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# The associations among *RARRES2* *rs17173608* gene polymorphism, serum chemerin, and non-traditional lipid profile in patients with metabolic syndrome

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## Abstract

**Background:** The adipokine chemerin retinoic acid receptor responder protein 2 (*RARRES2*) has been associated with insulin resistance, type II diabetes mellitus (T2DM), obesity, and metabolic syndrome (MetS). The impact of *RARRES2 rs17173608* gene polymorphism on MetS and chemerin levels is not completely elucidated. This study included 100 patients with MetS and 68 healthy subjects (non-MetS group). The *RARRES2 rs17173608* gene variant was analyzed by tetra amplification refractory mutation system polymerase chain reaction (T-ARMS-PCR). Circulating chemerin levels were determined by ELISA. Serum urea, creatinine, fasting blood glucose, glycosylated hemoglobin, and traditional lipid profile were measured by colorimetric methods. The estimated glomerular filtration rate (eGFR) and non-traditional lipid parameters were calculated.

**Results:** Serum chemerin levels were significantly higher in MetS than in non-MetS subjects, type II diabetics (T2DM) than non-diabetics, and overweight compared to lean subjects, but it did not differ significantly between patients with and without hypertension. Strikingly, newly diagnosed diabetic patients had significantly higher serum chemerin levels. Correlation and multiple linear regression analysis showed that serum chemerin levels and non-traditional lipid parameters were correlated significantly with the clinical criteria of MetS. Genotyping and allelic frequency distribution of *RARRES2 rs17173608* gene polymorphism showed its significant association with MetS. The TT genotype of *RARRES2 rs17173608* SNP was more distributed in T2DM in comparison with non-diabetics, and it was associated significantly with higher serum chemerin and higher glycosylated hemoglobin levels. *RARRES2 rs17173608* GG genotype and G allele frequency were less distributed in T2DM patients than in non-diabetic patients.

**Conclusions:** The *RARRES2 rs17173608* SNP might have an impact on chemerin levels and lipid parameters. The GG genotype and G allele may have a protective role towards the risk of T2DM but not for MetS. Serum chemerin and non-traditional lipid profile are significantly associated with MetS.

**Keywords:** Chemerin, *RARRES2 rs17173608*, Metabolic syndrome, T-ARMS-PCR, Diabetes mellitus, Obesity

## Background

Metabolic syndrome (MetS) is a cluster of three or more of the following conditions that take place together, including abdominal obesity, hyperglycemia, dyslipidemia and hypertension [1]. Obesity and type II diabetes

mellitus (T2DM) are the main contributors to MetS [2]. Among challenges imposed by MetS is the increasing incidence all over the world, about 25% in the Middle East [3], 35% of Americans adults [4], and 45.9% of the Gulf Cooperative Council suffer from it [5]. It is associated with various morbidities such as vascular diseases, osteoarthritis [6], psoriasis [7], chronic kidney disease [8], and pulmonary inflammations [9].

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The adipokine and chemokine chemerin (retinoic acid receptor responder protein 2 (*RARRES2*) is a multifunctional 16-kDa protein that is encoded by the *RARRES2* gene [10]. It modulates the immune response and has a regulatory role in lipid and glucose metabolism [11]. Chemerin is predominantly expressed in adipocytes [12, 13] and regulates their differentiation [14]. Furthermore, it can activate inflammatory response and oxidative stress in adipose tissue leading to insulin resistance [15]. The expression of chemerin is observed to be increased in diabetic, hypertensive, and dyslipidemic patients who may suffer from MetS [16].

Retinoic acid receptor responder protein 2 *rs17173608* single nucleotide polymorphism (SNP) is located in intron 2 of the *RARRES2* gene, which is a potential site for mutations [17]. It had been associated with increased risk of obesity and MetS [18, 19]. However, it was reported to be not associated with the risk of MetS-related diseases such as gestational diabetes, diabetic nephropathy, and polycystic ovary syndrome [20–22]. The impact of this gene polymorphism on chemerin levels is not completely elucidated.

The non-traditional lipid parameters total cholesterol (TC)/high-density lipoprotein cholesterol (HDL-C), triglycerides (TG)/HDL-C, total lipids, and non-HDL-C showed better associations with T2DM than traditional lipid parameters [23]. Currently, they have been confirmed to be independent predictors for vascular complications associated with MetS [24].

The relationship among non-traditional lipid parameters, serum chemerin level, and *RARRES2 rs17173608* SNP has not been adequately studied in patients with MetS. In this study, we aimed to evaluate the association of *RARRES2 rs17173608* gene polymorphism with serum chemerin, traditional lipid parameters, and non-traditional lipid parameters in MetS patients, elucidating their relationship with components of MetS (high blood glucose, hypertension, and T2DM).

## Methods

### Subjects and anthropometric parameters

The present study is a case-control study, conducted between May 2018 and September 2018. One hundred patients with MetS were recruited from the author's institution hospital outpatient clinics along with 68 age- and sex-matched control subjects (non-MetS group). Each participant signed a written informed consent for participation in the study. The study protocol was reviewed and approved by the medical ethics committee of the faculty of authors institution (registered as IRB no: IRB17200157), and all the study procedures were following the Helsinki declaration. All participants were subjected to routine physical and clinical examinations which include measurements of body weight (kg), waist

circumference (cm), height (cm), body mass index (BMI), and blood pressure (mmHg).

### Control group (non-MetS group)

Sixty-eight completely healthy subjects were enrolled in this group. They did not suffer from diabetes nor hypertension. According to their BMI, 32 had normal weight, 20 were overweight, and 16 were obese.

The diagnosis of MetS was based on the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) guidelines. The diagnosis of MetS was made if any three of the following risk factors were present: waist circumference (WC) more than 80 cm in women or more than 90 cm in men, elevated systolic blood pressure (SBP) more than 135 mmHg or elevated diastolic blood pressure (DBP) more than 85 mmHg, fasting blood glucose (FBG) more than 140 mg/dl, elevated triglycerides (TG) above 150 mg/dl, or decreased HDL-C levels less than 50 mg/dl.

Patient groups (with MetS) were sub-classified into subgroups: firstly, according to BMI (96 obese and 4 overweight); secondly, according to the presence or absence of T2DM, they were sub-classified to a diabetic subgroup (56 subjects) and non-diabetic subgroup (44 subjects); and thirdly, the MetS group sub-classified into hypertensive subgroup (40 subjects) and non-hypertensive subgroup (60 subjects).

The diabetic subgroup was further sub-classified according to the duration of T2DM into known diabetics (48 subjects) and newly diagnosed T2DM (8 subjects). According to the World Health Organization definition [25], the known diabetics group are those previously diagnosed as T2DM or on current treatment with insulin or oral hypoglycemic agents, as they were having either FBG  $\geq 7.0$  mmol/l ( $\geq 126$  mg/dl) and/or 2-h plasma glucose  $\geq 11.1$  mmol/l, with HbA1c ( $\geq 6.5\%$ ), whereas the newly diagnosed diabetes patients are those diagnosed within only 1 year and they were also having either FPG  $\geq 126$  mg/dl and/or 2-h postprandial plasma glucose  $\geq 11.1$  mmol/l.

