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# Prevalence of vitamin B12 deficiency among patients with Type 2 diabetes on metformin in Security Forces Hospital, Riyadh, Saudi Arabia: A cross-sectional study

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**Abstract**
**Background and Aim:** *The association between Vitamin B12 deficiency and metformin use among Type 2 diabetic patients (T2DM) were reported. We wanted to determine the prevalence of Vitamin B12 deficiency among T2DM patients who were on metformin seen in our institution.*
**Methods:** *We conducted a retrospective medical records review of Saudi patients diagnosed with Type 2 Diabetes Mellitus patient aged between 30-50 years who visited the Primary Care Center of Security Forces Hospital in Riyadh, Saudi Arabia during the last two years 2018-2019.*
**Results:** *A total of 289 T2DM patients, 161 (55.7%) males and 128 (44.3%) females with a mean age of 44.66 ± 4.49 years were included in the study. The mean Vitamin B12 level was 296.68 ± 114.79 pg/mL. There were 12 patients (4.2%) with Vitamin B12 deficiency, and the remaining 277 patients (95.8%) had normal Vitamin B12 level. The mean (SD) Vitamin B12 level of males was significantly higher among males than females (311.75 ± 115.34 pg/mL versus 277.72 ± 111.68 pg/mL, p=0.012). There was no significant difference in the mean (SD) Vitamin B12 level among patients <50 years old and patients ≥50 years old (292.40 ± 111.82 pg/mL versus 324.08 ± 130.52 pg/mL, p=0.109).*
**Conclusion:** *In summary, we found 19.72% prevalence of Vitamin B12 deficiency among patients seen at the family medicine clinics with 40.14% of our patients in the borderline Vitamin B12 status. Contrary to other previous studies, we found that females are more at risk for Vitamin B12 deficiency in this region. This study suggests the importance of measuring the Vitamin B12 levels of women especially and improve their Vitamin B12 status.*
**Keywords:** *Vitamin B12 deficiency, Type 2 diabetes, Metformin, prevalence, Saudi Arabia.*

## Introduction

Metformin is the first therapeutic choice for management of type 2 diabetes mellitus (T2DM), as recommended by the American Diabetes Association and the European Association for the Study of Diabetes.[1] Metformin acts as an insulin sensitizer on insulin-targeted tissues; liver, muscle, and adipose tissues and reduces insulin resistance, and it offers protection from cardiovascular diseases and heart failure.[2]

However, several studies have shown that long term use of metformin leads to malabsorption of vitamin B12, with a decrease in the concentration of serum vitamin B12 from 30% to 14%.[3] Vitamin

B12 deficiency secondary to long-term use of metformin has been associated with intestinal malabsorption of Vitamin B12 and can potentially increase the risk for cardiovascular, neurological and hematological outcomes among patients with T2DM.[4]

Vitamin B12 deficiency (<200 pg/mL) among long-term metformin users were found to be around 3.9% to as much as 10.5% compared to non-metformin users. [5-7] The incidence of Vitamin B12 deficiency was also reported to increaseby as much as 2-3x more among metformin users compared to non-metformin users. [8] On the contrary, one study showed that the level of homocysteine, as well as the VB12 level, hemoglobin concentration and mean corpuscular volume, did not differ significantly between the metformin users and non-metformin users. [9] Despite these reports, there are no national guidelines for Vitamin B12 deficiency screening and Vitamin B12 supplementation remained to be under prescribed.[10]

There is a scarcity of studies conducted on the prevalence of Vitamin B12 secondary to metformin use in Saudi Arabia. To date, there is only one study that showed a Vitamin B12 deficiency prevalence of 9.4% among metformin users. Furthermore, there are no guidelines to address how often individuals with T2DM who are being treated with metformin should be screened for vitamin B12 deficiency risk and, if appropriate, prescribed vitamin B12 supplements.[1] Therefore, we conducted this study to determine the prevalence of vitamin B12 deficiency amongT2DM patients on metformin at Security Forces Hospital, Riyadh, Saudi Arabia.

