

# Protein Intake and Single-Nephron GFR

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High protein intake can increase glomerular filtration rate (GFR) in response to excretory overload, which may exacerbate the progression of kidney disease. However, the direct association between glomerular hemodynamic response at the single-nephron level and dietary protein intake has not been fully elucidated in humans. In the present study, we evaluated nutritional indices associated with single-nephron GFR (SNGFR) calculated based on corrected creatinine clearance (SNGFR<sub>Cr</sub>). We retrospectively identified 43 living kidney donors who underwent enhanced computed tomography and kidney biopsy at the time of donation at Jikei University Hospital in Tokyo from 2007 to 2018. Total nephron number was estimated with imaging-derived cortical volume and morphometry-derived glomerular density. SNGFR<sub>Cr</sub> was calculated by dividing the corrected creatinine clearance by the number of non-sclerosed glomeruli (Nglom<sub>NSG</sub>). The mean ( $\pm$  standard deviation) Nglom<sub>NSG</sub>/kidney and SNGFR<sub>Cr</sub> were  $685\,000 \pm 242\,000$  and  $61.0 \pm 23.9$  nL/min, respectively. SNGFR<sub>Cr</sub> was directly associated with estimated protein intake/ideal body weight ( $P = 0.005$ ) but not with body mass index, mean arterial pressure, albumin, or sodium intake. These findings indicate that greater protein intake may increase SNGFR and lead to glomerular hyperfiltration.

Keywords: glomerular hyperfiltration ; nephron number ; protein intake ; single-nephron glomerular filtration rate

## 1. Introduction

Chronic kidney disease (CKD) is a global health concern because of increased morbidity and mortality [1]. Dietary interventions are an effective strategy to prevent or delay the progression of CKD, and current nutritional management recommendations include controlling the intake of protein, sodium, and phosphorus [2]. A high-protein diet is known to increase the risk of CKD development and progression through several mechanisms. In animal models [3][4] and humans [5][6], dietary protein was shown to increase intrinsic acid production, which can cause kidney injury due to acid retention-induced kidney endothelin and aldosterone production. Furthermore, increased dietary protein per se was shown to induce kidney injury through a hemodynamic mechanism of renal hyperfiltration in humans [7] and experimental animals [8]. However, the direct association between protein intake and glomerular hemodynamic response remains poorly understood.

Glomerular hyperfiltration, defined as an abnormal renal hemodynamic change at a single-nephron or whole-kidney level, may arise from metabolic disturbances and is a risk factor for progressive kidney damage. Among the various diseases and conditions associated with glomerular hyperfiltration are diabetes mellitus, polycystic kidney disease, secondary focal segmental glomerulosclerosis, pregnancy, obesity, and a high-protein diet [9]. While experimental studies using high protein loading in animals show that glomerular hyperfiltration at the single-nephron level precedes the subsequent albuminuria and glomerulosclerosis [10], the lack of available methods to measure single-nephron glomerular filtration rate (SNGFR) in humans has hindered clinical studies to assess glomerular hyperfiltration in humans [11]. Thus, most studies have utilized elevated glomerular filtration rate (GFR) at the whole-kidney level as an indicator of glomerular hyperfiltration.

Recent studies in humans have described a new method to calculate SNGFR, which is defined as GFR divided by the estimated total number of non-sclerosed glomeruli (Nglom<sub>NSG</sub>) [12][13]. Using this method, we previously demonstrated that the estimated total number of glomeruli (Nglom<sub>TOTAL</sub>) in Japanese living kidney donors was similar to that determined in a Japanese autopsy study which used the physical disector/fractionator method, the gold standard method for estimating total number of glomeruli in kidneys [14][15][16]. Additionally, in an autopsy study of Japanese subjects, we showed that SNGFR was higher in those with hypertension compared to normotensive subjects [14]. A higher SNGFR, which indicates glomerular hyperfiltration, is associated with certain risk factors for CKD and certain kidney biopsy findings such as glomerular hypertrophy and sclerosis [13][14]. Despite numerous clinical trials and observational nutritional studies on renal hyperfiltration using elevated whole-kidney GFR as a parameter, few studies reported the association of SNGFR with nutritional indices.

We hypothesized that a high protein intake would lead to glomerular hyperfiltration with an elevated SNGFR, leading to CKD either directly or indirectly through damage to the glomerular structure. In the present study, we calculated SNGFR by estimating the number of glomeruli in living kidney donors using the combined computed tomography imaging and kidney biopsy method [15] and explored the association between protein intake and SNGFR in healthy individuals without CKD.

## 2. Discussion and Findings

The major new finding of the present study, including 43 Japanese living kidney donors without CKD, is the positive correlation between protein intake and SNGFR, which persisted with the statistical trend analysis of the cohort categorized according to the PI/BW tertiles and after the consideration of confounders for glomerular and renal hyperfiltration. These findings suggest that greater daily protein intake may increase SNGFR and induce glomerular hyperfiltration.

