

The Habit of Eating Vegetables First Is Linked with a Lower Risk of Diabetic Retinopathy and Nephropathy: Cross-Sectional Study in Japanese Diabetic Patients

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Purpose: Although eating habits of “vegetables first” have been reported to be effective in suppressing postprandial hyperglycemia, its association with complications in diabetic patients remains unknown. This study aimed to examine the relationship between the habit of eating vegetables first and complications in diabetic patients.

Patients and Methods: This cross-sectional study included diabetic patients who were examined as outpatients at the Ise Red Cross Hospital from June to August 2023 and from June to August 2024. The complications were diagnosed according to the clinical guidelines of the Japan Diabetes Society. Participants completed a questionnaire about their eating order, classified into four groups: no order, vegetables first, protein first, and carbohydrates first. Logistic regression analysis was used to calculate odds ratios for complications based on eating order.

Results: The results revealed that 204 patients ate in no order, 438 patients ate vegetables first, 59 patients ate protein first, and 131 patients ate carbohydrates first. The adjusted odds ratios for diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, and cardiovascular disease for vegetables first with no order of eating as the reference were 0.64 (95% confidence interval [CI], 0.41–0.98; $P = 0.043$), 0.80 (95% CI, 0.53–1.20; $P = 0.289$), 0.47 (95% CI, 0.30–0.71; $P < 0.001$), and 1.28 (95% CI, 0.76–2.15; $P = 0.351$), respectively. Neither the protein first nor carbohydrates first groups showed a significant association with complications.

Conclusion: In diabetic patients, the habit of eating vegetables first may indicate a reduced risk of diabetic retinopathy and nephropathy.

Keywords: diabetes, diet therapy, complications, eating behavior, postprandial glycemia, cross-sectional study

Introduction

The number of people with diabetes continues to increase and is expected to reach 700 million by 2045.¹ One goal of diabetes treatment is to prevent complications,² which is important to improve life expectancy and maintain quality of life. Major complications in diabetic patients include microvascular complications, such as diabetic retinopathy, diabetic neuropathy, and diabetic nephropathy, as well as macrovascular complications, such as cardiovascular disease and stroke. Strict glycemic control is important to prevent the development of these complications.^{3,4} To achieve strict blood glucose management and reduce the risk of complications in diabetes mellitus, controlling postprandial hyperglycemia is paramount, alongside improving mean blood glucose levels.^{5,6}

In addition to exercise and drug therapy, diet therapy is key to quality glycemic control in diabetes treatment. In addition to the usefulness of adequate caloric intake in correcting postprandial hyperglycemia, previous studies of diabetic patients have reported the effect of order of eating (vegetables first, protein first, or carbohydrates last, etc.) in reducing postprandial hyperglycemia.^{7–11} Among such studies, it has been reported that the habit of eating vegetables

first is useful for correcting postprandial hyperglycemia,^{9,10} and there are high expectations for this habit in managing postprandial hyperglycemia in diabetic patients. Previous studies¹⁰ have reported that the “vegetables first” diet exerts physiological mechanisms such as the correction of postprandial hyperinsulinemia, delayed digestion due to dietary fiber, and the promotion of GLP-1 and GIP secretion.

In light of the above, it may be inferred that the habit of eating vegetables first, which is expected to suppress postprandial hyperglycemia in diabetic patients, may be associated with a lower risk of complications, although no reports of such associations have been published. No previous study has investigated the association between meal order and diabetic complications. We hypothesized that the “vegetables first” dietary habit may be associated with reducing the risk of complications. This study aims to examine the association between the habit of eating vegetables first and microvascular complications and macrovascular disease.

