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ORIGINAL RESEARCH

Non-Linear Relationship Between Fasting C-Peptide and Retinopathy in Patients with Type 2 Diabetes Mellitus - A Retrospective Study

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Background: Previous research has demonstrated that fasting C-peptide (FCP) serves as a protective element against diabetic retinopathy. But the protective effect of elevated FCP levels against diabetic retinopathy (DR) remains uncertain when these levels exceed specific thresholds. This research aimed to investigate the intrinsic link between FCP concentration and DR in individuals with T2DM.

Methods: A total of 1661 individuals diagnosed with type 2 diabetes participated in this observational analysis, where DR was assessed as the primary outcome and categorized according to FCP levels. Curve fitting analysis and two-part linear regression models were applied to assess the relationship between DR and FCP, and exploratory analysis was conducted to identify the threshold.

Results: Our study found a non-linear relationship between the two, as well as a threshold effect at an FCP of 4.11 ng/mL. Below the critical value, each 1 ng/mL increase in FCP levels was associated with a 24% lower risk of DR (OR: 0.74, 95% CI: 0.64–0.86). Above the cutoff, the relationship did not reach statistical significance (OR: 1.52, 95% CI: 0.87–2.66).

Conclusion: There was a nonlinear relationship between FCP level and DR risk, which was negatively correlated at first but stabilized at a lower level when FCP>4.11 ng/mL.

Keywords: diabetic retinopathy, type 2 diabetes mellitus, threshold effect, fasting C-peptide, diabetic retinopathy

Introduction

Diabetic retinopathy (DR) is a common and very specific microvascular health complication that frequently arises in patients with type 2 diabetes mellitus (T2DM), and approximately one-third of all individuals with diabetes globally suffer from DR.[1] DR is among the primary contributors to avoidable visual impairment in the adult population.[2] Therefore, early prevention and identification of DR is particularly important.

The C-peptide concentration in peripheral blood is generally considered to be the most suitable marker of insulin secretion, as it is released in equal amounts with insulin and reflects the overall health of β-cells by assessing their ability to produce insulin.[3,4] However, the changes in fasting C-peptide (FCP) concentration in individuals with DR, particularly in those diagnosed with T2DM, can reflect not only the reduction in β-cell function but also the degree of insulin resistance.[5,6]

Earlier research has indicated that C-peptide has an independent relationship with DR.[7,8] However, these studies revealed only an overall pattern of reduced DR risk when C-peptide levels were higher, but they failed to investigate the dose-response relationship between the two, nor did they determine if a linear relationship was present between DR risk and elevated C-peptide. Therefore, this research sought to explore the inherent connection between fasting C-peptide and the likelihood of DR in individuals with type 2 diabetes (T2D).

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Materials and Methods

Study Population

A total of 1661 individuals with type 2 diabetes participated in this study. These participants had been admitted to the Department of Endocrinology and Metabolism at the Bethune Second Hospital of Jilin University, China. The admission occurred from January 1, 2023, to December 31, 2023. This research is a retrospective observational analysis that was endorsed by the hospital's ethics committee, meaning that informed consent from participants was not required. The inclusion criteria were as follows: (1) participants older than 18 years; (2) those with complete clinical data and a confirmed diagnosis of T2DM. Exclusion criteria included: (1) individuals with incomplete or unclear clinical data and diagnosis; (2) Gestational diabetes or type 1 diabetes. Figure 1 illustrates the study flowchart.

Study Variables

By reviewing the electronic medical records, clinical as well as laboratory data were collected, including age, gender, duration of diabetes, education level, family history of diabetes, whether insulin was used, history of hypertension, smoking and drinking history, body mass index (BMI), Fasting C-peptide (FCP), high-density lipoprotein cholesterol (HDL-C), fasting blood glucose (FBG), triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and glycated HbA1c and urine albumin-creatinine ratio (UACR).

