

REVIEW OF LITERATURE / ПРЕГЛЕД ЛИТЕРАТУРЕ

Sex-specific differences in the epidemiology, progression, and outcomes of chronic kidney disease

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Higher prevalence of chronic kidney disease (CKD) in women than in men was reported all over the world. This difference could be partly explained by longer life expectancy and slower CKD progression rate in women. Potential factors associated with sex differences in CKD progression are as follows: difference in glomerular hemodynamic and the response to angiotensin II; sex hormones – estrogen has protective and testosterone deleterious effects on CKD progression; lifestyle. In most countries, the percentage of men is higher than that of women among incident and prevalent patients on hemodialysis (HD). In HD patients, the Kt/V index overestimates HD adequacy, secondary hyperparathyroidism is more common in women, and women require higher doses of erythropoiesis-stimulating agents for achieving and maintaining the hemoglobin target level. The survival of HD patients is equal for both sexes. In earlier years, an equal percentage of women and men started peritoneal dialysis, but in recent years, a higher percentage of women, especially at younger ages, start peritoneal dialysis. Initial peritoneal transport properties differ between men and women. A smaller percentage of women than men receive deceased donor kidneys, but women are more likely to be living kidney donors. Kidney allograft outcome depends on the sex and age of both the recipient and the donor. Cardiovascular diseases are the most common cause of death for renal replacement therapy patients of both sexes.

Although sex-specific differences have been described in CKD patients, the inequality of patients in access to medical care has not been found in most regions of the world.

Keywords: sex-specific differences; chronic kidney disease; prevalence; progression; renal replacement therapy

INTRODUCTION

Although many studies in humans and animals showed sex differences in kidney size, structure and function [1, 2], recommendations for the treatment of kidney diseases generally do not take into account the differences between the sexes. The National Institutes of Health has repeatedly mandated that women should be included in clinical trials, as well as in analysis and reporting of trial results [3].

World Kidney Day in 2018, titled “Kidneys and Women’s Health,” pointed out the significance of sex-specific differences in kidney diseases. Although this action was mostly aimed at the impact of kidney disease on women’s health, it also highlighted the importance of sex-sensitive prevention, detection and treatment of kidney disease. In recent years, the number of papers on the sex differences in kidney diseases, especially chronic kidney disease (CKD), has been increasing [4, 5, 6]. The significance of these studies is not only in discovering sex differences but in their impact on the development of guidelines in which the sex difference will be taken into account. It will enable more correct and effective treatment of kidney diseases.

This review presents the results of studies that dealt with the difference in the prevalence and progression of CKD between the sexes as

well as sex-specific differences in the epidemiology, response to the treatment, and outcome of patients on renal replacement therapy (RRT).

SEX-SPECIFIC DIFFERENCES IN THE EPIDEMIOLOGY OF CHRONIC KIDNEY DISEASE

During the most recent decades, an increase in the prevalence of CKD has been registered throughout the world. The Global Burden of Disease (GBD) study reports that the global all-age prevalence of CKD increased by 29.3%, while the global all-age mortality rate from CKD increased by 41.5% between 1990 and 2017 [7]. According to the data of the Institute for Public Health of Serbia, during the 2009–2018 period, the mortality rate from diseases of the genitourinary system increased from 28.23 to 33.81/100,000 inhabitants [8]. A secondary analysis of data collected in the 2013 National Health Survey showed that out of 14,587 respondents aged 15 years or older, 5.6% reported the presence of kidney disease. Among them, there was a higher proportion of females (61.2%), and female sex was selected as an independent predictor for the presence of kidney diseases [9]. A higher CKD prevalence in women than in men is reported in most

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countries, although there are differences in prevalence between individual countries. These differences could be explained by the existence of real differences in CKD prevalence, but also by differences in data collection, the use of different equation for estimating glomerular filtration rate (eGFR), but also due to the longer life expectancy and slower CKD progression rate in women [4, 10]. Although in most countries the prevalence of CKD is higher in women than in men, more men than women commence RRT for end-stage renal disease (ESRD) [4, 11]. GBD also reported higher prevalence of early stages of CKD in females but higher mortality in males, which could be a consequence of faster progression of CKD in males [7]. This prompted additional studies on sex-related differences of CKD progression and outcome.

SEX DIFFERENCES IN CHRONIC KIDNEY DISEASE PROGRESSION

Although two large meta-analyses have reported conflicting data on the sex difference in the progression of CKD [12, 13], the most subsequent studies reported slower decline of GFR with age, as well as slower CKD progression in women than in men [4, 14]. Thus, the study PREVENT, involving 5488 subjects, showed not only significant sex difference in the mean eGFR slope over time but also sex differences in the predictors of eGFR decline [15]. Similarly, a recent observational cohort study that analyzed data from the Swedish Renal Registry, including 26,279 incident CKD patients, found that women had slower CKD progression and mortality in comparison to men [10]. Although the factors and mechanisms underlying sex difference in CKD progression have not yet been fully elucidated, several factors have been pointed out (Table 1).

