Keynote Lecture Series

The role of sex hormones in abdominal aortic aneurysms: a topical review

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Sex discrepancies have been reported for patients with abdominal aortic aneurysm (AAA) for decades. Men have a higher prevalence of disease, earlier onset, less morphological features obstructing eligibility for repair and better survival, both short and long term. In more recent years, several attempts have been made to identify the biologic or pathogenic factors contributing to these sex differences, including socioeconomic factors though all have failed. The greatest challenge is to reveal the variable mechanism for development of disease for both women and men, and secondly to identify the factors contributing to the progression of disease, and eventual rupture. Evaluations of diagnosed patients have failed to detect any factors associated with development of disease which would give a distinct explanation for the profound sex differences. Considering the obvious earlier trigger for development in men compared to women, excluding smoking, hypertension, hyperlipidemia as certified sole triggers, the remaining factors to explore are sex hormones or biological mechanisms. This topical review explores the contemporary publications on sex hormones and their association with AAA in women and men. The findings confirm the lack of scientific evidence for the influence of female and male sex hormones on development or progression of aneurysm disease. Weak indications support that women probably benefit from a longer reproductive history as a contributing protection against AAA development, influenced by smoking and heredity. There is some evidence that could support that, as for other manifestations of cardiovascular diseases, low testosterone levels in men, can contribute to an increased risk for AAA development. The influence of higher circulating levels of female sex hormones on risk development in men remains to be evaluated. In conclusion, this area will expand during the next decade, by combining registry-based and translational databases in stratified analysis for women and men, giving us more evidence that will contribute to important risk factor estimations for future cohorts at risk of AAA development.

Keywords: Sex hormone; abdominal aortic aneurysm (AAA); treatment; gender; aortic disease; testosterone; estradiol

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Introduction

Profound sex differences in disease distribution

The question why such profound sex and gender differences are found in abdominal aortic aneurysm (AAA) patient groups has for decades remained unanswered. One can presume that there will not be one answer to such a question, but rather a multitude of responses. The key to exploring this will probably be to intensify the quest for defining the aneurysm phenotypes (1).

The four areas most intensely explored in the AAA field are prevalence rates, onset of disease development, treatment eligibility and mortality. Several of these areas will be reported elsewhere in this edition of the

