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High-Normal Protein Intake Is Not Associated With Faster Renal Function Deterioration in Patients With Type 2 Diabetes: A Prospective Analysis in the DIALECT Cohort

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OBJECTIVE

To study the prospective association between dietary protein intake and renal function deterioration in patients with type 2 diabetes (T2D).

RESEARCH DESIGN AND METHODS

Prospective analyses were performed in data of 382 patients of the Diabetes and Lifestyle Cohort Twente (DIALECT) study. Dietary protein intake was determined by the Maroni equation from 24-h urinary urea excretion. Renal function deterioration was defined as need for renal replacement therapy or a persistent increase of ≥50% in serum creatinine. Cox proportional hazards models were used to calculate hazard ratios (HRs) for the association between dietary protein intake and renal function deterioration. Threshold levels represent the dietary protein intake at which there was a significantly increased and reduced hazard of renal function deterioration.

RESULTS

Renal function deterioration occurred in 53 patients (14%), with a median follow-up duration of 6 (interquartile range 5–9) years. Mean dietary protein intake was 91 ± 27 g/day (1.22 ± 0.33 g/kg ideal body weight/day). Dietary protein intake was inversely associated with renal function deterioration (HR 0.62 [95% CI 0.44–0.90]). Patients with an intake <92 g/day had an increased hazard for renal function deterioration (HR 1.44 [95% CI 1.00–2.06]), while patients with an intake >163 g/day had a decreased hazard for renal function deterioration (HR 0.42 [95% CI 0.18–1.00]). Regarding dietary protein intake per kilogram body weight, patients with an intake <1.08 g/kg/day had an increased hazard for renal function deterioration (HR 1.63 [95% CI 1.00–2.65]).

CONCLUSIONS

In patients with T2D, unrestricted dietary protein intake was not associated with an increased hazard of renal function deterioration. Therefore, substituting carbohydrates with dietary protein is not contraindicated as a part of T2D management, although it may have a positive effect on body weight while minimizing loss of muscle mass.

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Because a high dietary protein intake has traditionally been considered as a factor that could enhance progression of chronic kidney disease (CKD) (1), dietary guidelines advise to limit dietary protein intake or even to maintain a dietary protein restriction in advanced CKD (2). In type 2 diabetes (T2D), renal function impairment is a prominent complication that occurs in 20–40% of patients (3,4).

Regarding diet in T2D, there is a strong tendency to focus on carbohydrate content (5). A low-carbohydrate diet is recommended in diabetes guidelines to manage glycemic control and to prevent complications (6,7). However, reducing carbohydrates will usually be accompanied by a shift toward increased dietary protein intake, which raises concerns about the effects of such a diet on kidney health (8). The current Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for patients with T2D and CKD (estimated glomerular filtration rate [eGFR] $<$60 mL/min/1.73 m^2) not treated with dialysis suggest to maintain a protein intake that does not exceed 0.8 g/kg/day (9). It remains unsettled, however, whether a higher protein intake would jeopardize renal function in the long-term in T2D with or without CKD. In this study, we investigated the prospective association between dietary protein intake and renal function deterioration in patients with T2D treated in secondary care.

RESEARCH DESIGN AND METHODS

Study Design

We performed prospective analyses using data of the Diabetes and Lifestyle Cohort Twente (DIALECT) study (10). DIALECT is an observational prospective cohort study performed in Ziekenhuis Groep Twente Hospital (Almelo and Hengelo, the Netherlands) that investigates the effect of lifestyle, including dietary habits, and medication use on outcomes in patients with T2D. Patients in DIALECT were included between September 2009 and January 2016. The study was performed according to the guidelines of good clinical practice and the Declaration of Helsinki. Written informed consent was obtained from all subjects before participation. The study has been approved by the local institutional review boards (METC registration numbers NL57219.044.16 and 1009.68020) and is registered in The Netherlands Trial Register (NTR trial code 5855).

