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Low levels of postprandial C-peptide are clinically significant in non-proliferative diabetic retinopathy and diabetic macular oedema in Iraqi patients with type 2 diabetes

Haider A. Alnaji

Medical Laboratory Technology Department, College of Medical Technology, The Islamic University, Najaf, Iraq
Email: Hgeoda995@gmail.com

Mohammed Qasim Al Nuwaini

Surgery Department, College of Medicine, Jaber Ibn Hayan University, Najaf, Iraq
Email: M.qasim@jmu.edu.iq

Al-karrar Kais Abdul Jaleel Duaibel

Medical Laboratory Technology Department, College of Medical Technology, The Islamic University, Najaf, Iraq
Email: alkkais50@gmail.com

giyath Al-Deen Thegil Neamah

Surgery Department, College of Medicine, Jaber Ibn Hayan University, Najaf, Iraq
Email: sogiyath80@yahoo.com

Abbas F. Almulla

Medical Laboratory Technology Department, College of Medical Technology, The Islamic University, Najaf, Iraq
Email: abbass.chem.almulla1991@gmail.com

Abstract---Objective: To evaluate if the low postprandial C-peptide levels are clinically significant and would it relate to the risk of diabetic retinopathy (DR) in Iraqi patients with type 2 diabetes. Methods: Forty-one patients with diabetes (28 male, 13 female) were included, and eight non-diabetic tests were present in this study: HbA1c and 2 h. Post-prandial C-peptide levels were measured in all patients and control groups. Results: In subjects both NPDR and DMO, patients with DR showed lower levels of postprandial C-peptide and higher HbA1c percent. Regression analysis between postprandial C-peptide and DR showed that postprandial C-peptide was negatively associated with DR with odds ratio: (0.569, CI: 0.370- 0.872, p = 0.01)

in Iraqi type 2 diabetes. Conclusion: Low postprandial C-peptide levels may predict NPDR and DMO in T2DM patients. Measuring the postprandial or non-fasting C peptide level offers uncomplicated and flexible testing for an outpatient or inpatient.

Keywords---C-peptide, Diabetic retinopathy, Non-proliferative diabetic retinopathy, Diabetic macular oedema, Type 2 diabetes mellitus.

Introduction

Diabetes mellitus (T2DM) type 2 prevalence has increased globally. Diabetes affects a range of tissue, including retinal endothelium capillaries, renal glomerular mesangial cells, and extend to neurons and Schwann cell (Brownlee, 2005; Tarboush2018.Pdf, n.d.). That leads correspondingly to diabetic retinopathy (DR), nephropathy, and neuropathy(Tarboush2018.Pdf, n.d.). Diabetic retinopathy (DR) is one of the most prevalent consequences of T2DM, it microvascular complications of T2DM (Zhang et al., 2010). And DR symptoms are present at the time of their diagnosis in one-third of T2DM patients (Nentwich & Ulbig, 2015). DR is the world's leading cause of adult blindness, and its pathogenesis develops early and silently in the course of T2DM (Atlas, 2015). Approximately 95 million diabetic patients worldwide suffer from DR, a third have vision-threatening DR, and macular oedema reaches 7,6% of them (Hristova et al., 2021). The DR may occur in any part of the retina as moderate non-proliferative alterations in vision, to severe retinal proliferative retinopathy that is characterized by severe hemorrhages to the retina and vascular changes; Proliferative retinopathy, characterized by abnormal neovascularization(Gurung et al., 2020). Another retinal complication of diabetes is diabetic macular oedema (DMO), which is often included under the umbrella of DR. It can occur at any stage of the disease's development from non-proliferative to proliferative with or without other DR signs (Gundogan et al., 2016).

Most diabetic vision loss is caused by two types of DR: proliferative diabetic retinopathy (PDR) and diabetic macular oedema (DMO). The PDR is characterized by retinal neovascularisation, and a distinctive feature is the beginning of dysregulated angiogenesis. In DMO, retinal vascular hyperpermeability causes blood plasma components to infiltrate into the retina (Duh et al., 2017; Whitehead et al., 2019). However, Patients with early DR are typically asymptomatic. Still, when the severity of the disease advances over time, visual abnormalities such as blurred vision and sometimes Acute vision loss can occur due to complications such as vitreous hemorrhage or tractional retinal detachment(Whitehead et al., 2019). On the other hand, NPDR is distinguished by developing microaneurysms and tiny dilation of retinal blood vessels, which are hallmarks of DR (Kang & Yang, 2020).

