BMC Endocrine Disorders

RESEARCH

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Association of dietary glycemic index and glycemic load with pancreatic steatosis: a case control study

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Abstract

Background Carbohydrate intake, its type and characteristics including glycemic index (GI) and glycemic load (GL) may be associated with the risk of pancreatic steatosis (PS), but there is no conclusive evidence. The aim of the present study was to investigate whether the intake of carbohydrates, GI and GL were associated with an increased risk of PS.

Methods To conduct this study, 278 patients with common bile duct stones (CBD) underwent endoscopic ultrasound, including 89 patients with PS (case group) and 189 healthy individuals (control group). In addition to demographic and anthropometric information, a 168-item questionnaire of food frequency was completed to calculate GL and GI.

Results With the increase of GI and GL, the number of patients with PS increased significantly ($P=0.013$, $P<0.001$, respectively) and the risk of PS increased significantly. A similar increase in risk of PS was found with increased risk of carbohydrate, simple sugar and fructose intake. After adjusting all the confounders, the risk of PS with increasing simple sugar and fructose intake was 4.3 times ($OR_{T3\ vs.\ T1}=4.3$, 95% CI: 1.7–10.6, P trend < 0.001) and 5.3 times ($OR_{T3\ vs.\ T1}=5.3$, 95% CI: 2.2–12.9, P trend < 0.001), respectively, compared to the first tertile. Conversely, increased fiber intake showed a reverse association with the PS, so that those in the second and third tertiles of fiber intake were 84% (OR = 0.16, 95% CI: 0.05–0.45) and 87% (OR = 0.13, 95% CI: 0.04–0.39) less at risk of developing PS, respectively (P trend = 0.001).

Conclusions These findings support the hypothesis of direct associations between GI and GL increased risk of PS.

Keywords Pancreatic steatosis, Glycemic index, GI, Glycemic load, GL

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Introduction

In 1933, the concept of pancreatic steatosis (PS) was introduced by Ogilvie, who observed that obese individuals have higher fat levels in the pancreas than non-obese individuals [1]. PS is a broad term that refers to the accumulation of fat in the pancreas and, when triggered by obesity, is known as non-alcoholic fatty pancreas disease (NAFPD) [2]. Extensive investigations in Asian populations have reported PS prevalence rates ranging from 16 to 35% [3], and a meta-analysis based on pooled data found an overall prevalence of 33% for NAFPD [4]. Moreover, research has yielded substantial evidence that establishes a direct correlation between pancreatic cancer and PS [5, 6]. Pancreatic cancer is the seventh most prevalent cause of cancer-related deaths worldwide and is responsible for over 331,000 deaths annually [7]. Previous studies have also demonstrated the association of PS with metabolic syndrome, type 2 diabetes mellitus, hypertension [8, 9], and obesity [8–10]. Nevertheless, there is currently no specific treatment for PS, and its management is primarily focused on addressing its underlying causes [11]. Diet has emerged as a crucial factor in the development of PS and its role seems to be promising in PS management [12].

The glycemic index (GI) and glycemic load (GL) of foods are two of the quality measures for carbohydrates that predict the glycemic response after meals. It is widely accepted that the quality and quantity of carbohydrates are the main factors that determine the glycemic response and the release of insulin after a meal [13, 14].

Current literature suggests that a low-glycemic index diet has potential benefits in reducing body weight, total body fat and visceral fat, levels of pro inflammatory markers and the occurrence of dyslipidemia and hypertension [15], all of which could influence the pathophysiology of PS [12]. Moreover, the advantageous impacts of low GI and GL have been examined in relation to similar conditions, such as fatty liver and it was determined that diets with low GI and GL may decrease the amount of fat in the liver [16].

Considering the relatively high occurrence of PS, the absence of targeted treatment methods, and its connection to pancreatic cancer, effectively managing PS is crucial. The primary objective of the present study is to provide further insights and improve the existing body of literature on dietary factors that are linked to PS. Specifically, our focus is to investigate the correlation between the quality and quantity of carbohydrates in one's diet and the risk of PS.

