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Evaluating the relationship between C-peptide levels and insulin resistance in patients with and without diabetic complications

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Abstract

The precise role of C-peptide remains a subject of ongoing research, particularly in the context of type 2 diabetes mellitus (T2DM), characterized by both insulin resistance (IR) and beta cell dysfunction. This study evaluates the association between C-peptide levels and IR, insulin secretion, and beta cell function independent of other risk factors in T2DM patients with and without complications. This cross-sectional study included 91 T2DM participants with or without diabetic complications. Clinical variables, routine biochemical tests, and serum C-peptide levels were measured after overnight fasting. The levels of biomarkers (fasting insulin, C-peptide, resistin, and tumor necrosis factor alpha [TNFα]) were measured using a Randox Evidence biochip analyzer. Homeostatic model assessment (HOMA) of IR and beta-cell function was calculated using the software HOMA 2 calculator. The C-peptide index was also computed using a widely accepted formula. The mean fasting insulin ($P < .001$), homeostatic model assessment of IR ($P = .001$), homeostatic model assessment of beta cell function ($P = .002$), C-peptide index ($P < .001$), and TNFα ($P = .022$) were significantly increased with tertiles of C-peptide. Patients with diabetic retinopathy and nephropathy had significantly higher levels of C-peptide. C-peptide levels significantly increased with the number of complications ($P = .010$). The C-peptide levels were significantly associated with fasting insulin ($P < .000$), homeostatic model assessment of beta cell function ($P = .011$), C-peptide index ($P < .000$), homeostatic model assessment of IR ($P < .000$), and resistin ($P = .018$) after adjustment for confounding factors such as age, gender, diabetes duration, body mass index, systolic blood pressure, low-density lipoprotein cholesterol, HbA1c, TNFα, and antidiabetic drugs (metformin and sulfonylurea) in diabetic patients with complications. This study illustrated the clinical utility of C-peptide in microvascular complications such as diabetic nephropathy and diabetic retinopathy. Moreover, C-peptide can be used as an appropriate index for identifying IR in T2DM patients with complications.

Abbreviations: BMI = body mass index, FBS = fasting blood sugar, HDL-C = high-density lipoprotein cholesterol, HOMA-B = homeostatic model assessment of beta cell function, HOMA-IR = homeostatic model assessment of insulin resistance, IR = insulin resistance, LDL-C = low-density lipoprotein cholesterol, SBP = systolic blood pressure, T2D = type 2 diabetes, T2DM = type 2 diabetes mellitus, TNFα = tumor necrosis factor alpha.

Keywords: beta cell function, C-peptide, complications, insulin resistance, type 2 diabetes

1. Introduction

Type 2 diabetes mellitus (T2DM) is a disease of glucose metabolism characterized by elevated blood glucose levels caused by insufficient insulin secretion and insulin resistance (IR). It is a major global health concern, with an estimated 463 million adults (20–79 years) affected worldwide, and the number is projected to reach 700 million by 2045.[1] In Saudi Arabia, Al Rubeaan et al showed that the prevalence of diabetes among those aged ≥30 years was 25.4%, with 40.3% being unaware of their condition.[2] The development of IR, a hallmark of T2DM,

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

The data for this retrospective cross-sectional study were obtained from a previous cohort study (E-10-154) conducted between 2010 and 2016 and approved by the Institutional Review Board (IRB), College of Medicine, King Saud University, Saudi Arabia, in accordance with the Declaration of Helsinki.

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is attributed to a complex interplay of various pathophysiological factors, including aging, oxidative stress, inflammation, dysfunction in adipose tissue, genetic changes, etc. In addition, the development of obesity in T2DM is contributed to by IR and hyperinsulinemia.[3] Important mechanisms associated with IR, overt diabetes, and related diabetic complications have been elucidated.[4]

Human insulin is made up of 2 peptide chains that are linked together by a connecting peptide (C-peptide). C-peptide plays a crucial role in insulin biosynthesis by aiding in the proper folding of the proinsulin molecule. C-peptide levels in patients with diabetes might vary based on insulin secretory responses, type of diabetes, and duration of diabetes, ranging from normal to decreased. As diabetes progresses, C-peptide levels tend to decline due to diminished glucose response or glucose sensitivity.[5]

Clinical studies have revealed various insulin-like effects, aside from a drop in blood glucose that may be directly linked to C-peptide.[6,7] As measured by fasting C-peptide levels, residual beta-cell secretion has been related to a lower risk of microvascular complications in type 1 diabetes.[8] These findings show that C-peptide treatment may be therapeutically relevant in protecting against diabetic complications and perhaps mitigating or reversing secondary microvascular complications.[9] Indeed, individuals receiving C-peptide therapy have shown a lower risk and improvement in their diabetic nephropathy, neuropathy, and retinopathy complications.[9,10] Furthermore, some researchers speculate that C-peptide could be a part of an auto-feedback mechanism that increases the release of insulin.[11]

