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Associations of dietary insulin load and dietary insulin index with diabetic nephropathy and reduced kidney function among women: a case–control study

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Abstract

Background Increased insulin levels lead to hyperinsulinemia and insulin resistance (IR). IR is one of the main causes of the onset and progression of Diabetic Nephropathy (DN) and kidney failure in type 2 diabetic patients. The present case–control study sought to investigate the relationship between dietary insulin load (DIL) and index (DII) and the odds of DN and kidney function decline.

Methods At the Kowsar Diabetes Clinic in Semnan, Iran, we enrolled 105 eligible women with DN and 105 controls (30–65 years old). Dietary insulin load (DIL) and index (DII) were assessed using a 147-item food frequency questionnaire (FFQ). Using standard protocols, biochemical variables and anthropometric measurements were evaluated for all patients. To investigate potential associations, binary logistic regression was used.

Results We found that higher DII was associated with 2.72 times higher odds of albuminuria (OR: 2.77; 95% CI 1.16, 6.63) and 1.92 times higher odds of DN (OR: 1.92; 95% CI 1.11, 3.32) compared to lower adherence. Additionally, DIL was found to be statistically highly connected with mild to severe reduction of glomerular filtration rate (GFR) in participants and 1.82 times greater odds of DN (OR = 1.82; 95% CI 1.01, 3.30).

Conclusion The findings from this research showed that a higher odds of DN were related to a higher level of adherence to DIL and DII. Increased adherence to DIL was strongly correlated with the likelihood of a decreased GFR. To clarify our findings, more prospective research is necessary.

Keywords Dietary insulin load, Dietary insulin index, Diabetic nephropathy, Case–control study, Women

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Introduction

Diabetic nephropathy (DN) is a primary microvascular complication of type 2 diabetes and the most common cause of end-stage renal disease (ESRD) [1]. Approximately 25–50% of patients with type 1 and 2 diabetes show clinical manifestations of DN, including glomerular hyperfiltration following a gradual increase in proteinuria, high blood pressure, and finally loss of glomerular filtration rate [2, 3].

Observational and clinical trial studies have determined that hyperglycemia and its associated metabolic consequences are involved in the initiation and progression of DN [4, 5]. Considering that recent data have indicated that kidney epithelial cells respond to insulin, insulin resistance (IR) plays an important role in the development of DN [6]. IR is often seen in patients with advanced renal failure or mild functional impairment [7]. Increasing the level of chronic inflammatory factors such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-alpha), and interferon-gamma is one of the main causes of IR in patients with kidney failure [8, 9]. In IR, the signal transmission cascade after insulin binding appears to be disturbed [10, 11]. Glomerular endothelial cells, in response to insulin, can increase nitric oxide production by stimulating endothelial nitric oxide synthase (eNOS) activity [12], which has been shown in animal models to be impaired by IR and diabetes [13, 14]. Albuminuria is one of the main manifestations of DN; indeed, the presence of albuminuria means that the glomerular filtration barrier (GFB) is damaged. IR is one of the main causes of damage to podocytes, which are the main component of GFB [15, 16].

Considering that hyperinsulinemia and IR are one of the main reasons for the onset and progression of DN and kidney failure, it is necessary to monitor type 2 diabetic patients [20] carefully. Therefore, this case–control study focuses on the relationship between dietary insulin index (DII), dietary insulin load (DIL), and diabetic nephropathy (DN). The glycemic index (GI) and glycemic load (GL) indicate the ability of foods to increase blood glucose levels compared to glucose or white bread [17]. Serum glucose level is related to insulin level, but GI and GL are not suitable for showing postprandial insulin levels because they only consider carbohydrates in food; foods containing amino acids and certain fatty acids can also stimulate insulin secretion [18, 19]. For this reason, the insulin index has been proposed to estimate postprandial insulin levels in response to the isoenergetic values of different foods [20]. The dietary insulin index (DII) and dietary insulin load (DIL) are determined by evaluating the DII of each meal according to its caloric content and intake frequency in the diet [21]. Studies in healthy populations have shown that DII and DIL are significantly associated with IR [22].

Increased insulin levels lead to hyperinsulinemia and, eventually, IR. In turn, IR is one of the main causes of kidney failure both in the healthy population and in type 2 diabetic patients. Specifically, elevated DII and DIL contribute to DN through several mechanisms: Firstly, they exacerbate hyperinsulinemia, leading to increased oxidative stress and inflammation within the kidneys. Secondly, the resultant insulin resistance impairs the normal function of podocytes and glomerular endothelial cells, disrupting the glomerular filtration barrier (GFB) and promoting albuminuria [23]. Although some recent investigations have evaluated the effect of dietary protein, fat, and acid load on reduced kidney function, the impact of insulin load on kidney function among diabetic patients is not known [24–26]. Therefore, the present case–control study was designed to investigate the individual and separate associations of dietary insulin index (DII) and dietary insulin load (DIL) with the odds of DN and kidney function decline among women. Investigating both DII and DIL separately allows for a comprehensive understanding of how the quality and quantity of dietary insulin-stimulating foods may impact DN risk.

