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## **Editorial**

### **Primary versus secondary prevention of chronic kidney disease: the case of dietary protein**

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The proclamation that “*the greatest medicine of all is to teach people how not to need it*” (Hippocrates. 460-370 BC, Greece), is the basic principle of primary disease prevention, which aims to prevent disease before it ever occurs. Preventing exposures to hazards that cause disease, such as altering unhealthy behaviours, is one example of primary disease prevention. Secondary or tertiary disease prevention, however, refer to reducing the impact of a disease that has already occurred, or limiting the impact of an ongoing illness that has lasting effects, respectively. Salutory diets or lifestyles for primary versus secondary/tertiary disease prevention may not necessarily align.

In patients with manifest chronic kidney disease (CKD), a low protein diet remains the first line of nutrition therapy for *secondary prevention* of CKD.<sup>1,2</sup> Potential effects of low protein diets are the preservation of residual renal function, better control of uremia, reduced kidney stone formation, hyperphosphatemia, or gut-derived uremic toxins.<sup>3,4</sup> However, there remains conflicting data on the benefits of low protein diets in retarding the progression to end-stage kidney disease (ESKD)<sup>5</sup> or lowering the risk of mortality,<sup>6</sup> and the potential to promote undernutrition in the elderly.<sup>2</sup> It is possible that conflicting evidence is explained by patient-centered experiences following this restrictive dietary approach.<sup>7</sup> In fact, compliance to a low protein diet is commonly between 14-50% in CKD trials,<sup>2</sup> and approximately 70% of nephrologists report hesitation in prescribing it.<sup>8</sup>

In contrast to the low protein diet advice in CKD, a high protein, low carbohydrate diet has been touted as a quick fix solution to today's epidemics of obesity and type 2 diabetes. Commentary has followed related to its safety, with several reports and lay media raising concern that such diets in the general population, may be detrimental to the healthy kidney.<sup>9-12</sup> Yet, the current state of the evidence is uncertain, with little to no evidence to support these claims. To date, randomized controlled trials of a high-protein diet in individuals free from CKD have generally observed no adverse effect on renal function decline (**Table 1**). Existing studies are nonetheless too short in duration to meaningfully detect eGFR changes (< 2 years), often include younger participants, and choose creatinine-based eGFR as a study outcome, which may be compromised when intervening on protein intake.<sup>13</sup> Similar conclusions were reached in a recent meta-analysis of randomized controlled trials, that showed that a high protein diet in populations free from CKD stimulated the renal reserve causing increases in eGFR, but no evidence of renal damage or eGFR decline was found.<sup>14</sup> Observational evidence also points to a lack of a clear association between a high-protein diet and renal function in the general population (**Table 2**). Finally, real world examples support this contention, within the body-building community<sup>11</sup> and in historical accounts of extreme protein intakes (for example, men in the famous Lewis and Clark expedition across America in 1804 reportedly ate as much as nine pounds of buffalo meat (>600 grams protein) each day with no ill effects<sup>15</sup>).

In this issue of *JREN*, we are presented with two studies examining the effects of dietary protein on the healthy kidney. Cirillo *et al.*<sup>16</sup> present a post-hoc analysis of the Gubbio study, an Italian population-based study of 4,679 adults. Dietary protein intake was measured from overnight urine urea nitrogen (UUN), with low protein intake defined as the lowest quartile of UUN distribution. CKD progression was defined as an eGFR reduction of less than or equal to one standard deviation from baseline. Over 16 years of follow-up, they found no association between low UUN and the odds of eGFR decline. Interestingly, when the analysis was restricted for those participants with reduced renal function at baseline (defined as eGFR decline from equal to or below a Z-score of -1 baseline eGFR), a low protein intake was significantly associated with lower odds of eGFR decline (odds ratio: 0.44 [95%CI 0.22, 0.85]). Also in this issue, Malhotra *et al.*<sup>17</sup> present another observational analysis based on

3,165 participants from the Jackson Heart study. The sample included African American adults who were mostly female (65%) and had dietary protein intake ascertained at baseline from food frequency questionnaires. Change in GFR was calculated as the final visit GFR minus the baseline GFR, using the CKD-EPI equation. The primary finding of this study was a lack of significant association between protein intake and GFR decline over 8 years of observation. However, when the analysis was stratified by diabetes status, participants with diabetes had a higher incidence of eGFR decline across the lowest ( $-20.0 \pm 1.7$  mL/min/1.73 m<sup>2</sup>) and highest ( $-15.9 \pm 2.8$  mL/min/1.73 m<sup>2</sup>) quintiles of protein intake, as compared to those with middle quintile ( $-12 \pm 1.6$  mL/min/1.73 m<sup>2</sup>).

