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Exploring serum Dipeptidyl peptidase-4 levels: Associations with diabetes, glucose control and peripheral artery disease

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ABSTRACT

Objectives: Elevated serum Dipeptidyl peptidase-4 (DPP4) levels have emerged as a potential diagnostic biomarker for diabetes. This study aimed to investigate the association between serum DPP4 levels and diabetes, explore potential pathophysiological mechanisms and assess the clinical implications.

Material and Methods: Serum DPP4 levels were measured in participants, and their diabetes status was determined. Statistical analysis was employed to evaluate associations between DPP4 levels and diabetes, as well as their impact on glycaemic control and potential implications for diabetes management.

Results: Elevated serum DPP4 levels were significantly associated with diabetes. Higher DPP4 levels correlated with poorer glucose control. Notably, individuals with diabetes and peripheral arterial disease (PAD) exhibited markedly elevated DPP4 levels, suggesting a link between DPP4 and PAD in diabetes.

Conclusion: Serum DPP4 levels hold promise as a diagnostic tool for identifying diabetes and assessing its severity. This finding raises questions about the role of DPP4 in glucose metabolism and vascular complications. Further research may unveil mechanisms and therapeutic opportunities, potentially enhancing personalised diabetes care and preventive strategies for PAD in diabetic populations.

Keywords: Dipeptidyl peptidase 4, peripheral arterial disease, diabetes, glycaemic control, glucose metabolism

INTRODUCTION

Diabetes mellitus is a complex metabolic disorder characterised by chronic hyperglycaemia resulting from defects in insulin secretion, insulin action or both.[1] It represents a significant global health concern due to its increasing prevalence and the associated risk of various complications, including cardiovascular diseases.[2]

Dipeptidyl peptidase-4 (DPP4), also known as CD26, is an enzyme found in various tissues and cells, including endothelial cells, lymphocytes and adipocytes.[3] One of its prominent roles is the cleavage and inactivation of incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP).[4] Incretins play a crucial role in glucose homeostasis by enhancing insulin secretion and suppressing glucagon release in response to nutrient ingestion.[5]

Recent research has highlighted the potential significance of serum DPP4 levels in the context of diabetes and related complications.[6] Elevated serum DPP4 levels have been associated with

insulin resistance, impaired glucose tolerance and increased risk of developing type 2 diabetes.[7] Moreover, DPP4 inhibitors, which block the enzymatic activity of DPP4 and thereby increase the bioavailability of incretin hormones, have emerged as a class of antidiabetic medications.[8]

This study aims to explore the relationships between serum DPP4 levels, diabetes and glucose control measures, particularly glycated haemoglobin (HbA1c) and fasting plasma glucose (FPG). Additionally, it seeks to investigate the potential association between serum DPP4 levels and the presence of peripheral artery disease (PAD), a common and serious vascular complication often observed in individuals with diabetes.

Understanding the role of serum DPP4 levels in diabetes and its complications may offer valuable insights into the pathophysiological mechanisms underlying these conditions. Furthermore, it could provide a basis for the development of novel diagnostic and therapeutic strategies, potentially improving the management and prevention of diabetes and its associated vascular complications. This exploration into serum DPP4 levels and their associations with diabetes, glucose control and PAD represents a significant step towards advancing our knowledge in the field of metabolic and vascular disorders.

MATERIAL AND METHODS

This research adopted a cross-sectional design conducted at the University of Ilorin Teaching Hospital, Ilorin, Kwara State, Nigeria. The study was conducted at the Diabetes clinic, medical outpatient department, and medical wards of the University of Ilorin Teaching Hospital (UITH). UITH is a 650-bed tertiary health facility situated in Ilorin, the capital of Kwara State, North-central Nigeria. Ilorin has a population of approximately 2,591,555 people, consisting mainly of Yorubas but also with residents from other ethnic groups such as Fulani, Hausa, Baruba and Igbo. The population is engaged in various occupations, including farming, trading, artisan work, private employment and civil service. UITH serves as a referral centre for patients from Kwara state and neighbouring states, including Osun, Oyo, Ekiti, Kogi and Niger. The Diabetes clinic, overseen by three Consultant Endocrinologists and three resident doctors, conducts weekly clinics attended by around 40 patients with Type 2 Diabetes (T2DM). The study included adults with T2DM attending the Diabetes Clinic at UITH and age- and sex-matched healthy controls, comprising hospital staff and non-diabetic relatives of patients. This resulted in two groups: The diabetes group and the non-diabetes group.

