THE ROLE OF GENDER IN CHRONIC KIDNEY DISEASE

Idan Goldberg,[1] *Ilan Krause[1,2]

1. Rabin Medical Center, Beilinson Campus, Petah Tikva, Israel.
2. Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel.
**Correspondence to ilank2@clalit.org.il*

Disclosure: The authors have declared no conflicts of interest.
Received: 09.02.16 **Accepted:** 16.03.16
Citation: EMJ. 2016;1[2]:58-64.

ABSTRACT

Chronic kidney disease (CKD) is a common disease worldwide and is associated with high rates of morbidity and mortality. This review discusses several aspects of the relationship between gender and CKD. While the prevalence of CKD tends to be higher in women, the disease is more severe in men, who also have a higher prevalence of end-stage renal disease. Most of the evidence in the current literature suggests a higher progression rate and mortality risk of CKD in men compared with women, except in post-menopausal women and diabetic patients. However, the decrease in glomerular filtration rate and the increase in the level of albuminuria are more prominent mortality risk factors among women. Sex hormones are thought to play a major role in the biological mechanisms associated with variability in CKD prevalence and characteristics between men and women. Animal studies have demonstrated the harmful influence of testosterone and protective influence of oestrogen on several biological processes that are involved in kidney injury. However, the role of sex hormones in explaining gender-related differences in CKD in humans has not yet been established. In summary, gender has an important influence on several aspects of CKD. Further research is needed to find additional gender-related characteristics in CKD and to identify the mechanisms of sexual dimorphism in CKD.

Keywords: Renal failure, glomerular filtration rate (GFR), sex hormones, end-stage renal disease (ESRD).

INTRODUCTION

Chronic kidney disease (CKD), defined by reduced estimated glomerular function rate (eGFR) and/or albuminuria levels, is a worldwide health problem due to the significant rate of morbidity and mortality associated with it. CKD is associated with an increased risk of all-cause mortality and cardiovascular mortality, and progression to end-stage renal disease (ESRD).[1] To establish better prevention strategies and enable early detection, much effort has been made to identify risk factors associated with CKD development. In this respect, various studies have been conducted to assess the effect of gender on the prevalence, progression, and characteristics of CKD. In this review, the main aspects of gender influence on CKD are discussed.

When addressing the difference between CKD in men and women, we must take note of the fact that eGFR (commonly used in studies) is based on a patient's sex, among other variables. The two most common equations for assessing eGFR, the MDRD (Modification of Diet in Renal Disease) and CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equations, both use sex as a variable. They are based on the assumption that for a given creatinine level, men will have higher levels of kidney function than women due to higher muscle mass and increased creatinine generation among men.[2] Thus, in the lack of studies using the gold standard measurement of glomerular filtration rate (GFR) (which is the measurement of inulin), results regarding gender influence on CKD are often biased due to the use of sex dependent equations.

PREVALENCE OF RENAL DISEASE AND END-STAGE RENAL DISEASE AMONG MEN AND WOMEN

Based on the most recent US Renal Data System (USRDS) annual data report,[3] the prevalence of chronic renal failure between the years 2007 and

2012 was higher in women (15.1%) than in men (12.1%). Women had a higher prevalence of high urinary albumin to creatinine ratio (9.6% versus 8.1% in men) and a higher prevalence of decreased GFR (7.6% versus 5.4% in men; decreased GFR is defined as eGFR <60 mL/min/1.73 m^2). It is important to mention that several previous studies have shown opposing data regarding this issue.[3-8] For example, a French epidemiologic study showed a higher incidence rate of chronic renal failure in men,[4] whereas a Chinese cross-sectional study[5] demonstrated similar CKD prevalence among men and women. There might be a geographic variability in the effect of gender on the prevalence of CKD, as shown in Table 1. Nonetheless, the incidence of ESRD appears to be higher in men than women. Based on the most recent US Renal Data System data,[3] 57.8% of the patients with a new onset ESRD were men. Furthermore, 56.3% of the prevalent dialysis patients were males, as were 59.7% of the kidney transplant recipients in the USA. Several other studies[9-11] found similar results, as shown in Table 2.

