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Role of chitotriosidase as inflammatory marker of endothelial dysfunction in type-2 diabetes mellitus

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Abstract
Background: The pathophysiology of diabetes mellitus (DM) has been related to the enzyme chitotriosidase (CHIT1). The increasing amount of research demonstrating that CHIT1 levels rise in pathological conditions like atherosclerosis, coronary artery disease, acute ischemic stroke, cerebrovascular dementia, nonalcoholic fatty liver disease, and osteolytic processes indicates its crucial role in the development and complications of diabetes mellitus (DM). The aim of this study is evaluation of CHIT1 serum in patients with type 2 diabetes for its role as early predictive marker for vascular complications.
Methods: On 60 type 2 DM patients, both with and without vascular problems (diabetic nephropathy and diabetic retinopathy), this prospective cohort study was done. Three groups of participants were created: Group I consisted of 20 people with recently diagnosed type 2 diabetes, Group II of 20 people with type 2 diabetes who also had vascular problems (diabetic nephropathy and/or diabetic retinopathy), and Group III of 20 people who looked to be in good condition. They completed tests in the lab, including fasting and two hours after eating, glycated haemoglobin (HbA1C), microalbuminuria, fasting serum insulin calculation of insulin resistance (HOMA-IR), and serum level of CHIT1.
Results: HDL and serum CHIT1 showed a statistically substantial negative association, indicating that higher levels of CHIT1 would be associated with higher cardiac risk. There was statistically significant positive correlation between serum CHIT 1 and FBS, 2hP.PBS, BMI, CRP, ESR, HbA1C, HOMA-IR, microalbuminuria, serum creatinine, SBP, Cholesterol, triglycerides and LDL. ROC curve analysis for CHIT1 in diagnosis of DM reveals an AUC of 0.984 using the cut-off (48.5 pg/ml) yielded a sensitivity of 100%, specificity of 92.5%, PPV of 92.5%, NPV of 100%, and an accuracy of 96%
Conclusions: Increased CHIT1 activity could be early predictive marker for vascular complications.

Keywords: Chitotriosidase, type-2 diabetes mellitus, endothelium

Introduction

High blood sugar is a symptom of a series of metabolic conditions known as diabetes mellitus that may be caused by problems with insulin production, action, or both. There are two main forms of diabetes mellitus (DM). Type 1 is caused by inadequate insulin production in the pancreas [1]. Insulin resistance, a condition where cells don't react to insulin appropriately, is where type 2 starts. A shortage of insulin may also occur as the condition progresses. Lack of exercise and excessive body weight are the main causes of type 2 diabetes [2].

The endothelium plays an essential role in preserving vascular integrity, which promotes metabolic homeostasis across the whole organ. Multiple endothelium-related dysfunctions have been related to DM. Diabetes is known to have an impact on how insulin-like growth factor-1, epidermal growth factor, or acidic fibroblast growth factor regulate the production of plasminogen activator in human endothelial cells [3]. Patients with diabetes have abnormal glycosylation of intracellular and plasma proteins, which impacts endothelial function [4].

Diabetes patients may develop diabetic nephropathy, a form of progressive kidney disease. Both type 1 and type 2 diabetics are susceptible, and risk rises with years of treating the condition as well as other risk factors including high blood pressure and a family history of kidney disease [5].

A little elevation in the amount of urine albumin is referred to microalbuminuria. Small

quantities of albumin from the kidney drain into the urine, or in other words, when the albumin permeability in the kidney's glomerulus is excessively high [6].

Chitotriosidase (CHIT1), which can only be produced by active macrophages, has been considered as a biochemical indicator of macrophage aggregation in a number of lysosomal conditions, including vascular angiopathy. Human chitinase CHIT1 belongs to the family 18 glycosyl hydrolases. It is produced as a 50-kDa protein with a hinge region, a 39-kDa catalytic domain, and a C-terminal chitin-binding domain. Although it is mostly secreted, some processing results in a 39-kDa form that builds up in lysosomes [7].

