Original Article

Vitamin B12 deficiency and the knowledge and practice of physicians regarding screening for vitamin B12 deficiency among type 2 diabetic patients on metformin in selected hospitals in Riyadh, Saudi Arabia

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Abstract

Background/Aim: The worldwide prevalence of diabetes is high including Saudi Arabia. One standard first-line treatment for diabetes is metformin, which was reported to increase the risk for vitamin B12 deficiency. We wanted to determine the prevalence of vitamin B12 deficiency in metformin-treated type 2 diabetes mellitus patients. **Methods:** We conducted a cross-sectional study at the diabetic clinics of four hospitals in Riyadh, Saudi Arabia. Type 2 diabetes mellitus patients who were on metformin for at least 1 year were included in the study. Associations between B12 deficiency and age, duration of type 2 diabetes mellitus (T2DM), duration of use and dosage of metformin, and use of proton pump inhibitors (PPIs) were determined. **Results:** Of 363 T2DM patients, 206 (56.7%) were males and 157 (43.3%) were females, mean age was 53.72 ± 11.31 years, the mean duration of T2DM was 9.89 ± 7.32 years, and the mean duration of metformin use was 9.84 ± 7.29 years. There were 205 patients 56.5% who had a daily dose of 750 mg of metformin. The most commonly used oral hypoglycemic agent was gliclizide only in 138 (38.4%) of patients. There were 107 patients (29.5%) who were on PPIs. There were 210 patients (57.9%) who were on vitamin B12 supplementation, of which 111 (30.6%) had a daily dose of 200 mcg. The use of vitamin B12 supplement, duration of T2DM and duration of metformin use was significantly higher among females. The use of vitamin B12 supplement was significant among patients who were 46 years old and above. There were only 16 patients (4.4%) who had available serum vitamin B12 levels. Only 44.0% of the physician respondents know the current recommendation of American Diabetes Association on vitamin B12 screening and supplementation among diabetic patients, and 21.0% never prescribe vitamin B12 to their patients. **Conclusion:** Routine testing for serum vitamin B12 level is not practiced in our institution. A large percentage of physicians are not aware of the current recommendations of the American Diabetic Association (ADA) regarding vitamin B12 supplementation and screening. Thus, there is a need for doctors involved in the management of diabetes to keep abreast with guidelines and current recommendations and routinely monitor vitamin B12 levels particularly those who were on long-term takers of metformin and the elderly patients to optimize management of diabetes and its complications.

Keywords: Metformin, type 2 diabetes, Vitamin B12 deficiency, Vitamin B12 screening, Vitamin B12 supplementation

Introduction

Diabetes mellitus (DM) is a chronic metabolic disease with increasing prevalence worldwide.[1]

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The number of persons with diabetes has risen from 108 million in 1980 to 422 million in 2014.[2] In 2015, diabetes was the leading cause of 1.6 million deaths and World Health Orgnization projects that diabetes will be the seventh most important cause of death by 2030.[2] The prevalence of diabetes in Saudi Arabia alone has increased to reach 7 million cases.[3]

Metformin has been one of the most widely used antidiabetic agents taken orally. Metformin is the base of medicine in the treatment of type 2 diabetes mellitus (T2DM) with estimates that it is frequently approved and recommended to 120 million patients with diabetes globally.[4] Both American and European guidelines recommend metformin as the first-line agent for the pharmacological management of T2DM. Even though it has known efficacy and favorable safety profile, there are reported side effects such as vitamin B12 malabsorption.[5,6] Reports have shown that vitamin B12 deficiency occurs in 5.8–30% of diabetic patients on long-term treatment with metformin.[7-13] Geographical studies conducted in the United Kingdom, Iran, Spain, China, and Mexico all showed significant association between long-term use of metformin and vitamin B12 deficiency.[14-18] Furthermore, there were several studies that quantified the prevalence of vitamin B12 deficiency among diabetics including the 7% prevalence in a US study,[19] 28.1% prevalence in a South African study,[20] 22.5% in Brazil,[21] 18.7% in New Zealand,[22] 9.7% in the Netherlands,[7] and 9.7% in Libya.[23]

