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Insulin and C-peptide response patterns in newly diagnosed Type 2 diabetes patients versus healthy controls: Demographic, anthropometric, and metabolic correlates

Umar Faruk Abdullahi

abdallahriko@gmail.com

Aminu Kano Teaching Hospital

Andrew Enemako Uloko

Bayero University Kano

Nura Hamidu Alkali

Abubakar Tafawa Balewa University

Adamu Girei Bakari

Ahmadu Bello University

Muhammad Arabi Saad

Modibbo Adama University

Jamila Mu'utassim Ibrahim

Aminu Kano Teaching Hospital Kano

Umar Musa Tambuwal

Usmanu Danfodiyo University Teaching Hospital

Zaitun Amin Hassan

Aminu Kano Teaching Hospital

Usain Abdullahi Ahmad

Federal University Dutse

Ibrahim Abdullahi Haladu

Muhammad Abdullahi Wase Teaching Hospital

Abdulgafar Lekan Olawumi

Aminu Kano Teaching Hospital Kano

Ibrahim Danjummai Gezawa

Bayero University Kano

Short Report

Keywords: Type 2 diabetes mellitus, Plasma insulin, C-peptide, β-cell function, HOMA-β, Insulin resistance

Posted Date: November 18th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11368690/v1

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Additional Declarations: No competing interests reported.

Abstract

Objective: To compare insulin and C-peptide levels between patients with newly-diagnosed Type 2 diabetes mellitus (T2DM) and non-DM controls, and to assess relationships between insulin, C-peptide and blood pressure, body mass index (BMI) and the homeostatic model assessment (HOMA) of insulin resistance (HOMA-IR) and beta cell function (HOMA-β).

Results: A case-control study of 100 newly-diagnosed, T2DM patients and 100 controls. Variables studied were fasting and 2-hour post-prandial (2HPP) glucose, insulin, C-peptide, HOMA-IR and HOMA-β. Compared to controls, cases had higher median BMI ($P < 0.001$) and blood pressure ($P < 0.001$), but lower plasma fasting insulin (FPI, 2.96 vs 10.87 μIU/ml; $P = 0.001$), 2HPP insulin (7.42 vs 13.21 μIU/Ml; $P < 0.001$), fasting C-peptide (0.17 vs 0.32 ng/ml; $P < 0.001$) and 2HPP C-peptide (0.60 vs 1.10 ng/ml; $P< 0.001$). Median FPI in cases was higher in men and correlated with HOMA-IR (Spearman $\rho = 0.45$; $P < 0.001$) and HOMA-β (Spearman $\rho = 0.46$; $P < 0.001$), but C-peptide didn't differ by gender, BMI or glycemic control. These findings show newly diagnosed T2DM patients in the study area had depleted β-cell function. Early assessment of β-cell reserve among Nigerians with T2DM could guide early insulin therapy.

Introduction

The prevalence of Type 2 diabetes mellitus (DM) is rising globally and across sub-Saharan Africa (SSA). The International Diabetes Federation has estimated that worldwide, 537 million adults had DM in 2021, which is projected to reach 783 million by 2045 [1]. The prevalence of Type 2 DM (T2DM) among adult Nigerians was estimated at 7.0%, corresponding to approximately 8 million people, although regional variations exist across the country [2].

The pathophysiology of T2DM involves peripheral insulin resistance combined with progressive pancreatic beta-cell secretory failure. Kahn's influential synthesis argued that while insulin resistance is typically present from an early, pre-diabetic stage, it is the decline in β-cell compensation, not insulin resistance per se, that determines the transition to overt hyperglycemia [3]. Subsequent work, including the Verona Newly Diagnosed T2DM Study, has shown that insulin resistance and β-cell dysfunction frequently coexist at DM diagnosis but β-cell dysfunction is more consistent [4].

The homeostasis model assessment (HOMA) of insulin resistance (HOMA-IR) and pancreatic β cell function (HOMA-β), derived from a single fasting glucose-insulin pair, is a widely used surrogate of insulin resistance and β-cell function in research settings due to its simplicity relative to clamp techniques [5, 6]. C-peptide, which is co-secreted with insulin from pancreatic β-cells in equimolar amounts but cleared far more slowly, offers a complimentary index of endogenous insulin secretion that is less distorted by hepatic extraction and exogenous insulin therapy [7]. Thus, fasting and stimulated C-peptide levels can be used as adjuncts or alternatives to insulin levels previously needed to characterize β-cell reserve, distinguish diabetes subtypes, and guide treatment decisions for DM patients [8].

