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ORIGINAL RESEARCH

Evaluation of Vitamin B12 Deficiency Among Patients with Type 2 Diabetes Mellitus on Metformin at Hoima Regional Referral Hospital, Uganda

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Background: Metformin is the cornerstone of type 2 diabetes mellitus (T2DM) management but has been linked to vitamin B12 deficiency (VB12D), a condition with potential hematological, neurological, and neuropsychiatric consequences. Despite this association, little is known about its burden in Uganda. This study aimed to determine the prevalence, associated factors, and clinical outcomes of VB12D among patients with T2DM on metformin at Hoima Regional Referral Hospital (HRRH).

Methods: A hospital-based cross-sectional study was conducted involving 257 adult T2DM patients on metformin attending the diabetic clinic at HRRH between February and April 2024. Data were collected using interviewer-administered questionnaires and chart reviews. Serum vitamin B12 levels were measured using an electrochemiluminescence immunoassay. Deficiency was defined as levels <150 pg/mL. Data were analyzed using STATA v17. Logistic regression was used to determine factors independently associated with VB12D.

Results: The prevalence of VB12D among participants was 10.1%. Independent factors associated with VB12D included metformin use ≥10 years (AOR 3.94; 95% CI 1.34–11.56), daily dose of 2000 mg (AOR 4.32; 95% CI 1.47–12.67), and elevated glycated hemoglobin (AOR 2.63; 95% CI 1.08–6.41). Clinical outcomes significantly associated with VB12D included peripheral neuropathy (76.9% vs 46.8%, p=0.005) and neuropsychiatric symptoms (50.0% vs 28.6%, p=0.042).

Conclusion: Vitamin B12 deficiency is relatively common among T2DM patients on metformin at HRRH. Longer duration and higher dosage of metformin, as well as poor glycemic control, were significantly associated with deficiency. Peripheral neuropathy and neuropsychiatric manifestations were more frequent among those deficient. Routine screening for VB12D, especially in patients on long-term and high-dose metformin, is recommended to reduce morbidity.

Keywords: vitamin B12 deficiency, diabetes mellitus, metformin

Introduction

Diabetes mellitus, particularly type 2 (T2DM), is a chronic metabolic disorder characterized by insulin resistance and impaired insulin secretion. Among oral hypoglycaemic agents, metformin remains the first-line treatment due to its effectiveness, affordability, and low risk of inducing hypoglycaemia. However, evidence linking metformin to vitamin B12 deficiency (VB12D) has grown over the past five decades. Reports as early as the 1970s have documented the association, and later randomized controlled trials confirmed that long-term metformin use leads to reduced serum B12 levels, with potential clinical

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manifestations such as neuropathy and cognitive dysfunction.[1–3] The underlying mechanism is thought to involve interference with B12 absorption in the terminal ileum, alterations in gut microbiota, and impaired calcium-dependent uptake.[3]

Globally, more than 463 million people are living with diabetes, with projections suggesting a substantial increase in the coming decades.[4] Prevalence of metformin-associated VB12D has been reported between 5.8% and 30%, depending on dose, duration of therapy, and patient characteristics.[5–7] In clinical practice, VB12D may mimic or exacerbate diabetic neuropathy, leading to diagnostic confusion and delayed interventions.[8] Consequently, international guidelines increasingly recommend periodic monitoring of B12 levels in metformin users, especially those with high dose exposure or long treatment duration.[3]

In Africa, the burden of diabetes is rising rapidly. The continent had an estimated 15.5 million diabetic adults in 2017, expected to increase to nearly 24 million by 2030.[9] Prevalence of VB12D among T2DM patients on metformin in sub-Saharan Africa has ranged from 6.6% to 28.1%, with similar associations observed between VB12D and long-term or high-dose metformin use.[10–12] Yet, many settings in Africa lack protocols for routine B12 assessment in diabetic patients, and VB12D remains an under-recognized cause of neurological and haematologic complications.