Vitamin B12 deficiency screening is recommended for diabetic patients on long-term treatment with biguanides including metformin.[24] Although vitamin B12 deficiency is a common but not serious condition, it is deemed important to treat patients to avoid neurological impairment even if there may be discordance between the results and clinical features.[25] There have been no studies that explored the knowledge and perceptions of physicians on vitamin B12 screening. Furthermore, because of the paucity of data on Saudi patients, this study aimed to find the prevalence of vitamin B12 deficiency in metformin-treated T2DM patients in selected Ministry of Health (MoH) hospitals in Riyadh, Saudi Arabia, and determine the knowledge and perception of physicians on vitamin B12 screening, to be able to make a recommendation for screening, as suggested by ADA and the European Association for the study of diabetes.[26,27]

Materials and Methods

Study patients

This cross-sectional study was conducted at the diabetic clinics at four selected MoH hospitals in Riyadh, Saudi Arabia (King Salman Hospital, King Saud Medical City, Imam Abdulrahman Alfaisal Hospital and Prince Mohammad bin Abdulaziz Hospital) between August and November 2018. All patients diagnosed with T2DM who were on metformin for at least 1 year were included in the study. Type 1 diabetics and patients who had a history of pernicious anemia, chronic renal insufficiency, prior bariatric surgery, prior gastrectomy, vitamin B12 supplementation with B12 injections or an oral dose of >500 μg/day, prior ileum resection, or Crohn's disease were excluded from the study. Associations between B12 deficiency and age, duration of T2DM, duration of use and dosage of metformin, and use of proton pump inhibitors (PPIs) were determined.

Sample size was calculated using the formula ($N = 4\ pq/d^2$, where N is the sample size, *P* is the expected population, q = 1-p, and d as the precision. Using an assumed proportion of 9.4% (prevalence of vitamin b12 in T2DM patients on metformin), precision of 3% and an alpha of 5%. The calculated sample size was 363. A multi-cluster random sampling technique was used. Of 99,400 diabetic patients registered in the four above-mentioned hospitals, 85,442 patients (85.95%) were from King Salman Hospital, 8,624 (8.67%) were from King Saud Medical City, 3,780 (3.80%) were from Imam Abdulrahman Alfaisal Hospital and 1,554 (1.56%) were from Prince Mohammad bin Abdulaziz Hospital. Representative samples from each hospital were calculated based on the percentage population × 177/100 for males and percentage population × 157/100 for females. We chose the four hospitals according to availability of Vitamin B12 test. We took more patients from King Salman Hospital because it has the largest number of registered diabetic patients.

Data was collected from the medical records of four tertiary MoH hospitals in Riyadh, Saudi Arabia (King Salman Hospital, King Saud Medical City, Prince Mohammed Bin Abdul-Aziz Hospital and Imam Abdurrahman Alfaisal Hospital). The data collection was done in the clinic using a data extraction form. The form was piloted on five medical records before using it. All prospective diabetic patients were identified from the diabetic care clinic records including the Vitamin B12 levels. Vitamin B12 deficiency was defined as serum levels less than 148 pmol/L or 200 pg/mL.[24]

Physician participants

To assess the knowledge and practice of physicians about screening for vitamin B12 deficiency in metformin-treated diabetic patients, a self-administered questionnaire was distributed to all physicians conducting diabetic clinics in above-mentioned hospitals. The questionnaire contained questions on their demographic profile, knowledge and practice of screening of Vitamin B12 level. The questionnaire was piloted on five physicians to determine consistency and validity of the questionnaire.