Studies on the association between C-peptide and diabetes complications were inconsistent.[12-15] Recently, C-peptide levels demonstrated a bidirectional relationship with cardiovascular risk in both nondiabetic persons and patients with newly diagnosed T2DM.[16] C-peptide levels were shown to be associated with the severity of peripheral atherosclerosis[17] and corneal neuropathy in patients with type 2 diabetes.[18] Moreover, postprandial C-peptide is a good predictor of diabetic retinopathy (DR).[19] Diabetic individuals with elevated blood C-peptide levels, an indicator of endogenous insulin production, may be at a higher risk of developing vascular disease.[20]

Even though C-peptide is widely accepted as a measure of beta-cell function, its potential in identifying IR is not well studied.[21] This study highlights the potential of C-peptide as an indicator of IR among type 2 diabetes patients with and without complications. Furthermore, measuring C-peptide levels in patients with long-term T2DM may help clinicians start insulin therapy to maintain good glycemic control.[22] Therefore, this study aimed to evaluate the association of C-peptide levels with IR and beta-cell function, independent of other risk factors, in patients with T2DM who were managing diabetes without insulin.

2. Materials and methods

The data for this retrospective cross-sectional study were collected from a previous study: a cohort study (E-10-154) conducted between 2010 and 2016 and approved by the Institutional Review Board (IRB), College of Medicine, King Saud University, Kingdom of Saudi Arabia, in accordance with the Declaration of Helsinki.[23,24] Study participants were recruited from the University Diabetes Centre at King Saud University Medical City. Written informed consent was obtained from each participant.

This study included both male and female participants with T2DM aged between 35 and 75 years. The duration of diabetes mellitus was more than 10 years. Participants having data available for glycemic markers (C-peptide, insulin, fasting blood sugar [FBS], and HbA1c) were included in this study. Patients receiving insulin treatment, pregnant women, those with a history of smoking, acute renal failure, pancreatic diseases affecting C-peptide levels, use of a glucocorticoid, chronic liver disease, infection, cancer, or a history of dialysis or renal transplantation were excluded from this study.

Diabetic nephropathy (DN) was identified by a glomerular filtration rate ≤ 60 mL/min/1.73m^2. Diabetic neuropathy was assessed by measuring nerve conduction velocity in the upper and lower limbs. The presence of at least 1 distinct microaneurysm in any of the fields studied was used to diagnose DR. The history of macrovascular complications was confirmed by a research physician.

Selected participants were on treatment with oral antidiabetic medications such as metformin, sulfonylurea, thiazolidinediones, and sitagliptin. Individuals were on antihypertensive medications such as AT-II-receptor antagonists, thiazide diuretics, angiotensin-converting enzyme inhibitors, beta-blockers, and calcium channel blockers. Statins are used to treat hyperlipidemia. Of the 480 T2D patients from the cohort, 320 were on insulin, and 58 did not have C-peptide findings. Additionally, 11 patients with missing data on demographic or clinical factors were excluded from the study. This study includes data from 91 patients with T2DM. Figure S1, Supplemental Digital Content 1 depicts a schematic of the study participants' flow.

2.1. Data collection

Demographic and clinical information, such as age, gender, diabetes duration, SBP, diastolic blood pressure, and body mass index (BMI), were collected.

Overnight fasting serum samples were utilized for biochemical tests, which include FBS, HbA1c, serum creatinine, and a lipid profile (triglycerides, high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], and total cholesterol). The biochemical analysis was carried out using an RX Daytona clinical chemistry analyzer (Randox Laboratories, Ltd., Crumlin, UK).

The level of serum biomarkers was analyzed using a Randox Evidence Biochip analyzer (Randox Laboratories Ltd., Crumlin, UK). Metabolic syndrome array I includes fasting insulin, C-peptide, resistin, and TNFα (Randox evidence, Catalogue No. EV3754). The C-peptide index is computed as 100 × serum C-peptide level (ng/mL)/plasma glucose level (mg/dL).[25] The HOMA 2 calculator was used to calculate IR and beta-cell function.[26] Triglyceride-glucose index (TyG index) and triglyceride-to-high-density lipoprotein cholesterol ratio (TG/HDL-C ratio) were calculated.[27]