Patients

The study population consists of patients with T2D aged ≥18 years treated in the outpatient clinic of the Ziekenhuis Groep Twente Hospital. Patients requiring renal replacement therapy or patients with insufficient knowledge of the Dutch language were excluded from participation. From the initial 433 patients with T2D with or without CKD included, we excluded those with missing follow-up data on renal function deterioration (n = 2) and with missing dietary protein intake data (n = 49), leaving 382 patients for analysis.

Dietary Assessment

Dietary protein intake was determined at baseline from urea excretion in 24-h urine by the Maroni equation: 6.25 * ([0.18 * urinary urea excretion (mmol/24 h)] + [0.031 * body weight (kg)]) + urinary protein excretion (g/24 h) (11,12). Ideal body weight was used to estimate dietary protein intake in g/kg/day on the basis of a BMI of 25 kg/m^2 (13). DIALECT is a strictly observational study, and participants did not receive dietary counseling other than their usual care.

Outcome Measurement

Renal function deterioration was defined as need for renal replacement therapy (i.e., kidney transplantation, initiation of peritoneal dialysis or hemodialysis) or a persistent increase of ≥50% in serum creatinine from the baseline visit for at least 3 months (14). Serum creatinine was routinely measured every 3 months. In case of nephrectomy, the surgery date was used as the censor date. Until time to surgery, patients were not at risk for a chronic renal function deterioration.

Covariates

During the study visit at which baseline assessments were performed, we collected information relevant to medical condition and pharmacological treatment. Weight (kg), height (cm), and waist and hip circumference (cm) were measured and BMI calculated (kg/m^2). Body surface area (BSA) was determined with the DuBois equation: weight (kg)$^{0.425}$ * height (m)$^{0.725}$ * 0.007184 (15). Information about lifestyle exposures (e.g., smoking, physical activity) was collected by a self-administered questionnaire. Physical activity was assessed by the previously validated Short Questionnaire to Assess Health Enhancing Physical Activity questionnaire (16). An activity score was calculated on the basis of minutes of activity per day multiplied by an intensity factor. From these data, we scored which patients met the Dutch healthy exercise norm of 30-min moderate intensity activity a day for at least 5 days a week (17).

Patients were asked to collect 24-h urine to obtain the urinary excretion of urea and sodium as objective measure of protein and sodium intake, respectively, by multiplying these concentrations with the volume of the 24-hour urine collection. Prevalent proteinuria was defined as ≥150 mg/24 h. For proper collection of the 24-h urine sample, patients were instructed to dispose of the first morning void and thereafter collect all urine in the provided canister, including the first morning void of the next day. Patients were instructed to store the canister in a dark, cool place, preferably in a refrigerator. Nonfasting venous blood was used for routine laboratory tests. Renal function at baseline was estimated with the serum creatinine–based Chronic Kidney Disease Epidemiology Collaboration equation from 2009 (18). Blood pressure was measured in a supine position by an automated device (Dinamap; GE Medical Systems, Milwaukee, WI) for 15 minutes with a 1-minute interval. Mean systolic and diastolic blood pressure of the last three measurements was used for further analysis.

Procedures

At baseline, laboratory tests and 24-h urine collection were used to identify the exposure variable and potential confounders. Urinary urea excretion was used to determine dietary protein intake, and urinary protein excretion was used to assess prevalent proteinuria (≥150 mg/24 h). Serum creatinine was assessed to estimate renal function because low eGFR at baseline is an independent risk factor for renal function deterioration among patients with T2D (19). During the follow-up period,

routine laboratory tests were used to identify a persistent increase of ≥50% in serum creatinine from baseline visit for at least 3 months. The need for renal replacement therapy was derived from the electronic patient file.

Statistical Analysis

All statistical analyses were performed using R 4.0.3 software (R Foundation for Statistical Computing, Vienna, Austria). Normally distributed data are presented as mean (SD), skewed variables are presented as median (interquartile range [IQR]), and categorical variables are presented as number (percent). A two-tailed $P < 0.05$ was considered to indicate statistical significance.

