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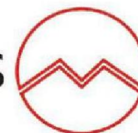

Protein Tyrosine Phosphatase 1B (*PTPN1*) Gene polymorphism (467T>C) and metabolic syndrome –A pilot study

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Abstract :Background: The metabolic syndrome (Met S) is a cluster of the most dangerous heart attack risk factors as diabetes, abdominal obesity, high cholesterol, and high blood pressure. Protein tyrosine phosphatase 1B (PTP1B), is negatively regulating the leptin and insulin signaling, with positive correlation with adiposity and contributes to insulin resistance. The effect of PTP1B on the obesity is still vague. This study aimed to study the effect of *PTPN1* genetic variations (467T>C) on susceptibility to Met S components and its metabolic traits by comparing the *PTPN1* gene (467T>C) alleles and genotypes between T2D patients with Met S and healthy Egyptian subjects. **Methods:** Polymerase chain reaction/restriction fragment length polymorphism (PCR-RFLP) analyses were carried out to detect the 467T>C variants of *PTPN1* gene in 100 Egyptian patients with obesity as compared to controls (n=80). **Results**: The results did not detect any significant difference in 467T>C *PTPN1* genotypes between patients and control groups (X^2= 0.674, P= 0.714). 467T>C *PTPN1* variants showed non-significant association with Met S components [diabetic metabolic traits in both groups ; plasma insulin levels, fasting blood glucose levels (FBG) , HOMA-IR , abdominal obesity [Waist circumference (WC) , body mass index (BMI)], the lipid profile parameters , diastolic blood pressure (DBP) and systolic blood pressure (SBP). C**onclusion**: The *PTPN1* promoter variant of 467T>C was not associated with Met S components and T2D metabolic related traits in Type 2 diabetic Egyptian patients. More studies are required on a larger scale to examine any potential metabolic association.

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Keywords: Metabolic Syndrome. Obesity, Diabetes mellitus, insulin resistance. protein tyrosine phosphatase gene polymorphisms.

1. Introduction

The metabolic syndrome (Met S) constitutes group of clinical phenotypes, including central obesity, hypertension, hyperglycemia, and Dyslipidemia. The metabolic syndrome (Met S) is a commonly encountered cluster of clinical phenotypes, including central obesity, hypertension, hyperglycemia, and dyslipidemia. Identifying genetic determinants of Met S will lead to better understanding of its progression and pathogenesis [1]. Egypt and the Middle East countries have experienced a rapid rise in the prevalence of obesity [2]. Obesity in the Eastern Mediterranean Region has reached ‘alarming levels’ according to the World Health Organization, nearly half of Egyptian women of reproductive age classified as obese [2]. Clearly, Egypt is facing extraordinary changes in the prevalence of overweight and obesity in a comparatively short period of time. However, most studies are highlighting on the experience of overweight and obesity in developed countries, with the appearance of obesity in developing countries that is little unexplained and understood [3]. White adipose tissue (WAT) is the main storage site of unneeded dietary energy, and has a crucial effect on the body glucose homeostasis [4]. Diabetes mellitus (DM) is the eighth disease causing death throughout the world with increasing to be the fifth recently, coming after communicable diseases, cardiovascular disease, cancer, and injuries [5]. The prevalence of DM is increasing worldwide, more than 300 million people are suffering from DM all over the world [6]. The correlation between the insulin resistance (IR) and type 2 diabetes has been identified for over half a century. IR is not important only in predicting the occurrence of type 2 diabetes, it is also a therapeutic

