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Assessment of Serum C-Peptide Level as a Risk Factor for Atherosclerosis and Myocardial Dysfunction in Egyptian Patients with Type 2 DM

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ABSTRACT

Background: C-peptide was thought to be physiologically inert until recent studies showed that it could stimulate intracellular signalling pathways in a variety of cell types[1]. In type 2 diabetes, the connection between C-peptide levels and macrovascular issues can be a good indicator of DM complications.
Aim of the study: The aim of this research was to see if the level of serum C-peptide was a risk factor for atherosclerosis and myocardial dysfunction in Egyptian type 2 diabetic patients.
Patients and Methods: A thorough clinical examination, carotid Doppler intimal thickness [CIMT], echocardiography, abdominal ultrasonography (US), blood glucose levels, HOMA IR, liver and kidney functions, complete lipid profile, and C-Peptide levels were performed on 60 patients with T2DM (the patient group) and 30 healthy individuals (the control group) in a cross-sectional comparative clinically controlled study. A comparison of the difference in C-peptide levels between patients with T2D and normal controls in the Egyptian population and its correlation with markers of atherosclerosis and myocardial dysfunction was performed.
Results: There had been a statistically significant (P <0.05) elevation in serum C-peptide levels in the T2DM group compared to the control group (mean 1.82±0.55 vs. 1.21±0.24). In the diabetic group, the correlation coefficient of C-peptide levels with various cardiovascular risk factors was statistically significant (p <0.05).
Conclusion: C-peptide has been linked to macrovascular complications such as atherosclerosis and can be used as a useful tool for the diagnosis of subclinical myocardial injury.

Keywords: *Serum c-peptide level; Atherosclerosis; Myocardial dysfunction; Type 2 DM.*

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INTRODUCTION

C-peptide was formerly dealt with as biologically inactive, but recent research has shown that it can activate intracellular signalling pathways in a variety of cell types[1]. It has been shown that binding of radioactively labelled C-peptide on the membranes of cells has binding effects that stimulate Na-K-ATPase. Similar to other hormone-like peptides like gastrin and cholecystokinin, the C-terminal pentapeptide completely replaces the whole molecule [2, 3]

When proinsulin is cleaved during insulin production, C-peptide is generated, which is a 31-amino-acid peptide. Proinsulin is made up of two chains, A and B, with a bridging peptide called C-peptide in the centre. Proinsulin is cleaved in beta pancreatic cells' endoplasmic reticulum. In addition, C-peptide is retained in Golgi secretory granules in response to glucose stimulation and co-secreted into the bloodstream with insulin at equimolar levels [2].

The impacts of the C-peptide have sparked some debate. Its favourable effects on long-term complications of T2D have been proven. For example, in T2D, substituting the C-peptide

promotes glomerular hyperfiltration, hypertrophy, as well as proteinuria. In type 2 diabetes, however, C-peptide has proinflammatory and proatherogenic effects.

According to previous studies, C-peptide can deposit in the sub-endothelial region of early lesions in people with insulin resistance and DM, enhancing the recruitment of inflammatory cells into the artery wall via its chemotactic impact. These mechanisms could be involved in lesion formation and explain why diabetic patients have a widespread and broad form of arteriosclerosis at a young age [5].

Furthermore, because of its chemotactic action on monocytes and CD4+ lymphocytes, C-peptide colocalized with vascular smooth muscle cells (VSMCs) in some patients with diabetes and improved VSMC proliferation in vitro, possibly boosting both the progression of arteriosclerotic lesions and the formation of neo-intima after coronary intervention.[5, 6]

Fasting blood C-peptide levels should be between 0.8 and 2.85 ng/mL (0.26 and 1.27 nmol/L). A level of less than 0.6 ng/mL (0.2 nmol/L) can indicate beta cell failure and type 1 diabetes. In healthy persons, blood levels rise to around 3–9 ng/mL (1–3 nmol/L or 3000–9000 pmol/L) after a meal. Postprandial C-peptide is the term for this measurement. Urine values are frequently measured during a 24-hour period. Urine values in the normal range are 14–156 ug/24h. [7]

The following conditions cause an increase in C-peptide levels: Insulinoma. Intoxication with sulfonylureas. Pancreatogenic hypoglycemia syndrome caused by non-insulinoma (NIPHS). Obesity, Cushing syndrome, and chronic renal disease are examples of insulin resistance states.