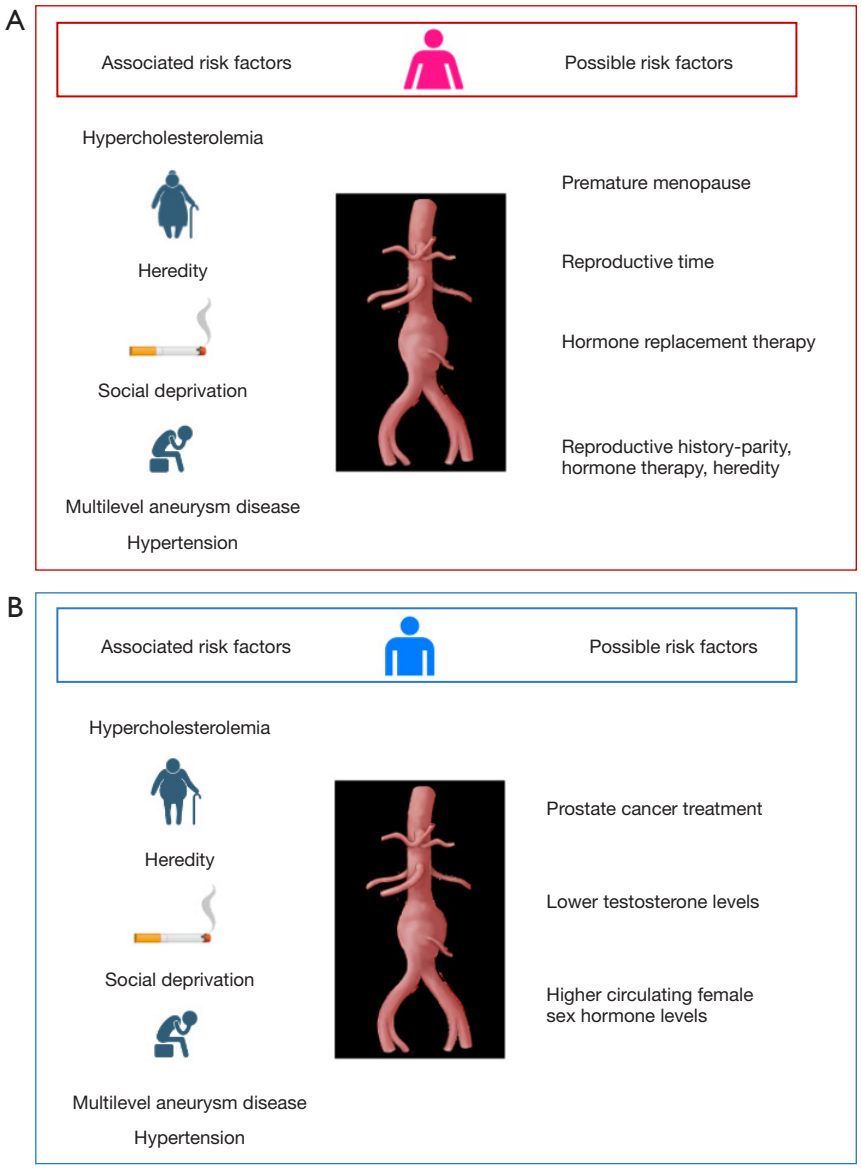

Figure 1 Schematic summary of findings regarding risk factors commonly found in cohorts with AAA patients, and possible sex hormone associated factors. (A) In women. (B) In men. AAA, abdominal aortic aneurysm.

Annals of Cardiothoracic Surgery. There are other factors of interest within the AAA field, which goes beyond these aforementioned, such as the rarely debated higher proportion of AAA women with multilevel aortic disease as compared to men, which could influence eligibility rates (1). Additionally, the lack of "catch-up" regarding the prevalence of AAA in women as compared to other cardiovascular disease (CVD) patient groups in that women will never develop AAA in a similar proportion as men, in any age group, also requires investigation. These areas could be associated either directly or indirectly with female and male sex hormones (2).

A number of risk factors, both modifiable and non-modifiable, that are associated with disease development or are commonly reported in the AAA patient population have been known for decades, though are commonly not reported in a sex-stratified analysis (1,3-10) (*Figure 1*). The modifiable risk factors commonly associated with the development and progression of aortic disease are smoking, obesity and hyperlipidemia (1,3-10). Several

reported non-modifiable factors in AAA patient groups are male sex, increasing age, heredity, depression, other aneurysms (thoracic/popliteal) and other manifestations of CVD disease (11) (*Figure 1*). The published reports on the distribution of these modifiable risk factors in the population, such as smoking or hyperlipidemia cannot be said to explain these profound sex differences regarding aneurysm development. If these gender differences partly explain the much higher proportion of women in rupture, patient groups with a lower ratio (3–4.1) remain to be explored further. One example serving as an illustration of these gender differences would be hyperlipidemia (12).

It is possible that the axis of hypercholesterolemia influencing the later development of AAA exists in some phenotypes, and in these subgroups contributes to explain AAA disease development (1,6,13). Since some population-based reports show a higher chance for men to obtain successful treatment, reaching target lipid-levels in greater proportions than women, it is unlikely that this explains the much higher rate of AAA in men in general. Regarding coronary disease, a small but higher association for disease development in men with hypercholesterolemia was reported than for women (14). Overall, there is a demonstrated influence of sex hormone levels on lipid levels, high-density lipoprotein (HDL) as well as low-density lipoprotein (LDL) in both women and men. There could be an even stronger contributing risk factor for AAA occurrence in women than men with respect to increased LDL (10). The challenge in understanding such an axis is the alterations in lipid levels at the menopausal transition in women, since women have increased LDL levels compared to their premenopausal state or men of the same age. Males with higher circulating testosterone concentrations had higher HDL cholesterol level, which decreases CVD risk (15,16). Which levels should be considered to influence the risk for disease development, and is the alterations in sex hormone levels to be considered as a surrogate for the influence of lipids?

