

Correlation of serum chitinase-3-like protein 1 level with cardiovascular complications in Egyptian patients with type 2 diabetes mellitus

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Background/aim

Diabetes mellitus (DM) represents a strong as well as independent risk factor toward cardiovascular diseases (CVDs), considered to be the primary reason for morbidity and mortality linked to type 2 diabetes mellitus (T2DM). DM may alter the production of many inflammatory cytokines, including chitinase-3-like protein 1 (CHI3L1). The present study aims to evaluate the correlation of serum level of CHI3L1 with cardiovascular complications in Egyptian patients with T2DM.

Participants and methods

A total of 90 participants were enrolled in this case–control study (age range 40–70 years). They were divided into three groups: Group 1, which included 30 T2DM patients with CVDs; group 2, which included 30 T2DM patients without CVDs; and group 3, which included 30 individuals as a control group. Comparison of groups in terms of demographic, laboratory, echocardiography, carotid intima-media thickness, and serum CHI3L1 levels was carried out for all participants.

Results

CHI3L1 was statistically found to be highly statistically significant in group 1 over group 2 ($P < 0.001$) and in group 2 over group 3 ($P < 0.001$). CHI3L1 was positively correlated with the duration of DM ($r = 0.009$; $P = 0.049$), triglyceride ($r = 0.866$; $P = 0.001$), low-density lipoprotein cholesterol ($r = 0.950$; $P = 0.001$) and albumin/creatinine ratio ($r = 0.386$; $P = 0.002$), while a negative correlation existed with high-density lipoprotein cholesterol. ($r = -0.408$; $P = 0.024$). On drawing an receiver operating characteristics curve between groups 1 and 2, the CHI3L1 cutoff point was less than or equal to $67.38 \mu\text{g/l}$, and the area under the curve was 0.9193 ($P = 0.001$) with 100% specificity and 60% sensitivity.

Conclusions

CHI3L1 has better specificity and positive predictive value in the differentiation between T2DM patients with cardiovascular complications and those without cardiovascular complications, which may add a new diagnostic biomarker for early detection of CV complications, proposing new efficient therapies for such patients.

Keywords:

cardiovascular diseases, chitinase-3-like-1, diabetes mellitus

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Introduction

Diabetes mellitus (DM) globally represents a widespread noncommunicable disease and is the fourth to fifth primary reason for death, particularly in developed countries [1]. A strong biological association exists between DM and cardiovascular diseases (CVDs), and several studies have shown that DM patients are more often vulnerable to myocardial infarction as well as stroke over those without DM [2]. Patients with type 2 diabetes mellitus (T2DM) usually have similar risk factors for CVDs, such as hyperglycemia, abnormal lipid profiles, changed inflammatory mediators, and coagulation/thrombolytic parameters, in addition to other nontraditional risk factors, where most of them show a potential close relation to insulin resistance (IR) [3]. New noninvasive diagnostic tools for early detection of

complications of CV in such patients and new efficient treatments are increasingly required nowadays.

Chitinase-3-like-1 (CHI3L1), an inflammatory biomarker, also referred to as YKL-40, is a chitin-binding glycoprotein that belongs to the chitinase protein family without having chitinase activity. Many cells, including local inflamed tissues, express and secrete CHI3L as adipose tissue in T2DM [4]. The abbreviated form YKL-40 is established using one-letter codes originating from the first three N-terminal amino

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acids, namely, tyrosine (Y), lysine (K), and leucine (L), whereas 40 refers to its molecular weight [5]. Numerous studies have shown an increase in CHI3L1 levels in the case of IR and obesity, in addition to other pathological conditions, including coronary artery disease, acute ischemic stroke, atherosclerosis, diabetic nephropathy, and retinopathy [6].