Measurements of C-Peptide

Because routine insulin injection therapy in some patients may affect the results of serum islet hormone measurement, we routinely check the level of serum C-peptide instead of measuring islet hormone. C-peptide measurement is performed as

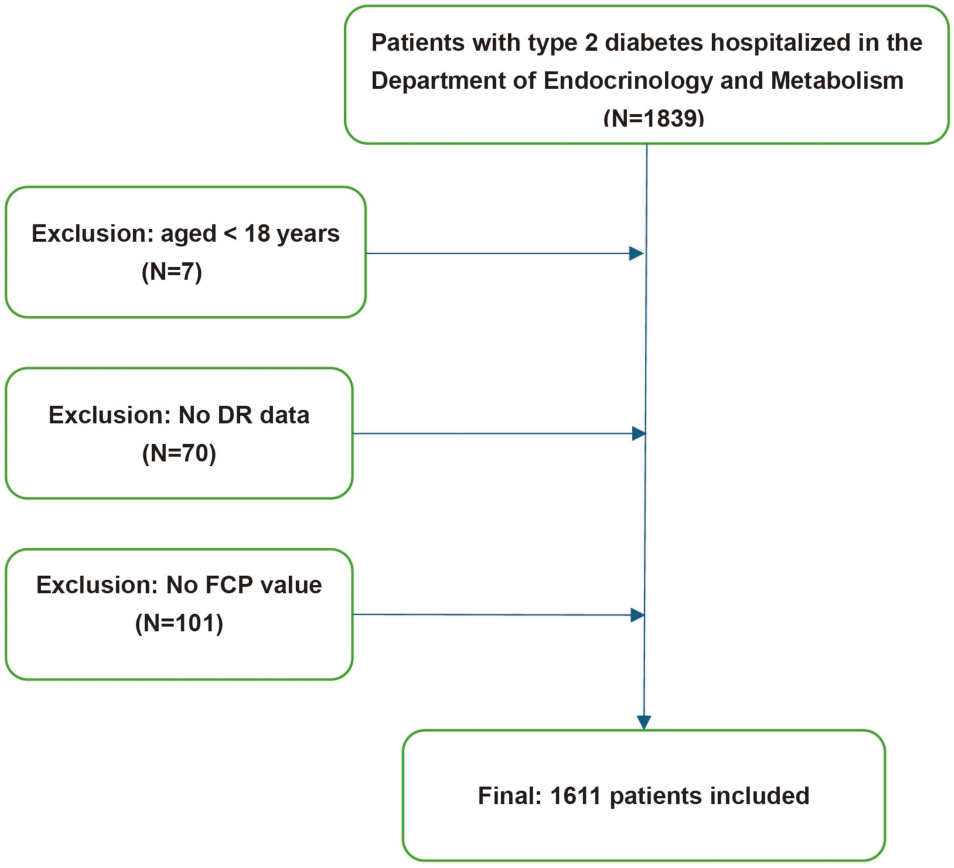

Figure 1 The study flowchart.

part of the initial diagnostic evaluation in newly diagnosed individuals with diabetes and annually thereafter during routine follow-up care.

Variable Definition

A fundus camera was used to capture 45° color fundus images centered on the optic disc and macula of both eyes. An ophthalmologist reviewed the images and determined whether the patient had DR based on the diagnostic criteria.[9] The diagnosis of type 2 diabetic retinopathy was in accordance with the diagnostic criteria published by the American Diabetes Association.[10]

Ethics

This research was authorized by the Ethics Committee of the Second Hospital of Jilin University and adhered to the principles of the Declaration of Helsinki. This retrospective analysis did not require gathering any personal data from patients. Given that the exemption of informed consent would not adversely affect the subjects, we obtained approval from the Ethics Committee (approval number: 2024–351).

Statistical Analysis

Statistical analyses were performed using R software (version 4.3.3) and EmpowerStats (version 6.0). Continuous variables were presented as mean ± standard deviation (SD), while categorical variables were expressed as frequencies and percentages. Differences across fasting C-peptide (FCP) tertiles were assessed using one-way analysis of variance (ANOVA) for continuous variables and chi-squared tests for categorical variables.

The dose-response relationship between FCP and diabetic retinopathy (DR) was examined using a generalized additive model (GAM), adjusting for potential confounding factors including age, sex, body mass index (BMI), duration of diabetes, hypertension, smoking and drinking history, family history of diabetes, education levels, lipid levels, UACR and insulin use. To identify potential threshold effects, we employed a two-piece-wise linear regression model. The optimal turning point for FCP was determined through exploratory analysis by iteratively evaluating potential turning points within a predefined interval and selecting the point that maximized model likelihood. A log-likelihood ratio test was conducted to compare the one-line linear regression model with the two-piece-wise linear model as previously described.[11,12] Additionally, mediation effect analysis shows that HbA1c mediates the correlation between FCP and DR.