Material & methods

Study design and ethics considerations

The present study was designed as a case-control with 278 participants. After the approval of the Research Ethics Committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.NNFTRI.REC.1402.689), sampling started in 2022 by consecutive-sampling method. Sampling, endoscopic sonography and other investigations were performed in the gastroenterology clinic of Ayatollah Taleghani Hospital, Tehran, Iran. Before commencement, the study protocol and objectives were explained to the patients. Each participant was assigned a code, while face-to-face interviews and measurements were conducted in a private room, and participants were assured of confidentiality. This study was conducted in accordance with the ethical guidelines of the Helsinki Declaration. All participants signed a written informed consent form.

Participants

The participants of the present study were selected from patients with common bile duct stones who underwent endoscopic ultrasound (EUS). Based on the diagnosis of a skilled gastroenterologist and hepatologist and according to relevant guidelines [17], 89 patients were diagnosed with PS and the other 189 patients were healthy in this respect. Conscious and interested adults over 18 years of age were included in the study. The study exclusion criteria can be mentioned as follows: Pregnancy or breastfeeding, active malignancy and severe concomitant diseases including hepatitis, cirrhosis and kidney failure.

Data collection

First, demographic and lifestyle information was completed using a questionnaire. In order to avoid random observer error, a skilled nutritionist with more than 5 years of research experience performed all anthropometric measurements for cases and control groups. Body weight was assessed using a digital scale (Seca, Germany) with an accuracy of ± 0.1 kg. For anthropometric measurements, participants were instructed to wear light clothing without shoes or hats. Participants' height was measured in a standing position with a wall-mounted stadiometer (Seca, Germany) and rounded to the nearest 0.5 cm. The body mass index (BMI) was computed by dividing the weight (kg) by the square of height (m^2).

Calculation of dietary intakes, GI and GL

Food consumption during the past year (before the diagnosis of PS for cases and before the interview in controls) was estimated using a reliable and valid semi-quantitative food frequency questionnaire (FFQ). The mentioned questionnaire was designed based on Willett's method [18] and its validity and reliability [19] have already been measured. After explaining the household measures, the participants were asked about the frequency of consumption of each food item. Then, using the USDA food composition table along with the Iranian food composition

table, the average daily intake of energy and macronutrients was evaluated for each participant.

GI values were estimated using the international table of GI and GL values [20]. For items not on these lists, GI values were estimated based on foods with similar nutritional composition or calculated using related formula [21]. To calculate the dietary GI of each participant, we multiplied the carbohydrate content of each food items by its GI and the frequency of consumption and divide the result by the total carbohydrate intake. Then GIs of individual food items were summed up. The GI for whole and refined grain, vegetables, fruits, dairy products, and seeds and nuts was obtained from the international table of GI [22], the GI online database of the University of Sydney [23], and the publication that lists the GI of Iranian foods [24]. To calculate GL, GI in total available carbohydrate was multiplied and divided by 100. Each unit of dietary GL represents the equivalent of 1 g carbohydrate from glucose.

Dietary GI = [(carbohydrate content of each food item) × (number of servings/d) × (GI)]/total daily carbohydrate intake.

Dietary GL= (carbohydrate content of each food item) × (number of servings/d) × (GI).

Statistical analysis

Statistical data analysis was conducted using SPSS version 21.0 (SPSS, Inc.). All hypothesis tests were 2-tailed, with P values < 0.05 considered statistically significant. Data were tertiled by GL and GI to best fit the data distribution, simplify interpretation, and perform a comparison between triplicates without extreme differences in sample size between groups. Quantitative variables were compared between GI and GL tertiles, as well as between case and control groups, respectively, using ANOVA and independent t-test, and the results were reported as mean ± standard deviation (SD). Chi-square test was used to compare quantitative variables and the values were reported as frequency and percentage. The association of GI, GL and different types of carbohydrate with PS was assessed using binary logistic regression with odds ratios (ORs) and 95% confidence intervals (CIs). Age, sex, BMI and energy intake were considered as confounding factors. Three statistical models were defined. In the first model, the results were reported without considering confounders (crude). The second model was adjusted for age and sex, and the third model was additionally adjusted for BMI and energy intake. In all analyses, the first tertile was considered as the reference.