The most important risk factors for DR include hyperglycemia, diabetes duration, child and youth obesity, puberty, high pressure, hyperlipidemia, and genetic predisposition (Raczyńska et al., 2014). The pathophysiological effects of DR are primarily due to hyperglycemia, including the thickness of the retinal capillary basement membrane, increased permeability of vessels of the retina of the cell,

ischemia of the tissue, and release of vasoactive materials that lead to neovascularization (Kang & Yang, 2020). The risk of the duration of diabetes mellitus is ≥ 10 years. The duration of diabetes can influence DR prevalence, the shortest period in the youngest age group (25-44 years, < 5 years) is 50 times greater. The most prolonged duration is the risk factor between the elders' diabetes age group (≥ 65 years, ≥ 15 years) (Alharbi & Alhazmi, 2020). A higher mean diastolic blood pressure was more critical than higher systolic blood pressure in the risk of DR (Wysocka-Mincewicz et al., 2021).

Yau et al. found that the prevalence of any subtype of DR was 18.0% in patients with glycated hemoglobin (HbA1c) $\leq 7.0\%$, compared to 51.2% in patients with HbA1c > 9.0 percent, in a pooled analysis of 35 global population-based studies (Yau et al., 2012). A large US study revealed that the DR risk for each 1-point HbA1c rise in children with T1D increased by 20 percent (95% CI 6-35%) (S. Y. Wang et al., 2017). Studies by Mosier MA and Subrata reported varying levels of C-peptide in Type 1 patients who had PDR and NPDR (Mosier, 1984; Nakanishi & Watanabe, 2008). Whereas Cai reported that as diabetic retinopathy progressed, patients had greater mean HbA1c but lower fasting and 2 hours postprandial C-peptide levels. (Cai et al., 2014). This study aims to investigate the link between 2 hours of postprandial C-peptide levels and diabetic retinopathy.

Methods

Subjects, materials, and methods

A total of 41 T2DM patients visited Amir Al-Muminin, Specialized in Najaf, Iraq, and eight non-diabetic tests were present in this study. The diabetic group had 28 men and 13 women, and the control group consisted of 5 males and three females. We acquired 2 mL of venous blood in K₂ EDTA vacutainers. Blood samples were processed immediately. For serum isolation, whole blood in a gel tube was centrifuged at 5000 rpm for 5 min at room temperature. Supernatants were then collected and stored at -20°C until investigated. Biochemical measurements including HbA1c (HumaNex A1c, Germany), 2 hours postprandial C-peptide (COBAS e 411, Roche Diagnostics Ltd. Switzerland)

Assessment of Diabetic Retinopathy

A complete ophthalmological examination was carried out for all participants; an ophthalmologist assessed the funduscopy results. Patients were divided into three groups based on the severity of their retinal disease; no apparent retinopathy (NDR), non-proliferative diabetic retinopathy (NPDR), and diabetic macular oedema (DMO); it also considers as NPDR with oedema.

Statistical Analysis

Continuous data were expressed in terms of mean and standard deviation, whereas categorical variables were expressed in percentages. Participants' characteristics were compared using the Mann-Whitney U test between the DR and non-DR groups. Multivariable logistic regression analyses were performed to assess the relationship between diabetic retinopathy and C-peptide levels. A *P*

value <0.05 at the two-tailed level was considered statistically significant. All statistical analyses were performed using SPSS software version 26.

