Original Article

The ENPP1 K121Q polymorphism is associated with obesity-related parameters in Iranian normoglycemic male subjects

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ABSTRACT

Objectives: The K121Q polymorphism of the Ectoenzyme Nucleotide Pyrophosphate Phosphodiesterase 1 (ENPP1) gene has been variably associated with obesity in several populations. However, this association has not been studied in Iranian subjects. It was hypothesized that the K121Q variant might be associated with obesity and related risk factors in subjects with normal glucose tolerance and normal fasting glucose.

Methods: The K121Q genotypes were determined by PCR-restriction fragment length polymorphism in 377 non-diabetic subjects.

Results: In males, the frequency of the Q allele was 20.8% and 15.9% (p=0.269) in obese and non-obese subjects, respectively. The ENPP1 genotype (KQ+QQ) was not associated with systolic and diastolic blood pressure, triglyceride, cholesterol, LDL-C, HDL-C, HOMA-IR, or insulin levels in both genders. Male carriers of the KQ+QQ genotype had significantly higher values for BMI (p=0.079), waist (p=0.01), and WHR (p=0.006) than subjects with the KK genotype. Obesity-related parameters were not significantly different between obese and non-obese female subjects.

Conclusion: Our results suggest that the ENPP1 121Q allele might be associated with obesity and related parameters only among Iranian normoglycemic male subjects.

Keywords: Iranian population, Obesity, K121Q, ENPP1

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Introduction

Obesity is the most common and rapidly growing health problem throughout the world. It increases the risk of morbidity from hypertension, type 2 diabetes, metabolic syndrome, and cardiovascular diseases (1). The incidence and prevalence of obesity are rising globally. According to a World Health Organization report, there are more than 300 million obese subjects in the world, and this number is expected to increase to 700 million by 2015 (2). In Iran, there is also an increasing prevalence of both obesity and type 2 diabetes (2). It is estimated that 25% of Tehranian people are obese (3). The etiology of the common form of obesity is poorly understood, but it appears that both genetic background and environmental factors play a role in the development of this condition.

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Genome-wide scans, as well as screening of candidate regions, have enabled identification of single nucleotide polymorphisms in various genes, which increase the risk of becoming overweight and obese. ENPP1, INSIG2, and PLIN are some of the genes that have been suggested to link to adiposity (4-6).

The ectoenzyme nucleotide pyrophosphate phosphodiesterase 1 (ENPP1, also known as plasma cell membrane glycoprotein 1, or PC-1) is a class II membrane glycoprotein that reduces both insulin receptor function and subsequent downstream signaling (7-9). The ENPP1 gene is located on 6q22-23, a locus linked to obesity and diabetes in several studies (8-10). It has been reported that PC-1 has a wide range of tissue expression, including skeletal muscle and liver (11, 12). In insulin-resistant subjects, the elevated level of PC-1 protein is correlated with whole-body insulin resistance (13). Liver-specific overexpression of PC-1 in mice also caused a defect in insulin signaling that leads to whole-body insulin resistance (7).

Several polymorphisms are located in the ENPP1 gene, with the one most frequently analyzed being located in exon 4, causing a change of lysine to glutamine at codon 121 (K121Q) (14, 15). *In vitro* studies have demonstrated that the Q variant decreases insulin receptor activity by interacting with the insulin receptor (16). Furthermore, it has been shown that overexpression of the Q allele in mouse muscle and liver tissues leads to insulin resistance and glucose intolerance *in vivo* (8).

Several human studies have been performed to find the association between the K121Q polymorphism and obesity and related metabolic traits in various populations. However, there has been controversy as to whether this polymorphism is correlated with obesity. The purpose of this study was to examine the possible association between the ENPP1 K121Q variant and obesity and related parameters in a sample of Iranian subjects with normal glucose tolerance and normal fasting glucose.

Materials and Methods

Subjects

A detailed description of the study population has been previously published (2). Initially, 639 unrelated Iranian individuals aged 23 to 79 years were recruited. After excluding individuals with abnormal glucose tolerance and type 2 diabetes based on the WHO 1997 criteria (17), 377 subjects with normal glucose tolerance and normal fasting glucose were included in the analyses. Written informed consent was obtained from all participants before enrollment in the study.