It should be noted that a natural decline in GFR with age is present in the healthy population.[12]

Table 1: Geographic variability in gender-associated prevalence of CKD.

Study	Year of publication	GFR assessment method	Percentage of women with CKD	Percentage of men with CKD	Sample size
Swedish National Study on Ageing and Care[6]	2014	Cystatin C	23.2	17.7	1,252
Swedish National Study on Ageing and Care[6]	2014	Creatinine	23.08	15.01	1,252
Ile de France district (France)[4]*	1996	Direct level of creatinine	0.0179	0.0348	10,660,000
USA NHANES population[3]	2007-2012	Lower estimated GFR and high urinary albumin creatinine ratio	15.1	12.1	No Data
Framingham (Massachusetts, USA)[7]	1999	Creatinine level (gender-specific cut-off)	8	8.7	6,233
Beijing (China)[5]	2008	Creatinine (using the MDRD equation), albuminuria	12.7	13.3	13,925
Middle and old-aged population of Beijing (China)[8]	2005	Creatinine (using the MDRD equation)	12.6	13.2	2,310

*The reported data is the annual incidence of CKD.
CKD: chronic kidney disease; GFR: glomerular filtration rate; MDRD: modification of diet in renal disease.

Table 2: Geographic variability in gender-associated cumulative incidence of ESRD.

Study	Year of publication	Percentage of women with ESRD	Percentage of men with ESRD	Sample size
Predictors of ESRD in Finland[9]	2010	0.27	0.46	25,821
Washington Country, Maryland[10]	2003	0.49	0.78	23,534
Japan[11]*	1999–2000	0.0189	0.032	No Data
USA white people[75]	2006	0.0139	0.0169	No Data
Norway[75]	2006	0.0036	0.007	No Data

*The reported data is the incidence of CKD (but not cumulative incidence).
ESRD: end-stage renal disease.

In a study which used the gold standard method for assessing GFR, a significant decrease in GFR with age among men, but not among women, was observed.[13] Furthermore, research from India showed a significantly higher mean eGFR among women aged 41–45 years, yet no significant difference between men and women in the 20–30 or 30–40 year age groups.[14] In contrast, in an Israeli longitudinal study[12] that assessed the natural rate of decline in renal function with age, no significant effect of gender on the natural decline of GFR with age was observed.

THE INFLUENCE OF GENDER ON DISEASE PROGRESSION

Though the prevalence of chronic renal failure may be higher in women, the incidence of ESRD seems to be higher in men, indicating that the progression rate of renal disease may be faster in men than women. Though the literature regarding this issue is conflicting and inconclusive, most studies support this assumption.

In a large meta-analysis published in 2000,[15] a significant correlation between male gender and disease progression of IgA nephropathy, membranous nephropathy, autosomal dominant polycystic disease, and 'chronic renal disease of unknown aetiology' was demonstrated. In addition, a Swedish cohort study[16] found that the male sex is associated with a greater risk of future need of renal replacement therapy among patients with chronic renal failure, in comparison with the female sex. In another study,[17] which examined the variation in GFR among patients with CKD Stage 3, a more rapid decline in GFR in men was demonstrated. Similar findings were observed in a large cohort of patients with CKD Stage 4.[18]