A major determinant of insulin resistance and DM risk in Africa is adiposity, especially central adiposity. A Ghanaian study has associated the waist-hip ratio with incident T2DM [9], while a systematic review, also from Ghana, has documented a rising burden of overweight/obesity, especially in women [10]. Although obesity is more prevalent in women, β-cell reserve and insulin sensitivity are better in women than in men, probably due to the protective role of estrogen on pancreatic islet cells [11].

Few studies from Africa have utilized fasting plasma glucose, stimulated insulin and C-peptide levels to assess β-cell function in newly-diagnosed T2DM patients [12, 13]. A study of C-peptide levels among Nigerians with DM has found poor residual β-cell function in almost 70% [12], while a multicenter study of new-onset T2DM in Uganda, which assayed stimulated plasma glucose, C-peptide and insulin, found a smaller rate of 20% [13]. Insulin deficiency in the Ugandan study was strongly associated with body-mass index and higher levels of HbA1c [13].

In this study, we aimed to determine the clinical profiles, fasting and stimulated plasma insulin and C-peptide levels of newly-diagnosed diagnosed, treatment-naive T2DM patients compared to non-DM controls. A secondary aim was to assess whether insulin and C-peptide secretion varied by sex, adiposity, or glycemic control. Findings from this study could help guide individualized care of Nigerians with T2DM.

Methods

Study population and sampling

This was a case-control study of newly diagnosed, treatment-naive or diet-controlled adult patients with T2DM and non-DM controls recruited at the DM Clinic and the General Outpatient Clinic (GOPC) of Aminu Kano Teaching Hospital (AKTH), a tertiary referral hospital in Kano City, Northwest Nigeria. The study was conducted from 3rd August to 30th October, 2020.

Sample size calculation

The sample size was calculated using Cochran's formula, $n = Z^2 \times (pq)/ d^2$ [14], where n is the minimum sample size, Z is the standard normal (1.96) corresponding to a 95% confidence interval, p is the prevalence of T2DM in Nigeria (5.8%) [15], q is the alternate probability (1–p) = 0.942, and d is the level of precision, placed at 5%. Thus, $n = (1.96)^2 \times (0.058) \times (0.942)/ (0.05)^2 = 84$. We anticipated a 15% attrition rate and added 13 patients, which raised the final sample size to 97, rounded to 100.

Inclusion and exclusion criteria

Patients were included in the study if they had T2DM, were aged 40 years or more, were registered at the DM Clinic and had consented to participate. Control subjects were non-DM patients attending the GOPC and had consented to participate. Controls were age and sex-matched to cases at 1:1 (± 2.5 years).

Patients were excluded from the study if they were pregnant, were on insulin therapy, had Type-1 DM, had a debilitating disease (such as dementia, chronic obstructive pulmonary disease, etc.) or had the potential for acute stress-induced hyperglycemia (acute stroke, heart failure, severe sepsis, etc.).

Study instruments and variables

The study utilized a structured questionnaire that noted participant sociodemographic data (age, sex, ethnicity, level of education, etc.), clinical history (duration of T2DM, treatment history, vascular risk factors), and measurements of weight, height, waist circumference and hip circumference to derive the body mass index (BMI) and waist/hip ratio. Others included blood pressure (BP), lipid profile, fasting plasma glucose (FPG), 2-hour postprandial (2HPP) glucose, fasting plasma insulin (FPI), 2HPP insulin, fasting C-peptide, and 2HPP C-peptide.

Operational terms and definitions

The BMI was derived from the weight in kilograms divided by the square of the height in meters, and was categorized as underweight (< 18.5 kg/m^2), normal (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obese (≥ 30.0 kg/m^2). The waist/hip ratio was interpreted using the WHO Expert Consultation cutoffs [16]. Hypertension and dyslipidemia were defined according to standard criteria. T2DM was defined according to the American Diabetes Association diagnostic glycemic criteria of FPG ≥ 126 mg/dL, 2HPP glucose ≥ 200 mg/dL, HbA1c ≥ 6.5%, or random glucose ≥ 200 mg/dL with classic symptoms [17] at the time of first diagnosis, prior to initiation of glucose-lowering pharmacotherapy beyond diet and/or a short interval of oral therapy. Controls had normal FPG at screening and no history of DM.

