Association of unhealthy dietary behaviors with renal function decline in patients with diabetes

Cheng-Wei Lin [ORCID] ,[1] I-Wen Chen,[1] Ying-Tzu Lin,[2] Hsin-Yun Chen,[2] Shih-Yuan Hung [ORCID] [1]

C-WL and I-WC contributed equally.

[1]Division of Endocrinology and Metabolism, Chang Gung Memorial Hospital Linkou Main Branch, Taoyuan, Taiwan
[2]Department of Medical Nutrition Therapy, Chang Gung Memorial Hospital Linkou Main Branch, Taoyuan, Taiwan

Correspondence to
Dr Shih-Yuan Hung;
9002053@gmail.com

ABSTRACT

Objective Balanced nutrition is important for patients with diabetes, and nutrition might well influence diabetes-related complications, although there is limited evidence for this supposition at present. Consequently, we investigate the association between dietary behaviors and renal function decline among patients with diabetes.

Research design and methods From 2011 to 2013, a total of 2797 patients with type 2 diabetes participated in the D*iabetes Shared Care* Program at Chang Gung Memorial Hospital. All received nutritional consulting by dieticians and an eight-item list of unhealthy dietary behaviors, which included the excessive intake of carbohydrates, fats, protein, fruit, pickled foods, dessert and alcohol, as well as inadequate dietary vegetable. Estimated glomerular filtration rate (eGFR) decline ≥40% was defined as a surrogate end point for kidney damage. Independent dietary risk factors predicting poor renal outcomes were assessed.

Results Stable mean glycated hemoglobin (A$_{1c}$) (7.78% to 7.75%, p=0.151), improved cholesterol (174.04 to 170.13 mg/dL, p<0.001) and low-density lipoprotein (104.19 to 98.07 mg/dL, p<0.001) were found in patients throughout 2 years of therapy. However, significant eGFR decline was noted (94.20 to 88.08 mL/min/1.73 m^2, p<0.001). A total of 125 subjects had eGFR decline ≥40% and 2672 had stable renal progression.

In regression analysis, 625 stable renal patients (selected via propensity score matching) and 125 subjects with eGFR decline ≥40% demonstrated excessive pickled foods to be predictive of poor renal outcomes (OR 1.861, 95% CI 1.230 to 2.814, p=0.003).

Conclusions Our study suggests that excessive pickled foods deteriorate renal function more than other unhealthy dietary behaviors in patients with diabetes.

Significance of this study

What is already known about this subject?

► Prevalence of kidney diseases is more severe in Asia, especially in Taiwan, where diabetes mellitus is a major contributor to end-stage renal disease cases, accounting for nearly half of the patient population.

What are the new findings?

► Among unhealthy dietary behaviors, excessive pickled foods intake had the most impact on renal function decline in patients with diabetes even under stable metabolic control.

How might these results change the focus of research or clinical practice?

► Given the evidence that pickled foods would deteriorate renal function, sodium restriction should be flagged for renal protection with the precise amount requiring further research.

drugs has benefitted blood sugar control and decreased major adverse cardiac events and mortality,[4–8] renal function decline has remained a serious problem for patients with diabetes.

The dietary behaviors in Taiwan are possibly associated with renal problems experienced by patients with diabetes. Several studies have investigated individual nutrient effects on renal function decline, including fat, protein, or sodium.[9–12] However, few studies have focused on the association between dietary behaviors and renal function decline outcomes. This study investigated the influence of unhealthy dietary behaviors on rapid renal function decline.

METHODS

Participants

From 2011 to 2013, patients with type 2 diabetes mellitus, participating in the D*iabetes Shared Care* Program (DSCP)[13] and attending the Chang Gung Memorial Hospital, a major medical center in Taiwan, were retrospectively

INTRODUCTION

Worldwide comparisons demonstrate the prevalence of kidney disease to be more severe in Asia, especially in Taiwan, the country with the leading incidence rate of end-stage renal disease (ESRD).[1] The incidence of ESRD has even increased while Taiwan has undergone medical service improvements.[2] Diabetes mellitus is a major contributor to ESRD cases in Taiwan, accounting for 43.2%.[3] Though the broad development of new antidiabetic

analyzed. All patients received nutrition evaluation from professional dietitians during the 2-year study, with participants who were pregnant or diagnosed with ESRD being excluded. The Institutional Review Board of Chang Gung Memorial Hospital approved this study (No 104-9221B).