2.2. Statistical analysis

Data analysis was carried out using the Statistical Package for the Social Sciences (SPSS) software version 21.0 (IBM Corp., Armonk). Categorical variables were described using frequencies and percentages, whereas continuous variables were expressed as mean and standard deviation (mean ± SD). The Student *t* test was used to compare diabetic individuals with and without diabetic complications. C-peptide tertiles were also computed (<0.4967, 0.4967–0.9567, and >0.9567 ng/mL) by picking cut points for 3 equal groups to measure variability, and the difference between groups was analyzed using analysis of variance (ANOVA). The Spearman correlation coefficient was used to assess the relationships between individual variables. In multiple linear regression analysis, C-peptide was used as the dependent variable, while glycemic parameters and IR indicators served as the independent variables. Various combinations of confounding variables, such as age, gender, DM duration, BMI, SBP, LDL-C, HbA1c, TNFα, and antidiabetic medications (metformin and sulfonylurea) were utilized to build multiple adjustment models. A *P*-value of ≤.05 indicates statistical significance.

3. Results

The demographic, clinical, and biochemical characteristics of patients with T2D according to the presence and absence of complications are summarized in Table 1. The number of patients categorized into each group was as follows: diabetic without complications, n = 33; and diabetic with complications, n = 58. In comparison with diabetics with and without complications, BMI (P = .047), triglycerides (P = .002), C-peptide (P = .032), resistin (P = .004), TyG index (P = .025), TG/HDL-C ratio (P = .012), and the inflammatory marker TNFα (P = .044) were significantly increased in the patients with diabetic complications.

Table 2 shows the classification of clinical and biochemical parameters of T2D based on C-peptide tertiles (tertile 1, <0.4967; tertile 2, <0.4967–0.9567; tertile 3, >0.9567). Fasting insulin (P < .001), HOMA IR (P = .001), homeostatic model assessment of beta cell function (HOMA-B; P = .002), C-peptide index (P < .001), and TNFα (P = .022) were found to be significantly increased with tertiles of C-peptide. However, BMI, DM duration, blood pressure (SBP and diastolic blood pressure), lipid profile (total cholesterol, LDL-C, HDL-C, and triglycerides), glycemic parameters (FBS and HbA1c), TyG index, TG/HDL-C ratio, and resistin were not significant across the tertiles of C-peptide.

C-peptide levels increased with an increase in the number of diabetic complications (no complications, 1 complication, 2 or more complications; P = .010; Fig. S2 Supplemental Digital Content 2). The mean levels of C-peptide in patients with various diabetic complications are presented in Figure 1. The levels of C-peptide significantly increased in T2D patients with DR (P = .004) and diabetic nephropathy (P = .050). In contrast, patients with and without diabetic complications such as diabetic neuropathy (P = .843) and macrovascular complications (P = .317) did not show any significant difference in C-peptide levels.

Table 3 illustrates the correlation analysis of C-peptide levels with different biochemical parameters and biomarkers in patients with and without diabetic complications. In patients without diabetic complications, C-peptide was significantly correlated with fasting insulin (r = 0.460; P = .007), homeostatic model assessment of IR (HOMA-IR; r = 0.468; P = .006), and C-peptide index (r = 0.816; P < .001). In contrast, in patients with diabetic complications, C-peptide was positively correlated with age (r = 0.319; P = .015), fasting insulin (r = 0.397; P = .002), HOMA-IR (r = 0.368; P = .004), HOMA-B (r = 0.416; P = .001), C-peptide index (r = 0.632; P < .001), and resistin (r = 0.276; P = .043). However, C-peptide was negatively correlated with glycemic parameters such as FBS (r = –0.325; P = .013) and HbA1c (r = –0.343; P = .010) in diabetic patients with complications.

Multiple linear regression analyses of HOMA models, fasting insulin, C-peptide index, and resistin with C-peptide as the

Table 1

Demographic, biochemical, clinical features, and inflammatory markers in type 2 diabetes patients.