To evaluate the robustness of our findings, we conducted stratified analyses to assess the association between FCP and DR across different participant subgroups and performed sensitivity analyses using multiple imputation for missing data.

Results

Basic Clinical Features

This research examined the data of 1661 individuals diagnosed with T2DM, among these patients, 712 developed diabetic retinopathy, while the remaining 949 did not which were categorized into three clusters based on FCP: low (0–1.44 ng/mL), medium (1.44–2.37 ng/mL), and high (2.37–6.91 ng/mL). The participants had an average age of 53.86 years, and the dispersion was 12.3 years. Of the total number of participants in the study, 960 (57.8%) were men and 701 (42.2%) were women. Table 1 offers a synopsis of the demographic traits, duration of diabetes, and other crucial clinical parameters among the various fasting C-peptide groups. In contrast to the group with the lowest tertile, those in the group with the highest tertile showed a younger age, a shorter duration of diabetes, a higher proportion of liver and kidney disease and a higher proportion of males. Furthermore, their HbA1c levels were markedly lower. Statistical significance was observed ($P < 0.001$) among these differences.

Identification of Nonlinear Relationships

We observed a nonlinear dose-response relationship between fasting C-peptide (FCP) levels and diabetic retinopathy (DR) through generalized additive model (GAM) (Figure 2). Using a two-piece-wise linear regression model, we identified a significant threshold effect at FCP level of 4.11 ng/mL (Table 2). In the linear model (Model I), each 1 ng/mL increase in FCP levels was associated with a 17% lower probability of DR (OR: 0.81, 95% CI: 0.71–0.92).

Table 1 Baseline Characteristics and DR According to the Tertiles of the FCP

	Overall N = 1661	**Low N = 553**	**Middle N = 553**	**High N = 555**	**p-value**	**Missing Data, n (%)**
		(<1.44)	**(1.44–2.37)**	**(>2,37)**		
Age, years	53.86 ± 12.30	57.19±11.18	53.55±11.61	50.85±13.19	<0.001	
Gender, n (%)					<0.001	
Man	960 (57.80%)	280(50.63%)	324(58.59%)	356(64.14%)		
Women	701 (42.20%)	273(49.37%)	229(41.41%)	199(35.86%)		
BMI, kg/m²	26.10 ± 3.68	24.50 ± 3.05	26.02 ± 3.28	27.78 ± 3.89	<0.001	(2,0.1%)
Duration, years	7.69 ± 7.14	10.24 ± 7.83	7.50 ± 6.78	5.33 ± 5.81	<0.001	(1,0.1%)
Insulin, n (%)					<0.001	(1,0.1%)
No	903 (54.40%)	212(38.34%)	299(54.07%)	392(70.76%)		
Yes	757 (45.60%)	341(61.66%)	254(45.93%)	162(29.24%)		
Hypertension, n (%)					0.007	(1,0.1%)
No	903 (54.40%)	330(59.67%)	292(52.80%)	281(50.72%)		
Yes	757 (45.60%)	223(40.33%)	261(47.20%)	273(49.28%)		
Smoking, n(%)					0.004	
No	1047(63.03%)	369(66.73%)	358(64.74%)	320(57.66%)		
Yes	614 (36.97%)	184(33.27%)	195(35.26%)	235(42.34%)		
Alcohol, n (%)					0.012	
No	1057(63.64%)	369(66.73%)	362(65.46%)	326(58.74%)		
Yes	604 (36.36%)	184(33.27%)	191(34.54%)	229(41.26%)		
Family, n (%)					0.094	(1,0.1%)
No	1056(63.61%)	338(61.12%)	346(62.57%)	372(67.15%)		
Yes	604 (36.39%)	215(38.88%)	207(37.43%)	182(32.85%)		
Education, n(%)					0.013	(2,0.1%)
Below high school	247 (14.89%)	102(18.48%)	75 (13.59%)	70 (12.61%)		
Above high school	1412(85.11%)	450(81.52%)	477(86.41%)	485(87.39%)		
UACR, n (%)					0.007	(60,3.6%)
No	1262(78.83%)	433(83.11%)	423(78.19%)	406(75.32%)		
Yes	339 (21.17%)	88 (16.89%)	118(21.81%)	133(24.68%)		
TG, mmol/L	2.83 ± 3.17	2.01 ± 2.17	2.79 ± 2.80	3.65 ± 4.01	<0.001	(121,7.3%)
TC, mmol/L	4.86 ± 1.25	4.82 ± 1.20	4.78 ± 1.18	4.99 ± 1.35	0.110	(121,7.3%)
HDL, mmol/L	1.06 ± 0.27	1.13 ± 0.29	1.04 ± 0.24	1.00 ± 0.26	<0.001	(122,7.3%)
LDL, mmol/L	2.64 ± 0.95	2.72 ± 0.95	2.60 ± 0.92	2.61 ± 0.97	0.137	(122,7.3%)
Glu, mmol/L	9.85 ± 3.82	9.09 ± 4.41	10.04 ± 3.47	10.37±3.42	<0.001	(129,7.8%)