Univariable and multivariable Cox proportional hazards models were used to calculate hazard ratios (HRs) for the association between dietary protein intake and renal function deterioration, expressed per incremental SD. Survival time was calculated as the difference in days between the baseline visit and date of renal function deterioration or censoring date, defined as the date of the last available routine laboratory test. Competing risk analysis was performed in which patients were censored in case of all-cause mortality. The proportional hazards assumption was verified visually with plots of the scaled Schoenfeld residuals and was not violated in any of the models. Potential nonlinear effects of dietary protein intake on the baseline hazard of renal function deterioration were modeled using natural cubic splines with 2 df, where boundary knots were set to the 5th and 95th percentiles of dietary protein intake. Potential modification of the effect of dietary protein intake on the baseline hazard for renal function deterioration by sex was explored by introduction of a product term into the model. Multivariable Wald tests were used to select an appropriate structure of the linear predictor. Potential confounders were selected on the basis of relevant differences in characteristics in the baseline table, biological plausibility, and previous literature.

The multivariable model was adjusted for age, sex, baseline eGFR, and prevalent proteinuria at baseline (≥150 mg/24 h). Results were graphically depicted to facilitate their interpretation. HRs for different levels of dietary protein intake were established by comparing the hazard of renal function deterioration for a hypothetical male patient of median age (65 years) with median eGFR (84 mL/min/1.73 m^2) and prevalent proteinuria (≥150 mg/24 h) with the hazard of renal function deterioration for a hypothetical patient who had the mean value for every covariate (including sex and prevalent proteinuria). Threshold levels represent the dietary protein intakes at which there was a significantly increased and reduced hazard of renal function deterioration on the basis of the 95% CI. In addition, we computed the expected cumulative incidence of renal function deterioration for two hypothetical patients, with dietary protein intakes below the value associated with an increased hazard of renal function deterioration (75 g/day) and above the value associated with a reduced hazard of renal function deterioration (180 g/day). Sensitivity analyses were performed in which BSA was added to the multivariable model, with blood pressure and use of antihypertensive agents added to the multivariable model, with use of urinary urea excretion as exposure instead of dietary protein intake, and with cystatin C–based eGFR instead of serum creatinine–based eGFR.

RESULTS

Baseline Characteristics

Mean ± SD age of the 382 participants (59% male) was 63 ± 9 years. Mean ± BMI, eGFR, and dietary protein intake were 32.8 ± 5.8 kg/m^2, 78 ± 24 mL/min/1.73 m^2, and 91 ± 27 g/day (i.e., 1.22 ± 0.33 g/kg/day), respectively (Table 1). Median (IQR) frequency rate of serum creatinine assessment was 3 (2–5) measurements per year. After a median (IQR) follow-up duration of 6 (5–9) years, 53 patients experienced renal function deterioration. Age (HR 1.39 [95% CI 1.02–1.89]), prevalent macrovascular complications (HR 2.07 [95% CI 1.20–3.55]), proteinuria (HR 1.98 [95% CI 1.09–3.59]), and use of any antihypertensive treatment (HR 2.41 [95% CI 1.09–5.34]) were associated with an increased hazard of renal function deterioration. In contrast, diastolic blood pressure (HR 0.72 [95% CI 0.55–0.97]); eGFR (HR 0.70 [95% CI 0.54–0.92]); and dietary protein intake, when expressed in g/day (HR 0.68 [95% CI 0.51–0.92]) and in g/kg/day (HR 0.71 [95% CI 0.53–0.96]), were associated with a reduced hazard of renal function deterioration.