Low-grade inflammation as well as activation of the innate immune system serve a function in the common pathogenesis of IR in addition to endothelial dysfunction, accompanied by type 2 diabetes as well as development of atherosclerosis [7]. Vascular endothelial dysfunction is a significant factor in diabetic the pathogenesis of micro- and macroangiopathy [8]. CHI3L1 was found to serve a function in endothelial dysfunction in terms of cell migration, reorganization, and tissue remodeling through atherogenesis. It causes chemotaxis promotion, cell attachment, and distribution, in addition to vascular endothelial cells migration, enhancing the formation of atherosclerotic plaque [5]. It also shows modulation for vascular endothelial cell morphology by developing branching tubules, revealing a function in angiogenesis through stimulated migration and reorganization for vascular smooth muscle cells. In addition, it can be obtained through the production as well as secretion of monocytes when differentiated to macrophages in addition to secretion by means of activated macrophages. Substantial evidence suggests that it is involved in differentiation of monocytes and activation of macrophages, exemplifying a role of endothelial dysfunction in early stages of atherosclerosis, and appears to have pathogenic significance in low-grade inflammation, preceding CVD development [9].

The aim of the present study was to evaluate the correlation of serum level of CHI3L1 with cardiovascular complications in Egyptian patients with T2DM.

Participants and methods

Patients

This case-control study was carried out on 90 participants, recruited from the inpatient and outpatient clinics in Al-Zahraa University Hospital Cairo, Egypt, from June 2017 to May 2019.

Ethical consideration

The present study was carried out according to the principles laid out in the Declaration of Helsinki. This study has been approved by the Ethics Committee of

the Faculty of Medicine for Girls, Al-Azhar University, with approval number 20/202619; a written informed consent was obtained from each participant before their inclusion in the study.

Study design

A total of 90 participants (59 females and 31 males) were enrolled in this study, age ranged 40–70 years; they were divided into three groups:

- (1) Group 1: 30 T2DM patients with CVD complications.
- (2) Group 2: 30 T2DM patients without clinically evident CVD complications. T2DM patients diagnosed based on the criteria of the American Diabetes Association [10].
- (3) Group 3: 30 individuals, apparently healthy, age and sex matched, served as the control group.

Exclusion criteria: T1DM patients, critically ill patients and patients with a known history of inflammatory and autoimmune diseases, malignancies, liver cirrhosis, and renal impairment were excluded from the study.

Methods

The participants in this study were all subjected to a full assessment of medical history, such as duration of DM, history of smoking, hypertension, dyslipidemia, current medications, and other comorbidities. Anthropometric measurements, such as BMI determined from weight in kilograms/height in square meters (m^2), in addition to waist circumference (WC), measured as the midpoint between the lowest rib as well as the iliac crest, were determined. Hypertension was confirmed by systolic blood pressure (SBP) greater than or equal to 140 mmHg and/or diastolic blood pressure (DBP) greater than or equal to 90 mmHg and/or current medication in the form of BP-lowering drug(s) prescribed for the treatment of high BP.

Carotid intima-media thickness (CMT) measurement was performed utilizing a high-resolution ultrasonographic scanner equipped with a 10-MHz linear-array transducer. The examination of the participants was conducted in the supine position, with the head somewhat hyperextended and turned away from the scanned side at 30–45°. Measurement of CMT was performed at the far wall of the right as well as left common carotid arteries 10–20 mm proximal to the carotid bulb. Measurements were performed on each side, and the mean CMT was reported.

Blood sampling and biochemical analysis

From all participants, 8 ml of venous blood was withdrawn, followed by division into three sample tubes after 12–14 h of overnight fasting: two for serum and the third in an EDTA tube. First, 4 ml in a serum separator tube for blood chemistry was left to clot. Serum was subjected to rapid separation using centrifugation (3000 rpm, 10 min). Serum was examined for fasting blood glucose (FBS) by the glucose oxidase method in addition to lipid profile by standard enzymatic procedures [total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-c), and low-density lipoprotein cholesterol (LDL-c)] using a Cobas 6000 supplied by Roche Diagnostics (Mannheim, Germany). HDL-c was assessed by the direct assay method [11], and Friedewald's formula was used to estimate LDL-c [12]. The second 2 ml in a separate EDTA vacutainer was used for HbA1c analysis by HPLC-high performance liquid chromatography-Biorad Variant II Turbo (Biorad Medical Diagnostics, Santa Rosa, CA, USA) [13]. The last 2 ml in serum separator tube was left to clot, and serum separation was performed by centrifugation (3000 rpm, 15 min). At -80°C , serum was stored until analysis of fasting insulin using a commercially available enzyme-linked immunosorbent assay technique according to the manufacturer's guidelines (DRG International Inc., Springfield, New Jersey, United States) [14]. CHI3L1 level was determined using the Sandwich Enzyme-Linked Immunosorbent Assay for the quantitative detection of Human YKL-40 Concentrations in serum (catalog # MBS824919; My BioSource Inc., USA). Assessment of IR index was performed using homeostatic model assessment (HOMA-IR) as follows: $\text{HOMA-IR} = \text{fasting plasma insulin } (\mu\text{U/mL}) \times \text{fasting plasma glucose (mg/dl)} / 405$ [15].

