Ann Med Res 2021;28(12):2134-9

Annals of Medical Research

DOI: 10.5455/annalsmedres.2021.02.129

Original Article

The effect of visfatin rs2110385 gene polymorphism over oral antidiabetic drug response

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Abstract

Aim: The aim of our study is to investigate the effects of rs2110385 polymorphism of the visfatin gene on obesity in Turkish study groups. The rs2110385 polymorphism was analyzed in terms of genotype frequencies, obesity-related parameters, demographic data, serum visfat-in levels and drug use in obese and non-obese subjects.

Materials and Methods: The PCR-RFLP method was used to determine the visfatin gene rs2110385 genotype. MicroELISA method was used to measure serum visfatin levels.

Results: Homozygous wild type (G / G), heterozygous (G / T) and homozygous polymor-phic (T / T) genotype frequencies of the visfatin gene rs2110385 polymorphism was found to be respectively as, 54.1%, 66.7%, 61.8% in obese and 45.9%, 33.3%, 38.2% in non-obese. There was no statistical difference between the groups in terms of genotype frequen-cies and serum visfatin levels. Homozygous wild type genotype frequency was higher than heterozygous and homozygous polymorphic genotype in obese group with type 2 diabetes mellitus using sulfonylurea and glinide, respectively. The rs2110385 mutation reduced the response to antidiabetics in obese patients with type 2 diabetes mellitus.

Conclusions: In conclusion, our results may indicate that obese type 2 diabetic patients with the visfatin gene T / T rs2110385 genotype may benefit more efficiently from oral an-tidiabetic drugs other than glinide or sulfonylurea.

Keywords: Glinide; obesity; rs2110385 polymorphsim; sulphonylurea; visfatin

INTRODUCTION

Obesity is due to the excessive food intake and unbalanced energy expenditure. In recent years, the prevalence of people suffering from obesity has increased. Obesity is as-sociated with T2DM, hypertension and cardiovascular disease. Adipose tissue known to be an endocrine organ, secreting adipocytokines such as leptin, adiponectin and visfatin (1,2). Visfatin is a new adipocytokin that is mainly synthesized from visceral adipose tissue and has insulin-mimetic effects (3). Several studies have shown the correlation between serum visfatin levels and body mass index (BMI) or visceral fat accumulation which is known to be the primary determinant of insulin resistance (IR) (4-6) and relationship between serum visfatin and IR in pathological obesity (7). It is uncertain whether circulating visfatin levels are in correlation with increased total or visceral fat mass. Conflicting data exist on the rela-tionship between visfatin and IR (8).

Visfatin is originally called PBEF1 or nicotinamide phosphoribosyl transferase (NAMPT) (9). Visfatin level is elevated in the development of obesity, and plasma visfatin level is strongly correlated with visceral fat mass (10). Visfatin gene is located on chromo-some 7q22.2, with 473–amino acid protein with a molecular mass of 52 kd (11) and con-tains 10 introns and 11 exons (12). -4689 G>T (rs2110385) polymorphism is located in the promoter region of the visfatin (PBEF1) gene.

It has been shown that plasma visfatin levels are increased in people with abdominal obesity and / or type 2 diabetes mellitus (13). Haider et al. according to their study, it has been shown that there is a relationship between circulating visfatin level and blood sugar levels. However, this may be affected by some antidiabetic drugs in the hypothesis (14).

In patients with type 2 diabetes, glycemic control lowers plasma visfatin levels, and changes in visfatin levels may

Received: 07.02.2021 **Accepted:** 23.06.2021 **Available online:** 16.12.2021
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be a compensatory mechanism in insulin deficiency (15). Several studies have reported SNPs in the promoter region of the visfatin gene which are in relation with susceptibility to T2DM, additionally other studies have shown correlation with glucose homeostasis (16). Research on the promoter and coding region generated genotypes explain promoter regions to be effective on insulin levels and plasma glucose (17-19). The most commonly used drugs in the treatment of Type 2 Diabetes are Metformin (20) from the insulin sensitizer (Biguanide) class and Glibenclamide (21) from insulin secretagogues (Sulfonylureas) class. Sulfonylurea agents close the adenosine triphosphate sensitive potas-sium channels in pancreatic I cells and leading to insulin triggering (22). Metformin im-proves reduce hyperinsulinemia and insulin sensitivity, resulting with significant minimiza-tion in plasma triglycerides, cholesterol, free fatty acid and leptin concentrations (23-25). According to some studies, it has been emphasized that SNPs are effective in response to antidiabetic drugs in patients with type 2 diabetes (26,27). It is still unknown whether an-tidiabetic drugs modulate visfatin actions (8). We aimed to study the effects of visfatin gene promoter gene rs2110385 variation on obesity, obesity related parameters, serum visfatin levels together with its pharmacogenomic interactions in the present study.