(*Continued*)

Table 1 (Continued).

	Overall N = 1661	Low N = 553	Middle N = 553	High N = 555	p-value	Missing Data, n (%)
		(<1.44)	(1.44–2.37)	(>2,37)		
HbA1c, %	8.76 ± 1.83	9.15 ± 1.98	8.56 ± 1.75	8.57 ± 1.68	<0.001	(208,12.5%)
Liver disease, n (%)					<0.001	(152,9.2%)
No	1457(96.55%)	477(98.96%)	498(98.22%)	482(92.69%)		
Yes	52 (3.45%)	5 (1.04%)	9 (1.78%)	38 (7.31%)		
Cardiac disease, n (%)					0.031	(176,10.6%)
No	1421(95.69%)	473(94.04%)	490(97.42%)	458(95.62%)		
Yes	64 (4.31%)	30 (5.96%)	13 (2.58%)	21 (4.38%)		
Kidney disease, n (%)					0.003	(22,1.3%)
No	1259(76.82%)	435(80.71%)	429(77.72%)	395(72.08%)		
Yes	380 (23.18%)	104(19.29%)	123(22.28%)	153(27.92%)		
DR, n (%)					<0.001	
No	949 (57.13%)	266(48.10%)	316(57.14%)	367(66.13%)		
Yes	712 (42.87%)	287(51.90%)	237(42.86%)	188(33.87%)		

Notes: Data are presented as mean ± SD, median (IQR), or percentage. With missing data: The amount of missing values for the variables were: 2 (0.1%) for BMI, 1 (0.1%) for disease duration, 1 (0.1%) for insulin use, 1 (0.1%) for hypertension, 1 (0.1%) for family history, 2 (0.1%) for education level, 60 (3.6%) for UACR, 121 (7.3%) for triglycerides, 121 (7.3%) for total cholesterol, 122 (7.3%) for HDL cholesterol, 122 (7.3%) for LDL cholesterol, 129 (7.8%) for glucose, 208 (12.5%) for HbA1c, 152 (9.2%) for Liver disease, 176 (10.6%) for Cardiac disease, and 22 (1.3%) for kidney disease.
Abbreviations: BMI, body mass index; DR, diabetic retinopathy; Glu, glucose; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TG, triglycerides; UACR, urinary albumin-to-creatinine ratio.

However, the two-piece-wise linear regression model (Model II) revealed that when FCP was < 4.11 ng/mL, each 1 ng/mL increase corresponded to a 26% lower likelihood of DR (OR: 0.74, 95% CI: 0.64–0.86), while at FCP levels ≥ 4.11 ng/mL, there was a non-significant trend toward increased DR risk (OR: 1.52, 95% CI: 0.87–2.66). The log-likelihood ratio test comparing the linear regression model with the two-piece-wise linear regression model yielded (P = 0.024), indicating that the two-piece-wise linear regression model should be used to fit the model. These findings suggest a complex relationship between FCP levels and DR, with different associations observed above and below the identified threshold of 4.11 ng/mL.