Another example, smoking, has historically been more common in men (17). In the last two decades, women in Sweden have been found to smoke more than men, though the AAA ratio between the sexes is not changing. By using contemporary data for AAA prevalence in men diagnosed by the population-based screening program for all 65-year-old men in Sweden (participation rate at 75%), a true declining rate in men is found (18-20). This can possibly partly be due to the decreasing proportion of smokers nationally but should presumably then change the male:female ratio, which is not true (8,18-20). A recent paper again also confirms the even more deleterious association between smoking and AAA in women as compared to men (10). Altogether, smoking habits cannot be the sole explanation for the vast sex differences in distribution of AAA (21). Other variables, such as alcohol consumption, obesity and others have been indirectly explored in patient series and cannot explain the four- to six-fold increased risk for men in the population. The remaining area to explore is therefore true biological sex-differences, where sex hormones must be a central factor to consider (2,22). There is clearly an unknown impact by sex hormones of the pathophysiology of AAA, which apart from influencing the onset of disease could also influence the sex differences with respect to outcome. This summary includes a topical review of the studies published on patients with AAA with a focus on sex hormone analysis or reproductive history in humans.

Methods

The search for relevant publications in the field was restricted to articles in English. The abstract of the articles in English were extracted by a literature search in the databases PubMed and Web of Science. The final search date was 10th April 2023. The studies were identified by using different combinations of keywords and the following chosen terms: “abdominal aortic aneurysm(s)”, “sex differences”, “gender differences”, “(o)estrogens”, “androgens”, “17bestradiol”, “testosterone”, “sex hormones”, “natural history”, and “risk factors” [controlled vocabulary medical subject heading (MeSH) and free text].

In total, 701 articles were primarily found, and 295 articles were determined to be relevant for this review after careful reading of the abstract and reference list by the author. All animal-based studies were excluded from the analysis. The remaining 26 abstracts were evaluated. Only human reports were included based on person-specific data (charts, registry or hormone levels). Due to the low number of reports and heterogeneity of methodology used, no further attempts to perform a meta-analysis was performed. The reports are presented for women and men separately. There is a summary and tabulation of the remaining included relevant reports (seven publications in women and four in men; *Tables 1-3*).

Sex hormones develops as a contributing factor to consider

The distribution of abdominal aortic disease is always in a ratio

Table 1 Reports regarding reproductive history, including HRT published for women with AAA

Author, publication year	Study design	Sample size	Study aim	Reproductive history defines as menarche and menopause	HRT treatment	Major finding
Villard, 2011, (23)	Case control questionnaire based	140 women with AAA, 140 controls with PAD; controls certified non-AAA	Reproductive history in controls *vs.* AAA women reproductive history in women with smaller and larger AAA	Menarche: 13.5 years (PAD) *vs.* 13.5 years (small AAA) *vs.* 13.8 years (large AAA) (P=0.60) Menopause: 49.7 *vs.* 49.9 *vs.* 47.7 years (P=0.011) Reproductive time: 36.7 *vs.* 36.4 *vs.* 33.9 years (P=0.003)	Ever used: 49% *vs.* 42% *vs.* 32% (P=0.13)	Women with larger AAA more frequently had an earlier menopause and shorter reproductive time compared to women with PAD and smaller aneurysms
Nyrønning, 2019, (24)	Prospectively collected characteristics in HUNT trial Prospectively collected serum levels of estradiol	201 women with AAA and 19,823 controls (not certified AAA-free)	Effect of female sex hormones compared with other risk factors for AAA development. S-estradiol levels collected prior to AAA development (n=376)	Menarche 13.7 *vs.* 13.6 years (P=0.17) Menopause 48.7 *vs.* 49.4 years (P=0.15) Estradiol levels detectable in AAA patients 17% *vs.* 24% in controls (P=0.075)	Never user: 77% in AAA women *vs.* 71.5% in controls (P=0.11)	Strongest risk factor for AAA was smoking, occurrence of CVD and hypertension HRT showed a non-significant protective effect. Estradiol levels measurable in more controls than AAA women
Chou, 2022, (25)	Extracted from the WHI database including observational data and three clinical trials	1,125 women with AAA and 101,119 controls (not certified AAA-free)	Determine if premature menopause and early menarche influences the risk for AAA, and influence of smoking	Menarche and menopause not presented separately Reproductive time not presented separately for AAA and controls Premature menopause 11.9.% in AAA women *vs.* 9.4% in control cohort Not significant after multivariable adjustment	HRT usage not presented for groups	The combined effect of smoking and premature menopause with increased risk for AAA development indicates the need for further analysis in the area

HRT, hormone replacement therapy; AAA, abdominal aortic aneurysm; PAD, peripheral arterial disease; HUNT, Nord-Trøndelag Health Study; CVD, cardiovascular disease.

