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Vitamin B12 Deficiency in Adults with Type-2 Diabetes Mellitus in Salmaniya Medical Complex - A Cross-Sectional Study

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ABSTRACT

Objective: To determine the prevalence of vitamin B12 deficiency in patients with type-2 diabetes mellitus attending secondary care endocrinology clinic and study the possible factors that might affect vitamin B-12 serum level.
Design: Retrospective cross-sectional study.
Setting: Salmaniya Medical Complex, Kingdom of Bahrain.
Methods: From January 2018 to December 2018, 306 patients with type-2 diabetes mellitus were included. Baseline demographic characteristics, physical and laboratory investigations were retrieved from electronic medical records. For statistical analysis, Prism (Graph Pad) software was used.
Results: Of the 306 cases, 62.1% of patients were female (vs. 37.9 % were male) and the mean age of the patients was 57.6years. This study found that around 93% (n=284) of patients with type 2 diabetes mellitus had normal or borderline vitamin B12 levels, whereas vitamin B12 deficiency was noticed in 7% (n=22) of the cases. No significant differences between these groups were found. Metformin use has been found to be significantly associated with vitamin B12 deficiency (P=0.0341).
Conclusion: The estimated prevalence of vitamin B12 deficiency in patients with type-2 diabetes mellitus was 7%. Use of metformin was significantly associated with vitamin B12 deficiency and thus routine screening should be considered in metformin users, particularly in patients with neuropathic symptoms.

Keywords: Diabetes mellitus, Vitamin B12 deficiency, Metformin, Cobalamin deficiency

INTRODUCTION

Vitamin B12, also known as Cobalamin, is a water-soluble vitamin that is found naturally in animal products [1]. This vitamin is essential for nucleic acids synthesis, cellular metabolism mitochondrial metabolism and neurological functions [2].

Low cobalamin levels may lead to significant hematological, gastrointestinal and neuropsychiatric complications, but asymptomatic subjects are not uncommon [1]. Periodic assessment of this vitamin should be considered in patients with risk factors including prolonged use of metformin, proton pump inhibitors (PPIs) and advanced age [2]. American Diabetes Association (ADA), for instance, recommends periodic assessment of serum B-12 levels in metformin-treated patients, particularly in the presence of anemia or peripheral neuropathy. Screening for vitamin B12 deficiency is not recommended in average-risk adults [3].

Cobalamin deficiency is more common in patients with T2DM not only due to metformin use, but also due to advanced age and nutritional deficiencies [3,4]. Due to cost-effectiveness, low risk of hypoglycemia and cardiovascular benefits, metformin is a first-line therapy for the treatment of T2DM. It is estimated that almost 120 million patients

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diagnosed with T2DM are taking Metformin [5,6].

Type-2 Diabetes Mellitus (T2DM) is one of the rapidly growing epidemics, especially in the Eastern Mediterranean and Middle East regions [7]. The prevalence of disease in Bahrain is reported to be between 14-17% [8] Most of the patients with T2DM are managed according to the standard guidelines in Primary Health Care (PHC), however, uncontrolled cases and/or patients with diabetes-related complications are referred to secondary care mostly at Salmaniya Medical Complex (SMC) for further management.

In Bahrain, a study was conducted among adult T2DM patients attending the primary care department diabetic clinic at the Bahrain Defense Force (Military Hospital) found that the prevalence of low vitamin B12 level was 43.6% among adults with T2DM patients on metformin [9]. The aim of this study is to determine the prevalence of vitamin B-12 deficiency among patients with T2DM, particularly in metformin-users and elderly patients attending endocrine clinic at SMC.

METHODS

Study design and participants

This retrospective cross-sectional study was conducted at SMC in the period between January 2018 and December 2018. All adults (≥ 18 years) with T2DM were enrolled. Those who have not had their vitamin B12 levels measured and patient who had gastrectomy were excluded from the analysis. All T2DM patients who presented to endocrinology clinics in the first week of every month between January 2018 and December 2018 were included. The protocol of this study was reviewed and approved by Secondary Healthcare Research Committee at Ministry of Health.