Dietary Protein Intake and Renal Function Deterioration

There was no indication for a nonlinear association between dietary protein intake and renal function deterioration ($P_{nonlinear}$ = 0.26). Adjusted for multiple potential confounders, dietary protein intake remained inversely associated with renal function deterioration (HR 0.62 [95% CI 0.44–0.90]) (Fig. 1*A*). The effect of dietary protein intake on renal function deterioration did not differ between males and females ($P_{interaction}$ = 0.27). Patients with an intake <92 g/day had an increased hazard for renal function deterioration (HR 1.44 [95% CI 1.00–2.06]), while patients with an intake >163 g/day had a decreased hazard of renal function deterioration (HR 0.42 [95% CI 0.18–1.00]). To facilitate clinical interpretation of the magnitude of the difference in hazards associated with low- versus high-protein intake, the expected cumulative incidence of renal function deterioration was graphically depicted for two hypothetical patients, i.e., one with a protein intake of 75 g/day and one with a protein intake of 180 g/day (Fig. 1*B*). After 4 years of follow-up, a protein intake of 75 g/day was associated with a higher expected cumulative incidence of renal function deterioration than 180 g/day. In a subgroup analysis of patients with CKD (*n* = 85, 22%), the point estimate for the association between protein intake and renal function deterioration was of similar magnitude, albeit not statistically significant (HR 0.59 [95% CI 0.32–1.08]).

Protein Intake per kg Body Weight and Renal Function Deterioration

Dietary protein intake in g/kg/day was inversely associated with renal function deterioration after accounting for relevant confounders. Patients with an intake <1.08 g/kg/day (*n* = 121, 32%) had an increased hazard of renal function deterioration (Fig. 2). Prevalent proteinuria (≥150 mg/24 h, *n* = 221) was associated with an increased hazard for renal function deterioration (HR 2.16 [95% CI 1.16–4.03]) (Table 2). Age, sex, and baseline eGFR were not associated with renal function deterioration after accounting for relevant confounders.

Table 1—Univariable HRs for renal function deterioration in patients with T2D included in DIALECT

	Total population	HR	95% CI	*P*
Age (years)	63 ± 9	1.39	1.02–1.89	0.035
Male sex	224 (59)	0.92	0.54–1.59	0.78
BMI (kg/m^2)	32.8 ± 5.8	0.93	0.70–1.22	0.59
BSA (m^2)	2.09 ± 0.22	0.79	0.59–1.05	0.10
Waist circumference (cm)†	112 ± 13	0.94	0.72–1.23	0.65
Current smoking status	68 (18)	1.62	0.89–2.95	0.12
Alcohol consumption†				
No (<1 unit/month)	135 (36)			
Moderate (1 unit/month–1 unit/day)	143 (38)	0.58	0.30–1.12	0.10
High (>1 unit/day)	96 (26)	0.94	0.48–1.83	0.86
Physical activity: adherence to the Dutch healthy exercise norm†	200 (53)	0.86	0.50–1.49	0.60
Systolic blood pressure (mmHg)†	136 ± 16	0.87	0.64–1.17	0.35
Diastolic blood pressure (mmHg)†	75 ± 9	0.72	0.55–0.97	0.023
HbA_{1c} (mmol/mol)†	57 ± 12	0.92	0.69–1.22	0.57
eGFR (mL/min/1.73 m^2)	78 ± 24	0.70	0.54–0.92	0.009
Macrovascular complications	143 (37)	2.07	1.20–3.55	0.009
Proteinuria	221 (58)	1.98	1.09–3.59	0.026
Urinary urea excretion (mmol/24 h)	417 ± 150	0.69	0.51–0.92	0.013
Pharmacological treatment				
RAASi	276 (72)	0.89	0.48–1.63	0.70
Any antihypertensive treatment	278 (73)	2.41	1.09–5.34	0.030
Nutritional intake				
Dietary protein intake (g/day)	91 ± 27	0.68	0.51–0.92	0.013
Dietary protein intake (g/kg/day)	1.22 ± 0.33	0.71	0.53–0.96	0.025
Estimated sodium intake (g/day)†*	4.32 ± 1.86	0.76	0.57–1.02	0.07

Data are mean ± SD or *n* (%). HRs for the association of continuous variables with incident renal function deterioration are expressed per incremental SD in the specific predictor concerned. HbA_{1c}, glycated hemoglobin; RAASi, renin angiotensin aldosterone system inhibitor. †Missing values for waist circumference (*n* = 3), alcohol consumption (*n* = 8), physical activity (*n* = 2), systolic and diastolic blood pressure (*n* = 11), serum HbA_{1c} (*n* = 1), and estimated sodium intake (*n* = 1). *Based on 24-h urinary sodium excretion.

