoms of metabolic syndrome. Proteinuria and albuminuria were also reduced in the OZR, and there no change in the glomerular injury compared to untreated OZR. By 32 weeks of age, there was an age-related increase in blood pressure in OZR, and unlike in the LZR, testosterone supplements caused a significant increase in blood pressure in the OZR.[8] We concluded from these studies that androgen supplements in obese men could be protective against metabolic syndrome, but that blood pressure needed to be monitored closely. A meta-analysis that included 32 of 824 retrieved articles that included the terms, “body composition” and “testosterone”, in obese men, aged 51.7± 6.1 years, showed testosterone supplements improved insulin resistance, reduced body fat and increased lean mass, and improved lipid profile.[9] The meta-analysis data also supported a reduction in blood pressure with testosterone supplements. Perhaps the difference between our study in the rats and those of the metaanalysis was the age-related increase in blood pressure in the control OZR that influenced the further increase in blood pressure with testosterone supplements.

Our data do not provide mechanisms by which chronic androgens increase blood pressure in the OZR. We have data that conversion of testosterone to estradiol may actually provide some protection against even higher blood pressure with androgens in the OZR, since anastrozole, the inhibitor of the conversion of testosterone to estradiol, in testosterone-treated OZR, causes a further increase in their blood pressure (Reckelhoff, unpublished data). Other mechanisms will be studied in the future.

## Androgens in females

Polycystic ovary syndrome (PCOS) is the most common endocrine abnormality in reproductive aged women and symptoms can occur as early as menarche.[10] One of the defining symptoms of PCOS is hyperandrogenemia, but PCOS is also characterized in many women by overweight or obesity, hyperlipidemia and metabolic syndrome, and elevated blood pressure. [4,11,12] Typically, the elevated blood pressure does not meet the guidelines for antihypertensive treatment, but is still elevated for young women compared to controls.[4]

Several years ago, Manneras and colleagues developed a model of PCOS in female rats by administering dihydrotestosterone (DHT) chronically, beginning prepubertally.[13] DHT was used rather than testosterone since DHT is not converted to estradiol. They used the DHT-treated female animal model of PCOS to evaluate the gynecological consequences of increased androgens.[13] We adopted this animal model to determine the cardiovascular and renal implications of androgens in females.

As in the Manneras model, female rats were implanted with DHT pellets at approximately 4 weeks of age, and increased serum DHT levels by 3-4 fold,[4] which is typical for women with PCOS.[12] It should be noted that the levels of DHT developed by the supplements are 20-fold lower than would be found in men. Furthermore, the levels of DHT are not sufficient to cause downregulation of endogenous sex steroids, so serum testosterone and estradiol levels in the model are not affected.[4] DHT caused a sustained increase in food intake of 3 grams per day in the model and this led to an increase in body weight, and an increase in subcutaneous fat but not visceral fat as determined by computed tomography. Along with the increase in body weight, the DHT-treated female rats developed hypercholesterolemia, hyperinsulinemia, hyperleptinemia and increase in OGTT. Note that these effects are opposite of the effects that androgens had in male OZR or LZR. What was similar between the males and females treated with androgens was the increase in blood pressure. Both males and females given androgens experienced sustained increases in blood pressure.[4,8]

## Mechanisms responsible for hypertension in hyperandrogenemic females

### Role of the sympathetic nervous system (SNS) and melanocortin-4 receptor (MC4R)

The SNS has been shown by numerous investigators to play a role in mediating hypertension in obese animal models.[14–16] In the hyperandrogenemic female rat model, we tested whether blockade of the adrenergic receptors would affect blood pressure. We found that hyperandrogenemic females treated with terazocin and propranolol, α1- and β1,2-adrenergic receptor antagonists, had greater reductions in blood pressure than did control females.[17] These data supported the role for the SNS in mediating the elevated blood pressure with DHT. Similarly, we found that renal denervation prevented the androgens from increasing

the blood pressure in the female rats,[17] suggesting that the SNS was working through the renal nerves to increase the blood pressure in the females in response to androgens.