Results

Table 1 shows the characteristics of the participants at the beginning of the study. With the increase of glycemic index and glycemic load, the number of patients with PS increased significantly ($P = 0.013$, $P < 0.001$, respectively). A total of 94 men and 184 women participated in the study. The comparison of the gender across the GI and GL tertiles showed that the quantity of men increased with the increase in GI and GL, although this increase was statistically significant only in the GL tertiles ($P = 0.011$). No difference was observed in terms of age, smoking (except for GI, $P = 0.021$) and alcohol consumption. Differences in anthropometric characteristics including height, weight and BMI also showed statistical differences between GI and GL tertiles, except for BMI in GL.

Table 2 shows the difference in dietary intakes of case and control groups. As shown, although the two groups do not differ significantly in terms of calorie intake, the intake of carbohydrates, simple sugar, and fructose in the patients is higher than the control group, and the intake of fiber is lower. Therefore, the glycemic index and glycemic load in the case group were estimated higher than the control group. The minimum and maximum GI values were 45.3 and 82.52, respectively, and the minimum and maximum GL values were 53.25 and 333.52, respectively.

Table 1 Baseline general characteristics of study participants

	Glycemic Index				Glycemic Load			
	Tertile 1 < 55 (*n* = 92)	Tertile 2 55–63 (*n* = 93)	Tertile 3 63 ≤ (*n* = 93)	P value	Tertile 1 < 151 (*n* = 92)	Tertile 2 151–210 (*n* = 93)	Tertile 3 210 ≤ (*n* = 93)	P value
Cases with PS, n (%)	18 (20)	33 (36)	38 (41)	0.013	20 (22)	28 (30)	41 (44)	0.001
Men, n (%)	30 (32)	30 (33)	34 (38)	0.673	23 (24)	27 (29)	44 (47)	0.012
Age (y)	57.5 ± 16.3	55.6 ± 14.8	53.8 ± 14.4	0.270	58.4 ± 13.7	55.3 ± 15.2	54.5 ± 15.6	0.194
Alcohol drinker, n (%)	2	4	3	0.710	2	3	4	0.419
Smoker, %	14 (15)	7 (8)	20 (22)	0.021	10 (11)	14 (16)	17 (19)	0.332
Weight, kg	71.4 ± 14	73.8 ± 15.2	78.6 ± 18.2	0.009	70.5 ± 13.3	74.5 ± 14.9	76.7 ± 19.1	0.040
Height, cm	162.3 ± 8.5	165.2 ± 8.7	165.2 ± 9.9	0.044	161.3 ± 7.7	164.8 ± 9	165.7 ± 9.4	0.003
BMI, kg/m^2	27.1 ± 4.9	26.9 ± 4.9	28.7 ± 5.6	0.045	27.1 ± 4.5	27.4 ± 5.3	27.9 ± 6	0.621

The results are described as mean ± standard deviation (ANOVA test) or number (%) (Chi-square test).

Abbreviations: BMI: body mass index; PS: pancreatic steatosis

Table 2 Mean ± Standard deviation of dietary factors among cases with pancreatic steatosis and matched controls

	Cases *N* = 89	Controls *N* = 189	*P* value
Calorie (Kcal/d)	2547 ± 779	2400 ± 684	0.128
Carbohydrate (g/d)	340 ± 79	291 ± 92	< 0.001
Fiber (g/1000 kcal)	11 ± 9	14 ± 9	0.008
Simple sugar (g/d)	138 ± 52	121 ± 48	0.009
Fructose (g/d)	28.5 ± 20.6	19.4 ± 11.2	< 0.001
GI	62 ± 6	59 ± 8	0.016
GL	213 ± 59	174 ± 61	< 0.001