Results

Among our samples, diabetic retinopathy was 40.8% in patients with type 2 diabetes. NPDR was 30.6%, and the number of patients with diabetic macular oedema (DMO) was 12.2%. The percentage of moderate and severe NPDR was 25% and 75%, respectively of total DR. Of the patients in this study, 65.3% were males. The average age was 56.1 ± 9.29 years, duration of diabetes was 11.2 ± 5.51 years, average BMI was 30.0 ± 6.57 kg/m², average HbA1c was 8.9 ± 2.31 %. The age at diagnosis of diabetes was 44.95 ± 10.58 years. The average C peptide level was 2.6 ± 1.90 %. The patients with primary hypertension were 69.4%, the smokers' patients were 10.2%

Demographic data and metabolic profile of patients with DR

Comparisons among patients with NDR, NPDR, and DMO or NPDR with oedema (NPDR+) showed that with the progression of diabetic retinopathy, patients have higher mean HbA1c, but with a lower 2-hour postprandial C-peptide level, and patients turned to have older age but younger age at diagnosis of diabetes. Details were shown in Table 1 and figure 1.

Table 1
Clinical characteristics of T2DM patients with or without DR.

Total n. of diabetic patients = 41					
	NDR (%)	NPDR (%)	DMO (%)	control	P
n.	21(51.2)	15(36.6)	5(12.2)	8	-
Gender: male	15(71.4)	11(73.3)	2(40)	5(62.5)	0.62
Age	55.9 ± 10.6	56.3 ± 7.4	56.0 ± 7.5	56.5 ± 11.3	0.97
Age at diagnosis of diabetes (years)	45.4 ± 10.4	41 ± 7.2	42.4 ± 6.1	52.8 ± 14.9	0.26
Diabetes duration*	10.5 ± 2.6	15.3 ± 3.9	13.6 ± 6.8	-	<0.001
BMI (kg/m ²)*	26.7 ± 4.8	33.1 ± 6.7	31.0 ± 8.2	32.1 ± 6.5	0.012
HbA1c (%)*	9.4 ± 2.3	9.7 ± 1.8	9.1 ± 1.8	5.9 ± 0.3	<0.001
Postprandial C-peptide (ng/ml)*	4.1 ± 1.7	1.7 ± 1.4	1.8 ± 1.3	1.2 ± 0.8	<0.001
Smoker*	2(9.5)	0	0	3(37.5)	0.035
Hypertension	3(14.3)	6(40)	2(40)	0	0.189

*comparison among groups showed significant differences

Abbreviations in the table: NDR: non-diabetic retinopathy, NPDR: non-proliferative diabetic retinopathy, DMO: diabetic macular oedema, BMI: body mass index and HbA1c: hemoglobin A1c.

Association between age at diagnosis of diabetes and DR

The clinical outcome of patients and demographic data from the lowest to the highest quartiles in terms of age at diabetes diagnosis are summarized in Table 2. findings indicate that when patients' age at diagnosis decreased, they had a longer duration of diabetes, a lower postprandial C peptide level, a higher BMI, and a younger age. Analysis between age at diagnosis and DR showed that there is no association.

Table 2
Comparisons between patients in different levels of age at diagnosis

	Q1	Q2	Q3	Q4#
Age*	46.9 ± 6.79	55.2 ± 3.11	61.7 ± 4.84	66.9 ± 8.62
Age at diagnosis of diabetes (years)*	33.2 ± 4.83	43.4 ± 2.38	48.1 ± 1.70	59.2 ± 8.29
Diabetes duration*	13.7 ± 4.21	11.9 ± 4.18	13.5 ± 5.94	7.7 ± 4.21
BMI (kg/m ²)	30.1 ± 5.95	29.9 ± 6.76	28.9 ± 7.88	27.7 ± 8.23
Postprandial C-peptide (ng/ml)	2.86 ± 2.17	3.5 ± 2.24	2.9 ± 1.38	2.5 ± 1.63
HbA1c (%)	8.7 ± 1.56	9.1 ± 1.35	9.5 ± 1.86	9..9 ± 3.97
DR	8	5	4	3
NPDR (%)	6(42.9)	4(25)	3(42.9)	2(16.7)
DMO (%)	2(14.3)	1(6.3)	1(14.3)	1(8.3)

*comparison among groups showed significant differences.

#lowest quartile (Q1): age at diagnosis ≤ **38** years old; second quartile (Q2): ≤ **44.9** years old third quartile (Q3): ≤ **50.5** years old; highest quartile (Q4): **73** years old, age at diagnosis.