CHIT1 activity is very low and comes from the circulating polymorphonuclear cells in a healthy population. Conversely, the enzymatic activity of CHIT1 substantially increases when acute/chronic inflammatory diseases occur. Diabetes mellitus (DM) etiology has also been related to CHIT1. A growing body of research demonstrating that CHIT1 levels rise in diseases like atherosclerosis, coronary artery disease, acute ischemic stroke, cerebrovascular dementia, nonalcoholic fatty liver disease, and osteolytic processes indicates to its crucial role in the development and complications of diabetes mellitus (DM) [8].

The purpose of this study is to evaluate serum CHIT1 levels in type 2 diabetes patients in order to determine if it serves as an early indicator of vascular problems.

Patients and Methods

The internal medicine department of Tanta University Hospitals' outpatient clinics and inpatient group of 60 people with type 2 diabetes with and without vascular problems (diabetic nephropathy and diabetic retinopathy) were used for this investigation.

Every person involved in this study gave their informed permission, and the study was given the ethics committee's approval.

Any indication of cardiovascular conditions, hypertension, dyslipidemia, rheumatoid or granulomatous disorders, as well as renal, hepatic, or thyroid dysfunction, was a need for exclusion.

Three groups of participants were created: Group I consisted of 20 people with newly diagnosed type 2 diabetes, Group II of 20 people with type 2 diabetes who also had vascular problems (diabetic nephropathy and/or diabetic retinopathy), and Group III of 20 people who seemed to be in good condition.

All patients had full history taking, detailed clinical examination, and BMI calculation.

They underwent laboratory investigations including: complete blood count (CBC) using ERMA INC. (model PCE-210N) full automatic blood cell counter, fasting blood glucose and 2-hour postprandial blood glucose using INDIKO PLUS, glycated hemoglobin (HbA1C) using ADAMSTM A1C automated glycated hemoglobin analyzer (Reversed- phase cation exchange chromatography), complete lipid profile using INDIKO PLUS, CRP using INDIKO PLUS., Erythrocyte sedimentation rate (ESR) by Westergren method, Microalbuminuria using INDIKO PLUS, kidney function test (serum creatinine and blood urea) using INDIKO PLUS and fasting serum insulin & estimation of Homeostasis Model Assessment–Insulin Resistance (HOMA-IR) [9].

Specific laboratory tests

Serum level of CHIT1 was measured by ELISA technique using Human CHIT1 ELISA kit from My BioSource- Cat. No. MBS923372 (San Diego - USA).

Statistical analysis

SPSS (Version 22) was used for the processing and analysis of the data. In order to describe quantitative variables, their means, standard deviations, or median were used. The chi-square test (2) was used to compare categories of variables and to indicate them using their absolute frequencies. To confirm beliefs for use in parametric tests, Kolmogorov-Smirnov (distribution-type) and Levene (homogeneity of variances) tests were utilized. The Mann-Whitney test (U) was developed to evaluate quantitative nonparametric data across two groups. One-way ANOVA (F) and the Kruskal Wallis (KW) tests were applied to compare quantitative data across more than two groups if the data were regularly distributed. In order to find at least one group that is different from the other groups, the Fisher LSD test and pairwise comparison were carried out. The magnitude and direction of the linear connection between two continuous variables were determined using the Pearson and Spearman rank correlation coefficients. The magnitude of the linear association between a dependent variable and one or more independent variables was assessed using a linear stepwise regression analysis. In order to determine the most effective cutoff value for certain characteristics utilized in the diagnosis of health issues, receiver operating characteristic (ROC) curve analysis was employed. The diagnostic effectiveness of these parameters was assessed as area under the curve (AUC). $p<0.05$ was chosen as the limit for statistical significance.