Unhealthy dietary behaviors

Eight unhealthy dietary behaviors were recorded, including excessive intake of dietary carbohydrate, fats, and protein; inadequate dietary vegetable; excessive fruit and pickled foods intake; and excessive dessert and alcohol consumption. Excessive carbohydrates, fats, and protein were defined as occupying more than 46%, 35%, and 30% of total daily calories, respectively. Inadequate vegetable intake was defined as less than three servings per day, with one serving defined as a half-cup of cooked vegetables or one cup of raw vegetables. The definition of excessive fruit intake was eating more than three servings per day, with one serving of fruit defined as a small whole fruit (eg, a small apple) or about a half-cup of frozen or canned fruit. Excessive pickled food indicated eating pickled foods three times per week. Excessive dessert was defined as eating dessert three times per week. Excessive alcohol consumption was defined as more than three cups of alcohol drunk per week.[14]

The objective evaluation of eating behaviors was based on the standardized self-administered questionnaire provided by the D*SCP*, implemented nationally in Taiwan since 2001. To minimize reviewer bias, registered dietitians, certified by the Taiwan Dieticians Association and DSCP, performed the dietary behavior assessments.

Clinical characteristics

The clinical characteristics of patients, including age, gender, smoking habits, and comorbidities, such as hypertension, dyslipidemia, cardiovascular disease, heart failure, and cerebral vascular accidents were recorded beginning at their initial clinic visit. Laboratory data for glycemic control, lipids, and renal function were recorded at initial visits and for a 2-year follow-up period. Estimated glomerular filtration rate (eGFR) decline of more than 40% was defined as a surrogate end point for kidney disease progression.[15]

Statistical analysis

Categorical variables were reported as numbers with percentages, and continuous variables were reported as means with SD. Comparisons between the two groups were performed using Pearson's χ^2 test for categorical variables or the Student's t-test for continuous variables, as indicated. A paired sample t-test was used to compare the biochemistry changes across the 2-year follow-up. All statistical tests were carried out at a two-tailed significance level of 0.05 using SPSS V.19 (IBM SPSS, Chicago, Illinois, USA).

Propensity score (PS) matching was executed to account for measured confounding. The PS used 1:5 matching stratified by age, gender, and variables known to

Table 1 Demographics and clinical characteristics of patients with diabetes with regularly clinic follow-up during 2011 to 2013

	Mean (SD) or n (%)
Patient numbers	2797
Age (years)	60.08 (11.41)
Gender	
Male	1421 (50.8)
Female	1376 (49.2)
Smoking	333 (11.9)
Comorbidities	
Hypertension	1686 (60.3)
Dyslipidemia	1200 (42.9)
Coronary heart disease	75 (2.7)
Heart failure	20 (0.7)
Cerebral vascular accident	43 (1.5)
Unhealthy dietary behaviors	
Excessive carbohydrate	1412 (50.5)
Excessive protein	902 (32.2)
Excessive fat	1822 (65.1)
Inadequate vegetable	1077 (38.5)
Excessive fruit	1178 (42.1)
Excessive pickled food	590 (21.1)
Excessive dessert	940 (33.6)
Alcohol consumption	237 (8.5)

influence renal outcome, including hypertension, dyslipidemia, initial glycemic and lipid control, and certain medications. Multivariate logistic regression analysis was used to find independent dietary factors predicting rapid renal function decline in PS-matched subjects.