Method and materials

Subjects

Participants in this study were gathered from the Kowsar Clinic in Semnan, Iran, between July and December 2016. The inclusion criteria were: Women with diabetes mellitus type 2 (DM2), between the ages of 30 and 65, with a history of DM2 lasting 3–10 years, and who were not adhering to a specific diet at the time of enrollment, were eligible to participate in this study [27]. The diagnosis of diabetes in this study was based on the updated diagnostic criteria of the American Diabetes Association (ADA), defined as a fasting blood sugar (FBG) of 126 mg/dl or higher, or a 2-h post-load blood glucose level of 200 mg/dl or higher. Autoimmune diseases, a history of malignancy, coronary angiography, hepatitis, myocardial infarction, or stroke were other disqualifying factors. A total daily calorie intake of 500 kcal or less was regarded as an exclusion criterion, as well as an incomplete food frequency questionnaire.

Urinary albumin-to-creatinine ratio (ACR) of 30 mg/g in a random spot urine sample was the standard utilized for DN in this study. Convenience sampling was used for the identification of 120 patients with DN. 105 patients with DN consented to take part in the investigation. Furthermore, the control group consisted of 105 diabetic women without DN from the same center who were matched 1:1 to the DN cases, by age at 1-year intervals,

and by duration of diabetes at 6-month intervals. To participate in the present study, every individual gave written informed consent. This work was approved by the Ethics Committee of Tehran University of Medical Sciences (Ethics Number: IR.TUMS.REC.1395.2644).

Data collection

Age, diabetes duration, smoking status, and other participant information were collected, and individuals were dressed comfortably and unshod while having their body weight (kg) measured. Body mass index (BMI) was determined as body weight divided by the square of the body height. Using a manual sphygmomanometer, blood pressure was taken once, on the left arm, while participants were seated and after 5 min of rest [28]. To measure physical activity, the International Physical Activity Questionnaire (IPAQ) was utilized [29]. This questionnaire's scoring criteria were as follows: "poor physical activity" (score 600 Metabolic Equivalent of Task-hours/week), "moderate physical activity" (score 600–3000 MET-h/Week), or "high physical activity" (score > 3000 MET-h/week) levels.

Blood parameters

From the participants' medical records from the preceding three months, biochemical data were gathered. Tests for blood sugar (FBG, 2hrBG, and HbA1c), lipid profile (triglycerides (TG), low-density lipoprotein (LDL), total cholesterol (TC), and high-density lipoprotein (HDL), as well as kidney function tests (total serum creatinine (Cr), and blood urea nitrogen (BUN)) were among these factors. To calculate the LDL/HDL ratio, the LDL level is divided by the HDL level.

Dietary assessment

Face-to-face interviews were used to measure dietary consumption using a valid and reliable food-frequency questionnaire (FFQ) [30]. Participants provided information on how often they eat—daily, weekly, monthly, or annually. Using standard measures, the final portion amounts were converted to grams per day. The residual approach was then used to account for calorie consumption at these levels. Dietary intakes were examined using the NUTRITIONIST 4 program (First Data Bank, San Bruno, CA) to estimate energy and nutrient intakes.

The US Department of Agriculture Food database was used to examine the daily dietary intake of nutrients and energy after being modified for Iranian cuisine. The compositions of various Iranian foods that were absent from the original USDA database are now available in the amended USDA nutrition database. These foods' components have already been evaluated. From prior research, BrandMiller calculated DII [21].

Generally, DII calculates the difference between the area under the curve after consuming a 1000 kJ test food divided by the area under the curve after consuming a 1000 kJ portion of the reference food over 2 h [20, 21, 31]. Based on the associations between the calorie, fiber, carbohydrate, protein, and fat contents of the food items in the current study and the Brand-Miller products, the food items were matched. The insulin of each item was determined by multiplying the insulin index by the calorie content of the food:

A food's insulin load is calculated by multiplying its insulin index by its daily calorie intake.

DIL was then calculated by adding up the items' total insulin loads.

Statistical analysis

The normal distribution of the quantitative variables was assessed and confirmed using the Kolmogorov–Smirnov test. Independent t-test and chi-square tests were used to compare quantitative variables and to determine the distribution of the qualitative variables across the median of DIL and DII, respectively. Energy-adjusted dietary macro and micronutrient intakes across the groups of DIL and DII were compared using analysis of covariance (ANCOVA). DIL and DII were separated into two groups based on their median (Low vs High) intake.

Binary logistic regression for matched analysis was used to determine whether dietary insulin load and index were associated with the odds of DN, abnormal GFR, and BUN. We also used Multinomial logistic regression to investigate the odds of albuminuria (severe and mild) between DIL and DII groups.

In adjusted models, age, energy intake, and hemoglobin level were controlled for. All data analysis was performed using SPSS software (Version 25, SPSS Inc., Chicago, IL, USA), and $P \leq 0.05$ was a priori considered statistically significant.

