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The *GPx-1* Gene Variants (rs1050450) in Obesity: Association with the Risk of Obesity and the GPx Activity in Females

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Abstract

Background: This study aimed to investigate the *GPx-1* gene polymorphism (rs1050450), the level of oxidative stress and antioxidant parameters, and the lipid profile in an obese Kurdish population in Sulaimani, Iraq.

Methods: In a case-control study,134 obese subjects and 131 normal BMI healthy individuals participated. The *GPx-1* gene polymorphism was assessed by Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP) method. The levels of biochemical and oxidative parameters were determined using photometric methods.

Results: The results showed that the fasting blood sugar (FBS), triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C) levels were significantly higher in obese subjects compared to the control group. Obese individuals had significantly lower levels of high-density lipoprotein cholesterol (HDL-C) than the controls. The GPx-1 activity and total antioxidant capacity (TAC) levels were significantly elevated in the obese group compared to the control group (P=0.006, and P<0.001, respectively). No significant difference was detected in genotype and allele frequencies of *GPx-1* (rs1050450) between obese and normal BMI groups. However, the presence of the *GPx-1* TT genotype enhanced the risk of obesity in females by 1.93-fold (95% CI 1.04-3.58, P=0.036). In the total population, the GPx activity increased in the presence of TT compared to CC+CT and CT genotypes.

Conclusions: The study indicated that obesity is linked to significantly higher levels of FBS, TG, LDL-C, TAC, and GPx activity and lower level of HDL-C. Also, we found the *GPx-1* gene polymorphism was associated with the risk of obesity in females and increased the GPx activity.

Keywords: Glutathione peroxidase-1, Obesity, Oxidative stress, Polymorphism.

Introduction

Obesity, body mass index (BMI) ≥ 30kg/m^2 according to World Health Organization (WHO) definition, is defined as abnormal fat tissue accumulation within adipose tissues which is estimated to affect about 650 million people worldwide (1-3). Obesity is recognized as a severe basic healthcare consequence that reduces the standard of living due to comorbidities such as diabetes, heart disease, malignancy, asthma, difficulty sleeping, hepatic malfunction, kidney dysfunction, or rather sterility (1). The etiology of obesity is complicated and environmental and genetic factors are playing roles in its pathogenesis and incidence. The results of clinical and animal observations indicated that obesity, by several mechanisms, could induce the oxidative stress (4, 5).

Oxidative stress is described as a condition that is associated with excessive production of

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reactive oxygen species (ROS) and reactive nitrogen species (RNS), insufficiency of an antioxidant defence system or both of them (6, 7). On the other hand, oxidative stress by increased fat deposition and alteration in food intake could be important in body weight control (4, 6, 8). Thus, the gene variants, which are associated with the antioxidant defense system, might have a crucial role in obesity pathogenesis and affect the activity of the encoding enzymes.

Glutathione peroxidase-1 gene (*GPx-1*) is located in the human chromosome 3p21.313 (9). The GPx-1 enzyme is also called selenocysteine peroxidase because its activity depends on selenium. The GPx-1 enzyme converts H_2O_2 into the water and catalyzes the reduction of lipid peroxides to alcohols in the cells (10). Single nucleotide polymorphism at nucleotide 594 of the *GPx-1* (C to T substitution, rs1050450) results in leucine to proline substitution at codon 198 of the protein that could alter the activity of GPx-1 enzyme (11-13). Considering these points and to the best of our knowledge, no study investigated this subject in the Kurdish population, we aimed to examine the C594T polymorphism of *GPx-1* and its association with GPx activity in an obese Kurdish population in Sulaimani province, Sulaimani, Iraq. Additionally, we assessed the oxidant/antioxidant parameters and lipid profile in these subjects.

Materials and Methods

Participants and sample collection

Two hundred and fifty-six individuals from Sulaimani, Kurdistan of Iraq participated in the present case-control study. Studied individuals consisted of 134 females and 131 males (20- 59 years). The subjects were divided into two sex-age matched groups based on their BMI. BMI was calculated by dividing weight to height square and was classified as underweight with BMI<18.5, normal range with BMI 18.5 to <25, overweight (pre-obese) with BMI 25-30, and obese with BMI>30 kg/m^2 (14). The individuals with normal BMI (18.5-24.9 kg/m^2) considered as control while subjects with BMI higher than 30 kg/m^2 considered as case.