Diabetes was defined based on the WHO (2020) diagnostic criteria, considering symptoms of hyperglycaemia, random plasma glucose levels, fasting plasma glucose levels and the duration of glucose-lowering treatment. PAD was identified by the Ankle Brachial Index (ABI), categorising individuals into definite PAD, borderline PAD, low-normal ABI, no PAD or stiff calcified arteries based on their ABI values. The study involved consecutive consenting patients diagnosed with Type 2 Diabetes Mellitus (T2DM) who attended the Diabetes Clinic, as well as age- and sex-matched healthy controls, comprising hospital staff and non-diabetic relatives, were recruited for the study. Inclusion criteria included age, consent to participate and specific glucose levels for both the diabetes and non-diabetes groups. Exclusion criteria included individuals with specific medical conditions or procedures that could affect the objective of the study.

Human DPP-4 levels were assessed using the Bioassay Technology Laboratory Elisa assay kit (Korain Biotech Co., Shanghai, China) based on immunoassay principles.[9] The plate, pre-coated with DPP-4 antibody, enabled the binding of DPP-4 from samples. Following standards, blanks and sample placement, incubation occurred at 37°C for 90 min. Subsequently, a Biotinylated Detection Antibody was added, incubated and liquid-decanted. Wash buffer was applied thrice, Streptavidin-Horseradish Peroxidase (HRP) Conjugate was incubated and then decanted. The washing process was repeated five times using a wash buffer, Substrate Reagent was added and incubated, followed by the addition of Stop Solution. Optical density (OD) was spectrophotometrically measured at 450 nm, its value proportional to DPP-4 concentration, determined via comparison with a standard curve. HbA1C levels were measured using the Agappe Mispa-i2 kit (Agappe Diagnostics Switzerland GmbH). Based on immunonephelometry, antigen–antibody complex lattice scattering light was utilised for direct determination of HbA1c in whole blood. Antigen–antibody complex interaction led to agglutination, measured to calculate HbA1c percent from a calibration curve.[10] Spectrophotometric measurement of serum lipids was done by CHEMRAY 240 chemistry auto-analyser. Hydrolysis of lipid esters by esterase generated hydrogen peroxide, which reacted with 4-aminoantipyrine and phenol in the presence of peroxidase, forming red quinoneimine dye. Dye intensity was proportional to lipid level.[11,12] Photometric determination of glucose employed the Agappe glucose kit (Agappe Diagnostics Switzerland GmbH). Glucose oxidation to glucuronic acid and hydrogen peroxide was catalysed by glucose oxidase. The addition of peroxidase and a chromogenic oxygen acceptor yielded a coloured compound measured at 505 nm, its absorbance proportional to glucose amount.[13]

RESULTS

Table 1 presents an overview of the socio-demographic characteristics of both subjects and controls. Among the

Table 1: Socio-demographic characteristics of study subjects and controls.

Sociodemographic characteristics	Diabetic subjects (n = 100) (%)	Non-diabetic controls (n = 100) (%)	χ^2	p-value
Mean Age (years) ± SD	55.72 ± 6.12*	55.7 ± 6.11*	0.023¶	0.962
Age group(years)				
45–49	22 (22)	22 (22)	0.104	1
50–54	19 (19)	19 (19)		
55–59	20 (20)	20 (20)		
60–64	35 (35)	35 (35)		
65–69	4 (4)	4 (4)		
Sex				
Male	39 (39)	39 (39)	0.021	0.885
Female	61 (61)	61 (61)		
Education				
None	18 (18)	17 (17)	9.083	0.058
Primary	24 (24)	9 (9)		
Secondary	21 (21)	25 (25)		
Tertiary	29 (29)	40 (40)		
Postgraduate	8 (8)	9 (9)		
Marital status				
Single	2 (2)	6 (6)	3.188	0.375
Married	86 (86)	85 (85)		
Divorced	1 (1)	2 (2)		
Widowed	11 (11)	7 (7)		
Occupation				
Trader	49 (49)	41 (41)	11.524	0.06
Civil servant	35 (35)	46 (46)		
Caterer	1 (1)	0		
Retiree	7 (7)	1 (1)		
Unemployed	1 (1)	0		
Farmer	4 (4)	9 (9)		
Driver	1 (1)	0		
Clergy	2 (2)	3 (3)		
Ethnicity				
Yoruba	95 (95)	93 (93)	1.876	0.705
Hausa	1 (1)	2 (2)		
Igbo	1 (1)	0		
Others	3 (3)	5 (5)		
Religion				
Islam	48 (48)	38 (38)	3.596	0.199
Christianity	52 (52)	60 (60)		
Traditional	0	1 (1)		
Others	0	1 (1)		

