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The association between urinary albumin excretion and nutrient status in patients with type 2 diabetes mellitus

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ABSTRACT

Introduction: Diet plays an important role in blood glucose control and management of vascular complications in patients with type 2 diabetes mellitus (T2DM). Excess food intake can be a burden to kidney function and, therefore increase diabetic nephropathy in T2DM.
Objectives: To determine the nutritional status and the association between nutrition regime and urinary albumin excretion in patients with T2DM in Vietnam.
Patients and Methods: The study was carried out on 594 outpatients with T2DM at military hospital 103, Hanoi, Vietnam from December 2020 to April 2021. Nutrient regime was calculated based on the guidelines of Vietnam national institute of nutrition. Urinary albumin concentrations were measured by enzymatic turbidimeter autoanalyzer.
Results: Twenty-four hours nutrient intake is as follows: mean total calorie intake of 1913.72 ± 235.87 kcal; protein of 80.76 ± 14.56 g, fat of 51.10 ± 13.97 g, carbohydrate of 284.83 ± 47.71 g, fiber of 7.35 g (5.85-8.87). Calorie, protein, fat, and carbohydrate intakes per kilogram of body weight (BW) are lower in men compared with women. In the univariate analysis, urinary albumin concentrations correlated with 24-hour protein intake (r = 0.391, $P=0.02$). In the univariate linear regression analysis, urinary albumin significantly correlated with protein intake (standardized B=0.616, $P=0.004$); fat intake (standardized B=0.601, $P=0.002$); diabetes duration (standardized B=0.441, $P=0.028$), and energy intake (standardized B=-0.467, $P=0.039$). Microalbuminuria (MAU) significantly correlated with protein intake (OR=1.042, $P=0.006$) and HbA1c (OR = 1.664, $P=0.013$).
Conclusion: In patients with T2DM in Vietnam, 24-hour calory intake is 1913.72 ± 235.87 kcal, fat and carbohydrate intakes are within the normal range. Urinary albumin concentrations and MAU had a significant correlation with protein, fat and calory intakes.

Implication for health policy/practice/research/medical education:
This study contributes to the reservoir of knowledge on the association between a high-protein diet and blood glucose control with the occurrence of microalbuminuria in patients with type 2 diabetes mellitus (T2DM). The results have implications in the treatment of diabetes, as dietary modification and good blood glucose control will contribute to protecting kidney function.
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Original

Introduction

Diabetic nephropathy is a popular complication of diabetes besides retinopathy and neuropathy, which is presented as diabetic microvascular complications (1). Diabetic nephropathy is a renal deterioration with albuminuria, occurs in 20% to 40% of patients with

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diabetes, and leads to end-stage renal disease (2). A patient who has a progression from microalbuminuria (MAU) to (3) macroalbuminuria is likely to riskily suffer from developing end-stage renal diseases in a few years. Balanced and sufficient nourishment is recommended for diabetes mellitus patients as a key factor of diet therapy. Diabetes mellitus patients should be recommended balanced and sufficient nourishment in their diet therapy, this can as well significantly improve their kidney function (4). A higher dietary inflammatory index score (a pro-inflammatory diet) has a close relationship with the risk of metabolic syndrome and its components such as fasting blood glucose, triglyceride, and waist circumference (5). Therefore, proper nutrition plays the management of diabetic microvascular complications such as diabetic nephropathy. The patient who suffers from diabetic nephropathic complications is in need of nutrition education to suitably manage the disease progression as well as to improve the quality of life (6).

Despite the role of high-protein diets in weight management of type 2 diabetes mellitus (T2DM) (7), it can lead to high intraglomerular pressure, glomerular injury, and albuminuria (8). Eating foods high in protein may reduce kidney size and body weight in humans (9). Besides, changes in hormonal mediators (e.g., glucagon and hormone-insulin-like growth factor -1) are proposed as underlying mechanisms to facilitate the increased excretion of excess nitrogen, leading to vasodilation, changes in neuroendocrine responses (such as tubuloglomerular feedback) within the kidney (4). In patients who have, or potentially have chronic kidney disease, their kidneys might be evoked disadvantageous effects when having a high intake of animal proteins (10). As a result, it may lead from micro- to macroalbuminuria, which is presented by an initial rise and a following rapid decrease in glomerular filtration rate (11). In contrast, a dietary protein restriction can effectively limit the progression of renal dysfunction and reduce albuminuria (12). According to a recent study, renal function deterioration could be prevented by proactive management right after being diagnosed. Therefore, it is important to customize the nutrition regime based on individual characteristics as soon as possible (2).