The exclusion criteria were smoking, alcohol consumption, neuropsychiatric disorders, the use of anorexigenic drugs or anabolic steroids, hypothyroidism, polycystic ovarian syndrome, chronic illness, and being pregnant or intending to become pregnant during the study period. Additionally, subjects with a history of hypertension, diabetes, renal disease, and/or cardiovascular disorders according to the files in the Public Health Laboratory of Sulaimani, Iraq that reviewed by a physician were excluded from the study. The ethics committee of the Kermanshah University of Medical Science, Kermanshah, Iran approved present study (Kermanshah, Iran, Ethics approval number: IR.KUMS.REC.1400.7141) and all procedures were in accordance with the 1964 Declaration of Helsinki (version 2013). Prior to the collection of data, permission was obtained from the administrative authorities based in the Sulaimani Public Health Laboratory according to the approval of research by the ethics committee of the Kermanshah University of Medical Science, Kermanshah, Iran.

Seven ml venous blood samples were taken from participants under 12 hours of fasting. Three ml of blood were collected in EDTA tubes, and four ml were collected in serum gel separator tubes. By centrifuging at 1000 x g for six minutes on refrigerator centrifuges, blood cells were separated from the plasma and were used for genotyping. The plasma and serum samples were aliquoted in several tubes (for oxidant/antioxidant and lipid profile measurement) and stored at -40° C, and then the samples were transported in a cold chain to the Department of Clinical Biochemistry, Medical School, Kermanshah University of Medical Science, Kermanshah, Iran.

Biochemical analysis

The serum levels of total cholesterol, high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C) and triglycerides (TG) were measured by standard enzymatic methods using automated (Biochemistry Analyzer) KENZA 450 TX (BIOLABO Diagnostics), France.

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Oxidant/antioxidant analysis

The activity of GPx-1(mU/ml), total antioxidant capacity (TAC) (mmol Trolox Eq./L), total oxidative status (TOS) (μmol H_2O_2 Eq./L) and malondialdehyde (MDA) (μmol/l) levels were determined by using Kiazist kits (Kiazist, Iran). Oxidative stress index (OSI) was calculated as OSI=TOS (μmol H_2O_2 Eq./L)/TAC (mmol Trolox Eq./L).

Genotyping

Extraction of DNA from the peripheral blood leukocytes were performed using the standard phenol–chloroform method (15). The DNA content of every sample was measured, and the purity of DNA was assessed by a NanoDrop spectrophotometer. The genotypes of the *Gpx-1* rs1050450 (596C>T) were identified using the polymerase chain reaction (PCR) followed by fragment length polymorphism (RFLP) method. Briefly, DNA was amplified using the PCR method by the specific forward primer of 5′ AGAAGTGCGAGGTGAACG 3′and the reverse primer of 5′ AGGACATACACACAGTTCTGC 3′ (obtained from Pishgam Biotechnology Company, Iran). PCR reaction (20 μL) included 1 μL of DNA (200–600 ng), 0.7 μL of each primer (100 pmol),7.6 μL of ddH2O and 10 μL of the optimized ready to use master mix 2X contained MgCl2, dNTPs, PCR buffer and Taq DNA polymerase (obtained from Sinaclon Company, Iran). The PCR process was done in 35 cycles started with initial denaturation (95 °C for 5 minutes), denaturation at each cycle (95 °C for 40 seconds), annealing step at each cycle (56 °C for 35 seconds), extension step at each cycle (72 °C for 40 seconds), and a final extension at 72 °C for 10 min. About 15 μL out of 20 μL of PCR product (314-bp) was digested with the ApaI restriction enzyme (obtained from Thermo Fisher Scientific, Lithuania). The RFLP products have been electrophoresed in 3.0% agarose gel. In presence of TT genotype, the 314-bp PCR product was not cleaved by the ApaI enzyme. In the presence of CT genotype, three fragments with 314-, 237-, and 77-bp were obtained after digestion of PCR products with the ApaI, and two fragments with 237- and 77-bp were detected in the presence of the CC genotype.

Statistical analysis

The SPSS software package version 16 was used for statistical analysis. The frequency of *GPx-1* genotypes in obese subjects and control group was determined and compared using the χ^2 test. The comparison of quantitative parameters between two groups was done by two-tailed Student's tests. The one-way ANOVA test was applied for comparing the biochemical and oxidant/antioxidant parameters between three genotypes of *GPx-1*. The linear fit plot with confidence intervals was used to evaluate the association between GPx-1 activity and BMI. The $P< 0.05$ was considered as a statistically significant level.