Data analysis

The collected data was entered and analyzed by using Statistical Package for Social Sciences (SPSS) version 23.0 (SPSS Inc., IBM, Armonk, New York, USA). Results were expressed as numbers and percentages for categorical variables and as mean and standard deviation (SD) for continuous variables. Associations between Vitamin B12 deficiency and age, duration of diabetes mellitus, duration of use and dosage of metformin, and use of PPIs or histamine H2 antagonists were determined using Pearson's

correlation test. Chi-square test was used to determine significant difference between two proportions or groups. Independent t-test was performed to determine the significant difference between continuous variables. Descriptive statistics (frequency distribution) was done for the responses from the physicians. A *P* value of < 0.05 was considered statistically significant.

Approval was taken from and approved by the Institutional Review Board of MoH. Approvals were taken from the directors of the four hospitals prior to data collection.

Results

A total of 363 T2DM patients who were on metformin were included in the study. The mean age of the patients was 53.72 ± 11.31 years (ranged from 25 to 84 years old). There were 206 (56.7%) males and 157 (43.3%) females, and 337 (92.8%) were Saudis. The mean duration of T2DM was 9.88 ± 7.32 years (range: 1–35 years). The mean HbA1c for all patients was 8.45 ± 2.01% (range: 4.23–16.0). The mean daily dose of metformin was 984.85 ± 320.96 mg (range: 500–2000 mg). The mean duration of metformin use was 9.84 ± 7.29 years (range: 1.0–35 years). Table 1 shows the clinicodemographic profile of all patients.

There were 205 patients 56.5%) who had a daily dose of 750 mg of metformin. The most commonly used oral hypoglycemic agent was gliclizide only in 138 (38.4%) of patients. There were 107 patients (29.5%) who were on PPIs. There were 210 patients (57.9%) who were on vitamin B12 supplementation, of which 111 (30.6%) had a daily dose of 200 mcg [Table 2].

The use of vitamin B12 supplement was significantly higher among females ($p < 0.001$). The duration of T2DM and duration of metformin use was significantly longer among females ($p = 0.025$ and $P = 0.018$, respectively) [Table 3]. The use of vitamin B12 supplement was significant among patients 46 years old and above [Table 4]. There were only 16 patients (4.4%) who had available serum vitamin B12 levels. The mean serum vitamin B12 level of all 16 patients was 558.46 ± 318.01 pg/mL (range of 174–1288 pg/mL). The mean age of these 16 patients was 53.8 ± 14.26 (range of 35–84 years old). The mean duration of T2DM was 10.27 ± 7.99 years (range of 2.0–26.0 years) and the mean duration of metformin use was 10.27 ± 7.99 years (range of 2.0–26.0 years). Their mean daily dose of metformin was 828.13 ± 150.52 mg (range of 500–1000 mg). A total of 6 of the 16 patients (37.5%) used PPI, and 11 (68.8%) had Vitamin

Table 1: Clinicodemographic profile of 363 T2DM patients on metformin use

Clinicodemographic variables	Mean (SD), range	*n* (%)
Age, in years	53.72 (11.31), 25-84	
HbA1c, in %	8.45 (2.01), 4.23-16.0	
Duration of diabetes, in years	9.88 (7.32), 1-35	
Duration of metformin use, in years	9.82 (7.29), 1-35	
Daily dose of metformin, in mg	984.85 (320.96), 500-2000	
Daily dose of vitamin B12, in ug	165.05 (92.26), 2.4-250	
Serum vitamin B12 level, in pg/mL	366.99 (139.95), 164.6-1288	
Gender		
Male		206 (56.7)
Female		157 (43.3)
Nationality		
Saudi		337 (92.8)
Non-Saudi		26 (7.2)
Use of proton pump inhibitors		107 (29.5)
Use of vitamin B12 <500 ug/day		213 (58.7%)

Table 2: Frequencies of daily doses of metformin, types of OHA used, PPI use, vitamin B12 supplement use, and daily doses of vitamin B12

