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ORIGINAL ARTICLE

Cobalamin Status In Patients With Type 2 Diabetes Mellitus At Primary Health Care Centers In Bahrain - A Cross-Sectional Study

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Abstract

Background and Objectives: Cobalamin, also known as vitamin B12, is essential for DNA synthesis and neurological functioning. Deficiency results in hematological and neurocognitive manifestations. One risk factor for vitamin B12 deficiency is the use of metformin, a common oral hypoglycemic agent. This study was conducted to determine cobalamin status in patients with type 2 diabetes mellitus at primary health care centers in Bahrain.

Methods: This cross-sectional study was conducted in five randomly selected health centers in Bahrain. Vitamin B12 levels below 148 pmol/L were categorized as deficient, levels ranging from 148 to 221 pmol/L were considered borderline, and levels exceeding 221 pmol/L were classified as normal.

Results: A total of 691 participants were included in the study, with a mean age of 58.7 years. The most common comorbid condition among our cohort was hypertension (63.1%), followed by dyslipidemia (53.1%). Analysis of the glycemic control showed that only 40% of the participants achieved control targets. Nearly 10% (9.4%, n=65) of the cohort had low levels of vitamin B12, and 31% had borderline values. A significant association was seen between low vitamin B12 levels and Bahraini nationality ($p<0.001$), and patients who engaged in weekly exercise ($P=0.007$). Furthermore, the analysis revealed that the use of metformin ($P=0.037$) and alcohol ($P=0.012$) was significantly associated with low levels of vitamin B12.

Conclusion: Although the overall prevalence of B12 deficiency among patients with type 2 diabetes in Bahrain was low, patients at high risk of B12 deficiency, including metformin users and alcohol consumers, should be periodically screened to prevent the associated neurological and hematological sequela.

Keywords: Bahrain, Cobalamin, Diabetes Mellitus, Primary Health Care, Vitamin B 12

Introduction

Type 2 Diabetes mellitus is one of the most prevalent chronic diseases in the world. Globally, an estimated 10% of the world's population has type 2 diabetes, and the prevalence is expected to increase to 11% by 2045.[1] The International Diabetes

Federation has reported most countries in the Gulf Cooperation Council region have high prevalence rates of diabetes, exceeding 20%.[2] Management of patients with type 2 diabetes takes into account not only the microvascular and macrovascular complications of the disease but also the medication side effects into consideration.[3]

Metformin has been the most widely used first-line pharmacological treatment for most patients with diabetes. (2) Despite its well-established long-term efficacy and favorable adverse effect profile, recent studies have shown a significant association between long-term metformin use and decreasing cobalamin values.[4] Cobalamin deficiency causes hematological abnormalities, including anemia and neurocognitive manifestations such as numbness, tingling, weakness, and psychiatric disorders. The presence of neuropathic symptoms among patients with type 2 diabetes could occur due to diabetic neuropathy, renal impairment, or due to metformin-linked low B12. Therefore, the American diabetes association recommends period assessment of B12 levels in patients on metformin, particularly among patients with numbness, weakness, and anemia, as it can be treated effectively.[3]

Cobalamin (also known as vitamin B12), a water-soluble vitamin, acts as a cofactor for enzymes and is essential for DNA synthesis and neuroprotection.(2) Cobalamin is primarily obtained through diet, animal-rich, and fortified foods and is absorbed in the terminal ileum as a complex with intrinsic factors. Although metformin use has been linked to vitamin B12 deficiency, the exact reason for this association remains unclear. One of the proposed theories suggests that metformin causes a decrease in the production of intrinsic factors and a reduction in intestinal motility, which in turn can result in bacterial overgrowth and B12 malabsorption.[5,6]

The association between vitamin B12 and metformin has been studied in the literature. The prevalence of vitamin B12 deficiency varies across the studies. In South Africa, it was 28.1%[7], while lower rates were reported in Brazil (22.5%),[8] New Zealand (18.7%),[9] and United States (7%), respectively.[10] Similar variations are also observed in the Gulf region, ranging from 10.8% in Oman[11] to 17.5% in Saudi Arabia.[12] The United Arab Emirates had the highest level of B12 deficiency among metformin users at 48%.[13]

The normal ranges of B12 levels were highly variable across the studies; however, optimal B12 status is usually defined as levels above 300 pg/ml (221 pmol/L). Values ranging from 200-300 pg/ml are considered borderline, whereas values below 200 pg/ml are considered low and consistent with deficiency.[14,15] This study aimed to identify the prevalence of cobalamin deficiency and its determinants among patients with type 2 diabetes mellitus attending primary healthcare centers in Bahrain.

