Prevalence and determinants of Vitamin B_{12} deficiency among subjects with Type 2 Diabetes in a tertiary institution in Southeast Nigeria

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Abstract

Vitamin B_{12} (Vit B_{12}) deficiency is very common among diabetic subjects, although with variable prevalence. The aim of this study is to determine the prevalence of Vit B_{12} deficiency and its associated factors among patients with Diabetes Mellitus (DM). This study is important because Vit B_{12} deficiency is associated with metformin, which is a bedrock in the management of diabetic subjects. Since peripheral neuropathy is a recognized complication of DM, and also occurs in Vit B_{12} deficiency, it would be important to ascertain the role of Vit B_{12} deficiency in the emergence of peripheral neuropathy. Appropriate measures like vitamin supplementation would then be instituted in diabetics who are on metformin. A cross-sectional study was conducted at Enugu State University Teaching Hospital in Enugu, Nigeria, between January to July 2019. A total of 422 patients who fit the eligibility criteria were included in the study. Data on demographics, medication use, and anthropometry were obtained from each subject, while blood was drawn to study Vit B_{12} levels, Haemoglobin (Hb), Mean Cell Volume (MCV), and Glycated Heamoglobin (HbA1c). Vitamin B_{12} deficiency was defined as serum B_{12} level of ≤200 pg/mL. The prevalence of vitamin B_{12} deficiency among Type 2 DM patients was 16.6% (n=364). Predictors of Vit B_{12} deficiency in Type 2 diabetic subjects included duration of metformin use of more than five years ($p<0.0001$). Other predictors of vitamin B_{12} deficiency include Body Mass Index (BMI), diabetes duration, and macrocytic anemia. This study suggests that the prevalence of Vit B_{12} deficiency among patients with DM in our population is substantial. This is more frequent among patients who have been on metformin for more than five years.

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Introduction

Diabetes Mellitus (DM) is a non-communicable disease characterized by hyperglycemia, with increasing prevalence all over the world.[1] Overall, the global burden of diabetes has increased significantly since 1990. Both the trend and magnitude of diabetes-related disease burden varied substantially across regions and countries. In 2017, global incidence, prevalence, death, and Disability-Adjusted Life-Years (DALYs) associated with diabetes were 22.9 million, 476.0 million, 1.37 million, and 67.9 million, with a projection to 26.6 million, 570.9 million, 1.59 million, and 79.3 million in 2025, respectively.[2]

Vitamin B_{12} (Vit B_{12}) is a complex water-soluble organic compound which is essential to a number of microorganisms and animals, including humans.[3] Vitamin B_{12} deficiency is prevalent all over the world, as shown by studies conducted across almost all continents.[4-7] The etiology of this vitamin deficiency includes autoimmunity,[8] malabsorption,[9] dietary insufficiency,[10] and medications, especially metformin, which is a common treatment for DM.[11] A deficiency of Vit B_{12} leads to disordered production of DNA and, hence, to the impaired production of red blood cells. Vitamin B_{12} also has a separate biochemical role, unrelated to folic acid, in the synthesis of fatty acids in the myelin sheath that surrounds nerve cells. The clinical presentations of Vit B_{12} deficiency include megaloblastic anemia and neurological deficits,[12] which include myelopathy, neuropathy, and, less frequently, optic nerve atrophy.[13,14] There is a paucity of data on Vit B_{12} deficiency in diabetic patients in Nigeria. Given the multiple possible etiology of neurologic deficits and anemia in diabetic subjects, it is particularly important to clearly define the clinical scenario occasioned by Vit B_{12} deficiency. This study sets out to determine the prevalence and risk factors of this common but largely overlooked condition

in DM patients, given the potentially harmful but preventable and largely treatable effect of lack of Vit B_{12}.

Materials and Methods

This was a cross-sectional observational study of subjects with Type 1 and Type 2 DM conducted at the Enugu State University Teaching Hospital (ESUTH), Enugu, Nigeria, between January and July 2019.

Subjects who were within the age range 18-70 years, diagnosed with Type 1 or Type 2 DM, and attended the outpatient diabetes clinics of ESUTH participated in the study. The minimum sample of 400 subjects was calculated using Fisher's formula.[15]

Exclusion criteria included pregnancy, subjects on Vit B_{12}-containing supplements (local examples include alphabetic and biobetic which are commonly taken by diabetic patients with a false belief that they are antidiabetics), or are known to have chronic kidney or liver disease. Their socio-demographic variables, including age, gender, smoking, and alcohol habits, were documented. This was followed by clinical history, including type and duration of diabetes, treatment type, history of hypertension, diabetic foot ulcer, and lower limb amputation (Table 1).