**Methods**

We conducted a retrospective medical records review of Saudi patients diagnosed with Type 2 Diabetes Mellitus patient aged between 30-50 years who visited the Primary Care Center of Security Forces Hospital in Riyadh, Saudi Arabia during the last two years 2018-2019. We excluded patients with history of any type of anemia, alcohol intake, patients on current parenteral or enteral nutritional support, prior transfusion and thyroid illness, patients of malabsorption syndrome, patients using vitamin supplements especially B12 or proton pump inhibitors and who are vegetarians as assessed on history or previous record., patients with chronic renal insufficiency defined by serum creatinine level less than 3, and patients with a prior history of gastrostomy, bariatric surgery, ileum resection or Crohn's disease.

Sample size was calculated based on the formula $Z_1\text{-}\alpha 2^2$ p(1-p)/$d^2$, where $Z_1\text{-}\alpha 2^2$ is the standard normal variate (at 5% type 1 error ($p<0.05$), p is the expected proportion in population, and d is the absolute error or precision. Assuming that the nationwide prevalence of type 2 diabetes in Saudi Arabia is 25.4% based on previous studies,[11] and using a precision absolute error of 5% and a type 1 error of 5%, the calculated sample size was 289.

Vitamin B12 deficiency were classified according to Vitamin B12 levels as: more than 300 pg/mL as normal, between 200 and 300 pg/mL as borderline, and Vitamin B12 levels below 200 pg/mL as deficient as reported by Ankar and Kumar in 2020.[12]

Data was analyzed using the Statistical Package for Social Sciences (SPSS) version 23.0 (IBM-SPSS, SPSS Inc, Armonk, New York, USA). Results are presented as number and percentages for categorical variables such as gender and age, and as mean and standard deviation for vitamin B12 levels. Independent samples t-test was used to determine the significant differences in the mean (SD) of Vitamin B12 levels across gender and age groups. Chi-square test was used to determine the significant difference in the proportion of Vitamin B12 deficiency across gender and age groups. A p value of <0.05 was considered statistically significant. IRB approval to conduct the study was granted by the IRB of Security Forces Hospital, Riyadh, Saudi Arabia.

**Results**

A total of 289 T2DM patients were included in the study, 161 (55.7%) males and 128 (44.3%) females. The mean age was 44.66 ± 4.49 years od (range: 33.0 to 52 years old). All included patients were Saudi nationals. The mean Vitamin B12 level for all 289 patients was 296.68 ± 114.79 pg/mL. There were 57 patients (19.72%) with Vitamin B12 deficiency, 116 (40.14%) with borderline Vitamin B12 level, and the remaining 116 patients (40.14%) had normal Vitamin B12 level. (Figure 1)

The overall mean (SD) Vitamin B12 level for all males regardless of Vitamin B12 classification was significantly higher among males than females (311.75 ± 115.34 pg/mL versus 277.72 ± 111.68 pg/mL, p=0.012). (Figure 2) On the other hand, there was no significant difference in the mean (SD) Vitamin B12 level among patients <50 years old and patients ≥50 years old (292.40 ± 111.82 pg/mL versus 324.08 ± 130.52 pg/mL, p=0.109). A significant correlation was observed between Vitamin B level and male gender (r=0.148, p=0.012) but age was not significantly correlated with Vitamin B12 deficiency (r=0.094, p=0.109).

Subanalysis of the 57 patients with Vitamin B12 deficiency showed a greater non-significant proportion of Vitamin B12 deficiency among females (n=31, 54.4%) females compared to males (n=26, 45.6%) (p=0.347). (Figure 2) There was no significant difference in the mean (SD) Vitamin B12 deficiency levels between males (168.12 ± 30.58 pg/mL) and females (162.16 ± 30.31 pg/mL) (p=0.465). (Figure 2) On the other hand, of the 57 patients with Vitamin B12 deficiency, there were significantly more patients who were below 50 years old (n=51, 89.5%) than ≥ 50 years old (n=6, 10.5%) (p<0.001), with no significant difference in the mean (SD) Vitamin B12 deficiency levels across age groups (p=0.919).

Subanalysis of the 166 patients who had borderline Vitamin B12 levels showed an almost equal proportion of males and females (males=57, 49.1% and females=59, 50.9%) (p=0.795). (Figure 2) There was no significant difference in the mean (SD) Vitamin B12 levels between males (245.93 ± 28.84 pg/mL) and females (250.07 ± 29.63 pg/mL) (p=0.448). Of the 116 patients with borderline Vitamin B12 levels, 100 (86.2%) were <50 years old and 13 (13.8%) were ≥50 years old (p<0.001). However, patients who were ≥ 50 years old had significantly lower Vitamin B12 levels compared to patients who were <50 years old (≥50 years od = 244.63 ± 28.15 pg/mL versus <50 years old = 269.31 ± 27.28 pg/mL).