Parameters	Total diabetic	Diabetic without complications	Diabetic with complications
n	91	33	58
Age, yr	60.92 ± 9.7	59.45 ± 10.22	61.76 ± 9.51
Sex, n (M/F)	45/46	17/16	28/30
BMI, kg/m^2	29.3 ± 5.57	27.81 ± 4.34	30.23 ± 6.03*
Duration of diabetes, yr	17.9 ± 7.08	19.18 ± 5.79	17.17 ± 7.67
SBP, mm Hg	137.32 ± 18.75	132.75 ± 15.00	139.93 ± 20.24
DBP, mm Hg	73.70 ± 8.95	74.06 ± 8.62	73.50 ± 9.20
Total cholesterol, mg/dL	167.07 ± 36.96	158.16 ± 34.41	172.14 ± 37.68
LDL, mg/dL	107.84 ± 46.27	104.48 ± 47.65	109.76 ± 45.78
HDL, mg/dL	44.39 ± 11.35	44.48 ± 9.75	44.34 ± 12.26
Triglycerides, mg/dL	136.31 ± 57.11	112.01 ± 42.36	150.14 ± 60.06*
FBS, mg/dL	158.30 ± 55.77	162.86 ± 40.31	155.70 ± 63.09
HbA1c, %	8.98 ± 1.67	8.67 ± 1.65	9.17 ± 1.67
Diabetic complications			
Diabetic neuropathy %	20	NA	31
Diabetic retinopathy %	33	NA	51
Diabetic nephropathy %	38	NA	60
Macrovascular diseases %	17	NA	28
Drugs			
Metformin%	39.6	45.5	36.2
T hiazolidinediones %	19.8	3	29.3*
Sulfonylureas %	36.3	57.6	24.1*
Sitagliptin %	19.8	9.1	25.9*
Markers for beta-cell function, insulin resistance and inflammatory markers			
Fasting insulin, median (IQR)	13.56 (8.24–20.44)	12.64 (7.94–18.18)	15.01 (8.45–22.35)
HOMA-B, median (IQR)	46.20 (29.27–71.35)	40.60 (27.85–66.00)	46.20 (30.50–81.27)
C-peptide index, ng/mg	0.38 (0.27–0.66)	0.35 (0.28–0.56)	0.46 (0.24–0.84)
HOMA-IR, median (IQR)	2.02 (1.19–2.97)	1.80 (1.11–2.71)	2.14 (1.23–3.28)
TyG index, median (IQR)	9.12 (8.83–9.61)	9.00 (8.67–9.34)	9.27 (8.86–9.70)*
TG/HDL-C ratio, median (IQR)	2.80 (1.85–4.10)	2.39 (1.61–3.15)	3.40 (2.35–4.32)*
C-peptide, ng/mL median (IQR)	0.67 (0.45–1.06)	0.53 (0.45–0.89)	0.76 (0.45–1.29)*
Resistin, ng/mL median (IQR)	5.33 (3.96–6.80)	4.45 (3.59–5.67)	5.82 (4.24–8.19)*
TNFα, pg/mL median (IQR)	7.15 (5.67–9.90)	6.42 (4.76–9.42)	7.43 (6.00–10.56)*

Data are presented as mean ± standard deviation for normally distributed variables and median (interquartile range [25th–75th]) for non-normally distributed variables. Categorical data are presented as frequencies and percentages.

BMI = body mass index, DBP = diastolic blood pressure, FBS = fasting blood sugar, HbA1c DCCT = hemoglobin A1c diabetes control and complication trial units, HDL = high-density lipoprotein, HOMA-B = homeostatic model assessment of beta cell function, HOMA-IR = homeostatic model assessment for insulin resistance, LDL = low-density lipoprotein, SBP = systolic blood pressure, TG/HDL-C ratio = triglyceride to HDL-C ratio, TNFα = tumor necrosis factor alpha, TyG index = triglyceride-glucose index.

*P-value ≤ .05 was considered as significant.

Table 2

Classification of clinical, biochemical parameters and glycemic markers in type 2 diabetes as per C-peptide tertiles.

Variables	Tertiles of C-peptide, ng/mL			*P*
	<0.4967	0.4967–0.9567	>0.9567	
N	30	32	29	
Age, yr	57.90 ± 8.03	62.28 ± 7.82	62.55 ± 12.58	.11
Sex, n (M/F)	13/17	22/10	10/19	.020*
BMI, kg/m^2	29.65 ± 5.63	29.33 ± 5.94	29.01 ± 5.24	.91
Duration of diabetes, yr	16.23 ± 6.03	20.06 ± 5.79	17.24 ± 8.80	.08
SBP, mm Hg	137.7 ± 21.28	134.59 ± 16.50	139.96 ± 18.53	.53
DBP, mm Hg	72.53 ± 9.23	73.56 ± 8.19	75.06 ± 9.57	.55
Total cholesterol, mg/dL	169.30 ± 40.25	155.33 ± 27.72	177.71 ± 39.78	.05
LDL, mg/dL	113.43 ± 50.56	103.57 ± 37.19	106.78 ± 51.46	.70
HDL, mg/dL	45.66 ± 10.53	43.05 ± 10.02	44.60 ± 13.54	.66
Triglycerides, mg/dL	131.28 ± 62.55	130.22 ± 51.75	148.24 ± 57.01	.39
FBS, mg/dL	163.81 ± 41.43	169.75 ± 49.34	139.95 ± 70.67	.09
HbA1c, %	9.09 ± 1.67	9.22 ± 1.64	8.59 ± 1.69	.32
Fasting insulin, median (IQR)	8.20 (5.75–14.61)	15.77 (9.45–22.95)	17.04 (12.72–26.47)	<.001*
HOMA-IR, median (IQR)	1.18 (0.85–2.18)	2.49 (1.44–3.16)	2.40 (1.80–3.51)	.001*
HOMA-B, median (IQR)	35.85 (23.45–57.80)	54.05 (30.32–93.42)	56.00 (37.20–107.60)	.002*
TyG index, median (IQR)	9.24 (8.69–9.47)	9.11 (8.86–9.62)	9.11 (8.83–9.86)	.83
TG/HDL-C ratio, median (IQR)	2.51 (1.61–3.98)	3.14 (2.34–3.65)	3.34 (1.92–4.53)	.58
C-peptide index, median (IQR)	0.24 (0.20–0.31)	0.41 (0.32–0.54)	0.85 (0.55–1.50)	<.001*
Resistin, ng/mL median (IQR)	4.14 (4.51–6.29)	5.19 (3.77–6.67)	6.30 (4.42–8.56)	.09
TNFα, pg/mL median (IQR)	6.83 (5.26–8.94)	6.78 (5.75–9.43)	8.75 (5.68–11.97)	.022*

