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Excess protein intake relative to fiber and cardiovascular events in elderly men with chronic kidney disease

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Abstract *Background and aims:* The elevated cardiovascular (CVD) risk observed in chronic kidney disease (CKD) may be partially alleviated through diet. While protein intake may link to CVD events in this patient population, dietary fiber has shown cardioprotective associations. Nutrients are not consumed in isolation; we hypothesize that CVD events in CKD may be associated with dietary patterns aligned with an excess of dietary protein relative to fiber.
Methods and Results: Prospective cohort study from the Uppsala Longitudinal Study of Adult Men. Included were 390 elderly men aged 70–71 years with CKD and without clinical history of CVD. Protein and fiber intake, as well as its ratio, were calculated from 7-day dietary records. Cardiovascular events were registered prospectively during a median follow-up of 9.1 (interquartile range, 4.5–10.7) years.

The median dietary intake of protein and fiber was 66.7 (60.7–71.1) and 16.6 (14.5–19.1) g/day respectively and the protein-to-fiber intake ratio was 4.0 (3.5–4.7). Protein-to-fiber intake ratio was directly associated with serum C-reactive protein levels. During follow-up, 164 first-time CVD events occurred (incidence rate 54.5/1000 per year). Protein–fiber intake ratio was an independent risk factor for CVD events [adjusted hazard ratio, HR per standard deviation increase (95% confidence interval, CI) 1.33 (1.08, 1.64)]. Although in opposing directions, dietary protein [1.18 (0.97, 1.44)], dietary fiber alone [0.81 (0.64, 1.02)], were not significantly associated with CVD events.
Conclusions: An excess of dietary protein relative to fiber intake was associated with the incidence of cardiovascular events in a homogeneous population of older men with CKD.

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Introduction

Poor lifestyle habits, including unhealthy diet, may contribute to the elevated cardiovascular disease (CVD) risk observed in individuals with chronic kidney disease (CKD) [1]. Excess protein intake has been associated with increased CVD morbidity and mortality in some [2–4] but not all community-based studies [5–7]. For patients with CKD, limiting protein intake remains an important modifiable risk factor for haltering CKD progression, but whether high protein intake is associated with cardiovascular risk in this patient population has not been established. In contrast, observational studies consistently report that a high fiber intake is associated with reduced cardiovascular risk and mortality in the community [8]. Moreover, this association appears to be stronger in adults with CKD [9,10].

Nutrients are not consumed in isolation. There is a considerable biological ground to support the notion that reducing protein intake and increasing the intake of fruit, vegetables and, in essence, dietary fiber, may mitigate the excess cardiovascular risk of CKD patients [11]. A significant difference in generation rates of two major nephrovascular toxins indoxyl sulfate and p-cresyl sulfate between omnivores and vegetarians has been demonstrated in the healthy population, presumably owing to their different protein and fiber profiles (i.e. higher protein:fiber ratio in omnivores) [12]. Furthermore, we showed that the ratio of dietary protein–fiber intake was strongly associated with the serum concentration of these toxins in CKD patients [13]. However, neither study found an association between the toxins and individual nutrients, suggesting the importance of considering the nutrients' combined effect [12,13]. We hypothesize that dietary patterns aligned with an excess of dietary protein relative to fiber may be more important than the component nutrients on CVD risk in CKD.

Methods

Study population

This study was performed in the Uppsala Longitudinal Study of Adult Men (ULSAM) (http://www2.pubcare.uu.se/ULSAM/). The present analyses are based on the third ULSAM examination cycle. During this examination, participants were 70–71 years of age (examinations performed during 1991–1995; $n = 1221$). A total of 692 individuals were identified as having CKD on the basis of cystatin C-estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 ($n = 506$) or urine albumin excretion rate (UAER) ≥ 20 μg/min ($n = 292$), or both these conditions ($n = 106$). Of those, we excluded individuals with a history of CVD ($n = 302$), defined as any CVD recorded in the Swedish Patient register (Inter-national Classification of Diseases (ICD)-8 codes 390–458 or ICD-9 codes 390–459). The remaining 390 participants were considered for the present study. The Ethics Committee at Uppsala University approved the study and all participants gave informed consent.

Demographics and co-morbidities

Investigations were performed under standardized conditions. Smoking status was defined as current smoking versus non-smoking. Regular physical activity was defined as the reporting of regular or athletic leisure time exercise habits according to four physical activity categories (sedentary, moderate, regular, and athletic). Blood pressure (BP) was measured in duplicate in the right arm with the subject in the supine position at rest. Hypertension was defined as BP $\geq$ 140/90 mmHg or the use of antihypertensive medications. Diabetes mellitus was defined as fasting plasma glucose $\geq$126 mg/dL (7.0 mmol/L), 2 h post-load glucose levels $\geq$200 mg/dL (11.1 mmol/L) or diabetes medication (insulin or oral). Hyperlipidemia was defined as serum cholesterol $>$250 mg/dL (6.5 mmol/L), serum triglycerides $>$200 mg/dL (2.3 mmol/L) or treatment with lipid-lowering medications.

Protein–fiber intake ratio assessment

Dietary habits were evaluated by a 7-day dietary record based on a validated pre-coded menu book, which was prepared and previously used by the Swedish National Food Administration (NFA). A dietitian gave the participants verbal instructions of how to complete the dietary record, and the amounts consumed were reported in household measurements or specified as portion sizes. The daily intake of protein and fiber as well as its ratio were calculated using a food composition database from the NFA. Other nutrients that are typically aligned with this ratio and considered in these analyses were saturated fatty acid intake (SFA), potassium and salt intake. Dietary salt was estimated as the natural salt-content of foods and, when reported by the participants, the salt added to cooking and at the table. In order to reduce extraneous variation, nutrient intake was corrected for total energy intake by regression analysis of the residual method [14].

Laboratory measurements

Venous blood samples were drawn in the morning after an overnight fast and stored at −70 °C until required for analyses. Serum cystatin C (N Latex Cystatin C, Dade Behring) was used to estimate GFR by the formula $y = 77.24 \times x^{-1.2623}$, which has been shown to be closely correlated with iohexol clearance in our previous study [15]. Urine albumin excretion rate (UAER) was calculated based on the amount of albumin in the urine collected during the night. The subjects were instructed to void immediately before going to bed and to record the time. All samples during the night and the first sample of urine after rising were collected and used for the analysis with radioimmunoassay kit (Albumin RIA 100; Pharmacia, Uppsala, Sweden). Serum high sensitivity C-reactive protein (hs-CRP) was measured by latex enhanced reagent (Dade Behring, Deerfield, IL) using a Behring BN ProSpec analyzer (Dade Behring).