To assess the robustness of our findings, we conducted sensitivity analyses using multiple imputation for missing data, which yielded results consistent with the primary analysis (Table S1).

Mediation of HbA1c

We conducted a mediation analysis to evaluate the potential mediating role of HbA1c in the FCP-Diabetic retinopathy relationship (Figure 3). After adjusting for all potential confounders, the analysis revealed significant direct and indirect effects. The total effect of Fasting C-peptide on Diabetic retinopathy was significant (β = −0.04; 95% CI: −0.01 to −0.001), comprising both direct and indirect pathways. The direct effect of Fasting C-peptide on Diabetic retinopathy remained significant after accounting for HbA1c (β = −0.035; 95% CI: −0.06 to −0.01), while the indirect effect through HbA1c was also significant (β = −0.005; 95% CI: −0.01 to −0.001). The proportion of the total effect mediated by HbA1c was 25.28% (95% CI: 2.42–39.18%), indicating partial mediation.

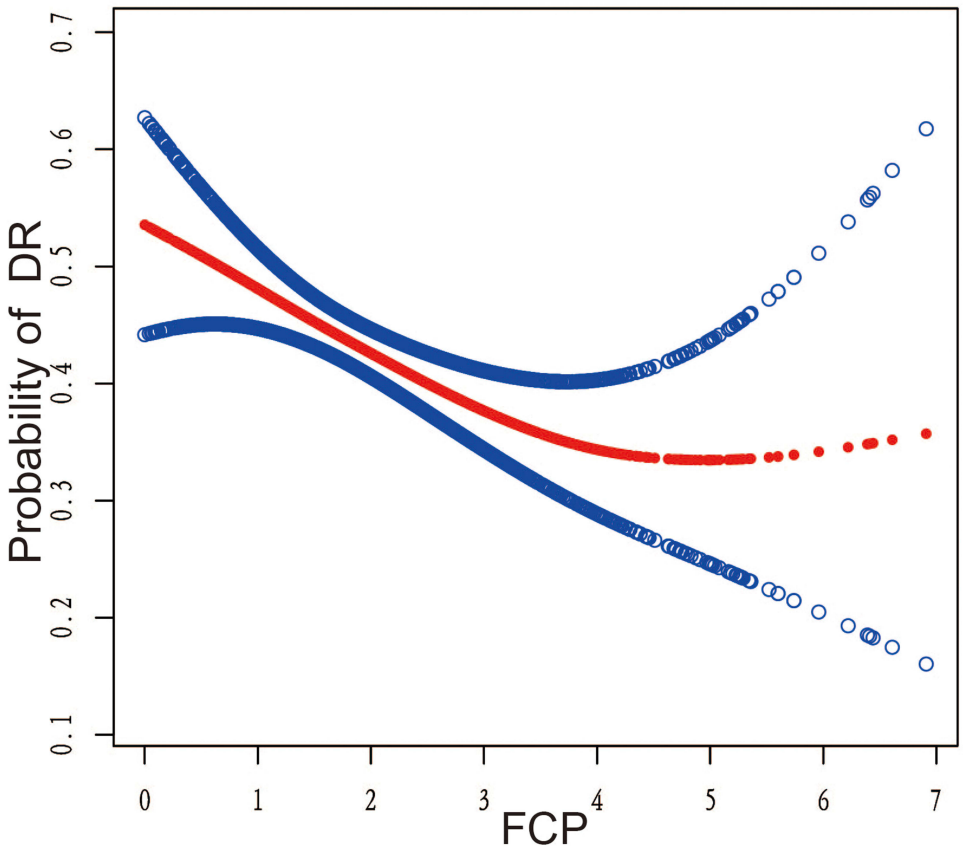

Figure 2 The link between FCP and DR prevalence was analyzed. A threshold, nonlinear association between the FCP and DR was found in a generalized additive model (GAM). The fitted curve is shown as a solid red line, with blue lines indicating the 95% confidence intervals. This analysis accounted for gender, age, BMI, diabetes duration, insulin use, alcohol intake, smoking status, education level, family history, hypertension, TG, TC, LDL, HDL, and UACR.

Subgroup Analysis

To validate our findings, we performed comprehensive subgroup analyses (Figure 4). Having identified a nonlinear relationship between FCP levels and DR, we stratified the study population at the FCP inflection point of 4.11 ng/mL.

