Clinical Kidney Journal

Clinical Kidney Journal, 2023, vol. 16, no. 9, 1369–1371

https://doi.org/10.1093/ckj/sfad163
Advance Access Publication Date: 7 July 2023
Editorial Comment

The Forgotten Sex
gender disparities in kidney disease

EDITORIAL COMMENT

Shedding a light on sex disparity in clinical trials in CKD patients

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ABSTRACT

Clinical studies do not include an adequate proportion of female participants, and research data on drug efficacy and safety are generally collected from studies including a majority of men and extrapolated to women. This article describes the imbalance of male and female distribution in clinical studies, including patients with chronic kidney disease. The lack of sex equity in clinical research is a real 'public health problem' because not reporting sex-specific results may result in the loss of information on how a drug works according to sex. Therefore, it is essential to plan more research in the field of sex disparities in clinical studies to identify why women are underrepresented and to promote initiatives to expand women's participation in clinical studies.

Keywords: chronic kidney disease, clinical studies, sex equity

The original paper, 'Women's representation in clinical trials of patients with chronic kidney disease', published in this issue of the *CKJ* [1], deals with a topic of paramount importance—the underrepresentation of women in chronic kidney disease (CKD) clinical trials, which occurs despite CKD being more prevalent in women than in men. Notably, CKD affects 8%–16% of adults worldwide (11.8% of all women, 10.4% of all men), thus conferring enormous healthcare costs and contributing to excess comorbidity and death. Moreover, CKD is the ninth leading cause of death (1.8% of deaths) for women, but it does not have the exact rank toll for men.

It is worth noting that CKD progression is faster in men than in women. When renal function has to be replaced by dialysis or renal transplantation, most patients are men, the female:male ratio being 4:6. This male predominance is attributed to sex peculiarities, for instance men's biological predisposition to a faster rate of CKD progression, but these are not the sole explanations to be taken into account [2]. Although most people with CKD are identified, followed and managed in primary care, evidence of differences by sex derives mainly from the minority of patients referred to nephrology specialist units. First, although women more often donate kidneys and show similar transplantation survival to men, women still have a lower probability of being kidney transplanted.

On the other hand, another explanation for this treatment discrepancy could be that women prefer conservative care, possibly for social and financial reasons. It is also essential to add that women on dialysis have higher hospitalization rates and lower reported quality of life. Finally, there are sex-related treatment differences, such as dialysis overdose or administration of inappropriate amounts of erythropoietin-stimulating agents, because information about drugs and therapeutic doses, in general, is derived from studies on male patients. To this end, recent changes in the federal Food and Drug Administration's (FDA) position regarding drug trials are intended to increase women's representation in those studies from which women were

Received: 12.4.2023; Editorial decision: 4.7.2023

excluded in the past [3]. The FDA has altered its policy that excluded most women with 'childbearing potential' from the earliest phases of clinical trials. In addition, the FDA will provide formal guidance to the drug industry emphasizing the need for women to be adequately represented in clinical studies. However, the FDA's attention is restricted primarily to new drugs and medical devices; therefore, increased inclusion of women may be limited to ongoing or future trials.

Then, why is this issue so important?

In a study by the European Commission entitled 'Structural change in research institutions: enhancing excellence, gender equality and efficiency in research and innovation', the reasons why sex and gender equality are so crucial are analysed. Primarily, it is because they generate wasted opportunities and cognitive errors in fields like know-how, technology and innovation. In addition, it was documented that research on sex and gender bias substantially impacts scientific content because it boosts the quality of research and improves the acceptance of innovation in the market. At this point, it is important to make a distinction between sex and gender. Sex refers to 'the different biological and physiological characteristics of males and females, such as reproductive organs, chromosomes, hormones and so on'. Gender refers to 'the socially constructed characteristics of women and men—such as norms, roles and relationships of and between groups of women and men'.