The mechanism by which the SNS was activated in the hyperandrogenic female rat model was not clear from these data, however. One mechanism for activation of the SNS is due to activation of MC4R.[15,17] Leptin and other mediators are thought to increase expression of α-MSH which in turn binds to MC4R in the pro-opiomelanocortin (POMC) neurons of the hypothalamus. Activation of the MC4R mediates satiety and causes an increase in sympathetic activity.[18] Thus if animals, or humans, develop leptin resistance or have leptin receptor deficiency as in the OZR, satiety is not reached when leptin is increased, and food consumption is increased compared to controls. In addition to food intake, MC4R activation causes an increase in sympathetic activity that can also affect thermoregulation and cause an increase in blood pressure.[19] Several years ago, Da Silva and colleagues reported that blockade of MC4R with an antagonist, SHU-9119, caused a reduction in blood pressure in male spontaneously hypertensive rats (SHR),[20] a model of essential hypertension in which it is well known that sympathetic activation contributes to the hypertension.[21]

We thus tested the hypothesis that the sympathetic activation in hyperandrogenemic female rats was mediated by activation of the MC4R.[17] DHT-treated females were given SHU-9119 intracerebroventricularly. Food intake increased considerably in both DHT-treated and control females, an indicator that the MC4R was indeed blocked. The blocker also reduced the blood pressure in the hyperandrogenemic female rats,[17] but not controls, suggesting that the SNS activation was mediated at least in part by activation of the MC4R. These data were interesting to us since we had previously shown that hypertension in both old and young female SHR was refractory to SHU-9119 blockade despite the fact that the drug reduced blood pressure in old male SHR,[22] just as had been shown previously in young males.[20] We have hypothesized that perhaps the presence of androgens increases activation of the MC4R in the PCOS model compared with female SHR. In support of this hypothesis, we found that the expression of the MC4R in the brain of DHT-treated females was significantly higher than in control females. We are now in the process of inhibiting the androgen receptor in the brain and then giving the MC4R antagonist to determine if our hypothesis is correct.

## Role of 20-hydroxyeicosatetraenoic acid (20-HETE)

Schwartzman and colleagues have studied the effect of increased androgens in 20-HETE synthesis and found that testosterone supplements in male animals increases cytochrome P450 (CYP) 4A ω-hydroxylase expression and activity, leading to increased synthesis of 20-HETE in the kidney.[23] We tested the hypothesis then that 20-HETE may also contribute to the elevated blood pressure in hyperandrogenemic female rats.[24] We determined that DHT-treatment in females increased endogenous 20-HETE levels and ω-hydroxylase activity in isolated renal microvessels, but not in cerebral vessels.[24] These data are important since the location of 20-HETE expression in the kidney determines whether it is pro-hypertensive or antihypertensive.[25] For example, if 20-HETE is present in the renal microvessels, this causes vasoconstriction and increase in GFR leading to elevated blood pressure. If 20-HETE is present in the tubules of the kidney, it blocks sodium reabsorption and thus is anti-hypertensive. In addition to the upregulation of 20-HETE and the ω-hydroxylase activity in

the renal microvessels of DHT-treated females, we also found that both 20-HETE and ω-hydroxylase activity were reduced in renal microsomal preparations (renal tubules) from DHT-treated females compared to control females.[24] We also found that the CYP4A2 expression was increased by 15-fold and that CYP4A8 was decreased by 50% in kidneys of DHT-treated females compared to controls. [24] Using female CYP4A2$^{-/-}$ rats and SS.BN5 wild type, we found that while androgen treatment increased blood pressure in the wild type females, androgens failed to increase blood pressure in the CYP4A2$^{-/-}$ females,[24] supporting the contention that CYP4A2 ω-hydroxylase was necessary for androgens to increase blood pressure. Since the Dahl salt sensitive (DS) rat is deficient in renal 20-HETE, [26] we also tested whether androgens would increase blood pressure in DS females, compared to Dahl salt resistant (DR) rats. We found that while androgens increased blood pressure in DR females, androgens failed to increase the blood pressure in DS females,[24] again supporting the importance of the 20-HETE in mediating the androgen-mediated elevation in blood pressure in the PCOS model. It does not appear that 20-HETE in the brain plays any role in mediating androgen-dependent sympathetic activity or the MC4R activation in the PCOS model since androgens had no effect on brain microvessel 20-HETE and actually reduced cerebral vessel ω-hydroxylase activity in these studies.[24]

## Role of the renin-angiotensin system (RAS)

Androgens are known to increase intrarenal expression of some of the components of the RAS.[27,28] For example, androgens upregulate the synthesis of angiotensinogen, and thus could impact renin activity. We have found that chronic DHT in females increased mRNA expression of angiotensinogen by 9-fold, increased angiotensin converting enzyme (ACE) mRNA by approximately 50%, and reduced angiotensin AT1 receptor mRNA expression in the cortex.[4] We have not measured ACE or plasma renin activity in our PCOS model, and we have only preliminary data that RAS blockade modestly reduces their blood pressure (Reckelhoff, unpublished data).