Results

The means of age was not different between study groups. Compared with non-obese individuals, the serum levels of biochemical parameters, FBS (P=0.03), TG (P<0.001), and LDL-C (P<0.001), were significantly higher in obese. Comparing total cholesterol, results were higher in obese but were not reach statistically significant level. In contrast, HDL-C concentration showed a significantly lower level in obese individuals (mean=44.7±11.3; P=0.02) (Table 1).

The biochemical and demographic parameters analysis showed that there was no difference between genders in obesity incidence (not shown in the table). Similar results were obtained regarding age in males (P=0.37) and females (P=0.22) compared with non-obese ones. Along with a significantly higher level of BMI in obese individuals (P<0.001), the serum levels of FBS (102.8±24.4; P=0.039), TG (175.9±101.3; P=0.002), total cholesterol (188.3±39.8; P=0.003), and LDL-C (129.3±36.9; P<0.001) were statistically higher in obese males than in the control males (Table 2).

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Table 1. Biochemical characteristics of studied individuals.

Parameters	Obese individuals (n=134) Mean±SD	Normal BMI subjects (n=131) Mean±SD	P value
Age (years)	40.7±10.2	38.9±8.7	0.13
BMI (kg/m^2)	35.7±4.9	23±1.8	<0.001
FBS (mg/dl)	99.7±20.6	95.5±8.4	0.03
Total cholesterol (mg/dl)	182.6±39.3	174±38.5	0.07
Triglycerides (mg/dl)	151.3±86.9	111.6±56.5	<0.001
HDL-C (mg/dl)	44.7±11.3	48±11.8	0.02
LDL-C (mg/dl)	126.7±34.2	105.9±30.6	<0.001

FBS: fasting blood sugar; HDL-C: High-density lipoprotein- cholesterol; LDL-C: low density lipoprotein- cholesterol.

Table 2. Biochemical characteristics of studied individuals according to the gender.

Parameters	Obese individuals Male= 66/ Female=68 Mean±SD	Normal BMI subjects Male= 65/ Female=66 Mean±SD	P value (Male/Female)
Age (year)(male/female)	40.6±10.5/40.7±9.9	38.7±9.3/39.2±8	0.37/0.22
BMI (kg/m^2) (male/female)	34.4±3.6/ 37±5.6	23.4±1.6/22.6±1.9	<0.001/<0.001
FBS (mg/dl) (male/female)	102.8±24.4/96.8±15.7	7.4/94.8±9.2±96.2	0.039/0.39
Total Cholesterol (mg/dl) (male/female)	188.3±39.8/177±38.4	167.8±39.1±180±37.1	0.003/0.61
Triglycerides (mg/dl) (male/female)	175.9±101.3/127.4±62	128.7±61.7/94.8±45.4	0.002/0.001
HDL-C (mg/dl) (male/female)	42.3±9/47.1±9	42±8.2/54±11.8	0.84/0.002
LDL-C (mg/dl) (male/female)	129.3±36.9/124.1±31.4	103.9±31/107.8±30.3	<0.001/0.003

FBS: fasting blood sugar; HDL-C: High-density lipoprotein- cholesterol; LDL-C: low density lipoprotein- cholesterol.

In the female population, only TG (127.4±62; P=0.001) and LDL-C (124.1±31.4; P=0.003) significantly increased in obese females compared with non-obese females. Serum HDL-C concentration was significantly lower in obese females (47.1±9; P=0.002) than non-obese ones, and it was not significantly different among the male population (obese and non-obese).

The value of oxidant/antioxidant parameters in the studied groups indicated that the GPx-1 activity in obese patients was significantly different compared to control group having normal BMI (P=0.006). Additionally, our findings indicated that the level of TAC in obese individuals was significantly higher compared to normal BMI group (P<0.001). However, there was no significant difference in MDA (P=0.502), TOS (P=0.817) and OSI (P=0.284) levels between obese patients and control group (Table 3).

Table 4 depicted the genotypes and allele frequencies of *GPx-1* (rs1050450) in the studied groups. The frequencies of *GPx-1* genotypes in obese patients were not statistically different compared with control group having normal BMI (χ^2=3.231, P=0.199). However, the analysis of male and female separately indicated a significantly higher frequency of *GPx-1* TT genotype in obese females than normal BMI ones (n=13, 219.1% vs. n=4, 6%, P=0.03). The presence of *GPx-1* TT genotype enhanced the risk of obesity in females by 1.93-fold (95%CI 1.04-3.58, P=0.036). Comparing TT with combined genotype of CC+CT genotype indicated the presence of *GPx-1* TT genotype increased the risk of obesity in women 3.66 times (OR=3.66, 95%CI 1.13-11.9, P=0.031). No significant difference in allele frequencies between obese individuals and control group was observed (P=0.42).