Table 1. Factors associated with sex-related differences in chronic kidney disease (CKD) progression

Sex-related difference in renal hemodynamics
Difference in renal vascular resistance
Difference in renal hemodynamic responses to angiotensin II
Effects of sex hormones on the following processes of importance for CKD progression
Collagen synthesis and matrix degradation
Transforming growth factor beta expression
Apoptosis of podocytes and proximal tubular cells
Nitric oxide syntheses
Oxidative stress
Sex-related differences in lifestyle
Tobacco use
Adherence to the prescribed diet
Hypertension control
Obesity

Factors associated with sex difference in the progression of chronic kidney disease

Difference in glomerular hemodynamics

Experimental studies showed lower whole-kidney GFR and renal plasma flow but higher renal vascular resistance in females than in male rats [16]. In humans, a difference

in the hemodynamic response to angiotensin II has been reported. Infusion of angiotensin II caused an increase in GFR and filtration fraction in men, while in women, GFR decreased and filtration fraction increased less than in men [17]. Neugarten et al. [12] considered that this angiotensin II response protects women from the increase in glomerular capillary pressure that occurs in the progression of CKD.

Sex hormones and CKD progression

Several experimental and clinical studies have shown that estrogen has protective and testosterone deleterious effects on CKD progression. Thus, testosterone increases and estrogen decreases the expression of TGF-beta, which consequently has an opposite effect on apoptosis of podocytes and proximal tubular cells, as well as on collagen synthesis [12]. The impact of sex hormones on oxidative stress is also significant. While testosterone inhibits antioxidant enzymes, estrogen has the opposite effect and reduces generation of superoxide anion [12]. Oxidative stress has a significant role in the progression of non-diabetic and diabetic kidney disease [18, 19]. Despite these favorable estrogen effects, it has been rarely used for slowing down the CKD progression and conflicting results have been obtained [12, 20].

Lifestyle and social factors

Differences in lifestyle between men and women could have an impact on CKD progression. Men are more likely to smoke, to keep their hypertension under control, they are less likely to adhere to the suggested dietary regimen, but women are more often obese [4, 12]. In our study conducted in collaboration with family doctors, we found that men come to the doctor's check-ups less often than women. However, among those with reduced kidney function, there was no difference in the frequency of the doctor's check-ups between men and women [21]. García et al. [6] described significant differences in risk factors for CKD between men and women, as well as sex-related social inequalities and access to medical care. However, these differences exist only in certain parts of the world, and our previous studies did not confirm that they exist in our region [21, 22].

SEX-RELATED DIFFERENCES AND RENAL REPLACEMENT THERAPY

The percentage of women who start RRT worldwide is lower than that of men. This is explained by the difference in the rate of CKD progression between women and men, as well as by the greater burden of men with risk factors for ESRD. The analysis of sex-specific differences in RRT incidence and prevalence in nine countries included in the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) Registry showed that in all analyzed countries the percentage of men was higher than that of women, both among incident and prevalent patients during the entire observed period from 1965 to 2015 [23].

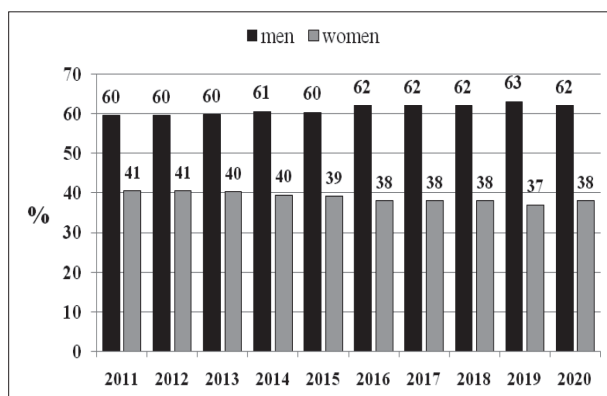


Figure 1. Percentage of men and women among prevalent patients on renal replacement therapy in Serbia in the period 2011–2020

Data from Serbia also showed a higher percentage of men among both incident and prevalent patients (Figure 1) [24]. The last annual report of the ERA-EDTA Registry shows that the percentage of men among incident RRT patients varies 52–74% and is similar among the prevalent patients. This registry also shows that hemodialysis (HD) is the most common method of RRT for ESRD patients [24].

