Gender Differences in Chronic Kidney Disease: Underpinnings and Therapeutic Implications

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Key Words

Compliance • Estrogen • Testosterone

Abstract

In nephrology, gender differences exist with regard to the epidemiology, evolution and prognosis of chronic kidney disease (CKD). In some cases, these differences run contrary to the general population trends. This review discusses such gender and sex disparities, including differing impact of traditional and novel risk factors, prescription patterns, differences in the responses to therapies, as well as hormonal factors, all of them potentially influencing propensity, progression and biochemical and psychological aspects of CKD. Through the integration of gender aspects in CKD research and management, we may be able not only to identify novel therapeutic targets but also improve existing treatment options.

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Introduction

Although physicians often are forced to generalize treatment options and medical care, we cannot neglect that men and women are physiologically different. These

differences are reflected in many varying aspects, with men and women diverging in the pathogenesis, clinical features and prognosis of many diseases. Moreover, diagnostic and therapeutic options are not necessarily identical. In recent years, gender-specific issues and how they influence health have increasingly attracted public attention, as well as interest from those working with health-care and prevention. We have learned that gender is of great relevance not only in research but also in day-to-day medical practice. A clear example lies in the higher incidence of cardiovascular disease in men than in women of similar age, and the menopause-associated increase in cardiovascular disease in women. Compelling data have indicated that sex differences in vascular biology are determined not only by differences in sex steroid levels, but also by sex-specific tissue and cellular differences that mediate sex-specific responses, as well as lifestyle differences [1, 2].

Gender and sex are often used indistinctly and incorrectly in the scientific literature. For consistency throughout this review, some definitions should be stated a priori: by 'sex' we refer to the property or quality by which organisms are classified as female or male on the basis of their reproductive organs and functions; 'gender' refers, on the other hand, to the way in which people perceive themselves and how they expect others to behave, and is

largely culturally determined. Therefore, sex-based differences are biologically based differences in men and women, whereas gender-based differences are distinctions shaped by the cultural and social environment (including differences in treatment prescriptions or disease perceptions) [3].

In nephrology, gender differences exist with regard to the epidemiology, evolution and prognosis of chronic kidney disease (CKD). In some cases, these differences run contrary to the general population trends. This review will present an overview of gender differences in CKD and also identify areas of overlap. Such gender dimorphism may involve differing impact of traditional risk factors and/or differences in the responses to therapies, as well as hormonal and genetic factors, all of them influencing propensity, progression and biochemical and psychological aspects of CKD. I will defend the thesis that through the integration of gender aspects in CKD research and management, we may be able not only to identify novel therapeutic targets but also improve existing treatment options. I will also try to show that there is still a gap between gender research and incorporation of the results into clinical practice.

Sex Differences in Progression to End-Stage Renal Disease

The progression rate of many renal diseases is affected by sex, and this is a topic excellently reviewed elsewhere in more detail [4]. The biggest meta-analysis to date, including more than 11,000 patients from 68 different studies, demonstrated that renal disease in women with polycystic kidney disease, IgA nephropathy, membranous glomerulopathy, and 'chronic renal disease of unknown aetiology' progresses at a slower rate than it does in blood pressure- and lipid levels-matched men with these diseases [5]. Recently, 2 additional population-based studies showed that men were associated with a worse CKD progression than women [6, 7]. In another study [8] with 840 non-diabetic patients, the loss of renal function was slower in women than in men, especially in women who were younger and predominantly premenopausal. However, the difference in renal disease progression was no longer significant after adjusting for baseline proteinuria, mean arterial pressure, and high-density lipoprotein levels. A few studies have also observed a worse renal prognosis in women [9], but the fact that most women in such analyses were postmenopausal may explain the divergent findings. Fur-

thermore, when the community-based PREVEND cohort [10] assessed which modifiable risk factors are associated with renal function decline, different results were found for men and women: in both men and women, plasma glucose and systolic blood pressure were independent risk predictors of renal function decline. Additionally in men, urinary albumin excretion was the strongest independent predictor of renal function decline, while low waist circumference and cholesterol/HDL ratio were associated with a better renal function outcome; in women, on the other hand, low triglycerides were associated with better renal prognosis. Consistent with this, a previous study also from PREVEND suggested that risk factors such as age, BMI and plasma glucose contributed to exacerbate the male progression to end-stage renal disease (ESRD) to a greater extent than for comparable women [11]. Additionally, a sex-dimorphic adipokine, adiponectin, was associated with renal function decline in men, but not in women [12, 13]. Altogether, there seem to be sex differences in the standard predictors of the decline in renal function, but little has been done with regard to whether these factors can be sex-specifically modified. Ahmed et al. [14] studied the renal plasma flow response in healthy humans to the nonspecific nitric oxide synthase inhibitor L-NAME. The authors observed that in men, the fall in renal plasma flow increased remarkably with increasing age, not observing such relationship in women. These results may suggest that any renal disease that interferes with nitric oxide production may, over time, cause existing kidney damage to progress more quickly in men relative to women.