Results

As regard gender and age, there were no substantial variations among the tested groups. In terms of body mass index (BMI), group 2 has a much higher BMI than group 3 and group 1. When compared to groups 1 and 3, group 2's systolic and diastolic blood pressure significantly increased. (Table.1)

Comparing the tested groups showed statistically substantial differences in FBS, TLC, CRP, ESR, total cholesterol, triglycerides, HDL, and LDL. The variance between the control group with no disease and each other group on Fisher LSD comparison/pairwise comparisons was substantial (patients' groups had substantially higher FBS, TLC, CRP, ESR, total cholesterol, triglycerides, and LDL levels).

Between the examined groups, there was a statistically substantial variance in HDL. In the sick groups compared to the control group and in group 2 compared to group 1, according to the Fisher LSD comparison, HDL is considerably lower. (Table.2).

Only (10%) of newly diagnosed diabetic patients have a mean HbA1C above 8.5%, while (75%) of group 2 have a mean HbA1C above 8.5%with a poor glycemic control.

Table 1: Baseline and clinical data of the study particpants

	Group 1	Group2	Group 3 Control group	χ2/F	p
	n=02	n=02	n=02		
Gender					
Female	21 (06%)	10 (50%)	10 (50%)	0.54	0.77
Male	8 (40%)	10 (50%)	10 (50%)		
Age (year)					
Mean±SD	4990±2691	6494±790	4794±2694	1961	6969
BMI					
(kg/m2): Mean±SD	1491±197	4196±696	1694±194	12946	0.001**
Age of onset of DM (year)					
Mean±SD	4996±2691	4796±94	---------	---------	----------
Duration of DM (month)					
Mean±SD	794±494	4496±1691	---------	---------a-	---------
SBP (mmHg)					
Mean±SD	21691±499	24294±794	229917±291	94941	0.001**
DBP (mmHg)					
Mean±SD	7999±194	4494±497	7496±294	41929	0.001**
Fundus examination:				---------	--------
Retinopathy	Zero (0%)	5 (25%)	----------		
Normal	20 (100%)	15(75%)			

χ^2 =Chi square test F= One-way ANOVA

Table 2: Comparison between the studied groups regarding laboratory parameters:

Parameter		Groups		Test	
	Group1	Group0	Group 3	F/KW	p
	n=20	n=20	n=20		
FBS					
(mg/dl): Range	266 – 246	216 – 126	76 – 266	6991	<0.001**
Mean±SD	24494±1497	20497±1496	4194±499		
LSD comparison	P1=69662**	P2=<0.001**	P3=<0.001**		
2h P.P BS					
(mg/dl): Range	266 – 466	206 – 496	269 – 246	4491	<0.001**
Mean±SD	16791±4794	17299±7492	21694±499		
LSD comparison	P1=69662**	P2=<0.001**	P3=<0.001**		
T. Cholesterol					
(mg/dL): Range	246 – 176	246 – 446	226 – 296	4696	<0.001**
Mean±SD	24696±4190	14099±4492	24694±1196		
LSD comparison	P1 =<0.001**	P2=<0.001**	P3=69661**		
Triglycerides					
(mg/dL): Range	266 – 146	246 – 146	06 – 246	4799	<0.001**
Mean±SD	26299±4494	24794±1992	26494±1492		
LSD comparison	P1=0.001**	P2=<0.001**	P3=<0.001**		
HDL Cholesterol					
(mg/dL): Range	46 – 61	42 – 44	46 – 66	1294	<0.001**
Mean±SD	44±691	4690±490	4499±499		
LSD comparison	P1=<0.001**	P2=<0.001**	P3=0.816		
LDL Cholesterol					
(mg/dL): Range	46 – 276	216 – 290	76 – 226	6294	<0.001**
Mean±SD	214±1999	20294±2497	91±2197		
LSD comparison	P1 =<0.001**	P2=<0.001**	P3 =<0.001**		
CRP (mg/L):	1 – 10	4.4 – 30	1 – 5	55.9	<0.001**
Range Median	5	12	2.1		
Pairwise comparison	P1 =<0.001**	P2=<0.001**	P3=0.01*		
TLC (x103/mm3):	4 – 21	491 – 24	4 – 4	494	<0.001**
Range Mean±SD	799±196	499±492	699±294		
LSD comparison	P1 =69246	P2=<0.001**	P3=0.004**		
ESR1st (mm/hr): Range	6 – 12	20 – 100	2 – 7	49.9	<0.001**
Median	9	38	5.5		
Pairwise comparison	P1 =<0.001**	P2=<0.001**	P3=0.412		

