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Serum visfatin levels are positively correlated with dietary carbohydrate and polyunsaturated fatty acid intakes in type 2 diabetes mellitus patients

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ABSTRACT

Aims: To investigate the relationship between dietary intake and biochemical parameters and anthropometric measurements and serum visfatin concentrations.
Study design: A case-control study.
Methods: The study was carried out in 30 type 2 diabetes mellitus (T2DM) and 30 sex, age and body mass index (BMI) matches healthy control subjects. Biochemical parameters (glycemic and lipid profile, insulin resistance), anthropometric measurements (weight and bioimpedance) and dietary intake evaluation were obtained. Visfatin was assayed with ELISA method.
Results: The mean BMI of the case group was 31.36 ± 4.37 kg/m^2 and 29.80 ± 3.53 kg/m^2 in the control group ($p = 0.134$). The results revealed a significant increase in the weight, waist circumference, waist/hip ratio, visceral fat ratio, fasting glucose level, HbA1c and fasting insulin as well as in insulin resistance (HOMA-IR) among T2DM patients when compared with controls ($p < 0.05$). Serum visfatin levels were higher in the subjects with T2DM than healthy control subjects ($p < 0.05$). There was no significant correlation between visfatin levels and biochemical parameters and anthropometric measurements in patients with T2DM. Serum visfatin level was positively correlated with carbohydrate (CHO) and polyunsaturated fatty acid (PUFA) in T2DM patients ($r = 0.406$, $p = 0.026$; $r = 0.404$, $p = 0.027$, respectively).
Conclusion: T2DM patients compares with healthy control group increased serum visfatin levels. PUFA and CHO intake was found to be positively associated with visfatin levels.

1. Introduction

Excess adiposity is regarded as the most important risk factor for insulin resistance and type 2 diabetes mellitus (T2DM).[1] Visceral fat is more dangerous than subcutaneous fat, especially in subjects with T2DM.[2] Adipose tissue releases different adipocytokines including leptin, adiponectin, resistin and seem to play an important role in the pathogenesis of diabetes.[1]

Visfatin, also known as pre-B-cell colony-enhancing factor (PBEF), is a cytokine that is predominantly expressed in visceral fat and was originally isolated as a secreted factor that from peripheral blood lymphocytes to promote the growth of B cell precursors.[3,4] Fukuhara et al. reported that visfatin inhibited decrease plasma glucose concentrations and imitate the effects of insulin by binding to insulin receptor.[5] However, since doubts were increased on the results of this study, it was later retracted.[6] Several studies were conducted for visfatin association with insulin resistance, diabetes. However, there are controversies in the results of these studies. In fact, some studies suggest that visfatin levels is

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increased in T2DM[7,8] whereas other have shown that visfatin is reduced in insulin resistance.[9] Several studies have shown significant correlations between circulating visfatin and fasting glucose,[3] insulin sensitivity, body mass index (BMI).[10] Other investigators have also found no significant correlations between circulating visfatin and fasting glucose, insulin sensitivity, BMI.[7,11] Due to mentioned findings, the association between serum visfatin and diabetes is not well understood.

Changes in dietary intake such as underfeeding, overfeeding plays an important role on adipose tissue metabolism and may affect visfatin concentrations. Although visfatin has important effects in diabetes, its relationship nutrition were lacking.[12] The effect of dietary determinants on adipocytokine levels are not well understood. Dietary intake of fatty acids might modify gene expression, metabolism and secretion of adipocytokines from adipose tissue. The effect of dietary monounsaturated fatty acid (MUFA) intake on serum of visfatin by its stimulating role on PPAR-g has been reported.[13] Studies assessing the effect of dietary factors on serum visfatin levels in diabetes are very limited. The aim of this study is to examine the relationship between serum visfatin levels and biochemical parameters and anthropometric measurements and nutritional status.