In Uganda, the diabetes burden continues to rise, with prevalence rates estimated at 16.1% in rural and 7.6% in urban populations.[13] More than half of all diabetic patients remain undiagnosed.[14] A study at Mulago National Referral Hospital reported VB12D in 10.7% of ambulatory T2DM patients.[15] However, this included individuals on various therapies, not specifically metformin. At Hoima Regional Referral Hospital (HRRH), a large proportion of T2DM patients are managed on metformin, yet B12 status is not routinely assessed, and the true prevalence and correlates of VB12D remain unclear.

The proposed mechanism linking metformin to vitamin B12 deficiency involves interference with calcium-dependent absorption of the intrinsic factor–B12 complex and alterations in gut microbiota, further supporting the rationale for this study.[15]

Although there is strong evidence linking prolonged metformin use to B12 deficiency, there are no national or institutional guidelines in Uganda mandating screening for this deficiency in T2DM patients. HRRH serves over 150 diabetic patients monthly, with the majority prescribed metformin. Without routine B12 testing, many cases of deficiency may remain undetected, leading to irreversible neurological damage, particularly in resource-limited settings. This study aimed to determine the prevalence of vitamin B12 deficiency among T2DM patients on metformin at HRRH, identify the associated factors, and assess its clinical impact, particularly on neuropathy and neuropsychiatric outcomes. The findings are expected to guide local screening protocols and contribute to policy development to improve patient outcomes.

Methodology

Study Design and Setting

This was a hospital-based cross-sectional study conducted at the outpatient diabetes clinic of Hoima Regional Referral Hospital (HRRH), a tertiary-level public hospital located in western Uganda. The hospital serves as the main referral centre for several surrounding districts and receives a high volume of patients with type 2 diabetes mellitus (T2DM), most of whom are treated with metformin. The study was conducted between April and June 2025.

Study Population and Sampling

The target population consisted of adult patients aged 18 years and above, with a confirmed diagnosis of T2DM, who had been on metformin therapy for at least three months. Patients were consecutively recruited during their routine outpatient visits. Exclusion criteria included patients who were critically ill, pregnant, or had known chronic kidney disease, in order to eliminate conditions that could independently affect vitamin B12 metabolism. The sample size was calculated using the Leslie Kish formula, based on a prior prevalence of 10.7% of vitamin B12 deficiency among diabetic patients in Uganda, yielding a total of 257 participants.

Data Collection

Data were collected using a structured and pre-tested interviewer-administered questionnaire. Information gathered included sociodemographic data (age, sex, education level, occupation), clinical characteristics (duration of diabetes,

duration and dose of metformin use, glycaemic control, presence of comorbidities), and potential symptoms of neuropathy or neuropsychiatric disturbances. Physical measurements such as weight, height, and blood pressure were taken using standard procedures. Peripheral neuropathy was assessed clinically, and neuropsychiatric symptoms were evaluated through self-report and confirmation with clinical records.

Laboratory Testing and Definitions

Blood samples were drawn aseptically and processed at the HRRH central laboratory. Serum vitamin B12 levels were measured using the ARCHITECT B12 immunoassay analyzer. Vitamin B12 deficiency was defined as a serum concentration below 150 pg/mL. Values between 150 and 399 pg/mL were considered borderline, and those ≥400 pg/mL were classified as normal.

Data Management and Analysis

Data were entered into a secure, password-protected SPSS version 26 software for analysis. Descriptive statistics, including means, medians, and proportions, were used to summarize demographic and clinical data. Bivariate analysis was performed to assess associations between independent variables and vitamin B12 deficiency. Variables with a p-value of <0.2 were included in a multivariate logistic regression model to identify independent predictors of vitamin B12 deficiency. A p-value <0.05 was considered statistically significant. Variables with p<0.2 at bivariable level were included in multivariable logistic regression, a threshold commonly applied in epidemiological modeling to avoid exclusion of potential confounders. Interaction terms were also checked to assess for effect modification, though none reached statistical significance.

