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Sexual Dimorphism of Abdominal Aortic Aneurysms

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Abstract

Sex is the largest nonmodifiable risk factor for the development of abdominal aortic aneurysms (AAAs) in humans and experimental models. Data from several studies consistently demonstrate a higher AAA prevalence in males than in females, contributing to divergent recommendations for AAA screening in men and women. Despite a higher AAA prevalence in males, females have more rapid rates of aneurysm dilation, and aneurysms rupture at smaller sizes. Unfortunately, no therapies have been effective to retard aneurysm dilation in either sex. Results from experimental AAA models indicate a protective role for estrogen in AAA development and progression, while male testosterone has been demonstrated to markedly promote angiotensin II (AngII)-induced AAAs. Potential mechanisms implicated in sex hormone regulation of AAAs include regulation of inflammation, matrix metalloproteinases, aromatase activity, oxidative stress, stem cells, and transforming growth factor-beta. In addition to sex hormones, sex chromosomes have been implicated in diseases of the aorta. Turner's syndrome (monosomy X) patients have a high incidence of thoracic aortic rupture. Recent studies indicate a novel approach to define the relative role of sex hormones versus sex chromosomes in experimental AAAs. Further studies are warranted to determine interactions between sex hormones and sex chromosomes in AAA development and progression.

Keywords: sex chromosomes, sex hormones, gender, AAA

1. Introduction

As defined by the Society of Vascular Surgery, abdominal aortic aneurysms (AAAs) are a permanent dilation of the infrarenal aorta (ratio of ≥ 1.5 -fold increase in normal abdominal aortic diameter) [1], leading to infrarenal aortic diameters >3 cm that can expand to more than 5.5 cm [2]. AAAs are typically asymptomatic, which is of concern due to the high mortality rate from aneurysm rupture. The prevalence of asymptomatic AAAs in geriatric men and women

ranged from 4 to 14.2% and from 0.35 to 6.2%, respectively [3–5]. Between the ages of 50 and 84 years, it has been estimated that AAA prevalence could be as high as 1.1 million people in the United States [6]. AAAs are responsible for 1.3% of all deaths in men between the ages of 65 and 85 years [7]. According to the Society of Vascular Surgery, in the United States, there are 200,000 people diagnosed with an AAA each year, and it is the 10th leading cause of mortality in men more than 55 years of age [8]. Impending rupture of AAAs is associated with sudden, severe, and constant groin, abdominal, and lower back pain. Because the aorta is the main supplier of blood throughout the body, AAA rupture can result in fatal bleeding with 85% chance of death. Depending on AAA expansion rate and size, treatment might vary from frequent monitoring (typically by ultrasound) to open or endovascular aneurysm repair. As AAA size increases (diameter > 5.5 cm), the probability of rupture also increases. While age, smoking, male sex, and family history are positively associated with AAA development, female sex, smoking cessation, and a healthy diet are negatively associated with AAA formation [6].

2. Sex differences in AAA prevalence in human and experimental models

Sex is considered a strong nonmodifiable risk factor for AAA formation. The incidence of AAAs has been reported to range from 4- to 5-fold higher in men compared to women [9, 10], with studies indicating that men are at a 10-fold higher risk to develop AAA compared to age-matched women [10]. Results from the Tromsø Study demonstrate that male sex contributes a 2.66 relative risk for AAA formation [11]. Epidemiological studies have shown an increased AAA incidence and rupture in men originating from western countries [12, 13]. In a community-based older population screening study, it was found that the AAA prevalence was 1.3% in women in comparison to 7.6% in men [14]. Correspondingly, the male:female ratio in a surgical series was $\approx 5:1$. Hospitalization for ruptured or intact AAA was 5 times more prevalent among men than women [9]. After controlling for time of surgery and age, men were around 1.8 times as likely to have an intact AAA treated surgically and 1.4 times to have a ruptured AAA in comparison to women. Current screening recommendations are to screen annually by ultrasound for men between the ages of 65 and 75 years with either a family history of AAA or who smoke. Conversely, studies have also shown that female sex decreases the AAA risk [10]. These results indicate that across a broad range of large-scale clinical trials, AAAs are much more prevalent in men as compared to women. In addition to male sex, the most predominant risk factors for AAAs are age, smoking, and family history.