Sensitivity Analysis

Multiple sensitivity analyses were performed, addressing the possible impact of either BSA, blood pressure, or use of antihypertensive agents on the association between dietary protein intake and renal function deterioration. Neither of these sensitivity analyses materially changed from those from the primary analyses. In addition, the results of the analyses with use of urinary urea excretion as exposure instead of dietary protein intake and with cystatin C–based eGFR instead of serum creatinine–based eGFR remained materially unchanged compared with the primary analyses.

CONCLUSIONS

In this prospective study among 382 patients with T2D, we investigated the relation between dietary protein intake and renal function deterioration. The main finding of this study was that a higher dietary protein intake is not associated with increased renal function deterioration. By contrast, a dietary protein intake <92 g/day (<1.08 g/kg/day) appeared to be associated with an increased hazard of renal function deterioration in patients with T2D.

Although our finding may seem controversial, a beneficial association between dietary protein intake and development of CKD has also been previously found in the Ongoing Telmisartan Alone and in Combination With Ramipril Global End Point Trial (ONTARGET), wherein diet had been assessed by food frequency questionnaires (20). Our study, using objective assessment of protein intake from 24-h urine urea excretion, provides an independent replication of the ONTARGET findings. Therefore, we urge that the existing recommendation for dietary protein restriction as prevention of CKD in T2D be reconsidered (21,22). The current KDIGO guidelines suggest maintaining a diet that does not exceed a protein intake of 0.8 g/kg/day for patients with T2D and CKD (eGFR <60 mL/min/1.73 m^2) not treated with dialysis (9). Although our results apply to the full range of kidney function in nondialysis-dependent patients with T2D, in subgroup analysis of patients with CKD, the point estimate for the association between protein intake and renal function deterioration was of similar magnitude, albeit of borderline significance (*P* = 0.08), which may be due to lack of power in this relatively small subgroup (*n* = 85). It would be interesting to see whether the beneficial association between protein intake and renal function deterioration observed can be replicated in a larger population, since concerns have been raised