RESULTS

In total, 2797 participants were enrolled in this study. The mean age was 60.08 (±11.41) years, and 50.8% of the patients were male (table 1). Hypertension was diagnosed in 39.0% of the patients, and 42.9% had dyslipidemia. The prevalence rates of coronary artery disease, heart failure, and stroke were 2.7%, 0.7%, and 1.5%, respectively, with current smokers accounting for 11.9% of these participants. Most had excessive carbohydrate (50.5%) and excessive fat (65.1%) intake. The next most common unhealthy dietary behaviors were excessive fruit (42.1%), inadequate vegetable (38.5%), excessive dessert (33.6%), and excessive protein (32.2%) intake. Excessive pickled food was recorded in 21.1% of the participants, and alcohol consumption was recorded only in 8.5% (table 1).

The diabetes control among these patients was moderate and remained stable over the 2-year follow-up period (glycated hemoglobin (A_{1c}) from 7.78% to 7.75%, p=0.151) with the lipid control receiving mild

Table 2 Biochemistry changes across the 2-year follow-up in these 2797 patients with diabetes

	Before	After	P value
A_{1c} (%)	7.78 (1.50)	7.75 (1.49)	0.151
Body mass index (kg/m^2)	25.98 (4.05)	25.96 (3.91)	0.841
eGFR (mL/min/1.73 m^2)	94.2 (35.60)	88.08 (34.81)	<0.001
Cholesterol level (mg/dL)	174.04 (35.62)	170.13 (47.16)	<0.001
Triglyceride level (mg/dL)	149.77 (118.92)	146.91 (106.07)	0.150
HDL cholesterol level (mg/dL)	46.06 (11.56)	45.36 (11.73)	<0.001
LDL cholesterol level (mg/dL)	104.19 (30.80)	98.07 (28.94)	<0.001
ALT (U/L)	27.92 (26.48)	27.8 (28.08)	0.835

A1c, glycated hemoglobin; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

improvement (cholesterol from 174.04 to 170.13 mg/dL, p<0.001; low-density lipoprotein from 104.19 to 98.07 mg/dL, p<0.001, respectively). However, a deterioration of renal function, measured via eGFR decline (from 94.20 mL/min/1.73 m^2 to 88.08 mL/min/1.73 m^2, p<0.001), was also documented (table 2). In total, 125 subjects had eGFR decline ≥40%, and their clinical data were compared with the other 2672 subjects who had stable renal progression.

Patients with stable renal progression (n=2672) had significantly lower prevalence of hypertension (38.5% vs 51.2%, p=0.004), a higher baseline eGFR (94.75 mL/min/1.73 m^2 vs 82.48 mL/min/1.73 m^2, p=0.016), and improved A_{1c} values (7.75% vs 8.60%, p=2.05) compared with the 125 patients with rapid eGFR decline ≥40% (table 3). After PS matching, no statistical differences in age, gender, body mass index, comorbidities, or medications was shown between the two groups (table 3). Furthermore, among the 750 PS-matched subjects, excessive pickled food intake was the only independent risk factor to predict rapid eGFR decline (OR 1.861, 95% CI 1.230 to 2.814, p=0.003; figure 1).

DISCUSSION

In this study, around 4.47% of patients had renal function decline even with stable glycemic and lipid control. During the 2-year follow-up, eGFRs were reduced by 6.12 mL/min/1.73 m^2 (average decline 3.06 mL/min/1.73 m^2 per year), similar to a previous report in the diabetes population but less than that in the population without diabetes.[16] Patients with rapidly declining eGFR also had higher prevalence of hypertension, worse glycemic control, and lower baseline eGFR, compatible with known risk factors for predicting renal deterioration.[17 18] Interestingly, excessive pickled food intake was the only independent dietary risk factor to predict renal function decline for the patients with type 2 diabetes in this study.

Pickled foods are popular garnishes in many countries, and some of them are fermented products believed to have health benefits because of their antioxidant, antimicrobial, antifungal, anti-inflammatory, antidiabetic, and antiatherosclerotic activities.[19] However, unlike western countries, pickled food in Asia always includes salted and pickled vegetables, fruits, and fish, but not fermented foods like yogurt or cheese. The salted pickled foods are therefore rich in sodium and thought to have adverse effects on renal function. The high sodium diet-associated renal damage involves a complex relationship between increased blood pressure, proteinuria, and higher intraglomerular pressure. The potential mechanisms included the activation of the local renin–angiotensin–aldosterone system (RAAS), endogenous inhibitors of Na/K ATPase, and epithelial damage in vascular and glomerulus by increasing oxidative stress and transforming growth factor beta-1 levels.[11 20] Our study provided additional evidence that pickled foods increase the odds for renal damage compared with other unhealthy dietary behaviors, and this is believed to be through association with the essentially high sodium content.