2. Materials and methods

2.1. Study population

This case-control study conducted at the Endocrinology and Metabolism Polyclinic of Erciyes University Medical Faculty Gevher Nesibe Hospital. The case group included 30 patients with T2DM (males 9, females 21), aged 25–64 were recruited from Department of Endocrinology. The control group was comprised of 30 healthy subjects (males 6, females 24), who regularly visited at our general clinic of the same hospital and compatible with the case group in terms of age, gender and BMI. Two different samples were calculated in order to make a statistically significant difference of 0.20 units between case and control group. According to the power of the test, the minimum number of subjects in each group was 23 (($\alpha = 0.05$); power of the test ($1 - \beta = 0.80$)) and 30 (($\alpha = 0.05$); test power ($1 - \beta = 0.90$)). Diagnosis of T2DM was made according to American Diabetes Society criteria. Exclusion criteria was including type 1 diabetes mellitus, gestational diabetes mellitus, cancer, hypertension, heart failure, acute or chronic infections, hepatic, renal disease and medications affecting glucose and insulin levels, major depressive disorder, being pregnant. Individuals with a disease diagnosed by a physician, regular medication and vitamin-mineral supplement use and a smoking-alcohol history were exclusion criteria for the control group. All individuals gave written informed consent before study beginning. The study was approved by ethical committee of Erciyes University Faculty of Medicine and was performed in agreement with Helsinki Declaration.

2.2. Measurement of body composition

The participants were on an empty stomach, and wore light indoor clothing without shoes. All measurements were taken by same researcher. Body weight was measured to an accuracy of 0.1 kg. Height was measured while they were standing in a vertical plane, with the head in the Frankfort horizontal plane. BMI was calculated as body weight (kg) divided by height (m) squared. Waist (narrowest diameter between the costal edge and iliac crest) and hip (greatest circumference around the buttocks) circumferences were measured to derive the waist-to hip ratio. Body compositions (fat-free mass (kg), body fat percentage (%), basal metabolic rate (BMR, kcal), visceral fat ratio (%)) was analyzed with the bioelectrical impedance method using the TANITA 730 BCE (TANITA, Japan).

2.3. Biochemical parameters and visfatin assay

Venous blood samples were taken after at least 8 h of fasting in the morning (between 8:30 and 10 A.M.). Samples analyzed in Erciyes University Central Laboratory, and fasting plasma glucose (FPG), glycosylated haemoglobin (HbA1c), insulin, serum total (TC), low-density (LDL-C), and high-density lipoprotein cholesterol (HDL-C) and triglyceride (TG) levels were determined. The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as fasting insulin (U/L) $\times$ fasting plasma glucose (mg/dL) / 405.[14] In order to determine serum visfatin levels, 5 mL blood sample was taken and centrifuged at 2500 rpm for 10 min at +4 °C. Blood samples whose serum was separated were placed into Eppendorf tubes and stored at −40 °C in the freezer until the analysis. Serum visfatin concentrations were measured in duplicate with a human visfatin ELISA Kit (MyBioSource, USA). Assay sensitivity was 0.1 ng/mL for visfatin. Visfatin test was evaluated by intra-assay precision ($\leq$10 %, CV %) and inter-assay precision (<12 %, CV %) according to the given information by kit manufacturer.

2.4. Dietary intake

The dietitian obtained daily dietary intake records of participants for 3 consecutive days (2 days week and 1 weekend). While first dietary intake record was received in Polyclinic, records of the following two days were collected through telephone interviews. A food catalogue was used to enhance portion size accuracy.[15] Dietitian provided with 10–15-min individual trainings about portion size. Records were analyzed with the computer-based data evaluation system and participants' daily intake amounts of energy and macro/micronutrients were calculated.[16]

2.5. Statistical analysis

The study data were analyzed using the IBM SPSS Statistics V.22.0. The data with normal distribution were shown as $\bar{x} \pm$ SD, whereas the data with non-normal distribution were shown as the median. The relationships between categorical variables were tested with the chi-square test. The Shaphiro-Wilk test was used to test whether the data was normally distributed. While the Student's *t*-test was used to compare variables with normal distribution in two groups, Mann-Whitney *U* test was used to compare variables with non-normal distribution in two groups. The relationship between the variables was analyzed with the Spearman Correlation Analysis if at least one of the variables had non-normal distribution. If both of the variables were normally distributed, Pearson correlation analysis was used to analyze the relationship between them. *p*-Values < 0.05 were considered statistically significant.