Student t-test

GI: Glycemic Index; GL: Glycemic Load

Table 3 describes the risk of pancreatic steatosis according to dietary intakes of some types of carbohydrates and GI and GL. With the increase of GI and GL, the risk of PS increased significantly. This increased risk was reinforced by adjusting the results for confounding factors. Also, in the pairwise tertile comparisons, it was found that those in the third tertile of GI and GL were significantly more at risk of PS compared to the reference group. Although this comparison was not significant between the second tertile and the reference group except for GL in the model 3 (OR = 2.1, 95%CI: 1.1–3.9). With the increase in carbohydrate intake, the number of patients and the risk of PS increased significantly. However, by adjusting the results for confounding factors, this increase in risk became a little weaker, so that in model 3, after adjusting the effect of all confounders, P was close to the significant level ($P = 0.049$).

A similar increase in risk of PS was found with increased risk of simple sugar and fructose intake. In model 3, after adjusting all the confounders, the risk of PS with increasing simple sugar and fructose intake was 4.3 times ($OR_{T3\ vs.\ T1}$ = 4.3, 95% CI: 1.7–10.6, P trend < 0.001) and 5.3 times ($OR_{T3\ vs.\ T1}$ = 5.3, 95% CI: 2.2–12.9, P trend < 0.001), respectively, compared to the first tertile. Conversely, increased fiber intake showed a reverse association with the PS. Logistic regression results after adjusting for all confounders indicated that those in the second and third tertiles of fiber intake were 84% (OR = 0.16, 95% CI: 0.05–0.45) and 87% (OR = 0.13, 95% CI: 0.04–0.39) less at risk of developing PS, respectively (P trend = 0.001).

Table 3 Odds and 95% confidence interval for occurrence of the pancreatic steatosis

	Tertiles of intake			*P* trend
Glycemic Index	**T1 (< 55)**	**T2 (55–63)**	**T3 (63 ≤)**	
No. of cases	18	33	38	0.013
Model 1	ref	1.1 (0.6-2)	1.9 (1.1–3.4)	0.007
Model 2	ref	1.3 (0.57–1.89)	2.3 (1.2–4.7)	0.015
Model 3	ref	1.4 (0.39–2.13)	2.5 (1.3–4.9)	0.031
Glycemic Load	**T1 (< 151)**	**T2 (151–210)**	**T3 (210 ≤)**	
No. of cases	20	28	41	0.001
Model 1	ref	1.4 (0.6–3.3)	2.8 (1.-6.1)	< 0.001
Model 2	ref	1.9 (0.9–3.6)	3.2 (1.4–7.3)	< 0.001
Model 3	ref	2.1 (1.1–3.9)	3.5 (1.5–7.9)	< 0.001
Carbohydrate	**T1 (< 257)**	**T2 (257–341)**	**T3 (341 ≤)**	
No. of cases	18	32	39	0.001
Model 1	ref	1.18 (0.6–2.1)	2.2 (1.1–4.3)	0.021
Model 2	ref	1.3 (0.7–2.3)	2.1 (1.1–4.1)	0.033
Model 3	ref	1.2 (0.6–2.6)	2 (0.86–4.7)	0.049
Fiber	**T1 (< 22)**	**T2 (22-33.8)**	**T3 (33.8 ≤)**	
No. of cases	43	29	17	0.010
Model 1	ref	0.32 (0.12–0.83)	0.28 (0.11–0.71)	0.022
Model 2	ref	0.29 (0.11–0.77)	0.26 (0.1–0.68)	0.016
Model 3	ref	0.16 (0.05–0.45)	0.13 (0.04–0.39)	0.001
Simple sugar	**T1 (< 99)**	**T2 (99–143)**	**T3 (143 ≤)**	
No. of cases	21	30	36	0.020
Model 1	ref	1.4 (0.76–2.8)	3.1 (1.1–9.2)	< 0.001
Model 2	ref	1.8 (0.97–3.4)	3.9 (1.6–9.2)	0.001
Model 3	ref	2.8 (1.3–6.2)	4.3 (1.7–10.6)	< 0.001
Fructose	**T1 (< 15.2)**	**T2 (15.2–24.2)**	**T3 (24.2 ≤)**	
No. of cases	12	36	41	< 0.001
Model 1	ref	1.93 (1.2–3.8)	4.78 (2.29–9.8)	< 0.001
Model 2	ref	2.44 (1.36–4.35)	5.68 (2.59–12.4)	< 0.001
Model 3	ref	3.45 (1.7–7.1)	5.3 (2.2–12.9)	< 0.001