Another mechanism by which the RAS could impact the blood pressure in DHT-treated females is via its effect to increase oxidative stress. In our original studies we found that mRNA expression of some of the submits of NADPH oxidase are increased in the PCOS model. For example, mRNA expression of gp91phox, p22phox, p47phox and NOX4 were all increased in kidneys of DHT-treated females.[4] We have also found that urinary nitrate/nitrite excretion, an index of whole body nitric oxide production, was also significantly lower in the DHT-treated females,[4] perhaps due to increases in oxidative stress particularly superoxide. However, the role of oxidative stress in mediating the elevated blood pressure in the PCOS model is not clear since tempol failed to reduce the blood pressure (Reckelhoff, unpublished data).

## Postmenopausal hyperandrogenemia and blood pressure

We have had a longstanding interest in the mechanisms responsible for postmenopausal hypertension.[29] Women with PCOS have increased risk factors for cardiovascular disease including hypertension, and androgen levels remain elevated in women with PCOS following menopause.[30] However, whether women who have had PCOS throughout their reproductive lives have accelerated cardiovascular disease after menopause compared to

their non-PCOS counterparts is not clear. A meta-analysis study published in 2013 showed that while women who had PCOS during their reproductive years continue to have cardiovascular risk factors, such as increased insulin, the majority was not at increased risk for cardiovascular morbidity and mortality compared to women who did not have PCOS.[31] However, the authors point out the limited number of studies performed in women with PCOS who are postmenopausal.

In order to evaluate whether the rat model of PCOS exhibits increased cardiovascular disease with aging, female rats were treated chronically with DHT from 4-5 weeks of age through cessation of estrous cycling to 13 months of age.[32] Plasma DHT levels were 3-fold higher than in age-matched control females, and estradiol levels were approximately 10-fold lower. Body weight, visceral adiposity and subcutaneous adiposity were higher in the PCOS model that the controls. Metabolic syndrome was still present compared to controls with increases in plasma insulin, glucose and OGTT. Mean arterial pressure was higher and heart rate was significantly lower in the PCOS model, suggesting even greater sympathetic activation than in age-matched controls or previously studied young females treated with DHT. GFR was slightly lower in the PCOS model than in the control rats at this age but there was little renal injury.

We allowed the female rats to age further to 22-24 months of age. Female Sprague Dawley rats are typically protected from renal injury compared to aging males.[33] However, in the chronically DHT-treated females, we found they had chronic kidney disease with 60% reductions in GFR and 40% reductions in renal plasma flow.[34] Mean arterial pressure was not dissimilar from the levels found at 13 months, however. The DHT-treated females also had higher KIM-1 and proteinuria than the control females and lower nitrate/nitrite excretion. The kidneys of the aged PCOS model had significant glomerular sclerosis and interstitial fibrosis. These data suggest that with advanced aging, women with PCOS may have more chronic kidney disease than do women who have not had PCOS. Unfortunately, as mentioned above there are few studies in aged women with PCOS, much less women with advanced age. More research is needed to determine if women who have had PCOS during the reproductive years develop a higher incidence of chronic kidney disease with aging.