Animal and experimental studies have tried to offer further mechanistic explanations for gender differences in disease progression. Besides the occurrence of sex specificities in kidney structure and glomerular hemodynamics [4], it has been suggested that the gender dimorphism of CKD progression may represent the effects of the interaction of circulating steroids with specific kidney receptors, an issue recently reviewed elsewhere [15]. Endogenous estrogens have in general been considered to have anti-fibrotic and anti-apoptotic effects on the kidney [16, 17]. Consequently, 17 β -estradiol administration in ovariectomized rats was shown to attenuate glomerulosclerosis and tubulointerstitial fibrosis [18], by protecting podocytes against injury through the upregulation of estrogen receptor β in an animal model of type-2 diabetes [19]. On the other hand, the faster kidney function decline in men has been attributed to the specific proapoptotic and profibrotic properties of andro-

gens [17, 20, 21]. Recently, testosterone administration was shown to promote the apoptosis of proximal tubule kidney cells by direct regulation of the c-Jun amino terminal kinase [22].

Thus, a direct extrapolation from the animal studies above described would suggest that exogenous estrogen administration may slow ESRD progression. However, clinical evidence in this regard is conflicting. An observational study on premenopausal women found a strong association between oral contraceptive use and macroalbuminuria [23]. Supporting this observation, postmenopausal women on hormone replacement therapy had a significantly reduced risk of albuminuria in comparison with those not on hormone therapies [24], and type-2 diabetic proteinuric hypertensive women who received hormone replacement therapy had less proteinuria and higher creatinine clearance [25]. However, evidence exists to the contrary, as a large case-controlled study found that oral contraceptive use in premenopausal women or estrogen replacement therapy in postmenopausal women were both associated with increased risk of microalbuminuria [26]. Also, a recent retrospective study suggested an independent dose-dependent association of oral estrogen use and loss of kidney function in elderly women [27]. Clearly, the implications of these studies need to be carefully considered in the context of their observational and, in the majority of the cases, retrospective nature [28]. It should also be noted that, in general, hormone replacement therapy is prescribed less frequently to postmenopausal ESRD patients than to the general population [29], possibly creating a selection and under-representation bias.

A final reflection is required regarding creatinine clearance-based formulas for estimation of renal function. Although the variable sex is included in some but not all such estimations, they do not differentiate an athletic woman or a small, lean man. In a retrospective study, the Modification of Diet in Renal Disease Study equation-estimated glomerular filtration rate (MDRD-eGFR) was suggested to differ between sexes and to vary with age more than the serum creatinine concentration does [30]. Thus, it is possible that incorrect GFR estimation may over/underestimate renal function, perhaps influencing results from large epidemiological studies (inferring misclassification of CKD stage) and/or clinical decisions such as medication prescription. These are personal speculations and the author is not aware of studies addressing this possible sex difference. However, the reported higher prevalence on CKD stages 3–5 in females [31], which flies in the face of ESRD statistics where men

are disproportionally affected (discussed below), may indeed depend on the limitations of the MDRD equation [31].

Cancellation of Female Survival Advantage during Dialysis

In the general population women have a longer life expectancy than men [32]. This may partly be explained by a lower prevalence of cardiovascular risk factors and events in women, who have also been found to have a longer life expectancy in populations with manifest atherosclerosis [33–36]. Likely because of the faster progression to ESRD in men, more men than women initiate dialysis [5, 10, 11]. Interestingly, men have somewhat higher eGFR at the start of dialysis compared to women [37–39], an issue that, although without apparent explanation, may link to gender differences in the physician's clinical judgment. However, once they start dialysis – and unlike in the general population – these women have as poor survival as men [40–42]. Interestingly, this cancelled survival advantage in ESRD women is not restored after transplantation [43]. This observation may be biased, however, by the fact that none of these studies differentiate between pre- and postmenopausal states. To the best of my knowledge, the reasons for this finding have not been fully investigated, while the explanation may increase our understanding of the causes and mechanisms of the increased mortality risk in ESRD. If so, they can potentially influence therapy.