Even though women have far lower AAA prevalence compared to men, women have worse prognosis than men, as AAAs in women progress faster and rupture at smaller sizes [15, 16]. Using the Vascular Study Group of New England database, Lo et al. have shown that women are older when diagnosed with an AAA, have smaller aortic diameters, and stay in the hospital longer than men diagnosed with an intact AAA [17]. Furthermore, women more frequently experience complications (e.g., leg and bowel ischemia) and have a higher mortality after 30 days than men after open AAA repair [17]. Also, according to the National Service hospitals in England, all cause and aortic-related mortalities were higher in women at all-time points (30 days, 1 year, and 5 years) in both open and EVAR surgeries [18]. Additional

studies have shown that the survival rate in women after surgical repair is lower than that of men; however, mechanisms for these effects are largely undefined [19, 20]. Differences in AAA rupture and progression between men and women could relate to vascular anatomy. For example, Lo and Schermerhorn noted that if the ratio of infrarenal to suprarenal diameter is ≥ 1.2 or a definition of ≥ 1.5 times the normal aortic diameter, then AAA prevalence in women could be as high as 6.2–9.8% [21]. This would indicate that using the same vascular anatomic criteria for men and women could lead to underdiagnosis of small AAAs in women [21]. While there is general consensus that men should be screened at 65 years of age or older, only the Society for Vascular Surgery recommends screening women (65 or older) who have smoked or have a family history of AAA [21]. In fact, some studies have indicated that women who smoke are more likely than nonsmoking men to develop AAAs [22]. An additional area of concern relates to recommendations for endovascular aneurysm repair as women having this procedure with a small AAA have poor outcomes (and also for open AAA repair) [17, 18]. Another issue related to the use of endovascular aneurysm repair in women is poor access to smaller vessels. These access-related complications lead to arterial injury of vessels which may result in additional surgeries and/or problems with stent engraftment.

In addition to anatomical differences, aortic wall stress differs between men and women. A recent study analyzed biomechanical and microstructural properties of nonaneurysmal human male and female aortas and concluded that male aortas are stiffer than female aortas [23]. Male aortas had higher failure load and tension than female aortas [23], which was suggested as a mechanism explaining rupture of AAAs in women at smaller sizes. Additionally, a small study (15 women and 15 men) examined peak wall stress (PWS) and peak wall rupture risk (PWRR) of AAA between men and women. Using computed tomography (CT) scans, results did not support differences in PWS between men and women; however, there was a trend for higher PWRR in females [24]. Future studies should utilize CT imaging to determine if criteria such as PWRR are informative for AAA diagnosis and in defining AAA growth.

An interesting study examined 140 Swedish women with an AAA compared to the same number of women with peripheral arterial disease (non-AAA) [25]. Results demonstrated smoking as a risk factor for AAA while diabetes was protective, but an interesting aspect of this study was the segregation of women who had an AAA ≥ 5 cm versus < 5 cm that showed differences in onset of menopause. Women who had large AAAs were approximately 2 years younger at age for menopause than those women who had smaller AAAs [25]. These data suggest that ovarian hormones may play a role in protection from large AAA development.

In addition to humans, experimental AAA models also exhibit sexual dimorphism, and have been used to define mechanisms of AAA formation and progression. Depending on the experimental model under study, AAAs recapitulate several facets of the human disease including medial degeneration, thrombus formation, and inflammation. The majority of experimental AAA models are evoked by genetic and/or chemical interventions, including increased degradation of collagen and elastin, defects in extracellular matrix maturation, aberrant cholesterol homeostasis, increased aldosterone, and salt levels, as well as enhanced generation of or exposure to angiotensin peptides [26–30]. Similar to humans, male mice infused with angiotensin II (AngII) exhibit a 4-fold higher prevalence of AAAs compared to female mice [31].