Data collection

Data collection sheet was developed and used to collect the following data from the electronic medical records. The primary outcome was vitamin B12 serum levels while the secondary outcomes were participants' baseline demographic characteristics (age, sex and nationality), diabetes control determined by A1C levels, diabetes medications, presence of underlying of comorbidities, blood pressure, lipid profile, renal function, thyroid stimulating hormone (TSH) and vitamin D status were recorded.

Serum vitamin b12 assays

B-12 level of ≤ 148 p mol/L was considered low (deficiency), more than 221 pmol/L was considered normal and borderline level was considered as serum B-12 level >148 to ≤ 221 pmol/L [10].

STATISTICAL ANALYSIS

All data were de-identified in the analysis process using serial numbers. Continuous variables were expressed as means with 95% confidence interval, while categorical variables were expressed as frequencies and percentages. Prism (Graph Pad) software was used for statistical analyses and differences with P value<0.05 were considered statistically significant. T-test was used to compare between continuous data. Differences, associations and interactions between categorical variables were analysed using the chi-square test and Fisher's exact test.

RESULTS

Baseline characteristics

A total of 387 records were reviewed but serum B-12 levels were available in 306 cases only. The baseline characteristics of the participants are shown in **Table 1**. Approximately two-third of the patients were female (62.1%; n=190), had hypertension (66.0%; n=202), hyperlipidemia (72.9%; n=223) and low vitamin D levels (64.1%; n=196).

Table 1. Baseline characteristics of participants.

	B12 deficiency* (n=22)	Normal B12 levels (284)	P value
Age, mean (95 CI)	58.3 (51.1-65.5)	57.6 (56.2-58.9)	0.7812
Sex			
Male	7	109	0.6512
Female	15	175	
Number of OHA			
1	6	105	0.3479
2	6	92	
3	10	87	

Metformin			
Yes	21	215	0.0341
No	1	69	
HbA1c			
<7	11	120	0.5851
>7	11	164	
Hypertension			
Yes	12	190	0.2385
No	10	94	
Hyperlipidemia			
Yes	17	206	0.6302
No	5	78	
PPIs			
Yes	8	82	0.4576
No	14	202	
Vitamin D status			
Low	14	182	0.9663
Normal	8	102	
LDL			
<2.6 mmol/L	18	195	0.2360
≥ 2.6 mmol/L	4	89	
Systolic BP			
<140 mm Hg	17	187	0.2733
≥ 140 mm Hg	5	97	
Diastolic BP			
<90 mm Hg	21	254	0.7107
≥ 90 mm Hg	1	30	

** B12 deficiency defined as B12 level of less than 148 pmol/L*
OHA: Oral Hypoglycemic Agents; HbA1c: Glycated Hemoglobin; PPI: Proton Pump Inhibitors; BP: Blood Pressure

B12 serum status

The vast majority of the patients had normal or borderline serum B12 levels (n=284; 94%) and only 7% (n=22) of the patient had low B12 levels **(Figure 1)**. No significant differences were found between patients with low and those with normal B12 results except for being on metformin (P=0.0341).

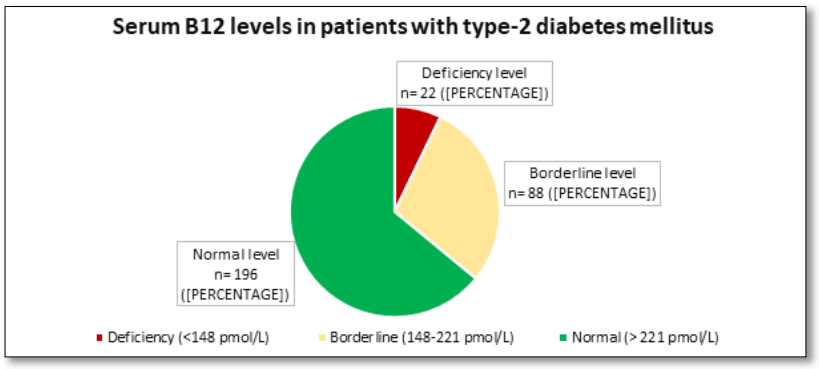

Figure 1. Serum B12 levels in patients with type-2 diabetes mellitus.