Table 2 Hormone replacement therapy and association with AAA in women, only studies in humans included

Author, publication year	Study design	Sample size	Study aim	Reproductive history	HRT treatment	Major finding
Hsia, 2004, (26)	RCT within the WHI	16,608 postmenopausal women. Definition of disease only including hospitalized for peripheral arterial disease; cases not specified	Effect on peripheral disease requiring hospitalization with estrogens and progestin *vs.* placebo	Not reported	Not reported in numbers Similar numbers of women with HRT suffered AAA (7 *vs.* 6) A non-significant higher risk for AAA in HRT group *vs.* placebo (HR 1.1)	No certified significant risk for AAA and HRT
Hsia, 2006, (27)	RCT with "Estrogen alone" *vs.* placebo	10,739 postmenopausal women with hysterectomy; cases not specified	Effect on disease development	Not reported	Not reported in numbers More women with HRT suffered AAA (14 *vs.* 6) A non-significant higher risk for AAA in HRT group *vs.* placebo (HR 2.40, 95% CI: 0.92–6.23)	No certified significant risk for AAA and HRT
Iribarren, 2007, (28)	Kaiser-permanent population, questionnaires, clinical and laboratory tests (28,29)	115 AAA women *vs.* 57,868 (490 AAA men and 46,945 controls)	Explore traditional and new risk factors for AAA	Not reported	19% HRT overall; nonsignificant protection with HRT in the multivariable model; 0.87 (95% CI: 0.55–1.37)	No certified protection for AAA with HRT
Lederle, 2008, (30)	Extracted from the WHI database including observational data and three clinical trials	184 AAA women *vs.* 161,808 controls	Assess association between risk factors and AAA events as repair or rupture	Not reported	HRT never user 62% AAA women 44% controls HRT current user in multivariable model and risk for AAA HR 0.48 (95% CI: 0.31–0.73)	Further studies will be needed to clarify the effect of hormone therapy on AAA. There are strong positive associations between age, smoking and AAA in women
Nyrønning, 2019, (24)	Prospectively collected characteristics in HUNT trial; prospectively collected serum levels of estradiol	201 AAA cases and 19,823 controls	See *Table 1*	See *Table 1*	HRT never user: 77% in AAA women *vs.* 71.5% in controls (P=0.11)	Strongest risk factor was smoking, CVD and hypertension. HRT showed a non-significant protective effect

AAA, abdominal aortic aneurysm; HRT, hormone replacement therapy; RCT, randomized controlled trial; WHI, Women's Health Initiative; HR, hazard ratio; CI, confidence interval; CVD, cardiovascular disease.

Table 3 Female and male sex hormone levels in men with AAA or without AAA, only including reports on humans