## The consequences of androgens in transgender humans

Few studies have evaluated long term effects of sex steroids in transgender individuals. In meta-analysis studies of transgender individuals, transgender men (female to male) have increases in plasma endothelin, which could have cardiovascular implications.[35,36] Some studies have shown that they have increases in blood pressure and LDL with reductions in HDL, but this is not entirely consistent among the studies. It seems to depend on the age of the participants in the studies and how long they have been taking androgen therapy. They also exhibit increases in the incidence of PCOS if their reproductive organs are intact. With regard to blood pressure, most studies show that transsexual men have increases in blood pressure with testosterone supplements.[36,37]

### The Four Core Chromosome Mouse as a model for future studies

The four-core chromosome mouse in which the Sry gene that determines maleness is on an autosome, such that there are XY and XX females, and XY and XX males, could be an important tool in the study of the effects of androgens.[38] In this model, by removing the sex organs, it is possible to separate chromosomal from the sex steroid-mediated effects. While most factors studied to date have been found to be sex-steroid mediated, Li and colleagues reported that XX mice have a poorer response to cardiac ischemia-reperfusion injury than do XY animals, a consequence of the number of X chromosomes, not lack of Y chromosomes, and independent of sex steroids.[39] The exploitation of this model may shed more light in the future on the mechanisms responsible for androgen-mediated adverse effects on cardiovascular disease in females, and elucidate the mechanisms by which androgens are metabolically protective, but cardiovascularly detrimental in males.

## Conclusion

As shown in Table 1, from our animal studies it is quite clear than androgens have different effects in males and females. Despite the sex differences in response to androgens, both males and females become hypertensive with androgen supplements. The implications of these differences are important not only in women who have PCOS, but also in transgender men since it appears that the differential responses to androgens persist and do not resolve even after long term testosterone treatment. Additional animal studies will be necessary to separate the cardiovascular-metabolic consequences of androgens that are chromosomally (genetically)-mediated from those that are sex steroid-mediated, and provide the potential for additional therapeutic options for hypertension.

## Acknowledgements

This work is supported by NIH grants R01HL66072, R01HL67028, P01HL51971. Research reported in this publication was supported by the National Institute of General Medical Sciences of the National Institutes of Health under Award Number P20GM121334 and P20GM104357. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.”

## CME questions:

## Objectives

Upon completion of this article, the reader should be able to:

**1)** Identify the symptoms of polycystic ovary syndrome, and the potential mechanisms by which they may develop hypertension.

**2)** Cite the cardiovascular and metabolic consequences of testosterone supplements in male obese rats that could impact humans.

**3)** Extrapolate the cardiovascular and metabolic consequences of androgen supplements from the animal studies to transgender men.

## Questions

1. A 24 year old woman comes into the OB/GYN Clinic with a complaint of missed periods and weight gain. During the physical examination, you notice the woman has facial hirsutism. You anticipate that she has polycystic ovary syndrome. What laboratory test would you order to make the diagnosis?

   **a)** Plasma lipids

   **b)** Plasma glucose

   **c)** Plasma sodium and potassium

   **d)** Serum testosterone

   **e)** Plasma estradiol

   Answer: d. Elevated serum testosterone is one of three symptoms of PCOS along with cystic ovaries and obesity. Plasma lipids and glucose may also be elevated if the patient has type II diabetes or metabolic syndrome. Plasma sodium and potassium should be normal even if the patient has elevated blood pressure. Plasma estradiol is likely to be normal or slightly decreased if she has PCOS.[1–3]

2. The serum testosterone levels are elevated in the woman. You refer her to the Endocrinology Clinic. Her body mass index is 31, and while her fasting plasma glucose is normal, you are concerned that she may be suffering from metabolic syndrome. What tests from above, and what additional tests would you use to strengthen your diagnosis?

   **a)** Plasma sodium and potassium, plasma lipids

   **b)** Plasma lipids, plasma insulin

   **c)** Plasma estradiol, plasma testosterone

   **d)** Plasma estradiol, plasma insulin

   **e)** Plasma sodium and potassium, plasma insulin

   Answer: b. Metabolic syndrome is characterized by hyperinsulinemia, hyperlipidemia, with or without hyperglycemia.[1]

3. The patient’s blood pressure is found to be 125/85. What would you prescribe for her blood pressure?

   **a)** Angiotensin receptor antagonists

   **b)** Weight loss program

   **c)** Beta adrenergic receptor blockers

   **d)** Anti-inflammatory medications

   **e)** Anti-androgens

Answer: B. Weight loss program. It is likely that the increase in body weight is mediating the increase in blood pressure, and even based on the new SPRINT Guidelines for aggressive therapy, medications are not appropriate. Anti-androgens, such as flutamide, have not been approved by the FDA for use to treat PCOS in the US.[1]

**4.** An 18 year old man comes to your Endocrinology Clinic requesting estradiol supplements claiming he wants to make the transition to become female. Based on the known consequences of estradiol therapy, what do you caution him about for his future health care?