MATERIALS and METHODS

Study subjects

We studied 63 obese (overweight + obese + morbid obese) and 41 non-obese indi-viduals who applied to Istanbul University-Cerrahpaşa Faculty of Medicine, Department of General Surgery (Istanbul, Turkey) between January-June 2013. Diagnosis of the disease was made by an expertise endocrinologist. Obesity, abdominal obesity, T2DM, dyslipidemia and hypertension and were diagnosed according to IDF guidelines (28). For the measure-ment of body fat, the lean body mass (LBM) was calculated separately for men and women according to the formula below according to Hume (29).

Females (kg): 0.29569 X weight (in kilograms) + 0.41893 height (in cm) -43.2933.

Males (kg): 0.32810 X weight (in kg) + 0.33929 X height (in centimeters) -29.5336.

Body fat measurement was calculated by subtracting lean body mass from whole body weight. Assessment of arterial blood pressure was made based on The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure criteria (30). Patients with metabolic syndrome (MS) were determined ac-cording to Adult Treatment Panel III (ATP III) criteria (31). The mean age was 57.36 ± 2.72 for obese group and 60.94 ± 2.98 for non-obese group. Excluded patients; patients had diabetic nephropathy, neoplasia, secondary hypertension, pseudohypertension, hypertension with endocrinopathy, and those who take illicit and oral contraceptives drugs.

Biochemical Analytical Methods

Using the glucose oxidase method with the Biotrol kit, plasma glucose concentra-tion was measured on the Bayer / opeRA analyzer. Serum T- Cholesterol was measured us-ing commercial kit of Biotrol; HDL- Cholesterol using by commercial Randox's kit; calcu-lated LDL-Cholesterol using Friedewald formula and for the determination of triglycerides (TG), lipase / glycerol kinase was performed with UV endpoint method on opeRA analyzer.

Determination of serum visfatin levels

Serum samples for visfatin were stored at -80 ° C until analysis. Serum visfatin lev-els of the samples were measured using Visfatin Human Enzyme Immunoassay Kit (Ray Biotech, Norcross, GA) according to the commercial kit protocol. Intra-assay and inter-assay coefficients of variation were less than 10% in enzyme immunoassays.

DNA isolation and genotyping

Genomic DNA isolation was done by salting out method using peripheral blood leu-kocyte cells (32). The obtained DNA purity was 1.8-2.0 in the 260/280 ratio and showed good deproteinization. Purified DNA (50 ng) was stored at -20°C. The rs2110385 geno-types were determined using the PCR-RFLP method. PCR primers are selected to specifi-cally target the human visfatin gene containing the -4689G/T (rs2110385) polymorphism in the distal promoter region. PCR mix conditions in 25 µl reaction: 50 ng genomic DNA, 0.15 ul 50 u mol/l primers, 0.5ul 100 mol/l dNTP and 0.1 unit Taq Polymerase (Fermentas). Pri-mer annealing temperature was 57°C. Restriction digestion was done overnight at 37 ° C to the PCR products. The visfatin gene rs2110385 primer sequences were as follows, respec-tively: left primer, 5'-TGCTAGCCCATATCAATGACTG-3'; right primer, 5'-AATGGGAGAAGAGGGGAAAA-3'. Restriction digested were overnight with 5 units of AluI (Fermentas). The digested DNA fragments were separated by 2% agarose gel electro-phoresis.