The C-peptide levels are reduced in the following ways: Diabetes mellitus type 1. Injections of exogenous insulin (factitious). Insulin-dependent hypoglycemia (hypoglycemia caused by impaired glucose mobilisation during fasting due to a defect in gluconeogenesis and/or glycogenolysis as in adrenal insufficiency and severe liver morbidities).

The aim of this research was to see if the level of serum C-peptide was a risk factor for atherosclerosis and myocardial dysfunction in Egyptian type 2 diabetic patients.

PATIENTS AND METHODS

A cross-sectional comparative clinically controlled study involved 60 patients with T2DM (the patient group) and another 30 normal healthy individuals (the control group), with both groups being age and gender matched. A comparison of the difference in C-peptide levels between patients with T2D and normal controls in the Egyptian population and its correlation with markers of atherosclerosis and myocardial dysfunction.

The study was conducted on the patients attending the Outpatient Clinic in the Internal Medicine Department at Al-Hussein University Hospital and Al Agouza Police Hospital; in a period of one year from February 2020 to February 2021.

Inclusion criteria: T2DM patients over the age of 35, both sexes included, BMI less than 30 kg/m2, and able to provide confirmed consent.

Exclusion criteria: Patients under the age of 35 with T1D, chronic liver disease, chronic renal disease, and autoimmune disorders such as sarcoidosis and systemic lupus erythematous (C-peptide levels are independently up-regulated in SLE and sarcoidosis), patients with known cardiovascular diseases, and patients who refuse to participate in the study.

Controls: Normal healthy volunteer individual's age and sex matched with the patients' group and also performed informed consent.

Complete assessment was done for each patient including:

Full history taking: Personal history. Present history: Onset and duration of the disease, its complications and treatment. Special habits. Associated diseases, and drug intake. Past history.

General Examination: (a) Cardiac examination: Blood pressure measurement, pulse heart rate, carotid Doppler intimal thickness [CIMT], electrocardiogram (ECG), and echocardiography. (b) Abdominal Examination: Abdominal Ultrasonography (US): For assessment of liver texture and presence of fatty infiltration of liver.

Laboratory investigation for both groups: Fasting and postprandial blood glucose, glycosylated hemoglobin (HBA1c), lipid profiles: LDL-Ch, HDL-Ch and triglycerides (TG), assessment fasting serum insulin levels for [HOMA-IR], fasting C-peptide level estimation, renal and liver function tests.

C-peptide level estimation:

A needle has been inserted into an arm vein to obtain a blood sample. If a 24-h urine sample is needed, all urine produced during that time will be collected.

Ethical considerations:

The study was conducted after approval of the protocol by the Local Research Committee & the Studies Committee as well as the Research Ethics Committee. Written informed consent has been acquired from each participant.

Statistical analysis:

The statistical tool SPSS version 20.0 has been employed to examine the data (SPSS Inc., Chicago,

IL, USA). The Kolmogorov–Smirnov test has been applied to see whether the variables have a normal distribution. To calculate the difference between two or more sets of qualitative variables, use the Chi square test (2). The mean and standard deviation (SD) were used to express quantitative data (Standard deviation). The independent samples t-test was used to compare two independent groups of normally distributed variables (parametric data). The differences in CCT across the three myopia groups were examined using multiple analysis of variance (ANOVA) with Bonferroni corrections (post hoc comparisons). The link between central pachymetry and the SE and the AL was investigated using linear regression, and the correlation coefficient (r) was calculated. To determine the link between the study variables, the Pearson correlation coefficient was performed. A P value of < 0.05 has been considered significant.