Variables	*n* (%)	Confidence intervals
Daily dose of metformin		
500	2 (0.6)	±0.79 (-0.19-1.39)
750	205 (56.5)	±5.1 (51.4-61.6)
1000	62 (17.1)	±3.87 (13.23-20.97)
1500	93 (25.6)	±4.49 (21.11-30.09)
2000	1 (0.3)	±0.56 (-0.26-0.86)
Other OHA used		
Glibenclamide only	5 (1.4)	±1.21 (0.19-2.61)
Gliclizide only	138 (38.0)	±4.99 (33.01-42.99)
Glimepride only	1 (0.3)	± 0.56(-0.26-0.86)
Gliclizide and glibenclamide	2 (0.6)	±0.79 (-0.19-1.39)
Gliclizide and insulin	50 (13.8)	±3.55 (10.25-17.35)
Glibenclamide and insulin	2 (0.6)	±0.79 (-0.19-1.39)
Glibenclamide and pioglitazone	1 (0.3)	± 0.56(-0.26-0.86)
Glimipride and insulin	1 (0.3)	± 0.56(-0.26-0.86)
Insulin only	91 (25.1)	± 4.46 (20.64-29.56)
None	72 (19.8)	±4.1 (15.7-23.9)
Proton pump inhibitor use		
Yes	107 (29.5)	±4.69 (24.81-34.19)
No	256 (70.5)	±4.69 (65.81-75.19)
Vitamin B12 supplement use		
Yes	210 (57.9)	±5.07 (53.63-63.77)
No	153 (42.1)	±5.07 (36.23-46.37)
Vitamin B complex use		
Yes	5 (1.4)	±1.21 (0.19-2.61)
No	358 (98.6)	±1.21 (97.39-99.81)
Doses of Vitamin B12		
2.4 mcg	42 (11.6)	±3.29 (8.31-14.89)
15 mcg	8 (2.2)	±1.51 (0.69-3.71)
200 mcg	111 (30.6)	±4.74 (25.86-35.3)
240 mcg	1 (0.3)	±0.56 (-0.26-0.86)
250 mcg	48 (13.2)	±3.48 (9.72-16.68)
None	153 (42.1)	±5.08 (37.02-47.18)
Vitamin B12 level below 200, (in 16 patients)	2 (0.6)	±0.79 (-0.19-1.39)

Table 3: Gender differences in the use of PPI, vitamin B12 supplements and duration of T2DM, duration and dose of metformin use, and vitamin B12 levels

Categorical variables	Males	Females	p	
Use of PPI				
Yes	67 (62.6)	40 (37.4)	0.145	
No	139 (54.3)	117 (45.7)		
Use of vitamin B12				
Yes	100 (46.9)	113 (53.1)	<0.001	
No	106 (70.7)	44 (29.3)		
Use of vitamin B complex, yes	3 (60.0)	2 (40.0)	Not significant	
Vitamin B12 level below 200 (in 16 patients)	1	1	Not significant	
Continuous variables	**Males**	**Females**	**95% CI**	***P***
HBA1c, mean and SD	8.40 (2.04)	8.51 (1.98)	-0.315-0.527	0.621
Duration of T2DM, years	9.13 (6.36)	10.87 (8.35)	0.219-3.259	0.025
Duration of metformin use, years	9.03 (6.36)	10.87 (8.35)	0.323-3.349	0.018
Daily dose of metformin	976.94 (317.79)	1000.0 (327.7)	-44.048-90.165	0.500
Vitamin B12 dose	172.86 (92.05)	158.22 (92.3)	-39.782-10.495	0.252

Table 4: The use of PPI, vitamin B12 supplements and duration of T2DM, duration and dose of metformin use, and vitamin B12 levels according to age groups