Statistical Analysis

Statistical analyses were performed using the SPSS 17.0 software (SPSS Inc., Chicago, IL) program. Data were expressed as mean ± SE. Categorical variables were expressed as the number of cases and percentage values. Kolmogorov-Smirnov and Shapiro Wilk test was used to examine whether the distribution of the variables with continuous measurement was normal or not. In the comparison of the two groups (obese and non-obese) Student's t-test was used if the variables showed normal distribution and the Mann Whitney U test was per-formed if variables were not in normal distribution. Comparisons of more than two groups (wild type homozygous, heterozygous, and polymorphic homozygous genotypes) one way ANOVA was used if the variables showed normal distribution and if variables were not in normal distribution Kruskal Wallis test was performed. Comparison of categorical variables was performed with Chi-square and Pearson's exact probability tests. $p < 0.05$ was conside-red as statistically significant.

RESULTS

The visfatin gene rs2110385 genotype frequencies for obese and non-obese groups are shown in Table 1. The frequencies of the visfatin gene rs2110385 wild type homozygous, heterozygous, and polymorphic homozygous genotypes, respectively as, 54.1 %, 66.7 %, 61.8 % in obese group; 45.9 %, 33.3 %, 38.2 % in non-obese group. Genotype frequencies of the rs2110385 polymorphism were not significantly different between study groups (χ2=1.192, p=0.551) (Table 1). The homozygous polymorphic and heterozygous genotype frequencies for obese patients were considerably high in comparison to non-obese individu-als (Table 1).

Table 1. rs2110385 genotype frequencies in Obese and non-Obese subjects

	Genotype Frequency		
	G/G, n(%)	G/T, n(%)	T/T, n(%)
Obese	20 (54.1)	22 (66.7)	21 (61.8)
Non-Obese	17 (45.9)	11 (33.3)	13 (38.2)

Results are presented as number (%). Disease frequencies of the study groups were com-pared according to Chi-square (χ2) test. n: Number of people. χ2 =1.192, p= 0.551

Table 2. Comparison of CVD risk factors between microalbuminuric and normoalbuminuric groups