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Table 3. Oxidant/antioxidant parameters in studied groups.

Parameters	Obese individuals (n=134) Mean±SD	Normal BMI subjects (n=131) Mean±SD	P value
MDA (µmol/L)	22.80±13.83	21.46±18.21	0.502
TAC (nmol/ml)	4.14±0.58	3.81±0.44	<0.001
TOS (nmol/ml)	4.56±2.58	4.49±2.19	0.817
OSI	1.11±0.55	1.18±0.53	0.284
GPx-1 activity (mU/ml)	8.46±3.18	7.15±4.36	0.006

MDA: Malondialdehyde, TAC: Total Antioxidant Capacity, TOS: Total Oxidative Status, OSI: Oxidative Stress Index.

Table 4. Genotype and allele frequencies of *GPx-1*(rs1050450) in studied groups.

Genotype	Obese individuals (n=134) n (%)	Normal BMI subjects (n=131) n (%)
CC	58 (43.3)	56 (42.7)
CT	51 (38.0)	60 (45.8)
TT	25 (18.7)	15 (11.5)
	χ^2=3.231, P=0.199	
Alleles		
C	167 (62.3)	172 (65.6)
T	101 (37.7)	90 (34.4)
	P=0.42	

The significant differences of GPx-1 genotypes and allele in obese individvals and control group with normal BMI was dermined using χ^2 test

In addition, we determined the oxidant/antioxidant parameters in different genotypes in all studied groups. No significant difference was observed in the levels of MDA, TAC, TOS, OSI and GPx-1 activity between different genotypes of GPx-1. However, considering all females, the GPx activity increased in the presence of TT than CC+CT genotype (8.67±3.6 vs. 6.97±2.66 mU/ml, P=0.014). Also, the GPx-1 activity in all females' carriers of TT genotype (8.67±3.60 mU/ml) was significantly higher than that in CT carriers (6.81±2.60 mU/ml) (P=0.043).

In the total population with normal BMI, the activity of GPx1 ascends with the BMI elevation. In contrast, in obese individuals, there was a reverse association between the BMI level and the GPx1 activity. In male population, the obtained result in normal BMI population was similar to all studied individuals with normal BMI; however, increased BMI level in obese males did not affect the GPx-1 activity. Results of the female population demonstrated the reversed association between BMI and the GPx-1 activity that by the rise in the BMI level, the GPx-1 activity decreased in both non-obese and obese individuals (Fig. 1).