Serum B12 levels, patient age, metformin use and dose

There was a weak positive correlation between the age and serum-B12 levels. Patients who were treated with metformin were younger (56.7 vs. 60.7 years; P=0.01), had lower HbA1c results (58.3 vs. 62.9; P= 0.01) and lower systolic BP (132.6 vs. 136.5; P=0.02). No significant differences between metformin-user and non-metformin users in sex ratio, ALT, LDL and total cholesterol levels. Most importantly, vitamin B12 deficiency was significantly associated with metformin use (8.9% vs. 1%; P=0.03). Metformin users who had low B12 levels were female (71.4%; n=15), using 2000 mg/day (61.9%; n=13) and had a reasonable A1C<7% (52.4%; n=11) **(Table 2 and Figures 2 and 3)**.

Table 2. Comparison of demographic and clinical characteristics between metformin and non-metformin users.

	Metformin user (n=236)	Non-Metformin users (N=70)	P value
Age, Mean (SE)	56.7 (0.79)	60.7 (1.30)	0.01
Male, n (%)	90 (38.1%)	26 (37.1 %)	0.88
Insulin use, n (%)	94 (39.8%)	49 (70%)	0.00
PPI use, n (%)	68 (28.8%)	22 (31.4 %)	0.67
Systolic BP (mmHg), Mean (SE)	132.6 (0.75)	136.5 (1.68)	0.02
Serum B12 deficiency (pmol/L), n (%) *	21 (8.9%)	1 (1%)	0.03
Serum B12 level (pmol/L), Mean (SE)	287.7 (11.7)	302.6 (17.6)	0.52
HbA1c (%), mean (SE)	58.3 (0.79)	62.9 (1.49)	0.01

** B12 deficiency defined as B-12 level of less than 148 pmol/L*
PPI: Proton Pump Inhibitors; BP: Blood Pressure; HbA1c: Glycated Hemoglobin; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein

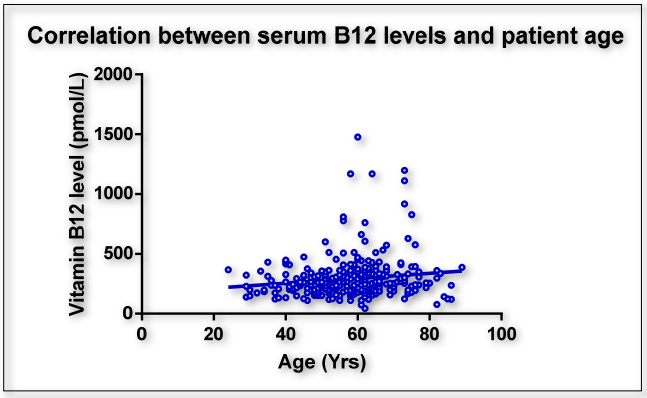

Figure 2. Scatter plot for vitamin B12 level and patient age.

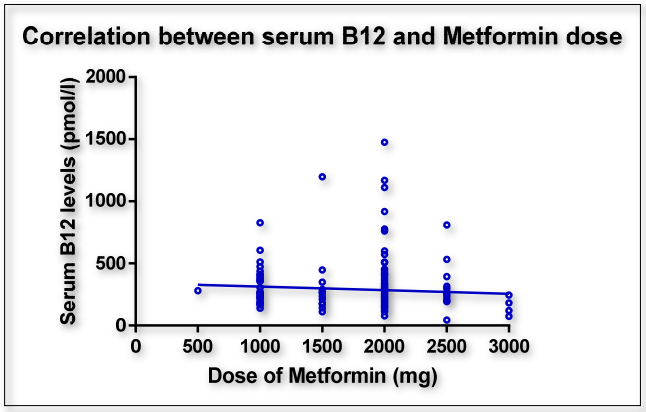

Figure 3. Scatter plot for vitamin B12 level and metformin dose.