These two studies add to the body of evidence that restricting protein intake may not be beneficial in the primary prevention of CKD. Nonetheless, they also suggest that a lower protein intake may be beneficial in some high-risk populations, including those with some mild degree of renal impairment or diabetes. This agrees with preceding observational reports, such as the Nurses' Health study, where an association of low protein intake with less rapid decline of kidney function over time was only observed in the subgroup of 489 participants with established mild renal impairment.<sup>18</sup> There is also the suggestion that quality of the ingested protein (animal versus plant-based ) within an overall healthy dietary pattern, may be more important than the total protein ingested.<sup>19</sup> Indeed, acute lab studies suggest that animal protein stimulates the renal reserve more so than plant-based proteins<sup>20</sup>. As recently shown in JREN<sup>21</sup> people consuming the highest quartile of vegetable protein had a 24% reduced risk of incident CKD over a 23-year follow-up period, but the analysis of overall protein intake yielded no association. When the analysis targeted individual food items, there was an increased CKD risk for those who consumed more protein from red and processed meats (HR 1.23;  $p < 0.01$ ), and a reduced CKD risk for those who consumed more protein from dairy products, nuts, and legumes. While an important limitation of all these studies is their observational nature, due to the lack of adequately powered and well-designed intervention trials. Such evidence forms the basis for many nutrition guidelines in primary and secondary prevention.

The Science of Nutrition is a science of "virtue in moderation", where any excess nutrient intake or deficit is a risk for more harm than good. Concerns relating to a high-protein diet are likely because of harmful effects other than kidney damage. Some of the adverse effects attributed to excessive protein intake include disorders of bone and calcium homeostasis, renal stone formation, possible increased risk of cancer, disorders of liver function, hypertension and coronary artery disease.<sup>10,22</sup> It is interesting, in this sense, that Malhotra and co-workers<sup>17</sup> observed a U-shape association between protein intake and mortality. Neither too little nor too much protein intake may be good for health, as it was similarly shown in other population-based studies.<sup>18,23</sup>

These two interesting studies leave us with two conclusions. First, they align with current evidence, which does not support the assertion that a high protein diet leads to incident CKD in the community, at least in those with normal renal function. Interestingly however, is a call for caution about prescribing high-protein diets in populations at high-risk of CKD, such as those with minimal renal impairment or diabetes. There is a need to better understand lifestyle advice for the primary prevention of CKD separately from secondary prevention, preferably in randomized controlled trials.

Second, these studies make us realize that although a healthy diet is likely to be effective for primary CKD prevention,<sup>24</sup> the characteristics of such a diet are, to date, poorly defined.<sup>25</sup> The case of dietary protein and CKD illustrated in these two studies is an excellent example that primary and secondary prevention strategies are not always aligned. There is still much

to be learned in the case of dietary protein, and more improvement is needed for effective strategies to minimize the burden of CKD in the community. After all, CKD afflicts one in 10 adults and causes as many deaths as diabetes.<sup>26,27</sup>

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**Table 1.** Results of studies examining high protein intake and renal outcomes in randomized controlled trials conducted in populations free from CKD with study durations greater than 3 months.