target of hyperglycemia [7]. The molecular mechanisms of IR are till now not fully explained, however the insulin receptor signal transduction pathway downstream defect may be accused [5]. Protein tyrosine kinases and protein tyrosine phosphatases are important regulators of insulin signal transduction pathway [8] [9]. Recently, more researches have been acting on clarifying the role of protein tyrosine phosphatase, non-receptor type 1 (*PTPN1*) on glucose homeostasis through IR and insulin sensitivity [10]. The *PTPN1* gene encodes protein tyrosine phosphatase enzyme (PTB)-1B (EC 3.3.3.48), which downregulates the insulin signaling pathway via de-phosphorylation of phosphotyrosine residues of the activated insulin receptor [11,12]. Mice deficient for *PTPN1* exhibited augmented insulin sensitivity and decreased diet-induced obesity [13], as well as general slimness with enhanced basal metabolic rate [14]. In vitro inhibition of PTP-1B augments insulin sensitivity [15,16]. These functional features, together with its genomic location under the chromosome 20q13 type 2 diabetes linkage, shore the *PTPN1* as a candidate gene affecting the predisposition to IR and type 2 DM [17]. Several studies have examined the association of *PTPN1* single-nucleotide polymorphisms (SNPs) with traits related to T2D and they have elucidated that *PTPN1* expression increases in obese people and those with T2D [18, 19]. The effect of genetic diversity on *PTPN1*gene expression is one of the most likely possibility to implicate on complex diseases likeT2D [9].The present study aimed to examine the effect of *PTPN1* genetic SNP (467T>C) on susceptibility to Met S compartments in T2D by comparing the *PTPN1* gene (467T>C) alleles and genotypes between diabetic patients with met S and healthy Egyptian subjects. Moreover, to investigate the effects of this polymorphism on obesity markers (BMI, WC), insulin sensitivity (FPI, FPG, HbA1c, HOMA), hypertension (SBP, DBP) and also on different quantitative metabolic parameters as total lipid profile parameters (TC, TG, HDL-C, and LDL-C).

2. Subjects and methods

Subjects, blood pressure, and anthropometric measurements:

This case–control study was conducted from June 2014 to December 2015. It is comprised of 180 subjects. They were recruited from Endocrinology outpatient clinics of the Internal Medicine Department, Zagazig University hospitals. All subjects were Egyptians from El-Sharkia province Egypt and they belonged to the same ethnic group. A written informed consent was obtained from all patients before enrollment in the study. The study was approved by Zagazig University's ethics committee.

The diagnosis of metabolic syndrome (Met S) was considered when criteria adopted by NCEP – ATP III was achieved: WC ≥ 102 cm for men, ≥ 88 cm for women; fasting blood glucose (FBG) ≥ 110 mg/dl; triglycerides (TG) ≥ 150 mg/dl; HDL-cholesterol < 40 g/dl for men, <50 mg/dl for women; systolic blood pressure (SBP) ≥ 130 mm Hg or diastolic blood pressure

(DBP) ≥ 85 mmHg [20].

Type 2 diabetes was identified by the World Health Organization (WHO) criteria (fasting blood glucose level >126 mg/dl and/or 2-h postprandial blood glucose level > 200 mg/dl) (World Health Organization, 2006). Patients who did not meet these criteria as under treatment but who gave a history of T2DM were also included in the study. Obesity was determined on the basis of a body mass index (BMI) more than >26 kg/m2. BMI was computed as weight (kg) divided by squared height (m2).

Subjects were classified into two main groups:

-Group I "control group ": 80 normal volunteers (38 females and 42 males). Their mean ages were ranged from 37 – 65 years with a mean value ± S.D of 47.16 ± S.D of 6.72 years, who had been matched for BMI, sex, age and socioeconomic background, they had no evidence of DM, hypertension, obesity, hypercholesterolemia, family history or previous history of stroke or transient ischemic attacks and smoking on the basis of their clinical history and physical examination.

-Group II " diabetic patients with Met S: included 100 patients (51 males and 49 females), aged from 38-65 with a mean value ± S.D of 51.45±9.37 years. Body mass index [BMI = weight (kg)/height (m) ^{2}] was calculated. Waist circumference (WC) was measured while the subjects were standing up, with a tape placed at the midpoint level between the lower intercostal border and the anterior superior iliac supine while the subject was gently exhaling.

-There was no statistical difference regarding age and sex among the groups (t= -2.909, P=0.064) (X^2= 0.040, P=0.480), respectively. (Table.2).

Biochemical analyses of blood samples

Sample collection:

Overnight fasting venous blood samples were collected from the subjects in EDTA-containing tubes using standardized protocol and equipment, separated into two samples one whole blood for DNA extraction, and *PTPN1* gene SNP detection and the measurement of glycated hemoglobin (HbA1c) (Abraham et al.1978) [21].The

other plasma specimen was used for measuring total lipid profile parameters, plasma insulin level, and FBG. Other basic biochemical blood tests were measured by standard chemical and enzymatic commercial methods in the Medical Biochemistry department and hospital laboratories.