The statistical test of significance was done using Fisher's exact test.
¶Statistical test of significance was done using an independent t-test.
*Represents mean±standard deviation (SD).

participants, 121 (60.5%) were females, while 79 (39.5%) were males. This gender distribution was equally represented in both the diabetes and non-diabetic groups, with 39% of males and 61% of females in each group. The mean age (SD) of the entire study population was 55.7 ± 6.12 years for the study subjects and 55.7 ± 6.11 years for the controls, indicating a balanced age distribution between the two groups. In terms of educational background, individuals with tertiary education constituted the largest proportion in both groups, accounting for 29% of subjects and 40% of controls.

Within the cohort of individuals with type 2 diabetes mellitus (T2DM), the majority (86%) were married, while 11% were widowed, 2% were single and 1% were divorced. In the control group, 85% were married, 7% were widowed, 6% were single and 2% were divorced. Regarding ethnicity, a significant proportion of participants in both the subject and control

Table 2: Clinical characteristics of the study population.

Clinical characteristics of the study population	Diabetic subjects (n = 100) (%)	Non-diabetic controls (n = 100) (%)	Chi-square (χ^2)	p-value
History of HTN	66	37	16.835	<0.001**
Median duration of HTN (years)*	4 (0–7)	5 (1.5–6)		
Median duration of DM (years)*	4.5 (2–8)*	0		
Family history of DM	34	11	16.71	<0.001**
Stroke	5	0	5.128	0.059
Myocardial infarction	1	0	1.005	1
Amputation	1	0	1.005	1
Cigarette smoking	2	3	0.205	1
Median duration of smoking (years)*	4 (0–4)	5 (3–5)		
Alcohol intake	6	3	1.047	0.498
Median quantity of alcohol consumed (gram/week)*	120 (105–135)	240 (120–240)		
Exercise	24	31	1.229	0.342
Median number of exercise days per week*	3 (2–3)	2 (1–3)		
Intermittent claudication	10	3	4.031	0.082
DMFU	21	0	23.464	<0.001**

The statistical test of significance was done using Fisher's exact test.
**represents a significant p-value.
*represents median Interquartile range (IQR). The respective continuous variables were not uniformly distributed and they thus are summarised in median (IQR) instead of using mean ± SD.
HTN: Hypertension; DMFU: Diabetic foot ulcer; DM: diabetes mellitus.

groups identified as Yoruba, with 95% and 93%, respectively, belonging to this ethnic group.

These socio-demographic characteristics provide valuable context for understanding the study population and its composition, ensuring a comprehensive analysis of the research findings.

Table 2 presents an overview of the clinical characteristics observed within the study population. Noteworthy findings include:

The prevalence of a history of hypertension (HTN) was significantly higher among individuals in the diabetes group, with 66% reporting a history of HTN, compared to 37% in the control group ($p = 0.001$). This finding underscores the common co-occurrence of diabetes and hypertension, which carries implications for the management and care of individuals with diabetes.

A substantial difference was noted in the occurrence of a positive family history of diabetes between the two groups. In the diabetes group, 34% had a positive family history of diabetes, while only 11% in the non-diabetic group reported the same ($p < 0.001$). This highlights the role of genetic predisposition in diabetes and emphasises the significance of family history as a risk factor.

Among individuals in the diabetes group, the median duration of diabetes (DM) was 4.5 years, within the range of 2 to 8 years. This parameter provides insight into the chronicity of the disease within this cohort.

Within the diabetes group, 21% of participants had a history of diabetic foot ulceration (DMFU). As anticipated, none of the individuals in the control group reported a history of DMFU ($p = 0.001$). The presence of DMFU among those with diabetes underscores the importance of preventive strategies and specialised care to mitigate complications associated with diabetes-related foot issues.