Based on multiple logistic regression model.

Model 1: crude

Model 2: adjusted for age and sex

Model 3: additionally adjusted for energy intake, BMI, smoking, alcohol

Discussion

To the best of our knowledge, the present study is the first to provide valuable insights into the association between the quality and quantity of carbohydrates and the risk of PS. Our results suggested that diets with a high GI, GL, carbohydrate, simple sugar, and fructose content may increase the risk of PS. Specifically, being in the last tertiles of GI and GL was associated with a 2.5-fold and 3.5-fold higher risk of PS. Likewise, our findings indicated that higher consumption of carbohydrate, simple sugar, and fructose is associated with a 4.3-fold, 2-fold, and 5.3-fold higher risk of PS, respectively. Conversely, our findings indicated that higher fiber intake appears to have a reverse association with the PS, possibly due to its role in improving insulin sensitivity [25, 26] and reducing inflammation [27, 28]. Remarkably, individuals with higher fiber consumption demonstrate an 87% lower risk of developing PS.

Although the relationship between high glycemic indices, carbohydrates, and PS is not well established, there

are some potential connections to consider that can explain our findings. Multiple investigations have demonstrated a clear correlation between obesity, elevated visceral adipose tissue, and pancreatic fat accumulation [9, 29]. Obesity is a triggering factor for insulin resistance [30, 31] and the current evidence suggests that there is an association between insulin resistance and PS. For instance, a study by Weng et al. [32] demonstrated that the homeostatic model assessment of insulin resistance (HOMA-IR) is an independent risk factor for NAFPD. Similarly, another study by van der Zijl et al. [33], which involved patients with impaired glucose tolerance, found an inverse correlation between pancreatic fat content and insulin sensitivity. Furthermore, Lee et al. [34] discovered that HOMA-IR tended to increase with the severity of NAFPD. Specifically, in multivariate logistic regression analysis, HOMA-IR was correlated with NAFPD after adjusting for age, BMI, and lipid profiles. Nonetheless, the significant correlation between NAFPD and HOMA-IR disappeared when further adjustments were made for visceral adipose, indicating that visceral adipose may have a more prominent role in either contributing to or mediating the connection between NAFPD and insulin resistance. Dysfunctional adipose tissues in obese individuals contribute to early-stage insulin resistance through the excessive release of free fatty acids (FFAs), reactive oxygen species (ROS), and pro-inflammatory cytokines [30]. This elevation in FFAs produces toxic lipids, such as ceramide, that disrupt cellular organelles, including mitochondria, endoplasmic reticulum, and lysosomes [30, 35]. The malfunction of these organelles leads to apoptosis, systemic dysfunction, and cellular impairment, which in turn increase the release of FFAs and pro-inflammatory substances [30]. This condition eventually exacerbates insulin resistance, which raises the levels of FFAs in the body and encourages the build-up of fat in organs such as the pancreas [12, 30]. Interestingly, diets high in free sugar and correspondingly high glycemic indexes have been linked to obesity and the development of insulin resistance [36, 37].