Author, publication year	Study design	Sample size	Study aim	Male sex hormones main findings	Female sex hormones main findings	Major finding
Yeap, 2010, (31)	Prospectively collected biobank within population-based screening program for men aged 65–83 years (questionnaires, laboratory tests)	262 men with AAA men and 3,358 controls without AAA	Association between male sex-hormone levels and risk for AAA measured by chemiluminescent immunoassays	AAA men had lower testosterone levels and higher LH levels than controls. Differences remained in multivariable analysis	Not included in study	Results reveals a significant and independent inverse association between circulating free testosterone and AAA
Villard, 2012, (32)	Prospectively collected pilot study	18 men with AAA; 36 women with AAA; 18 women with PAD	To investigate levels of established biomarkers for AAA in men and women, and to compare biomarker levels in women with and without AAAs	Not analyzed	Men with AAA had higher levels pf circulating estradiol than women (86.5 *vs.* 30.0 pmol/L, P<0.001)	The lower levels of estradiol in women with AAAs compared with men suggest that the possible protective effect of endogenous estrogen cannot be explained by a difference in circulating levels of estradiol
Villard, 2021, (33)	Prospectively collected biobank within population-based screening program for 65-year-old men (questionnaires, laboratory tests)	230 men with AAA and 222 controls without AAA	Association between male and female sex-hormone levels and risk for AAA measured by electrochemiluminescent immunoassay	AAA men had lower testosterone levels than controls, including more men with non-measurable levels. LH and SHBG similar. Differences did not remain in multivariable analysis	AAA men had higher progesterone and estradiol levels than controls. More controls had non-detectable levels of female sex-hormones. Strong association between progesterone levels and risk for AAA remain in multivariable analysis	The higher female sex hormone levels in men with AAA suggest an effect of sex hormones on aneurysm development. The association between progesterone and aortic diameter stresses the importance of focusing on this unconsidered female sex hormone on aneurysm formation
Ohlsson, 2022, (34)	Prospectively collected biobank within population-based screening program for 65-year-old men (questionnaires, laboratory tests)	147 men with AAA and 251 controls without AAA	Association between male and female sex-hormone levels and risk for AAA measured by high-performance sex steroid assay	AAA men had lower testosterone levels than controls, including more men with non-measurable levels. Differences did not remain in multivariable analysis	AAA men had lower progesterone and estradiol levels than controls. Strong association between low progesterone levels and risk for AAA occurrence remain in multivariable analysis	Measured by a high-performance sex steroid assay, progesterone and estradiol are inversely associated with AAA in men, independent of known risk factors

AAA, abdominal aortic aneurysm; LH, luteinizing hormone; PAD, peripheral arterial disease; SHBG, sex hormone-binding globulin.

of 3–6:1 in men *vs.* women, with a considerably lower mean age at diagnosis and development detected in men (1,10).

The apprehension of female sex as a protective risk factor for development of disease as well as the obvious delayed onset of disease, has intensified the quest for the female sex hormone as a protective underlying mechanism for disease development.

It is highly probable that the insight from the Women's Health Initiative (WHI) and other trials in cardiac disease was a trigger for such interesting studies (35-37). Few epidemiological or population-based studies have been performed in AAA patient groups, presumably mainly due to methodological challenges (mostly asymptomatic disease, slow progression, challenges in collecting reproductive history). The perspectives will be presented below from the large-scale population series to clinical series focused on sex hormones, finalizing with sex hormones analysis in aortic walls and some comments on the reported findings in animal models.

Sex hormones in women

The apprehension of female sex as a protective risk factor for AAA development has intensified the quest for the female sex hormone as a protective underlying mechanism for disease development. Few epidemiological or population-based studies have been performed, due to methodological challenges (2,22,38). Regarding sex hormones, one should discriminate between endogenous and exogenous female sex hormones. An overview of the published papers in the area reveals the paucity of knowledge and the contradictory findings (*Tables 1*,*2*; *Figure 1*).

Endogenous female sex hormones

Within other cardiovascular patient groups, premature menopause has been reported to increase the risk for earlier onset of events (36,39). It is also shown indirectly as a protective effect on longevity by having a late menopause (2,40). Interestingly, menarche, early or late, has not shown a similar clear association between development or risk for CVD as menopause, but more indirectly as a factor in the "reproductive time", that is, higher prolonged female sex hormone levels. In some reports, early menarche is associated with increased risk of diabetes and CVD. Later age at menopause and longer reproductive times have been associated with less risk for CVD, but the influence of smoking which lowers the "reproductive time" also influences CVD risk indirectly by influencing the hormonal axis (36,39,41).

This has been interpreted as a direct vascular effect especially by estradiol, both in the short and long term (40). Circulating estradiol will be considerably lower in the peri- and post-menopausal period, which accelerates the arteriosclerotic process. If higher endogenous female sex hormone levels would be protective for other CVDs, it could be postulated that this could contribute to the difference in AAA prevalence between the sexes as well. To explore if a life-span difference in the "reproductive time" (fertile period; length of time between ages at menarche and menopause) is different in women with AAA, a questionnaire-based investigation was performed in 2011 (23). The endogenous reproductive history was then explored for the first time for AAA patient groups. With consideration of the risk that earlier menopause can be triggered also by smoking, which can affect AAA development especially in women, a control group with similar smoking habits was chosen (41,42). The association with lower menopausal onset for smoker has been reported (43). The control group were women with peripheral arterial disease (PAD) and were certified to not have AAA by ultrasound (US) examinations (*Table 1*). Women with larger AAAs had an earlier menopause compared to non-AAA patients (47.7 *vs.* 49.9 years) (23). The data suggested that the reproductive time, i.e., lower menstruating period in a lifetime, could be interpreted as a surrogate for an overall shorter life-time period of lower levels of circulating estradiol.