Screening included standardized questionnaires on personal data and clinical measurements such as age, sex, obesity, drug consumption during the past month, and medical or family history of diabetes. All those who were not taking diabetes medication underwent a 2-h oral glucose tolerance test (OGTT) after an overnight fast. Criteria for control selection were fasting glucose <6.1 mmol/l and 2-h plasma glucose <7.8 mmol/l after OGTT. Diabetes was defined as fasting glucose ≥7.0 mmol/l, 2-h glucose ≥11.1 mmol/l after OGTT, or use of hypoglycemic medication. Systolic and diastolic blood pressure were measured twice in the right arm of subjects who had been resting for at least 10 min in a comfortable position. BMI was calculated as weight in kilograms divided by height in meters squared. Insulin resistance was assessed from glucose and insulin concentrations using the homeostasis model assessment of insulin resistance (HOMA-IR) equation (18). Subjects with BMI <30 kg/m2 were categorized as non-obese, and individuals with BMI ≥30 kg/m^2 were obese.

Laboratory measurements

Blood samples were taken at 0 and 120 min, and plasma was preserved with EDTA. Glucose measurements were carried out using the glucose oxidase method. Total cholesterol and triglyceride were determined using enzymatic methods. High-density lipoprotein (HDL) was measured in the supernatant after precipitation of apolipoprotein B (apoB)-containing lipoproteins using phosphotungstic acid and magnesium chloride. Low-density lipoprotein (LDL) was calculated using the Friedewald formula. Serum concentrations of insulin were determined by radioimmunometric assay. Plasma apoB concentrations were determined using the immunoturbidometric assay.

Genotyping

Genomic DNA was isolated from leukocytes using a commercial DNA isolation kit. The K121Q polymorphism of the ENPP1/PC-1 gene was determined using the PCR-RFLP method. Exon 4 was amplified using the following primer pairs: forward, 5'-GCAATTCTGTGTTCACTTTGGA-3'; and reverse, 5'-GAGCACCTGACCTTGACACA-3'. PCR was carried out in a final volume of 25 µl containing 100 ng genomic DNA, 1.5 mmol/l MgCl2, 0.5 mmol/l of each dNTPs, and 0.5 pmol of each primer. After an initial denaturation of 2 min at 94°C, the samples were subjected to 30 cycles at 94°C for 1 min, 55°C for 40 s, and 72°C for 40 s, with a final extension of 10 min at 72°C. The 208-bp product was digested with AvaII for 2 h at 37°C. The undigested 208-bp product represents the K allele, while the Q allele was cut into 53- and 155-bp fragments. The three genotypes were scored after running on a 2.5% agarose gel and staining with ethidium bromide.

Statistical analysis

All statistical analyses were carried out using the statistical program SPSS (version 10, SPSS, Chicago, IL, USA). P-values are two-sided throughout, and P<0.05 was considered significant, while a P-value between 0.05 and 0.1 was considered borderline significant. Genotypic and allelic frequencies were compared using the x2 or Fisher's exact test. Odds ratios (ORs) and 95% CI, with adjustment for age, were calculated by logistic regression analysis. Baseline quantitative results are expressed as mean±SD. Continuous variables that failed the normality test were logarithmically transformed before analysis. The variables transformed were triglyceride, insulin, and HOMA-IR. Analysis of covariance was used to determine associations while adjusting for age and BMI.

Results

All clinical and metabolic characteristics differed significantly between obese and non-obese groups. Obese subjects had significantly higher values for age, systolic and diastolic blood pressure, BMI, waist and waist-to-hip ratio (WHR), glucose, 2h glucose, cholesterol, triglyceride, LDL, apoB, insulin, and HOMA-IR, and lower levels of HDL than non-obese subjects (data not shown).