Data are presented as mean ± standard deviation for normally distributed variables and median (interquartile range (25th–75th)) for non-normally distributed variables. Categorical data are presented as frequencies and percentages.

BMI = body mass index, DBP = diastolic blood pressure, FBS = fasting blood sugar, HbA1c DCCT = hemoglobin A1c diabetes control and complication trial units, HDL = high-density lipoprotein, HOMA-B = homeostatic model assessment of beta cell function, HOMA-IR = homeostatic model assessment for insulin resistance, IQR = interquartile range, LDL = low-density lipoprotein, SBP = systolic blood pressure, TG/HDL-C ratio = triglyceride to HDL-C ratio, TNFα = tumor necrosis factor alpha, TyG index = triglyceride-glucose index.

**P*-value ≤ .05 was considered as significant.

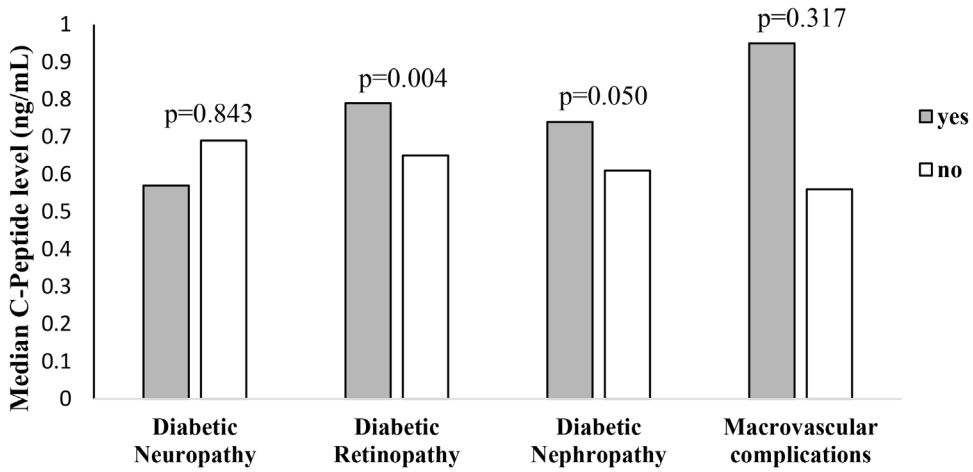


Figure 1. C-peptide levels in type 2 diabetic patients with various diabetic complications.

dependent variable in diabetic patients without and with complications are shown in Table 4. In patients without diabetic complications, fasting insulin (β = 0.431; *P* = .03), HOMA-IR (β = 0.443; *P* = .025), and C-peptide index (β = 0.899; *P* < .000) showed an association with C-peptide after adjusting for age, gender, DM duration, BMI, SBP, LDL-C, HbA1c, TNFα, and antidiabetic drugs (metformin and sulfonylurea) in different models. However, in patients with diabetic complications, C-peptide was associated with fasting insulin (β = 0.502; *P* < .000), HOMA-IR (β = 0.470; *P* < .000), HOMA-B (β = 0.465; *P* = .011), C-peptide index (β = 0.567; *P* < .000), and resistin (β = 0.329; *P* = .018) after adjusting for confounding factors such as age, gender, DM duration, BMI, SBP, LDL, HbA1c, TNFα, and antidiabetic drugs (metformin and sulfonylurea) in different models.