3. Results

This study was carried out with 60 participants. Of them, 30 were with type 2 diabetes (case group) and 30 were healthy individuals (control group). The mean age of the case group was 47.5 $\pm$ 6.61 years and the mean age of the control group was 46.0 $\pm$ 5.87 years. Of the participants, 30 % in the case group and 20 % in the control group were males ($p = 0.371$). Of the participants 43 % in the case group and 40 % in the control group were primary school graduates ($p = 0.999$). In each group, 93.3 % participants were married ($p = 0.999$). Of the participants 66.7 % in the case group and 53.3 % in the control group had income equal to their expenses ($p = 0.574$). The mean BMI of the case group was 31.36 $\pm$ 4.37 kg/m^2 and 29.80 $\pm$ 3.53 kg/m^2 in the control group ($p = 0.134$). There was no statistically significant difference between the groups in terms of age, gender, educational status, marital status, smoking, economic status and BMI ($p > 0.05$). The clinical characteristics of the case group were showed in Table 1.

There was an a highly significant increase in the levels of weight, waist circumference, hip circumference, waist/hip ratio, visceral fat ratio, FPG, HbA1c, insulin and CRP as well as in HOMA-IR of case group

Table 1
Clinical characteristics of the case group.

Variables	Type 2 diabetes ($n = 30$)
Age (yrs)	47.5 ± 6.61
Female (%)	21 (70.0 %)
Family history	26 (86.7 %)
DM duration (yrs)	5.73 ± 4.89
Age of onset (yrs)	41.80 ± 7.56
BMI (kg/m^2)	31.36 ± 4.37
Smoking status	
– Never	18 (60.0 %)
– Ex-smoker	7 (23.3 %)
– Current	5 (16.7 %)
Pattern of diabetes treatment	
– Diet control alone	0 (0 %)
– Oral antidiabetic medications	30 (100 %)
– Insulin therapy	0 (0 %)

compared with control group (Table 2). Serum visfatin levels of case group were higher than that control group ($p < 0.05$) (Table 2) (Fig. 1). There was no statistically significant difference in terms of dietary intake between the two groups ($p > 0.05$) (Table 4).

We analyzed the correlation between serum levels of visfatin and anthropometric measurements and biochemical parameters. Serum visfatin levels in case and control groups did not correlate with weight, BMI, waist circumference, hip circumference, waist-to-hip ratio, fat-free mass, body fat percentage, basal metabolic rate, and visceral fat ratio. Moreover did no significant correlation between serum visfatin and FPG, HbA1c, insulin, CRP, HOMA-IR, TG, TC, and LDL-C in both groups (Table 3).

When the relationship between serum visfatin and dietary intake is examined, there was a positive correlation between serum visfatin level

Table 2
Anthropometric measurements and biochemical parameters of the participants in both groups.

Variables	Case group (n = 30) $\overline{X}$ ± **SS** or median	Control group (n = 30) $\overline{X}$ ± **SS** or median	*p*
Weight (kg)	82.95 ± 12.37	76.70 ± 10.06	**0.036****
Height (cm)	162.47 ± 8.77	160.16 ± 7.33	0.275
BMI (kg/m^2)	31.36 ± 4.37	29.80 ± 3.53	0.134
Waist circumference (cm)	99.06 ± 9.19	85.87 ± 8.17	**0.000***
Hip circumference (cm)	111.60 ± 10.52	105.76 ± 7.03	**0.014****
Waist-to-hip ratio	0.89 ± 0.05	0.81 ± 0.07	**0.000***
Fat-free mass (kg)	49.55 ± 7.85	46.19 ± 7.53	0.096
Body Fat Percentage (%)	38.1 (27.3–43.9)	38.7 (31.0–41.6)	0.830
BMR (kcal)	1579.55 ± 230.58	1475.10 ± 212.55	0.076
Visceral fat ratio (%)	10.38 ± 2.67	8.85 ± 2.47	**0.025****
FPG (mg/dL)	138.40 ± 43.50	90.06 ± 6.46	**0.000***
HbA1c (%)	6.88 ± 1.10	5.13 ± 0.29	**0.000***
Insulin (μU/mL)	12.5 (7.8–22.8)	8.1 (6.9–11.1)	**0.015****
CRP (mg/dL)	3.9 (1.5–6.5)	1.35 (0.9–2.8)	**0.008***
HOMA-IR	4.4 (2.4–8.4)	1.8 (1.5–2 0.4)	**0.000***
TG (mg/dL)	144.5 (98.5–189.3)	116.5 (84.3–161.8)	0.124
TC (mg/dL)	193.96 ± 42.13	191.16 ± 36.58	0.784
LDL-C (mg/dL)	109.2 (72.9–137.6)	105.2 (93.5–133.2)	0.982
HDL-C (mg/dL)	48.13 ± 15.58	55.41 ± 11.54	**0.046***
Visfatin (ng/dL)	2.8 (0.7–4.2)	1.6 (0.9–1.9)	**0.030***