Typically, AAA incidence in male, hypercholesterolemic mice is 80% with females having a much lower incidence (20%) [31]. Our laboratory demonstrated previously that sex hormones are primary contributors to higher AAA susceptibility in male compared to female apolipoprotein E deficient (*ApoE*^{-/-}) mice, as ovariectomy had no effect on AAA formation while orchietomy decreased AAA incidence to the level of females [31, 32]. We also demonstrated that testosterone promotes AAA incidence in male and female mice associated with increased expression of angiotensin receptor 1a (AT1aR) expression specifically in abdominal aortas [32]. Similarly, in the elastase perfusion AAA model, male rats had larger and more frequent AAAs than females [33].

3. Influences of sex hormones on AAA development and progression

Limited studies have examined effects of sex hormone replacement therapy (HRT) in relation to AAA development, while experimental studies have focused primarily on therapeutics of sex hormones. Use of HRT for greater than 5 years in women decreased the odds ratio of developing an AAA [34]. However, other studies have shown no beneficial effect of HRT on AAA outcomes [35, 36]. Castration of male mice decreased AAA development and progression in both elastase and AngII-induced models [31–33, 37, 38]. In contrast, castration of female mice did not influence AAA development in either of these models [31, 37]. However, another study demonstrated ovariectomy of Wistar rats promoted elastase-induced AAAs [39].

In addition to effects of endogenous sex hormones, exogenous administration of estrogen inhibited AAA development and/or progression in AngII-infused male mice, while exogenous dihydrotestosterone administration also promoted AngII-induced AAAs in females [32, 37, 39–42]. Mechanisms of estrogen to protect against AAA formation and/or progression are multifactorial. Inflammation is frequently associated with AAAs [43], and recent studies demonstrated that peripheral blood monocytes contained sex and disease-specific inflammasome signatures that could be potential biomarkers to determine which patients may have AAAs [44].

In experimental AAAs, results demonstrated that estrogen replacement in ovariectomized female low density lipoprotein receptor deficient mice (*Ldlr*^{-/-}) decreased neutrophil AAA content [40]. Also, exogenous estrogen administration to AngII-infused male *ApoE*^{-/-} mice decreased nuclear factor-kappa B (NF-kappa B) activity and immune cell adhesion markers in the aorta [42]. Dietary phytoestrogens have also been demonstrated to decrease inflammation and AAA formation in elastase-induced male mice [45]. Plasmin activator inhibitor-1 (PAI-1) expression was increased in aortas from elastase-perfused female mice compared to males, while PAI whole body deficiency enhanced AAA development in both sexes [46].

An additional mechanism evoked in sex hormone effects on AAA development and/or progression is regulation of matrix metalloproteinase (MMP) activity. Results demonstrate that aortas from elastase-perfused female rats and mice have lower MMP activity than males [33, 47]. Likewise, ovariectomy of female Wistar rats increased aortic MMP-2 and -9 activity [39]. Conversely, administration of estrogen to male rats decreased aortic MMP-2 or MMP-9 activity compared to vehicle controls [33, 48]. An ability of estrogen to regulate MMP activity

differs according to the experimental model under study, as estrogen incubations in rat aortic smooth muscle cells (SMCs) did not alter MMP-2 activity, while estrogen stimulated MMP activity in aortic explants [48].