Table 2 Threshold Effect Analysis of FCP and DR

Models	OR (95% CI)	P value
Model 1		
One line effect	0.81(0.71,0.92)	0.001
Model 2		
Turning point (K)	4.11	
FCP<K	0.74(0.64,0.86)	<0.001
FCP≥K	1.52(0.87,2.66)	0.139
Log-likelihood ratio test		0.024

Notes: Adjustments were made for age, gender, BMI, diabetes duration, insulin usage, Hypertension, education level, smoking status, alcohol intake, family history, TG, TC, HDL, LDL and UACR. Logarithm likelihood ratio test (LRT) (P <0.05) signifies that the non-linear model significantly differs from the linear model.

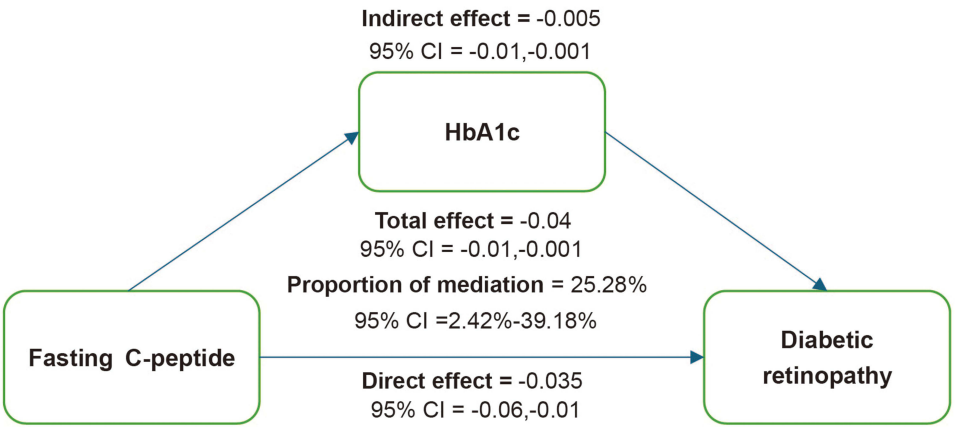

Figure 3 The proportion of the mediation effect in HbA1c.
Notes: Adjustments were made for age, gender, BMI, diabetes duration, insulin usage, Hypertension, education level, smoking status, alcohol intake, family history, TG, TC, HDL, LDL and UACR.

Analysis of the relationship between FCP and DR within each stratum revealed distinct patterns: a negative association below the threshold and a positive association above it, although the positive association above the threshold did not reach statistical significance. Further analysis showed no interaction effects on either side of the threshold (P for interaction > 0.05). This nonlinear relationship remained consistent across demographic and clinical subgroups, including age categories, insulin treatment status, and presence of hypertension. Similar patterns emerged when examining other relevant factors such as family history of diabetes and hypertension. The consistency of these associations was further verified across key biochemical parameters, including UACR and HbA1c.

Discussion

This cross-sectional study found a nonlinear relationship linking fasting C-peptide (FCP) levels with DR, and a threshold of 4.11 ng/mL was found. The study results show that after accounting for potential confounding factors, when FCP is higher than the threshold, due to the large confidence interval, this association is not clear despite OR=1.52, hile when FCP is lower than the threshold, the likelihood of DR decreases as FCP levels increase. There is a marked reduction as peptides rise, and each additional increase of 1 ng/mL deviation results in a 0.74-fold rise in the likelihood of developing DR. Meanwhile, subgroup analysis results showed that this nonlinear relationship remained stable across different subgroups (P for interaction > 0.05). This result emphasizes the value of FCP for risk stratification and intervention in patients with T2DM.

Previous studies demonstrated that FCP levels are an independent protective factor for DR. For example, Cai et al[13] showed that reduced FCP concentrations were significantly linked to an increased rate of DR among Chinese T2DM individuals, suggesting that C-peptide contributes to delaying DR onset. Furthermore, Li et al[8] observed that keeping higher FCP concentrations might lower the likelihood of DR progression.

While previous studies have examined the association between FCP and diabetic retinopathy (DR), the potential nonlinear nature of this relationship has remained largely unexplored. Through smooth curve-fitting analysis, our study identified a nonlinear dose-response relationship between FCP levels and DR.