Results

Characteristics of participants across cases and controls

Among 210 participants, 105 cases of DN were included. The mean (SD) age of participants was 55.37 (7.07) years, and the mean BMI was 28.09 (4.59) kg/m^2. According to characteristics of participants across cases and controls, serum albumin, Hb A1C, serum levels of TC, LDL, and

Cr, the usage of angiotensin receptor blockers and angiotensin-converting enzyme inhibitors was higher in cases than in controls (P value < 0.05).

Demographic characteristics between the DIL and DII groups

The demographic characteristics of the case and control groups between DIL and DII intakes based on median groups were presented in Table 1. As shown in this table, a significant mean difference was observed in terms of Hb A1C among low and high adherence of DIL between both cases (P = 0.03) and control (P = 0.02), and control among DII groups (P = 0.02). Individuals with high adherence to the DIL and DII scores had significantly higher HbA1C. Also, DN patients who consumed higher DIL showed higher blood sugar (P = 0.04), whilst patients with higher DII were heavier (P = 0.04). Moreover, controls with higher adherence to DIL had significantly higher Hb (P = 0.007) and lower diastolic blood pressure (DBP) (P = 0.04).

Dietary intakes of study subjects according to DIL and DII groups

Table 2 shows the mean differences in dietary intakes between the two groups of DIL and DII based on their median. The results show that the participants with high adherence to DIL had significantly higher intakes of energy, protein, carbohydrate, total fat, cholesterol, saturated fatty acids (SFA), Iron, magnesium, potassium, phosphorous, calcium, vitamin K, vitamin E, α-Tocopherol, vitamin B1, vitamin B2, vitamin B3, vitamin B5, vitamin B6, vitamin B12, biotin and lower monounsaturated fatty acids (MUFA) (P < 0.05). However, among DII groups, considering the energy intake attenuated all associations (P > 0.05).

The association between DIL and DII adherence with reduced kidney function

Crude and multivariable odds ratios and 95% confidence intervals of DN, albuminuria, decreased GFR, and increased BUN according to DIL and DII groups are shown in Table 3.

In the crude model, the odds of having high DII adherence were 1.92 times higher in women with DN (cases) compared to women without DN (controls) (OR: 1.92; 95% CI 1.11, 3.32; P = 0.02). In addition, after controlling for energy intake, age, and Hb, this association has remained significant (OR: 1.90; 95% CI 1.08, 3.33), and participants with higher compared to the lower DII adherence had 1.92 times higher odds of DN.

In the crude model, participants with higher adherence to the DII group had higher odds of severe albuminuria (OR: 2.77; 95% CI 1.18, 6.50) compared with those with lower adherence. Also, after controlling for energy intake, age, and Hb, this association remained significant (OR: 2.77; 95% CI 1.16, 6.63), and participants with higher compared to the lower DII adherence had 2.77 times higher odds of severe albuminuria.

The DIL median intake was not significantly associated with DN in the crude model (OR = 1.52; 95% CI 0.88, 2.62). However, after adjusting for confounding variables, energy intake, age, and Hb, participants with the higher DIL median had 1.82 times higher odds of DN (OR = 1.82; 95% CI 1.01, 3.30).

The DIL and DII median intake was not significantly associated with a mild to severe decrease in GFR in the crude model (OR = 1.36; 95% CI 0.78, 2.37) and (OR = 1.36; 95% CI 0.78, 2.37), respectively. However, after adjusting for potential confounding variables, energy intake, age, and Hb, participants with the higher DIL and DII median intake had 2.30 (OR = 2.30; 95% CI 1.17, 4.52) and 1.82 (OR = 1.82; 95% CI 1.09, 3.90) times higher odds of mild to severe decrease GFR, respectively. The significant associations between adherence to dietary insulin load and dietary insulin index with diabetic kidney outcomes are presented in Fig. 1.

Discussion

The present case–control study sought to assess the relationship between DII and DIL with the odds of DN and kidney function factors in Iranian women. Accordingly, we found a significant association between higher adherence to DII and with odds of DN and albuminuria. Furthermore, we showed a statistically significant association between DIL and the odds of DN and mild to severe reduction of GFR in participants. In the preceding three decades, DN prevalence has increased in all income levels in countries. Diabetes is known to impact all organ functions, including the digestive system, brain and nervous systems, cardiovascular system, skeletal muscle, the immune system, and the kidneys. DN is currently accountable for 31.1 percent of deaths in diabetic patients [32, 33].

The results of the present study showed that more DII consumption was related to increased odds of DN and albuminuria; also, higher DIL was associated with greater odds of DN in participants. Both greater intake of DIL and DII were associated with increased odds of reduced