Obesity was defined according to body mass index (BMI) (weight kg/height m<sup>2</sup>). The participants were classified as follows: normal weight (lean) if BMI was 18.5 to 24.9; overweight if BMI was 25 to 29.9; or obese if BMI was  $> 30$  kg/m<sup>2</sup>. Measurement of waist circumference was used as an indicator of abdominal fat mass; it was performed by placing a flexible tape midway between the lower edge of the ribs and the iliac crests and the subjects were standing with their feet about 23–30 cm apart, and the measurements were taken during gentle expiration [26].

### Blood samples and analysis of general biochemical markers

Five milliliters of venous blood was collected from all included subjects. One milliliter of blood was collected in

EDTA-containing tubes and used for DNA extraction and HbA1c assay. The remaining 4 ml of blood was used for serum separation by centrifugation at 3000 rpm for 10 min. The samples were kept at  $-20^{\circ}\text{C}$ .

The serum levels of total cholesterol (TC), triglyceride (TG), and high-density lipoprotein cholesterol (HDL-C) were measured using colorimetric methods by kits supplied by Bio-Diagnostics Company (cat no.CH1220, TR2030, and CH1232, respectively). Low-density lipoprotein cholesterol (LDL-C) serum concentrations were calculated using the Friedewald equation [27] ( $\text{LDL cholesterol} = \text{total cholesterol} - (\text{HDL cholesterol} + \text{triglyceride}/5)$ ). Very low-density lipoprotein cholesterol (VLDL) serum concentrations were calculated by dividing triglyceride/5 according to Friedewald equation [27]. Serum glucose levels were measured by Randox enzymatic glucose kit (catalog no.GL364). Quantitative diagnostic determination of serum creatinine was measured by spectrum diagnostics creatinine reagent (catalog no.235002). Serum urea was measured by Bio-Diagnostics reagent (catalog no.2110). The estimation of glycated hemoglobin (HbA1c) values was performed on a fresh EDTA blood by spectrum diagnostics turbidimetric immunoassay (catalog no.602001-I). The estimated glomerular filtration rate (eGFR) was calculated by the Modification of Diet in Renal Disease (MDRD4) equation that is based on age, sex, ethnicity, and serum creatinine, and the eGFR was expressed in milliliters per minute per  $1.73\text{ m}^2$ .

#### Determination of serum chemerin concentrations

Serum chemerin levels were measured by ELISA kit catalog no. WH-1371 supplied by Wkeamed supplies, Changchun, China.

#### DNA extraction

DNA was extracted from the peripheral whole blood samples by QIAamp DNA mini extraction kit, catalog no.51104, supplied by Qiagen Company and according to instructions provided by the manufacturer. The concentration and purity of extracted DNA were checked by nanodrop (Epoch, Biotek, USA). The concentration of DNA samples was calculated by using DNA absorbance at 260 nm. DNA samples were considered pure if the 260/280 ratio was 1.8–2. The DNA was kept at  $-20^{\circ}\text{C}$  till genotyping.

#### Genotyping

A tetra amplification refractory mutation system polymerase chain reaction (T-ARMS-PCR) for rapid and sensitive detection of *RARRES2 rs17173608* SNP was utilized. Polymerase chain reaction mixture of 25  $\mu\text{l}$  total volume contained 100 ng DNA and 1  $\mu\text{l}$  of each primer (100 pm/ $\mu\text{l}$ ), and 5  $\mu\text{l}$  DNase-free water was added to

Taq PCR master mix (catalog no. 201443, Qiagen). The primers of *RARRES2 rs17173608* gene polymorphism were as follows [18]; primers sequence (5' to 3')

FI: (G allele) ATTGCTATAGTCCAGTGCCCTTCG

RI : (T allele) CCAGTTCCCTCTGTCTGGCTTAA

F: (com).GTCAGACCCATGCAGTTTTCAAAC

R: (com). GAGTTCCTCTCTCAAGCATCAGGG

Amplification was done with an initial denaturation step at  $95^{\circ}\text{C}$  for 5 min, followed by 30 cycles denaturation at  $95^{\circ}\text{C}$  for 30 s, annealing at  $56^{\circ}\text{C}$  for 15 s, and extension at  $72^{\circ}\text{C}$  for 30 s, with a final extension step at  $72^{\circ}\text{C}$  for 10 min. PCR products were electrophoresed on a 2.0% agarose gel containing 0.5  $\mu\text{g}/\text{ml}$  ethidium bromide then viewed on the BIODOC gel documentation system. To certify genotyping quality, all polymorphisms in random samples were re-genotyped and the check confirmed the previous genotyping results by 100%.

#### Statistical analysis

Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, IL, USA). Quantitative data were expressed as mean  $\pm$  standard deviation (SD). Qualitative data were expressed as frequency and percentage. Independent-samples *t* test of significance was used for comparing two means. A one-way analysis of variance (ANOVA) followed by post hoc test was used when comparing more than two means. Correlation analysis between the biochemical parameters and MetS criteria was done using Pearson's correlation test. Multiple linear regressions were applied to show the association among serum chemerin levels, MetS criteria, and independent factors that may have effects on them.

Chi-square ( $\chi^2$ ) test of significance was used to compare proportions among qualitative parameters, genotype, and allelic frequencies between the study groups. Logistic regression analysis was applied to estimate odds ratio (OR) and to obtain 95% confidence intervals (CI) of associated MetS risk. The confidence interval was set to 95%, and the margin of error accepted was set to 5%. The receiver operating characteristic (ROC) curve of serum level of chemerin was performed to estimate its diagnostic performance between groups and subgroups.

#### Results

Demographic characteristics, MetS criteria, and biochemical parameters in both MetS ( $N = 100$ ) and non-MetS ( $N = 68$ ) groups are shown in Table 1. The age and sex of the two groups were matched. According to the guided MetS diagnosis criteria, the mean values of waist circumference, SBP, DBP, FBG, TC, TG, HDL-C, VLDL, and non-traditional lipid parameters (total lipid, TC/HDL, TG/HDL-C, non-HDL) were significantly higher in MetS group in comparison with non-MetS

**Table 1** Comparison between MetS group and non-MetS (control) group in relation to demographic data, MetS criteria, and biochemical parameters

Variables	MetS group(n, 100)		Non-MetS group (n, 68)		p value
	Mean/number	(%)/± SD	Mean/number	(%)/± SD	
Female	48	48.0%	29	42%	0.54
Male	52	52.0%	39	58%	
Age (years)	43.88	14.40	44.53	16.81	0.85
Waist (cm)	105.36	14.90	78.00	15.67	<b>&lt; 0.001</b>
SBP (mmHg)	123.80	16.74	115.88	7.83	<b>0.012</b>
DBP (mmHg)	82.20	9.16	76.47	7.13	<b>0.003</b>
FBG (mg/dl)	166.40	74.73	105.22	83.87	<b>0.02</b>
TC (mg/dl)	209.57	51.56	184.51	71.87	0.07
TG (mg/dl)	191.08	82.40	114.20	37.75	<b>0.002</b>
HDL-C (mg/dl)	39.40	29.46	55.66	20.47	<b>&lt; 0.01</b>
LDL-C (mg/dl)	132.24	65.87	103.54	69.91	0.06
VLDL	39.40	23.47	30.86	7.61	<b>0.04</b>
Total Lipid	611.69	128.27	528.77	173.68	<b>&lt; 0.01</b>
TC/HDL-C	11.41	17.05	3.64	1.64	<b>&lt; 0.01</b>
TG/HDL-C	12.33	2.85	3.18	1.51	<b>0.03</b>
LDL/HDL-C	7.90	1.70	2.07	1.41	<b>0.009</b>
Non HDL (TC-HDL-C)	170.16	62.58	128.85	70.23	<b>0.006</b>
Serum chemerin (ng/ml)	554.64	166.06	359.59	205.39	<b>&lt; 0.0001</b>
Serum creatinine (mg/dl)	0.83	0.35	0.82	0.29	0.846
Serum urea (mg/dl)	16.12	2.11	15.23	3.1	<b>0.018</b>
eGFR (ml/min/1.73 m <sup>2</sup> )	107.2	12.4	108.3	11.1	0.557