Data collection procedures

Weight and height were measured on a stadiometer, with participant wearing light clothing and no shoes. The BP was the average of three readings measured with a mercury sphygmomanometer applied to the arm. Venous blood samples were collected for FPG, FPI, fasting C-peptide, HbA1c and lipid profile after an overnight (> 10 hours) fast, and again 2 hours after a standard mixed-meal for measurement of 2HPP glucose, 2HPP insulin and 2HPP C-peptide levels. The values for HOMA-IR and HOMA-β were calculated from the FPG (mmol/L) and FPI (μIU/ml) using the standard Mathews' formula, where HOMA-IR = (FPI x FPG)/ 22.5, and HOMA-β (%) = (20 x FPI)/ (FPG – 3.5) [5, 6].

Statistical analysis

Data were analyzed with the Statistical Package for the Social Sciences (SPSS) software version 25 (IBM Corporation, New York, USA). Continuous variables were presented as means and standard deviations, or medians and interquartile ranges (IQR), as appropriate. Between-group differences were tested with the Student's t test or Mann-Whitney U test. Multiple independent groups were compared with the Kruskal-

Wallis test. Categorical variables were compared using the chi-square or Fisher's exact tests. Spearman's ranked correlation was used to assess associations between continuous variables and levels of insulin/C-peptide in those with T2DM. P values < 0.05 were considered significant.

Ethical considerations

The study was approved by the AKTH Human Research Ethics Committee in a letter dated 26th August, 2019 (Ref. No. NHREC/21/08/2008/AKTH/EC/2580). All participants signed written, informed consent, and the study protocol conformed with the Declaration of Helsinki and the STROBE guidelines [18].

Results

Demographic characteristics

We enrolled 100 T2DM cases, aged and sex-matched with 100 controls. There were no differences between cases and controls with regards to median age (43 vs. 45 years, respectively; *P* = 0.459), 10-year age-groups (*P* = 0.160) or gender (56% vs 56% female; *P* = 1.000). The sociodemographic characteristics of participants are shown on Table 1.

Table 1
Sociodemographic and physical findings in Type-2 DM cases and controls

Characteristic	T2DM (n = 100)	Control (n = 100)	P value
Sex, *n (%)*			
Male	44 (44.0)	44 (44.0)	1.000
Female	56 (56.0)	56 (56.0)	
Age, median years (IQR)	43.0 (40.0–51.0)	45.0 (41.0–49.0)	0.459
Age group, years, n (%)			
40–49	64 (64.0)	76 (76.0)	0.160
50–59	32 (32.0)	20 (20.0)	
60–69	4 (4.0)	4 (4.0)	
Occupation, n (%)			
Government worker	41 (41.0)	72 (72.0)	< 0.001*
Trader, business person, artisan, etc.	50 (50.0)	28 (28.0)	
Farmer	7 (7.0)	0 (0.0)	
Educational level, n (%)			
Postgraduate degree	19 (19.0)	18 (18.0)	0.069
University degree/diploma	32 (32.0)	20 (20.0)	
Secondary school certificate	29 (29.0)	48 (48.0)	
Primary school certificate	7 (7.0)	4 (4.0)	
No formal education	13 (13.0)	10 (10.0)	
Residence, n (%)			
Urban	89 (89.0)	94 (94.0)	0.310
Rural	11 (11.0)	6 (6.0)	
Waist–hip ratio	N.A.	N.A.	
BMI, kg/m², median (IQR)	30.8 (27.4–34.6)	27.5 (23.0–31.2)	< 0.001*
BMI category, n (%)			

* Significant *P* value; Continuous variables were compared using the independent samples t-test or Mann-Whitney U test, as appropriate; Categorical variables were compared using the chi-square test or Fisher's exact test (Fisher–Freeman–Halton for age group), as appropriate; BMI, body mass index; BP, blood pressure; DM, diabetes mellitus; IQR, interquartile range.