A smaller study performed on participants of the MDRD study[19] indicated a slower mean GFR decline in women compared with men, particularly among younger women. However, the association between gender and the rate of GFR decline became non-significant after adjusting for differences in blood pressure, proteinuria, and high-density lipoprotein (HDL) cholesterol. In this study, women had different renal diagnoses, less proteinuria, and lower serum creatinine levels for a given GFR compared with men. Conflicting results were found in a large meta-analysis performed on a database of patients enrolled in a randomised clinical trial for evaluating the efficacy of ACE (angiotensin-converting-enzyme) inhibitors in slowing renal disease progression,[20] in which a similar rate of progression in men and women was observed. Further, adjustment for other factors which affect the rate of renal progression suggested that progression may be faster in women. However, most of the female participants were of post-menopausal age, and therefore these findings may not extend to younger women. In a large cohort of 24,682 patients aged ≥50 years,[21] female sex was a risk factor for developing ESRD (hazard ratio: 1.48); most of the women in this study were also of post-menopausal age. The authors suggest that as the prevalence of cardiovascular mortality increases in both men and CKD patients, mortality in men might be higher occurring before the development of ESRD. A large meta-analysis performed on a global consortium[22] did not show a gender-related difference of eGFR with the risk of developing ESRD. For specific values of urinary albumin creatinine ratio, women showed a slightly higher risk of developing ESRD, compared with men. Results were obtained from a pooled analysis of 13 CKD cohorts containing over 38,000 participants.

The effect of gender on diabetic renal disease is much more debatable. Whilst a number of studies show that male gender is a risk factor for diabetic kidney disease (DKD),[23-25] others demonstrate that women are at higher risk of developing the disorder,[26,27] and some found no significant difference between men and women in terms of risk.[28,29] Recent research, which was designed to assess the influence of gender on the incidence of CKD among diabetic patients, concluded that diabetic women had a significantly higher incidence of CKD.[30] Furthermore, diabetic women had a higher (but not significant) incidence of microalbuminuria. This study included both Type 1 and Type 2 diabetic patients. In another study, which was conducted using the Pathways Study database, women had a similar prevalence of DKD in comparison with men, but had an increased prevalence of advanced DKD.[31]

In conclusion, current evidence regarding the effect of gender on DKD is contradictory, though it seems that a protective role of female sex on the kidney is lost in the case of DKD. One reason for this finding might be an imbalance in sex hormones associated with diabetes.[32]

GENDER ASPECTS REGARDING MORTALITY

Several studies have shown a reduced risk of mortality among women with CKD, compared with men.[17,33,34] Among CKD patients, the most common causes of death were cardiovascular disease, cancer, and infections.[34] In a large meta-analysis performed on a global consortium of over 2 million participants,[22] risks of all-cause mortality and cardiovascular-related mortality were higher among men for all levels of eGFR and for all levels of albuminuria. However, among participants with lower values of eGFR and participants with higher levels of albuminuria, the elevation in mortality risk was steeper for women. Thus, changes in GFR and albuminuria levels seem to be more significant risk factors for mortality (all-cause and cardiovascular-related mortality) in women. The similarity in the risk of developing ESRD for a given eGFR and level of albuminuria in both sexes leads us to speculate that the stronger correlation found between renal function and mortality among women was not due to renal disease-related mortality. It might reflect a higher risk of non-kidney disease mortality. Other specific risk factors might contribute to the higher risk of cardiovascular mortality among women with low GFR. These include hypertension, serum glucose level, serum lipids (total cholesterol level, low-density lipoprotein [LDL], triglycerides), and more. Further prospective studies are needed for evaluating these risk factors in large cohorts.

THE INFLUENCE OF GENDER ON OTHER RISK FACTORS FOR DEVELOPING CHRONIC KIDNEY DISEASE

Several risk factors for developing CKD among healthy people have been defined. Hypertension, diabetes, and cardiovascular disease are considered the most important risk factors for CKD. Other considerable risk factors for CKD are hyperlipidaemia, obesity, metabolic syndrome, and smoking.[35] Elevated levels of C-reactive protein[36] and of homocysteine[37] were both found to be independent risk factors for the development of CKD.