An initial explanation for this cancellation of survival advantage would entitle the existence of sex differences to be included in risk factors upon dialysis initiation. In other words, a worse risk profile in woman starting dialysis would probably justify, to some extent, the similar mortality to men. However, evidence exists for the opposite, as we recently observed that incident dialysis men had a 2-fold higher prevalence of cardiovascular disease and were more often smokers [42]. This worse risk profile would agree with the fact that in incident hemodialysis patients, men are more likely to develop left-ventricular hypertrophy [44]. Also, male gender predisposes to a higher risk of cardiovascular calcification on hemodialysis [45], while secondary hyperparathyroidism and adynamic bone disease (both linked to higher cardiovascular risk) are also reported to be more prevalent in male patients on dialysis [46, 47]. However, and despite this evidence for a worse risk profile in men, both sexes die at an equal rate. Because, in

agreement with the general population, women on hemodialysis present with increased leukocyte telomere length (a determinant of cell survival linked to cardiovascular disease and mortality [48]) as compared to men [49], this may suggest that the increased risk of women is not the result of a long-life risk exposure but rather a relatively short-term consequence of the disease/therapy. Interestingly, whereas a negative correlation between age and telomere length was reported in female hemodialysis patients, no such association was present in males, whose reduced telomere lengths seem to be more closely associated with inflammation [49]. Such results are in accordance with those by Fitzpatrick et al. [48], showing that in the general population CRP was associated with reduced telomere length in aged males, but not in matched females.

A following natural step towards an explanation is exploring whether the association of risk factors with mortality differs between sexes. In other words, the presence of certain risk factors may be more detrimental for women than for men, and vice versa [50]. For instance, women on dialysis have a higher incidence of gout, which is associated with increased cardiovascular risk [51]. By studying sex-specific differences, we could report on an interaction between sex and diabetes in hemodialysis patients, mediating excess mortality in women with concurrent diabetes [42]. Such findings are in line with reports in non-renal populations suggesting that diabetic women are at a higher mortality risk than diabetic men [52–54]. Also, a previous report on type 2 diabetic ESRD patients aged ≥ 60 years showed a slightly increased mortality risk in women compared with men [41]. The exact mechanisms of this high risk in diabetic women remain unknown, but recent literature [52] has speculated that an increased prevalence of CVD risk factors in diabetic women combined with possible disparities in the level of medical care between the sexes may be important factors to explain such risk. Our study provides an example of the potential of assessing risk through a sex perspective, as it identifies a high-risk group of patients (diabetic ESRD women) that may warrant further investigation and benefit from intensified therapeutic care.

Another putative area of interest in explaining sex survival differences concerns the relation between inflammation, muscle mass and outcome [55]. Interestingly, this area of research consistently suggests certain protection from these derangements in women as compared to men. For instance, in the presence of inflammation (CRP >10 mg/l), men on dialysis seem to have a worse

survival as compared to women with the same condition [56]. Markers of muscle strength and muscle mass were poor outcome predictors in women [57], signs of muscle atrophy are more commonly observed in women [58], and genetic variations in IL-1 gene, putatively associated to increased systemic inflammation, have been associated with poor nutritional status in men, but not in women [59]. Anorexia is one of the most common and early symptoms in the development of protein-energy wasting in CKD (partly due to systemic inflammation) which contributes to increased mortality, higher hospitalization rates, worse quality of life and depression [60, 61]. A sex-dimorphic pattern has been observed at this level, as anorectic women on hemodialysis exhibited a more favorable inflammatory and nutritional status than anorectic men [62], suggesting that uremic men may be more prone than women to inflammation-induced anorexia. In agreement with this, several studies have found sex differences in the regulation of appetite [63]. For instance, both feeding behavior during the ovarian hormone cycle and decreased food intake have been associated with elevated estradiol levels [64–66]. Also, higher anorectic signals and earlier satiety have been reported in men suffering from chronic illnesses [67, 68], perhaps contributing to a different response pattern to anorexigenic diseases (such as heart failure and cancer) among men and women [63]. Connected to this, megestrol acetate, a novel anorexigenic agent used in hemodialysis patients, has its origin in the chemical structure of sex hormones.