F= One Way ANOVA test , KW =Kruskal Wallis test
*$p \leq 0.05$ is statistically significant
P_1 The difference between Group 1 and group 2
P_2 the difference between group2 and group 3
P_3 The difference between group 1 and group 3

On Fisher LSD comparison, there were statistically substantial variations between the examined groups for both HbA1C and HOMA-IR, patients' groups have significantly higher HbA1C and HOMA-IR levels than control group

with significant higher level in group 2 than group 1. There was significant higher levels of Microalbuminuria, creatinine and urea in diabetic groups in comparison to group 3 (healthy control) with higher levels in group 2 than group 1 indicating deteriorating renal condition in this group. Comparison between CHIT1 levels in studied groups reveled a highly significant higher level in group 2 than both group 1 and group 3 with non-significant relation between group1 and control group (Table. 3)

Table 3: Comparison between the studied groups regarding glycemic control, renal assessment and chitotriosidase level

Parameter		Groups			Test
	Group 1	Group 2	Group 3	F	p
	n=20	n=20	n=20		
HbA1C (%): Range	097 – 9	797 – 22	494 – 696	4496	<0.001**
Mean±SD	796±6904	991±292	496±6942		
LSD comparison	P1=<0.001**	P2=<0.001**	P3=<0.001**		
HOMA-IR:	4 – 0	499 – 0	2 – 191	2696	<0.001**
Range Mean±SD	496±6902	692±6974	297±6941		
LSD comparison	P1 =69661**	P2=<0.001**	P3=<0.001**		
Microalbuminuria					
(mg/24 hour): Range	21 – 46	226 – 416	2 – 16	6199	<0.001**
Median	36	464	26		
Pairwise comparison	P1=<0.001**	P2=<0.001**	P3=0.424		
Serum Creatinine					
(mg/dL): Range	6974 – 292	2.5 – 1.8	697 – 2	49942	<0.001**
Mean±SD	6991±0.69	2.2±694	6947±6921		
LSD comparison	P1 =<0.001**	P2=<0.001**	P3=69404		
Blood urea(mg/dL): Range	16 – 44	52 – 96	27 – 16	4796	<0.001**
Mean±SD	1494±2.1	72.0±790	1694±194		
LSD comparison	P1=<0.001**	P2=<0.001**	P3=<0.001**		
Serum chitotriosidase					
(pg/ml): Range	66 – 246	266 – 416	46 – 226	449791	<0.001**
Mean±SD	4696±1694	11496±0490	0494±2790		
LSD comparison	P1 =<0.001**	P2=<0.001**	P3=69294		

F= One Way ANOVA test KW Kruskal Wallis test
*$p \leq 0.05$ is statistically significant
**$p \leq 0.001$ is statistically highly significant
P_1 The difference between Group 1 and group 2
P_2 the difference between healthy control and group 2 P_3 the difference between group 1 and healthy control group

Serum CHIT1 significantly correlated with FBS, BMI, CRP, ESR, HbA1C, HOMA-IR, microalbuminuria, serum creatinine, SBP, cholesterol, triglycerides, and LDL in a statistically significant way. HDL and serum CHIT1 indicated a substantial negative association. (Table.4)

Table 4: Relation between serum Chitotriosidase and the studied parameters in diabetic patients (Group 1& group 2)