Objectives

In Vietnam, the nutrition regime for patients with T2DM has recently been interested in by the government in many aspects such as energy intake per day, and nutritional composition for better T2DM management. However, dietary factors relevant to the occurrence of MAU in T2DM are not well defined. Therefore, we conducted this study to determine the nutritional status including energy and amount intakes of protein, fat, carbohydrates, and other factors in macronutrients, as well as the association between nutrition regime and urinary albumin excretion in patients with T2DM in Vietnam.

Patients and Methods

Study population and design

A cross-sectional descriptive study was implemented on 594 outpatients with T2DM in Military hospital 103 (Hanoi, Vietnam) from December 2020 to April 2021. All patients in the research were diagnosed with T2DM following the American Diabetes Association guideline – 2020 (13). We excluded T2DM with chronic organ failure (such as live, heart or kidney), hematological diseases (such as moderate-to-severe anemia, hemorrhagic conditions, hemolytic anemia), systemic disorders, infectious diseases and severe diabetic conditions (hyperosmolarity, diabetic ketoacidosis, lactic acidosis and hypoglycemia), and those who were currently prescribed with drugs affecting urinary albumin excretion (converting enzyme inhibitors).

Clinical and biochemical assessments

All participants were questioned about their comorbidity illnesses and use of drugs in history. Anthropometric measurements and clinical examination were likewise accumulated.

The patients were asked to not eat for at least 8 hours, their first blood and urine samples would be collected at 7:00 am the next morning. Fasting plasma glucose (FPG), two-hour postprandial glucose level (2h-PPG), total cholesterol, triglyceride, high low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), alanine transaminase (ALT), aspartate transaminase (AST), serum creatinine, and plasma HbA1c were measured as ISO protocol of the hospital laboratory. Urinary albumin was quantified by enzymatic turbidimeter autoanalyzer (Beckman AU680, USA) in a morning urine spot collection. MAU is defined as urinary albumin of between 30 and 300 mg.

The 24-hour diet recall interviews

The daily diet was investigated by volunteers using a form, which includes dietary energy and nutrients. The form records what patients eat and drink for three days composed of 2 weekdays and 1 weekend day including all meals, snacks, and beverages, and the time they eat or drink them. Participants are allowed to choose their days to record the survey (14).

Besides, we considered the dietary intake photo book of the institute of nutrition in 2014 as a reference build survey questionnaire about the type and amount of food. Our data is collected from four 24-hour recalls, they were analyzed by the national institute of nutrition's nutrition software, according the Vietnamese food composition databases. Energy and macronutrient (carbohydrate, lipid and protein) intakes were expressed as kcal/kg actual body weight (BW)/day, and g/kg actual BW/day, respectively. Evaluation of daily dietary status is as follows: the subject's diet was assessed by the total amount of food consumption, the nutritional value of the food, and the response level of the recommended diet for each age group based on the

table of dietary reference intakes recommendations for Vietnamese people in 2016.

Statistical analysis

Data were expressed as mean ± SD for normal distribution variables or Median (interquartile range, Q1-Q3). Student's T-test or Mann Whitney U test were employed to test the differences between groups. Correlations between serum MAU levels and other variables were measured with Pearson's and Spearman's analysis. The chi-square test was conducted to test if there is an association between two categorical variables. Multivariate linear regression was used to check the effects of related factors which affect urinary albumin concentrations. *P* values of less than 0.05 were set as significant. Statistical data analysis by the SPSS version 26.