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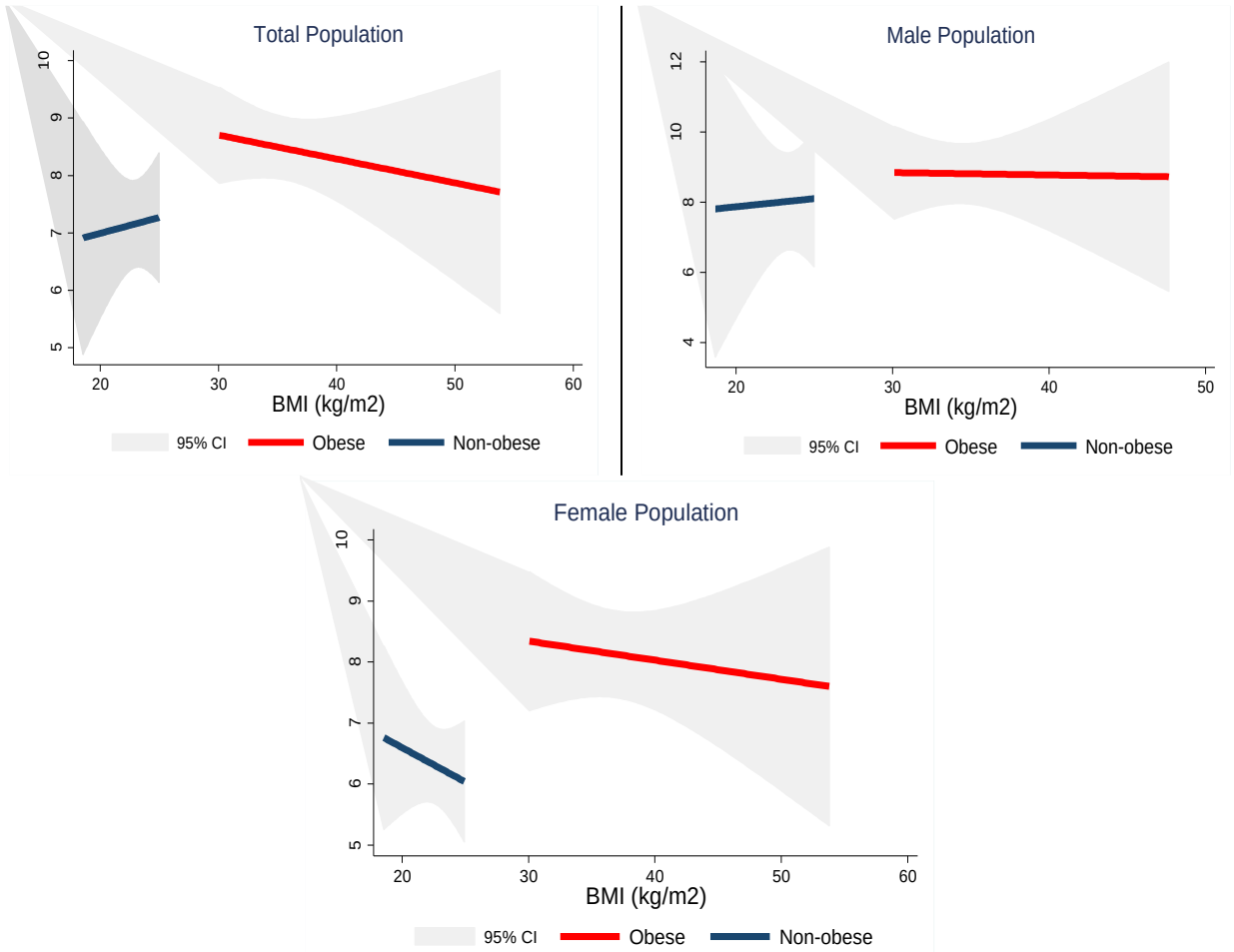

Fig. 1. Linear fit plot prediction with confidence intervals between GPx-1 activity and BMI in total, male, and female population. In the non-obese group in the total and male population, there was a positive relationship between GPx1 activity and BMI. Although in the female population, there was a reversed association between BMI and GPx-1 activity in both non-obese and obese groups.

Discussion

The current study investigated the *GPx-1* gene polymorphism, as an important gene with a crucial role in antioxidant defense system, in an obese Kurdish population in Sulaimani province, Sulaimani, Iraq. Moreover, we investigated the oxidant/antioxidant parameters and lipid profile in the studied groups. We found that the FBS level in the obese subjects was higher compared with the control group having normal BMI. Previous studies have indicated that the FBS level significantly increased during obesity (13, 14). The higher level of glucose in obese individuals compared to subjects with normal BMI might be associated with the effect of adipocytes on decreased glucose absorption by peripheral tissues (such as muscle tissue) through releasing free radicals (15).

Furthermore, obesity is usually accompanied by lipid metabolism disorder and dyslipidemia due to liver dysfunction (16). Our observation indicated that obese individuals had higher levels of triglycerides and LDL-C; while HDL-C level in obese individuals was lower compared to the control group. Additionally, our findings showed that obese men had a high level of FBS, total cholesterol, triglycerides and LDL-C compared to normal BMI males; while obese women had a low level of HDL-C compared to control group. Găman et al. reported the FBS level and lipid profile in obese subjects were significantly higher than those in subjects with normal BMI (17). It was shown that hypertriglyceridemia, which is present during obesity has a vital role in lipid metabolism abnormalities (18, 19). It

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might be partly due to the accumulation of triglycerides in liver tissue that leads to overproduction of VLDL-C which interferes with the metabolism of chylomicrons. On the other hand, it was suggested that the expression of lipoprotein lipase showed a significant decrease, which resulted in hypertriglyceridemia during obesity (19, 20). Furthermore, hypertriglyceridemia decreased the level of HDL-C and generation of small dense LDL-C by accelerating cholesterol ester and triglyceride exchange between HDL-C and VLDL-C and LDL-C (18, 21).