Parameter	Serum Chitotriosidase (pg/ml)	
	Diabetic Groups	
	r	p
BMI (kg/m2)	6947	2020*
FBS (mg/dL)	6940	2020*
2h P.P BS (mg/dL)	6966	20221*
CRP (mg/L)	2042	2021*
TLC (x103/mm3)	-0.10	20530
ESR (mm/hr)	0.70	<0.001**
HbA1C (%)	2060	<0.001**
HOMA-IR	2045	20223*
Microalbuminuria (mg/24 hour)	2003	<0.001**
Serum creatinine(mg/dL)	2060	<0.001**
Blood urea (mg/dl)	2060	<0.001**
Cholesterol (mg/dL)	2050	0.001*
Tiglycerides (mg/dL)	2.42	0.21*
HDL Cholesterol (mg/dL)	-0.80	<0.001**
LDL Cholesterol (mg/dL)	2.44	0.005*
SBP (mmHg)	2003	<0.001**
DBP (mmHg)	2001	<0.001**

r =Spearman rank correlation coefficient
*$p<0.05$ is statistically significant
**$p<0.01$ is highly statistically significant

Among the factors significantly correlated with serum CHIT1 in patient with DM, When using linear stepwise regression, only the HbA1C level was substantially and independently related to it. (unstandardized β=69619, p =0.001).
ROC curve analysis for CHIT1 in diagnosis of DM reveals an AUC of 0.984 using the cutoff (48.5 pg/ml) yielded a specificity of 92.5%, sensitivity of 100%, NPV of 100%, PPV of 92.5%, and an accuracy of 96% (table.5)

Table 5: Performance of serum chitotriosidase in diagnosis of diabetes among the studied patients:

Cutoff	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy
≥48.5 Pg/ml	0.984	100%	92.5%	92.5%	100%	96%

AUC: Area under curve
PPV: Positive predictive value NPV: Negative predictive value

Discussion

Study participants with complicated diabetes had significantly higher systolic and diastolic blood pressure than those with newly diagnosed DM and healthy controls with P-Value = (0.001). Similarly, Turan *et al.* [10] declare higher both systolic and diastolic blood pressure in patients with diabetes than healthy subjects. The same was denoted by Sonmez *et al.* [8] regard SBP, despite they found non-significant result according to BBP.
Demonstrating blood glucose levels in this study, showed

high significant difference between patients and healthy subjects with a p-value less than (0.001), and complicated DM patients had significant higher levels of both FBG&2h P.PBG (76361±5862 and 51762±1867) respectively more than both newly diagnosed DM and healthy subjects with P-value less than (0.001). The results, which supported the involvement of hyperglycemia in a number of diabetic problems, were in line with those of Elmonem *et al*. [11] who examined the association between CHIT 1 activity and the risk of nephropathy in type 2 diabetes.

In this study, results showed magnificent dyslipidemia among diabetic patients, DM patients who are very complex and have a P-value below 0.001 for all (T. Cholesterol, triglycerides and LDL-C levels). In agreement with this result, Zurawska-Plaksej *et al*. [12] identified imbalance in lipid metabolism with DM patients especially among complicated patients As compared with Elmonem *et al*. [11] who reported no differences in the lipid profile except for HDL-C levels being lower in nephrotic patients than in healthy or newly diagnosed individuals.

Regarding inflammatory markers in this study, CRP, ESR and TLC showed to be significantly higher in complicated DM patients than both newly diagnosed DM and healthy subjects with p-value below 0.001. Zurawska-Plaksej *et al*. [12] results were in agreement with present study to show body of evidence of inflammation in pathogenesis, finding a way to make since with CHIT1.

In this study, glycemic control was assessed by HbA1C and HOMA-IR, suggested a variance in HOMA-IR and HbA1C across the study groups that was of statistical significance

. Patients' groups had significantly higher HbA1C and HOMA-IR levels than control group with significant higher level in complicated DM patients than newly diagnosed ones. Moreover, 75% of patients in complicated DM group had poor glycemic control with mean HbA1C more than 8.5%. This outcome coincides with that of Elmonem *et al*. [11] who rationalize nephropathy as diabetic complication to prolonged hyperglycemia based on the enormous elevation in HbA1C in his study, similar results were obtained by Sonmez *et al*. [8].