RESULTS

This study involved sixty patients with T2DM (group 1); there were 28 females (46.7%) and 32 males (53.3%). The ages of group (1) ranged from 35 to 50 years, with a mean ± SD of (44.6 ± 5.36) years, and we selected 30 normal, healthy individuals as a control group (2); there were 15 males (50%) and 15 females (50%). The ages of the control group (2) varied from 37 to 49 years, with an average of (44.9 ± 6.42) years.

Comparison between the two groups concerning age and sex showed a statistically insignificant difference, indicating that both groups were age and gender matched. In diabetic patients, hypertension, hyperlipidemia and smoking habit were significantly increased than normal control subjects (P <0.001) (Table 1).

The diabetes group had significantly higher total cholesterol, triglycerides, and LDL-C than the normal control group (P <0.05), while the diabetic group had significantly lower HDL-C than the normal control group (P <0.05) (Table 2).

Uric acid and creatinine were significantly elevated in the diabetes group compared to normal control subjects (P <0.05). Estimated glomerular filtration rate showed statistically significant decrease in diabetes group compared to normal control subjects (P <0.05). (Table 3).

In terms of LV systolic function parameters such as LV diameters and ejection fraction, there have been no significant differences between groups. Increase of CIMT diameter in type 2 DM group than control (mean 0.61 ± 0.21 mm vs. 0.42 ± 0.17 mm, respectively). Fatty liver values were significantly elevated in the diabetes group compared to normal control subjects (P <0.05) (Table 4).

Serum C-peptide level is elevated in type 2 DM group than control group (mean 1.82 ±0.55 vs. 1.21 ±0.24, respectively) and it is statistically significant (P <0.05) .

The diabetic group has a higher HOMA IR level than the control group, with a mean of 3.35 ± 1.09 in the diabetic group and a mean of 2.87 ± 0.7 in the control group, and this difference is statistically significant (P <0.05) (Table 5).

The C-peptide level correlation coefficient with various risk factors for cardiovascular diseases revealed a statistically significant positive association (p <0.05). These risk factors were age, duration of type 2 diabetes, glycosylated hemoglobin, BMI, WC, blood glucose level, BP, total cholesterol, triglycerides, HDL-Ch, LDL-Ch, CIMT, and HOMA-IR (Table 6, Fig 1).

Groups / Item	Group (1) (n = 60)		Group (2) (n = 30)		Significance	
Gender	No.	%	No.	%	$\chi 2$	P
Males	32	53.3	15	50.0	0.102	0.749
Females	28	46.7	15	50.0	0.164	0.870
Total	60	100	30	100		
Age (years)	Min	Max	Min	Max	T	P
Range	35	50	37	49		
Mean ± SD	44.6 ± 5.36		44.9 ± 6.42		0.058	0.924
Risk factors	No.	%	No.	%	$\chi 2$	P
Hypertension	52	86.7	4	13.3	32.65	0.000*
Hyperlipidemia	48	80.0	3	10.0	12.65	0.000*
Smoking habit	45	75.0	8	26.7	10.84	0.000*
BMI (kg/m2)	26.9 ± 3.16		24.9 ± 3.81		0.851	0.012*
WC (cm)	92.02 ± 24.49		89.72 ± 21.94		0.127	0.065

Table 1: Patients demographics and risk factors of atherosclerosis of the two studied groups. (BMI: body mass index, WC: waist circumference χ^2 = Chi square, *P <0.001 = highly significant).

Item \ Groups	Diabetic (Group 1) Mean ± SD	Control (Group 2) Mean ± SD	Significance t	P
T. cholesterol (mg/dl)	202 ± 38.5	105.9 ± 26.5	4.125	0.001*
Triglycerides (mg/dl)	155 ± 44.39	82.17 ± 25.5	0.965	0.009*
HDL-C (mg/dl)	48.0 ± 7.57	57.0 ± 18.83	-0.323	0.031*
LDL-C (mg/dl)	124 ± 63	75.0 ± 28.07	1.372	0.007*

Table 2: Lipid profile of the two studied groups. (LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol).

