18. European Association For The Study Of The Liver. EASL clinical practice guidelines: management of hepatitis C virus infection. J Hepatol 2013; doi:10.1016/j.jhep.2013.11.003

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Is there a difference in metabolic burden between men and women?

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This question sounds trivial. Most lay people would probably say that men do eat more than women, because they are built differently in terms of body size and body composition. However, answers to how the metabolic burden differs between men and women are of great practical importance to practising nephrologists, not only in the dialysis setting, but also when managing kidney patient populations preceding dialysis. Men have a higher estimated glomerular filtration rate (eGFR) than women when they need to start dialysis [1, 2]. This finding has been taken as a suggestion that for the same level of eGFR in the pre-dialysis setting men may be more likely than women to develop complications that subsequently trigger dialysis initiation. One potential mechanism could be that men have a greater difficulty to maintain their homeostasis between food intake and uraemic solute clearance for the same level of eGFR.

Defining what level of nutrient intake is appropriate for a given GFR in men and women is very challenging because we do not know how to scale their GFR to their respective body compositions. For example, can a woman with a GFR of 15 mL/min eat the same amount of potassium compared with a man with the same GFR (holding other parameters constant, e. g. medication, primary renal diagnosis, diabetes control and age)? Would we allow in our calculations for weight differences between men and women, or should we scale to their respective body surface area (BSA), or to the total body water (TBW)? If we instead of potassium consider for example targets of protein intake for men and women, should we scale our recommendations to the lean body mass (LBM) of a man/woman rather than to their body weight? When giving recommendations on calorie intake, should it be scaled to resting energy expenditure (REE)? Of note is that the eGFR we use in clinical practice scales to estimated BSA [3, 4], and that existing recommendations currently do not explicitly distinguish by gender although men and women have different LBM, and REE [5].

In this issue, Ellam et al. attempted to provide more data on these question using cross-sectional data from three cohort studies: the Modification of Diet in Renal Disease (MDRD) trial [6], the Chronic Renal Insufficiency Cohort (CRIC) [7] and the NHANES survey (a study designed to represent the US general population) [8]. All studies had data on estimated dietary intakes of key nutrients, as well as serum and urine biochemistry; MDRD and CRIC were designed to investigate patients with chronic kidney disease (CKD) and therefore had measured iothalamate GFR. The authors were thus able to map average food intake between men and women across all stages of pre-dialysis CKD in well-known cohort studies from the USA.

The authors found unsurprisingly that there were gender differences in nutrient intakes which were consistent between cohorts, with men generally eating more calories, protein, phosphorus, sodium and potassium than women. The results for estimated nutrient intake are remarkably similar between the three different cohorts, with BSA-indexed protein, calorie, phosphate...
and sodium intake usually being about 11–15% higher in men than in women. Indexing to other measures (TBW, REE, LBM) reversed or abolished the gender difference. Data from food frequency questionnaires are often fraught with reporting errors despite every attempt of using validated questionnaires in all three cohorts. It was therefore reassuring to see that the estimated protein intake differences were reflected in the 24-h urine urea nitrogen results with ratios of 10–13% higher in men than in women when indexing to BSA. Estimated fractional excretions of sodium and phosphate were 12 and 23% higher, respectively, for men than women when indexed to BSA, and men had increased odds of hyperphosphataemia, hyperkalaemia and acidosis per mL/min/1.73 m² eGFR. These results attenuated or reversed when indexing to TBW, REE and LBM rather than BSA. The authors used data from the NHANES study to look at the ‘normal’ associations in the general US population—the mean eGFR was the same in men and women using the CKDEPI formula (this formula is not biased by gender [4]), and BSA was also similar for both genders in the general population. For a given level of eGFR, men participating in NHANES had a 16% higher serum urea than female participants of the same age and ethnicity.

The authors argued that if GFR truly indexes to BSA as is assumed by using eGFR, then men at all stages of CKD do eat more protein, calories, sodium, phosphate and potassium than women per mL/min/1.73 m² eGFR. They point out that our nutritional guidelines do not set explicit gender-specific nutrient targets. The authors then speculate that their observations may also explain the higher cardiovascular mortality for men at earlier stages of CKD, and that women may be better off as they excrete more nutrients per mL/min/1.73 m² eGFR than men. The authors do acknowledge that gender differences are less marked when GFR is scaled to other measures instead of BSA, which may imply using a gender-specific GFR cut-off for nutritional purposes.