GFR. Hyperinsulinemia, or even IR, is one of the main agents for the progression of DN and kidney failure [34]. DII and DIL are two factors that are related to IR, which in turn contributes to metabolic syndromes and type 2 diabetes [35]. To our knowledge, there is no currently available study on DII and DIL on DN; however, there are some previous studies performed in diabetic patients, including a randomized controlled trial by Zhang 2022, that have compared the association between insulin groups and Exenatide for 52 weeks. In Zhang 2022, the authors observed that, in insulin groups, eGFR was lower than in patients administered with Exenatide [36]. In a cross-sectional observational study involving 1,413 subjects with type 2 diabetes, a higher triglyceride-glucose (TyG) index was significantly associated with the presence of nephropathy. Additionally, the study observed that insulin use was more prevalent among individuals with nephropathy, suggesting a potential link between insulin resistance, hyperinsulinemia, and the progression of diabetic nephropathy [37]. Additionally, in a study by Jang et al., the results on 60,047 participants showed that IR was associated with the development of albuminuria in relatively healthy subjects [38]. Whilst in a national cohort of 855,133 veterans with type 2 diabetes by Grube et al., more advanced chronic kidney disease (CKD) was associated with greater insulin use. Indeed, both insulin use and advanced CKD were risk factors for serious hypoglycemic events [39]. Perhaps, insulin administration, like insulinogenic, plays a role in nephropathy. Moreover, a previous study reported that lower insulin sensitivity is related, longitudinally, to hyperfiltration and causes albumin excretion [40]. According to a randomized, crossover feeding trial study by Juraschek 2016 on 163 overweight/obese adults, without diabetes or kidney disease, a significant association between reducing GI and increasing intake of fat and proteins and promoting GFR was found [41].

Hyperglycemia is known to result in vascular endothelial cells. The biggest detriment happens in intracellular hyperglycemia [42], which can cause cellular damage by acute changes in cellular metabolism, as well as cumulative changes in long-lived macromolecules. Hyperglycemia is associated with rapid increases in reactive oxygen species (ROS) and lipid peroxidation. Consequently, ROS decreases nitric oxide levels by activation of aldolase reductase enzymes. This enzyme converts active aldehydes to inactive alcohol forms, and nitric oxide downregulates the activity of aldolase reductase by converting cysteine residues in the enzyme's active site. In addition, ROS seems to reduce nitric oxide levels and convert aldolase reductase to a higher status [43–45]. On the other hand, some studies have reported that ROS activates protein kinase C (PKC) by producing hydrogen peroxide (H2O2). PKC causes a thickening of basement membranes, vascular occlusion and permeability, and activates angiogenesis [46, 47]. Some studies posit that other mechanisms play a role in DN, implicating the production of advanced glycation products (AGEs). AGEs damage target cells by altering protein functions, changing extracellular matrix (ECM) function, producing cytokines and hormones by binding to macrophages, inducing ROS production, activating NF-κ B, and increasing expression of pathogenic cells [48]. Other mechanisms for DN concentrate on DIL and DII. In addition, higher insulin levels are associated with renal injury and predispose the patient to mild hypertension [49]. Some studies have reported a relationship between lower circulating irisin and IR and CKD and diabetes, whereas diabetic patients with abnormal fasting blood sugar present with higher levels of irisin [50–52]. The impaired insulin signaling, resulting from tyrosine phosphorylation that causes protein degradation and muscle wasting, is typically followed by a reduction in protein kinase B (PKB) or Akt kinase (Akt) activations and phosphatidylinositol 3 kinases [53–55]. CKD, by activating the ubiquitin–proteasome system, causes degradation of insulin receptor substrate 1 (insulin auto-phosphorylates tyrosine by these receptors) and decreases Akt phosphorylation and finally causes protein, lipid, and glycogen synthesis impairment [56]. Activation of the mineralocorticoid receptor in CKD raises asymmetric dimethyl arginine that impairs the signaling of insulin in adipocytes of rodents with renal dysfunctions. Moreover, angiotensin II promotes the suppression of cytokine signaling 3 (SOCS3) that leads to decreased IRS1 and impaired insulin signaling (in this pathway, increasing IR followed by enhancing ubiquitin protease system and degrading insulin receptor substrate 1 (IRS1) and reduction of phosphorylation Akt [57–60]). Podocyte cells prevent plasma proteins from entering the urine [61]; indeed, their decrease can be used as a predictive marker for a decrease in kidney function in diabetic patients, and the remaining cells are not able to compensate for the function of GFR and can cause glomerulosclerosis [62, 63].

To our knowledge, this is the first study to have assessed the relationship between DII and DIL and albuminuria, reduction of GFR, and DN. However, several limitations warrant consideration. First, the use of convenience sampling for the recruitment of participants

Table 1 Characteristics of participants across median of DIL and DII across case and control groups