Categorical variables	25-30	31-35	36-40	41-45	46 and above	p
Use of PPI, *n* (%)						
Yes	1 (0.9)	4 (3.7)	8 (7.5)	6 (5.6)	88 (82.2)	0.155
No	6 (2.3)	7 (2.7)	21 (8.2)	36 (14.1)	186 (72.7)	
Use of vitamin B12						
Yes	1 (0.5)	4 (1.9)	14 (6.6)	20 (9.4)	174 (81.7)	0.007
No	6 (4.0)	7 (4.7)	15 (10.0)	22 (14.7)	100 (66.7)	
Continuous variables						
HBA1c, mean and SD	8.47 (2.77)	9.27 (2.18)	8.85 (2.21)	8.18 (2.16)	8.41 (1.94)	0.435
Duration of T2DM, years	2.43 (0.98)	4.41 (3.33)	6.76 (5.85)	4.79 (3.88)	11.40 (7.41)	<0.001
Duration of metformin use, years	2.43 (0.98)	4.41 (3.33)	6.76 (5.85)	4.79 (3.88)	11.40 (7.41)	<0.001
Daily dose of metformin	1178.60 (400.89)	863.64 (233.55)	939.66 (303.66)	950.00 (337.86)	992.70 (323.73)	0.307
Vitamin B12 dose	200	113.70 (130.13)	143.05 (98.54)	133.92 (114.20)	171.11 (88.06)	0.285
Serum vitamin B12 level	-	583.0	174.00	382.5 (119.3)	664.83 (347.84)	0.301

Table 5: Demographic profile of 100 physicians who participated in the study on knowledge and perception about vitamin B12 screening

Demographic variables	*n*	Percentage
Gender		
Male	41	41.0
Female	59	59.0
Age groups, in years		
25-30	32	32.0
31-35	22	22.0
36-40	19	19.0
41-45	15	15.0
46 or more	12	12.0
Specialty		
Internal medicine	29	29.0
Family medicine	46	46.0
Others	25	25.0
Years of experience		
Less than 5 years	39	39.0
5-10 years	41	41.0
11 years or more	20	20.0

B12 supplementation. Of the 16 patients who had vitamin B12 levels, two (12.5%) had vitamin B12 level below 200 pg/mL.

Physicians' responses

A total of 100 physicians responded and consented to participate in the study. There were 41 (41.0%) males and 59 (59.0%) females. A total of 46 (46.0%) were family physicians, 29 (29.0%) were internal medicine doctors, and 25 (25.0%) were from other specialties. Table 5 shows the demographic profile of the 100 respondents.

Forty-four (44.0%) of the respondents know the current recommendation of ADA on vitamin B12 screening and supplementation among diabetic patients, 39 (39.0%) do not know about the current recommendation, whereas 17 (17.0%) have no idea about the recommendation. [Figure 1] A total of 51 (51.0%) order vitamin B12 testing supplementation only if they have symptoms of neuropathy, 9 (9.0%) if patients have anemia, 19 (19.0%) routinely order vitamin B12

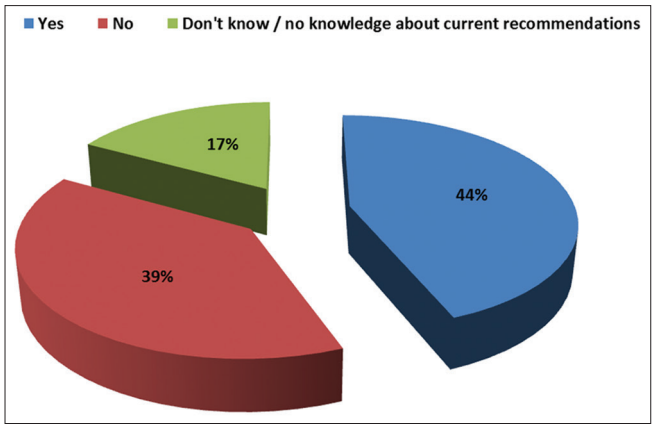

Figure 1: Knowledge of physicians about the current ADA recommendations on vitamin B12 supplementation and screening for T2DM patients

testing, and 21 (21.0%) never prescribe vitamin B12 to their patients [Figure 2].