Urine sample and biochemical analysis

A random urine sample was collected in a sterile cup to measure microalbumin and creatinine in urine and calculate the microalbumin/creatinine (A/C) ratio using the Cobas 6000 supplied by Roche Diagnostics (Mannheim, Germany) [16].

Statistical analysis

Data analysis was carried out using the IBM program SPSS 20.0 Package (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean $\pm$ SD and compared using a *t*-test when normally distributed, and as median and range using the Mann–Whitney *U*-test when not normally distributed. Categorical data were represented as frequencies (%). The differences in frequencies of categorical parameters

were analyzed using the χ^2 test. Correlations were determined using Pearson's correlation coefficient test (*r*) or Spearman's coefficient. *P* values less than 0.05 were considered statistically significant. Standard diagnostic indices including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic efficacy were calculated. An receiver operating characteristics (ROC) curve was constructed, with area under the curve (AUC) analysis carried out to detect the best cutoff value of CHI3L1.

Results

The present study was carried out on 90 participants (30 T2DM patients with CVD complications, 30 T2DM patients without clinically evident CVD complications and 30 individuals who served as the control group). There were 59 females (65.6%) and 31 males (34.4%). Among males, 22 (71%) were smokers and nine (29%) were nonsmokers.

Demographic and laboratory characteristics of all studied groups are presented in Table 1. In terms of age, a statistically significant difference was observed in group 1 versus group 2 and group 2 versus group 3 ($P < 0.05$). BMI was statistically significantly higher in group 1 than group 3 ($P = 0.002$). WC showed a significant difference in all the studied groups. SBP and DBP were statistically significant in all the studied groups, except between group 2 and group 3; no statistically significant differences were observed in terms of DBP ($P = 0.056$). Comparing FBS, HbA1c, and HOMA-IR between the three groups, a statistically significant difference was observed between all groups ($P < 0.05$). In terms of lipid profile, cholesterol showed significant difference among all the studied groups, but TG and LDL-c were statistically significantly higher in group 1 than groups 2 and 3 ($P = 0.043$, 0.003 , 0.003 , and 0.001 , respectively), with no statistically significant differences between all groups in HDL-c ($P > 0.05$). The A/C ratio was significantly different between the three groups ($P < 0.05$). In terms of the CHI3L1 level, there was a highly statistically significant difference between all the studied groups ($P < 0.01$).

Comparison of serum CHI3L1 level between males and females showed no statistically significant difference ($P = 0.476$), as shown in Table 2.

In terms of echocardiography characteristics in T2DM patients with CVD complications (group 1), hypokinetic wall was the most common finding (13 patients), 11 patients had left ventricular hypertrophy

Table 1 Comparison between all the studied groups in terms of demographic and laboratory characteristics

Parameters	Group 1: T2DM with CVD	Group 2: T2DM without CVD	Group 3: control	P		
				P ₁	P ₂	P ₃
Age (years)	54.9±10.7	48.4±6.8	60.3±8.4	0.001*	0.770	0.016*
Sex (male/female)	10/20	9/21	12/18	0.781	0.592	0.416
BMI (kg/m ²)	37.8±7.3	35.4±8.2	33.1±3.9	0.246	0.002*	0.167
Female WC (cm)	116.2±13	112±12	101.2±14.3	0.037*	0.001*	0.016*
Male WC (cm)	116.5±11	100.2±8.2	98.9±9.1			
Systolic BP (mmHg)	141.5±27	117±19.1	110±8.3	0.001*	0.001*	0.014*
Diastolic BP (mmHg)	92.5±9	78.7±7.9	74±5.2	0.001*	0.001*	0.056
FBS (mg/dl)	217.6±73.5	160±70.2	86.7±6.6	0.003*	0.001*	0.001*
HbA1c (%)	8.69±1.7	7.17±1.8	4.38±0.4	0.009*	0.001*	0.001*
Fasting insulin (pmol/l)	10.3±6.17	7.87±3.07	3.64±0.99	0.001*	0.001*	0.001*
HOMA-IR	5.53±2.1	3.1±2.6	0.77±0.21	0.002*	0.001*	0.015*
Cholesterol (mg/dl)	209±40	175.5±29	124±34	0.001*	0.001*	0.001*
TG (mg/dl)	195±66	150±59	133±23	0.043*	0.003*	0.133
LDL-c (mg/dl)	136±38	110±26	97±35	0.003*	0.001*	0.110
HDL-c (mg/dl)	41±12	42±15	61±11	0.565	0.209	0.299
A/C ratio	521±231.6	121±111	21±3.9	0.001*	0.001*	0.001*
Chitinase-3-like-1 (μg/l)	119.96±24	62.96±35.8	33.69±13.7	0.001*	0.001*	0.001*