Data are represented as mean ± SD or number (n) and percentage. The independent samples t test was used to compare between means of different parameters in MetS and non-MetS groups. Chi-square test was used to analyze the significance between the percentages

p < 0.05 is considered to be a significant value

SBP systolic blood pressure, DBP diastolic blood pressure, eGFR estimated glomerular filtration rate, FBG fasting blood glucose, HDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol, TC total cholesterol, TG triglyceride, VLDL very low-density lipoprotein cholesterol

group (all  $p < 0.05$ ). The serum levels of LDL-C were not significantly different between the two groups. Chemerin serum level was significantly higher in the MetS group ( $p$  value = 0.0001) than the control group.

Correlation analysis by Pearson's correlation test among serum chemerin levels, demographic data, and non-traditional lipid parameters with MetS criteria (waist circumference, elevated blood pressure, high blood glucose, high TG, low HDL-C) and other measured markers was performed. Table 2 showed that serum chemerin levels were significantly correlated with age, BMI, HbA1c, SBP, TG, and VLDL. The non-traditional lipid indices levels (TC/HDL-C, TG/HDL-C) showed significant positive correlations with DBP, TG, HDL-C levels, and HbA1c. Total lipids and LDL/HDL-C values also showed significant positive correlations with HbA1c.

Multiple linear regression analysis showed that TG, VLDL, and age were the only independent variables of chemerin serum level ( $\beta = 0.404$ ,  $p = 0.004$ ), ( $\beta = 1.69$ ,  $p = 0.000$ ), ( $\beta = 0.53$ ,  $p = 0.001$ ), respectively (Table 3).

Analysis of determinants of MetS criteria by multivariate linear regression analysis revealed that BMI, HDL-C, non-traditional lipid parameters (TC/HDL-C, TG/HDL-C, total lipid) and glycated hemoglobin (HbA1c) were independent factors of waist circumference (WC). Elevated SBP and DBP as dependent factors, were not affected by chemerin, non-traditional lipid parameters or traditional lipid parameters. High blood glucose was found to be associated with non-traditional lipid parameters but not related to traditional lipid parameters by regression analysis (Table 3).

Evaluation of chemerin serum levels in the subclasses of MetS group (subgroups) revealed significantly higher levels of chemerin in diabetics compared to non-diabetics ( $p$  = value < 0.001), as well as in between obese, overweight, and lean subjects ( $p$  value = 0.005). However, trend to significance appeared between hypertensive and non-hypertensive patients ( $p$  value = 0.08) as shown in Figs. 1 and 2. Remarkably, the newly diagnosed diabetic subgroup showed higher serum chemerin levels

**Table 2** Correlation between chemerin serum levels and non-traditional lipid indices with age and other studied parameters in MetS group

Variables	Chemerin (ng/ml)	TC (mg/dl)	TG (mg/dl)	HDL-C (mg/dl)	LDL-C (mg/dl)	VLDL	Total Lipid	TC/HDL-C	TG/HDL-C	LDL/HDL-C	Non HDL-C (TC-HDL-C)
Age (year)	<b>.426**</b>	<b>.283*</b>	<b>.515**</b>	.257	– .028	<b>.355*</b>	<b>.554**</b>	<b>.295*</b>	<b>.308*</b>	.276	.112
	<b>.002</b>	<b>.047</b>	<b>.000</b>	.071	.844	<b>.011</b>	<b>.000</b>	<b>.038</b>	<b>.030</b>	.053	.440
BMI (weight kg/height m <sup>2</sup> )	<b>.369**</b>	.150	– .187	– .005	.190	– .144	.010	– .061	.041	– .089	.126
	<b>.008</b>	.299	.193	.973	.185	.319	.943	.676	.777	.538	.384
Waist (cm)	– .181	.102	.101	<b>.345*</b>	– .072	.042	.156	– .031	.107	– .076	– .078
	.207	.481	.485	<b>.014</b>	.618	.774	.281	.829	.459	.598	.590
SBP (mmHg)	<b>.330*</b>	– .066	.083	.207	– .190	.088	– .007	.179	.172	.166	– .152
	<b>.019</b>	.650	.565	.149	.186	.542	.963	.213	.234	.250	.293
DBP (mmHg)	.220	– .173	.032	– .027	– .149	.061	– .120	<b>.281*</b>	<b>.294*</b>	.259	– .130
	.125	.230	.826	.853	.301	.672	.405	<b>.048</b>	<b>.039</b>	.070	.369
Serum chemerin (ng/ml)	1	– .080	<b>.424**</b>	– .049	– .203	<b>.469**</b>	.210	.203	.174	.188	– .042
		.583	<b>.002</b>	.736	.157	<b>.001</b>	.143	.158	.226	.192	.770
Glucose (mg/dl)	.152	.105	– .070	<b>.320*</b>	– .011	– .164	.035	.148	.101	.167	– .064
	.292	.469	.630	<b>.023</b>	.942	.256	.808	.306	.485	.245	.657
HbA1c (%)	<b>.303*</b>	.131	<b>.643**</b>	– .041	– .052	<b>.541**</b>	<b>.528**</b>	<b>.395**</b>	<b>.545**</b>	<b>.318*</b>	.127
	<b>.032</b>	.366	<b>.000</b>	.778	.719	<b>.000</b>	<b>.000</b>	<b>.005</b>	<b>.000</b>	<b>.024</b>	.380
TC (mg/dl)	– .080	1	– .043	– .128	<b>.848**</b>	– .046	<b>.772**</b>	.201	.087	.240	<b>.884**</b>
	.583		.769	.374	<b>.000</b>	.749	<b>.000</b>	.161	.548	.093	<b>.000</b>
TG (mg/dl)	<b>.424**</b>	– .043	1	– .110	– <b>.340*</b>	<b>.953**</b>	<b>.600**</b>	<b>.369**</b>	<b>.550**</b>	.259	.017
	<b>.002</b>	.769		.446	<b>.016</b>	<b>.000</b>	<b>.000</b>	<b>.008</b>	<b>.000</b>	.070	.908
HDL-C (mg/dl)	– .049	– .128	– .110	1	– <b>.478**</b>	– .225	– .179	–	–	–	– <b>.576**</b>
								<b>.488**</b>	<b>.428**</b>	<b>.489**</b>	
LDL-C (mg/dl)	.736	.374	.446		<b>.000</b>	.117	.213	<b>.000</b>	<b>.002</b>	<b>.000</b>	<b>.000</b>
	– .203	<b>.848**</b>	– <b>.340*</b>	– <b>.478**</b>	1	–	<b>.470**</b>	.273	.094	<b>.346*</b>	<b>.924**</b>
VLDL	.157	<b>.000</b>	<b>.016</b>	<b>.000</b>		.031	<b>.001</b>	.055	.518	<b>.014</b>	<b>.000</b>
	<b>.469**</b>	– .046	<b>.953**</b>	– .225	– <b>.305*</b>	1	<b>.568**</b>	.274	<b>.446**</b>	.163	.068
Total lipid	<b>.001</b>	.749	<b>.000</b>	.117	<b>.031</b>		<b>.000</b>	.055	<b>.001</b>	.257	.641
	.210	<b>.772**</b>	<b>.600**</b>	– .179	<b>.470**</b>	<b>.568**</b>	1	<b>.396**</b>	<b>.420**</b>	<b>.358*</b>	<b>.721**</b>
TC/HDL	.143	<b>.000</b>	<b>.000</b>	.213	<b>.001</b>	<b>.000</b>		<b>.004</b>	<b>.002</b>	<b>.011</b>	<b>.000</b>
	.203	.201	<b>.369**</b>	– <b>.488**</b>	.273	.274	<b>.396**</b>	1	<b>.938**</b>	<b>.988**</b>	<b>.396**</b>
TG/HDL	.158	.161	<b>.008</b>	<b>.000</b>	.055	.055	<b>.004</b>		<b>.000</b>	<b>.000</b>	<b>.004</b>
	.174	.087	<b>.550**</b>	– <b>.428**</b>	.094	<b>.446**</b>	<b>.420**</b>	<b>.938**</b>	1	<b>.876**</b>	.273
LDL/HDL	.226	.548	<b>.000</b>	<b>.002</b>	.518	<b>.001</b>	<b>.002</b>	<b>.000</b>		<b>.000</b>	.055
	.188	.240	.259	– <b>.489**</b>	<b>.346*</b>	.163	<b>.358*</b>	<b>.988**</b>	<b>.876**</b>	1	<b>.428**</b>
Non-HDL (TC-HDL)	.192	.093	.070	<b>.000</b>	<b>.014</b>	.257	<b>.011</b>	<b>.000</b>	<b>.000</b>		<b>.002</b>
	– .042	<b>.884**</b>	.017	– <b>.576**</b>	<b>.924**</b>	.068	<b>.721**</b>	<b>.396**</b>	.273	<b>.428**</b>	1
	.770	<b>.000</b>	.908	<b>.000</b>	<b>.000</b>	.641	<b>.000</b>	<b>.004</b>	.055	<b>.002</b>	