Discussion

In this study, we found that only 4.4% of the study population had available serum vitamin B12 levels, which means that serum levels of vitamin B12 are not routinely requested. We expected more number of patients to undergo vitamin B12 testing. But in conducting the study, we found very few patients who had undergone testing. So, it was not possible to get a valid estimate of the deficiency prevalence. Therefore, we focused on the other objectives of the study.

It has been suggested that healthy people can have low levels of vitamin B12, and much more vitamin B12 deficiency commonly occurs in around 6% of elderly patients aged ≥60 years with prevalence increasing with age.[28] Type 2 diabetics particularly those on metformin are at risk for metabolically lower levels of vitamin B12. Liu *et al.* suggested that the mechanism for this vitamin B12 deficiency is caused by the slowed intestinal transit time among diabetics causing bacterial overgrowth and eventually B12 malabsorption.[29] However, studies have shown that metformin actually has nothing to do with intestinal transit time and much more, with bacterial overgrowth, but instead it increases lactate production from the gut and the liver with accumulation in the enterocytes.[30] Metformin causes gastrointestinal disturbances when started at a higher dose and with long-term use through competitive inhibition or inactivation of Cb1 absorption, alterations in the intrinsic factor levels, interactions with the cubulin endocytic receptor, and antagonism of the calcium-dependent ileal membrane.[31]

Despite our study was not able to establish the relationship between vitamin B12 level and duration of T2DM and duration of metformin use, we were able to highlight some considerable facts including the use of PPI among T2DM patients. It was thought that the use of PPI contributes to vitamin B12 deficiency,[32] which may add to the vitamin B12 deficiency status

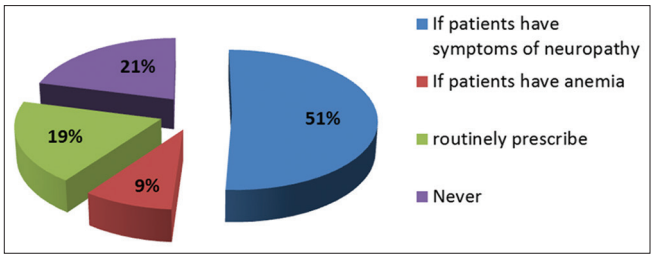

Figure 2: Responses of 100 physicians on "when do they order vitamin B12"

of T2DM patients. General multivitamins (6 μg) was found to be not enough to correct vitamin B12 deficiency particularly among those with diabetes.[8]

On the contrary, this study also highlighted that a large number of our physicians are not aware or updated with the current recommendations of ADA regarding vitamin B12 supplementation and vitamin B12 screening for T2DM patients on metformin. This issue maybe debatable to some, but we think that there is a need for physicians to keep abreast with the latest recommendations and guidelines pertaining to management of diabetes.

There are some limitations of this current study. For one, this study was done retrospectively, thus the vitamin B12 status of the patients was all based on the medical records, and for this reason vitamin B12 levels were not available. We were not also able to draw a solid conclusion on the association of vitamin B12 deficiency with vitamin B12 supplementation since we do not have enough number of patients who had vitamin B12 levels. Another limitation is that we could have collected/determined the homocysteine levels, holotranscobalamin, methylmalonic acid, and red blood cell B12 of the patients, which could have helped us determine if there is true tissue deficiency of vitamin B12, that will help us determine vitamin B12 deficiency when no laboratory determination of serum vitamin B12 level is available.

Conclusion

Routine testing for serum vitamin B12 level is not practiced in our institution. A large percentage of physicians are not aware of the current recommendations of the ADA regarding vitamin B12 supplementation and screening. Thus, there is a need for doctors involved in the management of diabetes to keep abreast with guidelines and current recommendations and routinely monitor vitamin B12 levels particularly those who were on long-term takers of metformin and the elderly patients to optimize management of diabetes and its complications.

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Conflicts of interest

There are no conflicts of interest.

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