Among the 116 patients with normal Vitamin B12 levels, 78 (67.2%) were males and 38 (32.8%) were females (p<0.001). However, their mean Vitamin B12 levels was not significantly different across genders (males=407.73 ± 85.02 pg/mL versus females=414.92 ± 94.58 pg/mL, p=0.681). (Figure 2) Of the 116 patients with normal Vitamin B12 level, 99 (85.3%) were <50 years old and 17 (14.7%) were ≥50 years old (p<0.001). There was no significant difference in the mean Vitamin B12 level across age groups among the 116 patients with normal Vitamin B12 level (<50 years old= 406.28 ± 81.16 versus ≥50 years old = 432.24 ± 120.83, p=0.263).

**Discussion**

This study investigated the prevalence of Vitamin B12 deficiency among T2DM patients seen at our institution and explored the spectrum of Vitamin B12 levels according to age and gender. For physicians particularly family medicine specialists, it is important to recognize Vitamin B12 deficiency as a serious disorder which needs to be treated. Vitamin B12 deficiency can lead to severe consequences including neurological symptoms,[12-14] depression and anxiety among adolescents and children, [15] abnormalities in lipid metabolism,[16] and many other outcomes.

This study showed a Vitamin B12 deficiency among T2DM patients on metformin prevalence of 19.72%, lower than other previous international studies conducted by Shivaprasad et al in 2020 (24.5%) [17] but higher than the reported rate by

Miyan and Waris in 2020 (3.9%). [18]This rate 24.5% among metformin users. On the other hand, a similar study conducted in Oman showed a Vitamin B12 deficiency prevalence of 10.5%. [19]In contrast with studies conducted in Saudi Arabia, our prevalence rate is significantly higher to prevalence rate reported by Jajah et al in 2020 (10.4%), [20] 10.4% from a study conducted in Taif, Saudi Arabia by Althaqafi,[21] and 3.6% prevalence rate reported by AlSaeed in 2021.[22]

Interestingly, we found that females had a higher prevalence of Vitamin B12 deficiency. This is in contrast to many previous studies that have elucidated that Vitamin B12 deficiency among metformin users is higher among men compared to women. Margalit et al in 2018 investigated 7,963 healthy individuals and found that men had a greater tendency for deficiency compared to women with an OR of 2.26. [23]Alvarez et al in 2016 also had a similar result that diabetic men who are on metformin are at higher risk for Vitamin B12 deficiency than women.[24] However, one study reported a greater tendency for Vitamin B12 deficiency among women because of the concomitant deficiency in holotranscobalamin, which is a protein that delivers cobalamin to the tissues and is considered a more sensitive diagnostic marker for cobalamin deficiency. [25]Whether the differences in the prevalence of Vitamin B12 deficiency according to gender varies so much, possible associated factors that has to be considered include the effects of pregnancy and lactation,[26] the positive effect of exercise, [27] and other confounding factors such as diet, income and age in women.[28]

Our study has several important limitations. First, this study used a retrospective cross-sectional design which may intercede with establishing relationships. Second, we were not able to extract very important information on the diabetes duration, duration of metformin use and the dose of metformin to establish the effects of these variables on the outcome (Vitamin B12 deficiency). Third, measurement of holotranscobalamin may be used as a more sensitive assessment of Vitamin B12 levels compared to plasma Vitamin B12 measurement.