Results

The mean age was 63.83 ± 10.05 years. The mean FPG was 7.55 mmol/L (6.50-8.82). The percentage of MAU was 25.44%. The percentage of T2DM patients who achieved the control target was 58.8% for HbA1c, 41.9% for FPG, and 18.9% for PPG. Mean weight, FPG, Aspartate transferase (AST), and Alanine transferase (ALT), urinary albumin concentrations, and percentage of MAU were significantly higher in men than in women. The means of age, cholesterol, and creatinine levels in women were significantly higher than those in men (Table 1).

24-Hour nutrient intake was as follows: mean total calorie intake of 1913.72 ± 235.87 kcal; protein of 80.76 ± 14.56 g, fat of 51.10 ± 13.97 g, carbohydrate of 284.83 ± 47.71 g, the fiber of 7.35 g (5.85-8.87). Total calorie, protein, fat, and carbohydrate intakes calculated per kg body weight of men were significantly lower than those of women ($P < 0.001$). The difference in dietary fiber intake between men and women was not significant. Dietary lipid and carbohydrate levels of men and women were within normal limits (Table 2).

Univariate regression analysis indicated that urinary albumin concentrations positively correlated with 24h dietary protein intake ($r = 0.391$, $P = 0.02$), duration of T2DM disease ($r = 0.432$, $P = 0.009$), FPG ($r = 0.386$, $P = 0.022$), creatinine ($r = 0.459$, $P = 0.008$), but inversely correlated with cholesterol ($r = -0.350$, $P = 0.042$). Multivariate regression analysis outlined that the concentration of urinary albumin was significantly related to the amount of protein intake (standardized B = 0.616, $P = 0.004$), lipid intake (standardized B = 0.601, $P = 0.002$), duration of T2DM (standardized B = 0.441, $P = 0.028$), and 24h dietary energy intake (standardized B = -0.467, $P = 0.039$; Table 3).

Multivariate logistic regression analysis indicated that

Table 1. The clinical and subclinical characteristics of the participants

Variables, unit	Men	Women	All
Age, years	62.33 ± 10.51[a]	65.60 ± 9.19[a]	63.83 ± 10.05
Duration of diabetes, years	6 (3-10)	6 (3-11)	6 (3-10)
Weight, kg	63.22 ± 8.48[a]	54.60 ± 7.93[a]	59.25 ± 9.29
Weight loss during 6 months, kg	0.64 (0-10)	0.69 (0-8)	0.66 (0-10)
BMI, kg/m^2	23.22 ± 2.57	23.00 ± 3.03	23.12 ± 2.79
BMI ≥ 23 kg/m^2, %	53.3	47.3	50.5
FPG, mmol/L	7.60 (6.56-9.13)[b]	7.40 (6.48-8.46)[b]	7.55 (6.50-8.82)
FPG < 7.2 mmol/L, %	39.8	44.4	41.9
2h-PPG, mmol/L	13.89 ± 5.15	14.61 ± 4.73	14.21 ± 4.97
PPG < 10.0 mmol/L, %	22.5	14.3	18.9
HbA1c, %	6.6 (6.0-7.5)	6.8 (6.1-7.7)	6.7 (6.1-7.6)
HbA1c < 7.0%, %	60.4	56.9	58.8
Urea, mmol/L	6.09 (5.66-8.02)	5.20 (4.98-6.73)	5.97 (5.13-8.20)
Creatinine, µmol/L	91.0 (80.9-101.0)[a]	71.0 (65.0-78.1)[a]	81.5 (71.0-93.7)
Cholesterol, mmol/L	4.62 ± 1.15[b]	4.90 ± 1.12[b]	4.73 ± 1.14
Triglyceride, mmol/L	1.75 (1.25-2.81)	2.01 (1.45-2.73)	1.91 (1.34-2.78)
AST, UI/L	24.2 (20.4-30.2)[b]	22.2 (18.6-27.5)[b]	23.5 (19.4-29.2)
ALT, UI/L	25.9 (19.7-35.7)[a]	21.2 (16-29.9)[a]	23.8 (17.6-33.9)
Urinary albumin, mg/day	10.19 (6.16-45.26)[b]	8.29 (4.72-19.56)[b]	9.54 (5.04-31.61)
MAU, %	33.0[a]	16.0[b]	25.4