Item \ Groups	Diabetic (Group 1) Mean ± SD	Control (Group 2) Mean ± SD	Significance T	P
Uric acid (mg/dL)	6.05 ±1.03	5.33 ± 0.92	0.316	0.045*
Creatinine (mg/dl)	1.52 ± 0.94	1.02 ± 0.39	0.428	0.019*
eGFR (mL/min/1.73m2)	81.36 ± 16.78	92.24 ± 19.1	-0.298	0.041*

Table 3: Blood chemistry for renal function of the two studied groups.

Item \ Groups	Diabetic (Group 1) Mean ±SD	Control (Group 2) Mean ±SD	t	p
ECHO findings:				
LVESD mm	29.4 ± 2.25	28.2 ± 4.96	0.264	0.51
Ejection fraction (EF%)	65.9 ± 7.91	67.8 ± 8.15	0.717	0.26
LVEDD mm	47.3 ± 5.24	46.4 ± 6.06	1.439	0.12
Sonographic examination:				
CIMT (mm)				
• Mean ± SD	0.61 ± 0.21	0.42 ± 0.17	0.558	0.044*
• Range	0.40 – 0.76	0.33 ± 0.64		
Ultrasonography findings: Fatty liver No. (%)	48 (80%)	5 (16.7%)	16.72	0.000*

Table 4: Echocardiographic findings and sonographic examination of the carotid arteries of the studied groups. (CIMT: Carotid artery intimal media thickness measured by echocardiography. *P <0.05: significant).

C-peptide (ng/mL):				
Mean ± SD	1.82 ± 0.55	1.2 ± 0.24	0.628	0.006*
Range	1.13 – 2.48	0.78 – 1.86		
HOMA IR	Diabetic group	Control group	T	P
Mean ± SD	3.35 ± 1.09	2.87 ± 0.7	0.719	0.011*
Range	1.99 – 5.89	1.85 – 4.89		

Table 5: C- peptide and HOMA- IR levels in the studied groups.

Risk factor	Correlation (r)	P
Age (years)	0.3563	0.001*
Duration of T2D (years)	0.5191	0.000*
BMI (kg/m2)	0.4935	0.000*
WC (cm)	0.4487	0.001*
Fasting blood glucose (mg/dL)	0.4927	0.000*
Postprandial blood glucose (mg/dL)	0.5924	0.000*
Glycosylated hemoglobin (HbA1c %)	0.5076	0.000*
Systolic blood pressure (mmHg)	0.3148	0.001*
Diastolic blood pressure (mmHg)	0.2987	0.002*
Total cholesterol (mg/dL)	0.2872	0.003*
Triglycerides (mg/dL)	0.1994	0.012*
HDL-C (mg/dL)	-0.312	0.001*
LDL-C (mg/dL)	0.3659	0.001*
Carotid artery intima-media thickness (mm)	0.4357	0.001*
HOMA-IR	0.4744	0.000*

Table 6: The C-peptide level correlation coefficient with various cardiovascular risk factors in diabetic patients. (* P <0.05 = statistically significant. r: correlation coefficient).