Oxidative stress has also been implicated as a mechanism for sex hormone regulation of AAAs. Superoxide dismutase (SOD) is an enzyme that converts superoxide radical to either oxygen or hydrogen peroxide. Deletion of SOD abolished sex differences in myogenic tone of mesenteric arteries from male compared to female mice [49]. Additional studies demonstrated that SMCs harvested from male and female rat aortas respond differently to ultraviolet B (UVB)-induced radiation [50]. Male SMCs were shown to produce more superoxide anion and SOD levels were lower in SMCs from male than female mice [50]. UVB-induced radiation resulted in apoptosis of SMCs that was also greater in male compared to female mice [50]. Interestingly, nitric oxide regulates SOD levels, but results using a carotid injury model demonstrated that males increase SOD levels in response to nitric oxide whereas females do not [51]. A recent study demonstrated that UVB-induced radiation resulted in upregulation of survival proteins in the nucleus of SMCs from female rats, but increased proapoptotic proteins and reduced mitochondrial membrane potential in SMCs from males [52].

Differences in estrogen formation and signaling such as aromatase activity and levels of estrogen receptors (ERs) could also contribute to sex differences in AAAs. Deletion of aromatase abolished the protective effects of female gender on elastase-induced AAAs [53]. Aortas from female mice had higher expression levels of ER α compared to male mice by day 3 of elastase perfusion [47]. Increased ER α expression was also detected in female human AAA patients compared to males [47]. Tamoxifen, a selective estrogen receptor modulator, decreased AAA development in male rats associated with decreased aortic neutrophil content, MMP-9 activity, and oxidative stress [54].

Sex differences have also been found in transforming growth factor-beta (TGF- β) and other members of the bone morphogenetic protein family (BMPs) related to AAA development [40, 55]. Elastase-perfused aortas from female rats had decreased TGF- β expression compared to males [55]. Moreover, exposure of murine SMCs to exogenous estrogen increased TGF- β expression and enhanced wound healing [40]. Deletion of the androgen receptor (AR) in either macrophages or SMCs lowered TGF- β 1 expression levels and suppressed AAA development in male mice [56]. In contrast, antibody-based depletion of TGF- β increased AAA ruptures in male mice [57, 58]. Mechanisms for these discrepancies are unclear, but may relate to sex hormones, sex chromosomes, or an interplay thereof [59].

Recent studies indicate that bone marrow-derived mesenchymal stem cells (MSCs) exhibit sex-dependent effects that influence AAA development [60]. When female MSCs were injected into male mice, elastase-induced AAAs were attenuated [60]. Furthermore, when conditioned media from MSCs was injected (i.v.) to male mice AAA formation was attenuated [60]. Moreover, the 5-alpha-reductase inhibitor, finasteride, decreased proinflammatory cytokine expression in male MSCs [60]. In humans, endothelial progenitor cells from AAA patients are impaired [61]. Taken together, these studies suggest that stem cells may have therapeutic potential for AAAs depending on patient sex.

In addition to protective effects in females, results indicate that male sex hormones may have detrimental effects on AAA formation and/or progression. For example, high levels of luteinizing hormone were positively associated with AAA outcomes [62]. Interestingly, lower testosterone levels have been linked to coronary artery disease and peripheral arterial disease in older men, but show little association when grouped with younger men [63–65].