There are several possible reasons why women's representation in CKD clinical trials may be lower than their representation in the overall CKD population. One reason could be that women are often excluded from clinical trials due to being of childbearing age or to hormonal fluctuations that, in the case of the latter, are perceived to interfere with study outcomes. Additionally, women may be less likely to participate in clinical trials due to a higher family and social burden than men [4]. Therefore, for all these reasons, papers like the one we are discussing should be welcome in the scientific world and have a high priority for publication. Furthermore, this study is well-documented and has a proper statistical approach supporting the author's results and conclusions. Indeed, the reluctance to involve women in scientific research has worrying consequences, such as a superficial and often inappropriate diagnosis and therapeutical approach in women who, and this cannot be forgotten, are the majority of human beings on our planet. Therefore, any effort should be taken to improve and stimulate women's enrolment into clinical trials in order to enable sex and also sex-disaggregated analysis. This strategy is fundamental in identifying potential differences in treatment responses between women and men. Therefore, having a representative sample of women in clinical trials is crucial to determine how treatments may affect them differently. For example, a systematic review published in 2016 found that women were underrepresented in cardiovascular disease clinical trials, including CKD-related trials. This was partly due to exclusion criteria related to pregnancy and hormonal status [5].

This study's main message and findings were that women's participation in CKD clinical trials is consistently lower than their representation in the underlying CKD population. Moreover, it was pointed out that sex-disaggregated efficacy and safety outcomes were rarely reported in the studies analysed in this paper. Under-representation of women in clinical trials and scientific reporting, in general, should not be disregarded and ignored any longer because it is a public health concern that can compromise the generalizability of study results and limit the development of effective treatments for women [6]. Moreover, 'the exclusion of women from clinical trials not only undermines women's health but also serves to reinforce gender inequities', as pointed out by The World Health Organization (WHO). The results of the present study are significant in the context of CKD, as women constitute a substantial portion of the CKD patient population.

This article comprehensively overviews the sex disparities in CKD epidemiology and outcomes. The authors discuss the differences in the prevalence, incidence and progression of CKD between men and women, as well as the disparities in access to healthcare, quality of life and mortality rates. This paper underlines the importance of taking sex into account when studying CKD. In addition, it highlights that sex-disaggregated efficacy and safety outcomes are rarely reported, which further emphasizes the need for more sex-specific analysis in clinical trials. By not reporting sex-specific outcomes, there is a risk of missing valuable information on the possible differential impact of treatments in men and women with untoward consequences in patient care.

Therefore, it seems mandatory other than ethical, to promote more research in this neglected field to understand why women are underrepresented in research studies. The authors of this interesting and inspiring original paper conclude that 'improving women's enrollment in clinical trials is essential to enable sex-disaggregated analysis and identify potential differences in treatment response between women and men. Doing so can help ensure that treatments are safe and effective for all patients, regardless of sex or gender.'

Whatever the findings, i.e. finding that there are or are not any sex differences in clinical research, this approach will help improve clinical care and clinicians' ability to treat their patients. Thus, women's underrepresentation in medical studies is a hot topic. Moreover, the suspicion that even in studies that include women, analysis by sex and gender are often not undertaken or not reported may imply a guilty attitude of consideration for women's health.

Finally, reviewers must always suggest that the authors provide information about the efficacy and safety of a given treatment not only in the whole study sample of a specific clinical trial but also by relevant patients strata (e.g. in males and females) by using forest plots [7]. A forest plot is a graph that provides the magnitude of a given effect (for example a relative risk or a mean difference, always accompanied by the 95% confidence interval) by subgroups of patients (e.g. by gender) and allows an understanding of whether the treatment effect is homogenous or heterogenous among strata. For example, suppose the effect of the drug being investigated significantly differs among subgroups (for example, between males and females). In that case, an effect modification by a specific effect modifier can be claimed and discussed. Otherwise, it can be concluded that the drug effect among subgroups can be considered a random fluctuation of the overall effect found in the whole study sample. Thus, given the importance of data analysis by sex, when presenting the results of clinical trials, it would be desirable to systematically include sex among the potential effect modifiers reported in the forest plots of clinical trials, and such a recommendation should be contemplated explicitly in the CONSORT statement and adopted by all international scientific journals.

CONFLICT OF INTEREST STATEMENT

F.M. is member of the *CKJ* editorial board.

(See related article by Pinho-Gomes et al. Women's representation in clinical trials of patients with chronic kidney disease. *Clin Kidney J* (2023) 16: 1457–1464.)

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Received: 12.4.2023; Editorial decision: 4.7.2023