Ethical Considerations

Ethical approval for the study was obtained from the Institutional Research and Ethics Committee (IREC) of Kampala International University Western Campus. Administrative clearance was granted by the director of Hoima Regional Referral Hospital. All participants provided written informed consent. Confidentiality and privacy were upheld throughout the research process. Participants found to have vitamin B12 deficiency were referred for clinical management and supplementation.

Result Presentation

During the study period, a total of 270 diabetic patients were screened for eligibility. Initially, seven patients were excluded for not meeting the inclusion criteria. Among these, one had chronic kidney disease, three were critically ill, and three were below 18 years of age. Subsequently, the remaining 257 patients were approached, and all provided informed consent to participate in the study. Finally, Vitamin B12 levels were assessed in these 257 eligible and consenting participants, as illustrated in Figure 1 below.

Characteristics of the Study Participants

In this research, we included 257 participants, majority of whom were above 45 years of age (47.9% aged 46–59 years, while 33.5% aged 60+ years). There were slightly more men than women (51.0% versus 49%). Only 5.4% were taking 2000 mg of metformin per day. Only 12.8% had taken metformin for at least 10 years. The details of the participant characteristics are shown in Table 1 below.

Prevalence of VB12D Among Patients on Metformin for T2DM at HRRH

Among 257 participants, VB12D was diagnosed in 26, representing a prevalence of 10.1% with a 95% confidence interval of 6.6–14.0%. Overall, 136 (52.9%) had normal Vitamin B12 levels, 95 (37.0%) had borderline while 26 (10.1%) had low and hence diagnosed as Vitamin B12 deficiency as shown in Figure 2 below.

Factors Associated with VB12D Among Patients on Metformin for T2DM at HRRH

The variables considered for multivariate analysis (P<0.2) were: alcohol intake, duration of DM, metformin dose, metformin use duration, BMI, HbA1c category and FBG category as shown in Table 2 below.

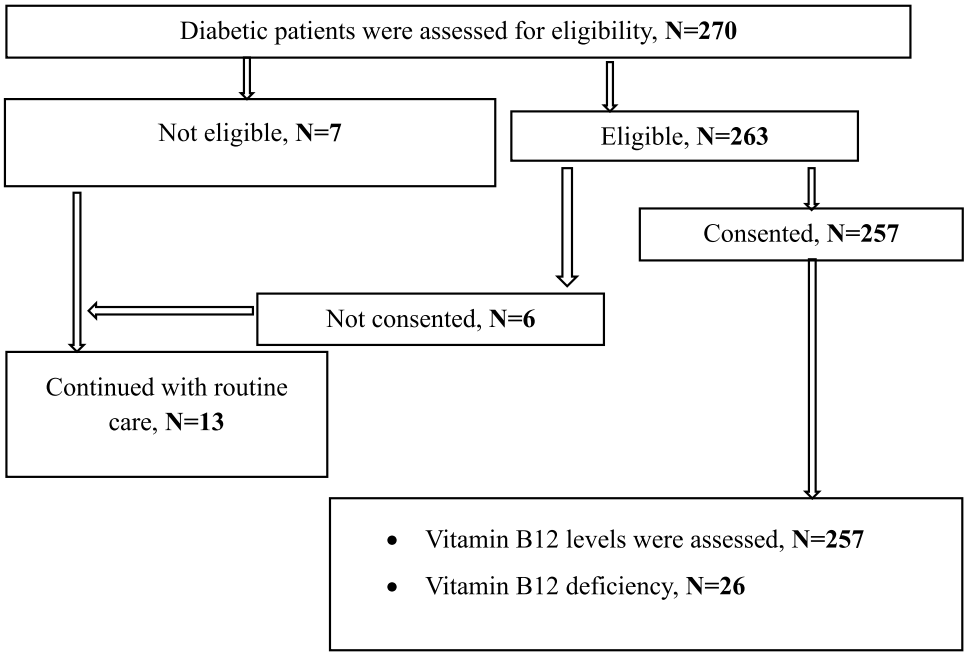

Figure 1 Flow chart showing eligible and consenting participants.