The other potential explanation for our findings is related to inflammation. In a study in which 30 obese and 30 lean female mice were compared, the obese mice exhibited a higher fat content, triglycerides, free fatty acids, cholesterol, and pro-inflammatory cytokines (IL-1β and TNF-α) in their pancreas [38]. Research has demonstrated that obesity induces chronic low-grade inflammation, which in turn results in an increase in pro-inflammatory cytokines, including interleukin-1β (IL-1β) and tumor necrosis factor-alpha (TNF-α) [12]. In addition, obesity disrupts the delicate equilibrium of cytokines by decreasing the production of the anti-inflammatory cytokine IL-10 in the spleen [12, 39]. Notably, diets that have high glycemic indexes have been linked to causing chronic, low-grade inflammation in the body, both directly and indirectly. The consumption of high-glycemic index foods leads to excessive postprandial blood glucose excursions, which in turn generate nitric oxide, which, in combination with superoxide, produces peroxynitrite (a potent and long-lasting pro-oxidant molecule) [40]. Therefore, the consumption of foods with a high glycemic index can induce oxidative stress and chronic low-grade inflammation [41]. Overall, these inflammatory responses (due to either obesity or diet) lead to elevated levels of triglycerides, FFAs, cholesterol, and fat accumulation in the pancreas [12]. Additionally, a study conducted by DiNicolantonio et al. [42] highlighted that inflammation triggered by fructose intake leads to an increase in intracellular cortisol, which, in turn, contributes to the development of visceral adiposity. This means that fat cells release fatty acids into visceral organs such as the liver and pancreas, disrupting metabolic processes and organ function.

The current study possesses several noteworthy strengths. First, the present study provides the first evidence of an association between the quality and quantity of carbohydrates and PS odds. Second, a validated FFQ was used for dietary data collection by an expert dietitian who was unaware of the diagnosis. Third, a specialist performed the diagnosis, and it was similar for both groups to control information bias. Nonetheless, there are several limitations to this study. Selection bias, measurement bias, and recall bias for FFQ may lead to misleading findings in a case-control study. Additionally, while we examined adjusted models to account for potential confounding factors, it was not possible to assess genetic factors and other potential factors so it is crucial to recognize the possibility of undiscovered confounding factors. Physical activity levels and inflammatory biomarkers, which can influence insulin resistance and fat deposition, were also not taken into account. Finally, the study design restricts the establishment of a causal relationship, and the generalizability of the findings may be restricted to the specific population under investigation.

Conclusion

In conclusion, this case-control study highlights that diets high in GI, GL, carbohydrates, simple sugar, and fructose may increase the risk of PS, while higher fiber intake is associated with a lower risk of PS. Nevertheless, further prospective studies are warranted to confirm these associations and explore the underlying mechanisms in more detail.

Acknowledgements

This study is related to the project NO. 1402/73348 from Student Research Committee, Shahid Beheshti University of Medical Sciences, Tehran, Iran. We also appreciate the "Student Research Committee" and "Research &

Technology Chancellor" in Shahid Beheshti University of Medical Sciences for their financial support of this study.

Author contributions
Conceptualization, ZY and AH; Formal analysis, ZY; Methodology, MB, MC and AS; Project administration, DF and AH; Writing– original draft, MB, DF and ZY; Writing– review & editing, ZY and AH. All authors read and approved.

Funding
This project was funded by grant NO. 1402/73348 from Student Research Committee, Shahid Beheshti University of Medical Sciences, Tehran, Iran. The funding body has no role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

Data availability
The datasets analyzed in the current study are available from the corresponding author on reasonable request.

Declarations

Competing interests
The authors declare no competing interests.

Ethics approval and consent to participate
The study was approved by the Research Ethics Committee of Shahid Beheshti Medical University of Iran, under protocol number IR.SBMU.NNFTRI.REC.1402.689. All methods were carried out in accordance with relevant guidelines and regulations and all participants enrolled in the study provided written informed consent.

Consent for publication
Not applicable.

Received: 24 September 2024 / Accepted: 17 March 2025
Published online: 31 March 2025

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