The effect of gender on these risk factors has also been examined. Several studies have shown that obesity (high body mass index) is a risk factor for developing CKD among women but not among men.[38,39] Other studies have yielded the opposite results.[40,41] Lately, it has been shown that the correlation between homocysteine and CKD is similar in men and women, in contrast to the results of a previous Japanese study in which elevated homocysteine was a risk factor for CKD only in women.[42] An Italian study[43] demonstrated gender differences regarding recognised risk factors for CKD: men had a higher prevalence of overweightness, having a higher waist circumference, and a higher blood pressure, whereas women had a higher prevalence of haematuria and leukocyturia, which are early manifestations of CKD.

PROTECTIVE AND PATHOGENIC MECHANISMS

Many possible mechanisms for the protective effect of female gender on CKD patients have been suggested. These include gender differences in kidney anatomy, kidney haemodynamic stress response, effect of sex hormones, diet, lipid metabolism, and blood pressure.[44,45] Anatomically, the kidney is usually larger in men, due to a larger body surface area. Some studies have shown a smaller number of glomeruli in female kidneys.[44] The haemodynamic stress response of the kidney differs between men and women; men may develop higher filtration fraction in response to angiotensin II infusion.[46] During hyperglycaemia, women exhibited a reduction in renal blood flow and an increase in renal vascular resistance and filtration fraction, whereas males exhibited no significant renal haemodynamic changes.[47] These findings may explain the lack of renal protection among diabetic women.

Lifestyle differences between men and women has been suggested as another possible explanation for the influence of gender on CKD. A high protein and high caloric dietary intake, which characterises men more than women, is associated with the development and the progression of kidney disease. High levels of LDL, triglycerides, and uric acid, and low levels of HDL are associated with accelerated kidney disease progression.[48] These trends are more common in men, and are influenced by nutrition and lifestyle.

The role of sex hormones in the pathogenesis of renal injury has gained a lot of attention. Several animal studies demonstrate a harmful influence of testosterone and protective influence of oestrogen on processes involved in kidney injury.[49] Testosterone induces podocyte apoptosis

(playing an important role in the development of glomerulosclerosis),[50] and TGF-β1 expression[51] (which is connected to tissue fibrosis), while oestradiol inhibits these processes.[52,53] It was demonstrated that testosterone induces proximal tubular cell apoptosis in human cells *in vitro*.[54] In addition, oestradiol has a direct influence on mesangial cells, decreasing extracellular matrix production and glomerulosclerosis.[44]

Nitric oxide (NO) synthase activity is also influenced by sex hormones. For example, oestrogen depletion has been associated with a decrease in the level of NO synthesis (endothelial and inducible NO synthase) in the kidney medulla.[55] Another study found an age-dependent reduction in NO synthase activity in the kidney cortex of male rats,[56] but not in female rats. Generally, NO synthase inhibition is associated with renal injury.[57] Recent animal studies have shown a protective role of NO in acute kidney injury.[58,59] However, there is some evidence of malicious influence of NO on kidney disease.[60] Thus, the role of NO in renal injury is complex as it varies depending on cell type and NO isoform. Additional influences of sex hormones on key factors in kidney injury have been noted: the renin–angiotensin system is induced by testosterone and inhibited by oestrogen; oestradiol inhibits the synthesis of endothelin, as well as its vasoconstrictor and inflammatory effects;[44] oestrogen also plays a role in decreasing kidney oxidative stress by suppressing NADPH oxidase activity.[61]

To summarise, various animal studies have shown that testosterone is associated with a rapid progression of kidney injury by several mechanisms. This could explain the faster progression rate of CKD among men compared with women. However, extrapolation of these findings to the human kidney is problematic. Testosterone levels in men, for example, decrease as kidney disease worsens.[62,63] Advanced CKD is associated with lower levels of testosterone, prolactin, and anti-Müllerian hormone,[64] as well as higher levels of gonadotropin. Some evidence suggests that testosterone has a protective role on the kidneys.[65] Androgen deprivation therapy, a treatment for advanced prostate cancer, is associated with an increased risk of acute kidney injury.[66] In a pig model, testosterone induced renal blood flow by enhancing NO production.[67] It has been shown that low testosterone levels in CKD in men can predict mortality.[68] Testosterone deficiency is associated with several cardiovascular risk factors, including metabolic syndrome, diabetes, hypertension, obesity, and atherosclerosis.[69] Thus, the decrease in levels of male androgens among CKD patients might play a role in the higher cardiovascular mortality rate among men with CKD.[63]