Characteristic	T2DM (n = 100)	Control (n = 100)	P value
Sex, *n (%)*			
Underweight	2 (2.0)	1 (1.0)	< 0.001*
Normal	10 (10.0)	33 (33.0)	
Overweight	29 (29.0)	37 (37.0)	
Obese	59 (59.0)	29 (29.0)	
Systolic BP, mmHg, median (IQR)	130.0 (120.0–142.5)	120.0 (110.0–130.0)	< 0.001*
Diastolic BP, mmHg, median (IQR))	80.0 (78.0–90.0)	77.0 (70.0–80.0)	< 0.001*

* Significant *P* value; Continuous variables were compared using the independent samples t-test or Mann-Whitney U test, as appropriate; Categorical variables were compared using the chi-square test or Fisher's exact test (Fisher–Freeman–Halton for age group), as appropriate; BMI, body mass index; BP, blood pressure; DM, diabetes mellitus; IQR, interquartile range.

Anthropometric measures and blood pressure

Compared to controls, cases had significantly higher rates of obesity (59% vs. 29% respectively; $P < 0.001$), median systolic BP (130mmHg vs. 120mmHg, respectively; $P < 0.001$) and median diastolic BP (80mmHg vs. 77 mmHg, respectively; $P < 0.001$).

Fasting and stimulated plasma insulin, C-peptide, and other glycemic indices

Median levels of FPG, 2HPP glucose and HbA1c were significantly higher in cases compared to controls, whereas median FPI (2.96 vs. 10.87 μIU/mL, respectively; $P < 0.001$), 2HPP insulin (7.42 vs 13.21 μIU/mL; P < 0.001), fasting C-peptide (0.17 vs 0.32 ng/mL, respectively; $P < 0.001$) and 2HPP C-peptide (0.60 vs 1.10 ng/mL, respectively; $P < 0.001$) were significantly lower.

Subgroup analyses of T2DM cases

We examined cases for differences in the levels of insulin and C-peptide based on gender, glycemic control and BMI category. Compared to women, men had significantly higher levels of FPI (median 3.11 vs 2.77 μIU/mL, $P = 0.018$) and HOMA-IR ($P = 0.028$), but no differences were observed in 2HPP insulin and HOMA-β values. Splitting cases at the median HbA1c (8.6%) into good and poor DM control showed no difference in 2HPP insulin, HOMA-IR or HOMA-β (Table 2). Although FPI showed a trend for association with obesity, this was not significant (Kruskal-Wallis $P = 0.057$). Fasting and 2HPP C-peptide levels showed no difference with regards to gender, glycemic control or BMI category (Table 2).

Table 2
Comparisons of C-peptide and insulin secretion/sensitivity indices within the T2DM group by sex, glycemic control, and BMI category

Comparison by Sex					
Parameter	**Male (n = 44)**		**Female (n = 56)**		**P value**
Fasting C-peptide, *ng/mL*	0.15 (0.09–0.29)		0.17 (0.09–0.25)		0.684
2HPP C-peptide, *ng/mL*	0.60 (0.30–0.80)		0.55 (0.28–0.90)		0.732
FPI, *μIU/mL*	3.11 (2.68–3.74)		2.77 (2.52–3.26)		0.018*
2HPP insulin, *μIU/mL*	7.39 (6.99–7.79)		7.43 (6.93–7.83)		0.876
HOMA-IR	1.94 (1.51–2.50)		1.67 (1.37–2.05)		0.028*
HOMA-β, %	6.55 (4.56–8.67)		6.54 (4.57–8.54)		0.843
Comparison by Glycemic Control (HbA1c)					
Parameter	**HbA1c < 8.6% (n = 44)**		**HbA1c ≥ 8.6% (n = 56)**		**P value**
Fasting C-peptide, *ng/mL*	0.14 (0.09–0.23)		0.18 (0.09–0.32)		0.178
2HPP C-peptide, *ng/mL*	0.60 (0.40–0.90)		0.50 (0.20–0.80)		0.237
FPI, *μIU/mL*	2.96 (2.54–3.67)		2.97 (2.57–3.34)		0.892
2HPP insulin, *μIU/mL*	7.45 (6.92–7.88)		7.39 (6.93–7.73)		0.496
HOMA-IR	1.88 (1.50–2.30)		1.73 (1.36–2.32)		0.507
HOMA-β, %	5.60 (4.61–8.60)		6.68 (4.57–8.54)		0.562
Comparison by BMI Category					
Parameter	**UW (n = 2)**	**NW (n = 10)**	**OW (n = 29)**	**OB (n = 59)**	**P value**
FPI, *μIU/mL*	2.53 ± 0.11	2.52 ± 0.73	3.26 ± 0.81	3.10 ± 0.66	0.057
2HPP insulin, *μIU/mL*	8.38 ± 1.91	7.44 ± 1.25	7.37 ± 0.70	7.70 ± 1.06	0.445