**a)** Potential for increased libido.

**b)** Potential for decreased facial hair.

**c)** Potential for thomboemboli, ischemic stroke, myocardial infarction

**d)** Potential for narcolepsy.

**e)** Potential for decrease in physical ability.

Answer: C. Transgender women who take estradiol have a 5-fold higher incidence of venous thromboemboli compared to cis-gender women.[4–6]

**5.** The most common cause of mortality in transsexual women is:

**a)** Suicide

**b)** Myocardial infarction

**c)** Stroke

**d)** Pulmonary embolism

**e)** Car accidents

Answer: A. Transsexual women have a 51% increase in mortality compared to cis-gender women, and while cardiovascular events are more common, the major causes of death are suicide, drug overdoses, and AIDS.[5]

## References:

1. Christakou CD, Diamanti-Kandarakis E. Role of androgen excess on metabolic aberrations and cardiovascular risk in women with polycystic ovary syndrome. Women's Health. 2008;4:583–694.
2. Diamanti-Kandarakis E. Polycystic ovarian syndrome; pathophysiology, molecular aspects and clinical implications. Exp Rev Mol Med. 2008;10:1–21.
3. Azziz R, Carmina E, Dewailly D, et al. Position statement: Criteria for defining polycystic ovary syndrome: An Androgen Excess Society guideline. J Clin Endocrinol Metab. 2006;91:4237–5. [PubMed: 16940456]
4. Maraka S, Singh Ospina N, Rodriguez-Gutierrez R, et al. Sex steroids and cardiovasdular outcomes in transgender individuals: A systematic review and meta-analysis. J Clin Endocrinol Metab. 2017; 102:3914–3923. [PubMed: 28945852]

5. Streed CG Jr, Harfouch O, Marvel F, et al. Cardiovascular disease among transgender adults receiving hormone therapy: A Narrative review. Ann Intern Med. 2017;167:256–267. [PubMed: 28738421]
6. Getahum D, Nash R, Flanders WD, et al. Cross-sex hormones and acute cardiovascular events in transgender persons: A cohort study. Ann Intern Med. 2018;169:205–213. [PubMed: 29987313]

## Abbreviations:

| | |
|---|---|
| **CYP** | cytochrome P450 |
| **DR** | Dahl salt resistant |
| **DS** | Dahl salt sensitive |
| **GFR** | glomerular filtration rate |
| **LZR** | lean Zucker rat |
| **MC4R** | melanocortin 4 receptor |
| **OGTT** | oral glucose tolerance test |
| **OZR** | obese Zucker rat |
| **PCOS** | polycystic ovary syndrome |
| **RAS** | renin-angiotensin system |
| **SNS** | sympathetic nervous system |

## References:

1. Biswas M, Hampton D, Turkes A, Newcombe RG, Aled Rees D. Reduced total testosterone concentrations in young healthy South Asian men are partly explained by increased insulin resistance but not by altered adiposity. Clin Endocrinol (Oxf) 2010; 73:457–462. [PubMed: 20550541]
2. Liu P, Death A, Handelsman D. Androgens and cardiovascular disease. Endocrinol Rev. 2003; 24:313–340.
3. Christakou CD, Diamanti-Kandarakis E. Role of androgen excess on metabolic aberrations and cardiovascular risk in women with polycystic ovary syndrome. Women's Health. 2008; 4:583–694.
4. Yanes LL, Romero DG, Moulana M, et al. Cardiovascular-renal and metabolic characterization of a rat model of polycystic ovary syndrome. Gender Med. 2011:8:103–115.
5. Shabsigh R, Arver K, Channer KS, et al. The triad of erectile dysfunction, hypogonadism and the metabolic syndrome. Int J Clin Prac. 2008; 62:791–798.
6. Traish AM, Kypreos KE. Testosterone and cardiovascular disease: An old idea with modern clinical implications. Atherosclerosis. 2011; 214:244–248. [PubMed: 20869058]
7. Buvat J, Maggi M, Guay A, Torres LO. Testosterone deficiency in men: systematic review and standard operating procedure for diagnosis and treatment. J Sex Med 2013: 10:245–284. [PubMed: 22971200]
8. Davis DD, Lopez Ruiz A, Yanes LL, et al. Testosterone supplementation in male obese Zucker rats reduces body weight and improves insulin resistance but increased blood pressure. Hypertension. 2012;59:726–731. [PubMed: 22275530]
9. Corona G, Giagulli VA, Maseroli E, et al. Testosterone supplementation and body composition, : results form a meta-analysis of observational studies. J Endocrinol Invest. 2016; 39:967–981. [PubMed: 27241317]