ALT; Alanine transferase, AST; Aspartate transferase, BMI; Body mass index, FPG; Fasting plasma glucose, 2h-PPG; 2-hour postprandial plasma glucose, MAU; microalbuminuria.
Data are expressed as mean ± SD or median (Q1-Q3); [a]*P* <0.001 and [b] *P* <0.05 (between male and female groups).

the occurrence of urinary albumin concentrations was associated with 24-hour dietary protein intake (OR = 1.042, $P = 0.006$), ALT (OR = 1.027, $P = 0.047$), weight (OR = 1.05, $P = 0.018$), weight loss at 6 months (OR = 1.477, $P = 0.027$), age (OR = 1.081, $P = 0.002$), and HbA1c (OR = 1.664, $P = 0.013$; Table 4).

Discussion

Nutritional status

WHO recommends maintaining a protein intake range of 0.8-1 g/kg body weight for adults (15). The ministry of health (MOH) of Vietnam has recommended nutritional supply according to age, in which adults should achieve protein intake from 1-1.13 g/kg body weight/24h, equivalent to 60-70 g protein/24 h (16). At our hospital, outpatient T2D cases are examined monthly to adjust medication and receive advice on diet and exercise. The procedure is applied according to the treatment guidelines of the ministry of health and is regularly updated. Our study showed that the daily protein intake of patients with T2DM was 79-81 g/24h (equivalent to 1.3-1.5 g/kg BW/24h). The general dietary energy level of both men and

Table 2. Nutrient intake determined through 24-hour recall and per kilogram of body weight per day

Variables, unit	Men	Women	All
Intake, kcal/day	1922.42 ± 232.40	1903.48 ± 239.92	1913.72 ± 235.87
Intake, kcal/kg BW/day	31.0 ± 5.8[a]	35.6 ± 7.1[a]	33.1 ± 6.9
Protein, g/day	81.81 ± 14.63	79.53 ± 14.42	80.76 ± 14.56
Protein, g/kg BW/day	1.32 ± 0.30[a]	1.49 ± 0.35[a]	1.40 ± 0.33
Fat, g/day	50.32 ± 13.39	52.02 ± 14.59	51.10 ± 13.97
Fat, g/kg BW/day	0.78 (0.63-0.95)	0.92 (0.74-1.15)	0.85 (0.68- 1.05)
Carbohydrates, g/day	286.95 ± 46.61	282.34 ± 48.94	284.83 ± 47.71
Carbohydrates, g/kg BW/day	4.62 ± 0.98[a]	5.29 ± 1.23[a]	4.93 ± 1.15
Fiber, g/day	7.42 (5.89-9.14)	7.26 (5.85-8.54)	7.35 (5.85-8.87)
Fiber, g/1000 kcal intake/day	3.82 (3.10-4.69)	3.69 (3.01-4.58)	3.76 (3.09-4.62)

Data are expressed as mean ± SD or median (Q1-Q3); [a]$P < 0.001$ and [b]$P < 0.05$ (between male and female groups).

Table 3. The association between urinary albumin concentrations and diet and the clinical and biomedical characteristics in the poor control HbA1c group (HbA1c >7%)

Variables	Univariate		Multivariate		
	r	*P* value	Standardized B	*P* value	VIF
Intake, kcal/d	0.205	0.238	-0.467	0.039	2.707
Protein, g/d	0.391	0.02	0.616	0.004	2.213
Fat, g/d	0.307	0.073	0.601	0.002	1.803
Carbohydrates, g/d	-0.038	0.829			
Fiber, g/d	-0.096	0.581			
Age, years	0.07	0.689			
Duration of T2DM, years	0.432	0.009	0.441	0.028	2.102
Body weight, kg	-0.276	0.108	0.214	0.449	4.637
Height, m	-0.037	0.835			
BMI, kg/m^2	-0.262	0.128	-0.006	0.977	2.989
FPG, mmol/L	0.386	0.022	0.449	0.073	3.398
2h-PPG, mmol/L	0.207	0.233	-0.474	0.059	3.389
HbA1c, %	0.075	0.669			
Creatinine, µmol/L	0.459	0.008	-0.113	0.491	1.553
Cholesterol, mmol/L	-0.350	0.042	-0.195	0.292	1.959
Triglyceride, mmol/L	-0.123	0.49			
AST, UI/L	0.156	0.372			
ALT, UI/L	0.085	0.627			

BMI; Body mass index, FPG; Fasting plasma glucose, 2h-PPG; 2-hour postprandial plasma glucose, HDL-C; high density lipoprotein cholesterol, VIF; Variance inflation factor, ALT; Alanine transferase, AST; Aspartate transferase.