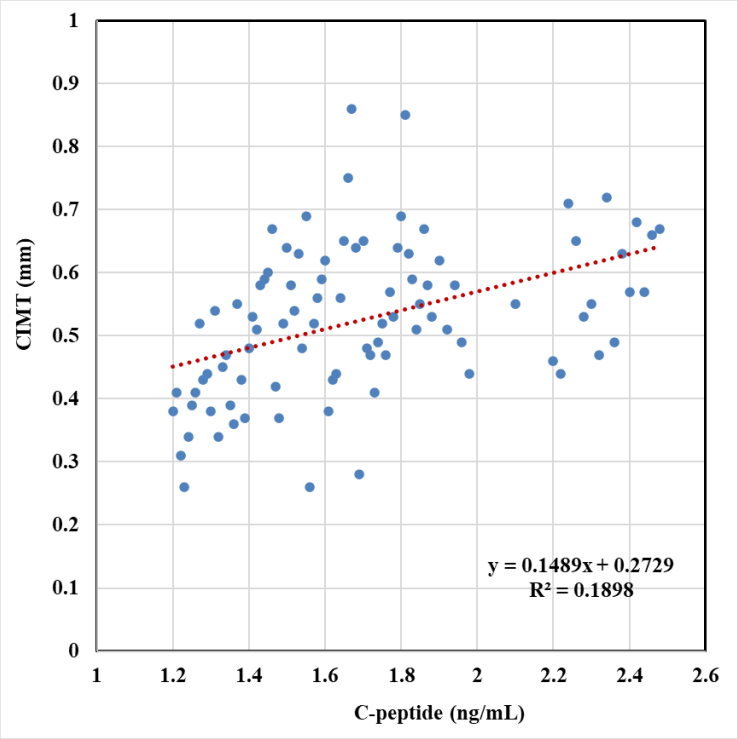

Fig 1: Correlation coefficient (r) and regression line between serum C-peptide level and carotid artery intimal media thickness (CIMT). There is a strong positive association (r = 0.43566, p <0.001)..

DISCUSSION

C-peptide was formerly C-peptide was formerly assumed to be biologically inert, but recent research has shown that it may stimulate intracellular signalling pathways in a variety of types of cells. types. The relationship between C-peptide levels and macrovascular issues in T2D can be a good indication of DM complications. In recent years, it has been discovered that this short 31-amino-acid peptide plays a function in the aetiology of atherosclerosis and may be a risk factor for CAD.

Our study involved sixty patients with T2DM (group 1); they were 28 females (46.7%) and 32 males (53.3%) and a selected 30 normal healthy individuals as a control group (2); they were 15 males (50%) and 15 females (50%). The ages of group (1) ranged from 35 to 50 years with a mean ± SD of (44.6 ± 5.36) years and the ages of group (2) varied from 37 to 49 years with an average of (44.9 ± 6.42) years.

This study showed that in diabetic patients; hypertension, hyperlipidemia, smoking habit and kidney dysfunction were significantly increased compared to normal control subjects (P <0.001). This study showed that BMI and CIMT showed a statistically significant increase in the diabetes group compared to normal control subjects (P <0.05).

In the same line with our findings, Wang et al.[8] discovered that BMI, hypertension, total cholesterol, HDL-Ch, LDL-Ch, and renal dysfunction were all statistically significant (P<0.05) in diabetics with cardiovascular problems when compared to controls. Triglycerides, SBP, DBP, and HBA1c levels, on the other hand, exhibited no significant association. In addition, smoking was statistically non-significant in the patients group (P = 0.138).

Bo et al.9 discovered no link between C-Peptide and cardiovascular death after controlling for age, sex, BMI, smoking, insulin treatment duration, glycosylated haemoglobin, systolic blood pressure, HDL-C , triglycerides, as well as prior vascular problems. Controlling for other metabolic cardiovascular risk variables, on the other hand, might have restricted causative pathways between C-Peptide and fatality, resulting in an underestimation of the relationship.

Parallel to our findings, the majority of patients in the Uzunlulu et al.[10] trial were obese, particularly abdominally obese, and had poor glycemic control.

This study showed that the mean blood glucose level and glycosylated hemoglobin showed statistically significant increase in diabetes group compared to normal control subjects (P <0.05). It also revealed that the mean total cholesterol levels, triglycerides, and LDL-C were significantly higher in the diabetes group compared to the normal control group (P <0.05), while HDL-C was significantly lower in the diabetic group compared to the normal control group (P <0.05).