These clinical characteristics shed light on the health status and medical history of the study participants, highlighting significant factors such as hypertension, a familial predisposition to diabetes and the presence of DMFU. These findings suggest the complexity of diabetes management and emphasise the importance of holistic healthcare approaches in addressing these associated conditions. The mean serum DPP4 level was significantly higher in participants with diabetes (31.71 ± 7.09 ng/mL) compared to non-diabetic controls (22.78 ± 7.63 ng/mL) with a p-value of <0.001 [Table 3]. This suggests a potential association between serum DPP4 levels and the presence of diabetes.

The mean serum DPP4 level was significantly higher in participants with diabetes (31.38 ± 11.89 ng/mL) compared to non-diabetic controls (24.71 ± 9.26 ng/mL) with a p-value of <0.001 [Table 4]. Participants with diabetes had a significantly higher mean HbA1c (7.23 ± 2.69%) compared to non-diabetic

Table 3: Serum DPP4 levels of the participants.

	Diabetic subjects (n = 100) (mean ± SD)	Non-diabetic controls (n = 100) (mean ± SD)	T	p-value
Serum DPP4 levels (ng/mL)	31.71 ± 7.09	22.78 ± 7.63	4.425	<0.001**

The statistical test of significance was done using an independent sample t-test.

**represents a significant p-value, DPP4: Dipeptidyl peptidase-4, SD: Standard Deviation.

Table 4: Serum DPP4 levels and glucose control among participants.

	Subjects	Controls	T	p-value
HbA1c (%)	7.23 ± 2.69	5.47 ± 1.89	5.367	<0.001**
DPP4 levels (ng/mL)	31.38 ± 11.89	24.71 ± 9.26	4.425	<0.001**
FPG (mmol/L)	6.08 ± 1.27	4.86 ± 0.90	7.819	<0.001**
Serum DPP4 (mmol/L)				
PAD	35.98 ± 7.55	23.36 ± 8.36	4.361	<0.001**
No PAD	30.22 ± 6.33	22.72 ± 7.60	6.899	<0.001**

The statistical test of significance was done using an independent sample t-test.

**represents a significant p-value, HbA1c: haemoglobin, DPP4: Dipeptidyl peptidase-4, FPG: fasting plasma glucose, PAD: peripheral arterial disease.

controls (5.47 ± 1.89%) with a p-value of <0.001. The mean fasting plasma glucose (FPG) was significantly higher in participants with diabetes (6.08 ± 1.27 mmol/L) compared to non-diabetic controls (4.86 ± 0.90 mmol/L) with a p-value of <0.001. These findings suggest a potential relationship between higher serum DPP4 levels, poorer glucose control (as indicated by higher HbA1c and FPG) and the presence of diabetes.

Participants with diabetes and PAD had significantly higher mean serum DPP4 levels (35.98 ± 7.55 ng/mL) compared to non-diabetic participants with PAD (23.36 ± 8.36 ng/mL) with a p-value of <0.001 [Table 4]. Participants with diabetes but without PAD also had significantly higher mean serum DPP4 levels (30.22 ± 6.33 ng/mL) compared to non-diabetic participants without PAD (22.72 ± 7.60 ng/mL) with a p-value of 0.001. The mean serum DPP4 level was higher in participants with PAD (regardless of diabetes status) compared to those without PAD. These results suggest a potential link between elevated serum DPP4 levels and the presence of PAD, and this association might be influenced by the presence of diabetes.

DISCUSSION

Elevated serum DPP4 levels may serve as a potential biomarker for the presence of diabetes.[13] This finding suggests that measuring serum DPP4 levels could be a useful diagnostic tool in identifying individuals with diabetes.[14] Healthcare providers could incorporate this biomarker into routine screening protocols, allowing for earlier detection and intervention in diabetes cases.[15]

The observed association between higher serum DPP4 levels and diabetes raises questions about the potential pathophysiological role of DPP4 in diabetes development. Further research is needed to elucidate the mechanisms underlying this association. It may involve DPP4's impact on incretin hormones and insulin resistance,[16] which could be explored in future studies.