Methods

This is a cross-sectional study conducted in 5 primary healthcare centers in Bahrain. A total of 27 health centers are distributed among five health regions. One center from each health region was randomly selected. As the study population was patients with type 2 diabetes mellitus, patients who attended the specialized diabetes clinics in each of the selected health centers (non-communicable diseases clinics and central diabetes clinics) were included. The proposal for this research was approved by the primary healthcare research and ethics committees, and written consent was obtained from all participants. All data were coded during analysis.

All patients who were 18 years and above, with type 2 diabetes mellitus, attending the specialized diabetes clinics at the time of data collection were approached for enrollment. We excluded pregnant participants, patients with intellectual disabilities, and those with language barriers from the study. A sample size of 384 patients was calculated to predict statistical significance, considering a 95% confidence interval and a 5% margin of error.

Vitamin B12 levels below 148 pmol/L were categorized as deficient, levels ranging from 148 to 221 pmol/L were considered borderline, and levels exceeding 221 pmol/L were classified as normal.

A pilot study was performed on 10 patients to predict possible challenges during data collection. Based on patients' responses, the sequence of the questions was modified. The data analysis was

performed using the Statistical Package for the Social Sciences program for Windows (Version 25.0; IBM Corp, Armonk, New York, USA). Categorical variables were analyzed by calculating frequencies and percentages, while continuous variables were described using means and a 95% confidence interval. The associations between two categorical variables were evaluated using Chi-Square or Fisher's exact tests, while associations involving continuous variables were assessed using T-test. A p-value of less than 0.05 was considered statistically significant.

Results

A total of 691 participants were included in the study. The majority of the research subjects were Bahraini (513/691, 74.2%), females (349/691, 50.5%), and married (565/691, 81.8%) with a mean age of 58.7 years. The most common comorbid condition among our cohort was hypertension (436/691, 63.1%), followed by dyslipidemia (367/691, 53.1%). Regarding microvascular complications, retinopathy, nephropathy, and neuropathy were observed in 13%, 11%, and 2% of the cohort, respectively. Among the patients included in this study, a significant proportion were prescribed oral hypoglycemic agents, with metformin being the most frequently used medication (635/691, 91.9%), followed by Sulphonylurea (356/691, 51.1%), (Table 1).

Table 1: Baseline Characteristics of the Patients with Type-2 Diabetes Mellitus, TN= 691

Variable		Number (%)
Nationality	Bahraini	513 (74.2)
Sex	Female	349 (50.5)
Age, mean (95% CI)		58.7 (57.8-59.5)
Education level	Primary level or less	149 (21.6)
	Intermediate/Secondary	356 (51.5)
	University/College	186 (26.9)
Marital status	Unmarried	126 (18.2)
	Married	565 (81.8)
Clinic type	Non-Communicable Diseases Clinic	64 (5.4%)
	Central Diabetes Clinic	198 (16.7%)
Duration of diabetes mellitus		12.8 (12.2-13.4)
Comorbidities	Hypertension	436 (63.1)
	Dyslipidemia	367 (53.1)
	Heart diseases	93 (13.5)
Micro-vascular complications	Retinopathy	90 (13.0)
	Nephropathy	76 (11.0)
	Neuropathy	14 (2.0)
Treatment measures	Lifestyle modifications	382 (55.8)
	Weekly exercise	337 (48.8)
	Diet control	100 (14.5)
	Oral agents	661 (95.7)
	Metformin	635 (91.9)
	Sulphonylurea	356 (51.5)
	Insulin	291 (42.1)
	Other injections	10 (1.4)
	Statins	589 (85.2)
Smoking		56 (8.1)
Alcohol		24 (3.5)

As illustrated in Figure 1, analysis of the glycemic control showed that only 40% (276/691) of the participants achieved control targets. As depicted in Figure 2, more than half of the patients had normal B12 values (59.9%), nearly one-third had borderline values (30.7%), and 9.4% (65/691) had low levels of vitamin B12.