Correlation is given as the parametric Pearson's correlation (*r*) with the corresponding *p* values. Correlation was significant at the 0.01 level (2-tailed)

FBG fasting blood glucose, TC total cholesterol, TG triglycerides, HDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol, SBP systolic blood pressure, DBP diastolic blood pressure

\*\**p* value less than 0.01, \**p* value less than 0.05



**Table 3** Multiple linear regression analysis of the predictor variables of serum chemerin, waist circumference, systolic blood pressure, diastolic blood pressure, triglyceride levels, and fasting blood glucose in MetS group

Independent variables of chemerin serum levels			Independent variables of SBP		
	Beta coefficient	p value		Beta coefficient	p value
(Constant)		0.766	(Constant)		0.000
WC (cm)	− 0.163	0.275	Total lipid	0.142	0.601
SBP (mmHg)	0.286	0.126	TC/HDL-C	− 3.774	0.540
DBP (mmHg)	− 0.043	0.812	TG/HDL-C	1.178	0.570
FBG (mg/dl)	0.194	0.177	LDL/HDL-C	2.891	0.499
HbA1c (%)	0.291	<b>0.04</b>			
TC (mg/dl)	− 0.066	0.630	Non HDL-C (TC-HDL-C)	− 0.328	0.227
TG (mg/dl)	0.404	<b>0.004</b>	Chemerin (ng/ml)	0.306	0.076
HDL-C (mg/dl)	− 0.086	0.592	LDL-C (mg/dl)	− 1.189	0.254
VLDL(mg/dl)	1.689	<b>0.000</b>	HDL-C(mg/dl)	− 0.280	0.538
Age(years)	0.534	<b>0.001</b>	TG (mg/dl)	− 0.313	0.426
BMI (weight kg/height m <sup>2</sup> )	− 0.257	0.098	TC (mg/dl)	0.893	0.279
Independent variables of waist circumference			Independent variables of DBP		
(Constant)	−	0.226	(Constant)	−	0.000
BMI	0.670	<b>0.000</b>	Total lipid	− 0.030	0.116
Chemerin (ng/ml)	− 0.032	0.757	TC/HDL-C	1.513	0.640
Glucose (mg/dl)	0.134	0.201	TG/HDL-C	− 0.171	0.824
HbA1c	0.301	<b>0.004</b>	LDL/HDL-C	− 1.472	0.623
TC (mg/dl)	− 0.018	0.853	Non HDL-C (TC-HDL-C)	0.012	0.756
HDL-C (mg/dl)	0.321	<b>0.004</b>	Chemerin (ng/ml)	0.012	0.194
Total lipid	0.537	<b>0.032</b>	LDL-C (mg/dl)	− 0.093	0.526
TC/HDL-C	− 14.756	<b>0.006</b>	HDL-C(mg/dl)	− 0.102	0.482
TG/HDL-C	5.383	<b>0.003</b>	TG (mg/dl)	− 0.024	0.587
LDL/HDL-C	9.702	<b>0.010</b>	TC (mg/dl)	0.061	0.682
Independent variables of blood glucose			Independent variables of TG		
(Constant)	−	<b>0.326</b>	(Constant)	−	<b>0.226</b>
Total lipid	0.570	<b>0.034</b>	Chemerin (ng/ml)	<b>.001</b>	<b>0.426</b>
TC/HDL-C	− 15.639	<b>0.011</b>	TC (mg/dl)	− <b>0.636</b>	<b>0.000</b>
TG/HDL-C	4.599	<b>0.025</b>	HDL-C (mg/dl)	− <b>0.349</b>	<b>0.000</b>
LDL/HDL-C	11.573	<b>0.007</b>	LDL-C (mg/dl)	− <b>0.780</b>	<b>0.000</b>
Non HDL-C (TC-HDL-C)	− 0.568	<b>0.032</b>	DBP (mmHg)	<b>0.239</b>	<b>0.131</b>
Chemerin (ng/ml)	0.171	0.296	VLDL	<b>0.12</b>	− <b>0.276</b>
LDL-C (mg/dl)	0.858	<b>0.394</b>	Age (Years)	<b>0.391</b>	<b>0.023</b>
HDL-C (mg/dl)	0.694	<b>0.120</b>	BMI (weight kg/height m <sup>2</sup> ).	− <b>0.103</b>	<b>0.580</b>
TG (mg/dl)	0.276	<b>0.469</b>	Waist (Cm)	<b>0.085</b>	<b>0.664</b>
TC (mg/dl)	− 0.523	<b>0.511</b>	SBP (mmHg)	<b>0.058</b>	<b>0.732</b>

p value less than 0.05 is considered significant. Significant results are marked bold

WC waist circumference, FBG fasting blood glucose, TC total cholesterol, TG triglycerides, HDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol, SBP systolic blood pressure, DBP diastolic blood pressure

(with *p* value < 0.001, results not shown) compared to known T2DM subgroups.