Table 4. The association between MAU and dietary regimen and the demographic and biomedical characteristics

Variables	B	SE	*P*	OR	95% CI
Protein, g/d	0.041	0.015	0.006	1.042	1.012 - 1.072
Carbohydrates, g/d	-0.007	0.005	0.162	0.993	0.984 - 1.003
Fat, g/d	-0.019	0.017	0.268	0.981	0.949 - 1.015
Fiber, g/d	-0.108	0.08	0.177	0.898	0.767 - 1.05
ALT, UI/L	0.027	0.013	0.047	1.027	1.00 - 1.054
Body weight, kg	0.049	0.021	0.018	1.05	1.008 - 1.094
Weight loss during 6 months, kg	0.39	0.176	0.027	1.477	1.045 - 2.086
Age, years	0.078	0.026	0.002	1.081	1.028 - 1.137
HbA1c, %	0.509	0.205	0.013	1.664	1.113 - 2.49
Constant	-13.273	3.412	0	0	

MAU, Microalbumiuria; ALT, alanine aminotransferase; SE, standard error; OR, odds ratio.

women was similar to the recommendation (15). However, total calorie, protein, fat, and carbohydrate intakes calculated per kg of body weight were significantly lower in men than in women in patients with T2DM. Possibly, in Vietnam, women mainly do housework, therefore they pay more attention to the nutrition regimen than men. Furthermore, male patients are less likely to adhere to the recommended nutritional regimen than women. In fact, the application of health counseling advice depends on the characteristics of the individual. This is especially true in the case of diet. Evidence suggests that no perfect regime with a precise percentage of calories from macro nutrition to prevent diabetes is established; therefore, the suitable idea is to build a diet based on individual characteristics (2). Our results indicated that the patient's mean current protein intake was 1.4 g/kg BW/24h which was higher than the WHO recommendation (0.8-1 g/kg BW/24 h). This was partly due to the fact that patients with T2DM were aware that the diet for patients with T2DM must contain little amount of carbohydrates. And as a result, the patients consumed more protein to compensate for energy demand and maintain body weight (17).

The levels of adherence to the recommended diet and achievement of glycemic control among patients with T2DM depend closely on the proportion of dietary fiber in the total amount of food intake (18). It is evidently proven that the overall quality of food consumed, especially for high-fiber food such as whole grains, fruits, and vegetables and the limitation of using refined and processed foods, is associated with a lower risk of developing T2DM (19). The continuous consumption of adequate dietary fiber is associated with a reduction in all-cause mortality in patients with T2DM. Hence, patients with T2DM are advised to consume minimally 14 g of fiber per 1000 kcal intake, with whole intact grains accounting for at least half of the consumption amount (20). Our results indicated that the average fiber intake was 3.76 g/1000 kcal. This was a low level compared to the recommended level, especially for patients with T2DM who need more fiber in the diet to reduce glycemic index in their diet. Patients tend to consume little amount of the food group that supplies carbohydrates and increase in the group that provides protein. However, the former mainly supplies fiber, especially food derived from plants. Besides, it is likely that patients pay no attention to choosing foods that provide carbohydrates with a low glycemic index and rich in fiber. Hence, their diet does not provide the adequate amount of fiber (21).