Sex-specific differences in hemodialysis patients

Kt/V – index adequacy

HD adequacy is most often assessed using the Kt/V index, where V is the urea distribution volume, which is approximately equal to total body water. Using V as denominator in the formula results in an overestimation of HD adequacy in woman, as well as in all small patients. We and others have confirmed that Kt/V was significantly higher in women than in men, which can only be a consequence of overestimating the adequacy by the formula [11, 25]. Therefore, women and generally small patients on HD with the minimal recommended value of Kt/V may be underdialyzed. This encouraged many authors to search for a more adequate parameters for evaluating HD adequacy (body surface area, resting energy expenditure, bioelectrical resistance, etc.) [26].

Hemodialysis vascular access

Although arteriovenous fistula (AVF) is recommended as the optimal vascular access for HD, there are large regional differences in the percentage of patients who are dialyzed via AVF among incident (32–85%) as well as prevalent HD patients (49–92%) [27]. HD centers in Serbia can boast of a high percentage of patients who are dialyzed via AVF, although this percentage has decreased in several previous years from 92% to 77% [28]. However, sex difference in the vascular access has only recently been examined. Three large longitudinal studies from different parts of the world have reported that fewer women than men start HD with AVF [29, 30, 31]. This difference was tried to be explained by differences in the size and structure of blood vessels, underlying kidney disease, comorbidities, and social differences

between men and women [32]. In our retrospective longitudinal closed cohort study involving 441 incident HD patients from 28 HD centers in Serbia, no significant difference in vascular access between men and women was found [11].

Secondary hyperparathyroidism

Several studies have shown that in HD patients secondary hyperparathyroidism is more common and more aggressive in women than in men, although this difference varied depending on the region and patient age [11, 33, 34]. Although the cause of this difference is not yet fully explained, it is considered that estrogen increases the *PTH* gene expression and consecutively *PTH* secretion. In addition, a higher serum phosphate level was found in women than in men, so women require higher doses of phosphate binders [11, 33].

Anemia and erythropoiesis stimulating agent response

It is known that in the general population, women have lower hemoglobin level than men, and such a difference also exists in patients in all stages of CKD. The use of erythropoiesis-stimulating agents (ESA) enabled the effective treatment of anemia in CKD patients, but it was reported that women on maintenance HD require higher doses of ESA agents for achieving and maintaining the hemoglobin target level [12, 34, 35, 36]. As lower hemoglobin levels are associated with higher mortality [37, 38], the investigation of the causes of more severe anemia and weaker response to ESA in women requires further investigation.

Hemodialysis patient outcome

While in the general population women have a longer life expectancy than men, several studies have shown that survival of HD-dependent ESRD patients is equal for both sexes [29, 34]. Nevertheless, there are regional differences in male-to-female mortality rate among HD patients [34, 39]. Our study showed equal survival time between men and women and no difference in causes of death between the sexes [11]. Cardiovascular diseases are the most common cause of death in HD patients of both sexes, which is another difference as compared to the general population. Data on the change in the male-to-female mortality rate in HD patients over time are contradictory. We did not find that this ratio changed over five years [11], while analysis of the ERA-EDTA registry showed equal mortality of women and men only in the first months, and thereafter survival of women increased [23]. In contrast, a recent large retrospective study of HD patients from Australia and New Zealand for the period 1998–2018 showed that women have a higher risk of all-cause mortality in the first five years from the onset of HD, but not later [40].

Although we have shown certain differences between men and women on HD, it should be emphasized that the existence of inequality between the sexes has not been established [11]. Nevertheless, there are parts of the world where sex-related social inequalities as well as access to

medical care are described, which requires further efforts to overcome such differences [6].

Sex-specific difference in peritoneal dialysis

Peritoneal dialysis is insufficiently used globally, especially in low-income and lower-middle-income countries [41]. Also, there is not much data on the sex difference in peritoneal dialysis (PD). The United States Renal Data System reported that among incident patients on RRT, 86.1% were on HD and 11% were on PD [42]. Similarly, according to the ERA registry, among the incident patients, there were 82% on HD and 14% on PD [24]. Both of these registries show large regional variations in these percentages. A longitudinal study showed that both PD incidence and prevalence increased more in men than in women during the previous years [43].

The male-to-female ratio among incident PD patients changed over the time. While in earlier years there was no difference in the percentage of men and women starting PD [4], in recent years a higher percentage of women start PD [24, 44]. The male-to-female ratio also depends on age and younger women more often choose PD as the initial RRT [43].

The risk of all-cause death, noncardiovascular and non-infections death was found to be lower in women than in men on PD [39]. However, due to the negative effect of diabetes on death, which is greater in women than in men, women with diabetes have higher all-cause, noncardiovascular and noninfections mortality than males [39]. Cardiovascular diseases are the main and equally frequent cause of death in both sexes, but women had higher infection-specific mortality than men [39, 41].

Although many studies have addressed peritoneal transport, only recently has the sex impact on peritoneal transport been examined. It has been shown that at the beginning of PD treatment, women had lower dialysate-to-plasma ratio of creatinine at four-hour peritoneal equilibration test, better ultrafiltration ability and higher Kt/V [45]. The mechanism of these sex differences in peritoneal transport requires further elucidation.