Laboratory investigations, including:
(a) Fasting plasma glucose levels (FPG) according to *Trinder* (1969) [22] using glucose enzymatic (GODPAP)- liquizyme Kits (Biotechnology, Egypt).

(b) Determination of HbA1c in blood [21]

(c) Lipid profile: plasma levels of total cholesterol (TC), Triglyceride (TG), and HDL-C (Assmann et al.1983) [23]. LDL cholesterol (LDL-C) was measured According to ***Friedewald et al.(1972)***. LDL was calculated as follows: LDL=TC-HDL-TG\5. [24]

(d)Fasting plasma insulin (FPI) by enzyme amplified sensitivity immunoassay according to Starr et al. (1978) [25] using KAP1251-INSEASIA (Enzyme Amplified Sensitivity Immunoassay) Kits (BioSource Europe S.A., Belgium).

(e) HOMA-IR: homeostasis model assessment (where HOMA= (fasting insulin (µU/ml) x fasting plasma glucose (mg/dl) /405 [26].

Genotyping:

Genomic DNA was isolated using the Wizard Genomic DNA Purification Kit purchased from Promega. After extraction, the quality of the extracted material was visualized in 1% agarose gel and the concentration was obtained by a spectrophotometer. -467T>C variants were genotyped using the polymerase chain reaction–restriction fragment length polymorphism (PCR–RFLP). Primer sequences (Iontec, Bioron). Amplification reactions of 467T>C variants of *PTPN1* gene were set up for polymorphic sites of promotor gene using (Meshkani et al) [10] (Table 1).

The PCR was done using Taq PCR Master Mix kit (Qiagen, GmbH) as following: 25 ml of Taq PCR master mix was dispensed into each PCR tube, and then the following materials were added to each tube containing 100 ng of extracted DNA, 25 mM forward primer, and 25 mM reverse primer (Operon Biotechnologies, Inc.) and then 19 ml dd H_2O was added giving a final volume of 50 ml. Following initial denaturation at 94ºC for 5 min, amplification was performed by 35 cycles of denaturation at 94°C for 30 sec, annealing at 57 °C for 30 sec extension at 72°C for 30 sec. Final extension step was adjusted at 72°C for 5 min; 8 ml of the PCR products were digested overnight at 37°C and for 3 h with 10 U *Ava*I enzyme -467T>C SNPs. The digested PCR products were resolved on 3% agarose gels stained with ethidium bromide.

Table (1): PCR-RFLP pattern of (467T>C) of *PTPN1* Gene polymorphisms.

Polymorphisms	Primers	Annealing Temp (̊C)	PCR-RFLP products
-467T>C SNP	**Forward 5'-TTC ATT CCTGCA GCA CCC AAG-3' Reverse: 5'-GTT GAG TCACAG AGT GAG TGG-3'**	**57°C**	**CC-269-bp segment. CT -269, 163, and 106 bp. TT-163 and 106 bp**

3.Statistical analysis

The statistical analysis was conducted by applying the software program (SPSS 16.0, SPSS Inc., Chicago, Illinois, USA). Descriptive data were expressed as the mean and standard deviation (SD). The differences between mean value for each parameter between controls and diabetic patients were tested by student's "*t*" test. One-way analysis of variance (ANOVA, F- test) was used to examine the variation in different metabolic and anthropometric variables with the genotypes. To examine the variations of the gene alleles frequencies between the diseased and control populations, the allele and genotype frequencies were compared via applying the Chi-square (X^2) test. Where significant *P*- values were generated, the odds ratio (OR) was calculated. Odds ratios and 95 confidence intervals (CI) were calculated to examine the association between the disease and genotypes. Statistical significance was assumed when p values were < 0.05.

4. **Results**

Demographic, clinical, and laboratory characteristics of the all studied groups are summarized in table 2.