We believe that the nonlinear relationship between the two might result from the dual influence of C-peptide on DR.[14] The defensive impact of C-peptide on DR stems from these mechanisms. C-peptide has the potential to avert retinopathy through suppressing intracellular ROS accumulation, lowering the formation of stress fibers, preserving the integrity of endothelial cells, and limiting the VEGF-triggered rise in microvascular permeability.[15] At the same time, previous studies have shown that in the presence of T2DM, elevated endogenous C-peptide levels can have harmful effects.[14,16,17] For instance, studies indicate that C-peptide concentrations show a positive association with CCL2, E-selectin, and triglyceride concentrations, while displaying an inverse relationship with IL-10 concentrations in the early stages of T2DM, and could participate in modulating adipokine activity.[18,19] First, multiple studies have found that CCL2 and other proteins are

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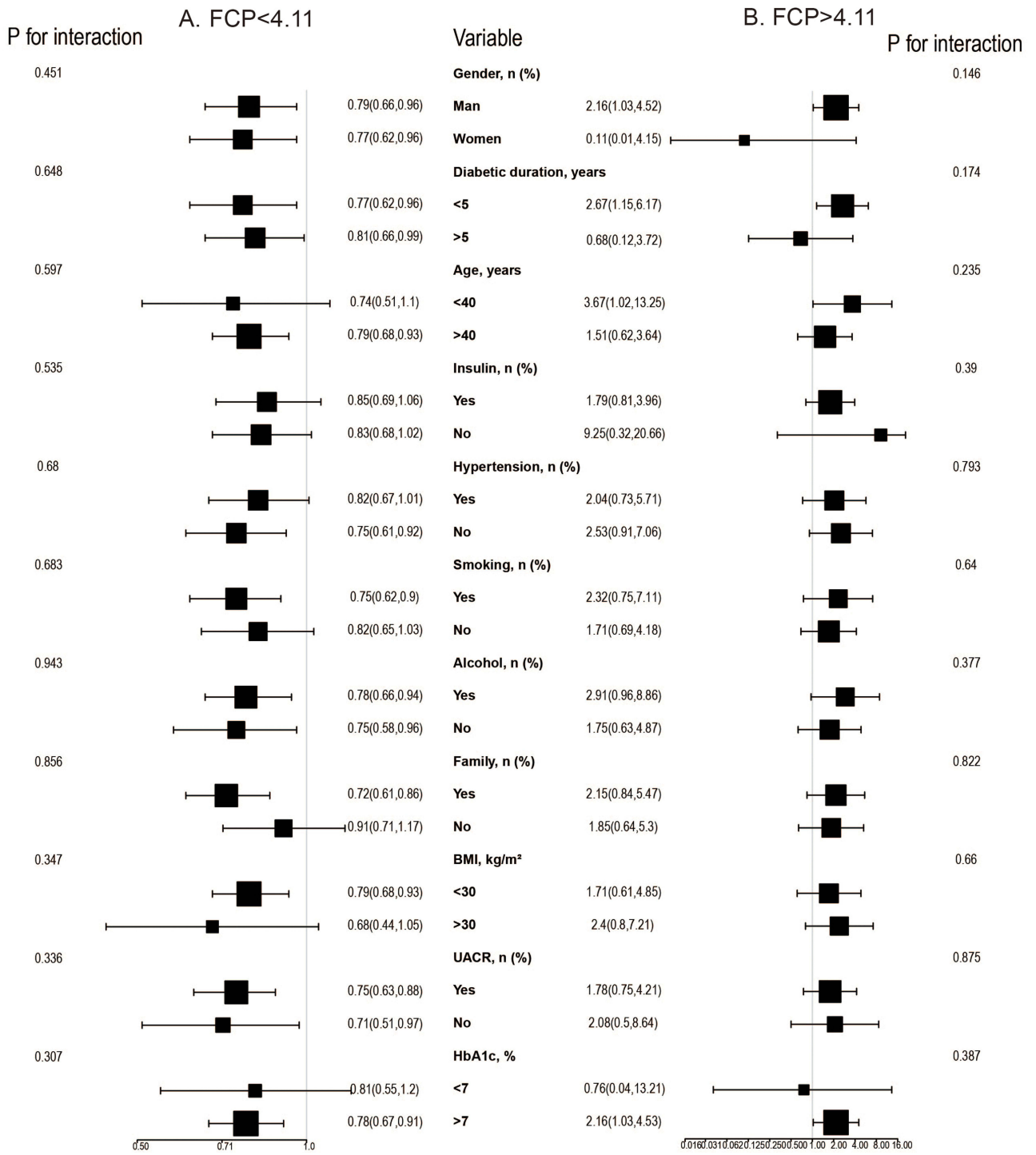