4. Discussion

This study assessed the level of C-peptide in patients with and without diabetic complications. In addition, a relationship between C-peptide and IR in T2DM was investigated using HOMA-IR, the TyG index, the TG/HDL-C ratio, and resistin, a marker used to evaluate IR. An association between C-peptide and markers of beta-cell function, such as the C-peptide index, HOMA-B, fasting insulin, and glycemic indices (FBS and HbA1c), was also investigated.

In this study, individuals with T2DM and complications had substantially higher BMI, C-peptide, resistin, and TNFα levels. Seppälä-Lindroos et al found that fat accumulation in the liver occurs independently of obesity and is more closely associated with IR.[28] IR is associated with increased hepatic fat storage, which changes hepatic lipoprotein secretion by

Table 3

Correlation of C-peptide as dependent variables in type 2 diabetes patients with and without complications.

	Diabetes without complications		Diabetes with complications	
Variables	***r***	***P***	***r***	***P***
Age, yr	–0.061	.73	0.319	.015*
Sex, n (M/F)	0.064	.72	0.096	.47
BMI, kg/m^2	–0.293	.10	–0.222	.10
Duration of diabetes, yr	–0.039	.82	–0.079	.55
SBP, mm Hg	0.024	.89	0.052	.69
DBP, mm Hg	0.142	.43	0.179	.17
Total cholesterol, mg/dL	0.075	.67	0.049	.71
LDL, mg/dL	0.199	.51	–0.137	.30
HDL, mg/dL	0.142	.43	–0.024	.86
Triglycerides, mg/dL	0.224	.21	0.135	.31
FBS, mg/dL	0.232	.19	–0.325	.013*
HbA1c, %	0.231	.19	–0.343	.010*
Fasting insulin, median (IQR)	0.460	.007*	0.397	.002*
HOMA-IR, median (IQR)	0.468	.006*	0.368	.004*
HOMA-B, median (IQR)	0.142	.43	0.416	.001*
TyG index, median (IQR)	0.26	.14	–0.03	.80
TG/HDL-C ratio,median (IQR)	0.16	.37	0.08	.51
C-peptide index, median (IQR)	0.816	<.001*	0.632	<.001*
Resistin, ng/mL median (IQR)	0.102	.57	0.276	.04*
TNFα, pg/mL median (IQR)	0.162	.36	0.209	.11

BMI = body mass index, DBP = diastolic blood pressure, FBS = fasting blood sugar, HbA1c DCCT = hemoglobin A1c diabetes control and complication trial units, HDL = high-density lipoprotein, HOMA-B = homeostatic model assessment of beta cell function, HOMA-IR = homeostatic model assessment for insulin resistance, LDL = low-density lipoprotein, SBP = systolic blood pressure, TG/HDL-C ratio = triglyceride to HDL-C ratio, TNFα = tumor necrosis factor alpha, TyG index = triglyceride-glucose index.

*P-value ≤ .05 was considered significant.

Table 4

Regression analysis of C-peptide as dependent variable in type 2 diabetic patients.

	Type 2 diabetes without complications													
	Fasting insulin		HOMA-IR		HOMA-B		C-peptide index		Resistin		TyG index		TG/HDL-C ratio	
	β	*P*	β	*P*	β	*P*	β	*P*	β	*P*	β	*P*	β	*P*
Model 1	0.235	.22	0.256	.18	0.192	.37	0.910	<.000*	0.145	.48	0.24	.23	0.07	.70
Model 2	0.377	.06	0.393	.05	0.348	.11	0.898	<.000*	–0.018	.93	0.17	.49	–0.009	.96
Model 3	0.431	.03*	0.443	.025*	0.431	.05	0.899	<.000*	–0.068	.76	0.06	.80	–0.18	.49
	Type 2 diabetes with complications													
	Fasting insulin		**HOMA-IR**		**HOMA-B**		**C-peptide index**		**Resistin**		**TyG index**		**TG/HDL-C ratio**	
	β	*P*	β	*P*	β	*P*	β	*P*	β	*P*	β	*P*	β	*P*
Model 1	0.421	.001*	0.395	.002*	0.348	.012*	0.551	<.000*	0.291	.027*	0.06	.66	0.12	.38
Model 2	0.435	.001*	0.420	.001*	0.347	.013*	0.563	<.000*	0.305	.027*	0.05	.74	0.10	.48
Model 3	0.502	<.000*	0.470	<.000*	0.465	.011*	0.567	<.000*	0.329	.018*	0.23	.21	0.23	.14

Model 1: age, gender, DM duration; Model 2: age, gender, DM duration, BMI, SBP, LDL-C; Model 3: Age, gender, DM duration, BMI, SBP, LDL-C, HbA1c, TNFα = antidiabetic drugs (metformin and sulfonylurea).