Weight and height were measured by a stadiometer placed on a firm floor with the feet joined and the measuring surface reached by the back of the head, buttocks, calves, heels, and shoulder blades. The gaze was directed forward. Body Mass Index (BMI) was calculated as a ratio of weight to the square of height in kilo-

Table 1. Baseline characteristics of the study population. A total of 422 were studied, of which about two-thirds were female. Three-fifths were in the middle age category, while about a third were elderly, with a mean age of 57.6±10.1 years. The mean duration of diabetes in the subjects was 7.4±5.9 years, while 86.3% and 26.8% were on metformin and insulin, respectively. About two-thirds of the subjects had poor glycaemic control with a mean HbA1c of 8.4±2.1%. There was no association between the use of metformin, dose of metformin >2 g/day, insulin use, or smoking on Vitamin B_{12} deficiency. Neither alcohol intake, arterial hypertension, and HbA1c also associated with the deficiency of this vitamin.

Variable	N	Percent	Mean ± SD
Gender			
Male	133	31.5	
Female	289	68.5	
Age (years)			
<45	36	8.5	57.6±10.1
45-64	255	60.4	
<65	131	31.0	
Cigarette smoking			
Yes	59	14.0	
No	363	86.0	
Alcohol use			
Yes	178	42.2	
No	244	57.8	
Body Mass Index			
Normal	131	31.0	27.8±5.5
Overweight	163	38.6	
Obese	128	30.3	
Hypertension			
Yes	258	61.1	
No	164	38.9	
Type of diabetes			
Type 1	12	2.8	
Type 2	410	97.2	
Duration of diabetes (years)			
<10	306	72.5	7.4±5.9
>10	116	27.5	
Treatment with metformin			
Yes	364	86.3	
No	58	13.7	
Duration of metformin use (n=364) (years)			
<5	199	54.7	6.3±5.7
>5	165	45.3	
Treatment with insulin			
Yes	113	26.8	
No	309	73.2	
Glycated Hemoglobin			
Good (<7%)	132	31.3	8.4±2.1
Poor (≥7%)	290	68.7	

grams per square meter. It was classified as normal (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2), or obese (≥30 kg/m^2) categories.

Serum radio-ligand binding assay, a commonly used and sensitive method, for B_{12} level, hemoglobin concentration, and MCV were measured in all DM patients with the inclusion criteria. The assay was done at a specialist laboratory in the hospital. B_{12} deficiency was defined as B_{12}<200 pg/mL, or 200-299 pg/mL, with hematological abnormalities (macrocytosis and/or pancytopenia).[16] Serum B_{12} levels between 200 and 299 pg/mL without hematological abnormalities were regarded as borderline $B_{12,}$ while those with 300 pg/mL and above, irrespective of hematological abnormalities, were adjudged to have normal B_{12} (Table 2, Table 3).

Statistical analysis

Demographic, clinical, and laboratory characteristics were presented as means ± standard deviation or proportions. Comparisons between groups were made using the Chi-squared test for categorical variables and the Student *t*-test for continuous variables. A value of p<0.05 was considered statistically significant. Following bivariate analysis, variables that were statistically associated were subjected to multivariate logistic regression. Data obtained were entered and analyzed using the Statistical Package for Social Sciences (SPSS) version 21.0 software 9 (IBM Corporation, Armonk, NY, USA).

Discussion

The prevalence of B_{12} deficiency among diabetic patients in this study was 16.6%, while 20.1% had borderline deficiency (Figure 1). There is limited data on this subject presently in Nigeria. Other studies were on Type 2 diabetics who were taking metformin and excluded Type 1 diabetic subjects. Owhin *et al*. in South-South Nigeria found a prevalence of 41% and 20% among metformin-treated and metformin-naïve Type 2 diabetes mellitus groups.[17] This study had a different design from ours. However, another study done in Ibadan, Southwest Nigeria, found Vit B12 deficiency and borderline deficiency in 8.6% and 26.0% of the patients, respectively.[18] The findings in the latter study could have been explained by the fact that they not only studied Type 2 diabetic patients on metformin, but also had a smaller sample size (81) compared with our study. In Uganda, the prevalence was 10.7%,[19] while another study in Egypt found a prevalence of 6.7% in Type 1 diabetics and 10% in type 2 diabetics.[20] At a large military hospital in the USA, Pflipsen *et al*. found a prevalence of 22%.[21] The lower prevalence in Uganda might be due to cultural and dietary differences between the studied subjects. The prevalence in Egypt is similar to what is found in this study. The higher prevalence in the USA could be explained by the fact that they had a smaller sample size of 203 subjects. They also used patients that were aged 45 years and above, and age is an established risk factor for Vit B_{12} deficiency.[22,23] Owhin *et al*. had a sample size of 200, while the studies in Uganda, Egypt, and Ibadan had sample sizes of 280, 150, and 81, respectively. These wide differences in sample sizes for different researchers may have been responsible for these noted discrepancies in the prevalence.