Regarding renal function assessment, there was significant higher levels of microalbuminuria, creatinine and urea in diabetic groups in comparison to healthy control. With higher levels in complicated DM patients than newly diagnosed ones (*p*-value<0.001) indicating deteriorating renal conditions among these patients. This finding coincides with studies by El-Horany *et al*. [13] who examined the relationship between oxidative stress and inflammatory indicators in diabetic nephropathy patients. Additionally, Chen *et al*. [14] discovered that difficult cases had higher levels than recently diagnosed and healthy participants.

In present study, a comparison between CHIT1 levels in studied groups reveled highly significant higher levels in complicated DM (55362±6666 pg/ml) than both newly diagnosed patients (8262±5266 pg/ml) and healthy control(6863±7166 pg/ml) with non-significant-difference-between newly diagnosed patients and control group. Turan *et al*., 2017 [10] results agreed with present study, Comparing to controls (p = 0.014) and patients with no complications (p = 0.009), we discovered a substantial rise in CHIT1 activity in patients with any type of medical condition (neuropathy, nephropathy, and retinopathy, coronary heart disease, ischemic stroke). Compared to our results, Sonmez *et al*. [8] found that patients with newly diagnosed diabetes had an increase in CHIT1 activity. They did not include participants whose ChT activity levels were lower than 10 nmol/ml/h, therefore their findings are not comparable to those from our study.

In the present study, there was a substantial positive connection between serum CHIT 1 and FBS, BMI, CRP, ESR, HbA1C, and HOMA-IR, microalbuminuria, serum creatinine, SBP, Cholesterol, triglycerides and LDL, and significant negative correlation between HDL and serum CHIT 1. These results were similar to Turan *et al*. [9] They assessed CHIT1 activity in relationship to the HbA1c level of the patient group since diabetes complications are strongly associated to the quality of glycemic management and discovered a substantial positive association between them.

In contrast, Cutaș *et al*. [15] demonstrated that was no correlation between HbA1C and CHIT1. Also, El-Horany [13] *et al*. didn't found a correlation between them. Elmonem *et al*. [11] supported our findings and observed that absence of substantial variance in CHIT1 levels between normoalbuminuric diabetic patients and non-diabetic controls in our study indicated that the enzyme levels are mainly related to the onset of glomerular insult rather than the earlier tubular phase of the disease. A positive substantial relationship between serum CHIT1 activity and CRP was found in the current investigation, which is interesting since CHIT1 has previously been believed as an inflammatory marker. It is thus possible to infer that CHIT1 activity reflects the chronic inflammatory state prevalent in type 2 diabetes [8, 16].

Only the HbA1C level was substantially independently connected with serum CHIT 1 in this study's DM patient population after completing linear stepwise regression (unstandardized =0.019, p =0.001). in agreement with our findings, Zurawska-Plaksej *et al*. [12] found that CHIT 1 activity was significantly higher in the plasma of patients with ongoing type 2 diabetes than in the control group and was positively correlated with hyperglycemia and hypertension (independent of other metabolic risk factors for diabetes progression).

The results of our investigation for CHIT1 in DM diagnosis show an AUC of 0.984 utilizing the cutoff (48.5 pg/ml), which produced a sensitivity of 100%, specificity of 92.5%, PPV of 100%, NPV of 100%, and accuracy of 96%. High effectiveness of CHIT1 supports and directs our efforts as we assess serum CHIT1 in type 2 diabetes patients for its ability to serve as an early warning indicator for vascular problems.

Conclusions

This study highlights the need for rummage predictor for endothelial dysfunction, which is a cornerstone in progression of vascular complications of T2DM. The highly significant higher level of CHIT in complicated DM patients than both newly diagnosed DM and healthy subjects and its positive correlation with inflammatory markers (CRP, TLC and ESR), HOMA-IR for insulin resistance, dyslipidemia presence as well as hyperglycemia via HbA1C; these results imply that increased CHIT1 activity could be early predictive marker for vascular complications.

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Nil

Conflict of Interest

Nil

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