Receiver-operator characteristic (ROC) curve was applied for testing the diagnostic utility of serum chemerin

as potential diagnostic biomarker for MetS and T2DM. Receiver-operator characteristic curve for serum chemerin in different subgroups is shown in Fig. 3. Diagnostic performance of chemerin (ng/ml) in discriminating

control and metabolic syndrome showed the best cutoff value of chemerin was  $> 209$  ng/ml, with sensitivity of 86%, specificity of 35.3%, positive predictive value (PPV) of 66.2%, negative predictive value (NPV) of 63.2%, a diagnostic accuracy of 56.5%. Discrimination between diabetics and non-diabetics showed that the best cutoff value of chemerin was  $> 297$  ng/ml, with sensitivity of 97.6%, specificity of 100%, PPV of 100%, NPV of 97.7%, and a diagnostic accuracy of 98.5%. Discrimination between newly diagnosed diabetics and known diabetics showed that the best cutoff value of chemerin was  $\leq 522$  ng/ml, with sensitivity of 75%, specificity of 100%, PPV of 100%, NPV of 55.6%, and a diagnostic accuracy of 91.3%.

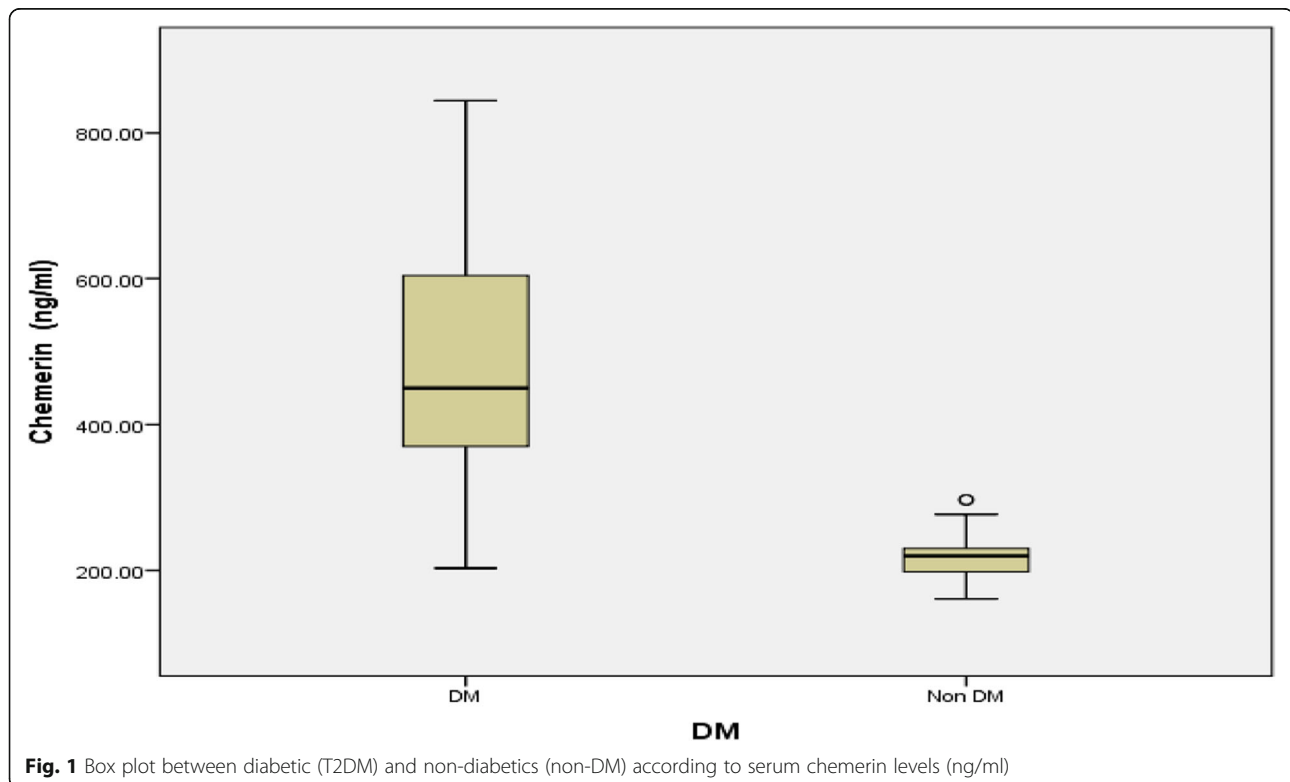
The T-ARMS-PCR analysis of *RARRES2* rs17173608 gene polymorphism followed by agarose gel electrophoresis demonstrated that the PCR product sizes of *RARRES2* rs17173608 polymorphism were 262 bp for the G allele, 332 bp for the T allele, and 549 bp for the two common primers, as shown in Fig. 4.

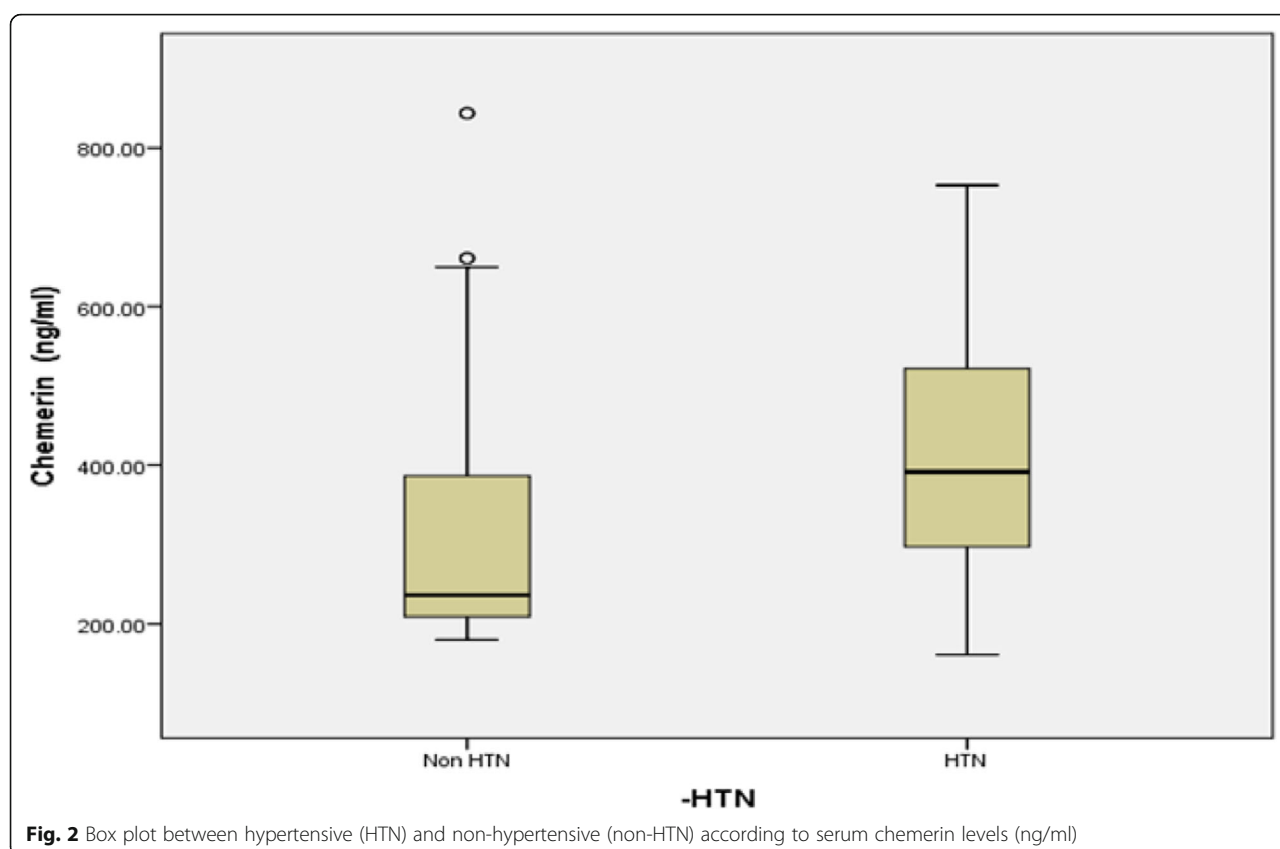
Genotypes of *RARRES2* rs17173608 gene polymorphism demonstrated that the homozygous TT genotype was more distributed in the control group (55.88%) in comparison with the MetS group (36%), while GG genotypes was more distributed in MetS group (32% vs. 11.8%). There was a significant association between the homozygous GG genotype and increased risk of MetS (RR = 4.222, 95% CI = 1.7185 to 10.3738,  $p$  value = 0.0017) as