All studied biomarkers were significantly higher in diabetic patients when compared to non-diabetic controls. Except for HDL-C which showed significantly decreased levels (P<0.05) (Table 2).

4.2. Distribution of 467T>C of *PTPN1* Gene polymorphism:

-The allele and genotype frequency distribution and carriage rate of 467T>C *PTPN1*Gene among patients and controls were shown in table 3and figure 1.

The present results did not find any significant association between patients with Met S and controls regarding the 467T>C *PTPN1* genotype and allele distributions (X^2 =0.674, P=0.74 and X^2 =0.015, P= 0.522) odds ratio (OR) and 95% CI = 0.96 (0.466-1.962).

In addition, I also compared the 467T>C *PTPN1* Gene genotypes with different biochemical and clinical phenotypes in the Met S patients and control groups separately. No significant differences (*P* >0.05) in anthropometric or biochemical features were observed between the wild-type and heterozygous individuals at 467T>C *PTPN1* variants in the T2D with Met S group or controls, data is shown in table 4 and 5.

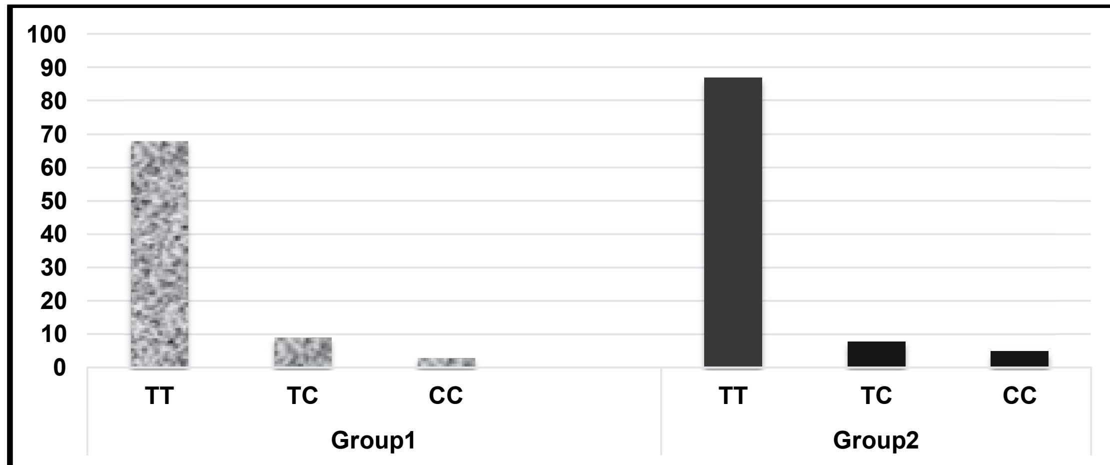

Figure1: Genotype and Allele frequency for PTPN1gene polymorphisms at 467T>C in all studied groups

Table (2): Basic Characteristics of all participant groups .

Parameters	Controls (n=80)	Diabetic with Met S group (n=100)	t-test	P value
Age (years)	47.16± 6.72	51.45±9.34	-2.909	P =0.064
Sex	38 F (47.5 %) 42M (52.5 %)	49 F (49%) 51 M (51%)	X^2= 0.040	P =0.480
FPI (µU/ml)	16.91±2.75	28.24±6.40	- 14.78	P =0.000
FPG (mg/dl)	100.27±9.62	140.69±8.46	- 26.643	P =0.000
HbA1c %	5.72±1.34	12.08±2.3	- 24.995	P =0.000
HOMA-IR	4.24±0.94	10.65±2.38	- 20.95	P =0.000
TC(mg/dl)	200.86±19.46	321.38±68.25	-15.013	P=0.000
TG(mg/dl)	141.58 ±15.46	230.3 ±53.49	- 13.84	P=0.000
LDL-C(mg/dl)	105.51 ±10 .76	244.37±31.14	- 39.87	P =0.000
HDL-C (mg/dl)	53.66 ±9.41	39.27±5.1	12.113	P= 0.000
SBP (mmHg)	110.4 ±12.4	132.24 ± 10.28	-11.756	P =0.000
DBP (mmHg)	76.68 ±8.11	94.47± 18.51	- 9.6	P =0.000
WC (cm)	90.7±9.07	108.47±10.3	- 11.1	P =0.000
BMI (kg/m^2)	21.37 ± 2.55	32.15 ± 3.16	-23.134	P =0.000

FPI: Fasting plasma insulin; FPG: Fasting plasma glucose; HbA1c: Glycated hemoglobin; TC: Total Cholesterol ; TG :Triglyceride; LDL-C: Low density lipoprotein Cholesterol; HDL-C: High Density Lipoprotein-Cholesterol; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; WC: Waist Circumference; BMI: Body Mass Index; X^2= Chi –square for non- parametric values.