Materials and Methods

Study Design and Subjects

This was a cross-sectional study of diabetic patients attending the outpatient services of Ise Red Cross Hospital in Ise City, Mie Prefecture, Japan. This study was approved by the Ethical Review Board of the Ise Red Cross Hospital and conducted in accordance with the principles of Helsinki Declaration. Written informed consent was obtained from all participants before enrolment. Eligibility criteria included patients with diabetes who were examined during outpatient visits from June to August 2023 and from June to August 2024. Exclusion criteria were alcoholism, severe mental illness, and those unable to cooperate with the survey on their own.¹²

Measuring Complications

The following complications were assessed based on the clinical guidelines of the Japan Diabetes Society.^{13,14} The presence of diabetic retinopathy was established by an ophthalmologist upon diagnosis of simple retinopathy, preproliferative retinopathy, or proliferative retinopathy. Diabetic neuropathy was considered to be present when there was decreased Achilles tendon reflex, decreased vibratory sensation in the medial ankle (<10 seconds on the C128 tuning fork), subjective symptoms (numbness, pain, or abnormal sensation in the bilateral lower extremities), or nerve conduction test abnormality (ie, grade 1 or higher by the Baba classification). Diabetic nephropathy was defined as a urinary albumin/creatinine ratio ≥ 30 mg/g Cre or an estimated glomerular filtration rate < 30 mL/min/1.73 m². Cerebrovascular disease was judged to be present in patients with ischemic heart disease, such as angina pectoris and myocardial infarction, chronic heart failure, and cerebrovascular disease, such as cerebral infarction.

Evaluation of Eating Habits with Respect to the Order in Which Food Is Eaten

A self-administered questionnaire was completed by the subjects to investigate their eating habits with respect to the order in which food is eaten.¹² The subjects were asked to select one of the following four types of eating habits: (1) eating vegetables first (vegetables first), (2) eating protein (including milk and yogurt) first (protein first), (3) eating carbohydrates (rice, bread, noodles, etc.) first (carbohydrates first), or (4) no order of eating (no order of eating). In a previous study using this question targeting diabetic patients,¹² eating order, particularly the habit of eating vegetables first, was shown to be significantly associated with ADL.

Measurement of Other Variables

Age, sex, body mass index (BMI) (weight (kg)/height (m²)), smoking habit, alcohol consumption habit, exercise habit, diabetes classification (type 1 and type 2), duration of diabetes, hemoglobin A1c (HbA1c), hypertension, dyslipidemia, loneliness, and diabetic medications were investigated. Diabetes mellitus was classified into type 1 and type 2 based on the diagnostic criteria of the Japan Diabetes Society.¹³ Systolic and diastolic blood pressure were measured in the examination room, and hypertension was defined as either systolic blood pressure ≥ 130 mmHg, diastolic blood pressure ≥ 80 mmHg, or taking antihypertensive medication. Regarding lipids, patients with dyslipidemia are defined as having triglycerides ≥ 150 mg/dL, high-density lipoprotein-cholesterol < 40 mg/dL, low-density lipoprotein-cholesterol (LDL-c)

≥ 120 mg/dL (LDL-c ≥ 100 mg/dL in the case of coronary artery disease), or taking lipid-lowering medication. Exercise habits were assessed by asking, “Do you have a habit of exercising at least once a week?” If the answer was “yes”, the respondent was considered to have an exercise habit. Loneliness was measured using the short version of the Japanese Loneliness Scale developed by Igarashi et al.¹⁵ The scale consists of three items and is answered according to a three-point scale: rarely (1 point), occasionally (2 points), and often (3 points). The total is calculated on a scale of 3–9, with higher scores indicating greater loneliness. In this study, following previous studies, we defined a score of ≥ 6 as having a sense of loneliness.¹⁶ Previous studies^{17,18} have reported that loneliness is associated with decreased dietary balance and ADL.

Statistical Analysis

Participants were classified into four groups (no order of eating, vegetables first, protein first, and carbohydrates first), and their background factors were recorded. Continuous variables were compared between the groups using the analysis of variance method (Bonferroni method for multiple comparisons) and binary variables using the χ -square test. Using logistic regression analysis with complications as the dependent variable and order of eating as the explanatory variable (based on no order of eating), the odds ratios for vascular complications associated with the order of eating were calculated. Variables to be adjusted were age, sex, BMI, diabetes classification, diabetes duration, HbA1c, exercise habit, smoking habit, alcohol consumption habit, loneliness, hypertension, dyslipidemia, and diabetic medications, with reference to previous studies^{14,17,18} and based on clinical judgment. Participants with missing data were excluded. Based on prior research,¹² we estimated an outcome prevalence rate of 20% and approximately 15 adjustment variables, leading us to infer a sample size of around 800 cases. The significance level (two-sided) was less than 0.05. STATA version 16.0 (Stata Corporation LP, College Station, TX) was used for analysis.