In the multivariable analysis, the independent factors linked to VB12D among individuals on metformin for T2DM at HRRH were: metformin dose of 2000 mg/day (aOR=4.634, CI=1.124–19.105, P=0.034), metformin use for 10+ years (aOR=4.044, CI=1.441–11.353, P=0.008) and high glycated hemoglobin (aOR=2.448, CI=1.041–6.238, P=0.021). The odds for Vitamin B12 deficiency were increased by over 4 times for those who were taking 2000 mg per day, by about 4 times for those who had used metformin for at least 10 years and by over two times for those whose glycated hemoglobin level was high as detailed in Table 3 below.

Table 1 Characteristics of Study Participants

Characteristic	Frequency	Percentage
Age category		
≤45	48	18.7
46-59	123	47.9
60+	86	33.5
Sex		
Male	131	51.0
Female	126	49.0
Residence		
Urban	78	30.4
Rural	179	69.6
Education		
None	62	24.1
Primary	142	55.3
Secondary	44	17.1
Tertiary	9	3.5
Religion		
Anglican	118	45.9
Catholic	114	44.4
Muslim	13	5.1
Others	12	4.7

(*Continued*)

Table 1 (Continued).

Characteristic	Frequency	Percentage
Occupation		
Formal	48	18.7
Peasant	141	54.9
Business	48	18.7
Other	20	7.8
Any comorbidity		
No	68	26.5
Yes	189	73.5
Hypertension		
No	125	48.6
Yes	132	51.4
Smoking		
No	254	98.8
Yes	3	1.2
Alcohol intake		
No	243	94.6
Yes	14	5.4
DM duration		
<10 years	186	72.4
10+ years	71	27.6
Metformin dose (mg/day)		
<1000	122	47.5
1000	121	47.1
2000	14	5.4
Metformin duration		
<10 years	224	87.2
10+ years	33	12.8
Non neuropathy complications		
No	251	97.7
Yes	6	2.3
BMI		
Normal	65	25.3
Overweight/obese	192	74.7
HbA1c		
Normal	178	69.3
High	79	30.7
FBG		
Normal	228	88.7
High	29	11.3

Abbreviations: DM, Diabetes mellitus; BMI, Body mass index; HbA1c, Glycated hemoglobin; FBG, Fasting blood glucose.

Effect of VB12D on Clinical Outcomes Among Patients on Metformin for T2DM at HRRH

Of the 257 participants, peripheral neuropathy was present in 125 (49.8%, 95% CI 43.2–55.6). The proportion of peripheral neuropathy was importantly increased of the subjects that had VB12D (76.9% versus 46.8%, P=0.004) as shown in Table 4 below.

Of the 257 participants, neuropsychiatric conditions were present in 79 (30.7%, 95% CI 24.9–36.2). The proportion of neuropsychiatric conditions was significantly higher among the participants that had vitamin B12 deficiency (50.0% versus 28.6%, P=0.041) as shown in Table 4 below.

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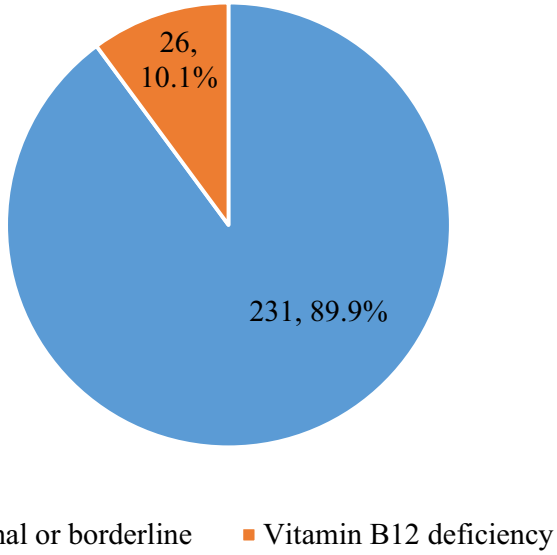

Figure 2 Prevalence of VB12D among patients on metformin for T2DM at HRRH.