Table (3): Genotype and Allele frequency for *PTPN1* gene polymorphisms at 467T>C in all studied groups.

467 T>C		
Genotype	**Groups**	
	Group I (N=80) N (%)	**Group II (N=100) N (%)**
TT	**68 (85.0%)**	**87 (87.0%)**
TC	**9 (11.2 %)**	**8 (8.0 %)**
CC	**3 (3.8 %)**	**5 (5.0 %)**
X^2 P – value	**0.674** **0.714 (NS)**	
	N (%)	**N (%)**
T allele	**145 (90.63%)**	**182 (91.0 %)**
C allele	**15 (9.37%)**	**18 (9.0 %)**
X^2 P OR (95%CI)	**0.015** **0.522** **0.96 (0.466-1.962)**	

Table (4): Different clinical and anthropometric parameters with different *PTPN1*gene polymorphisms at 467T>C in control group

Parameters	**467T>C Genotypes**			
	TT (n=68)	**TC (n=9)**	**CC(n=3)**	**Anova -F value** **P -value**
FPI (µU/ml)	**16.84 ±2.62**	**18.36±3.38**	**14.16±0.84**	**2.92** **0.06**
FPG (mg/dl)	**100.35±9.9**	**101.11±8.31**	**96.0±8.18**	**0.326** **0.723**
HbA1c %	**5.76 ±1.35**	**5.37±1.38**	**5.96±1.45**	**0.366** **0.695**
HOMA-IR	**4.22±0.89**	**4.31±1.27**	**4.5±1.11**	**0.151** **0.860**
TC (mg/dl)	**200.4±20.24**	**200.6±14.7**	**211.6±13.9**	**0.468** **0.628**
TG(mg/dl)	**142.1±16.3**	**139.8±9.99**	**135.5 ±8.54**	**0.325** **0.724**
LDL-C(mg/dl)	**105.77±1.34**	**102.82±3.2**	**107.67±3.2**	**0.355** **0.703**
HDL-C(mg/dl)	**54.3±9.5**	**51.84±9.1**	**45.0±2.35**	**1.616** **0.205**
SBP (mmHg)	**111.35±12.1**	**106.1±14.1**	**101.6±10.4**	**1.51** **0.228**
DBP (mmHg)	**76.98±8.11**	**76.66±8.66**	**70.0±5.0**	**1.06** **0.349**
WC(cm)	**91.11±8.85**	**89.97±11.23**	83.66±6.35	**1.00** **0.373**
BMI (Kg /m^2)	21.43±2.57	21.26± **2.9**	20.36±**0.68**	**0.256** **0.775**

FPI: Fasting plasma insulin; FPG: Fasting plasma glucose; HbA1c: Glycated hemoglobin; TC: Total Cholesterol; TG: Triglyceride; LDL-C: Low density lipoprotein Cholesterol; HDL-C: High Density Lipoprotein-Cholesterol; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; WC: Waist Circumference; BMI: Body Mass Index.

Table (5): Different clinical and anthropometric parameters with different *PTPN1*gene polymorphisms at 467T>C in diabetic patients with Met S.