Results

A total of 929 patients were screened, of whom 832 were included, while 97 were excluded due to missing eating order questionnaire and complication data. The patient background of the 832 patients included in the analysis is shown in Table 1. The mean age was 66 (13.3) years, 57% were male, and the mean HbA1c was 7.5 (1.1%). The results revealed that 204 patients (24.5%) ate in no order, 438 patients (52.6%) ate vegetables first, 59 patients (7.1%) ate protein first, and 131 patients (15.8%) ate carbohydrates first. Compared with the other groups, the “vegetables first” group tended to have a lower mean age, a smaller proportion of males, a shorter duration of diabetes, and a lower prevalence of hypertension.

Table 1 Characteristics of the Analysis Population

	No Order of Eating n = 204 (24.5%)	Vegetables First n = 438 (52.6%)	Protein First n = 59 (7.1%)	Carbohydrates First n = 131 (15.8%)	P value
Age (years), mean (SD)	69.6 (11.3) ^b	62.4 (13.8) ^{a,c,d}	71.1 (7.0) ^b	70.1 (13.3) ^b	<0.001*
Male, %	63.5	52.3	53.4	65.3	0.012*
BMI (kg/m ²), mean (SD)	25.1 (4.7) ^d	25.2 (4.9)	23.9 (4.5)	24.0 (3.8) ^a	0.021*
T1DM, %	10.2	14.8	8.4	16.7	0.181
Duration of diabetes (years), mean (SD)	17.8 (11.9) ^b	14.5 (11.6) ^{a,d}	18.4 (12.0)	18.3 (13.4) ^b	<0.001*
HbA1c (%), mean (SD)	7.6 (1.3)	7.4 (0.9)	7.2 (1.2)	7.6 (0.9)	0.108
Exercise habit, %	45.7	53.1	44.8	43.8	0.139
Alcohol consumption, %	27.8	27.5	25.4	22.4	0.674
Smoking, %	35.8	32.0	22.0	38.7	0.002*
Loneliness, %	17.2	21.1	25.4	22.9	0.460
Hypertension, %	70.5	52.0	61.0	61.8	<0.001*
Dyslipidemia, %	59.9	60.2	54.2	66.4	0.405
Retinopathy, %	37.7	24.6	40.6	33.5	0.001*

(Continued)

Table 1 (Continued).

	No Order of Eating n = 204 (24.5%)	Vegetables First n = 438 (52.6%)	Protein First n = 59 (7.1%)	Carbohydrates First n = 131 (15.8%)	P value
Neuropathy, %	48.5	40.1	35.5	39.6	0.142
Nephropathy, %	56.3	35.6	50.8	51.9	<0.001*
Cardiovascular disease, %	22.5	15.7	27.1	28.2	0.004*
Oral hypoglycemic agents, %	89.5	76.2	84.7	75.5	0.001*
Insulin, %	81.0	78.8	69.4	77.0	0.281

Notes: *Significantly different from No order of eating. ^bSignificantly different from Vegetables first. ^cSignificantly different from Protein first. ^dSignificantly different from Carbohydrates first. *P < 0.05.

Abbreviations: SD, standard deviation; BMI, body mass index; T1DM, type 1 diabetes mellitus; HbA1c, hemoglobin A1c.