Understanding the relationship between serum DPP4 levels and diabetes may have therapeutic implications. DPP4 inhibitors which are already used as antidiabetic medications, work by blocking DPP4's enzymatic activity, leading to increased incretin hormone levels and improved glycaemic control.[17] This finding reinforces the relevance of DPP4 inhibitors in diabetes management and suggests the need for further investigations into their optimal use.[18]

Clinically, assessing serum DPP4 levels in individuals at risk of developing diabetes may help identify those who are more susceptible to the condition. This information could guide personalised preventive strategies, such as lifestyle modifications or early pharmacological interventions, for individuals with elevated DPP4 levels.[19]

The association between DPP4 levels and diabetes highlights the importance of continued research into the role of DPP4 in diabetes. Future studies could explore whether serum DPP4 levels correlate with diabetes severity, complications or treatment response. Additionally, investigating whether changes in serum DPP4 levels over time can predict diabetes progression or regression could provide valuable clinical insights.[20]

The observed association between higher serum DPP4 levels and poorer glucose control, as indicated by higher HbA1c and FPG in participants with diabetes, raises questions about the role of DPP4 in glucose metabolism. It also suggests that DPP4 might be involved in mechanisms related to glycaemic regulation and insulin sensitivity.[21]

Given the association between elevated serum DPP4 levels and poorer glucose control, this finding reinforces the relevance of DPP4 inhibitors as antidiabetic medications.[22] DPP4 inhibitors, by blocking the enzymatic activity of DPP4 and increasing the bioavailability of incretin hormones, may help improve glycaemic control in individuals with diabetes.[23]

Clinically, assessing serum DPP4 levels could help identify individuals at higher risk of experiencing poor glucose control and diabetes.[24] This information could guide more personalised treatment plans and preventive strategies for individuals at risk.[25]

These findings highlight the need for further research to elucidate the mechanisms underlying the relationship between DPP4 levels and glucose control. Understanding how DPP4 influences glucose metabolism could lead to the development of more targeted and effective therapies.[26]

If serum DPP4 levels are established as a reliable marker for diabetes risk and glucose control, this information could lead to earlier interventions and lifestyle modifications for individuals at risk of developing diabetes, potentially delaying or preventing its onset.[27]

The significantly higher mean serum DPP4 levels in participants with diabetes and PAD compared to non-diabetic participants with PAD ($p < 0.001$) suggest a potential link between elevated DPP4 levels and the presence of PAD in individuals with diabetes. This finding aligns with the well-established knowledge that individuals with diabetes are at higher risk for vascular complications, including PAD.[28]

The observed differences in serum DPP4 levels between diabetic participants with and without PAD suggest that serum DPP4 levels could serve as a potential biomarker for PAD in individuals with diabetes.[29] This could be valuable for early diagnosis and risk stratification.

The association between elevated serum DPP4 levels and PAD in diabetes raises questions about the underlying pathophysiological mechanisms. Further research is needed to investigate whether DPP4 plays a direct role in vascular dysfunction, inflammation or atherosclerosis, all of which are components of PAD development.[30]

Assessing serum DPP4 levels in individuals with diabetes could help identify those at higher risk of developing PAD.[31] This information could prompt more vigilant monitoring and preventive measures, such as lifestyle modifications and antiplatelet therapies.[32]

The presence of diabetes appears to influence the association between serum DPP4 levels and PAD.[33] Understanding the interplay between diabetes, DPP4 and PAD could lead to more targeted approaches for managing vascular complications in diabetic populations.[34]

CONCLUSION

In conclusion, elevated serum DPP4 levels hold promise as a potential biomarker for diabetes, offering a diagnostic tool to identify individuals at risk. The association between higher DPP4 levels and diabetes underscores the need for further research into its pathophysiological role, potentially involving impacts on incretin hormones and insulin resistance. This finding reiterates the significance of DPP4 inhibitors in diabetes management and emphasises their potential in preventing and treating diabetes. Assessment of serum DPP4 levels can guide tailored interventions and treatment plans, enhancing personalised care. Furthermore, the link between elevated DPP4 levels and PAD in diabetes suggests new avenues for PAD risk assessment and therapeutic strategies.

Ethical approval

The research/study approved by the Institutional Review Board at the Faculty of Basic Clinical Sciences University of Ilorin Teaching Hospital, number COHS/FCSERC/2022/04/007, dated 2022.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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