Parameters	467T>C Genotypes			
	TT (n= 87)	**TC(n=8)**	**CC(n=5)**	**Anova (F-value) P -value**
FPI (µU/ml)	**28.76±6.41**	**29.93±3.95**	**35.64±4.6**	**2.957 0.057**
FPG (mg/dl)	**140.34±8.44**	**137.89± 8.52**	**138.7± 5.0**	**0.386 0.681**
HbA1c %	**12.17± 2.24**	**12.83±1.43**	**13.38±2.23**	**0.978 0.380**
HOMA	**10.78± 2.37**	**11.9±1.14**	**12.83± 1.05**	**2.642 0.076**
TC (mg/dl)	**326.1±69.2**	**341. 94 ± 54.52**	**351.58± 77.04**	**2.578 0.232**
TG (mg/dl)	**230.25±51.41**	**229. 22±12.9**	**242.1±43.54**	**0.140 0.870**
LDL-C (mg/dl)	**258.47±35.53**	**264.0 ±35.76**	**270.7±18.54**	**1.63 0.167**
HDL-C (mg/dl)	**39.5± 5.28**	**40.05± 4.61**	**37.42± 4.07**	**0.442 0. 644**
SBP (mmHg)	**132.4±10.03**	**136.88±9.61**	**132.0±7.58**	**0.760 0.470**
DBP (mmHg)	**95.2±16.16**	**101.16±16.89**	**109.6±14.5**	**2.325 0.103**
WC (cm)	**107.87±10.13**	**113.1±7.17**	**107.16± 9.23**	**1.071 0.347**
BMI (Kg/m^2)	**32.3±3.26**	**33.18±2.95**	**31.92±3.78**	**0.320 0.727**

FPI: Fasting plasma insulin; FPG: Fasting plasma glucose; HbA1c: Glycated hemoglobin; TC: Total Cholesterol; TG: Triglyceride; LDL-C: Low density lipoprotein Cholesterol; HDL-C: High Density Lipoprotein-Cholesterol; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; WC: Waist Circumference; BMI: Body Mass Index.

5. Discussion

Several definitions of the Met S exist, and it is confused if the risk factors having a higher cardiovascular risk [27]. Met S has confirmed to link the obesity, IR and related traits in relation to cardiovascular disease risk. Furthermore, the Met S as defined by the National Cholesterol Education Program appears to have a component of heritability, which suggests a genetic basis [27].The prevalence of diabetes has been increased to reach 382 million people throughout the world, about 35 million people in Middle East region suffered from diabetes in the year of 2013 and expected to increase to 592 million by the year of 2035 [28].IR plays a vital role in the development of Met S components such as impaired glucose tolerance, type 2 diabetes, central obesity, and hyperlipidemia [29].

PTPN1regulates negatively the insulin signaling pathway in skeletal muscles [30]. PTPN1 effects on several metabolic pathways have been discovered in PTPN1 deficient mice [31]. These multiple research studies opened the door for the negative effect of the PTPN1 on the insulin signal transduction [32].

The effects of PTPN1 promoter polymorphisms on the gene regulation may strengthen the link of that gene with the T2D disease, obesity and Met S [32]. Interestingly many types of research have been directed toward PTPN1 regulation on the insulin receptor phosphorylation, trying to clarify the effect of PTPN1on insulin sensitivity [9].The effect of

PTPN1 genetic polymorphisms on gene expression is considered to contribute to metabolic diseases such as T2D and metabolic syndrome [33].

The aim of the present study was to determine the relationship between the (467T>C) *PTPN1SNP* and Met S components by comparing the *PTPN1* gene (467T>C) alleles and genotypes between T2D patients with Met S and healthy Egyptian subjects. The study examined also the effects of that SNP on the insulin sensitivity (FPI, FPG, HbA1c, and HOMA index), obesity markers (BMI, WC), hypertension (SBP, DBP) and also on different quantitative metabolic parameters as total lipid profile parameters (TC, TG, HDL-C, and LDL-C).

A Non-significant association was detected by the present study among patients with Met S and the healthy volunteers for the 467T>C PTPN1 genotype and allele variants. Meshkani et al. [10] results on Iranian subjects were in harmony with the present findings, who stated that none of the PTPN1 gene SNPs were significantly associated with T2D except that of 1023C>A SNP.

In accordance with this study results, meta-analysis study included 7883 Europeans (from US, Poland, and Scandinavia) in three case-control studies, could not find any association for PTPN1 SNPs or haplotype with T2D [33].