The results of the logistic regression analysis and forest plot are shown in Table 2 and Figure 1, respectively. The adjusted odds ratios for diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, and macroangiopathy for those who ate vegetables first in reference to those who had no order of eating were 0.64 (95% confidence interval [CI], 0.41–0.98; P = 0.043), 0.80 (95% CI, 0.53–1.20; P = 0.289), 0.47 (95% CI, 0.30–0.71; P < 0.001), and 1.28 (95% CI, 0.76–2.15; P = 0.351), respectively. On the other hand, when the order of eating was used as the criterion, neither the protein first group nor the carbohydrates first group was significantly associated with each complication. In addition, sensitivity analysis of patients with type 2 diabetes mellitus showed no association with retinopathy, but did reveal an association between the “vegetable first” diet and a reduced risk of nephropathy (0.47 [95% CI, 0.30–0.72; P = 0.001]).

Discussion

The results of this study in diabetic patients showed that the habit of eating vegetables first was associated with a lower risk of diabetic retinopathy and diabetic nephropathy. To the extent of our knowledge, this is the first report to find these associations in diabetic patients.

In a previous study of diabetic patients, it was reported that the habit of eating “vegetables first” contributed to suppression of postprandial hyperglycemia,^{9,19} reduction of mean amplitude of glycemic excursions,²⁰ a marker of blood glucose variability, and suppression of atherosclerosis.⁹ Additionally, a recent report showed that eating carbohydrates last (ie, eating vegetables early in the meal) improved time above range, time below range, and time in range.⁶ These results, while still, suggest that the practice of consuming vegetables first in a meal may help correct postprandial hyperglycemia.⁶ In the present study, multivariate analysis adjusting for age, sex, preference history, exercise habits, and diabetes treatment, which have been shown to be associated with complications, as well as HbA1c, a control measure of average blood glucose levels, revealed that the habit of eating vegetables first was associated with a lower risk of diabetic retinopathy and diabetic nephropathy. This suggests that chronic hyperglycemia and reducing blood glucose fluctuations, such as postprandial hyperglycemia control, are important in managing diabetic retinopathy and diabetic nephropathy.

In the present study, we found an association between the habit of eating vegetables first and reduced risk of diabetic retinopathy and diabetic nephropathy but no association with diabetic neuropathy or cardiovascular disease. In previous studies of diabetic patients,¹⁷ it has been reported that postprandial hyperglycemia (high blood glucose variability) is closely associated with diabetic retinopathy and diabetic nephropathy in particular. On the other hand, the impression regarding the association between postprandial hyperglycemia (high blood glucose variability) and diabetic neuropathy and cardiovascular disease was inconsistent.^{17,18} The risk of developing microvascular complications and cardiovascular disease is increased not only by hyperglycemia and blood glucose fluctuations but also by additional factors such as hypertension, dyslipidemia, smoking, and obesity.^{14,21} In this study, despite being relatively elderly and having multiple comorbidities, smoking habits, and diabetes, only about half of the patients maintained an exercise routine, indicating the presence of numerous vascular disease risk factors. This coexistence of vascular risk among the participants may explain the lack of association between the eating habit of “vegetables first” and diabetic neuropathy or cardiovascular disease.

Table 2 Unadjusted and Adjusted Logistic Regression Analyses with Complications as the Outcome

	Retinopathy					Neuropathy					Nephropathy					Cardiovascular Disease				
	Unadjusted OR (95% CI), n = 832	P value	Adjusted OR (95% CI), n = 727	P value	GOF, P = 0.130	Unadjusted OR (95% CI), n = 832	P value	Adjusted OR (95% CI), n = 727	P value	GOF, P = 0.470	Unadjusted OR (95% CI), n = 832	P value	Adjusted OR (95% CI), n = 727	P value	GOF, P = 0.487	Unadjusted OR (95% CI), n = 832	P value	Adjusted OR (95% CI), n = 727	P value	GOF, P = 0.584
Eating order																				
No order of eating	1.00		1.00			1.00		1.00			1.00		1.00			1.00		1.00		
Vegetables first	0.53 (0.37–0.77)	0.001*	0.64 (0.41–0.98)	0.043*		0.71 (0.50–0.99)	0.047*	0.80 (0.53–1.20)	0.289		0.42 (0.30–0.6)	<0.001*	0.47 (0.30–0.71)	<0.001*		0.64 (0.42–0.97)	0.037*	1.28 (0.76–2.15)	0.351	
Protein first	1.13 (0.62–2.04)	0.683	1.31 (0.67–2.55)	0.423		0.58 (0.32–1.06)	0.081	0.59 (0.30–1.14)	0.121		0.80 (0.44–1.43)	0.453	0.87 (0.45–1.70)	0.702		1.27 (0.65–2.47)	0.467	1.68 (0.77–3.64)	0.185	
Carbohydrates first	0.83 (0.52–1.32)	0.440	0.86 (0.50–1.47)	0.585		0.69 (0.44–1.08)	0.113	0.69 (0.42–1.15)	0.161		0.83 (0.53–1.29)	0.423	0.96 (0.56–1.62)	0.881		1.35 (0.81–2.23)	0.239	1.73 (0.94–3.16)	0.074	