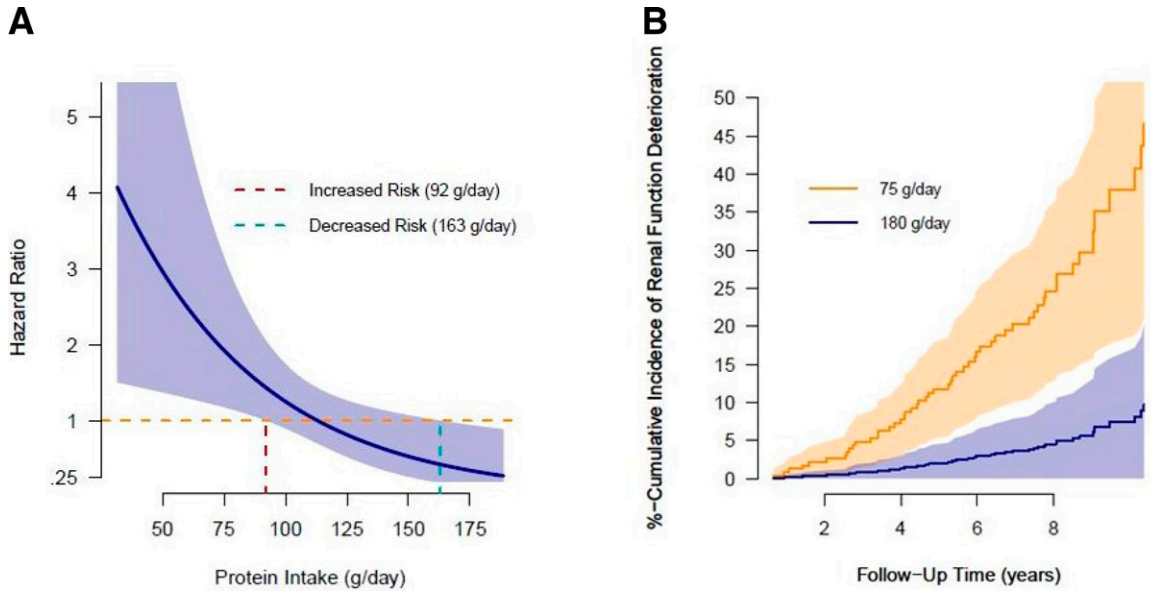

Figure 1—*A*: Association between dietary protein intake (g/day) and the hazard of renal function deterioration. HRs for different levels of dietary protein intake were established by comparing the hazard of renal function deterioration for a hypothetical male patient of median age (65 years) with median eGFR (84 mL/min/1.73 m^2) and prevalent proteinuria (≥150 mg/24 h) with the hazard of renal function deterioration for a hypothetical patient who had the mean value for every covariate (including sex and prevalent proteinuria). The HR is shown as a solid line, and the associated pointwise 95% CIs are represented by the shaded area. The null effect (HR 1) is shown by the orange dashed line. The red and green dashed lines represent the dietary protein intakes at which there was a significantly increased and reduced hazard of renal function deterioration, respectively. *B*: Expected cumulative incidence of renal function deterioration for two hypothetical 65-year-old male patients with prevalent proteinuria and a median eGFR of 84 mL/min/1.73 m^2 and dietary protein intakes of 75 g/day and 180 g/day.

about kidney health due to the strong focus on a low-carbohydrate diet as recommended in diabetes guidelines, and the usually higher dietary protein intake that accompanies such a diet (8). In addition, the recommended protein intake in patients with chronic diseases amounts to 1.2 g/kg/day (23), and our results indicate that unrestricted dietary intake of protein is not associated with an increased hazard of renal function deterioration, suggesting that this recommendation suits patients with T2D not treated with renal replacement therapy to prevent renal function deterioration.

A protein restriction in patients with CKD is based on a trade-off between the need to prevent renal function deterioration on the one hand and the need to maintain adequate nutritional status and prevent malnutrition on the other. A low-protein intake increases the risk of protein malnutrition, which may result in low muscle mass and mortality (24, 25). Previous findings from DIALECT showed that patients with a low-protein intake also have a low muscle mass and are less physically active (26). It is plausible that this cluster of characteristics represents less healthy patients who are at higher risk of renal function deterioration. Therefore, although consuming dietary protein might play an important role, it is likely not a single cause. In addition, our results did not indicate a nonlinear association between dietary protein intake and renal function deterioration ($P_{nonlinear}$ = 0.26). Therefore, we were able to conclude that a higher dietary protein intake (>163 g/day) is associated with preservation of renal function, although the beneficial effect of higher dietary protein intake was not found when using dietary protein intake in g/kg/day.

Compared with other European diabetes populations, mean dietary protein intake in our study population was more or less similar (91.0 vs. 94.2 g/day) (27). However, compared with the general Dutch population, dietary protein intake was somewhat higher in our study population (99 vs. 95 g/day in men, 79 vs. 72 g/day in women) (28). This might reflect diet adaptations related to diabetes, emphasizing restriction of calories and carbohydrates. Of note, it is unlikely that patients in the cohort have previously received dietary counseling aimed at protein restriction because dietary counseling regarding CKD is limited to the predialysis clinic (i.e., patients with eGFR <30 mL/min/1.73 m^2). Since only 3% of the DIALECT participants had eGFR <30 mL/min/1.73 m^2, we are not able to draw conclusions on the risks or benefits of dietary protein content in CKD stage IV.

A low dietary protein intake may lead to vasoconstriction of the afferent arterioles in the glomeruli, which has been observed to diminish glomerular damage (8). A high dietary protein intake may result in an increased glomerular pressure and glomerular hyperfiltration, which may lead to proteinuria (29). We found that patients with proteinuria have a higher dietary protein intake than those without (95 vs. 85 g/day), and prevalent proteinuria was independently associated with an increased hazard for renal function deterioration. Nevertheless, we found that the beneficial association between dietary protein intake and renal function deterioration was most clearly present in patients with proteinuria (Table 2). Previous literature also irrefutably showed that poor blood pressure management is associated with unfavorable renal outcomes (30). Somewhat unexpectedly, no evidence of this association was found in our population possibly because there is a strong clinical