Sex-specific differences in kidney transplantation

As there is a higher percentage of men on maintenance HD, a higher percentage of men receive deceased donor kidneys [5, 6]. This was confirmed by data from various regions of the world, but in recent studies a more detailed analysis of sex differences in kidney transplantation was examined.

Organ donation and sex-specific differences

Many studies have shown that women are more likely to be living kidney donors than men and women are also more often donors to their spouses [4, 46]. This was explained both by the higher proportion of women in the general population, traditional relationships in the family, and perhaps by the longer life of women. On the other hand, men more often suffer from diseases that make them unsuitable for donation [46, 47]. However, there are studies, including

ours, in which either no sex difference was found among donors or those differences changed over time [46, 48].

Sex-specific differences and kidney transplantation outcome

Kidney allograft outcome depends on the sex of the recipient, but even more so on the sex of the donor. Data on renal allograft outcome in recipients of a different sex are inconsistent. On the other hand, the survival of female donor kidney allografts is worse than that of male donor kidney allografts. In addition, a worse outcome has been described in male recipients of kidneys from female donors than in the reverse case [49]. However, it was recently described that this is not found in all age groups, because graft survival also depends on the recipient's age [5, 46, 47]. These differences in allograft outcome have been described as a consequence of the sex-specific differences in immune reactivity, the number of nephrons in the donor allograft, metabolic demands, hormonal differences, sensitization during pregnancy, differences in the post-transplant incidence of various diseases, psychosocial factors including compliance in the use of therapy, and controls [4, 5, 47]. All these factors should be taken into account when treating patients after transplantation in order to achieve the best possible outcome for both the recipient and the allograft.

CONCLUSION

A higher prevalence of CKD in women than in men was reported in most countries. This difference could be explained by longer life expectancy and slower CKD progression rate in women than in men. Differences in glomerular hemodynamics, sex hormones, and lifestyle are reported as factors associated with sex difference in the progression of CKD. Although the prevalence of CKD is higher in women than in men, more men than women have to start RRT in most countries. In HD patients, the Kt/V index overestimates HD adequacy, secondary hyperparathyroidism is more common in women than in men, and women require a higher dose of ESA to maintain the hemoglobin target level. Earlier, an equal percentage of women and men started PD, but in recent years, a higher percentage of women, especially at younger ages, start PD. Sex inequalities in kidney transplantation rates were reported: a smaller percentage of women than men receive deceased donor kidneys, but women are more likely to be living kidney donors than men. Kidney allograft outcome depends on the sex and age of the recipient, but also on the sex of the donor. Survival of men and women on RRT is similar and cardiovascular diseases are the most common cause of death. Although sex-specific differences in CKD patients were described in most regions of the world, the inequality of patients in access to medical care requires additional research.

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Разлике међу половима у епидемиологији, прогресији и исходу хроничне болести бубрега

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САЖЕТАК

Широм света забележена је већа преваленца хроничне болести бубрега (ХББ) код жена него код мушкараца. Ова разлика се објашњава дужим животним веком и споријом прогресијом ХББ код жена него код мушкараца. Сматра се да разлику у прогресији ХББ међу половима узрокују разлика у гломерулској хемодинамици и одговору на ангиотензин II; сексуални хормони – естроген има протективан, а тестостерон негативан утицај на прогресију ХББ; начин живота и навике. У већини земаља света више мушкараца него жена је међу инцидентним и превалентним болесницима који се лече редовним хемодијализама. Код болесника на хемодијализи индекс Kt/V прецењује адекватност хемодијализе, секундарни хиперпаратироидизам је чешћи код жена него код мушкараца, а жене захтевају примену већих доза стимулатора еритропоезе за постизање и одржавање циљних вредности хемоглобина. Раније је подједнак број жена и му-

шкараца започињао лечење перитонеумском дијализом, али последњих година већи проценат жена, посебно у млађим узрастима, бира перитонеумску дијализу као почетни метод лечења. Постоје разлике међу половима и у карактеристикама перитонеалног транспорта. Испитивање разлике међу половима у трансплантацији бубрега је показало да мањи проценат жена добија бубрег од можда мртве особе, али су жене чешће даваоци бубрега. Исход калема бубрега зависи од старости и пола и примаоца и даваоца. Кардиоваскуларне болести су најчешћи узрок смрти за болеснике који се лече методама за замену функције бубрега оба пола. Иако су откривене разлике међу половима у карактеристикама ХББ, у већини региона света није откривена неједнакост међу половима у приступу здравственој нези и лечењу. **Кључне речи:** разлике међу половима; хронична болест бубрега; преваленца; прогресија; методе за замену функције бубрега