10. Witchel SF. Puberty and polycystic ovary syndrome. Mol Cell Endocrinol. 2006; 254255:146–53.
11. Diamanti-Kandarakis E Polycystic ovarian syndrome; pathophysiology, molecular aspects and clinical implications. Exp Rev Mol Med. 2008;10:1–21.
12. Azziz R, Carmina E, Dewailly D, et al. Position statement: Criteria for defining polycystic ovary syndrome: An Androgen Excess Society guideline. J Clin Endocrinol Metab. 2006; 91:4237–5. [PubMed: 16940456]
13. Manneras L, Cajander S, Holmang A, et al. A new rat model exhibiting both ovarian and metabolic characteristics of polycystic ovary syndrome. Endocrinol. 2007; 148:3781–91.
14. Thorp AA, Schlaich MP. Relvance of sympathetic nervous system activation in obesity and metabolic syndrome. Relevance of sympathetic nervous system activation in obesity and metabolic syndrome. J Diabetes Res. 2015; 2015:341583. [PubMed: 26064978]
15. Hall JE, do Carmo JA, da Silva AA, Wang Z, Hall ME. Obesity-induced hypertension: interaction of neurohumoral and renal mechanisms. Circ Res. 2015; 116:976–990. [PubMed: 25767284]
16. Smith MM, Minson CT. Obesity and adipokines: effects on sympathetic overactivity. J Physiol. 2012; 590: 1787–1801 [PubMed: 22351630]
17. Maranon R, Lima R, Spradley FT, et al. Roles for the sympathetic nervous system, renal nerves and CNS melanocortin-4 receptor in the elevated blood pressure in hyperandrogensmic female rats. Am J Physiol Regul Integr Comp Physiol. 2015; 308:R708–R713. [PubMed: 25695289]
18. Girardet C, Butler AA. Neural melanocortin receptors in obesity and related metabolic disorders. Biochim Biophys Acta. 2014;1842: 482–494. [PubMed: 23680515]
19. Lute B, Jou W, Lateef DM, et al. Biphasic effect of melanocortin agonists on metabolic rat and body temperature. Cell Metab, 20 (2) (2014), pp. 333–345 [PubMed: 24981835]
20. da Silva AA, do Carmo JM, Kanyicska B, Dubinion J, Brandon E, Hall JE. Endogenous melanocortin system activity contributes to the elevated blood pressure in spontaneously hypertensive rats. Hypertension. 2008; 51:884–89 [PubMed: 18285617]
21. Iliescu R, Yanes LL, Bell W, Dwyer T, Baltatu OC, Reckelhoff JF. Role of the renal nerves in control of blood pressure in spontaneously hypertensive rats. Am. J. Physiol. Regul. Integr. Comp. Physiol 2006; 290:R341–R344. [PubMed: 16166211]
22. Maranon RO, Lima R, Mathbout M, et al. Postmenopausal hypertension: role of the sympathetic nervous system in an animal model Am J Physiol Regul Integr Comp Physiol. 2014; 306:R248–R256. [PubMed: 24381180]
23. Wu C, Schwartzman ML. The role of 20-HETE in androgen mediated hypertension. Prostaglandins Other Lipid Mediat. 2011; 96: 45–53. [PubMed: 21722750]
24. Dalmasso C, Maranon R, Patil C, Moulana M, Romero DG, Reckelhoff JF. 20-HETE and CYP4A2 ω-hydroxylase contribute to the elevated blood pressure in hyperandrogenemic female rats. Am J Physiol Renal Physiol. 2016; 311: F71–F77. [PubMed: 27194719]
25. Roman RJ. P-450 metabolites of arachidonic acid in the control of cardiovascular function. Physiol Rev. 2002; 82:131–85. [PubMed: 11773611]
26. Williams JM, Fan F, Murphy S, et al. Role of 20-HETE in the antihypertensive effect of transfer of chromosome 5 from Brown Norway to Dahl salt-sensitive rats. Am J Physiol Regul Integ Comp Physiol. 2012;302:R1209–18.
27. Chen Y- F, Naftilan AJ, Oparil S. Androgen-dependent angiotensinogen and renin messenger RNA expression in hypertensive rats. Hypertension. 1992;19:456–63. [PubMed: 1568764]
28. Ellison KE, Ingelfinger JR, Pivor M, Dzau VJ. Androgen regulation of rat renal angiotensinogen messenger RNA expression. J Clin Invest. 1989;83:1941–5. [PubMed: 2723066]
29. Reckelhoff JF, Fortepiani LA. Novel mechanisms responsible for postmenopausal hypertension. Hypertension 2004; 43:1–6. [PubMed: 14676222]
30. Shah D, Bansal S. Polycystic ovaries-beyond menopause. Climacteric 2104;17:109–115.
31. Welt CK, Carmina E. Clinical review: Lifecycle of polycystic ovary syndrome (PCOS): from in utero to menopause. J Clin Endocrinol Metab. 2013; 98:4629–4638. [PubMed: 24064685]
32. Dalmasso C, Maranon R, Patil C, et al. Cardiometabolic effects of chronic hyperandrogenemia in a new model of postmenopausal polycystic ovary syndrome. Endocrinology. 2016;157:2920–7. [PubMed: 27145003]