Abbreviations; BMI, body mass index; BMR, basal metabolic rate; FPG, fasting plasma glucose; HOMA-IR, insulin resistance; TG, triglyceride; TC, serum total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.
Data are expressed as mean ± standard deviation or median (25.percentile–75. percentile).
Bold font indicates statistical significance.
* $p < 0.01$.
** $p < 0.05$.

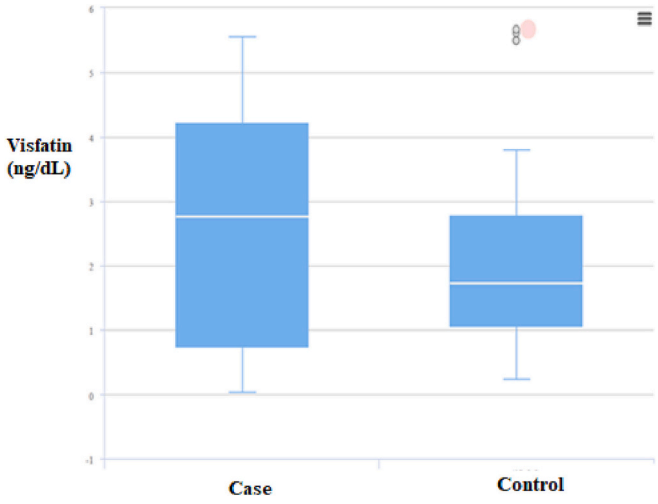

Fig. 1. Visfatin levels in both groups.

Table 3
Correlations between serum visfatin levels with anthropometric measurements and biochemical parameters of the participants in both groups.

Visfatin	Case group ($n = 30$)		Control group ($n = 30$)	
	r	*p*	*r*	*p*
Weight (kg)	−0.091	0.631	−0.134	0.481
Body height (cm)	−0.079	0.679	−0.335	0.071
BMI (kg/m^2)	0.054	0.777	0.157	0.407
Waist circumference (cm)	0.059	0.756	−0.127	0.503
Hip circumference (cm)	−0.015	0.938	0.234	0.214
Waist-to-hip ratio	0.153	0.418	−0.266	0.155
Fat-free mass (kg)	−0.058	0.761	−0.285	0.127
Body fat percentage (%)	−0.241	0.200	0.297	0.111
BMR (kcal)	−0.091	0.640	−0.294	0.115
Visceral fat ratio (%)	0.121	0.523	−0.148	0.436
FPG (mg/dL)	0.060	0.752	0.029	0.878
HbA1c (%)	−0.256	0.172	0.051	0.787
Insulin (μU/mL)	−0.001	0.998	−0.027	0.889
CRP (mg/dL)	0.348	0.075	−0.023	0.903
HOMA-IR	0.045	0.824	−0.008	0.965
TG (mg/dL)	0.117	0.537	0.003	0.987
TC (mg/dL)	−0.134	0.479	0.163	0.389
LDL-C (mg/dL)	−0.082	0.673	−0.007	0.972
HDL-C (mg/dL)	−0.307	0.105	0.377	**0.040***

Abbreviations; BMI, body mass index; BMR, basal metabolic rate; FPG, fasting plasma glucose; HOMA-IR, insulin resistance; TG, triglyceride; TC, serum total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.
Pearson correlation was used for analysis.
Bold font indicates statistical significance.
* $p < 0.05$.

and carbohydrate (CHO) and polyunsaturated fatty acid (PUFA) in the case group ($r = 0.406$, $p = 0.026$; $r = 0.404$, $p = 0.027$, respectively) (Figs. 2,3.) However, there wasn't correlation between serum levels of visfatin and other dietary intakes (Table 5).