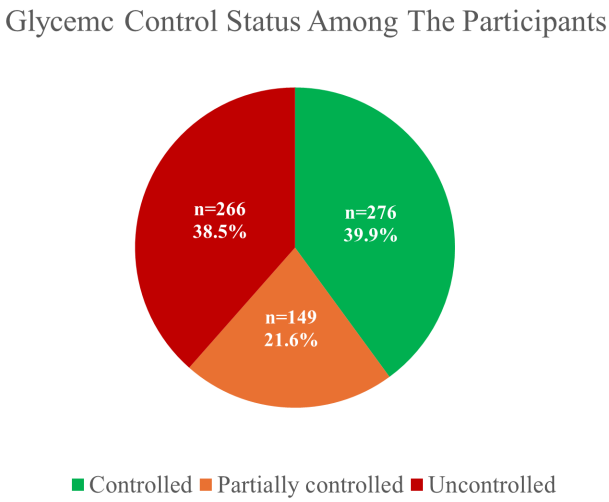

Figure 1: Glycemic Control Status Among Patients with Type-2 Diabetes Mellitus

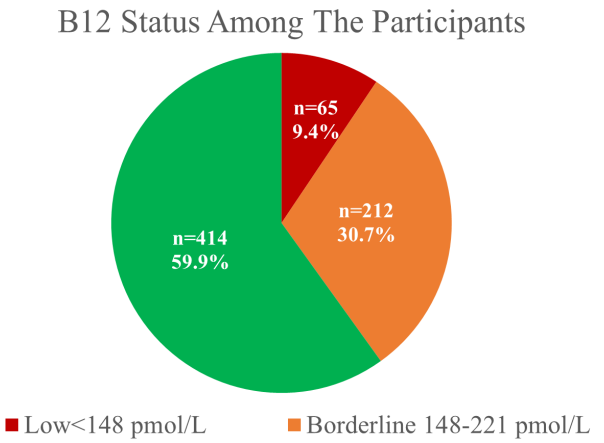

Figure 2: B12 Status Among Patients with Type-2 Diabetes Mellitus

Table 2 demonstrates the association between vitamin B12 levels and the patient's characteristics. As illustrated, a significant association was seen between low vitamin B12 levels and Bahraini nationality (P<0.001). Such association was also observed in patients who exercised weekly (P=0.007). Furthermore, the analysis revealed that the use of metformin and alcohol were both significantly associated with low levels of vitamin B12 (P= 0.037, P= 0.012, respectively).

Table 2: Association Between Vitamin B12 Levels and Patients' Characteristics, TN= 691

Variable	Type of Drug	Low B12 TN= 65	Borderline B12 TN= 212	Normal B12 TN= 414	P value
Nationality	Bahraini	40(7.8)	176(34.3)	297(57.9)	<0.001
	Non-Bahraini	25(14)	36(20.2)	117(65.7)	
Sex	Male	36(10.5)	99(28.9)	207(60.5)	0.448
	Female	29(8.3)	113(32.4)	207(59.3)	
Age, mean (95% CI)		56.2 (53.2-59.2)	59.59 (58.1- 61.1)	58.47 (57.3-59.6)	0.086
Education level	Primary level or less	8(5.4)	44(29.5)	97(65.1)	0.507
	Intermediate/Secondary	39 (10.9)	112(31.5)	205(57.6)	
	University/College	18(9.7)	56(30.1)	112(60.2)	
Marital status	Unmarried	10(7.9)	41(32.5)	75 (59.5)	
	Married	55(9.7)	171(30.3)	339(60)	
Duration of diabetes mellitus		11.5(9.8-13.3)	12.64(11.4-13.8)	12.9(12.1-13.7)	0.448
Comorbidities	Hypertension	39(8.9)	135(31)	262(60.1)	0.868
	Dyslipidemia	28(7.6)	122(33.2)	217(59.1)	0.109
	Heart diseases	6(6.5)	25(26.9)	62(66.7)	0.325
Micro-vascular complications	Retinopathy	7(7.8)	23(25.6)	60(66.7)	0.381
	Nephropathy	5(6.6)	20(26.3)	51(67.1)	0.357
	Neuropathy	0(0)	4(28.6)	10(71.4)	0.606

Treatment measures	Lifestyle modifications	35(9.2)	122(31.9)	225(58.9)	0.666
	Weekly exercise	40(11.9)	87(25.8)	210(62.3)	0.007
	Diet control	7(7)	29(29)	64(64)	0.562
	Oral agents	61(9.2)	205(31.0)	395(59.8)	0.569
	Metformin	60(9.4)	203(32)	372(58.6)	0.037
	Sulphonylurea	31(8.7)	113(31.7)	212(59.6)	0.725
	Insulin	27(9.3)	82(28.2)	182(62.5)	0.446
	Other injections	1(10)	2(20)	7(70)	0.797
	Statins	57(9.7)	176(29.9)	356(60.4)	0.515
Smoking		9(16.1)	14(25)	33(58.9)	0.171
Alcohol		5(20.8)	2(8.3)	17(70.8)	0.012