BMI = body mass index, HbA1c = hemoglobin A1c, HDL-C = high-density lipoprotein cholesterol, HOMA-B = homeostatic model assessment of beta cell function, HOMA-IR = homeostatic model assessment of insulin resistance, LDL-C = low-density lipoprotein cholesterol, SBP = systolic blood pressure, TNFα = tumor necrosis factor alpha.

*P-value ≤ .05 was considered significant.

increasing low-density lipoprotein secretion while lowering high-density lipoprotein secretion.[29] In this study, individuals with T2DM complications had a greater BMI and a higher level of IR (HOMA-IR, TyG index, TG/HDL ratio, and resistin). Furthermore, these patients' lipid profiles and LDL levels were elevated but not statistically significant. Individuals with T2DM complications had higher levels of the inflammatory marker TNFα. Increased chemokines and interleukin-6 production can induce liver and systemic IR.[30] Overstimulation of the inflammatory process commonly leads to altered insulin signaling, which can significantly contribute to IR.[3]

The relationships between C-peptide and diabetic complications are poorly understood. Early studies suggested that C-peptide replacement therapy could prevent and ameliorate diabetic vasculopathy and organ-specific complications by preserving vascular function and preventing endothelial cell death, microvascular permeability, vascular inflammation, and neointima formation.[31] However, recent studies have found that C-peptide in atherosclerotic lesions could have proatherogenic effects, such as stimulation of monocytes and T-cell chemotaxis.[32,33] The C-peptide-induced smooth muscle cell proliferation, in the context of IR and hyperinsulinemia, accelerated atherosclerosis and its consequences in T2DM patients.[34]

The C-peptide index is the ratio of serum C-peptide to plasma glucose levels to assess beta-cell function in T2DM.[35,36] Histological examination of human pancreatic tissues showed a

substantial correlation between the C-peptide index and beta-cell area.[37] In this study, HOMA-B and C-peptide indices were shown to be significantly increased with tertiles of C-peptide in T2DM patients. C-peptide was positively correlated with HOMA-B and the C-peptide index in individuals with T2DM and complications. Our results were consistent with the findings of a prior study.[38] The positive correlation between HOMA-B indices and postprandial C-peptide levels indicates that fluctuating levels of C-peptide can measure residual beta-cell function. This suggests that the HOMA formula is useful for evaluating beta-cell functions in T2DM.[39]

In addition to the findings mentioned above, C-peptide correlated positively with fasting insulin and HOMA-IR in T2DM patients with and without complications. Furthermore, tertiles of C-peptide were observed to significantly raise mean fasting insulin and HOMA-IR in T2DM patients. Possible causes of hyperinsulinemia (increased C-peptide) include disruptions in the classical insulin signaling system, and persistent insulin exposure can either induce or maintain IR as a compensatory response.[40] In this regard, the current study found that increased C-peptide production, along with fasting insulin, represents a compensatory response to IR in T2D. Crisman et al demonstrated that hyperglycemia stimulates both endogenous insulin and C-peptide secretion in T2DM patients with IR.[6]

Dyslipidemia in patients with T2D is characterized by elevated triglyceride levels, resulting in IR as well as increasing the risk of atherosclerotic cardiovascular disease.[41-43] The TyG index and TG/HDL-C ratio have become emerging novel indicators of IR and are associated with the development and progression of T2D and its complications.[44-49] The association of these markers with C-peptide was also evaluated in this study. A previous study reported an association of C-peptide with dysregulation of lipid metabolism, especially with elevated triglycerides.[44] This study observed no association between C-peptide and TyG index or TG/HDL-C ratio among participants with and without T2D complications. The involvement of C-peptide in the dysregulation of lipid metabolism in patients with diabetes needs to be explored.

Furthermore, this study's findings revealed a correlation between C-peptide and resistin, a marker used to assess IR. Resistin, a hormone produced mostly in adipocytes, has been associated with obesity, inflammation, and IR.[50] TNFα is known to harm beta-cells in vitro, particularly when paired with other cytokines like interleukin-1 beta or interferon-gamma (IFN-γ).[51] In the current study, C-peptide was found to be positively correlated with TNFα and significantly increased with C-peptide tertiles in T2DM. A prior study found that TNFα in overweight or obese patients supports its function in obesity-related IR.[52]

The correlation analysis revealed a negative relationship between HbA1c, FBS, and C-peptide levels. Previous studies suggest that the decline in beta-cell function in T2DM is mostly caused by beta-cell mass loss or beta-cell death triggered by low pancreatic duodenal homeobox 1 expression.[53,54] However, in this study, the inverse relationship of HbA1c and FBS with C-peptide levels, as well as the positive relationship of C-peptide with HOMA-B and the C-peptide index, indicates that C-peptide levels were associated with hyperinsulinemia-induced IR and a progressive decrease in insulin sensitivity, but no beta-cell dysfunction. Previous studies have also found a substantial inverse relationship between C-peptide levels and glycemic indicators, supporting the gradual beta-cell degeneration of T2DM.[55] Earlier, Banu et al proved an inverse relationship between C-peptide, HbA1c, and FBS, although it was not statistically significant.[56] In this study, the link identified between glycemic indices and C-peptide may be due to hyperinsulinemia-induced IR rather than beta-cell function impairment.