Variables	Control (N = 105)						Case (N = 105)					
	DIL			DII			DIL			DII		
	Low adherence (N = 58)	High adherence (N = 47)	P	Low adherence (N = 61)	High adherence (N = 44)	P	Low adherence (N = 47)	High adherence (N = 58)	P	Low adherence (N = 44)	High adherence (N = 61)	P
Demographic and anthropometric characteristics												
Age (year)	56.14 ± 7.32	54.51 ± 6.87	0.24	56.38 ± 6.99	54.07 ± 7.19	0.1	56.74 ± 5.8	54.19 ± 7.76	0.05	56.43 ± 6.73	54.54 ± 7.2	0.17
Body weight (kg)	72.29 ± 11.77	70.71 ± 11.21	0.48	71.97 ± 11.73	71.05 ± 11.27	0.68	75.12 ± 13	72 ± 14.42	0.25	71.04 ± 13.07	76.65 ± 14.33	0.04
Height (cm)	160.72 ± 5.82	161.72 ± 6.03	0.39	161.08 ± 5.89	161.30 ± 6.01	0.85	160.3 ± 5.98	160.98 ± 6.56	0.58	160.66 ± 6.1	160.69 ± 6.46	0.98
BMI (kg/m^2)	28.01 ± 4.63	26.89 ± 4.02	0.19	27.74 ± 4.6	27.18 ± 4.09	0.51	29.30 ± 5.31	28.18 ± 4.19	0.23	27.95 ± 3.97	29.70 ± 5.52	0.06
Diabetes duration	7.53 ± 2.14	7.60 ± 2.21	0.87	7.63 ± 2.14	7.45 ± 2.21	0.68	7.57 ± 2.18	7.63 ± 2.24	0.9	7.40 ± 2.19	7.75 ± 2.22	0.42
Blood pressure												
SBP (mmHg)	137.98 ± 132.22	118 ± 14.74	0.25	118.66 ± 16.13	143.43 ± 151.39	0.2	127.38 ± 16.21	125.95 ± 18.18	0.64	127.98 ± 16.08	125.59 ± 18.13	0.48
DBP (mmHg)	82.12 ± 11.99	77.60 ± 11.07	0.04	80.52 ± 11.72	79.50 ± 11.91	0.66	83.98 ± 12.49	81.84 ± 13.57	0.41	83.70 ± 11.82	82.15 ± 13.98	0.55
Blood parameters												
Albumin (mg/dl)	9.37 ± 7.2	7.15 ± 6.03	0.09	9.43 ± 7.27	6.91 ± 5.75	0.05	13.6 ± 9.46	15.05 ± 13.66	0.53	13.98 ± 9.51	14.70 ± 13.49	0.76
Vitamin D3 (mcg)	29.28 ± 19.52	27.43 ± 14.7	0.59	29.17 ± 20.12	27.47 ± 13.1	0.62	27.16 ± 18.2	26.44 ± 18.95	0.71	26.74 ± 17.75	26.78 ± 19.22	0.99
Hemoglobin (g/dl)	12.34 ± 1.18	12.98 ± 1.19	0.007	12.45 ± 1.27	12.86 ± 1.12	0.09	12.58 ± 1.33	12.63 ± 1.4	0.84	12.60 ± 1.29	12.61 ± 1.42	0.97
FBS (mg/dl)	159.1 ± 44.27	148.13 ± 45.69	0.21	155.15 ± 44.04	152.86 ± 46.84	0.79	157.3 ± 51.75	175.05 ± 48.86	0.07	166.61 ± 58.02	167.46 ± 45.02	0.93
BS (mg/dl)	215.78 ± 56.48	196.38 ± 50.13	0.06	209.64 ± 56.35	203.57 ± 51.87	0.57	206.62 ± 45.51	226.78 ± 57.55	0.04	214.07 ± 54.98	220.41 ± 52.21	0.54
Hb A1C (%)	7.72 ± 1.02	8.28 ± 1.42	0.02	7.68 ± 1.01	8.27 ± 1.41	0.02	8.33 ± 1.32	8.92 ± 1.43	0.03	8.58 ± 1.42	8.71 ± 1.4	0.65
TC (mg/dl)	174.31 ± 34.22	176.7 ± 30.35	0.71	172.74 ± 31.54	179.05 ± 35.6	0.32	181.98 ± 38.98	187.72 ± 37.54	0.44	182.45 ± 33.84	187.10 ± 41.09	0.54
TG (mg/dl)	171.69 ± 63.21	150.60 ± 48.75	0.06	163.59 ± 64.51	160.39 ± 64.51	0.78	163.55 ± 63.92	170.26 ± 67.48	0.6	167.39 ± 62.35	167.16 ± 68.49	0.98
LDL (mg/dl)	95.21 ± 31.77	93.85 ± 26.67	0.81	94.23 ± 30.35	95.11 ± 28.53	0.88	103.77 ± 31.1	109.36 ± 32.35	0.37	105.32 ± 27.58	107.97 ± 34.66	0.67
HDL (mg/dl)	46.10 ± 8.30	46.70 ± 10.38	0.74	47.02 ± 9.48	45.48 ± 8.94	0.4	46.77 ± 9.63	43.66 ± 8.77	0.08	45.41 ± 8.85	44.79 ± 9.6	0.73
LDL/HDL	2.09 ± 0.72	2.09 ± 0.67	0.95	2.05 ± 0.72	2.14 ± 0.66	0.49	2.31 ± 0.86	2.59 ± 0.89	0.11	2.38 ± 0.73	2.52 ± 0.99	0.43
TC/HDL	3.89 ± 1.11	3.92 ± 0.88	0.91	3.81 ± 1.11	4.03 ± 0.83	0.28	4.04 ± 1.16	4.43 ± 1.12	0.08	4.14 ± 1.01	4.34 ± 1.24	0.37
Kidney function blood markers												
Creatinine (mg/dl)	0.88 ± 0.18	0.86 ± 0.14	0.64	0.86 ± 0.15	0.88 ± 0.18	0.41	0.89 ± 0.15	0.94 ± 0.16	0.07	0.92 ± 0.16	0.92 ± 0.16	0.89
ACR (mg/g)	18.66 ± 5.98	18.67 ± 5.9	0.98	19.26 ± 6.1	17.84 ± 5.62	0.23	234.83 ± 114.3	230.07 ± 114.85	0.83	226.20 ± 106.99	236.52 ± 119.61	0.64
BUN (mg/dl)	15.22 ± 3.81	15.11 ± 3.95	0.87	14.64 ± 3.03	15.91 ± 4.7	0.09	15.22 ± 3.89	16.26 ± 5	0.24	15.82 ± 4.03	15.78 ± 4.91	0.96
GFR (ml/min)	100.5 ± 29.92	101.04 ± 29.04	0.92	101.21 ± 29.11	100.09 ± 30.09	0.84	100.15 ± 25.1	93.19 ± 26.27	0.17	99.43 ± 25.99	94.06 ± 25.75	0.29