It was shown that obesity might be important in oxidative stress induction by several mechanisms including hyperglycemia, chronic inflammation, high level of lipids in tissues and antioxidant defense system insufficiency (22). For example, previous observations proposed that hyperglycemia by overproduction of NADPH and ROS had an essential role in the progression of oxidative stress during obesity (23). Furthermore, it was suggested that the oxidative stress condition during obesity might be associated with inadequate antioxidants providing for compensating the excess level of oxidant compounds (8, 24). It was shown that lipid peroxidation increased during obesity due to increased circulating lipids. Thus one way to evaluate the oxidative damage is through assessing products such as MAD (14). Several investigations observed that the levels of thiobarbituric acid reactive substances (TBARs), as indicators of lipid peroxidation during oxidative stress conditions, and oxidative stress parameters are increased during obesity; while, the others showed no significant increases in TBARs level in obese subjects compared to healthy individuals with normal BMI (14, 25-27). Our results showed that TOS, OSI and MDA (as oxidant markers) levels in case group had no significant differences compared with the subjects with normal BMI and this observation is in line with the results of Brown et al. which indicated that the oxidant/antioxidant parameter was not changed in obese patients (28). However, we observed that TAC level (as antioxidant marker) and GPx-1 enzyme activity in the obese group were higher than those of subjects with normal BMI; these findings repeated in Tinahones et al. study that they observed that GPx-1 activity significantly increased in severely obese patients (14). We proposed that the lack of significant difference in MDA level between obese individuals and subjects with normal BMI might be associated with increased activity of GPx-1 enzyme in the obese group. The GPx-1 enzyme has an important role in elimination of free radicals, and increasing its activity in obese individuals in the present study might be explained by counteracting with an excess level of free radicals in obese group although we did not determine the level of ROS in our studied groups. Enhanced systemic oxidative stress is one of the major clinical manifestations of obesity. Oxidative stress is involved in tissue damage and increased oxidative stress is strongly related to metabolic disorders such as atherosclerosis, thrombosis, and diabetes mellitus, which are frequently observed in morbid obesity (31). We found an inverse association between BMI and the GPx activity in all obese individuals and in obese women. Decreased GPx activity has been reported in obese diabetics compared to non-obese diabetics, which could demonstrate higher levels of oxidative stress in obese diabetic patients (32).

Since we found that the *GPx-1* rs1050450 variant significantly increased the risk of obesity only in studied females and also a considerably lower level of HDL-C, as an anti-inflammatory factor, (29) was found in obese females, it seems that the obesity as a comorbidity is associated with more adverse metabolic effects in females.

By considering the key role of oxidative stress in obesity pathogenesis, single nucleotide polymorphism at nucleotide 594 (C to T substitution) of *GPx-1* gene could affect GPx-1 activity (12). Several pieces of the literatures showed an association between rs1050450 and pathologic conditions such as breast cancer, diabetic neuropathy, and diabetes mellitus (30-32). For example, the findings of Tang et al. indicated that the presence of the T allele significantly

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enhanced the risk of diabetic neuropathy in comparison with the C allele (32). In a cohort study by Kuzuya et al., it was found that the *GPx-1* genotypes (rs1050450) were associated with the risk of metabolic syndrome in Japanese men although significant findings were not observed for Japanese women (33). Our results showed that genotypes and alleles distribution of *GPx-1* were not significantly different between obese and normal BMI subjects. Although, when male and female genders were separately analyzed, we found that the TT genotype in female gender significantly increased the risk of obesity. Additionally, our findings showed that significant increase in the activity of GPx-1 enzyme in females with TT genotype compared to heterozygote genotype. Consistent with our findings, the results of Hernández Guerrero et al., indicated that *GPx-1* polymorphism is associated with morbid obesity (27).

One of the most important limitations of our study was the lack of information about family history of the obese and normal BMI subjects, food intake, and consumption of antioxidant supplements, which could affect on the results.

The findings of the present work indicated that obesity is linked to significantly higher levels of FBS, TG, LDL-C, TAC, and GPx activity and lower level of HDL-C. According to our findings, the *GPx-1* gene polymorphism (rs1050450) was not associated with the risk of obesity in the Kurdish population of Iraq. However, the GPx-1 gene polymorphism was associated with the risk of obesity in females and increased the GPx activity.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical Statement

The study was approved by the ethics committees of Kermanshah University of Medical Sciences (IR.KUMS.REC.1400.7141), Kermanshah, Iran. All participants entered the study after being fully aware of the study process and informed of written consent.

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