There were not any further attempts to replicate this study, until 2022 (25). A WHI-based investigation did an identical analysis in a considerably larger cohort. Unfortunately, the "controls" were not US-examined, and therefore a degree of uncertainty about how many of the control populations had AAA remains. Although there are several draw-backs with WHI-based investigations, such as the lack of certified AAA cases and AAA-free controls [by US or computed tomography (CT)] leading to a large underestimation of the AAA prevalence, the report confirms again the importance of smoking on a woman's risk of developing AAA (25). Smoking is, in itself, such a strong contributor to a lower menopausal age, and it is difficult to separate the influence of smoking on AAA development or its action on disease development by altering the reproductive time in these women.

In the population-based Norwegian Nord-Trøndelag Health Study (HUNT) database, the association between

postmenopausal hormone therapy (HT) was also evaluated, as well as menarche and menopause were also analyzed (24). A non-significant lower menopausal age was detected (48.7 *vs.* 49.4 years, P=0.15) and a higher menarche age (13.7 *vs.* 13.6, P=0.15). Unfortunately, this database did not include the reproductive time individually for AAA patients *vs.* controls, since this was not the objective of the paper (*Tables 1*,*2*).

The hypothetically very appealing thought that the reproductive time, serving as a prolonged protection against AAA development by estradiol in premenopausal women, is still not scientifically proven, though the literature does indicate that this could be a factor to consider and include in all future population-based trials in women.

Exogenous female sex hormones

If the pilot trial on reproductive history published in 2011 was an indication that a lower circulating female sex hormone levels (a shorter individual reproductive time) would indicate an increased proportion of larger aneurysms, one could suspect that exogenous hormone replacement therapy could decrease the risk for development of AAA (23,32).

One could also replicate other reported knowledge regarding hormone replacement therapy for example in CVD patient groups to AAA (17,35,40). Could exogenous HT contribute with a protection of onset of disease? These explorations have predominantly been performed within larger other trials in the US (*Table 2*).

Interestingly, the three studies performed in the same WHI cohort from the US showed quite contradictory results (26,27,30). The investigation published in 2008, which identified 184 women with AAA, suggested a protective effect by HRT on AAA risk, in a population of 160,000 women (30). In a smaller subset of the WHI women, published earlier, they failed to demonstrate such association (2004 and 2006) (26,27). During the same time period one population-based study showed a trend, but non-significant protective effect by HRT on AAA risk, and as always smoking dominated as risk factor (*Table 2*) (28).

In an attempt to catch the temporal effects by HRT and AAA development a combined clinical registry-based and laboratory analysis was performed in Norway in 2019. This was the hitherto largest study within the field, with >200 women with AAA and >20,000 women in the baseline group as controls (24). Smoking, hypertension and heart disease have a strong correlation with AAA risk in women, but not HRT (n=201/20,024) (24) (*Tables 1*,*2*).

It is not confirmed that exogenous hormones protect against AAA development, but it is unlikely that it would hold negative effects for development of aneurysm disease.

It has never been clarified if female sex hormones, endogenous or exogenous, would influence rupture risk, growth of AAA or mortality in women with AAA with any higher degree of scientific certainty. The overarching methodological challenge is the study design with control populations without US-verified normal aortas as well as the recall bias for reproductive history outside parity.

Male and female sex hormones in men

Considering the relatively higher risk that men confer for aneurysm disease development earlier in life and their 3–6-fold higher risk overall, the lack of investigation in the area is astonishing (1). Historically, some attempts to explore the group of men with prostate cancer, with an iatrogenic induced hormonal imbalance of both estrogen and androgen has been published (29). Due to obvious methodological complexity, little can be extracted from this in order to certify the associations. Secondly, again it is highly probable that sex hormones influence individuals differently, and the phenotyping of AAA patient groups would probably contribute to a better understanding.