Discussion

This study aimed to determine the cobalamin status and its determinants among individuals with type 2 diabetes mellitus. The study found that one in every 10 patients with type-2 diabetes had low B12, and one-third of the cohort had borderline B12. Patients who were Bahraini, doing regular exercises, taking Metformin, and alcohol consumers had a higher prevalence of B12 deficiency compared to their counterparts.

Compared to many studies, a lower prevalence of cobalamin deficiency in patients with type 2 diabetes mellitus was found in the present study. [7-9, 11-13] The variability of deficiency in cobalamin levels across the studies, ranging from 9% to 48%, can be attributed to several factors, including the lack of consensus on cut-off variations for deficiency, variability in immune assays, different settings, and different dietary patterns.

Following the patient's demographics analysis, we reached some observations consistent with those of other studies. No association was found between metformin use and age, sex, marital status, or comorbidities, whereas a correlation was observed between nationality (specifically Bahraini) and low levels of vitamin B12. This can be attributed to the fact that the majority of our cohort were Bahrainis and to the different dietary habits among various cultures and nationalities. Previous studies investigated the association between age and duration of diabetes, and it has been shown to correlate with cobalamin status negatively. These linkages were not found among our patients.

The adverse effect of metformin on cobalamin status in our study is comparable to the results seen in the literature. Here, the results revealed that metformin therapy resulted in low cobalamin concentration. The clinical impact of metformin-related cobalamin deficiency has been increasingly studied in the literature. Emphasis on metformin-induced B12 deficiency has been shown to exacerbate pre-existing neuropathy. Therefore, patients taking metformin should be screened for B12 deficiency, especially in the presence of hematological or neurological symptoms.

Where other studies concluded that treatment by metformin was significantly associated with more incidence of diabetes peripheral neuropathy, this was not evident in our results. Supplementation with multivitamins has been associated with a higher cobalamin status and lower prevalence of deficiency in patients on metformin.[12]

A duration-dependent correlation has shown inconsistent findings in the literature between metformin and cobalamin status.[12]. However, our results did not show any association between cobalamin status and the duration of diabetes. It is interesting to note that recent literature has shown that the additive effect of both metformin dose and duration using a Metformin Usage Index (MUI) was determined to be the most significant predictor of cobalamin deficiency.[18]

Interestingly, we found an association between exercise and low levels of vitamin B12. However, according to Herrmann and colleagues, individuals who engage in regular exercise may exhibit

functional deficiencies in vitamin B12 despite having normal or even elevated levels of B12.

In agreement with prior research, our findings indicate an association between alcohol consumption and decreased levels of vitamin B12, which is believed to be due to its interference with the absorption of B12 from the intestine.

This study supports the adopted guidelines to monitor cobalamin status among metformin users frequently. We regard these findings as valuable for the implication of international and local policies amongst our centers. In light of the associated health concerns of cobalamin deficiency, clinicians must continue monitoring cobalamin status as a vital element in managing type 2 diabetes mellitus, especially in patients on longer and higher dosages of metformin. In patients with low B12 levels, early treatment using parenteral or oral cobalamin supplements is necessary to prevent the associated neurological and hematological sequela. In most patients, post-treatment monitoring of B12 is not recommended.[15]

This study has some limitations. Additional biomarkers of cobalamin deficiency, such as methylmalonic acid and homocysteine, details of the patient's diet, presence of malabsorptive disease/ prior gastrointestinal surgeries, history of use of vitamin supplements, and proton pump inhibitors were not assessed. These conditions might result in B12 levels. In addition, some factors, such as duration and dose of metformin, were not assessed.

Conclusion

Although B12 deficiency is relatively uncommon among patients with type 2 diabetes mellitus attending primary care centers in Bahrain, Bahraini patients, metformin-users, Alcohol-drinkers, and patients who exercise weekly had higher rates of B12 deficiency compared to their counterparts. Screening patients for B12 deficiency, especially with hematological and neurological symptoms, is crucial. Further studies are needed to determine the association between metformin dose and duration on B12 status, as well as the mechanism of metformin-induced B12 deficiency.

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