The duration of metformin use correlated with Vit B_{12} deficiency in this study. Similar findings have been reported in previous studies. Akinlade *et al*. in Ibadan, Western Nigeria, also found that metformin use for up to 10 years positively correlated with low Vit

Table 2. Associations between subjects' variables and B12 concentration. Following bivariate analysis, variables that were found to be associated with B_{12} deficiency were subjected to multivariate analysis, as shown in Table 3. Haemoglobin <12 g/dL, BMI ≥25 kg/m^2, and duration of metformin >5 years predicted Vitamin B_{12} deficiency.

Variable	B_{12} concentration (pg/mL) <200 (n=70)	≥200 (n=352)	p
Age (years)	58.4±9.8	57.5±10.2	0.503
Gender (female)	46 (65.7)	243 (69.0)	0.673
Cigarette smoking	15 (21.4)	44 (12.5)	0.059
Alcohol use	30 (42.9)	148 (42.0)	1.000
Body Mass Index (Kg/m^2)	23.5±4.6	28.6±5.3	<0.001
Hypertension (yes)	47 (67.1)	211 (59.9)	0.285
Diabetes Type (Type 2)	69 (98.6)	341 (96.9)	0.700
Diabetes duration (years)	10.6±6.7	6.8±5.5	<0.001
On metformin (yes)	65 (92.9)	299 (84.9)	0.088
Duration of metformin use (years)	10.4±7.2	5.4±4.8	<0.001
Daily metformin dosage (g)	1.6±0.5	1.5±0.5	0.503
On insulin (yes)	25 (35.7)	88 (25.0)	0.078
On vitamin supplements (yes)	24 (34.3)	138 (39.2)	0.502
Hemoglobin (g/dL)	10.7±1.1	11.4±1.3	<0.001
Mean Cell Volume (fl)	87.0±8.5	84.6±7.3	0.014
Glycated Hemoglobin (%)	8.2±1.7	8.5±2.1	0.251

Table 3. Predictors of B_{12} deficiency.

Variable	O.R	95% C.I for O.R Lower	Upper	p
Age >50 years	0.89	0.386	2.055	0.785
Treatment with metformin	1.41	0.711	2.805	0.324
On supplements	0.99	0.503	1.962	0.984
Hemoglobin <12 g/dL	2.85	1.185	6.871	0.019
Macrocytosis	2.15	0.611	7.535	0.233
Glycated Hemoglobin ≥7%	0.95	0.479	1.891	0.888
Body Mass Index ≥25 kg/m^2	0.13	0.068	0.255	<0.001
Duration of metformin >5 years	3.36	1.740	6.487	<0.001
Metformin dosage ≥2 g/day	1.40	0.733	2.667	0.309