shown in Table 4. The minor allele (G allele) frequency was 48% in the MetS group and 27% in the non-MetS, and it was associated with increased MetS risk (OR = 2.38, 95% CI = 1.493–3.79,  $p$  = 0.0003). Furthermore, this significant risk was still noted in MetS when testing dominant (TG + GG vs. TT), recessive (TT + TG vs. GG), and additive (GG vs. TT) models of inheritance ( $p$  < 0.05 each). In our study, even though *RARRES2* rs17173608 had a minor allele frequency (MAF) = 0.048 in the MetS group which is not consistent with the Hardy Weinberg equilibrium (HWE), yet it had a MAF = 0.28 in the non-MetS group and 0.24 in T2DM ( $p$  value = 0.105, 0.76 respectively), where both were consistent with HWE.

Striking results obtained with testing the distribution of *RARRES2* rs17173608 SNP in between the T2DM and non-diabetics subgroups are shown in Table 4. The variant G allele and the homozygous GG genotype were more distributed in non-diabetics than in diabetics (52.38% and 38.1%, respectively); this was confirmed by odds ratio calculation (OR = 0.137, 95% CI = 0.055–0.338,  $p$  < 0.001) (OR = 0.293, 95% CI = 0.184–0.467,  $p$  < 0.000) and suggests a protective role towards T2DM.

Interestingly, the homozygous TT genotype was more distributed in the T2DM (60.71%) in comparison with non-diabetics. The association between different genotypes of *RARRES2* rs17173608 gene polymorphism and criteria of MetS group found in Table 5 showed that





**Fig. 2** Box plot between hypertensive (HTN) and non-hypertensive (non-HTN) according to serum chemerin levels (ng/ml)

serum chemerin levels were higher in TT genotype, and the GG genotype showed the lowest chemerin levels ( $p$  value for ANOVA  $< 0.001$ ).

## Discussion

The present study showed highly significant differences in circulating chemerin levels in the MetS group in comparison with the healthy controls. This could be explained by the effect of chemerin on lipid and glucose metabolism and its role in modulating immune responses. A study by Wang et al. [28] reported similar differences in serum chemerin levels in Chinese patients with and without MetS. Chemerin is an adipokine that regulates adipocyte differentiation [11]. Serum levels of chemerin might give an idea about adipocyte droplet size, its metabolic hemostasis, and total fat mass [29].

Our results showed that serum chemerin had a significant positive correlation with BMI, but not with the WC. This positive correlation with BMI was lost in the regression analysis. Zylla et al. [30] observed a positive relationship between chemerin and subcutaneous adipose tissue mass. Also, a similar correlation to our results was reported between chemerin and BMI, despite the absence of correlation with WC by Ba et al. [31]. Another large cohort cross-sectional study revealed that chemerin may be strongly correlated to MetS more than

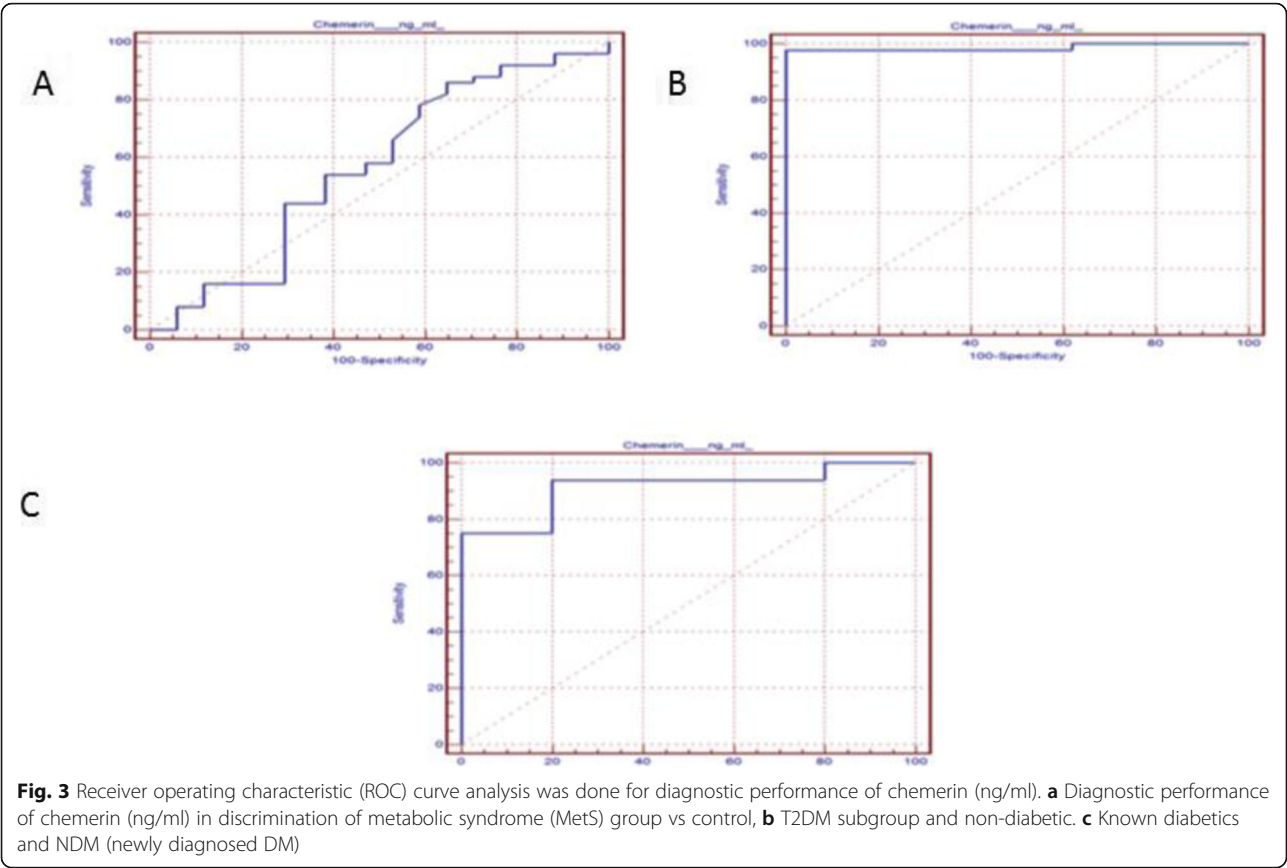
the traditional biochemical parameters [32]. Weigert et al. [33] study found no association between chemerin and BMI.