DISCUSSION

The main objectives of the current study it to determine the prevalence of B12 deficiency and the risk factors for this condition. Similar to multiple regional observations, our results showed that the prevalence of B12 deficiency in patients with T2DM was around 7% [11]. While B12 deficiency was more prevalent (43.6%) in the study conducted at Royal medical services military hospital. This might be partly explained by the different cut-off points used to define B12 deficiency (300 pmol/L) [12,13]. In addition, this difference in prevalence could be attributed to the differences in study population managed at primary care level and those referred to secondary care specialized endocrinology clinics that tend to have more complications and less stringent control. Moreover, having higher prevalence of B12 deficiency among T2DM metformin users should be cautiously interpreted in view of small number of cases in the non-metformin users in such studies.

Consistent with most of the studies, we found a statistically significant association between cobalamin deficiency and metformin use. For example, a systematic review found an increase in the incidence of B12 deficiency in metformin users compared to non-users [12]. In another study in Saudi Arabia, the overall prevalence of B12 deficiency among patients with T2DM was estimated to be 7.8% with statistically significant higher prevalence among metformin users [13]. However, interestingly, a recent study conducted in Qatar found comparable serum B12-levels between Metformin and non-Metformin users with T2DM [13]. Presently, although the exact mechanism of this association remains unclear, proposed mechanisms include alterations in small bowel motility, competitive inhibition of B12 absorption and alterations in intrinsic factor levels [14].

Additionally, the results of the present study have demonstrated a weak negative correlation between B-12 level and metformin dose. Such a relationship was also seen and evaluated in some observations. For instance, a study conducted in Netherlands concluded that higher doses of metformin were strongly associated with lower cobalamin levels [15]. This effect was found even in persons at high risk for type 2 diabetes who used metformin [16]. Studies have reported that PPIs use and patients' age decrease the serum level of B12 but this effect was not obvious in this analysis [17,18].

The clinical significance of B12 deficiency is to be determined particularly in asymptomatic individuals. In addition, the sensitivity and specificity of current assays and one reading B12 serum level remains limited in excluding or confirming the diagnosis. Methyl-Malonic Acid levels (MMA) and homocysteine are additional markers that can be utilised to improve the accuracy of the diagnosis in symptomatic patients with normal B-12 levels [19,20]. However, none of these tests is specific for the diagnosis [21].

This study has several strengths. It is the first study to investigate the prevalence of B12 deficiency in patients with T2DM in a public hospital in Bahrain. The most important parameters were evaluated and patients with different baseline characteristics were included. One of the limitations of this study is that some factors that could affect B12 level have not been evaluated. These include duration of metformin use; duration of diabetes and the presence of underlying gastric pathologies could not be obtained retrospectively in our setting. Because elevated level of MM Aim proves the diagnostic accuracy, another limitation was the lack of MMA measurements.

CONCLUSION

In conclusion, this study estimates the prevalence of cobalamin deficiency to be around 7%. Among adults with T2DM, there was a statistically significant association between metformin use and B12 deficiency. Given the accumulating evidence associating metformin use to cobalamin deficiency, periodic measurement of serum B12 should be considered in metformin-users, especially in the presence of neurological and/or anemia symptoms. Further studies to assess the feasibility and cost-effectiveness of

screening all T2DM and the role of prophylactic cobalamin in this setting.

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AUTHOR CONTRIBUTIONS

HT and MA contributed to the study conception and design; HA, RF, RA and HF collected the data; MA and HA analysed the data and drafted the article. All authors reviewed the manuscript and approved the final version of this study.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

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