4. Discussion

Serum visfatin plays significant role in numerous physiological and pathological processes T2DM. The present study aimed to assess the levels of serum visfatin in patients with T2DM. It is aimed also to examine the correlations between serum visfatin and anthropometric/biochemical parameters and nutritional status. The results of the study reveal that serum visfatin levels were higher in the subjects with T2DM than healthy individuals (as shown in Fig. 1). Previous studies showed

Table 4
Dietary intake of the participants in both groups.

Energy and macronutrient	Case group ($n = 30$) $\overline{X} \pm$ SS veya median	Control group ($n = 30$) $\overline{X} \pm$ SS or median	p
Energy (kkal/day)	1436.2 (1239.5–1642.8)	1447.7 (1155.4–1667.7)	0.824
CHO (g/day)	166.7 (146.8–216.4)	171.2 (123.5–210.7)	0.712
Fiber (g/day)	20.50 ± 7.21	19.22 ± 5.73	0.465
Protein (g/day)	53.4 (43.4–62.9)	48.20 (43.00–54.58)	0.179
Fat (g/day)	57.9 (47.3–64.9)	57.7 (44.80–63.86)	0.734
SFA (g/day)	19.73 ± 6.53	19.55 ± 6.38	0.917
MUFA (g/day)	22.11 ± 7.01	22.11 ± 7.31	0.999
PUFA (g/day)	13.5 (8.9–17.0)	9.9 (6.9–18.6)	0.408
Dietary cholesterol (mg/day)	232.4 (140.78–334.7)	211.2 (183.6–282.9)	0.790
Omega-3 fatty acids	0.9 (0.7–1.33)	0.9 (0.7–1.3)	0.888
Omega-6 fatty acids	11.7 (7.27–16.21)	8.8 (5.9–15.9)	0.473

Abbreviations; CHO, carbohydrate; SFA, saturated fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid.
Data are expressed as mean ± standard deviation or median (25.percentile–75. percentile).

Table 5
Correlations between serum visfatin levels with dietary intake of the participants in both groups.

Visfatin	Case group ($n = 30$)		Control group ($n = 30$)	
	r	p	r	p
Energy (kcal/day)	0.341	0.065	−0.316	0.089
CHO (g/day)	0.406	**0.026***	−0.290	0.120
Fiber (g/day)	−0.086	0.653	−0.119	0.530
Protein (g/day)	0.250	0.184	−0.402	**0.028***
Fat (g/day)	0.222	0.239	−0.241	0.200
SFA (g/day)	0.245	0.192	−0.226	0.230
MUFA (g/day)	0.047	0.807	−0.168	0.376
PUFA (g/day)	0.404	**0.027***	−0.147	0.439
Dietary cholesterol (mg/day)	0.331	0.074	−0.102	0.593
Omega-3 fatty acids	0.059	0.756	0.078	0.681
Omega-6 fatty acids	0.327	0.078	−0.109	0.566

Abbreviations; CHO, carbohydrate; SFA, saturated fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid.
Pearson correlation was used for analysis.
Bold font indicates statistical significance.
* $p < 0.05$.