Abbreviations in the table: DR: diabetic retinopathy, NPDR: non-proliferative diabetic retinopathy, DMO: diabetic macular oedema, BMI: body mass index, and HbA1c: hemoglobin A1c.

Association between the level of C-peptide and DR

The clinical outcome of patients and demographic data from the lowest to the highest quartiles in terms of postprandial C-peptide are summarized in Table 3; according to the findings, patients with the lowest level of postprandial C-peptide had a younger age at diabetes diagnosis, a longer duration of diabetes, a lower BMI, and a higher HbA1c. Analysis between postprandial C-peptide and DR showed that postprandial C-peptide was negatively associated with DR with odds ratio: (0.569, CI: 0.370- 0.872).

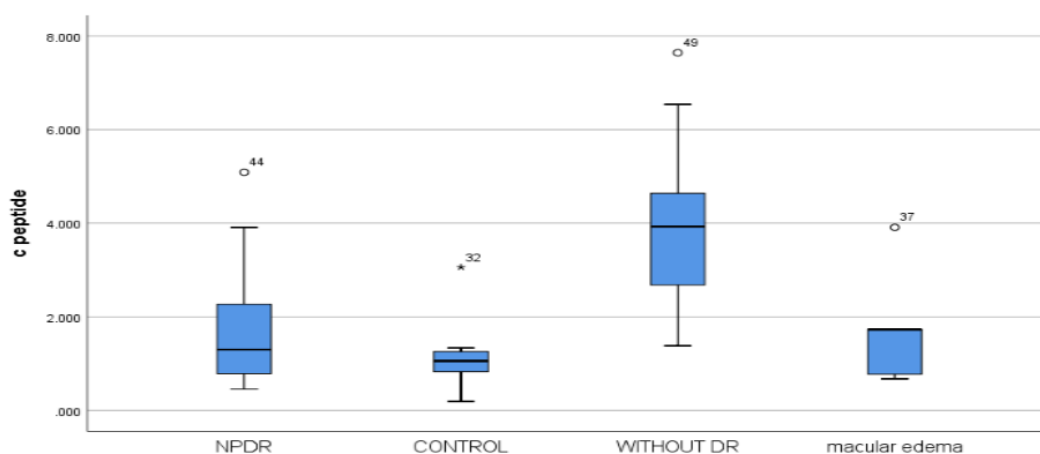


Figure 1: Comparison of C peptide NPDR, DMO and control

Table 3
Comparisons between patients in different levels of postprandial C-peptide

	Q1	Q2	Q3	Q4#
Age	55.9 ± 8.9	57.2 ± 12.07	56.29 ± 4.61	55.3 ± 10.7
Age at diagnosis of diabetes (years)	44.6 ± 13.32	43.8 ± 11.74	46.9 ± 7.10	44.5 ± 10.18
Diabetes duration	10.9 ± 6.53	13.4 ± 7.08	28.7 ± 3.9	10.8 ± 3.35
BMI (kg/m ²)	32.9 ± 6.54	30.7 ± 8.49	32.1 ± 6.5	27.6 ± 5.77
Postprandial C-peptide (ng/ml)*	0.68± 0.23	1.5 ± 0.41	3.1 ± 0.49	5.3 ± 1.25
HbA1c (%)	8.7 ± 2.78	9.2 ± 3.16	8.6± 1.79	9.04 ± 1.67
DR*	8	7	4	1
NPDR (%)	6(50)	5(38.5)	3(25)	1(8.3)
DMO (%)	2(16.7)	2(15.4)	1(8.3)	0(0.0%)

*comparison among groups showed significant differences

#lowest quartile (Q1): postprandial C-peptide ≤ 1.02 ng/dl; second quartile (Q2): > 1.02 ng/dl, postprandial C-peptide ≤ 2.32 ng/dl; third quartile (Q3): > 2.32 ng/dl, postprandial C-peptide ≤ 3.92 ng/dl; highest quartile (Q4): > 3.92 ng/dl, postprandial C-peptide.