Notes: Adjusted variables are as follows: Age, sex, body mass index, classification of diabetes, duration of diabetes, hemoglobin A1c, exercise habit, smoking habits, drinking habits, loneliness, hypertension, dyslipidemia, and antidiabetic drugs. *P < 0.05.

Abbreviations: OR, odds ratio; CI, confidence interval; GOF, goodness-of-fit.

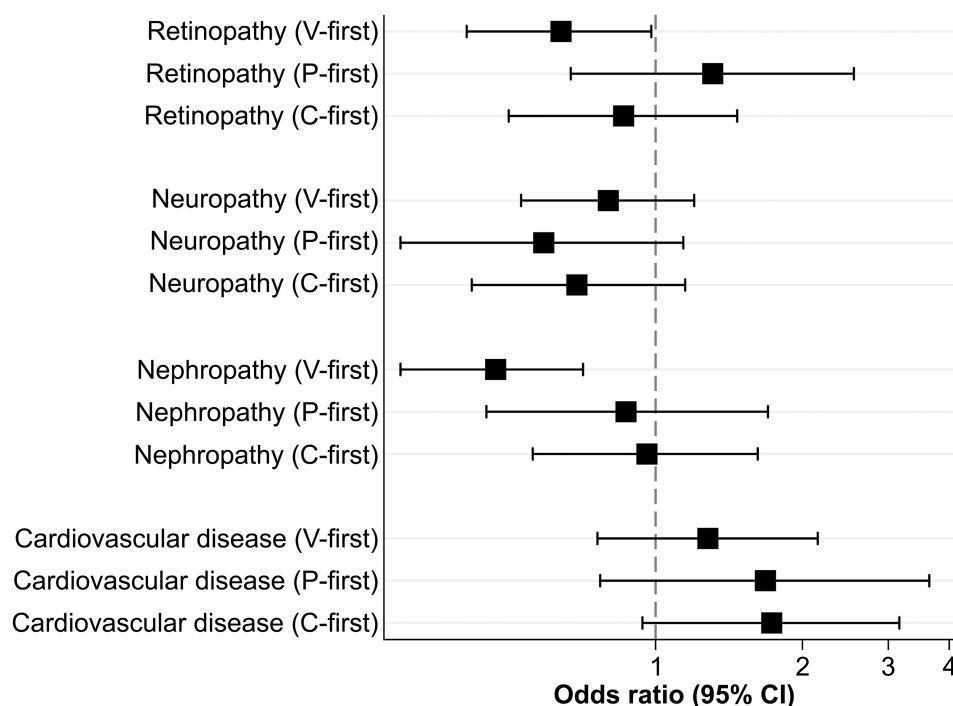


Figure 1 Eating order and complications.

Abbreviations: OR, odds ratio; CI, confidence interval; V-first, Vegetables first; P-first, Protein first; C-first, Carbohydrates first.

Mechanisms underlying the association between vegetables first eating habits and complications include the following. Postprandial hyperglycemia or increased glycemic variability has been suggested to induce inflammatory cytokines, oxidative stress, and insulin resistance, leading to vascular complications and organ damage.^{19,22} The habit of eating vegetables first has been shown to correct postprandial hyperinsulinemia, and the sesamin and dietary fiber in vegetables have been shown to promote the secretion of glucagon-like peptide 1 and glucose-dependent insulintropic polypeptide.¹⁰ However, the study did not measure postprandial blood glucose, inflammatory cytokines, or incretin in patients, and further studies are needed to address these factors.