* Statistically significant P value. Data are presented as median (interquartile range) for sex and glycemic-control comparisons, and as mean ± standard deviation (SD) for BMI category comparisons. Group sizes shown in parentheses. UW, underweight; NW, normal weight; OW, overweight; OB, obese. FPI, fasting plasma insulin; 2H-PPI, stimulated 2-hour plasma insulin; HOMA-IR, homeostatic model assessment of insulin resistance; HOMA-β, homeostatic model assessment of β-cell function.

Correlations among T2DM cases

The FPI positively correlated with HOMA-IR (Spearman's $\rho = 0.45$; $P < 0.001$, Fig. 1) and HOMA-β (Spearman's $\rho = 0.46$, $P < 0.001$), while 2HPP insulin levels positively correlated with age (Spearman's $\rho =$

0.21; $P = 0.032$). Neither FPI nor 2HPP insulin correlated with BMI, waist-hip ratio, FPG, 2HPP glucose, or HbA1c. Fasting C-peptide and 2HPP C-peptide levels didn't correlate with FPI, 2HPP insulin, HOMA-IR or HOMA-β, but fasting C-peptide did correlate with HbA1c (Spearman's $\rho = 0.20$, $P = 0.045$).

Discussion

In this study of newly-diagnosed, treatment-naïve T2DM patients, cases had higher BP and BMI, and higher rates of obesity compared to controls, which agrees with previous studies [9, 10]. T2DM cases had significantly lower fasting and stimulated insulin and C-peptide levels than controls, but lower HOMA-IR values and 22 times lower HOMA-β values (6.5% versus 147.6%). The low levels of HOMA-IR among cases is attributable to low FPI rather than enhanced insulin sensitivity, as the HOMA model is unreliable when β-cell reserve is markedly depleted [5, 6]. These findings suggest that secretory failure is the major defect at T2DM diagnosis, consistent with Kahn's model [3] and the Verona Newly Diagnosed T2DM Study [4].

Previous studies have shown the benefits of early insulin therapy in newly-diagnosed T2DM patients with severe β-cell secretory failure [19]. For instance, a Chinese study found that insulin therapy at T2DM diagnosis in those with depleted β-cell function resulted in drug-free remissions in half of patients after 12 months [19]. Thus, our findings could have therapeutic implications for T2DM care in Nigeria.

Insulin deficiency at T2DM onset is being increasingly reported in Africans. For instance, a Ugandan study found insulin deficiency associated with lower BMI and higher levels of HbA1c in 20% adults with newly-diagnosed T2DM [13]. A subsequent analysis of data from the same study showed the prevalence of insulin deficiency was up to 66.7% among underweight patients [20]. In contrast, 88% of our cases were overweight/obese, but there was no correlation between BMI and FPI. Thus, secretory defects in our study were not due to leanness or malnutrition. African immigrants in the United States have shown similar patterns, with insulin-deficient T2DM the most common subtype (45%) and often co-occurring with central obesity [21]. Black Americans are also 1.83 times more likely to have severe insulin-deficient DM compared to White Americans [22, 23]. In another study from Lagos, Nigeria, approximately 70% patients with hyperglycemic emergencies had poor residual β-cell function [12].

These findings challenge the view that African populations mostly exhibit hyperinsulinemia, a belief largely based on studies of African-Americans and Southern Africans [24, 25]. However, research in West Africa has shown that healthy men have lower insulin secretion relative to insulin sensitivity [26], just as men with T2DM exhibit lower levels of insulin secretion after a mixed meal or during clamp studies compared to European men [27]. In another study from Tanzania, the incretin effect was preserved in T2DM patients, unlike the reduced effect seen in Europeans. This suggests that hyperglycemia in Africans with T2DM is largely due to intrinsic defects in β-cell secretion, rather than impaired gut-hormone signaling [28].