Previous studies in our laboratory demonstrated that testosterone is a primary mediator of higher AAA prevalence in adult AngII-infused male mice, as orchietomy decreased AAA incidence to the level of adult females [32]. Additional studies demonstrated a greater abundance of AT1aR mRNA in abdominal compared to thoracic aortas of male, but not female *Apoe*^{-/-} mice [32]. Moreover, castration of male mice decreased AT1aR mRNA abundance in abdominal aortas, which was restored when castrated male mice were administered dihydrotestosterone [32]. Administration of dihydrotestosterone to female mice also increased abdominal aortic AT1aR mRNA abundance, and promoted AngII-induced AAAs. To explore mechanisms contributing to regional differences in AT1aR abundance along the aortic length, we initiated studies examining developmental influences of testosterone. The rationale for these studies was based on diversity of SMC origin along the aortic length [66], coupled with expression of AR in abdominal aortic SMCs derived from mesenchymal stem cells [67]. Using a novel model whereby neonatal female mice were exposed to a single dose of testosterone (e.g., to mimic testosterone surges after birth in males), we demonstrated a robust increase in adult AAA susceptibility in females that was associated with increased abdominal aortic AT1aR expression [31, 32]. Since increased abdominal aortic AT1aR mRNA abundance and high AAA susceptibility persisted in adult females exposed transiently to testosterone during development despite a low-level of circulating testosterone, these results indicate that the simple presence of testosterone does not define sex differences in AAA susceptibility. Finally, in addition to influencing AAA formation, recent studies from our laboratory demonstrated that castration of male *Apoe*^{-/-} mice after an AAA was established halted progressive increases in abdominal aortic lumen diameter but had no effect on maximal AAA diameters [38]. Castration of male mice was associated with increased aortic wall rigidity through increases in collagen and smooth muscle α -actin [38].

As an alternative approach to administering exogenous sex hormone, genetic deficiency of AR decreased elastase-induced AAA formation in male mice associated with decreasing aortic mRNA abundance of proinflammatory cytokines IL-1 α , IL-6, and IL-17 [68]. In different studies, whole body AR deficiency in male *Apoe*^{-/-} mice was demonstrated to suppress IL-1 α expression in aortic tissue, while AngII infusion stimulated aortic IL-1 α expression in wild type male controls [56]. Deletion of the AR specifically from macrophages or SMCs decreased AngII-induced AAAs in male *Apoe*^{-/-} mice that could be partially restored by administering recombinant IL-1 α [56]. Male mice have increased abdominal aortic IL-1 β mRNA and protein levels when perfused with elastase [69], and increased levels of c-Jun-N-terminal kinase (JNK), proMMP-9, proMMP-2, and active MMP-2 [70]. While it is unclear if these sex differences relate to testosterone, results consistently indicate differences in aortic inflammatory pathways that may contribute to sexual dimorphism of AAAs.

Several sex hormone-mediated effects that may relate to AAA development have been demonstrated in SMCs. For example, testosterone stimulated oxidative stress of SMCs harvested from

male mice [41]. Moreover, SMCs harvested from male mice exhibited increased MMP-2 and 9 activity and AKT phosphorylation [71], increased levels of phosphorylated extracellular signal-regulated kinase (p-Erk), and elevated proMMP-2 levels when exposed to elastase [72]. Male SMCs exhibit increased levels of MMP-2 compared to female rats when stimulated with IL-1 β [48]. Additionally, MMP-9 mRNA abundance was 10-fold higher in male compared to female SMCs.

4. Potential influence of sex chromosomes on AAA development

Sex chromosomes can also contribute to sexually dimorphic responses of the cardiovascular system [73]. However, as described above, sexual dimorphism of AAAs has primarily been attributed to direct or indirect effects of sex hormones, even though sex hormones do not fully explain all sexual dimorphism. Studies have shown that there are large sex differences of gene expression in somatic tissues of mice [74]. Sex hormones are known to be important in differentiation of the reproductive system and also impact sex differences in gene expression in somatic tissues. However, differences in pregonadal embryo size between males and females are also influenced by sex chromosome complement [75, 76]. Moreover, before gonadal differentiation, a large number of genes are expressed differentially in preimplantation embryos [77]. These results indicate that sex chromosome genes in addition to sex hormone regulation influence development.