		G/G, (Obese n=20; non-obese n=17) Mean ± SE; Median (Range)	G/T, (Obese n=22; non-obese n=11) Mean ± SE; Median (Range)	T/T, (Obese n=21; non-obese n=13) Mean ± SE; Median (Range)	ANOVA p
Weight (kg)	Obese	80.75 ± 3.20; 76 (64-120)	81.70 ± 2.59; 80 (65-103)	79.85 ± 2.98; 77 (62-115)	0.697
	Non-obese	63.79 ± 2.00; 62 (54-87)	62.09 ± 2.94; 62 (50-80)	64.62 ± 2.26; 64 (50-77)	
Height (m)	Obese	1.62 ± 0.02; 1.60 (1.5-1.8)	1.61 ± 0.02; 1.58 (1.5-1.8)	1.62 ± 0.02; 1.63 (1.4-1.8)	0.828
	Non-obese	1.65 ± 0.02; 1.63 (1.5-1.9)	1.64 ± 0.03; 1.65 (1.5-1.8)	1.62 ± 0.02; 1.63 (1.5-1.7)	
Waist (cm)	Obese	100.45 ± 2.68; 100.5 (71-131)	101.82 ± 2.92; 100 (80-130)	96.35 ± 3.02; 102 (72-115)	0.572
	Non-obese	79.41 ± 1.99; 82 (67-95)	76.55 ± 2.41; 72 (69-92)	80.91 ± 2.93; 76 (67-106)	
BMI (kg/m²)	Obese	49.91 ± 1.75; 47.12 (40.24-68.18)	49.61 ± 1.51; 48.46 (39.21-63.74)	49.84 ± 1.60; 48.20 (38.62-66.89)	0.327
	Non-obese	23.28 ± 0.30; 23.50 (20.95-24.91)	23.01 ± 0.73; 22.22 (20.01-29.38)	24.60 ± 0.93; 23.01 (22.03-33.32)	
LBM (kg)	Obese	30.59 ± 1.09; 29.36 (25.09-42.29)	31.49 ± 0.99; 29.76 (25.39-42.87)	30.39 ± 1.00; 29.97 (25.25-41.66)	0.806
	Non-obese	46.55 ± 1.47; 44.58 (37.18-62.29)	45.95 ± 2.20; 47.45 (34.33-53.50)	46.42 ± 1.21; 47.12 (37.76-53.13)	
FM (kg)	Obese	30.83 ± 1.91; 28.46 (22.59-51.80)	32.09 ± 1.66; 32.09 (18.91-46.15)	30.01 ± 1.93; 28.06 (18.26-48.10)	0.270
	Non-obese	17.24 ± 0.77; 16.92 (12.20-24.20)	16.14 ± 1.30; 15.67 (11.48-27.30)	18.19 ± 1.36; 17.57 (12.23-29.70)	
T-Col (mmol/L)	Obese	2.39 ± 0.10; 2.49 (1.77-3.09)	2.23 ± 0.10; 2.17 (1.46-3.32)	2.21 ± 0.11; 2.19 (1.40-3.09)	0.485
	Non-obese	2.17 ± 0.08; 2.24 (1.76-2.57)	2.15 ± 0.10; 2.20 (1.71-2.63)	2.00 ± 0.16; 1.98 (1.28-3.02)	
TG (mmol/L)	Obese	1.70 ±0.14; 1.44 (1.03-2.89)	1.60 ± 0.11; 1.66 (0.75-2.61)	1.75 ± 0.20; 1.48 (0.88-4.32)	0.770
	Non-obese	1.69 ± 0.46; 1.28 (0.76-5.80)	1.43 ± 0.12; 1.27 (1.13-2.23)	1.42 ± 0.21; 1.36 (0.81-2.94)	
HDL- Chol (mmol/L)	Obese	0.54 ± 0.03; 0.55 (0.27-0.75)	0.55 ± 0.02; 0.51 (0.33-0.83)	0.49 ± 0.02; 0.46 (0.27-0.66)	0.132
	Non-obese	0.58 ± 0.03; 0.55 (0.31-0.74)	0.49 ± 0.03; 0.50 (0.38-0.66)	0.60 ± 0.04; 0.59 (0.47-0.90)	
LDL-Chol (mmol/L)	Obese	1.23 ± 0.13; 1.29 (0.33-2.06)	0.09 ± 0.11;1.10 (0.37-1.96)	1.02 ± 0.12; 0.99 (0.28-1.96)	0.520
	Non-obese	0.91± 0.14; 1.06 (0.30-1.79)	0.97 ± 0.15; 1.06 (0.38-1.69)	0.94 ± 0.11; 1.07 (0.38-1.46)	
Fasting glu-cose (mmol/L)	Obese	8.33 ±1.17; 6.85 (3.44-19.53)	5.82 ± 0.90; 4.34 (3.16-13.70)	4.70 ±1.16; 3.22 (2.55-16.03)	0.869
	Non-obese	6.56 ± 0.97; 5.38 (3.16-10.71)	7.09 ± 2.19; 3.88 (2.22-16.48)	5.53 ± 1.02; 5.61 (3.71-7.72)	
SBP (mmHg)	Obese	146.5 ± 4.11; 150 (115-180)	143.86 ± 5.55; 135 (120-22-)	138.33 ± 5.58; 140 (90-190)	0.213
	Non-obese	128.24 ± 4.56; 125 (100-170)	119.09 ± 4.95; 115 (100-160)	134.23 ± 5.09; 130 (110-160)	
DBP (mmHg)	Obese	85.25 ± 2.77; 82.5 (60-110)	80.23 ± 1.85; 80 (70-100)	80.95 ± 2.96; 80 (60-110)	0.308
	Non-obese	76.47 ± 2.18; 80 (60-90)	72.73 ± 3.26; 70 (60-100)	79.23 ± 3.09; 80 (60-100)	

Values are represented as mean ± SE; Median (Minimum-maximum). n: Number of people. BMI: Body mass index, LBM: Lean body mass, FM: Fat mass, T-Chol: Total cholesterol, TG: Triglycerides, HDL-Chol: High-density lipoprotein, LDL-Chol: Low-density lipopro-tein, SBP: Systolic blood pressure, DBP: Diastolic blood pressure. Waist, T-Chol, HDL-Chol and LDL-Chol comparisons among genotypes were estimated by one way ANOVA whereas other parameters with kruskal-wallis test

Serum visfatin levels of the obese and non-obese groups were found to be similar (p=0.365) (Table is not included). In detail, serum visfatin levels were detected in the obese 7.91±0.17 ng/ml and non-obese 7.62±0.28 ng/ml.