Relationship between nutrient status and urinary albumin concentrations in patients with T2DM

Among those patients who did not meet the HbA1c treatment target (i.e, HbA1c >7 mmol/L), the univariate analysis outlined that urinary albumin positively correlated with 24h dietary protein intake ($r = 0.391$, $P = 0.02$). In patients with T2DM, dietary protein intake might affect renal diseases in some ways (22), it can be similarly expressed as a percentage of total food energy intake, which is provenly associated with albuminuria excretion rate (23). A low-protein in patients with T2DM with nephropathic complications maintains low-grade inflammation, proteinuria, and albuminuria. Besides, it leads to a positive protein balance toward an increase in protein and amino acid biosynthesis (24). Due to the distortion of news from social media, the effectiveness of low-carbohydrate and high-protein diets in inducing weight loss and achieving glycemic targets is likely to be blown up. In chronic kidney disease, a high-protein diet may have detrimental effects on kidney function and long-term kidney health (25). Many studies have shown that glomerular hyperfiltration is associated with high protein consumption. In early stages, glomerular hyperfiltration expresses through a rise in proteinuria, which may result in a reduction of kidney function over time, particularly in people who are having risk factors of chronic kidney disease (4,25). In the present study, multivariate analysis showed that urinary albumin positively correlated with 24h dietary protein intake (standardized B of 0.616, p

= 0.004), lipid intake of the 24h diet (standardized B of 0.601, $P=0.002$), and duration of T2DM (standardized B of 0.441, $P=0.028$). This may be due to either the damage to the microvasculature in the progression of T2DM or the contribution of a long-term unreasonable diet (21,25). Participants who consume excess protein in the regimen of a low-carbohydrate and high-protein diet would be more likely to have chronic kidney disease. Furthermore, high protein in food related to poor glycemic control in patients with diabetes, which is correspondingly one of the factors promoting the progression of kidney disease (26). Previous studies suggest that a diet with a high proportion of dietary lipid/fatty acid might be effective in reducing serum acid uric in patients with chronic kidney disease (4,27). High dietary fiber intake is likely to pose a lower risk of both inflammation and mortality in patients with kidney disease. However, the underlined mechanism has not been fully elucidated. Therefore, interventional trials are in need to confirm this causal effect (28). Our results showed that dietary fat and fiber intakes were not associated with MAU, which indicates that the daily nutrition of T2DM in Vietnam is focusing on protein and carbohydrate contents rather than lipid/fat and fiber. Therefore, in the diet with very low fiber content (7.35 g (5.85-8.87)), the lipid content was not reasonable. This increases the risk of developing MAU as well as chronic kidney disease.

Conclusion

In Vietnam, although mean 24-hour total calories, carbohydrates, and fat intakes were within the recommended range, T2DM patients consumed high protein and low fiber levels. Moreover, urinary albumin concentrations significantly correlated with protein, fat, and energy intakes. MAU significantly correlated with protein intake and HbA1c. All in all, this fact could affect the function of the kidney in T2DM in Vietnam.

Limitations of the study

Our study has limitations. First, this was a descriptive study, therefore it was not possible for us to evaluate the causal relationship between urinary albumin concentrations and nutrient regime. Moreover, our study did not mention the role of dietary habits and lifestyle in the nutrient regimen. Finally, patients might underestimate or overestimate the consumption of certain foods via eating diaries.

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Authors' contribution

Conceptualization: MPD, KXN, TDL.
Methodology: MPD, KXN, TDL and TBT.
Validation: KXN, TDL
Formal analysis: MDP, KXN, TDL and TBT.
Investigation: TTV and TBT.
Resources: TTV, TDL and MPD.
Data curation: KXN and MPD.
Writing-original draft : MDP and TDL.
Writing-review and editing: MPD, KXN, TDL, STN and TTV.
Visualization: KXN, TDL, AVN, BVN, STN, TLC, NMN, NPTN and TTV.
Supervision: NMN, TTV and TBT.
Project administration: MDP and TBT.

Conflicts of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data availability statement

The data used to support the findings of this study are available from the corresponding author upon request.

Ethical issues

All participants were provided with written informed consents and agreed to join our study; and the protocol was approved by the Ethical Review Committee of Vietnam Military Medical University, Vietnam (Ethical code #55/2021/IRB-VMMU). The study was also conducted using good clinical practice following the Declaration of Helsinki. Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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