Beyond their effects on sex determination and reproduction, there is little known about the role of genes residing on sex chromosomes in disease development, especially in the vasculature. The sex chromosomes are designated as X and Y. In mammals, there are 23 pairs of chromosomes, one pair of sex chromosomes that are either XX or XY, and 22 pairs of autosomes. The Y chromosome is responsible for sex determination, because it has the Sex determining Region of the Y (Sry) gene that resides in the male-specific region of the Y chromosome (MSY). The MSY represents 95% of Y chromosome content and does not recombine with the X chromosome during meiosis. This region of the Y chromosome is responsible for testis formation; however, if the Sry gene is absent, the fetus will be female even in the presence of the Y chromosome. The Sry gene has been demonstrated to regulate the expression of several components of the renin-angiotensin system. It has been shown that Sry increases the promoter activity for angiotensinogen, renin, and angiotensin-converting enzyme 1 (ACE1) and decreases angiotensin-converting enzyme 2 (ACE2) promoter activity in Chinese Hamster Ovary (CHO) cells [78]. It is unclear if these effects are related to sex differences in AAAs and/or other cardiovascular diseases associated with an activated renin-angiotensin system.

The sex chromosomes do not recombine normally like autosomes; they usually recombine at their tips which are called pseudoautosomal regions (homologous regions of nucleotide sequences that recombine with each other during meiosis). The most important characteristic feature of sex chromosomes is that the Y chromosome is missing a large number of genes compared to the X chromosome. As a result, male and female cells have a different dosage of X and Y genes that could influence cell function differently in gonadal and nongonadal tissues.

In addition to sex hormones, genes present on the sex chromosomes are thought to be a primary mechanism for differences between males and females. While the Y chromosome is

small and has few genes, the X chromosome is large and contains 1098 genes [79]. X-linked genes, including components of the renin-angiotensin system such as ACE2 and angiotensin type 2 receptors (AT2R), are present in males and females, but two X chromosomes in females can cause gene-dosage differences for X-linked genes between males and females. The possible difference in expression of genes on the X chromosome is typically compensated for by X chromosome inactivation, in which one of the two X chromosomes becomes silenced transcriptionally. However, some genes escape X-inactivation, or are differentially expressed depending on which X chromosome is inactivated (maternal or paternal) and can lead to gene-dosage effects between XX and XY cells.

Genes on sex chromosomes have been linked to inherited forms of cardiovascular diseases [80, 81], but it is still unclear what role sex chromosomes and their interaction with sex hormones have on the development of these diseases. Recently, an experimental study demonstrated that the numbers of X chromosomes influences protection from cardiac ischemia, because mice with two X chromosomes were more vulnerable to myocardial infarction when compared to mice with one X and one Y chromosome [82]. Klinefelter syndrome (47 XXY), the most common abnormality of sex chromosomes in males due to the presence of an extra X chromosome, is associated with increased cardiovascular risk and mortality [83, 84]. Turner syndrome (45X) in females, or monosomy X (XO), is a common chromosomal disorder that is due to partial or complete loss of one of the X chromosomes. Females with Turner syndrome exhibit a 100-fold increased risk of aortic dissection [85]. These results suggest that sex chromosome complement can influence the vasculature, but mechanisms for these effects are unknown.

AAAs are also an aortic disease that can be genetically inherited [86–89]. First degree relatives of AAA patients are at 11.6-fold higher risk of developing aneurysmal degeneration compared to non-AAA families [86]. Moreover, in a multinational study that investigated a large number of families, each family that contained at least two individuals with a diagnosed AAA were predominately male (77% of patients) and the most common relationship was being a male sibling [90]. Since the Y chromosome is passed only from father to son, this suggests a potential role for the Y chromosome in male AAA susceptibility. However, despite the strong predisposition for AAA formation in males compared to females, the contribution of sex chromosome effects to AAA inheritance and sexual dimorphism of this vascular disease has not been explored.