Currently, some evidence has demonstrated the benefits of reduced dietary salt for renal protection.[21 22] Though still controversial, dietary salt restriction for diabetic nephropathy[23 24] remains a common professional recommendation.[25] Restricted salt intake has been shown to benefit blood pressure because of decreased volume retention and a potential escape from RAAS cycle-related adverse effects.[21 26] Good hypertension control also has strong evidence for preventing diabetic nephropathic deterioration.[27 28] In experimental studies, a low-sodium diet reduced proteinuria and the development of glomerulosclerosis. Additionally, renoprotective and cardioprotective effects due to medications of RAAS blockade were more predominant in patients with diabetes who received low-sodium diet (RENAAL (reduction of endpoints in NIDDM with the angiotensin II antagonist losartan) and IDNT (irbesartan diabetic nephropathy trial)).[29 30] Nevertheless, the RAAS blockade confounding is minimal in this study, because we analyzed the impact of dietary behaviors by matching medications including RAAS blockade.

Table 3 PS matching for patients with eGFR decline ≥40% in comparing patients with stable renal function

	Before PS matching			After PS matching		
	Stable renal function	eGFR decline ≥40%		Stable renal function	eGFR decline ≥40%	
	n=2672	n=125	P value*	n=625	n=125	P value†
Characteristic						
Age	60.09 (11.42)	59.78 (11.21)	0.763	58.92 (11.60)	59.78 (11.21)	0.450
Male gender	1355 (50.7%)	66 (52.8%)	0.648	343 (54.9%)	66 (52.8%)	0.670
Hypertension	1028 (38.5%)	64 (51.2%)	0.004	356 (57.0%)	64 (51.2%)	0.236
Dyslipidemia	1146 (42.9%)	54 (43.2%)	0.945	262 (41.9%)	54 (43.2%)	0.791
A_{1c}	7.75 (1.46)	8.6 (2.05)	<0.001	8.47 (1.74)	8.6 (2.05)	0.516
BMI	25.95 (4.01)	26.51 (4.77)	0.133	26.6 (4.3)	26.51 (4.77)	0.831
eGFR	94.75 (34.28)	82.48 (55.83)	0.016	86.47 (35.61)	82.48 (55.83)	0.443
Medication						
Sulfonylurea	1276 (47.8%)	77 (61.6%)	0.002	371 (59.4%)	77 (61.6%)	0.641
Metformin	1643 (61.5%)	71 (56.8%)	0.293	369 (59.0%)	71 (56.8%)	0.642
Acarbose	240 (9.0%)	24 (19.2%)	<0.001	101 (16.2%)	24 (19.2%)	0.405
Glinide	104 (3.9%)	10 (8.0%)	0.023	43 (6.9%)	10 (8.0%)	0.656
TZD	182 (6.8%)	5 (4.0%)	0.219	24 (3.8%)	5 (4.0%)	0.933
DPP4i	750 (28.1%)	53 (42.4%)	0.001	261 (41.8%)	53 (42.4%)	0.895
Insulin	340 (12.7%)	39 (31.2%)	<0.001	167 (26.7%)	39 (31.2%)	0.306
RAAS blockade‡	1147 (42.9%)	89 (71.2%)	<0.001	446 (71.4%)	89 (71.2%)	0.971
Statin	759 (28.4%)	38 (30.4%)	0.629	195 (31.2%)	38 (30.4%)	0.860
Fibrate	148 (5.5%)	5 (4.0%)	0.46	30 (4.8%)	5 (4.0%)	0.699

*Compare data between patients with stable renal function before PS matching (n=2672) and patients with eGFR decline ≥40% (n=125).
†Compare data between patients with stable renal function by PS matching (n=625) and patients with eGFR decline ≥40% (n=125).
‡RAAS blockade include ACE inhibitor, angiotensin receptor blocker or direct renin inhibitor.
A1c, glycated hemoglobin; BMI, body mass index; DPP4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; PS, propensity score; RAAS, renin–angiotensin–aldosterone system; TZD, thiazolidinedione.