Alterations in the Hypothalamic-Pituitary-Gonadal Axis

The kidney is a potent endocrine organ, a key modulator of endocrine function and an important target for hormonal action. Thus, alterations in signal-feedback mechanisms and in production, transport, metabolism, elimination and protein binding of hormones rather commonly occur in this disease. As a direct consequence, the uremic state is associated with abnormalities in the synthesis or action of many hormones, including those in the hypothalamic-pituitary-gonadal axis [69]. Some of the differences above mentioned, while no data exists as yet, may relate to deficiencies at this level. Young uremic women usually experience premature menopause, approximately 4.5 years earlier on average than their non-uremic counterparts [70], and postmenopausal women on dialysis also have abnormally low serum

estrogen levels [71]. Hypogonadism in women has been linked to sleep disorders, depression, urinary incontinence and, in the long term, to osteoporosis, impaired cognitive function and increased cardiovascular risk [70]. Interestingly, a recent report suggested that preeclampsia, a disorder of pregnancy characterized by elevated blood pressure and proteinuria, was a risk factor for the development of ESRD later in life [72], suggesting sex-specific factors that predispose to kidney failure. It is uncertain, however, whether these associations are explained by adverse effects of preeclampsia itself or by underlying risk factors that predispose women to both preeclampsia and later cardiovascular and renal disease. The atheroprotective effects of estrogen include alterations in serum lipids as well as modulation of bone health, adhesion molecules, pro-inflammatory cytokines and chemokines after endothelial injury, and may thereby protect blood vessels [73]. In this direction, persistent amenorrheic young women on dialysis had lower bone mineral density and evidence of increased bone resorption when compared with normal menstruating women on dialysis [74], and 1-year administration of the selective estrogen receptor modulator raloxifene, increased bone mineral density and decreased bone resorption markers and LDL-cholesterol values in postmenopausal hemodialysis women [75]. Also, genetic variations in the estrogen receptor α were associated with increased mortality in women starting dialysis [76]. Phenotypically, this group of patients presented with higher prevalence of protein-energy wasting, increased serum triglyceride, lower serum albumin and higher CRP concentrations [76]. Supporting this, megestrol acetate, an estrogen agonist, has successfully been used in ESRD patients as an effective therapy to treat protein-energy wasting [77, 78]. However, a recent hypothesis-generating review has suggested a possible increased risk of encapsulating peritoneal sclerosis (EPS) in women undergoing peritoneal dialysis [79]. Such hypothesis is based on experimental evidence suggesting that many cases of EPS have shown improvement with tamoxifen therapy, an antiestrogen compound [80]. Surprisingly, all except 1 of the larger EPS studies fail to report on sex distribution. The CKD literature counts with many EPS case reports and EPS case series, and clearly there is in those a higher prevalence of women, often premenopausal [79].

In men, I described above how some experimental studies associated testosterone with the faster male progression to ESRD. However, once the kidney function is lost, ESRD in men is characterized by a marked testos-

terone deficiency, with this condition present in approximately 50% of patients on dialysis and substantial number of others at risk of deficiency [81]. Testosterone deficiency in ESRD is the result of reduced prolactin clearance [82], inhibition of luteinizing hormone signaling [83] and perhaps increased inflammation [84]. The consequences of uremic testosterone deficiency on sexual dysfunction [82] and anemia [85] have been explored in a few studies, but little attention has been given to the growing body of evidence suggesting that testosterone deficiency may contribute to the onset and progression of cardiovascular disease [86] and to the pro-catabolic environment of uremia [87]. Recently, low endogenous testosterone values in male hemodialysis patients were associated with increased risk of death [84, 88], and novel links between low testosterone values in ESRD patients and bone disorders [89] or endothelial activation [90] have been suggested. Despite this, there is limited quantitative evidence regarding the prevalence and consequences of a clinical condition of testosterone deficiency in men with ESRD. Whether restoration of testosterone levels or supraphysiological administration would diminish cardiovascular risk or improve nutritional status requires further investigation. Encouragingly, androgen therapy in uremic patients has resulted in amelioration of muscle mass, improved nutritional status [91, 92] and attenuated anemia [85], all of which could indirectly improve patient's cardiovascular risk [93, 94].