Table 1 (continued)

Variables	Control (N = 105)						Case (N = 105)					
	DIL			DII			DIL			DII		
	Low adherence (N = 58)	High adherence (N = 47)	P	Low adherence (N = 61)	High adherence (N = 44)	P	Low adherence (N = 47)	High adherence (N = 58)	P	Low adherence (N = 44)	High adherence (N = 61)	P
Drug history and physical activity												
CVD (yes)	11 (47.8%)	12 (52.2%)	0.48	12 (52.2%)	11 (47.8%)	0.63	10 (41.7%)	14 (58.3%)	0.81	11 (45.8%)	13 (54.2%)	0.81
ARB drug user (yes)	21 (46.7%)	24 (53.3%)	0.16	22 (48.9%)	23 (51.1%)	0.07	24 (40%)	36 (60%)	0.32	25 (41.7%)	35 (58.3%)	0.55
ACIE drug user (yes)	10(47.6%)	11(52.4%)	0.47	11(52.4%)	10(47.6%)	0.36	20 (45.5%)	24 (54.5%)	0.53	17 (38.6%)	27 (61.4%)	0.35
Beta-blocker drug user (yes)	9 (50%)	9 (50%)	0.4	12 (66.7%)	6 (33.3%)	0.29	10 (50%)	10 (50%)	0.59	11 (55%)	9 (45%)	0.3
Metformin user (yes)	57 (54.8%)	47 (45.2%)	0.55	60 (57.7%)	44 (42.3%)	0.58	47 (45.2%)	57 (54.8%)	0.55	44 (42.3%)	60 (57.7%)	0.58
Sulfonylurea drug user (yes)	33 (53.2%)	29 (46.8%)	0.38	36 (58.1%)	26 (41.9%)	0.57	31 (43.7%)	40 (56.3%)	0.45	29 (40.8%)	42 (59.2%)	0.45
Insulin user (yes)	22 (62.9%)	13 (37.1%)	0.18	21 (60%)	14 (40%)	0.47	14 (53.8%)	12 (46.2%)	0.19	11 (42.3%)	15 (57.7%)	0.56
PA low	21 (56.8%)	16 (43.2%)	0.88	21 (56.8%)	16 (43.2%)	0.95	11 (35.5%)	20(64.5%)	0.45	9 (29%)	22 (71%)	0.08
Moderate	15 (53.6%)	13 (46.4%)		16 (57.1%)	12 (42.9%)		20 (47.6%)	22 (52.4%)		17 (40.5%)	25 (59.5%)	
High	22 (55%)	18 (45%)		24 (60%)	16 (40%)		16 (50%)	16 (500%)		18 (56.3%)	14 (43.8%)	

The demographic characteristics of the case and control groups between DIL and DII intakes based on median groups

BMI body mass index, *ACIE* angiotensin-converting enzyme inhibitors, *ACR* albumin-to-creatinine ratio, *ARB* angiotensin receptor blockers, *BMI* body mass index, *BS* blood sugar, *CVD* cardiovascular disease, *DBP* diastolic blood pressure, *FBS* fasting blood sugar, *HB* hemoglobin, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *SBP* systolic blood pressure, *TC* total cholesterol, *TG* triglyceride, *SD* standard deviation

Cut off for Control DIL (149,866.95) and DII (114.6), Cut off for Case DIL (168,700.31) and DII (124.14)