All data are expressed as mean±SD. A/C, albumin/creatinine ratio; BP, blood pressure; FBS, fasting blood sugar; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment; LDL-c, low-density lipoprotein cholesterol; P₁, group 1 in comparison with group 2; P₂, group 1 in comparison with group 3; P₃, group 2 in comparison with group 3; TG, triglycerides; WC, waist circumference; *Statistically significant at $P<0.05$.

Table 2 Comparison between males and females in serum chitinase-3-like-1 levels

Parameter	Males (N=31)	Females (N=59)	P
Chitinase-3-like-1 (μg/l)	69.23±61	73.91±59.36	0.4762

All data are expressed as mean±SD.

and the same number had systolic dysfunction. Also, nine patients were diagnosed with coronary heart disease, while three patients were diagnosed with old myocardial infarction. Diastolic dysfunction was found in seven patients; six of them had right-sided dilatation.

CIMT was evaluated in all studied groups. About 20 (66.66%), 29 (33.34%), and 30 (100%) patients had normal CIMT in groups 1, 2, and 3, respectively, while 10 (33.34%), 1 (3.34%), and 0 patients had abnormal CIMT in groups 1, 2, and 3, respectively (Table 3).

Comparison between right and left CIMT revealed a statistically significant difference between all groups under study ($P<0.05$) (Table 4).

ROC curve was used for defining the best cutoff value of CHI3L1 in discrimination of groups 1 and 2, which was less than or equal to 67.38 μg/l, having 100% specificity, 60% sensitivity, 99% PPV and 84.3% NPV in addition to 91.93% diagnostic accuracy, while the area under curve is (0.9193, $P=0.001$) (Fig. 1).

In T2DM patients with CVD (group 1), considering the correlation between serum CHI3L1 with demographic parameters, a statistically significant positive correlation existed with duration of diabetes ($r=0.009$; $P=0.049$), with no statistically significant correlations with age, BMI, WC, SBP and DBP ($P>0.05$). Also, considering the correlation between serum CHI3L1 with laboratory parameters, a statistically significant positive correlation was observed with TG ($r=0.866$; $P=0.001$), LDL-c ($r=0.950$; $P=0.001$), and the A/C ratio ($r=0.386$; $P=0.002$), while a statistically significant negative correlation existed for HDL-c ($r=-0.408$; $P=0.024$) without statistically significant correlations with FBS, HbA1c, HOMA-IR and cholesterol ($P>0.05$). Finally, considering the correlation between serum CHI3L1 and CIMT, no statistically significant correlations were revealed ($P>0.05$) (Table 5).

Discussion

T2DM accounts for over 90% of diabetic cases worldwide, adversely affecting patients' prognosis due to a marked increase in hospitalization and mortality rates [17]. CVDs are considered to be a primary reason for T2DM-related morbidity and mortality [18]. While common risk factors for CVDs in addition to T2DM, including resistance to insulin, obesity, dyslipidemia, thrombophilia, and inflammation, can be detected in most affected patients, it is less understood how they affect both

Table 3 Normal and abnormal carotid intima-media thickness (CIMT) in all studied groups