33. Reckelhoff JF, Samsell L, Dey R, et al. The effect of aging on glomerular hemodynamics in the rat. Am J Kidney Dis. 1992;20:70–5. [PubMed: 1621681]

34. Patil CN, Racusen LC, Reckelhoff JF. Consequences of advanced aging on renal function in chronic hyperandrogenemic female rat model: implication for aging women with polycystic ovary syndrome. Physiol Rep. 2017;5 pii: e13461. doi: 10.14814/phy2.13461. [PubMed: 29051304]

35. Maraka S, Singh Ospina N, Rodriguez-Gutierrez R, et al. Sex steroids and cardiovascular outcomes in transgender individuals: A systematic review and meta-analysis. J Clin Endocrinol Metab. 2017; 102:3914–3923. [PubMed: 28945852]

36. Streed CG Jr, Harfouch O, Marvel F, Blumenthal RS, Martin SS, Mukherjee M. Cardiovascular disease among transgender adults receiving hormone therapy: A Narrative review. Ann Intern Med. 2017;167:256–267. [PubMed: 28738421]

37. Irwig MS. Cardiovascular health in transgender people. Rev Endocr Metab Disord. 2018: 8 3 Doi: 10.1007/s11154-018-945403 (Epub ahead of print).

38. Itoh Y, Mackie R, Kampf K, et al. Four core genotypes mouse model: localization of the Sry transgene and bioassay for testicular hormone levels. BMC Res Notes. 2015;8:69. doi: 10.1186/s13104-015-0986-2. [PubMed: 25870930]

39. Li J, Chen X, McCluskey R, et al. The number of X chromosomes influences protection from cardiac ischaemia/reperfusion injury in mice: one X is better than two. Cardiovasc Res. 2014;102:375–84.. [PubMed: 24654234]

**Table 1**

Effect of androgens

| | Obese males with androgen supplements | Females with increased endogenous androgens |
|---|---|---|
| Food intake | Decreased[8] | Increased[4] |
| Body weight | Decreased[8] | Increased[4] |
| Activity | Increased[8] | ? |
| Plasma Lipids | decreased[8] | Increased[4] |
| Inflammatory mediators (TNFα) | Decreased[8] | Increased[4] |
| Sympathetic nervous system activation | ? | Increased[17] |
| Renal nerve activation | ? | Increased[17] |
| Melanocortin-4 receptor activation | ? | Increased[17] |
| RAS activation | ? | ? [4] |
| Increased renal microvascular 20-HETE | ? | Increased[24] |
| Increased oxidative stress | ? | Increased[4] |
| Blood pressure | Increased[8] | increased[4,17,24] |

Abbreviations: RAS = renin-angiotensin system; TNFα = tumor necrosis factor-alpha. Numbers are the references cited.