Table 2 Dietary intakes of participants across DIL and DII intake

Variables	DIL		P^a	DII		P^a
	Low adherence (*N* = 105)	High adherence (*N* = 105)		Low adherence (*N* = 105)	High adherence (*N* = 105)	
Macronutrients						
Energy (kcal/d)	1340.63 ± 242.01	1519.27 ± 306.77	**< 0.001**	1459.72 ± 306.36	1400.18 ± 270	0.13
Protein (g/d)	45.2 ± 9.14	48.76 ± 8.98	**0.005**	47.99 ± 10.06	45.98 ± 8.8.20	0.11
Carbohydrate (g/d)	234.04 ± 46.01	268.54 ± 60.16	**< 0.001**	256.77 ± 61.93	245.82 ± 49.4	0.15
Dietary lipids						
Cholesterol (mg/d)	5.38 ± 6.56	8.09 ± 9.40	**0.01**	7.80 ± 8.82	5.66 ± 7.42	0.06
SFA (g/d)	5.81 ± 1.45	6.60 ± 1.74	**< 0.001**	6.39 ± 1.58	6.02 ± 1.69	0.09
MUFA (g/d)	10.13 ± 2.14	11.97 ± 3.63	**< 0.001**	11.10 ± 2.68	11.01 ± 3.49	0.82
PUFA (g/d)	10.32 ± 2.62	10.78 ± 2.08	0.15	10.85 ± 2.49	10.24 ± 2.22	0.06
Vitamins						
B1 (mg/d)	1.61 ± 0.32	1.76 ± 0.32	**0.001**	1.61 ± 0.32	1.76 ± 0.32	0.35
B2 (mg/d)	0.92 ± 0.16	1.02 ± 0.20	**< 0.001**	0.92 ± 0.16	1.02 ± 0.20	0.84
B6 (mg/d)	0.92 ± 0.16	1.02 ± 0.20	**< 0.001**	0.92 ± 0.16	1.02 ± 0.20	0.27
Folate (µg/d)	377.98 ± 98.94	390.02 ± 92.34	0.36	377.98 ± 98.94	390.02 ± 92.34	0.3
B12 (µg/d)	0.12 ± 0.11	0.17 ± 0.16	**0.01**	0.12 ± 0.11	0.17 ± 0.16	0.05

Cut off for DIL (162006.80) and DII (116.71)

DIL dietary insulin load; DII dietary insulin index, *SFA* saturated fatty acid, *MUFA* monounsaturated fatty acid, *PUFA* polyunsaturated fatty acid

Data are presented as mean ± SD; significant items with P 0.05 are bolded. P value was adjusted to energy intake. Independent sample T-test was used

might have introduced selection bias, potentially limiting the generalizability of our findings**.** Indeed, this study is a case–control study and cannot infer a causal relationship. Furthermore, given that dietary intake was assessed retrospectively using a food frequency questionnaire, it is plausible that women diagnosed with diabetic nephropathy may have altered their dietary habits after receiving their diagnosis, potentially in an attempt to manage their condition. This could have influenced their reported dietary intake at the time of the study. In addition, this study cannot provide real-time insight due to its nature. Although we adjusted for several covariates, it is entirely plausible that some unknown confounders exist. This study can be used as an evidence base for performing future randomized controlled trials and cohort studies with large populations.

Conclusion

This case–control study demonstrates that higher adherence to DII and DIL is associated with higher odds of DN. Furthermore, higher DII scores are related to albuminuria incidence in diabetic patients, whilst higher DII and DIL are negatively associated with GFR. However, further randomized controlled trials are required in the future to confirm the veracity of our findings.

Table 3 Association between intake of DIL and DII and odds of DN and reduced kidney function

	DIL						DII					
	Crude model			Adjust model			Crude model			Adjust model		
	OR	0.95% CI	p-value	OR	0.95% CI	p-value	OR	0.95% CI	p-value	OR	0.95% CI	p-value
Nephropathy												
Control	Reference						Reference					
Case	1.52	0.88, 2.62	0.13	1.82	1.01, 3.30	0.04	1.92	1.11, 3.32	0.02	1.90	1.08, 3.33	0.02
ACR												
Normal	Reference						Reference					
Microalbuminuria	1.48	0.82, 2.69	0.19	1.79	0.94, 3.44	0.07	1.67	0.92, 3.03	0.09	1.65	0.89, 3.04	0.1
Severely albuminuria	1.61	0.71, 3.65	0.25	1.89	0.78, 4.57	0.15	2.77	1.18, 6.50	0.01	2.77	1.16, 6.63	0.02
GFR												
Normal	Reference						Reference					
Mild to severe decrease	1.36	0.78, 2.37	0.26	2.30	1.17, 4.52	0.01	1.36	0.78, 2.37	0.26	2.06	1.09, 3.90	0.02
BUN												
Normal	Reference						Reference					
Mild to severe increase	1.27	0.57, 2.79	0.54	1.54	0.66, 3.6	0.31	1.49	0.67, 3.31	0.31	1.53	0.67, 3.48	0.3

The control group for Nephropathy, Normal < 30 for ACR, Normal ≥ 90 for GFR, and Normal < 20 for BUN was considered as a reference group

Binary logistic and multinomial regression were used, and the P-value was adjusted for Age, energy intake, and Hb

ACR albumin-to-creatinine ratio, *DN* diabetic nephropathy, *DIL* dietary insulin load, *DII* dietary insulin index, *GFR* glomerular filtration rate