The effects of visfatin gene rs2110385 genotypes on obesity, hypertension and type 2 diabetes mellitus phenotypes together with demographic characteristics in study groups (obese and non-obese) are shown in Table 2. The heterozygous genotype carrier obese pa-tients were found to be not having higher weight, waist, and fat mass measurements in comparison to homozygous polymorphic genotypes carriers. In the obese group, the poly-morphic allele has been found to have a reducing effect on fasting glucose levels compared to the wild type allele (Table 2). Visfatin rs2110385 genotypes were analyzed for their in-fluence on obesity, hypertension and type 2 diabetes mellitus phenotypes together with de-mographic characteristics the non-obese group (Table 2). Table 2 shows that the homozy-gous polymorphic (T / T) genotype has a lowering effect on fasting glucose, total cholesterol and triglyceride levels in non-obese individuals.

The effective drug use for the obese patients as a function of rs2110385 genotypes is given in Table 3. The wild type genotype of obese type 2 diabetic patients were found to respond positively to sulphonylurea and glinide therapy, whereas the homozygous polymor-phic genotype carriers were not found to respond well to antidiabetic drugs of sulphonylu-rea and glinide class (Table 3).

Table 3. rs2110385 genotype effect over drug use in obese patients

Drug	rs2110385 Genotypes			
	G/G, n(%)	G/T, n(%)	T/T, n(%)	p
Diuretic	4 (20)	8 (36.4)	6 (28.5)	0.503
ACE	4 (20)	6 (27.3)	5 (23.8)	0.858
BB	7 (35)	9 (40.9)	8 (38.1)	0.925
ASA	10 (50)	10 (45.5)	7 (33.3)	0.434
Sulphonylurea	8 (40)	2 (9.1)	1 (4.8)	0.005*
Glinide	15 (75)	11 (50)	4 (19.0)	0.002*
Metformin	8 (40)	11 (50)	6 (28.5)	0.357

Results are presented as number (%). n: Number of people.
ACE: Angiotensine converting enzyme inhibitor, BB: Beta blocker, ASA: Acetyl salicylic acid. *p<0.01
Drug frequency comparisons were applied with Chi-Square test, except for sulphonylurea in which Pearson's exact test was used

DISCUSSION

The main aim of our study is to determine the genotypic frequencies of the visfatin rs211085 variation in obese and non-obese individuals. We could not confirm any correla-tion of rs2110385 variation with any measure of obesity and serum visfatin levels, whereas significant association was detected with drug use.

Bailey et al. (17) reported the role of promoter region visfatin gene variants on obe-sity-related phenotypes within 13 SNPs in the of the visfatin gene. rs2110385 allele fre-quencies in study group 33.6% for homozygous wild type genotype (G/G), 50.2% for het-erozygous (G/T) and 16.2 for homozygous polymorphic genotype (T/T) in Quebec Family Study group. According to study they were not able to report significant genotype frequen-cies for the visfatin gene rs2110385 polymorphism among the study groups (17). Mirzaei et al. (33) reported the frequencies wild type genotype (G/G), heterozygous (G/T) and homo-zygous polymorphic (T/T) genotypes as 37.5%, 43.8% and 18.8%, respectively in type 2 diabetic patients. In Chinese Han population the rs2110385 G/G, G/T and T/T genotype frequencies were reported to be 78.6%, 14.3% and 7.1% respectively in type 2 diabetes mellitus group; 67.3%, 15.4% and 17.3% in type 2 diabetes was higher than that of normal glucose tolerant control ($\chi2=4.315$,$P<0.05$;$\chi2=6.621$,$P<0.05$) (34). In the present study, T/T genotype frequencies were found to be 51.4% and 45.97%; the heterozygous genotype frequencies 66.7% and 33.3% and homozygous polymorphic genotype 61.8% and 38.2% for the study groups (obese and non-obese), respectively. The serum visfatin levels between obese and non-obese groups were not statistically significant (p=0.365). Similar to the re-sults with most literature research, moreover, we could not detect a significant association of rs2110385 polymorphism with obesity.