As mentioned previously, according to many animal studies, oestrogen might have a protective role on the kidney. In humans, the higher risk of CKD progression among post-menopausal women (concluded from the fact that studies using post-menopausal women did not show a higher progression rate of CKD in men)[20,21] supports the protective role of oestrogen. We would expect that hormonal therapy (either hormone replacement therapy in post-menopausal women or contraceptive use in pre-menopausal women) would improve kidney function. Clinical studies that examined this assumption yielded opposing results. Several demonstrated that post-menopausal hormonal replacement therapy was associated with a lower risk of albuminuria and a higher creatinine clearance.[70,71] In contrast, one study[72] showed a dose related association of post-menopausal oestrogen replacement therapy with loss of kidney function, whilst another[73] found that oral contraceptives are associated with a development of macroalbuminuria among Type 1 diabetic patients. Furthermore, a case report study performed on historical data found that the use of oral contraceptives and hormone replacement therapy is associated with increased risk of microalbuminuria.[74]

CONCLUSIONS

Despite conflicting data regarding the influence of gender on CKD, some conclusions can be made. The prevalence of CKD tends to be higher in women, whereas the disease in men is more severe. Much of the evidence in the current literature indicates a higher progression rate of CKD in men, with the exception of post-menopausal women and diabetic patients. Mortality rate in patients with CKD is higher among men. The findings of Nitsch et al.[22] demonstrate that as kidney disease progresses in women, the elevation in mortality risk increases. This effect has not been shown in men, and further research is needed to understand the role of gender in the association between renal disease severity and mortality.

It seems that the influence of sex hormones on several biological processes involved in kidney injury plays a major role in creating gender differences in CKD; many animal and *in vitro* studies support this assumption. However, the same role has not been demonstrated in human-based research, and numerous studies refute this theory. In our opinion, as the level of sex hormones is influenced by several variables (diseases, medications, age, etc.) in addition to gender itself, it is difficult to extrapolate the findings from animal studies to the human population. Further research is therefore needed in this area.

REFERENCES

1. Foley RN et al. Chronic kidney disease and the risk for cardiovascular disease, renal replacement, and death in the United States Medicare population, 1998 to 1999. J Am Soc Nephrol. 2005;16(2):489-95.

2. Pounds LL, Teodorescu VJ. Chronic kidney disease and dialysis access in women. J Vasc Surg. 2013;57(4 Suppl): 49-53S.

3. United States Renal Data System. 2015 USRDS annual data report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. 2015. Available at: http://www.usrds.org/adr.aspx. Last accessed: 9 February 2016.

4. Jungers P et al. Age and gender-related incidence of chronic renal failure in a French urban area: a prospective epidemiologic study. Nephrol Dial Transplant. 1996;11(8):1542-6.

5. Zhang L et al. Prevalence and factors associated with CKD: a population study from Beijing. Am J of Kidney Dis. 2008;51(3):373-84.

6. Werner KB et al. Male sex and vascular risk factors affect cystatin C-derived renal function in older people without diabetes or overt vascular disease. Age Ageing. 2014;43(3):411-7.

7. Culleton BF et al. Cardiovascular disease and mortality in a community-based cohort with mild renal insufficiency. Kidney Int. 1999;56(6):2214-9.

8. Li ZY et al. Prevalence of chronic kidney disease in a middle and old-aged population of Beijing. Clin Chim Acta. 2006;366(1):209-15.

9. Kastarinen M et al. Risk factors for end-stage renal disease in a community-based population: 26-year follow-up of 25 821 men and women in eastern Finland. J Intern Med. 2010;267(6):612-20.