The positive correlation of protein intake with SNGFR is in agreement with previous reports. Early studies in rats demonstrated that an increase in SNGFR depended on protein intake during systemic amino acid infusion [17][18]. Although the exact mechanism for the glomerular hemodynamic responses to a high-protein diet, as well as the multiple mediators and factors affecting this mechanism, is yet to be settled, several studies reported that neuronal nitric oxide synthase [19][20] and tubuloglomerular feedback (TGF) [21][22] played pivotal roles in high-protein diet-induced glomerular hyperfiltration [23]. Specifically, TGF was a key player in the control of glomerular hemodynamics. Micropuncture data showed that a high-protein diet induced a 21% increase in SNGFR with TGF but no significant change in SNGFR in the absence of TGF [8].

High protein intake increases the filtration of amino acids and their reabsorption in proximal tubules. As the reabsorption of most amino acids is sodium-dependent [24], concomitantly increased sodium reabsorption leads to reduced sodium chloride concentrations in macula densa and results in reduced TGF signaling, which increases the SNGFR [25][26]. High protein intake also leads to increased urea excretion, which creates an osmotic load in the renal tubule lumen. As the most abundant solute in urine, urea plays an important role in the urinary concentrating mechanism [27]. Vasopressin, which is secreted to prevent urea-dependent osmotic diuresis, affects urea channels, resulting in the reabsorption of urea into the inner medullary interstitium. Sodium reabsorption that occurs simultaneously to create and maintain the osmotic gradient in the medulla [27][28] leads to increased SNGFR, as mentioned above.

Although not observed in this study, an association between high protein intake and elevated eGFR has been reported in several studies [7][29]. This discrepancy might be caused by a difference in glomerular hyperfiltration between the single-nephron level and the whole-kidney level [5]. In addition, in the early stage of CKD, whole-kidney GFR is preserved within the normal range, whereas SNGFR increases to compensate for nephron loss [30]. Furthermore, in this study, the subjects were healthy kidney donors with preserved kidney function and a mean PI/BW of  $1.0 \pm 0.2$  g/kg/day, whereas other studies defined a high-protein diet as a PI/BW of  $>1.2$  or  $1.5$  g/kg/day [31][32]. According to the International Society of Renal Nutrition and Metabolism Commentary on the National Kidney Foundation and Academy of Nutrition and Dietetics KDOQI Clinical Practice Guideline for Nutrition in Chronic Kidney Disease, a moderately high protein diet was defined as  $1.2$ – $1.5$  g/kg/day; this was the reported average protein intake of adults without CKD in the United States [33]. In this updated guideline, the recommended range for adults without CKD but who are at high risk for CKD was  $0.8$ – $1.0$  g/kg/day. The optimal daily protein intake for healthy individuals is a topic of much debate.

Unlike a previous study that determined the SNGFR based on urinary iothalamate clearance in healthy adult subjects [13], we used creatinine clearance to calculate SNGFR as we were able to correct most of the data based on 24-h urine collection. Creatinine clearance is known to lead to the overestimation of GFR because of the tubular secretion of creatinine [34]. Applying a correlation coefficient [35] to calculate SNGFR based on creatinine clearance allowed us to address this issue in the present study.

Moreover, SI and MAP did not show a significant correlation with  $\text{SNGFR}_{Cr}$  in the present study. In fact, the direct association of SNGFR with SI and hypertension is not fully understood. Certain studies have shown that salt intake increased GFR at a whole-kidney level and mean arterial pressure [36][37]. A recent study calculating SNGFR in 1388 living kidney donors showed that a higher SNGFR was associated with higher BMI, increased height, and family history of end-stage renal disease, although it was not associated with mild hypertension [13]. In an autopsy study of Japanese patients, we previously reported that SNGFR was higher in hypertensive subjects than normotensive subjects [14]; however, the blood pressure of the subjects in the present study was well controlled with medications or dietary interventions. In

addition, the mean SI was within the normal range ( $8.0 \pm 2.9$  g/day) compared to the mean SI of 10.1 g/day reported in the Japanese population. Of note, the recommended SI is less than 7.5 g/day for males and 6.5 g/day for females according to the 2020 recommendations of the Japanese Ministry of Health, Labor, and Welfare.

The present study has several limitations that should be acknowledged. First, parameters representing dietary acid load were not included. Second, we estimated SNGFR based on only creatinine clearance, and dietary protein intake was estimated from 24-h urinary urea excretion at one point. Third, the causal relationship between dietary protein intake and SNGFR could not be determined due to the correlation analyses and the observational nature of the study. Finally, the study cohort included Japanese subjects with normal kidney function, and the generalization of the results require further studies. Recently, in our latest study, we proposed a new method to estimate nephron number using unenhanced computed tomography and biopsy-based stereology [38]. Therefore, further study on a larger number of subjects, including CKD patients who are often unsuitable for contrast media administration, is expected with this new method.

Despite these limitations, a major strength of the present study is the measurement of SNGFR in humans as a representative parameter of renal hemodynamic change at the single-nephron level. Few studies previously investigated SNGFR in association with protein intake. We also examined the correlation of SNGFR with diet-related parameters to reveal the strong association between protein intake and glomerular hyperfiltration.

### 3. Conclusions

The present study, including healthy Japanese living kidney donors, reveals that greater protein intake might lead to increased SNGFR and glomerular hyperfiltration. These findings gave us a new insight to understand the critical role of a high-protein diet in inducing glomerular hyperfiltration.

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