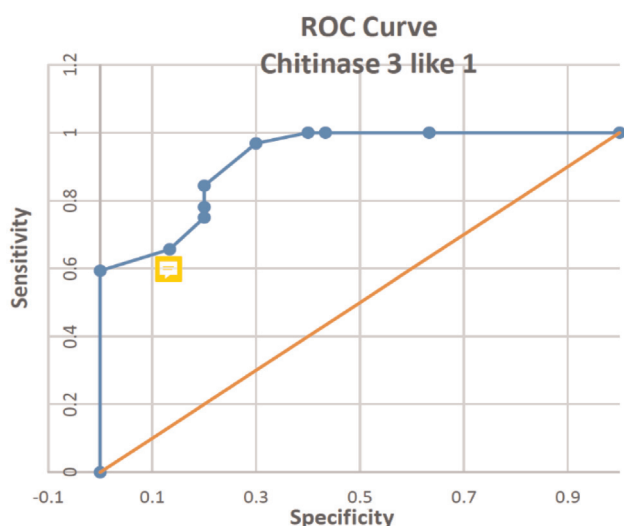
CIMT	Group 1: T2DM with CVD [n (%)]	Group 2: T2DM without CVD [n (%)]	Group 3: control [n (%)]
Normal CIMT (mm)	20 (66.6)	29 (96.66)	30 (100)
Abnormal CIMT (mm)	10 (33.34)	1 (3.34)	0 (0)

Categorical data are represented as frequencies (%) analyzed by the χ^2 test. CIMT, carotid intima-media thickness; CVD, cardiovascular disease; T2DM, type 2 diabetes mellitus.

Table 4 Comparison between all studied groups in right and left carotid intima-media thickness (CIMT)

Parameters	Group 1: T2DM with CVD	Group 2: T2DM without CVD	Group 3: control	P		
	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	P ₁	P ₂	P ₃
Right CIMT (mm)	0.932 $\pm$ 0.149	0.708 $\pm$ 0.130	0.612 $\pm$ 0.063	0.001*	0.001*	0.001*
Left CIMT (mm)	0.925 $\pm$ 0.215	0.673 $\pm$ 0.139	0.602 $\pm$ 0.069	0.001*	0.001*	0.016*

CVD, cardiovascular disease; T2DM, type 2 diabetes mellitus; P₁, group 1 in comparison with group 2; P₂, group 1 in comparison with group 3; P₃, group 2 in comparison with group 3. *Statistically significant at P<0.05.

Figure 1

Receiver operating characteristics curve.

conditions. As a consequence, efforts to better understand this correlation are required [19]. CHI3L1, an evolving biomarker included in endothelial dysfunction and inflammatory reactions, serves a significant function for DM in terms of development as well as complications [6].

In the current study, among the demographic and laboratory characteristics of all the studied groups, BMI showed high statistical significance and the highest value in group 1 (37.76 $\pm$ 7.3 kg/m²) over group 3 (33.08 $\pm$ 3.9 kg/m²) (P=0.002). Obesity-related T2DM represents 90–95% of diabetes in adults. Indeed, diabetes and resistance to insulin are found to be efficient predictors of cardiovascular morbidity as well as mortality, and in the case of patients with heart failure, they are independently considered risk factors for death [20]. Men as well as women with WCs above 102 and 88 cm,

Table 5 Correlation between serum chitinase-3-like-1 with demographic, laboratory, and CIMT parameters in the group of T2DM with CVD

Parameters	Chitinase-3-like-1	
	r	P
Age (year)	-0.021	0.435
Duration of DM	0.009	0.049*
BMI (kg/m ²)	-0.031	0.738
WC (cm)	0.080	0.069
Systolic BP (mmHg)	-0.031	0.737
Diastolic BP (mmHg)	-0.008	0.396
FBS (mg/dl)	-0.029	0.696
HbA1c (%)	0.008	0.272
Cholesterol (mg/dl)	-0.003	0.349
TG (mg/dl)	0.8663	0.001*
LDL-c (mg/dl)	0.950	0.001*
HDL-c (mg/dl)	-0.408	0.024*
A/C ratio	0.386	0.002*
HOMA-IR	-0.032	0.801
Right CIMT	-0.035	0.980
Left CIMT	-0.032	0.759

A/C, albumin/creatinine ratio; BP, blood pressure; CIMT, carotid intima-media thickness; CVD, cardiovascular disease; DM, diabetes mellitus; FBS, fasting blood sugar; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment; LDL-c, low-density lipoprotein cholesterol; T2DM, type 2 diabetes mellitus; TG, triglycerides; WC, waist circumference; *Significant at P<0.05.