Studies have demonstrated an inverse association between fasting C-peptide levels and the occurrence of microvascular complications in individuals with type 1 diabetes.[8] In contrast, the role of C-peptide is not well defined in T2DM, in which both IR and insulin secretion defects exist. Previous research has proven that lower levels of postprandial C-peptide and younger age at diagnosis may imply a higher prevalence of DR in Chinese T2DM.[57] It is commonly acknowledged that alterations in the activity of C-peptide-regulated intracellular enzymes (Na+, K+-ATPase) in several cell types contribute to the pathogenesis of diabetic complications.[58] A low delta C-peptide quartile was linked to a higher severity of retinopathy in the Korean population.[15] In this study, C-peptide levels were considerably greater in individuals with DR and nephropathy. Furthermore, C-peptide levels were significantly increased with an increase in the number of complications. Similarly, in an earlier study, participants with a longer diabetes duration demonstrated a strong association between C-peptide and albumin creatinine ratio and microalbumin levels.[59] Patients with chronic renal disease, IR, and early T2DM have all been reported to have elevated levels of C-peptide.[60] Mavrakanas et al demonstrate that C-peptide levels are associated with diabetic nephropathy and vascular disease. In IR, high amounts of C-peptide circulate through the glomeruli and may deposit in the juxtaglomerular apparatus, where they may exert a mitogenic impact on mesangial cells and contribute to the thickening and scarring of the glomeruli.[55]

C-peptide is a commonly used measure of pancreatic beta-cell activity. Although it is produced in equimolar amounts to endogenous insulin, it is excreted at a more constant rate over a longer period.[61] In this study, C-peptide levels were found to be significantly associated with variables of beta-cell function, such as fasting insulin, HOMA-B, and C-peptide index, after adjusting for confounding factors such as age, gender, diabetes duration, BMI, SBP, LDL, HbA1c, TNFα, and antidiabetic drugs in T2DM with complications. In patients without complications, C-peptide levels were associated with the C-peptide index and fasting insulin. Hu and Li showed a positive association between HOMA-B indices and postprandial C-peptide levels, suggesting that fluctuation levels of C-peptide can measure residual beta-cell activity.[38] In the current study, C-peptide levels were substantially correlated with resistin and HOMA-IR in diabetic patients with complications, even after controlling for confounding variables such as age, gender, duration of diabetes, BMI, SBP, LDL, HbA1c, TNFα, and antidiabetic drugs. In T2DM, elevated C-peptide levels indicate the consequence of IR.[62] According to Bo et al, individuals with elevated C-peptide levels had a combination of risk factors, including obesity, hypertension, low HDL cholesterol, and hypertriglyceridemia. These conditions may be the result of both IR and C-peptide resistance.[9] Earlier studies have shown the significance of C-peptide in the identification of IR in individuals with T2DM as well as the onset and advancement of metabolic syndrome.[56,63,64] Both healthy individuals and those with diabetes may benefit from using C-peptide as a suitable indicator to identify IR.[64,65] Overall, the study's results were consistent with earlier findings showing a significant and positive correlation between C-peptide and HOMA-B and HOMA-IR. This suggests that elevated C-peptide levels may predict IR in patients with diabetic complications. In addition to this, a negative correlation between glycemic indices and C-peptide may indicate hyperinsulinemia-induced IR in T2DM patients with complications.

The study limitations include the cross-sectional study design with a limited sample size. The effects of C-peptide on microvascular problems require confirmation by prospective investigations. Furthermore, as the research participants in this study were not under insulin therapy, the findings of this study will not apply to those who were under insulin therapy. As all our research participants had a longer duration of diabetes, we did not assess the function of C-peptide in the development of IR and the occurrence of chronic diabetic complications.

5. Conclusion

In conclusion, fasting C-peptide levels predict the presence of IR in T2DM patients with complications in those who were not under insulin therapy. Our findings suggest a clinically important utility of C-peptide in T2DM patients with diabetic nephropathy as well as in DR. Large prospective studies should be conducted to define the causal relation of C-peptide in patients with diabetic complications.

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