10. Haroun MK et al. Risk factors for chronic kidney disease: a prospective study of 23,534 men and women in Washington County, Maryland. J Am Soc Nephrol. 2003;14(11):2934-41.

11. Wakai K et al. Trends in incidence of end-stage renal disease in Japan, 1983–2000: age-adjusted and age-specific rates by gender and cause. Nephrol Dial Transplant. 2004;19(8):2044-52.

12. Cohen E et al. A longitudinal assessment of the natural rate of decline in renal function with age. J Nephrol. 2014;27(6):635-41.

13. Berg UB. Differences in decline in GFR with age between males and females. Reference data on clearances of inulin and PAH in potential kidney donors. Nephrol Dial Transplant. 2006;21(9):2577-82.

14. Barai S et al. Do healthy potential kidney donors in India have an average glomerular filtration rate of 81.4 ml/min? Nephron Physiol. 2005;101(1):21-6.

15. Neugarten J et al. Effect of gender on the progression of nondiabetic renal disease a meta-analysis. J Am Soc Nephrol. 2000;11(2):319-29.

16. Evans M et al. The natural history of chronic renal failure: results from an unselected, population-based, inception cohort in Sweden. Am J of Kidney Dis. 2005;46(5):863-70.

17. Eriksen BO, Ingebretsen OC. The progression of chronic kidney disease: a 10-year population-based study of the effects of gender and age. Kidney Int. 2006;69(2):375-82.

18. Levin A et al. Variability and risk factors for kidney disease progression and death following attainment of stage 4 CKD in a referred cohort. Am J Kidney Dis. 2008;52(4):661-71.

19. Coggins CH et al. Differences between women and men with chronic renal disease. Nephrol Dial Transplant. 1998;13(6):1430-7.

20. Jafar TH et al. The rate of progression of renal disease may not be slower in women compared with men: a patient-level meta-analysis. Nephrol Dial Transplant. 2003;18(10):2047-53.

21. Van Pottelbergh G et al. The evolution of renal function and the incidence of end-stage renal disease in patients aged ≥50 year. Nephrol Dial Transplant. 2012;27(6):2297-303.

22. Nitsch D et al. Associations of estimated glomerular filtration rate and albuminuria with mortality and renal failure by sex: a meta-analysis. BMJ. 2013;f324.

23. Gall MA et al. Risk factors for development of incipient and overt diabetic nephropathy in patients with non-insulin dependent diabetes mellitus: prospective, observational study. BMJ. 1997;314(7083):783.

24. Ravid M et al. Main risk factors for nephropathy in type 2 diabetes mellitus are plasma cholesterol levels, mean blood pressure, and hyperglycemia. Arch Intern Med. 1998;158(9):998-1004.

25. Jacobsen P et al. Progression of diabetic nephropathy in normotensive type 1 diabetic patients. Kidney Int. 1999;56:S101-5.

26. Laron-Kenet T et al. Mortality of patients with childhood onset (0–17 years) Type I diabetes in Israel: a population-based study. Diabetologia. 2001;44(Suppl 3):B81-6.

27. Zoppini G et al. Higher HDL cholesterol levels are associated with a lower incidence of chronic kidney disease in patients with type 2 diabetes. Nutr Metab Cardiovasc Dis. 2009;19(8):580-6.

28. Monti MC et al. Familial risk factors for microvascular complications and differential male-female risk in a large cohort of American families with type 1 diabetes. J Clin Endocrinol Metab. 2007;92(12):4650-5.

29. Rossing P et al. Risk factors for development of incipient and overt diabetic nephropathy in type 1 diabetic patients a 10-year prospective observational study. Diabetes Care. 2002;25(5):859-64.

30. Yu MK et al. Associations between sex and incident chronic kidney disease in a prospective diabetic cohort. Nephrology. 2015;20(7):451-8.