B_{12} levels.[18] In Ghana, metformin use of 5-9 years inversely correlated with Vit B_{12} levels[24] while in Canada Vit B_{12} deficiency also correlated with metformin duration of >6 months.[25] A study by Bauman *et al*. at a medical center in New York, USA, found that 12 out of 14 T2DM patients presented with reduced serum total Vit B_{12} levels after 3 months of metformin therapy.[26] Another study in Hong Kong also found that using metformin for more than 3 years was associated with more than two-fold increased risk of developing Vit B_{12} deficiency.[27] Similarly, a study conducted in three non-academic hospitals in the Netherlands found that the absolute risk of vitamin B_{12} deficiency after a period of 4 years was 7.2% higher in T2DM patients on metformin.[28] The pathogenic mechanisms of vitamin B_{12} deficiency in metformin treatment have not been fully elucidated. However, bacterial overgrowth in the small intestine attributable to diabetes mellitus, changes in small bowel motility, alterations in the bacterial flora, competitive inhibition, the inactivation of Vit B_{12} absorption, or the effect of calcium on cell membranes have been suggested to play a role.[24,29] Our findings contrasted with that of Owhin *et al*., who found that duration of metformin use did not correlate with Vit B_{12} deficiency.[17] Similarly, Kim *et al.* also found that in South Korea, the duration of metformin intake did not correlate with Vit B_{12} deficiency.[30] The differences may be explained by the fact that the former researchers had more stringent exclusion criteria than our study. Patients with a history of gastrectomy, colectomy, inflammatory bowel disease, or pernicious anemia, an acute illness characterized as severe infection, cancer or acute coronary syndrome within the last 3 months, as well as serious organ damage characterized by liver cirrhosis, Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥3 times the upper limit of the normal range, estimated Glomerular Filtration Rate (GFR) <30 mL/min/1.73m^2, or symptoms of heart failure were all excluded. Also, patients with hematological disorders other than anemia, pregnant women, and vegetarian patients were excluded. They also excluded subjects on medication that affect cytochrome P450, like omeprazole, rifampicin, and anticonvulsants. The smaller sample size of Owhin *et al*. may also be responsible for this discrepancy. The South Korean study may have excluded and also missed subjects with a longer duration of metformin use, and with the higher cutoff mark for B_{12} deficiency (300 pg/mL), could also have excluded patients with a long duration of metformin intake.

We found a significant relationship between hemoglobin <12 g/dL and B_{12} deficiency in this study. This is similar to the finding in an earlier study in Nigeria.[17] Aroda *et al*. also had similar findings in their study,[31] while another study in Japan noted that high doses of metformin might result in a moderate decrease in the circulating Vit B_{12} level, as well as in anemia in elderly individuals.[32] This contrasts with another study in India[33] where anemia had no positive correlation with Vit B_{12} deficiency. The smaller sample size of the Indian study and the fact that their subjects were aged above 30 years may have made them miss patients with anemia. Moreover, the Indian menu is replete with fermented foods, with most meals incomplete without lacto-fermented achaars. Traditionally fermented foods are rich sources of Vit B_{12}.[34]

There was a significant relationship between BMI and B_{12} concentration in this study, which is similar to findings in Nigeria and Asia.[18,35,36] However, a study in Palestine on 400 T2DM subjects found no relationship between BMI and B_{12} deficiency.[37] The reason for this discrepancy is not clear, considering the fact that 88.2% of their subjects had abnormal BMI while the prevalence of B_{12} deficiency was also quite high (39.5%). Genetic, cultural, and dietary factors may have contributed to this. Another study done on 252 subjects in Pahang district, Malaysia, also found no correlation between BMI and Vit B_{12} deficiency among T2DM subjects on metformin.[38] The fact that they studied only T2DM subjects and the smaller sample size may have eliminated subjects with high BMI and Vit B_{12} deficiency.

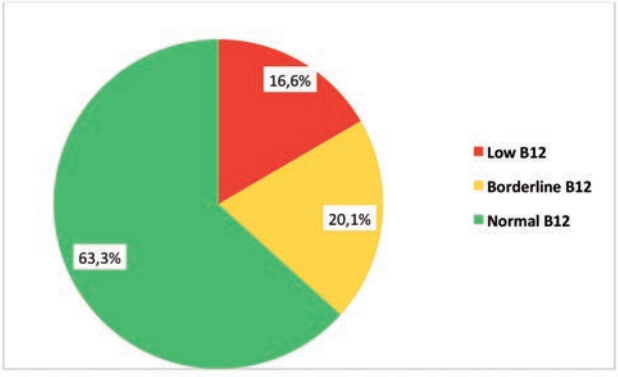

Figure 1. Prevalence of Vitamin B12 deficiency. About two-thirds of the subjects had normal B12 levels. However, about a fifth had borderline, while about 16% had B12 deficiency

Conclusions

Vitamin B_{12} deficiency is highly prevalent among diabetic patients in our study. We recommend screening our diabetes patients, who have been on metformin for about 5 years, for B_{12} deficiency to ensure early diagnosis and supplementation where necessary. Further studies need to be done on whether Vit B_{12} supplementation would improve B_{12} deficiency as well as glycemic control.

Limitations of the study

Due to financial constraints, we were not able to screen for Vit B_{12} deficiency using more sensitive methods like serum homocysteine and methylmalonic acid. Moreover, this study may not represent the situation in the entire southern Nigeria in view of the fact that data was only gotten from subjects in one tertiary center in Enugu, Southeast Nigeria.

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