respectively, are more vulnerable to cardiometabolic disease [21]. A statistically significant difference existed in WC in all studied groups, and the highest value was found in group 1. In agreement with our results, Maharana *et al.* [22], in their prospective observational study of cardiovascular risk assessment in T2DM patients, concluded that the visceral adiposity index and WC led to a considerably high risk of cardiovascular risk. In addition, elevated blood pressure was found to be a primary risk factor for CVD. Combined hypertension and diabetes in patients give rise to double the risk of developing CVD [23]. SBP

and DBP were statistically significant in all studied groups, except between group 2 and group 3, in which no statistically significant differences were identified for DBP ($P=0.056$). Only group 1 was hypertensive, and similar results were noted by Tamba *et al.* in Cameroon [24]. In disagreement with our results, Yeluri and Dharma [25] reported an insignificant difference in SBP in diabetic patients with no complications and diabetic patients with complications compared with healthy individuals.

HbA1c is an important indicator of long-term glycemic control. The HOMA index is extensively utilized to assess IR as a valid surrogate of the hyperinsulinemic-euglycemic clamp, the gold-standard method. It has been shown to be a reliable tool to predict the risk of coronary events [26]. The current study showed that on comparing FBS, HbA1c, and HOMA-IR between the three groups, a statistically significant difference was identified ($P<0.05$). Our results were consistent with those reported in 2010 [27] in a matched cohort research on the basis of a multicenter, observational study including retrospective medical chart reviews of patients with T2DM in Europe. In contrast, in 2007, Pradhan *et al.* [28] reported that HbA1c predicts diabetes but not CVD in nondiabetic women.

Diabetic dyslipidemia comprises a triad of elevated triglycerides, reduced HDL and excess of LDL. Herein, cholesterol showed a significant difference among all the studied groups, but TG and LDL-c showed a statistically significant increase in group 1 over groups 2 and 3, without statistically significant differences between the groups in HDL-c ($P>0.05$). However, Yeluri and Dharma [25] reported that the lipid profile was deranged in T2DM with or without complications, as the serum cholesterol and triglyceride values were significantly higher in uncomplicated and complicated diabetic patients when compared with healthy individuals.

Diabetic patients with kidney disease have extremely high cardiovascular morbidity as well as mortality. The underlying mechanisms for the significant correlation between diabetic kidney disease and various types of CVD remain unclear [29]. Our data revealed that the A/C ratio showed a significant difference between the three groups ($P<0.05$). A prospective epidemiological analysis on the basis of the Heart Outcome Prevention Evaluation study demonstrated that for every 0.4 mg/mmol of upsurge in the albumin-to-creatinine ratio, the adjusted hazard ratio for major CV events increased by 5.9% [30].

In terms of CHI3L1 level, a highly statistically significant difference existed between all studied groups ($P<0.01$), with a higher level in group 1 than groups 2 and 3 (119.96 ± 24 , 62.96 ± 35.8 , and $33.69\pm13.7\mu\text{g/l}$, respectively). Our results are in agreement with Rathcke *et al.* [31], who found that the median CHI3L1 level was $\sim 77\%$ higher in CHF patients. Also, Kulkarni *et al.* [32] found a significant increase in serum levels of sCD36, PPAR- γ and CHI3L1 in Indian T2DM patients (>5 years) with hypertension compared with healthy controls ($P<0.05$). Furthermore, comparison of serum CHI3L1 level between males and females showed no statistically significant difference ($P=0.476$). In previous researches it was found that the median serum CHI3L1 in healthy individuals was $43\mu\text{g/l}$ (range: $20\text{--}184\mu\text{g/l}$; 5–95% interval, $20\text{--}124\mu\text{g/l}$); values of CHI3L1 increase with age without a difference between men and women and no circadian variability in their levels [33].

CIMT represents a surrogate measure for atherosclerosis related to cardiovascular risk factors in addition to cardiovascular outcomes [34]. In the present study, comparison between right and left CIMT revealed a statistically significant difference between all studied groups, with a higher level in group 1 than groups 2 and 3.