The first unique paper within the field already in 2010, reported lower levels of testosterone in men with AAA *vs.* controls (31) (*Table 3*). The second larger paper in the field also included female sex hormones and confirmed the above-mentioned association between lower testosterone and secondly higher levels of female sex hormones. It had been preceded by a smaller pilot study including estradiol measurements in women and men (32,33). These findings support those shown for other CVD patient groups; a low testosterone level is associated with more and earlier disease development (17,31) (*Table 3*, *Figure 1*).

This paper was followed by an analysis based not on the standard immunohistochemical analysis but using the highly scientific but non-standardized Mass spectroscopy test for hormonal analysis (34). This showed that men with AAA had a lower level of female sex hormones compared to controls. How these methodological challenges should be interpreted and used in clinical practice is not clear, but they highlight that this area needs further exploration.

One factor seldom addressed in population-based risk factor evaluations is prostate cancer treatment (29). In the above-mentioned study on screened men, with analysis of sex hormone levels, six men in the control group had been treated for prostate cancer, none of whom were

AAA patients (33). In the Australian study these were excluded (31). These groups are much too small to give any support for the analysis of such associations. Some reports have tried to explore these associations in larger cohorts but have failed to reach any sharp conclusions.

So, this question remains unanswered: is a subset of men more susceptible for aneurysmal disease due to deranged circulating sex hormone levels, either female or male? Few studies actually report on prostate cancer, detection or treatment in AAA populations, and vice versa, how is the risk of disease development influenced by prostate cancer treatment such as castration? (29). How is the risk for AAA expansion and rupture influenced by such risk? Would there be a long-term higher risk for AAA development due to lower circulating testosterone levels in analogue with the reported higher general CVD risk for these patients? Regarding the high general risk for middle-aged and elderly men to develop AAA, CVD and prostate cancer, the lack of knowledge based on cohort studies or registries is also somewhat astonishing, also when considering the large registries within cancer research that exist internationally (44). The growing area of cardio-oncology will certainly include these aspects more in the coming decade.

Wall analysis

There is a noticeable lack of investigations on the human aortic wall and sex hormone receptors with respect to sex difference, presumably due to the methodological challenges and scarcity of laboratory know-how (37). Sex hormones influence the composition of the wall with respect to elastin, collagen and probably also the vascular smooth muscle cell (VSMC). Estrogen lowers collagen deposition, but increases the elastin deposition, both contrasting the testosterone effect (45)

The estrogen receptor (ER) beta receptor is similarly expressed in human VSMC for men and women (46). In aortic aneurysm wall material, a higher expression of androgen receptor (AR) and lower expression of ERβ compared to normal aortic walls could mean that sex hormone vessel wall activity is associated with aneurysm development (47). These results are in accordance with the observed susceptibility to AAA formation in men and women with ERβ gene polymorphism (38).

Prior biomarker analysis of aneurysm patients show that women had higher plasma levels of matrix metalloproteinase 9 (MMP9) than men with equivalent aortic diameters (32).

There are three published reports regarding elastin and collagen in the aortic wall of women and men with AAA, with somewhat contradictory findings, but this is presumably due to methodological issues. The group from Austria showed low elastin and high collagen component in the wall under the thrombus in men compared to women, in contrast to higher elastin in men and similar collagen content in a Swedish study (48-50).

The contradictory findings in these unique but small studies suggest that more molecular and histological studies are called for in AAA and non-AAA populations in order to understand if the wall structure is truly different between the sexes, before and after onset of disease (48).

One of the most challenging issues is that wall samples are collected at the end stage of the aneurysm disease, optimal analysis regarding the influence of sex hormones and receptor activity would be performed in the early period of aneurysm development (2,22).

The lack of coherence between human and animal models

Studies of animal models for AAA development, growth and rupture have increased the general understanding of hormonal mechanisms and underlying sex differences in AAA (51-55). In general, endogenous and exogenous estrogens have protective effects on experimentally induced AAAs, with results differing dependent on the model under study (2,22).