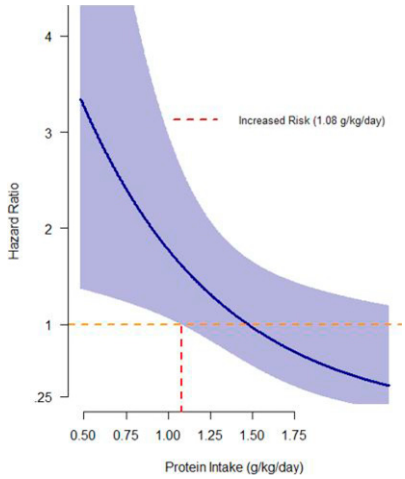

Figure 2—Association between dietary protein intake (g/kg/day) and the hazard of renal function deterioration. HRs for different levels of dietary protein intake were established by comparing the hazard of renal function deterioration for a hypothetical male patient of median age (65 years) with median eGFR (84 mL/min/1.73 m^2) and prevalent proteinuria (≥150 mg/24 h) with the hazard of renal function deterioration for a hypothetical patient who had the mean value for every covariate (including sex and prevalent proteinuria). The HR is shown by the solid line and the associated pointwise 95% CIs are represented by the shaded area. The null effect (HR 1) is shown by the orange dashed line. The red dashed lines represent the dietary protein intakes at which there was a significantly increased hazard of renal function deterioration.

focus on a lower blood pressure target in patients with proteinuria. In line with this notion, the percentage of patients using antihypertensive treatments is high in our population (73%).

The strength of the DIALECT cohort is that it reflects the real world of patients with T2D, with minimal loss to follow-up, and it was specifically designed to evaluate lifestyle characteristics such as dietary habits. Our study population appears to be a representative T2D population since renal function impairment was present in 22% of the patients compared with a prevalence rate of 20–40% in other T2D populations (3,4). In addition, we were able to assess dietary protein intake objectively, which is more reliable than subjective dietary protein assessment. Another strength is that we were able to adjust for baseline kidney function on the basis of cystatin C–based eGFR, which is independent of muscle mass, although follow-up data on cystatin C–based renal function were not available. Obviously, our observational design limits us in determining causation, and we were not able to check whether our results are mainly the result of dietary protein intake. Also, 24-h urine specimens might have been collected with error. Finally, protein intake was assessed at baseline only, and we did not monitor whether patients had changed their dietary protein intake during the follow-up period.

Table 2—Multivariable HRs for the association between dietary protein intake and renal function deterioration in patients with T2D included in the DIALECT population

	HR	95% CI	*P*
Dietary protein intake (g/kg/day)	0.67	0.48–0.94	0.017
Age (years)	1.16	0.82–1.64	0.40
Sex (female)	0.98	0.56–1.72	0.95
eGFR (mL/min/1.73 m^2)	0.83	0.60–1.14	0.24
Prevalent proteinuria (yes)	2.16	1.16–4.03	0.015

The multivariable model was adjusted for age, sex, baseline eGFR, and prevalent proteinuria at baseline (>150 mg/24 h). Continuous variables were expressed per incremental SD.

With regard to the potential impact on population health, substituting carbohydrates with dietary protein seems a rational approach in T2D management, which may have a positive effect on body weight while minimizing loss of muscle mass (31). A specific note is that dietary recommendations should take into account individual nutritional needs. Patients with T2D and CKD often have multiple comorbid diseases, which requires more complex dietary recommendations. In addition, to conform a sustained effect of dietary protein intake over the long term, assessment of dietary compliance will be a challenging aspect.

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Author Contributions. M.M.O. performed statistical analyses and wrote the manuscript. D.G. supervised the statistical analyses, interpreted the outcome measures, contributed to the discussion, and reviewed/edited the manuscript. G.N. and S.J.L.B contributed to the discussion and reviewed/edited the manuscript. G.D.L. was principal investigator of this study, coordinated the study, contributed to the discussion, and reviewed/edited the manuscript. M.M.O. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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