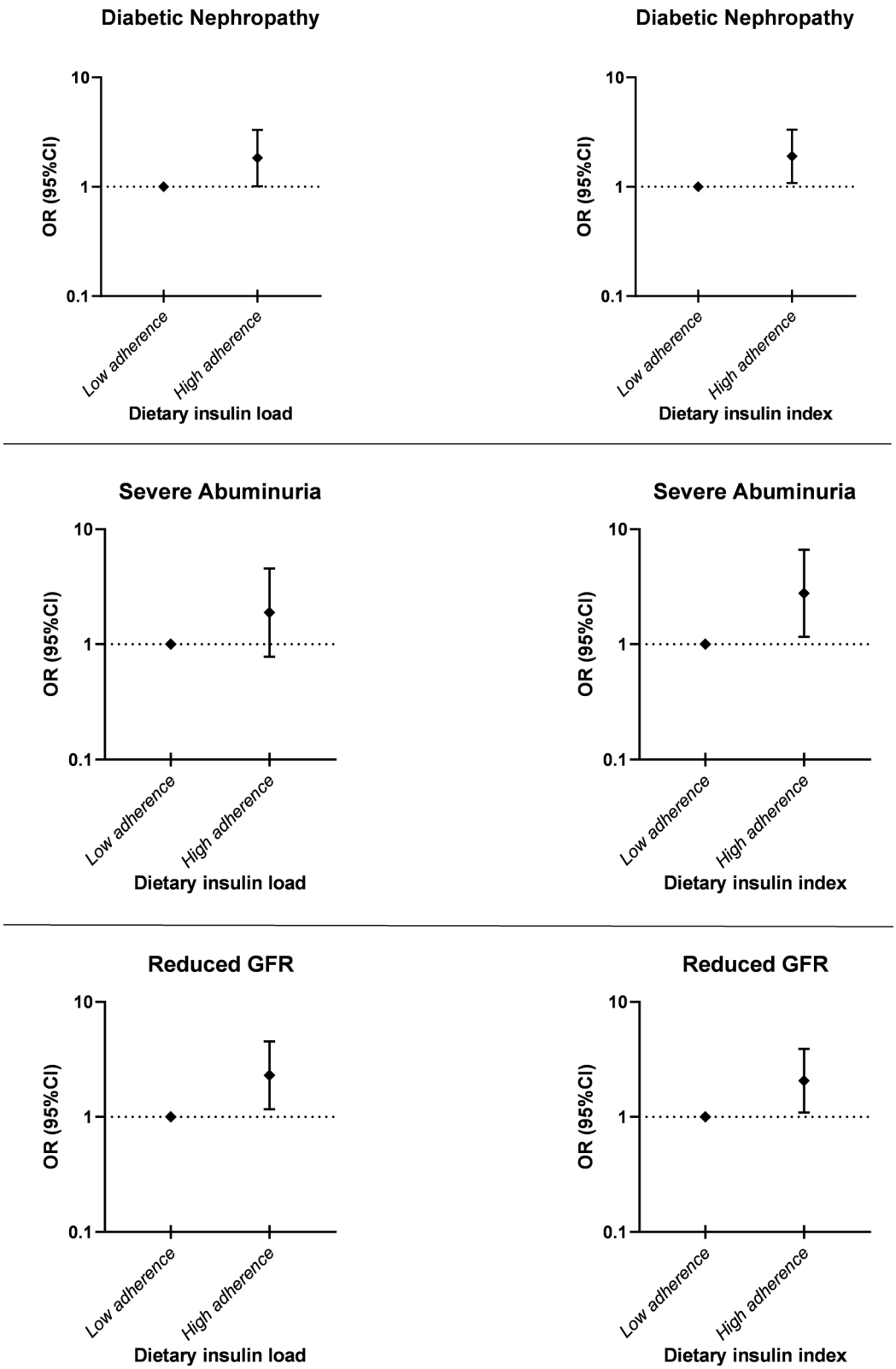

Fig. 1 Associations of Dietary Insulin Load and Dietary Insulin Index with Diabetic Nephropathy, Severe Albuminuria, and Reduced Glomerular Filtration Rate (GFR)

Abbreviations

ACR	Albumin-to-creatinine ratio
DM	Diabetes mellitus
DN	Diabetic nephropathy
DIL	Dietary insulin load
DII	Dietary insulin index
DBP	Diastolic blood pressure
e-GFR	Estimated glomerular filtration rate
ESRD	End-stage renal disease
FBS	Fasting blood sugar
FFQ	Food frequency questionnaire
Hb-A1C	Hemoglobin A1c
Hs-CRP	High-sensitivity C-reactive protein
T2D	Type 2 diabetes
MUFA	Monounsaturated fatty acids
SFA	Saturated fatty acids

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Author contributions
The project was designed and managed by FA and AM. The manuscript was written by FA, MG, YA, and RAK. Data were analyzed and interpreted by FA. The manuscript was edited by AM, PJ and CC. KM supervised the overall project. MG and PJ has revised and visualized the article. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study protocol has been approved by the ethics committee of Tehran University of Medical Sciences (TUMS) with the following identification: IR.TUMS.REC.1395.2644.

Consent for publication
Each participant was completely informed about the study protocol and provided a written informed consent form before taking part in the study.

Competing interests
The authors declare no competing interests.

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