It is problematic that animal models today still fail to include the postmenopausal aspects of biological sex differences (40,53). There are no models including the effect of the human menstrual cycle and menopausal transition phase on the aortic wall. Consequently, human studies are crucial to perform. Animal models with ovariectomy does not mimic menopause, since it suddenly eliminates all hormone activity, such as luteinizing hormone (LH), follicle-stimulating hormone (FSH) and progesterone/testosterone. In menopause, if not-surgically induced, the ovarian follicle diminishes over time.

The dominating risk for males to develop AAA, also at a younger age, led to the hypothesis testing and generation of different animal models that confirm that castration of male mice will reduce AAA development in angiotensin II-induced AAA models (22,53). Reduced growth rates and lower rupture rates in castrated male mice as well as studies showing increased disease development and growth by exogenous androgen substitution supported the hypothesis

that male sex hormones contribute to the pathological increased risk detected in men. Further refinement in animal models move towards identifying that the true carrier of the risk could be AR dysfunction rather than the circulating levels of male sex hormones that influence the risk in male mice. The ARs modulate the inflammatory responses by elevating IL-1α and possibly TGFβ1 (56).

The animal models have in later years also included other species, such as swine, which introduces a model which is somewhat more similar to human aneurysm formation based on a surgically induced elastase-based aneurysm infrarenally (57). These studies confirm the higher risk for increased aneurysm growth in animals with intact androgen levels as compared to females and castrated male swine (58). In fact, there is notably a pronounced lower growth in castrated *vs.* female swine. The study elegantly also reports on higher elastin degradation in intact male swine compared to lower in females and castrated specimens, and lower collagen levels overall in females. Estrogen levels were highest in females, but lowest in castrated males. Testosterone was highest in males, and lowest in females, no significant difference between castrated and un-castrated (57,58).

It is possible that the animal models for AAA development and rupture, although well designed and hypothesis generating, also has led the vascular community astray; since the models are very far from imitating AAA development in the aging population, men and women, smokers and non-smokers. Although evidence from animal models suggests a clear role for testosterone to promote AAA, there is little known about a role for endogenous or exogenous testosterone on human AAA, our reports as well as others, rather suggest that too low testosterone levels can be significant for CVD and AAA risk. Here, animal models stand in contrast with the association between low testosterone in human reports (31,33) (*Table 3*).

New perspectives

In a recent publication from a Dutch group the possible importance of FSH was stressed (59). The hormones FSH and LH are essential hormones that stimulate the function of ovaries in females and testis in males, contributing to a normal reproduction. These hormones are derived from the pituitary gland, not the reproductive organs, and increase in women after menopause (59). In three prior publications on men with AAA, LH has been investigated (31,33,34). Higher LH has been reported to be associated with increased risk for CVD and AAA (31,56). The authors suggest that increased FSH levels in women during a prolonged period could contribute with an increased AAA risk (59). As for all sex hormone circulating levels and AAA risk prediction, much remains to be explored before such an association could be confirmed.

Other factors to explore further are the differences between circulating sex hormone levels as compared to AR activity and also the different ERs. There is a vast lack of understanding on the effects of testosterone on CVD risk in men and women, for example, showing contradictory findings compared to the more simplified direct effects reported from mouse models (40).

New perspectives and understanding of disease development could also emerge from inclusion of patient groups with different hormone levels as compared to the average population, such as groups with women diagnosed with Turners syndrome, treated or not with estradiol or in transgender groups treated with sex hormones (60). The possible influence of lipid levels and lipoprotein(a) [Lp(a)] is also investigated and could be the target molecule in future trials (61). Associations between AAA onset and expansion with metformin treatment in diabetic or non-diabetic patients have not been analyzed with a sex and gender perspective (62). This could be essential to include in future randomized controlled trials (RCTs).

Conclusions

Vast sex differences regarding onset of disease, prevalence, eligibility, and treatment rates and outcomes regarding untreated and treated AAA patients are reported in the literature. The largest remaining key to understanding the basic sex and gender differences is to explore female and male sex hormones. This summary confirms the need for such explorations on all levels: molecular, temporal, registry-based and population-based in women and men. It also stresses the need to use the acquired knowledge obtained in animal models on presumed biological sex hormone wall differences and to apply this in translational research in humans. There is a need for collaborative networks in the field in order to succeed in large enough sample sizes in order to perform and succeed in such translational projects.

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Footnote

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