In this study, plasma C-peptide levels were lower in cases compared to controls, as reported by Polonsky et al. [7], but did not correlate with insulin-based indices. Several factors could explain it. Plasma C-

peptide assays are not standardized, with inter-platform variability as high as 30–36% [8, 29]. People of African ancestry have reduced and variable hepatic insulin clearance [25, 26], and our T2DM cases had a narrow range of values due to a high rate of insulin deficiency. Lastly, some of our patients may have had ketosis-prone atypical DM characterized by reversible insulin deficiency, which is common in SSA [30].

Compared to women in this study, men had higher levels of FPI and HOMA-IR, but not C-peptide, possibly due to gender differences in insulin clearance [11, 25]. Insulin and C-peptide levels did not differ by HbA1c, suggesting that the secretory defect was already established at diagnosis rather than driven by severe hyperglycemia as previously reported in Nigeria [12]. However, the narrow range of HbA1c levels (IQR, 8.1–9.5%) may also have masked any association between higher levels of HbA1c and insulin deficiency previously reported in Uganda [13].

Strengths and limitations

A major strength of this study was the case-control design that allowed for valid comparisons of pancreatic β cell function between newly-diagnosed T2DM patients and non-DM controls in a Nigerian population that was not previously studied. The study also had some limitations. Being a case-control study conducted at one center, we couldn't make causal inferences, and the generalizability of our findings were limited. We assessed β-cell function using a mixed-meal test and HOMA surrogates instead of the oral glucose tolerance test or clamp techniques that are more reliable. Lastly, we did not assay islet cell autoantibodies and plasma ketones to identify latent autoimmune DM or ketosis-prone DM.

Conclusion

Newly-diagnosed T2DM patients had impaired β-cell function compared to controls, as shown by the severe and significant reductions of fasting and stimulated plasma insulin and C-peptide levels. Low levels of HOMA-β among cases provide further evidence of β-cell failure. Other studies have shown the benefits of early insulin therapy in newly-diagnosed T2DM patients. Thus, C-peptide assays could guide early insulin therapy for improved care of new T2DM in Nigeria.

Abbreviations

2HPP2 - hour post-prandial

AKTH - Aminu Kano Teaching Hospital

BMI - Body Mass Index

BP - Blood Pressure

DM - Diabetes Mellitus

FPG - Fasting Plasma Glucose

FPI - Fasting Plasma Insulin

GOPC - General Outpatient Clinic

HbA1c - Glycated Hemoglobin

HOMA - IRHomeostasis Model Assessment of insulin resistance

HOMA-β - Homeostasis Model Assessment of β-cell function

IQR - Interquartile Range

SPSS - Statistical Package for the Social Sciences

SSA - Sub-Saharan Africa

STROBE - Strengthening the Reporting of Observational Studies in Epidemiology

T2DM - Type 2 Diabetes Mellitus

WHO - World Health Organization

Declarations

Ethics approval and consent to participate

The study was approved by the Human Research Ethics Committee of Aminu Kano Teaching Hospital, Kano, Nigeria (Ref. No. NHREC/21/08/2008/AKTH/EC/2580; 26 August 2019). Written informed consent to participate was obtained from all participants before enrolment. The study was conducted in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Authors' contributions

• UFA, AGB, IDG and AEU conceived and designed the study.

• MAS, MUT, IAH and UAA conducted the literature search.

• UFA, JMI, IAH, MAS and ZAH supervised the collection and assembly of data.

• ALO, NHA, UFA and AEU analyzed the data.

• JMI, MAS, ZAH, UAA and MUT proofread the manuscript.

• Writing-Original draft: UFA, NHA, AEU, IDG and AGB

• All authors drafted and revised the manuscript.

• All authors approved the final version of the manuscript.

Acknowledgements

The authors thank the staff and members of the Department of Chemical Pathology and the Diabetes Outpatient Clinic of Aminu Kano Teaching Hospital, Kano, for their support during the study.