Study citation	Population	Duration	Protein exposure	High protein intake and change in renal function
Randomized controlled trials				
Campos-Nonato et al 2017 <sup>28</sup>	Mexican adults; 20-60 years; BMI 25-45kg/m <sup>2</sup> ; metabolic syndrome; n=118	6 months	High protein: 1.3 g/kg Low protein: 0.8 g/kg	No significant change in renal function
Freidman et al 2012 <sup>29</sup>	Adults; 18-65 years; BMI 27-40kg/m <sup>2</sup> ; n=307	24 months	High protein: >15% Low protein: 15%	No significant change in renal function
Krebs et al 2012 <sup>30</sup>	Adults; 30-75 years; type 2 diabetes; BMI >27kg/m <sup>2</sup> ; n=419	24 months	High protein: 30% Low protein: 15%	No significant change in renal function
Larsen et al 2011 <sup>31</sup>	Adults; type 2 diabetes; BMI 27-40kg/m <sup>2</sup> ; n=99	12 months	High protein: 30% Low protein: 15%	No significant change in renal function
Li et al 2010 <sup>32</sup>	Adults; >30 years; BMI 27-40kg/m <sup>2</sup> ; n=100	12 months	High protein: 30%; 2.2g/kg Low protein: 15%; 1.1g/kg	No significant change in renal function
Noakes et al 2005 <sup>33</sup>	Adults; 20-65 years; BMI 27-40kg/m <sup>2</sup> ; n=100	3 months	High protein: 37% Low protein: 17%	No significant change in renal function
Skov et al 1999 <sup>34</sup>	Adults; BMI 25-34kg/m <sup>2</sup> ; n=65	6 months	High protein: 25% Low protein: 12%	Increase in GFR of 5ml/min.  No adverse renal effects reported
Tay et al 2015 <sup>35</sup>	Adults; type 2 diabetes; n=115	12 months	High protein: 28% Low protein: 17%	No significant change in renal function
Tirosh et al 2013 <sup>36</sup>	Adults; 40-65 years; BMI >27kg/m <sup>2</sup> ; n=318	24 months	High protein: 22% Low protein: 19%	High protein increased eGFR by 5%  Albuminuria decreased in the low protein intervention.  No adverse renal effects reported
Wycherley et al 2012 <sup>37</sup>	Adults; 20-65 years; BMI 27-40kg/m <sup>2</sup> ; n=68	12 months	High protein: 35%; 1.2g/kg Low protein: 17%; 0.8g/kg	No significant change in renal function



**Table 2.** Results of studies examining high protein intake and renal outcomes in observational studies conducted in populations free from CKD.

Study citation	Population	Duration	Protein exposure	High protein intake and change in renal function
Dunkler et al 2013 <sup>38</sup>	ONTARGET cohort; n=6123	5.5 years	Protein intake analysed across tertiles High protein: 1g/kg Low protein: 0.4g/kg	Lowest tertile of total and animal protein intake had an increased risk of CKD compared with participants in the highest tertile
Halbesma et al 2009 <sup>23</sup>	PREVEND cohort; n=8461	6.4 years	Protein intake analysed across quintiles. High protein quintile = 3.3g/kg	No significant change observed in renal function
Haring et al <sup>39</sup>	ARIC cohort; n= 11,952	23 years	Protein intake analysed across quintiles. High protein quintile: 110g/day	No significant change observed in renal for total protein intake  Red and processed meat consumption associated with risk of CKD  Protective associations from plant, egg and fish protein sources
Knight et al 2003 <sup>18</sup>	Nurses' Health Study cohort; n=1624	11 years	Protein intake analysed across quintiles. High protein quintile: 93g/day	No significant change observed in renal function in non-CKD  Significant association to renal function decline in those with established CKD
Lew et al 2016 <sup>40</sup>	Singapore Chinese Health Study cohort; n=63,257	15.5 years	Protein intake analysed across quartiles of animal, poultry, fish and plant sources High protein quintile: 64g/day Low protein quintile: 53g/day	Red meat consumption associated with risk of ESRD  Protective associations from plant, egg and fish protein sources
Cirillo et al 2018 <sup>16</sup>	Gubbio study cohort; n=4679	15.9 years	Lowest protein: 20% of the sample's UUN distribution	No significant change observed in renal function in non-CKD  Significant association to renal function decline in those with established CKD
Malhotra et al 2018 <sup>17</sup>	Jackson Heart study cohort; n= 3165	8 years	Protein intake analysed across quartiles High protein quintile: 19%; 1g/kg Low protein quintile: 10%; 0.6g/kg	No significant change observed in renal function in non-CKD  Significant association to renal function decline in those with uncontrolled diabetes

Abbreviations – NHANES: US National Health Nutritional Examination Survey, ARIC: Atherosclerosis Risk in Communities, ONTARGET: The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial, PREVEND: Prevention of Renal and Vascular End-Stage Disease, ESRD: end-stage renal disease, UUN: urine urea nitrogen.