Kim et al. (35) evaluated the relationship between metabolic syndrome and visfatin in postmenopausal women. The study subjects consisted of 110 postmenopausal Korean women (35). Serum visfatin level (mean ± SD) of patients with metabolic syndrome was higher with a value of 2.74 ± 1.70 ng / ml than subjects without metabolic syndrome ($p <0.01$) (35). The researchers concluded serum visfatin levels to be incorporated to metabolic syndrome in postmenopausal women (35). A study performed on 76 newly diagnosed type 2 diabetes mellitus patients and 76 healthy subjects have evaluated the association of serum visfatin, leptin and adiponectin with T2DM in the context of the role of insulin re-sistance/obesity and detected serum visfatin levels were higher in T2DM patients compared with controls (5.49±2.4 and 3.58±2.2 ng/ml, respectively, $p < 0.01$) (36). Ersoy et al. (8) have explored the association between visfatin and obesity related parameters such as BMI and waist circumference and IR in 81 healthy female subjects and they were divided into four groups accordingly their BMI and waist circumference rates. Serum visfatin levels did not differ between groups, and they showed that serum visfatin levels did not detect any significant relationship between obesity and metabolic parameters (8). Luis et al. (37) have reported a population of 228 obese non-diabetic patients with low, median and high rates of visfatin values. In a multivariate analysis with age- and sex- adjusted basic visfatin level as a dependent factor, only weight and leptin survived as an independent factor for obesity with a reverse relation ($p < 0.05$) (37). Zahorska-Markiewicz et al. (38) have compared se-

rum visfatin levels in 21 obese women with 16 normal-weight control individuals, where serum visfatin levels were significantly higher in the obese group (38). There was a positive correlation between serum visfatin and insulin in obese group and a positive correlation be-tween serum visfatin and glucose in the non-obese group (38). Jin et al. (39) studied the effect of adolescent obesity on circulating visfatin levels in Chinese adolescents and meas-ured serum visfatin concentrations in 72 obese and 76 non-obese adolescents (39). When serum visfatin concentrations were compared between the groups, serum visfatin levels in obese subjects were significantly higher than in non-obese subjects (P = 0.002) 28.67 ng / ml and 34.68 ng / ml, respectively (39). In our study we observed similar serum visfatin con-centrations in obese (7.91 ± 0.17) and non-obese (7.62 ± 0.28) groups.

In the Quebec Family Study, Bailey et al. (17) have evaluated the effects of visfatin gene rs2110385 SNP on some clinical measures of obesity and related parameters such as BMI, body fat, total-cholesterol and were not able to report significant associations. In accordance with results of Bailey et al. (17), it was found that the visfatin gene rs2110385 polymorphism did not affect any of the obesity-related parameters analyzed among study groups in the present study.

Mirzaei et al. (40) investigated the role of the rs2110385 polymorphism on oral anti-diabetic drug doses in patients with T2DM. The study declared that the rs2110385 poly-morphism altered insulin secretion with glibenclamide treatment (40). The dose of glibenclamide required for regulation of glucose homeostasis was found to be lower in indi-viduals with the G / G genotype compared to those with other genotypes, but no difference was found between genotypes for metformin dosage (40). In our study we detected visfat-in gene rs2110385 polymorphism to be effective on drug use in the obese patients. Obese type 2 diabetic patients with G/G genotype were found to respond positively to sulphonylu-rea and glinide treatment, whereas T/T genotype carriers were not found to reply well to antidiabetic drugs belonging to sulphonylurea and glinide subtypes.

CONCLUSION

In conclusion, this study declares the influence of rs2110385 polymorphism visfatin gene on drug use. Therefore, our results may indicate that obese type 2 diabetic patients with the visfatin gene T / T rs2110385 genotype may benefit more efficiently from oral antidiabetic drugs other than glinide or sulfonylurea.

Competing Interests: The authors declare that they have no competing interest.

Financial Disclosure: This work was supported by the Marmara University Scientific Research Projects Commis-sion (Project No: FEN/E-050608-0147).

Ethical Approval: Written consent was taken from each patient following a full explanation of the study, which has been approved by the local Ethics Committee of Marmara University (05.06.2008-0147).

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