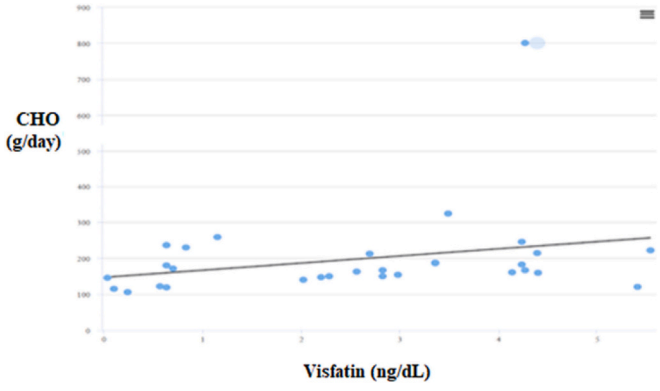

Fig. 2. Correlation between serum visfatin level and carbohydrate (CHO) intake in case group.

that the serum level of visfatin is higher in patients with T2DM compared to controls.[2,3,7] In addition, Kara et al. found that there was a significant positive correlation between serum levels of visfatin and BMI and HOMA-IR.[10] Sandeep et al. reported that serum visfatin were positively associated with BMI, HOMA-IR and waist circumference even after adjusting for age, sex, and type 2 diabetes mellitus.[17] Samiha et al. showed that serum concentration of visfatin increased along with rising insulin levels and HOMA-IR.[18] In contrast, Naithani et al. and Haddad et al. revealed that serum visfatin weren't associated with BMI, HOMA-IR and fasting insulin in T2DM patients.[11,19] Similarly, in our results, no association between serum visfatin levels and any anthropometric or biochemical parameters.

The effect of obesity status and HOMA-IR on circulating visfatin concentration is not clear.[10] Studies found an association between serum visfatin levels and obesity.[10,17] In contrast, we found no significant correlation between serum visfatin and obesity. Although this finding has also been inconsistency in different studies, it has been hypothesized that with obesity adipose tissue is exposed to hypoxia, which can secrete the inflammatory mediators. This is could in turn lead to the increase in serum visfatin levels.[19] There are studies showing correlation between serum visfatin and insulin resistance[10,17,18]; on the contrary, we could not observe a correlation. Esteghamati et al. found that increase of visfatin levels in T2DM is independent of insulin resistance, which is in agreement with the results of us.[2] Although clinical evidence regarding the correlation of serum visfatin with insulin resistance has been inconsistent, it has been showed that serum visfatin inhibited insulin signalling via the STAT3 and NF-κB pathways. Insulin may or may not have any role in the elevation of serum visfatin.[19]

Little is known about the effect of dietary factors influence circulating visfatin levels indirectly or directly. De Luis et al. found that serum visfatin was not significantly affected after hypo-energetic diet in obese patients.[20] Khanna et al. reported prevent decreases in visfatin following an exercise and diet intervention for 11 weeks.[21] Another study conducted by Tok et al. that diet and exercise-induced weight loss decreases in visfatin.[22] These inconsistencies in changes in visfatin could be explained by different inclusion criteria of subjects and the average BMI was different in previous studies.

It is not yet clear whether visfatin which has an insulin-mimetic effect plays a role in type 2 diabetes as a compensatory mechanism or as a marker of increased adipose tissue. In the this unclear relationships, dietary intake could play a main role.[23] Our main finding is an positive effect of PUFA and CHO intake on visfatin levels. Intakes of energy, protein, MUFA, saturated fatty acid (SFA) and fiber were not independently associated with serum visfatin concentration.

The acute effect of CHO intake on plasma visfatin is not clear. Bala et al., showed serum visfatin levels to be significantly decreased after oral glucose intake. All individuals in this study, however, were healthy and insulin-sensitive volunteers with a normal homeostasis model assessment (HOMA) index.[24] Zhaoxia et al. found visfatin levels increased in women with gestational diabetes mellitus following an oral glucose tolerance.[25] In the current study, plasma visfatin was significantly increased by CHO intake. These results suggest that visfatin may mediate glucose uptake when insulin function is impaired. Haider et al. reported that the level of visfatin release by adipocytes was dependent on duration and magnitude of glucose elevation.[26] Mellick et al. showed plasma visfatin was unchanged by CHO intake. The subjects used in this study, however, were insulin sensitive in healthy young men.[27] The reason for the discrepancy in studies is likely due to the heterogeneity of subjects used in the different studies.