ROC curve has been utilized for defining the best cutoff value for CHI3L1, which was less than or equal to $67.38\mu\text{g/l}$, with 60% sensitivity, 100% specificity, 99% PPV and 84.3% NPV, with 91.93% diagnostic accuracy, while area under curve was 0.9193, $P=0.001$. In 2017, El-Attar *et al.* [35] found that the best cutoff value for CHI3L1 is 91.78 ng/ml in the ROC curve between diabetic patients without and with cardiovascular complications. The sensitivity, specificity, PPV, NPV, and efficiency were 82.81, 87.50, 96.36, 56.0, and 83.75, whereas area under the curve for CHI3L1 was 0.743 ($P=0.004$).

In T2DM patients with CVD (group 1), considering the correlation between serum CHI3L1 with demographic parameters, a statistically significant positive correlation was observed of CHI3L1 with duration of diabetes ($r=0.009$; $P=0.049$), with no statistically significant correlations with age, BMI, WC, SBP and DBP ($P>0.05$). In accordance with our results, El-Attar *et al.* [35] reported an insignificant correlation between CHI3L1 and age in T2DM patients with cardiovascular complications. Similar results were noted by Kim *et al.* [36], who assessed potential correlation of

coronary artery disease and CHI3L1 in asymptomatic T2DM patients, and they found no significant correlation between CHI3L1 and BMI. Simultaneously, a significant but weak correlation existed with SBP and DBP. However, Røndbjerg *et al.* [37], who examined CHI3L1 level in patients with T2DM with increasing albuminuria levels, found significant correlations of CHI3L1 with age and SBP. With respect to duration of diabetes, Røndbjerg *et al.* [37] found significant positive correlations of CHI3L1 with duration of diabetes. Similarly, El-Attar *et al.* [35] found a significant positive correlation between CHI3L1 and duration of DM in diabetic patients with cardiovascular complications ($r=0.371$, $P=0.009$).

Besides, on studying the correlation between serum CHI3L1 with laboratory parameters, a statistically significant positive correlation was observed of CHI3L1 with TG ($r=0.866$; $P=0.001$), LDL-c ($r=0.950$; $P=0.001$), and the A/C ratio ($r=0.386$; $P=0.002$), while a statistically significant negative correlation was observed for HDL-c ($r=-0.408$; $P=0.024$), with no statistically significant correlations with FBS, HbA1c, HOMA-IR, and cholesterol ($P>0.05$). Our results are in agreement with those of Kim *et al.* [36], who found no significant correlation between CHI3L1 and fasting insulin or HOMA-IR, with no significant correlations with LDL-c or HDL-c in diabetic patients with suspected coronary artery stenosis, while Røndbjerg *et al.* [37] found significant correlations of CHI3L1 with lipid levels, HbA1c, and HOMA-IR. Moreover, considering the A/C ratio, in agreement with our results, Røndbjerg *et al.* [37] stated that the association found between CHI3L1 and albuminuria in T1DM and T2DM could represent common determinants, including inflammation, or a causal link where inflammation results in an upsurge in CHI3L1, and subsequent generalized vascular damage revealed using albuminuria. However, El-Attar *et al.* [35] found an insignificant correlation between CHI3L1 and the albumin-to-creatinine ratio and microalbuminuria estimated glomerular filtration rate in diabetic patients with cardiovascular complications.

Finally, considering the correlation between serum CHI3L1 with CIMT, no statistically significant correlations were revealed ($P>0.05$), and our findings are not consistent with those of Bakırcı *et al.* [38], who found that CIMT was strongly correlated with serum CHI3L1 level ($r=0.694$, $P<0.001$) in their study.

Conclusion

The current study showed that the inflammatory biomarker CHI3L1 was elevated in T2DM patients than healthy individuals, and greater increase was observed in those T2DM patients with cardiovascular complications. Also, the cutoff point of CHI3L1 was less than or equal to $67.38 \mu\text{g/l}$ with a specificity of 100% and a sensitivity of 60%. It was positively correlated with the duration of DM, TG, LDL-c, and A/C ratio, while a negative correlation was observed with HDL-c, which may be a new diagnostic and noninvasive tool to early detect CV complications in diabetic patients in addition to new efficient treatments for such pathological conditions that may help to improve the quality of life for these patients. However, further prospective large-scale studies on Egyptian type 2 diabetic patients with and without CVD are needed to detect the exact role of CHI3L1 in glucose homeostasis and other diabetic complications.

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Conflicts of interest

There are no conflicts of interest.

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