The genotype and allele frequency of the K121Q variant were evaluated in the case-control samples. Genotypes were in Hardy-Weinberg equilibrium for both obese cases and controls and in the total cohort. For the Q allele, only four individuals (1 obese and 3 non-obese subjects) were homozygous; therefore, for statistical purposes, these subjects (Q/Q) were combined with the heterozygous subjects (K/Q), and this combined group was then compared with the subjects homozygous for the K allele (K/K). There was no significant difference in genotypic or allelic distribution between obese and non-obese subjects. The frequency of the 121Q variant was 16.6% and 16.7% in the non-obese and obese groups, respectively. After gender stratification, the 121Q allele frequency did not significantly differ between obese and non-obese individuals in both genders, although male obese subjects tended to have a higher rate of the 121Q allele than the non-obese group (20.8% vs 15.9%, OR 1.414; 95%CI 0.665-3.001, p=0.269).

A general linear model analysis was used to assess the relationship between the genotypes of K121Q with anthropometrical and biochemical parameters. Covariates in the analysis were age and BMI. When the data were analyzed in male and female groups separately, no significant difference in blood pressure, plasma glucose, 2h glucose, total cholesterol, triglyceride, HDL-C, LDL-C, apo B, insulin, and HOMA-IR was observed between the K121Q genotypes in both groups. In male subjects, the KQ+QQ genotype was associated with higher BMI with borderline significance versus the KK genotype (25.77±3.48 vs. 24.78±3.24, p=0.079, respectively). Male carriers of the KQ+QQ genotype had significantly higher values for waist and WHR than subjects with the KK genotype (waist 90.4±8.8 vs 87.2±8.9, p=0.01; WHR 0.90±0.05 vs 0.88±0.05, p=0.006) (Table 2). Mean BMI, waist, and WHR values were not significantly different in the KQ+KQ (n=53) compared to the KK genotype (n=111) groups in female subjects (Data not shown).

Discussion

The ENPP1 K121Q variant is a functional missense polymorphism, with the Q variant binding the insulin receptors stronger than the 121K variant (16). Several studies in different populations have been conducted

Table 1: Genotype and allele frequency of the K121Q variant

Variant	Non-obese subjects (%)	Obese subjects (%)	OR (95%CI)	p value
Male				
Genotype				
KK	128 (68.8)	14 (58.3)		
KQ+ QQ	58 (31.2)	10 (41.7)	1.598(0.667-3.826)[a]	0.223
Allele				
K	84.1%	79.2%		
Q	15.9%	20.8%	1.414(0.665-3.001)	0.269
Female				
Genotype				
KK	83 (65.4)	29 (74.4)		
KQ+ QQ	44 (34.6)	10 (25.6)	0.691(0.293-1.633)[a]	0.400
Allele				
K	82.3%	85.9%		
Q	17.7%	14.1%	0.789(0.368-1.693)	0.543

Data are presented as n (%). All p-values and odds ratios are adjusted for age. [a]OR between K/Q + Q/Q vs. K/K.

Table 2: Clinical and biochemical parameters of male subjects according to the K121Q genotypes

	KK 141	KQ+QQ 67	p value
Systolic blood pressure, mmHg	118.45 ± 16.71	117.62 ± 13.98	0.888
Diastolic blood pressure, mmHg	78.40 ± 9.01	77.77 ± 10.31	0.789
Body mass index, kg/m^2	24.78 ± 3.24	25.77 ± 3.37	**0.079**
Waist (cm)	87.20±8.9	90.47±8.8	**0.013**
Waist to hip ratio (WHR)	0.88±0.05	0.90±0.05	**0.006**
Glucose, mmol/L	5.07 ± 0.52	5.03 ± 0.55	0.941
2h Glucose, mmol/L	5.21 ± 1.49	5.18 ± 1.41	0.920
Cholesterol, mmol/L	5.11± 1.1	5.15 ± 1.05	0.812
Triglyceride, mmol/L	1.58 ± 1.01	1.60 ± 1.04	0.846
HDL, mmol/L	1.01 ± 0.23	1.06 ± 0.22	0.599
LDL, mmol/L	3.80 ± 1.00	3.75 ± 1.18	0.734
Apolipoprotein B, mmol/L	1.02 ± 0.32	1.03 ± 0.34	0.790
Insulin, µU/mL	9.35± 4.02	9.32 ± 4.46	0.740
HOMA-IR	2.13 ± 0.98	2.10 ± 1.01	0.756

Data are presented as mean±SD. All comparisons are adjusted for age, BMI.