Figure 4 A Subgroup analysis was carried out to evaluate the possible influence of modifiers on the link between FCP and DR prevalence.
Notes: The analysis included two groups: (**A**) FCP < 4.11 and (**B**) FCP > 4.11. Adjustments were made for age, gender, BMI, diabetes duration, insulin usage, Hypertension, education level, smoking status, alcohol intake, family history, TG, TC, HDL, LDL and UACR. P for interaction < 0.05 indicates that the effect of FCP on DR differs within subgroups.
Abbreviations: BMI, body mass index; HbA1c, glycated hemoglobin.

elevated within the retinas of DR patients, triggering inflammatory pathways and VEGF production.[20–23] Secondly, adipose factors also promote the occurrence and development of DR by promoting inflammatory response, angiogenesis and oxidative stress response.[24] Finally, IL-10 is a key anti-inflammatory cytokine that reduces inflammation and promotes

tissue repair by inducing M2 macrophage polarization, while maintaining the stability of BRB, reducing retinal edema and restoring retinal morphology.[25–27] In summary, excessive C-peptide may lead to antagonism between the protective and harmful impacts of C-peptide concerning the onset and progression of DR, resulting in no significant protective effect on DR when C-peptide exceeds the threshold level.

Compared with previous studies, we explored in depth and found a nonlinear relationship between FCP and DR based on the previous work. This finding has several important clinical implications that could transform our approach to DR management. Meanwhile we found disease duration exhibited a significant negative correlation with C-peptide levels, thus demonstrating the dynamic fluctuations in C-peptide levels during the natural progression of type 2 diabetes. In the early stages of the disease, when the duration is relatively short, higher C-peptide levels frequently indicate insulin resistance.[28] This phenomenon can be attributed to the body's compensatory response to insulin resistance, whereby the pancreas increases its secretion of insulin and C-peptide to maintain synchronised levels in the plasma.[29] This compensatory hypersecretion state may serve as an indicator of the underlying degree of insulin resistance. However, as the disease progresses, there is the potential for gradual β-cell dysfunction, which can be seen in a progressive decline in C-peptide levels.[30] This finding not only facilitates a more comprehensive understanding of the natural progression of diabetes, but also underscores the necessity for clinicians to consider disease duration when interpreting C-peptide levels. This is because the same C-peptide level may have different clinical implications at different stages of the disease. In patients with a shorter duration of the disease, elevated C-peptide levels may necessitate more intensive efforts to enhance insulin sensitivity. Conversely, in patients with a longer duration of the disease, declining C-peptide levels may serve as a marker of the extent of β-cell dysfunction. This underscores the necessity for more personalised monitoring strategies that take into account both C-peptide levels and disease duration. Importantly, this finding indicates that maintaining C-peptide within an optimal therapeutic window is crucial, as levels outside this range may accelerate retinal damage through different pathophysiological mechanisms. This understanding could influence clinical decision-making regarding the timing and intensity of β-cell preservation treatments, while also emphasizing the importance of regular C-peptide monitoring as part of comprehensive diabetes care, particularly in high-risk patients for DR development or progression. However, this study still has limitations. First, the inpatients we analyzed may not be representative of outpatients. In fact, we conducted a single-center small sample study, and the results cannot represent populations in other regions. Finally, due to potential misdiagnosis, some patients may actually have Type 1 diabetes. Future research should focus on large multi-center studies to improve the general applicability of the results.

Conclusion

This research uncovered a nonlinear association between FCP concentrations and the likelihood of DR in individuals with T2DM.

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Disclosure

The authors report no conflicting interests in this work.

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