Gender Differences in Dialysis Therapy, Adequacy and Patient Attitudes towards Disease

Discrepancies in the response to medical or dialysis care between sexes may also contribute to the observed cancellation of the female survival advantage. The analysis of this issue should start by possible gender differences in attitude towards the disease, directly referring to the compliance with the dialysis treatment, medication and lifestyle restrictions. Needless to say, poor compliance dramatically increases the death hazards of dialysis patients [95]. Patient compliance is, however, hard to measure. Traditionally, routine clinical parameters like blood urea nitrogen (indicating protein intake), serum potassium (indicating potassium intake) and interdialytic weight gain (reflecting fluid and sodium intake) have been used [96]. This 'objective' patient compliance can be compared with the patient's perceived compliance, also called self-efficacy, and defined as 'the belief that one is

capable of executing a given course of action'. In general, greater self-efficacy is thought to result in better compliance. In a Japanese study of chronic hemodialysis patients [97], the authors assessed gender differences in the relationship between self-efficacy and objective compliance, finding that female patients who had higher self-efficacy were less compliant. Interestingly, the association between self-efficacy and interdialytic weight gain was stronger for men than for women. There is evidence suggesting the existence of gender differences in stress and coping with the disease. Some studies suggest that women on dialysis feel higher stress than males in response to physical symptoms and disease status [98, 99]. Additionally, it seems that more men than women rely on avoidance (smoking, irregular overeating and drinking) as means of coping with the stress of their illness [100]. These differences may translate into systemic stress, increased risk and further poor compliance, all likely increasing death hazards. Supporting this, women undergoing hemodialysis have been reported to experience a higher prevalence of depressive symptoms and anxiety traits [101, 102].

Various reports exemplify the need to take the patient's sex into account when taking medical decisions. It is evident that men and women differ in their responses to drug treatment as a result of physiological differences such as body weight, height, body surface area, total body water, and the amount of extracellular and intracellular water, as well as differences in pharmacokinetics or pharmacodynamics [103]. However, treatments are often universal and we seldom vary dosage according to the patient's sex. When prescribing dialysis, for instance, an overestimation of adequacy in women as estimated by Kt/V has been suggested [104]. This overestimation is thought to result from sex limitations of the denominator of the formula (V , urea distribution volume) [105]. This issue may help to explain the surprising secondary observations from the HEMO study and others, which showed that women with $Kt/V \geq 1.53$ had a significantly lower mortality than those with $Kt/V \geq 1.16$, an effect opposite to that seen in comparable men [106–108]. In fact, when dialysis doses are recalculated in the HEMO study by applying body surface area instead of V , such differences are much reduced [109].

Other studies have also demonstrated that women more often receive short dialysis (<12 h/week) than men [110] or that women are less likely to receive arteriovenous fistulas (AVF) [111, 112]. Concerning the latter, some reports showing increased AVF failure in women [113, 114] may have created uncertainty on its use, despite

an equal number of studies showing no gender difference, or the opposite [115, 116]. A traditional fear of smaller vessels in women may have prevented some nephrologists from considering AVF in female patients. However, published data using duplex Doppler ultrasonography have demonstrated that vessel diameter does not differ among sexes [117]. Likely, surgical training is the key to both fistula placement and survival, as recent studies, almost a decade after the original observations, do not observe sex differences in AVF failure, perhaps reflecting an improvement in both technique and physician experience [118, 119]. Finally, sex differences exist with regard to hemoglobin and hematocrit due to factors such as sex hormones, iron utilization, and menstrual blood losses. [120]. Despite these differences in the general population, guidelines for the treatment of ESRD anemia suggest the same target for men and for women. Thus, it may not be surprising that previous studies have almost unanimously reported higher EPO resistance in women than in men. However, this resistance may be dependent upon menopause, since in premenopausal women, EPO resistance was explained by iron deficiency after menses [121].

Summary and Conclusions

Currently, scant attention is paid to the important biological and psychological differences between men and women with CKD. The author suggests that closer attention to sex and gender differences regarding progression of disease, risk factor inter-play, prescription patterns and patient attitudes towards the disease may help to elucidate novel pathways to benefit all CKD sufferers, as well as be of assistance in improving patient care. Clearly, there is a scarcity of information about the role of menopause in modifying risk profiling and the involvement of sex hormones in the disease. The fact that most CKD women are postmenopausal may have contributed to overlooking these issues. However, sex hormones still have a role after menopause and sex-specific tissue responses and cellular differences also exist [1].

Current knowledge shows us that CKD patients behave differently from the general population, lacking a female survival advantage during renal replacement therapy. When integrating the gender perspective in future studies in CKD patients, it is also important to keep in mind differences in medical care, including overestimation of dialysis dose. Undoubtedly, there is still plenty of

work to be done on this topic, but it is the hope of the author that this review work will awaken some interest in what makes CKD men and women differ, especially as a means to improve patient outcome.

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