Unlike the consensus of sodium intake, the appropriate amount of dietary protein remains inconsistent for patients with diabetic nephropathy. Two meta-analyses revealed that dietary protein restrictions prevented renal function decline.[12 31] By contrast, a third meta-analysis and a Cochrane systemic review both concluded that a low-protein diet demonstrated no significant improvement in renal function.[10 32] Though the benefits of protein restriction are still debatable, dietary protein intake should be maintained at 0.8 g/kg/day according to the American Diabetes Association.[25] High dietary protein intake is thought to increase the nitrogen load, glomerular filtration rate, and renal hypertrophy.[33] Malhotra *et al* also proved that increased dietary protein was

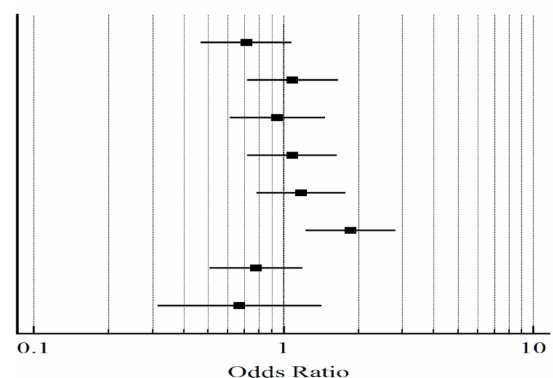| Unhealthy dietary behaviors	Odds ratio	95% CI	*P* value
Excessive carbohydrate	0.711	0.468-1.082	0.111
Excessive protein	1.089	0.716-1.656	0.690
Excessive fat	0.946	0.609-1.467	0.803
Inadequate vegetable	1.084	0.718-1.637	0.701
Excessive fruit	1.179	0.785-1.769	0.427
Excessive pickled food	1.861	1.230-2.814	0.003
Excessive dessert	0.778	0.506-1.197	0.254
Alcohol consumption	0.668	0.315-1.420	0.295

Figure 1 Forest plot of the impact of unhealthy dietary behaviors on rapid renal function decline via logistic regression model. Excessive pickled food intake independently predicted rapid renal function decline.

associated with the incidence of end-stage kidney disease in patients with diabetes.[34] This study also demonstrated that patients with diabetes with excessive dietary protein may increase the 8.9% incidence of eGFR decline, ≥40%, but this finding was not statistically significant (OR 1.089, 95% CI 0.716 to 1.656, p=0.690).

Aggressive glycemic control has influenced diabetes-related microvascular complications, including nephropathy in UK Prospective Diabetes Study,[35] and advanced glycated end products are known to increase glucotoxicity, leading to kidney injury.[36] In our study, excessive carbohydrate intake did not deteriorate renal function if glycemic control was performed well. In addition, other dietary factors, including a lipid-enriched diet,[9 37] alcohol consumption,[38] vegetables and fruit,[39] had limited effects on renal function.

There were several limitations in this study. First, although dietary behaviors were analyzed, the amount of each dietary element was not quantified. Though we showed that pickled foods would deteriorate renal function, the precise amount of sodium restriction needed for renal protection requires further research. Additionally, the study population was limited to patients with diabetes, and therefore, the result cannot be generalized to a population without diabetes.

In conclusion, among the different unhealthy dietary behaviors analyzed, excessive intake of pickled foods had the most impact on renal function decline in patients with diabetes. Beyond glycemic and hypertension control, patients with diabetes should avoid such intake to prevent the deterioration of kidney function.

ORCID iDs
Cheng-Wei Lin http://orcid.org/0000-0001-8922-7030
Shih-Yuan Hung http://orcid.org/0000-0002-9243-6586

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