As mentioned above, several studies have examined the association between eating order and the inhibition of postprandial hyperglycemia.^{9,19,22} However, to the best of our knowledge, this study is the first to identify an association between the order of eating and the occurrence of diabetic retinopathy and diabetic nephropathy. The strength of this study is that it found that the habit of eating “vegetables first” was associated with a lower risk of diabetic retinopathy and diabetic nephropathy after adjusting for age, sex, BMI, preference history, and exercise habits, which have been identified as factors associated with diabetic vascular complications in previous studies. Clinical findings obtained in the present study include the finding that the habit of eating “vegetables first” is associated with a decreased risk of diabetic retinopathy and diabetic nephropathy in diabetic patients, suggesting the importance of the habit of eating “vegetables first”. The habit of eating vegetables first is considered easy to engage in and has high retention rates.^{9,23} Japanese food is often served in the style known as “Ichiju-sansai” (one soup and three dishes), consisting of rice, soup, and main dishes rich in vegetables. In other words, Japanese dietary culture facilitates the practice of “vegetables first” dietary habit, and the feasibility of implementing this habit is high. It was considered clinically crucial that a highly adherent habit of eating vegetables first, which can be implemented in the long term, can reduce the risk of complications in diabetic patients.

There are several limitations to this study. First, the subjects of this study were patients attending the outpatient services of specialist diabetes clinics, and many had relatively severe diabetes mellitus. Therefore, careful judgment must be exercised as to whether the results of this study can be applied to patients with stable blood glucose levels or who are attending their family physicians. Second, although educational background, economic situation, dietary content (total calories, nutrient distribution), and the intensity of physical activity were measured in this study, no analyses adjusting for

these factors were conducted. In particular, dietary content may have influenced postprandial blood glucose, which in turn could have affected the results. Another concern regarding the analysis is the potential for type I error in the regression analysis. Therefore, the results, although statistically significant, must be interpreted with caution. Third, lower limb symptoms, which are subjective indicators, were included in determining diabetic neuropathy. Therefore, objectivity may be lacking, raising concerns about validity. Fourth, although the questionnaire on the order of eating used in this study has been validated, its reliability has not been examined. Fifth, exercise habits in this study were measured using a simple self-reported questionnaire, which may compromise validity. Sixth, the sample size was small; in particular, the number of participants in the protein-first and carbohydrate-first groups was limited, and the possibility of insufficient power cannot be ruled out. Finally, this study is cross-sectional, making it difficult to refer to causal relationships. It seems necessary to verify the causal relationship through a longitudinal study of diabetic patients in the future.^{24–26}

Conclusions

The results of this study in diabetic patients showed that the habit of eating vegetables first is associated with a lower risk of diabetic retinopathy and diabetic nephropathy. In terms of reducing the risk of complications in diabetic patients, the habit of eating vegetables first was considered important. Future prospective cohort studies are warranted to address the above-mentioned limitations.

Data Sharing Statement

Data and materials related to the results and analyses presented in this paper are available from the corresponding author, Satoshi Ida, upon reasonable request.

Ethics Approval

This study was approved by the Ethical Review Board of the Ise Red Cross Hospital (Approval No. ER2023-41) and conducted in accordance with the Helsinki Declaration. Written informed consent was obtained from all participants before enrolment.

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Author Contributions

Kanako Imataka: Investigation, Resources, Writing – Original draft. Satoshi Ida: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Software, Visualization, Writing – Review & Editing. Kazuya Murata: Investigation, Resources, Supervision, Writing – Review & Editing, Validation. Kentaro Azuma: Investigation, Resources, Supervision, Writing – Review & Editing. Tatsuya Tanaka: Investigation, Resources, Supervision, Writing – Review & Editing. All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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