Discussion

This study evaluated the prevalence, associated factors, and clinical outcomes of vitamin B12 deficiency (VB12D) among individuals with type 2 diabetes mellitus (T2DM) on metformin at Hoima Regional Referral Hospital (HRRH). The findings expand local understanding of a well-documented but often underdiagnosed complication of long-term metformin therapy.

The prevalence of VB12D in this study population was 10.1%. This is consistent with similar reports from Uganda (10.7%),[16] Brazil (6.9%),[17] and Nigeria.[18] This range reflects the established association between metformin use and impaired B12 absorption.[5,7,8] The relatively high prevalence found in this study may be attributable to multiple factors, including the duration of metformin use and glycemic control. Notably, 12.8% of participants had used metformin for over ten years, which is significant, as longer durations are strongly linked to B12 depletion due to interference with its ileal absorption.[19]

Table 2 Bivariable Analysis of Factors Associated with VB12D Among Patients on Metformin for T2DM at HRRH

Characteristic	No B12 Deficiency n (%)	B12 Deficiency n (%)	Total (N)	cOR	95% CI	P-value
Age category						
≤45	42 (87.5)	6 (12.5)	48	Ref		
46–59	111 (90.2)	12 (9.8)	123	0.757	0.267–2.146	0.600
60+	78 (90.7)	8 (9.3)	86	0.718	0.234–2.207	0.563
Sex						
Male	116 (88.5)	15 (11.5)	131	1.352	0.596–3.068	0.471
Female	115 (91.3)	11 (8.7)	126	Ref		
Residence						
Urban	70 (89.7)	8 (10.3)	78	Ref		
Rural	161 (90.0)	18 (10.0)	179	0.978	0.406–2.356	0.961

(*Continued*)

Table 2 (Continued).

Characteristic	No B12 Deficiency n (%)	B12 Deficiency n (%)	Total (N)	cOR	95% CI	P-value
Comorbidity						
No	59 (86.7)	9 (13.3)	68	Ref		
Yes	172 (91.0)	17 (9.0)	189	0.648	0.274–1.532	0.323
Hypertension						
No	114 (91.2)	11 (8.8)	125	Ref		
Yes	117 (88.6)	15 (11.4)	132	1.329	0.585–3.016	0.497
Smoking						
No	229 (90.1)	25 (9.9)	254	Ref		
Yes	2 (66.7)	1 (33.3)	3	4.580	0.401–52.321	0.221
Alcohol intake						
No	222 (91.4)	21 (8.6)	243	Ref		
Yes	9 (64.3)	5 (35.7)	14	5.873	1.802–19.137	0.003
DM duration						
<10 years	170 (91.4)	16 (8.6)	186	Ref		
10+ years	61 (85.9)	10 (14.1)	71	1.742	0.750–4.045	0.197
Metformin dose (mg/day)						
<1000	113 (92.6)	9 (7.4)	122	Ref		
1000	109 (90.0)	12 (10.0)	121	1.382	0.560–3.412	0.482
2000	9 (64.3)	5 (35.7)	14	6.975	1.926–25.260	0.003
Metformin duration						
<10 years	207 (92.5)	17 (7.5)	224	Ref		
10+ years	24 (72.7)	9 (27.3)	33	4.566	1.835–11.365	0.001
Non-neuropathy complications						
No	226 (90.0)	25 (10.0)	251	Ref		
Yes	5 (83.3)	1 (16.7)	6	1.808	0.203–16.097	0.595
BMI						
Normal	63 (96.9)	2 (3.1)	65	Ref		
Overweight/Obese	168 (87.5)	24 (12.5)	192	4.500	1.033–19.596	0.045
HbA1c						
Normal	165 (92.1)	13 (7.9)	178	Ref		
High	66 (83.5)	13 (16.5)	79	2.500	1.101–5.677	0.029

(*Continued*)

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Table 2 (Continued).