31. Yu MK et al. Risk factor, age and sex differences in chronic kidney disease prevalence in a diabetic cohort: the pathways study. Am J Nephrol. 2012;36(3):245-51.

32. Maric C. Sex, diabetes and the kidney. Am J Physiol Renal Physiol. 2009;296(4):F680-8.

33. Roderick PJ et al. CKD and mortality risk in older people: a community-based population study in the United Kingdom. Am J Kidney Dis. 2009;53(6):950-60.

34. John R et al. Unreferred chronic

kidney disease: a longitudinal study. Am J Kidney Dis. 2004;43(5):825-35.

35. Levey AS et al. Chronic kidney disease as a global public health problem: approaches and initiatives-a position statement from kidney disease improving global outcomes. Kidney Int. 2007;72(3):247-59.

36. Kugler E et al. C reactive protein and long-term risk for chronic kidney disease: a historical prospective study. J Nephrol. 2014;28(3):321-7.

37. Levi A et al. Elevated serum homocysteine is a predictor of accelerated decline in renal function and chronic kidney disease: A historical prospective study. Eur J Intern Med. 2014;25(10):951-5.

38. Cohen E et al. Association between the body mass index and chronic kidney disease in men and women. A population-based study from Israel. Nephrol Dial Transplant. 2013;28(Suppl 4):iv130-5.

39. Komura H et al. Gender difference in relationship between body mass index and development of chronic kidney disease. BMC Res Notes. 2013;6(1):463.

40. Shankar A et al. Association between body mass index and chronic kidney disease in men and women: population-based study of Malay adults in Singapore. Nephrol Dial Transplant. 2008;23(6): 1910-8.

41. Iseki K et al. Body mass index and the risk of development of end-stage renal disease in a screened cohort. Kidney Int. 2004;65(5):1870-6.

42. Ninomoya T et al. Hyperhomocysteinemia and the development of chronic kidney disease in a general population: the Hisayama study. Am J Kidney Dis. 2004;44(3):437-45.

43. Fabbian F et al. Risk factors for renal disease and urinary abnormalities in men and women: data from the world kidney day in the province of Ferrara, Italy. Ren Fail. 2013;35(4):440-5.

44. Neugarten J, Golestaneh L. Gender and the prevalence and progression of renal disease. Adv Chronic Kidney D. 2013;20(5):390-5.

45. Silbiger S, Neugarten J. Gender and human chronic renal disease. Gend Med. 2008;5:S3-S10.

46. Miller JA et al. Impact of gender on renal response to angiotensin II. Kidney Int. 1999;55(1):278-85.

47. Cherney DZ et al. Gender differences in renal responses to hyperglycemia and angiotensin-converting enzyme inhibition in diabetes. Kidney Int. 2005;68(4):1 722-8.

48. Kummer S al. The influence of gender and sexual hormones on incidence and outcome of chronic kidney disease. Pediatr Nephrol. 2012;27(8):1213-9.

49. Sandberg K. Mechanisms underlying sex differences in progressive renal disease. Gend Med. 2008;5(1):10-23.

50. Doublier S et al. Testosterone and 17β-estradiol have opposite effects on podocyte apoptosis that precedes glomerulosclerosis in female estrogen receptor knockout mice. Kidney Int. 2011;79(4):404-13.

51. Elliot SJ et al. Gender-specific effects of endogenous testosterone: female α-estrogen receptor-deficient C57Bl/6J mice develop glomerulosclerosis. Kidney Int. 2007;72(4):464-72.

52. Zdunek M et al. Protein kinase CK2 mediates TGF-b1-stimulated type IV collagen gene transcription and its reversal by estradiol. Kidney Int. 2001;60(6):2097-108.

53. Negulescu O et al. Estradiol reverses TGF-b1-induced mesangial cell apoptosis by a casein kinase 2-dependent mechanism. Kidney Int. 2002;62(6): 1989-98.