Chemerin serum levels in this present study were also positively correlated with TG and VLDL in the MetS group. This co-relation was proved also by Bozaoglu et al. [34] study that was conducted in a large cohort and showed that serum TG was correlated with serum chemerin. Ye et al. [35] suggested that chemerin is involved in the metabolic changes associated with obesity.

Regarding the association of chemerin with HDL-C level, the present study showed that serum chemerin was not correlated with HDL-C levels. In contrast to our results, Er et al. [36] found that chemerin levels were negatively correlated with HDL-C plasma levels in MetS patients.

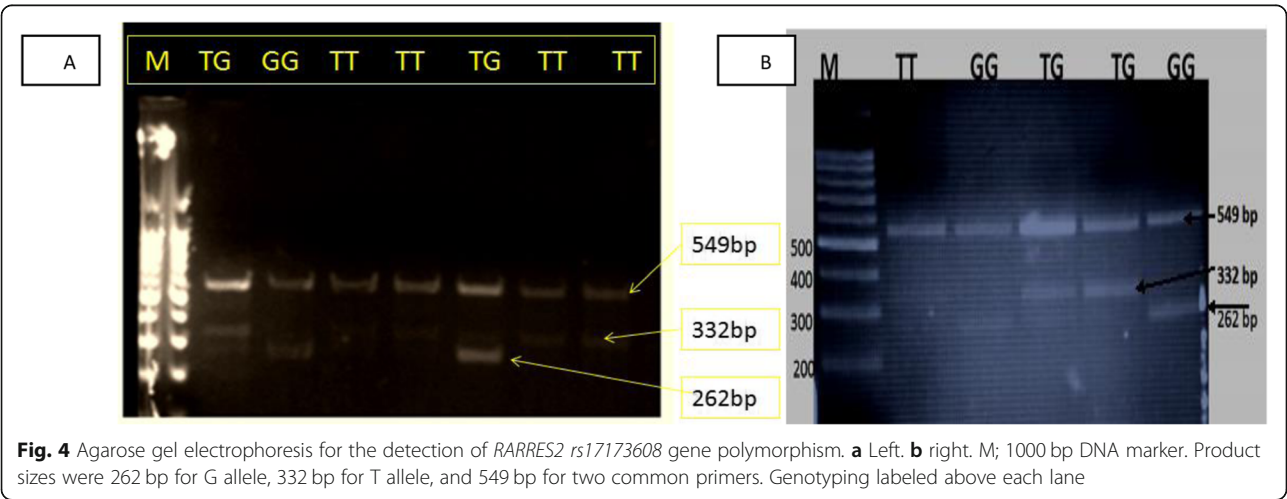
In the current study, there was positive correlation between serum chemerin and glycated hemoglobin (HbA1c) in the MetS group. Furthermore, our results showed significantly higher serum chemerin values in the diabetic subgroup compared to the non-diabetic subgroup. Chemerin levels were found to be markedly increased in newly diagnosed T2DM patients. These findings were supported as well by the results of Cheon et al. [37], Yang et al. [38], and Vasilenko et al. [39]; they confirmed different actions of chemerin in the sensitivity





of tissues to insulin. Against our results, a number of previous studies claimed that the chemerin serum levels did not show a significant difference between healthy control, pre diabetics, and diabetics [40, 41].

The role of chemerin in the pathogenesis of hypertension is not fully elucidated. Serum chemerin levels tend to be high in hypertensive patients with MetS; the present results showed a positive correlation between chemerin and mean values of SBP in the MetS group that was lost in regression analysis. This is in accordance with Jialal et al. [42], Wang et al. [28], and Dong et al. [43] who reported weak positive correlations between blood pressure and chemerin levels in T2DM subjects with hypertension and in patients with MetS. Other studies such as Gu et al. [32], Hah et al. [44], and Shin et al. [45] documented that subjects with hypertension



**Table 4** Genotyping and allelic frequencies distribution of *RARRES2 rs17173608* gene polymorphism between controls (non-MetS) and metabolic syndrome (MetS) group, and between T2DM and non-diabetics patients

Genotype	Non-MetS group (n = 68) (%)	MetS group (n = 100) (%)	OR	95% CI	p value	Non-diabetics (84)	T2DM (n = 84)	Odds ratio	95% CI	p value
TT*	38 (55.88%)	36 (36.0%)	<b>Ref</b>	<b>Ref</b>	<b>Ref</b>	28 (33.33%)	51 (60.71%)	<b>Ref</b>	<b>Ref</b>	<b>Ref</b>
TG	22 (32.36%)	32 (32.0%)	1.5354	0.75 to 3.12	0.2358	24 (28.57%)	25 (29.76%)	0.58	0.28 to 1.18	0.131
GG	8 (11.8%)	32 (32.0%)	4.2222	1.7185 to 10.374	<b>0.0017</b>	32 (38.1%)	8 (9.52%)	0.137	0.055 to 0.338	<b>0.0001</b>
Recessive TT + TG	60 (88.23%)	68 (68%)	3.5294	1.5101 to 8.249	<b>0.00364</b>	52 (61.9%)	76 (90.47%)	0.171	0.0730 to 0.4007	<b>0.0001</b>
GG	8 (11.76%)	32 (32%)				32 (38.1%)	8 (9.52%)			
Dominant TT	38 (55.88%)	36 (36%)	0.4441	0.2367 to 0.833	<b>0.00141</b>	28 (33.33%)	51 (60.71%)	0.323	0.172 to 0.608	<b>0.0005</b>
TG + GG	30	64 (64%)				56 (66.67%)	33 (39.3%)			
Additive TT	38 (55.88%)	36 (36%)	4.2222	1.7185 to 10.374	<b>0.0017</b>	28 (33.33%)	51 (60.71%)	0.137	0.055 to 0.338	<b>0.0001</b>
GG	8 (11.76%)	32 (32%)				32 (38.1%)	8 (9.52%)			
Alleles T*	98 (72.06)	104 (52%)	2.3806	<b>1.4937 to 3.7941</b>	<b>0.0003</b>	80 (47.62%)	127 (7%5.6)	0.293	0.1845 to 0.467	<b>0.000</b>
G	38 (27.94)	96 (48%)				88 (52.38%)	41 (24.4%)			

Data are represented as numbers and percentages.  $p < 0.05$  is considered to be significant

Numbers in bold indicated significant values

OR odds ratio, CI confidence interval

had significantly higher chemerin serum levels. This association was explained by Neves et al. [46] who documented that chemerin is responsible for vascular remodeling as it is expressed in the vascular endothelium and smooth muscles. Also, Kennedy et al. [47] added that chemerin may provoke vasoconstriction through chemokine-like receptor-1.

In this present study, we also assessed the associations of traditional and non-traditional lipid parameters with the risk of MetS. Non-traditional lipid parameters were associated significantly with the risk of MetS in a better manner than traditional lipids parameters; they correlated significantly with criteria of MetS (waist circumference, FBG, and HbA1c). So, we suggested that non-traditional lipid parameters may be better indices than traditional lipid profile, especially in MetS and diabetic patients. Our findings confirm and encourage their use in assessing the risk of T2DM and MetS in recent studies.

In the current study, we tried to investigate the possible interplay and associations among the circulating cell signaling molecule of adipose tissue, chemerin, and *RARRES2 rs17173608* gene polymorphism with the risk of MetS and T2DM in a sample of upper Egyptian population. We present in this study a novel finding of an association between *RARRES2 rs17173608* SNP G allele and decreased risk of T2DM. We also confirm the previous results of increased risk of MetS.