Characteristic	No B12 Deficiency n (%)	B12 Deficiency n (%)	Total (N)	cOR	95% CI	P-value
FBG						
Normal	207 (90.8)	21 (9.2)	228	Ref		
High	24 (82.8)	5 (17.2)	29	2.054	0.709–5.945	0.185

Abbreviations: Cor, Crude odds ratio; CI, Confidence interval; DM, Diabetes mellitus; BMI, Body mass index; HbA1c, Glycated hemoglobin; FBG, Fasting blood glucose.

Table 3 Multivariable Analysis of Factors Associated with VB12D Among Patients on Metformin for T2DM at HRRH

Characteristic	Bivariable Analysis			Multivariable Analysis		
	cOR	95% CI	P value	aOR	95% CI	P value
Alcohol intake						
No	Ref					
Yes	5.873	1.802–19.137	0.003	3.958	0.993–15.777	0.051
DM duration						
<10 years	Ref					
10+ years	1.742	0.750–4.045	0.197	1.249	0.244–2.955	0.797
Metformin dose (mg/day)						
<1000	Ref					
1000	1.382	0.560–3.412	0.482	1.103	0.416–2.924	0.843
2000	6.975	1.926–25.260	0.003	4.634	1.124–19.105	0.034
Metformin duration						
<10 years	Ref					
10+ years	4.566	1.835–11.365	0.001	4.044	1.441–11.353	0.008
BMI						
Normal	Ref					
Overweight/obese	4.500	1.033–19.596	0.045	3.517	0.763–16.209	0.107
HbA1c						
Normal	Ref					
High	2.500	1.101–5.677	0.029	2.448	1.041–6.238	0.021
FBG						
Normal	Ref					
High	2.054	0.709–5.945	0.185	1.270	0.347–4.645	0.718

Abbreviations: cOR, Crude odds ratio; aOR, adjusted odds ratio; CI, Confidence interval; DM, Diabetes mellitus; BMI, Body mass index; HbA1c, Glycated hemoglobin; FBG, Fasting blood glucose.

Table 4 Effect of VB12D on Clinical Outcomes Among Patients on Metformin for T2DM at HRRH

Outcome	Overall	No B12 Deficiency, N=231	B12 Deficiency, N=26	P value
Neuropathy				0.004
No	129(50.2)	123(53.2)	6(23.1)	
Yes	128(49.8)	108(46.8)	20(76.9)	
Neuropsychiatric conditions				0.041
No	178(69.3)	165(71.4)	13(50.0)	
Yes	79(30.7)	66(28.6)	13(50.0)	

High levels of glycated hemoglobin (HbA1c), observed in 30.7% of participants, were also associated with increased risk of B12 deficiency. Poor glycemic control may aggravate metformin-induced B12 malabsorption through mechanisms such as oxidative stress and enterocyte dysfunction.[20] The presence of comorbidities, seen in 73.5% of study subjects, is another contributing factor. Gastrointestinal disorders, renal insufficiency, or chronic inflammation can exacerbate B12 malabsorption and requirements.[21,22]

Prevalence findings in this study are similar to those reported from Pakistan (13.9%),[23] Oman (10.5%),[24] and Botswana (6.6%),[25] supporting the reliability of these results. Differences from studies in Saudi Arabia (3.6%)[26] and Libya (20.67%)[27] may stem from variations in cut-off values for B12 deficiency, use of supplements, and population demographics. In Saudi Arabia, for example, over 60% of patients were using vitamin B supplements, likely reducing the observed deficiency rate.[26]

In this study, metformin dose, duration of use, and HbA1c levels were independently associated with VB12D. Patients taking 2000 mg/day were over four times more likely to have deficiency, which agrees with findings from Oman, Nigeria, and Brazil, where higher daily dosages correlated with lower B12 levels.[18,24,28] Metformin impairs the calcium-dependent uptake of the intrinsic factor-B12 complex and affects intestinal motility and microbial balance, all contributing to malabsorption.[29,30]

Furthermore, our exclusion of patients on proton pump inhibitors (PPIs), B12 supplementation, or multivitamins helped ensure that the observed B12 deficiency was attributable to metformin rather than other confounding factors. In contrast, studies from Korea and Saudi Arabia observed lower prevalence in populations where supplementation was routine.[26,31]