We use in clinical practice eGFR and fractional excretions to obtain an indirect understanding of filtration capacity and current nephron mass. Autopsy studies suggest that men have a 17% higher nephron endowment than women [9]. This number fits the gender differences remarkably well in observed protein intake and urea excretion rates scaled to BSA in the three observational studies. Taking these findings together, I could therefore speculate that men were constructed by nature to maintain their body shape, composition and size with more protein, calories, sodium, phosphate and potassium per mL/min/1.73 m² eGFR than women. The authors do acknowledge that gender differences are less marked when GFR is scaled to other measures instead of BSA, which may imply using a gender-specific GFR cut-off for nutritional purposes.

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The patients we see in clinic have a life-long history of nutrition, changes in body shape (typically gain in fat and loss of muscle mass), underlying other comorbidities and a number of medications that can affect their eGFR. Hence, adults with CKD will not have the same nephron number as they had at birth, and the prior life-long history of environmental renal insults will have impacted on how an eGFR relates to nephron number by gender. Hence, although it may be that nature may have originally catered to men’s increased protein requirements in terms of nephron endowment, the conclusion of Ellam and colleagues remains valid in particular with regards to people with advanced CKD. For a given eGFR in mL/min/1.73 m² men with CKD need to clear more nutrients than women.

I am not sure that this paper proves that men are just unfortunate and therefore inevitably end up on dialysis sooner than women due to men’s increased nutritional needs.

Firstly, this paper only looked at intake/excretion, and assumed that the observed data suggest that men have a different nutritional homeostasis than women. Whether this is indeed the case, or whether this paper just shows that men eat more than they require which in turn negatively affects their homeostasis is unclear. Society’s gender stereotyping and in particular food advertising may affect men differently than women [10]. It is extremely difficult to define dietary requirements using cross-sectional observational studies. To answer the question of gender-specific requirements to maintain homeostasis in the presence of CKD longitudinal data is required.

Second, we do not know whether the study cohort observations for male and female patients with CKD were equally associated with their renal nutritionists’ advice. Study participants in CRIC and MDRD may have been from a generation in which a sizable subset of men may not have learnt to cook their own meals. It may be that Ellam’s findings are confounded by whether the male participants had a partner or family member providing their food or not. It may be that men found it more difficult to follow dietary advice given by renal nutritionists when compared with women. How men and women respond to renal nutrition advice needs to be investigated in more detail to inform future nutritional guidelines.

Third, the authors were unable to adjust for differences in medication intake. Men have more cardiovascular morbidity and thus more cardiovascular medication than women which may confound the findings for nutrition. Hence more studies in other settings and adjusting for medication data are needed.

In a recent meta-analysis of eGFR by gender on renal and cardiovascular outcomes there was no evidence of a gender difference for a given eGFR in long-term progression to end-stage renal disease [11]. This meta-analysis took into account cardiovascular risk behaviours between men and women [11]. This finding suggests that the long-term higher renal metabolic burden for men for a given eGFR is probably captured by common cardiovascular risk factors including BMI. Indirect and suggestive evidence for a higher metabolic burden in men derives instead from epidemiological findings of nephrolithiasis which is more predominant in men than women [12]. When contrasting the findings of the meta-analysis [11] with the present study by Ellam et al., it is worth remembering that the meta-analysis looked at long-term outcomes, whilst Ellam...
et al. and the other studies [1, 2] looked at cross-sectional data or results directly preceding dialysis.

Ellam and his colleagues have to be congratulated for a thorough effort highlighting gender differences in nutritional burden by level of eGFR. Their study raises a number of important questions that should be investigated further, such as longitudinal changes in nutritional needs by gender and the important role of gender and societal context on how renal nutritional advice is being implemented.

CONFLICT OF INTEREST STATEMENT

None declared.


REFERENCES


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Soluble Flt-1 release response to heparin use: implications for dialysis patients?

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Soluble Flt-1 is the soluble form of the vascular endothelial growth factor (VEGF)-receptor 1 (sVEGF-R1), which results from an alternative splicing of the VEGF-R1 transcript, as well as from the cleavage and ectodomain shedding of membrane-bound VEGF-R1 [1, 2]. The primary (known) function of sFlt-1 is to antagonize VEGF and placental growth factor (PIGF), acting as a trap for the agonist and for signalling receptor components [1]. Since VEGF, a protein with a high specificity for endothelial cells, is important, even crucial, for both angiogenesis (the growth of new blood vessels) and the maintenance of endothelial cell health and microvasculature...