In our previous study of Mackawy et al. [34] we investigated the association of PTPN1 gene polymorphisms (1023C>A and 467T>C) with Type 2 Diabetes in Egyptian patients and concluded that *PTPN1* promoter variant 1023C>A was associated with presence of T2D, but it had no correlation with any of metabolic traits and obesity and we could not detect any association between 467T>C variants and T2D Egyptian patients nor related traits.

This results also are in agreement with those of Weng et al [35], Santaniemi et al [36] and Wanic et al [37] who did not determine any association in a Chinese or a Finnish and Polish population, respectively.

In contrary, Bento et al. [38] had discovered associations between T2D and several *PTPN1* SNPs of noncoding genetic variants at this locus.

Furthermore, this study failed to find any significant association between anthropometric or biochemical features with the homozygous and heterozygous individuals at 467T>C PTPN1 variants in the T2D with Met S group or healthy subjects. This finding was in harmony with Meshkani et al [10].

On the other hand, several other studies have detected a significant association of PTPN1 SNPs with T2D metabolic traits as in Mok et al. [39] who discovered an association between an SNP in exon 8 and impaired glucose tolerance and T2D in Canadian aboriginal individuals. Paola et al. [40] reported significant association with IR in obese Italian individuals. Other studies of Bento et al. [38] and Palmer et al. [41] had found associations with T2D and IR variants with PTPN1 gene SNPs.

The Bento et al [38] and Palmer et al [41] reported different results among Hispanic Americans from the Insulin Resistance Atherosclerosis Study Family Study (IRASFS) IRASFS, they found a significant association of PTP- 1B gene polymorphisms with metabolic traits of T2D. Moreover, Florez et al. [33] and the Cheyssac et al. [42] discovered that significant association but in European populations.

The present study results did not match with the hypothesis of the possible effect of 467T>C *PTPN1* SNP on Met S traits such as insulin sensitivity, HOMA-I, and hypertension which are characteristics of the metabolic syndrome.

No significant association between PTPN1 gene SNP (467 T> C) and obesity markers (BMI, WC) was detected in the present study. In agreement with present study results was the study of Echwald et al. [43] who recorded no association between *PTPN1* SNPs and metabolic syndrome traits in the Danish or Swedish nondiabetic subjects.

In contrary, Cheyssac et al [42] displayed an association between SNP rs914458 and moderate obesity and severe obesity for SNP rs6126033 located in the first intron, those findings supported the corporation of the *PTPN1* genetic SNPs with insulin sensitivity and metabolic syndrome traits. In addition, several associations between *PTPN1*gene variants and insulin sensitivity quantitative traits were observed by Spencer-Jones et al [44].

In the present study, findings could not detect any association between T2D patients with Met S and 467T>C SNP *PTPN1* genetic variations. This was in disagreement with Kipfer-Coudreau et al [45] who confirmed that association between *PTPN1* genetic variation and dyslipidemia in the French population. An association was also be found between the Pro387Leu variant and increase in blood glucose levels in a German population [46]. Associations of *PTPN1* gene variants with BMI and TC level in an Asian population were observed by Olivier et al [47].

The findings of all those studies can be explained by the dephosphorylation effect of *PTPN1*

On the JAK2 kinase that is a crucial step in leptin signaling cascade and regulating the expression of the lipogenic genes [48].

Those variable results open the window for the effect of the *PTPN1* gene SNPs on the risk of Met S in T2D in subjects of different ethnic origin. These conflict results could be due to heterogeneity

of Met S etiology among the different populations, perhaps driven by variations in genetic or environmental modifiers. No single gene or cluster of genes has been responsible for Met S among different populations, likely due to the complex interaction between gene and environment necessary for expression of this phenotype [49]. Further adjustment of patient phenotypes, matching for all possible factors on increased sample size, will be needed to examine the possible effect of *PTPN1* gene SNPs on Met S in type 2 diabetes and related metabolic traits.

Conclusion

The present study could not detect any association between 467T>C variants of *PTPN1* gene with T2D Egyptian patients nor metabolic related traits. Further studies must be done on a larger population size to detect any potential metabolic association between different *PTPN1* gene variants and metabolic syndrome.

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Conflict of interest

There is no conflicts of Interest.

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3/2/3021