Clinical outcomes further emphasize the significance of B12 monitoring. Peripheral neuropathy was present in 49.8% of the total sample and was significantly more prevalent in the VB12D group (76.9% vs 46.8%). Similarly, neuropsychiatric manifestations occurred in 30.7% of participants, with a higher proportion among those with B12 deficiency (50.0% vs 28.6%). These results are in agreement with a Colombian study where altered B12 levels were seen in 64% of patients with diabetic neuropathy versus only 17% without neuropathy.[32]

The strength of this study lies in its being the first in Uganda to evaluate VB12D specifically among metformin users. It provides foundational data to support screening interventions. However, the cross-sectional design limits causal inference, and the single-centre scope may affect generalizability to other regions.

Based on these findings, routine screening for vitamin B12 levels should be incorporated into the standard care protocol for patients on long-term or high-dose metformin therapy, especially those with poor glycemic control or presenting with neuropathic or neuropsychiatric symptoms. Clinicians should consider vitamin B12 supplementation where deficiency is confirmed or suspected. Health policymakers and hospital administrators should prioritize development of local guidelines for VB12D monitoring, integrate testing into diabetic care packages, and enhance patient education on the risks associated with prolonged metformin use. Additionally, future multicenter studies are recommended to validate these findings and guide nationwide policy formulation.

Conclusion

This study established that vitamin B12 deficiency is relatively common among patients with type 2 diabetes mellitus receiving long-term metformin therapy at Hoima Regional Referral Hospital, with a prevalence of 10.1%. Key factors significantly associated with VB12D included higher metformin dosage (2000 mg/day), prolonged duration of therapy (≥10 years), and poor glycemic control as indicated by elevated HbA1c. Furthermore, VB12D was significantly linked to adverse clinical outcomes, particularly peripheral neuropathy and neuropsychiatric symptoms. These findings underscore the clinical importance of early identification and management of VB12D in metformin-treated diabetic patients to prevent complications and improve quality of life.

Data Sharing Statement

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

Ethical Approval and Consent to Participate

The study received ethical approval from the Research Ethics Committee of Kampala International University (Ref No: KIU-2024-687). Written informed consent was obtained from all participants prior to their inclusion in the study. This study was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from the participants for the publication of this study and any accompanying data.

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Author Contributions

Hassan Omar Ali contributed to study conceptualization, methodology development, data curation, and writing—both original draft preparation and critical review and editing of the manuscript. Agwu Ezera contributed to conceptualization, supervision, and writing—review and editing. Mutaz Abdullahi Ali contributed to methodology, formal analysis, validation, and writing—review and editing. Yahya Mohamed Jama participated in data curation, investigation, resource provision, and writing—review and editing. Abdullahi Hussein Ahmed contributed to investigation, data curation, and writing—review and editing. Mohamed Abdi Yusuf contributed to supervision, validation, and writing—review and editing. Abdirahman Ali Araye was involved in methodology, formal analysis, and writing—review and editing. Isse Muse Osobow contributed to data curation, investigation, visualization, and writing—review and editing. Abdisalam Ahmed Sandeyl participated in resource acquisition, data curation, and writing—review and editing. Zakaria Ali Ahmed contributed to data curation, investigation, and writing—review and editing. Nixson Onyanga contributed to formal analysis, validation, visualization, and writing—review and editing. Abukar Husein Mohamed contributed to project oversight and writing—review and editing. Abishir Mohamud Hirsi contributed to data curation and writing—review and editing. Ayan Ahmed Mohamed participated in visualization and writing—review and editing. Fatima Ibrahim Nor contributed to resource provision, original draft preparation, and writing—review and editing. Mohamed Jayte contributed to conceptualization, supervision, project administration, and writing—review and editing. All authors have read and approved the final version of the paper and agree to be accountable for all aspects of the work.

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Disclosure

Fatima Nor reports personal fees from Kiu during the conduct of the study and outside the submitted work. The authors declare that they have no other competing interests.

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