to find an association between the K121Q variant and obesity and its related parameters. Conflicting results have been reported about the effect of the ENPP1 K121Q variant on the risk of developing obesity. While reports from Dane (19), UK (20), Spanish (21), and Korean (22) populations show no effect of the K121Q variant on body weight, an association was found between the Q allele and lower BMI in the United States in individuals of European (23) and African descent (23). In contrast, in French (24), Chinese Han (25), German (26), and Turkish (27) populations, an association was observed between the Q allele and increased BMI. The molecular mechanism by which the K121Q variant might affect BMI has not yet been studied. It has been suggested that individuals carrying the 121Q allele develop brain insulin resistance, where insulin has potent anorectic actions, increasing appetite and body weight (28).

In the present study, it appears that there is an association between the ENPP1 K121Q variant and obesity and related parameters only in male subjects. Although the Q allele was not significantly associated with obesity in male subjects, male individuals carrying the 121Q genotypes had higher values of BMI, waist, and WHR than individuals with the 121KK genotype. The reason for inconsistency in the results might be due to insufficient power of the study for detecting the effect of the K121Q variant on obesity; therefore, a larger population is required to establish a definitive role for this variation in the Iranian population. A gender difference in association studies has been previously observed for the K121Q variant in Turkish and Chinese populations. In a study of Han Chinese, the Q allele frequency was higher in obese females (25), whereas the same association was observed only in Turkish male subjects (27). The reason for apparent discrepancies between studies, including this one, can be attributed to several factors such as study design, population heterogeneity, sample size, and gene-environment interactions.

The results did not show any association of the K121Q variant with cardiovascular risk factors. Particularly, no association was found between the K121Q polymorphism and insulin resistance assessed by HOMA-IR, in contrast to the results of previous reports (14, 15, 29). The K121Q polymorphism was reported to be associated with insulin resistance in some (15, 29-31), but not all populations (15, 21). It should be noted that some studies have demonstrated an association of the Q121 allele with insulin resistance in adults but have failed to show an association with obesity (15, 29). The reasons for these discrepancies are unknown and, as previously discussed for the association with obesity, differences in genetic and/or environmental background as well as recruitment procedures of the studied populations may have played a role (32). In this regard, it is emphasized that the frequency of the K121Q polymorphism varies considerably between different ethnic groups. A relatively low frequency of the 121Q allele was reported from Japanese (33) and Chinese populations (10.5% and 9.8%, respectively) (25). In Caucasians, the frequency of the Q121 allele ranges from 10 to 17.8% (34), starting from the lowest (9.8% and 10.5%) found in two unrelated non-diabetic Finnish groups (29), to median (13.8% and 14%), as demonstrated for subjects from Finland, Sweden (15), and Spain (21), to the highest prevalence (17.8%) found in subjects from Sicily (14). Furthermore, higher frequencies of the Q121 allele have been reported in African-American (78.5%) (35) and Dominican-Republic populations (54.2%) (31). In this study, the frequency of the 121Q allele (16.6%) is comparable to those reported from Caucasians. Given the low frequency of the Q allele in this population, a larger sample is needed to detect the possible impact of the K121Q variant on insulin resistance.

This study had some strengths and limitations. A homogeneous sample of well-characterized cases and controls was collected, which increases sensitivity for

detecting associations. Most studies performed on the K121Q variant did not include normoglycemic subjects, and obese individuals with either impaired glucose tolerance or overt type 2 diabetes were included in the samples analyzed. This point raises the possibility that the K121Q polymorphism tends to be more prevalent in hyperglycemic individuals. In this study, the healthy subjects included in the analyses were all normal glucose tolerance and normal fasting glucose. It is acknowledged that the number of obese subjects, as well as the QQ genotype, is small in the population, and this does not allow drawing any definitive conclusions in this population. Although false-positive results cannot be excluded, it should be pointed out that the association of the Pro12Ala variant of the PPAR-γ gene with insulin resistance was confirmed in the same population sample (2), which validates the results of this present analysis.

In conclusion, the findings of this study revealed that the ENPP1 K121Q polymorphism seems to influence the risk of obesity in Iranian male individuals.

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