In a meta-analysis of observational studies, Danesh et al.[11] found that individuals with C-reactive protein in the highest tercile had a greater chance of

cardiovascular events (OR 1.45; CI95 percent 1.25–1.68).

This study showed that the mean uric acid, was significantly elevated in the diabetes group compared to normal control subjects (P <0.05). When compared to normal control subjects, the estimated glomerular filtration rate in the diabetes group was statistically significant lower (P <0.05).

Wang et al.[8] found that eGFR and uric acid were considerably greater in the patient group compared to the controls, which is consistent with our findings.

This study shows elevation of serum C-peptide levels in type 2 DM group than control group (mean 1.82 ±0.55 vs. 1.21 ±0.24, respectively), and it is statistically significant (P <0.05).

In agreement with our study, a study by Wang et al [8]. was conducted on 539 type 2 diabetic patients. They were 47% females with an average age of 65 8 and discovered a link between C-peptide levels and cardiovascular risk. This agreed with our study, proves that the C-peptide represents a cardiovascular risk factor.

According to Cabrera et al.[12], elevated C-peptide is linked to the risk of myocardial infarction and CAD in the overall population. It may be a better predictor of heart attacks and strokes than impaired fasting glucose.

According to Marx et al. [13], blood levels of C-Peptide were linked to whole (HR 1.46 CI 95 percent 1.15–1.85) and cardiovascular (HR 1.58 CI 95 percent 1.15–2.18) mortality in individuals undergoing coronary angiography.

C-peptide, according to Patel et al.[14], has been linked to cardiovascular (HR 1.60, CI 95 percent 1.07–2.39) and total (HR 1.72, CI 95 percent 1.34–2.21) death in people with fasting glycemia less than 70 mg/dL.

In a retrospective study of 179 T2D patients who had already been detected and were receiving therapy, the average C-peptide levels have been determined to be 2.71 ng/mL, with 6.7 percent of cases having inadequate beta cell reserves (C-peptide 0.5 ng/mL), and 39.1 percent having borderline (C-peptide: 0.5-2 ng/mL) and adequate (C-peptide > 2 ng/mL) beta cell reserves. Gokhan et al. [15] observed that 81 percent of diabetics have borderline C-peptide levels (ranging from 1.44 to > 2.1ng/dL) in their study, which indicated that the mean C-peptide is 1.82 0.55.

Elevated concentrations of c-peptide were linked to a higher incidence of cardiovascular and all-cause deaths in adults without diabetes. [16,17] This is most likely due to the fact that elevated c-peptide concentrations are a sign of insulin resistance and the phenotype of metabolic syndrome. Some observational studies in T2DM have found similar results, although not all. [13, 18]

A statistically significant difference (p0.05) was found in the correlation coefficient of C-peptide levels with several cardiovascular risk variables. Age, type 2 diabetes duration, glycosylated haemoglobin, BMI, WC, BP, total cholesterol, triglycerides, HDL-Ch, LDL-Ch, and CIMT were all risk variables.

According to Uzunlulu et al.[10], C-peptide concentrations are also favorably connected with waist circumference (r: 0.282; p = 0.001), hip circumference (r: 0.251; p = 0.001), BMI (r: 0.279; p = 0.001), fasting glucose level (r: 0.309; p = 0.001), and triglyceride levels (r: 0.358; p = 0.001).

CONCLUSION

Although C-peptide was previously assumed to be biologically inactive, new research has shown that it may stimulate intracellular signalling pathways in a variety of types of cells.

It has been linked to macrovascular problems including atherosclerosis and can be utilised to diagnose subclinical myocardial damage.

In some cases, C-peptide could be used as a screening instrument to eliminate the requirement for autoantibody testing to verify or rule out the diabetes diagnosis and the necessity for insulin therapy. Although a lower c-peptide, particularly lower than 0.2 nmol/l, is a good sign of beta cell activity and can most likely anticipate insulin requirements, could values be employed to estimate the probable time until insulin is prescribed?

Conflict of interest : none

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