Abbreviations in the table: DR: diabetic retinopathy, NPDR: non-proliferative diabetic retinopathy, DMO: diabetic macular oedema, BMI: body mass index, and HbA1c: hemoglobin A1c.

Discussion

A prior study suggested that younger onset of diabetes was linked to DR. A data show that patients with age less than 30-35 years were associated with a greater risk of retinopathy (Chuang et al., 2006; Yokoyama et al., 1997). Age at diagnosis of diabetes is the patient's age when the physician in the medical record first documented the diagnosis. The duration of diabetes was defined as the period from the time of diagnosis and the assessment time. (Sari & Balci, 2005). In this study, the results show a significant correlation between the diabetes duration and DR. It was suggested that patients with longer disease duration worsen the health of eyes by increasing the period of dysregulated in angiogenesis, glycemic control, and more ever infiltrate blood plasma components into the retina; therefore, higher rates of retinopathy. Cai (Cai et al., 2014) reported that in Chinese patients, the age at diagnosis of diabetes was negatively associated with DR. our data show no significant association between age at diagnosis and DR.

In this study, we observed a significant inversed relationship between serum postprandial C peptide concentrations and the development of diabetic retinopathy in patients with type 2 diabetes. According to the findings of this study, type 2 diabetes patients with lower blood C-peptide levels have a greater incidence of retinopathy. Our results are consistent with those found in a previous study of type 2 diabetic patients (Cai et al., 2014; Chung et al., 2015).

In type-2 diabetes, the link between C peptide and chronic problems is not well understood. A low amount of C peptide in the serum may contribute to the development of diabetic angiopathies. Macrovascular and microvascular diabetes problems have been studied in connection to C-peptide levels (Sari & Balci, 2005). The presence of residual insulin secretion was a protective effect in certain studies, whereas it was not strongly related to microvascular complications (Kim et al., 2012), (Williams et al., 2019), (Panero et al., 2009). The C peptide level greater than 10 pmol/L was linked to decreased risk of microvascular problems in clinical populations. A C-peptide value of less than 10 pmol/l was statistically significant as a risk factor for diabetic complications ($P = 0.03$). (Kuhntreiber et al., 2015). These findings from the study by Kuhntreiber et al. show that preserved C-peptide levels is associated with improved glycemic control (Kuhntreiber et al., 2015). However, glycemic control was equivalent between individuals with and without detectable c-peptide in the study reported by Williams et al. (Williams et al., 2019). On the other hand, modest amounts of endogenous stimulated C-peptide (less than 30 pmol/l) may be beneficial in maintaining fasting blood glucose levels, lower hemoglobin A1C, and prevent severe hypoglycemia (Vantyghem et al., 2012). Our results show elevated C-peptide levels might help prevent diabetic complications, which is consistent with prior studies (Cai et al., 2014; Kuhntreiber et al., 2015; Y. Wang et al., 2020). The results demonstrating an inversed connection between C-peptide blood levels and the development of NPDR and DMO (DR forms) in Random non-fasting sampling patients with type 2 diabetes mellitus strongly support the critical function of C-peptide in the etiology and pathophysiology of DR. However, we could not find any association between serum C-peptide levels and HbA1c, age at diagnosis of diabetes, diabetes duration and BMI. A previous study demonstrated that increases in serum C-peptide are associated with increases in BMI, blood pressure, serum triglyceride, and insulin

levels, indicating that elevated C-peptide levels are associated with an increased risk of metabolic syndrome (Kim et al., 2012). C-peptide level in random non-fasting sampling rCP has been shown to link with fasting c-peptide (fCP) and post-glucagon stimulation test (GST) samples in type 1 or type 2 diabetes. Furthermore, it has been reported that rCP connects with c-peptide responses measured during a 90-minute mixed meal tolerance test (MMTT) (Leighton et al., 2017). Postprandial C peptide or non-fasting C peptide levels may be considered the most straightforward, flexible approach for diabetic retinopathy diagnostics. In conclusion: the low postprandial C-peptide levels may be a biomarker for at-risk NPDR and DMO in T2DM patients.

Conflict of interest

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial or non-financial interest in the subject matter or materials discussed in this manuscript.

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