Our current results showed that the *RARRES2 rs17173608* GG genotype and G allele were more distributed in MetS and were associated with increased risk for MetS. The GG genotype also showed a significant association with age, higher BMI, and LDL-C levels in comparison with TT and TG genotypes. The G allele also showed significant association with the age and higher BMI values. Mehanna et al. [19] also found higher G allele frequency in the MetS group. Our results are in accordance with a previous study by Hashemi et al. [18] that documented that G allele of *RARRES2 rs17173608* was associated with about two times risk susceptibility of MetS when compared to T allele in their cohort study. Movahed et al. [22] also indicated that the effect of *RARRES2 rs17173608* gene polymorphism on polycystic ovary syndrome was through obesity and in association with BMI.

Striking results obtained with testing the distribution of *RARRES2 rs17173608* SNP between T2DM subgroup and non-diabetics, GG genotype, and G allele might have a protective role towards risk of T2DM, whereas the homozygous variant GG genotype and the G allele were more distributed in the non-diabetic subgroup. Testing the recessive model of inheritance (GG vs TT + TG) ensured the distribution of *RARRES2 rs17173608* G allele in the non-diabetic subgroup. Interestingly, the homozygous TT genotype was more distributed in the T2DM in comparison with non-diabetics; this result could be explained by

**Table 5** Comparison between genotypes of *RARRES2 rs17173608* gene polymorphism according to demographic characters, criteria of MetS, and chemerin level in the MetS group ( $n = 100$ )

Variables	TT ( $n,36$ )		GG ( $n, 32$ )		TG ( $n, 32$ )		ANOVA	$p$ value
	Mean	$\pm$ SD	Mean	$\pm$ SD	Mean	$\pm$ SD		
Age (year)	51.56	15.52	37.63 <sup>#</sup>	11.07	41.50	12.79	4.97	<b>0.011</b>
BMI (weight kg/height m <sup>2</sup> )	35.85	3.41	<b>40.91<sup>#§</sup></b>	6.78	35.71	4.25	5.803	<b>0.006</b>
Waist (cm)	103.44	13.36	110.00	17.84	102.88	13.07	1.154	0.324
SBP (mmHg)	129.44	22.55	122.50	8.56	118.75	14.08	1.863	0.166
DBP (mmHg)	84.44	11.74	78.13	3.59	83.75	8.85	2.499	0.093
Chemerin (ng/ml)	<b>437.00</b>	132.10	228.88 <sup>#§</sup>	48.08	387.75	204.49	9.627	<b>&lt; 0.001</b>
FBG (mg/dl)	177.98	82.68	136.64	46.38	183.14	83.32	1.960	0.152
HbA1C (%)	9.47	3.69	6.15 <sup>#</sup>	1.86	7.90	2.89	5.351	0.008
TC (mg/dl)	203.90	54.59	233.65	49.99	191.86	42.64	3.028	0.058
TG (mg/dl)	212.30	78.52	151.79	27.37	206.50	109.56	2.905	0.065
HDL-C (mg/dl)	50.00	42.07	38.26	17.86	28.63	15.78	2.374	0.104
LDL-C (mg/dl)	113.52	82.69	<b>164.75</b>	37.27	120.78	57.86	3.177	<b>0.049</b>
VLDL (mg/dl)	40.61	17.30	30.64	5.32	46.80	35.92	2.014	0.145
Total lipid	620.33	135.15	619.09	110.87	594.56	142.47	0.203	0.817
TC/HDL-C	13.79	22.37	6.93	2.13	13.22	18.60	0.812	0.450
TG/HDL-C	18.25	36.29	4.68	1.73	13.32	16.03	1.417	0.253
LDL/HDL-C	9.17	15.17	4.99	1.87	9.39	15.77	0.611	0.547
Non HDL-C (TC-HDL-C)	153.90	85.14	195.39	38.05	163.24	45.64	2.095	0.134

The parametric one-way analysis of variance (ANOVA) followed by post hoc test was used to compare between the three genotypes of *RARRES2 rs17173608* polymorphism and all parameters. Data are represented as mean  $\pm$  SD.  $p < 0.05$  is considered to be a significant value

<sup>#</sup> $p$  value for comparison between GG vs TT

<sup>§</sup>Significant  $p$  value for comparison between GG vs TG

the association of this TT genotyping with the higher chemerin levels. Our results agreed with Olt et al. [40], who also found that TT genotype ratio was higher in the T2DM subjects and the G allele frequency in the T2DM group was lower than in the healthy control group.

Reports that discussed the influence of *RARRES2 rs17173608* on its serum level are few. The *RARRES2 rs17173608* SNP has a site on intron-2 which gives high chance for arising of mutation [17]. Interestingly, in our study, the TT genotype was associated with significantly higher serum chemerin levels compared to the GG and TG genotype ( $p < 0.001$ ); also, it was more distributed in T2DM in comparison with non-diabetics. The T allele also in the current study was associated with higher serum chemerin levels and higher glycated hemoglobin levels; this may point to its association with T2DM. A previous study by Er et al. [36] in the Taiwanese population reported that *RARRES2 rs17173608* was not associated with serum chemerin levels; this controversy may be due to different ethnicity.

## Conclusions

The findings of our present study underline the indispensable role of the adipokine chemerin in the pathogenesis of T2DM and MetS. Our results showed that novel

adipokine chemerin may be a mediator linking the association of MetS, T2DM, and obesity, as serum chemerin levels were significantly higher in MetS than in subjects without MetS, diabetics than non-diabetics, and in overweight subjects compared to lean subjects. The *RARRES2 rs17173608* SNP might have an impact on chemerin levels, BMI, and lipid parameters. The G allele and GG genotype frequency distribution in dominant, recessive, and additive models of inheritance showed a significant association and increased risk of MetS. In this current study, TT genotype showed a significant association with higher serum chemerin levels and higher glycated hemoglobin levels; this may point to the increased distribution of TT genotype in the T2DM in comparison with non-diabetics. Our study to the best of our knowledge is the first Egyptian study that demonstrated that *RARRES2 rs17173608* GG genotype and G allele frequency in T2DM subgroup were lower than in non-diabetics; the GG genotype and G allele might have a protective role towards the risk of T2DM, yet further studies with a large sample size are needed and recommended to confirm these results.

## Abbreviations

DM: Diabetes mellitus; eGFR: Estimated glomerular filtration rate; FBG: Fasting blood glucose; HbA1c: Glycated hemoglobin; HDL-C: High-density

lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; MetS: Metabolic syndrome; SNP: Single nucleotide polymorphism; T2DM: Type 2 diabetes mellitus; TG: Triglycerides; TC: Total cholesterol; WC: Waist circumference

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#### Authors' contributions

MD was involved in protocol development, researched the literature, and conceived the study and laboratory work, then helped and revised the statistical work and results, and wrote the first draft of the manuscript. GE conceived the study and was involved in the laboratory work and revised the statistical work and results. MA and NA helped in gaining ethical approval and patient recruitment. All of the authors help in data analysis. All authors reviewed and edited the manuscript and approved the final version of this manuscript.

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#### Availability of data and materials

All related data and materials are available on request.

#### Ethics approval and consent to participate

The study protocol was reviewed and approved by the Authors Institution Medical Ethics Committee (registered as IRB no: IRB17200157) and in accordance with the Helsinki declaration (1975); a written consent for participation in the study was obtained from all included subjects.

#### Consent for publication

Not applicable

#### Competing interests

The authors report no competing interests.

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