Several studies have reported dietary fatty acids can be modulate visfatin gene expression. In randomized cross-over clinical trial, serum visfatin levels increased during SFA-rich diet but decreased during MUFA-rich diet. These findings emphasize the importance of dietary macronutrients composition for changes in serum visfatin levels.[28] Piers et al. suggest that consumption of a MUFA-rich diet as compared with a SFA-rich diet observed greater fat oxidation rate, could result in reduction visceral fat accumulation.[29] This is could in turn lead to the decrease in serum visfatin levels.[28] MUFA oleate and SFA palmitate significantly decreased visfatin mRNA expression in 3 T3-L1 adipocytes as well as preadipocytes.[30] In the present study, intakes of MUFA and SFA were not associated with serum visfatin levels. Discrepancy in

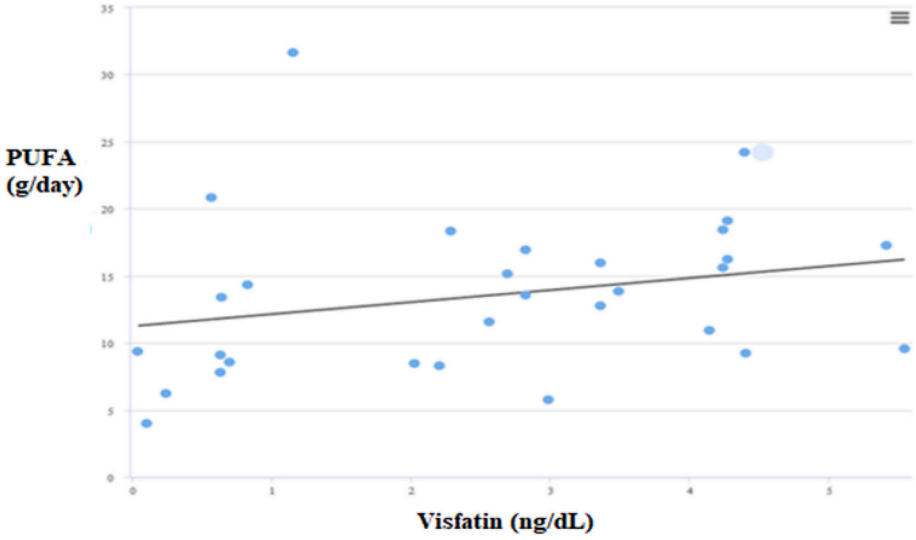

Fig. 3. Correlation between serum visfatin level and polyunsaturated fatty acid intake (PUFA) in case group.

findings might be attributed to sample sizes and duration of these studies. PUFA stimulated AMP-activated protein kinase and increased the effect of these acids on visfatin release by cultured adipocytes.[31] It has been showed an increase in visfatin level along with receiving Omega-3.[4] The same findings have also been reported by this study. Serum visfatin was significantly increased by PUFA intake. This result suggest that visfatin could be considered as a nutrient sensor secreted from adipocytes.[23]

The present study has some limitations. First, the sample size is not large enough to represent all patients with T2DM. Second, only one measurement of serum visfatin level may indicate short-term status. Third, we used a three-day weighed food record for dietary data collection.

5. Conclusions

The results of this study indicate increased serum visfatin levels in T2DM and this elevation of visfatin is independent of obesity and insulin resistance. It has been concluded that the increase in visfatin levels from the healthy control group to diabetes can be an indicator of the probability of developing metabolic diseases that accompany glucose metabolic abnormalities. Including visfatin in therapeutic agents could be considered as a new target in the management of diabetes. Additionally PUFA and CHO intake was found to be positively associated with visfatin levels. This result suggests that visfatin could be considered as a nutrient sensor secreted from adipocytes. Further research examining associations of nutrition with circulating visfatin in T2DM is need.

CRediT authorship contribution statement

N. Konyalıgil Öztürk, B. Çiçek and T. Tekin have been involved in the planning, execution and writing of the study. N. Konyalıgil and T. Tekin collected data. C. Yazıcı and İ. Güntürk has worked with visfatin ELISA kit. Z. Karaca has identified patients with type 2 diabetes. M. Sönmez made statistical analyzes. All authors read and approved the final manuscript.

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Declaration of competing interest

The authors have no conflicts of interest to disclose.

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