Since XX chromosomes are most commonly presented in nature with ovaries (females) while XY chromosomes exist in males with testes, previously it has not been possible to examine the role of sex chromosome complement independent of gonadal hormone effects in experimental animal models. However, there are now experimental models, such as the four core genotype model in mice, which can be used to understand the relative influence of sex chromosomes in the absence or presence of gonadal hormones. The four core genotype model is produced from male mice with a natural mutation of Sry, where this gene was reinserted on autosomes. Breeding of male mice with autosomal Sry to females produces four genotypes, XX and XY females (with ovaries) and XY and XX males (with testes) [91]. Recent studies using this model identified that blood pressure responses to infusion of AngII were influenced by both sex hormones and sex chromosomes, as blood pressure responses to AngII were greater

in gonadectomized XX than XY females [92]. Furthermore, vasodilation of iliac arteries was greater in XX than XY females and this effect appeared to be AT2R-dependent [93].

Since sex chromosome complement also influences the blood pressure response to AngII, it is highly likely that sex chromosome effects on gene expression influence other AngII-mediated responses, such as AAAs. Moreover, uncovering the basic knowledge of the interplay between sex hormones and sex chromosomes on aortic vascular biology and disease may lead to discovery of novel drug targets that have efficacy in a sex-specific manner.

5. Summary

It is clear that AAAs are sexually dimorphic in prevalence and prognosis. The majority of studies defining mechanisms for sexual dimorphism of AAAs have focused on potential roles for sex hormones (see **Table 1** for summary), with estrogen generally thought to be protective while testosterone exerts detrimental effects that promote AAA formation and progression. However, given a strong inheritance for AAAs, coupled with an association of sex chromosome abnormalities with aortic vascular disease, additional studies defining potential roles for sex chromosome genes in AAA development are warranted.

Gender	Study [Ref.]	Model	Intervention	Effect on AAA
Males	Martin-McNulty et al. [42]	AngII-induced AAA in mice	17 Beta-estradiol administration	Decrease
Males	Henriques et al. [31]	AngII-induced AAA in mice	Orchidectomy	Decrease
Males	Grigoryants et al. [54]	Elastase perfusion in rats	Tamoxifen (selective estrogen receptor modulators) administration	Decrease
Males	Laser et al. [47]	Elastase perfusion in mice	Low ER α expression	High AAA
Males	Zhang et al. [38]	AngII-induced AAA in mice	Orchidectomy	Decrease the progression of established AngII-induced AAAs
Males	Cho et al. [37]	Elastase perfusion in rats	Estrogen administration or orchidectomy	Decrease AAA diameter
Males	Huang et al. [56]	AngII-induced AAA in mice	ASC-J19 (androgen receptor degradation enhancer)	Decrease
Males	Huang et al. [56]	AngII-induced AAA in mice	Androgen receptor knockout in macrophage or smooth muscle cells	Decrease
Males	Huang et al. [56]	AngII-induced AAA in mice	Androgen receptor knockout in endothelial cells	No effect
Males	Davis et al. [68]	Elastase perfusion in mice	Flutamide (androgen receptor blocker)	Decrease
Males	Davis et al. [68]	Elastase perfusion in mice	Ketoconazole (androgen receptor blocker)	Decrease

Gender	Study [Ref.]	Model	Intervention	Effect on AAA
Males	Davis et al. [68]	Elastase perfusion in mice	Deletion of androgen receptor	Decrease
Females	Cho et al. [37]	Elastase perfusion in rats	Testosterone administration or oophorectomy	No effect
Females	Zhang et al. [41]	AngII-induced AAA in mice	Neonatal testosterone administration	Increase
Females	Laser et al. [47]	Elastase perfusion in mice	High ER α expression	Low AAA
Females	Thatcher et al. [40]	AngII-induced AAA in mice	17 Beta-estradiol administration	Decrease the progression of established AngII-induced AAA in ovariectomized females
Females and Males	Laser et al. [47]	Human	ER α protein level	ER α protein levels 80% higher in female human AAA patients than those in male counterparts
Females and Males	Johnston et al. [53]	Elastase perfusion in mice	Aromatase knockout	Increase in females and no effect in males

Table 1. Influence of sex hormone manipulation on experimental AAAs.

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