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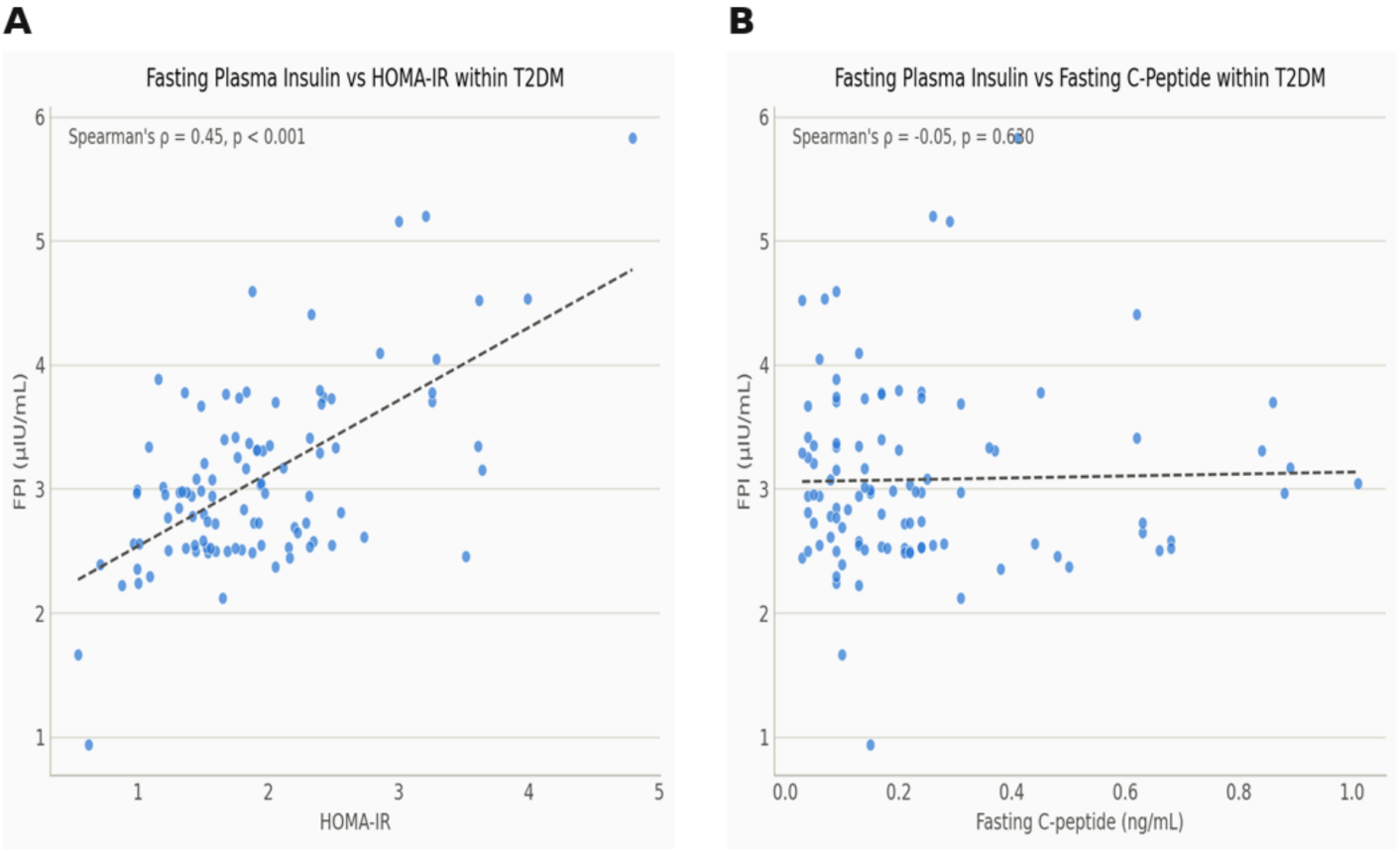
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Figures



A. Fasting plasma insulin versus HOMA-IR within the T2DM group.

B. Fasting plasma insulin versus fasting C-peptide within the T2DM group.

Figure 1

A scatter diagram of (A) fasting plasma insulin levels versus HOMA IR, and (B) fasting plasma insulin versus fasting C-peptide levels among T2DM patients.