54. Verzola D et al. Androgen-mediated apoptosis of kidney tubule cells: role of c-Jun amino terminal kinase. Biochem Biophys Res Commun. 2009;387(3): 531-6.

55. Maric C et al. Age-related renal disease in female Dahl salt-sensitive rats is attenuated with 17^2-estradiol supplementation by modulating nitric oxide synthase expression. Gend Med. 2008;5(2):147-59.

56. Baylis C. Sexual dimorphism in the aging kidney: differences in the nitric oxide system. Nat Rev Nephrol. 2009;5(7):384-96.

57. Zatz R, Baylis C. Chronic nitric oxide inhibition model six years on. Hypertension. 1998;32(6):958-64.

58. Declèves AÉ et al. Protective effect of nitric oxide in aristolochic acid-induced toxic acute kidney injury: an old friend with new assets. Exp Physiol. 2016;101(1):193-206.

59. Koul V et al. Investigation of the role of nitric oxide/soluble guanylyl cyclase pathway in ascorbic acid-mediated protection against acute kidney injury in rats. Mol Cell Biochem. 2015:406(1-2):1-7.

60. Goligorsky MS, Noiri E. Duality of nitric oxide in acute renal injury. Semin Nephrol. 1999;19(3):263-71.

61. Ji H et al. Female protection in progressive renal disease is associated with estradiol attenuation of superoxide production. Gend Med. 2007;4(1):56-71.

62. Hylander B, Lehtihet M. Testosterone and gonadotropins but not SHBG vary with CKD stages in young and middle aged men. Basic Clin Androl. 2015;25(1):9.

63. Yilmaz MI et al. Endogenous testosterone, endothelial dysfunction, and cardiovascular events in men with nondialysis chronic kidney disease. Clin J Am Soc Nephrol. 2011;6(7):1617-25.

64. Eckersten D et al. Anti-Müllerian hormone, a Sertoli cell-derived marker, is decreased in plasma of male patients in all stages of chronic kidney disease. Andrology. 2015;3(6):1160-4.

65. Meuwese CL, Carrero JJ. Chronic kidney disease and hypothalamic-pituitary axis dysfunction: the chicken or the egg? Arch Med Res. 2013;44(8): 591-600.

66. Lapi F et al. Androgen deprivation therapy and risk of acute kidney injury in patients with prostate cancer. JAMA. 2013;310(3):289-96.

67. Molinari C et al. The effect of testosterone on regional blood flow in prepubertal anaesthetized pigs. J Physiol. 2002;543(Pt 1):365-72.

68. Grossmann M et al. Sex steroids levels in chronic kidney disease and kidney transplant recipients: associations with disease severity and prediction of mortality. Clin Endocrinol. 2015;82(5): 767-75.

69. Traish AM, Kypreos KE. Testosterone and cardiovascular disease: an old idea with modern clinical implications. Atherosclerosis. 2011;214(2):244-8.

70. Szekacs B et al. Postmenopausal hormone replacement improves proteinuria and impaired creatinine clearance in type 2 diabetes mellitus and hypertension. BJOG. 2000;107(8):1017-21.

71. Agarwal M et al. The relationship between albuminuria and hormone therapy in postmenopausal women. Am J Kidney Dis. 2005;45(6):1019-25.

72. Ahmed SB et al. Oral estrogen therapy in postmenopausal women is associated with loss of kidney function. Kidney Int. 2008;74(3):370-6.

73. Ahmed SB et al. Oral contraceptives, angiotensin-dependent renal vasoconstriction, and risk of diabetic nephropathy. Diabetes Care. 2005;28(8):1988-94.

74. Monster TB et al. Oral contraceptive use and hormone replacement therapy are associated with microalbuminuria. Arch Intern Med. 2001;161(16):2000-5.

75. Hallan SI et al. International comparison of the relationship of chronic kidney disease prevalence and ESRD risk. J Am Soc Nephrol. 2007:17(8):2275-84.