**Figure 1** Vitamin B12 levels in 291 T2DM patients on metformin

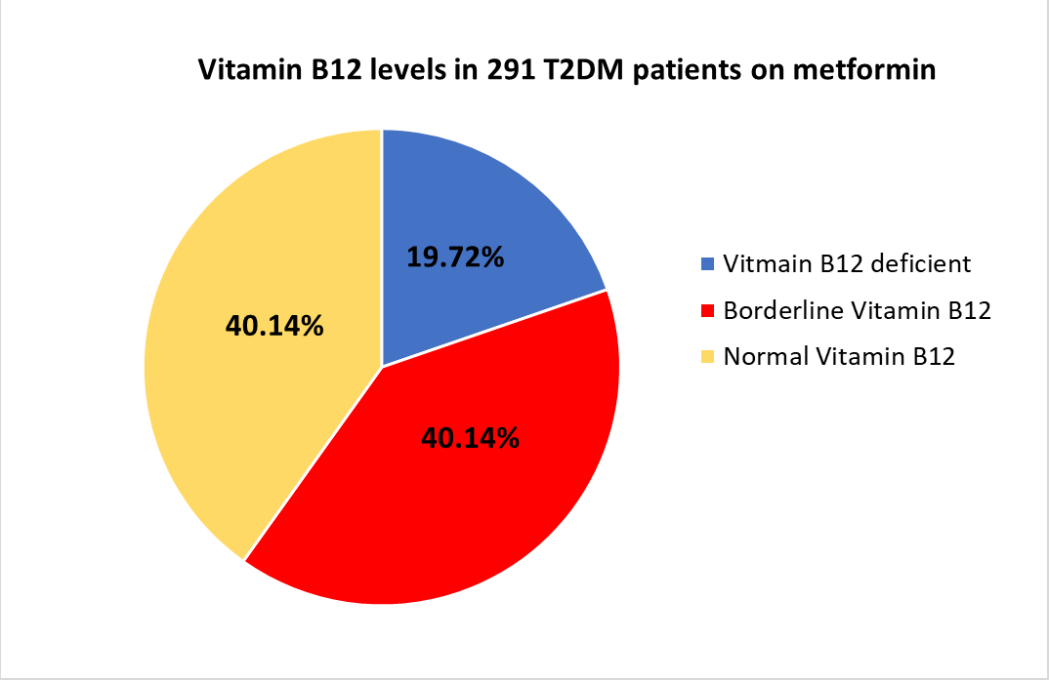


**Figure 2** Categories of mean Vitamin B12 levels according to gender

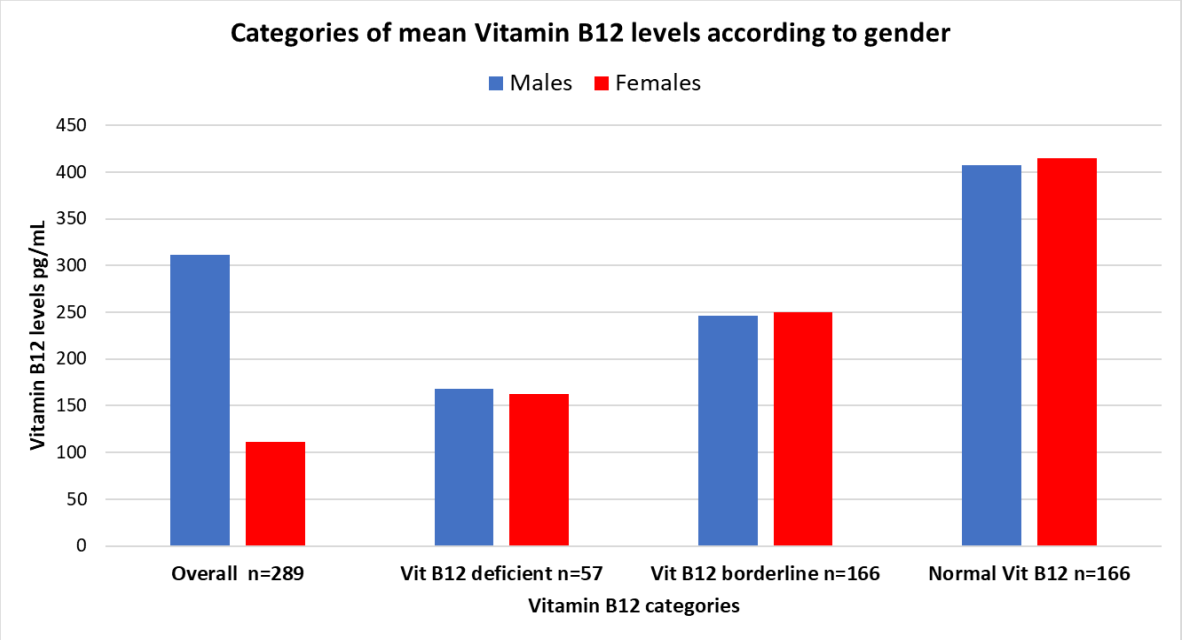
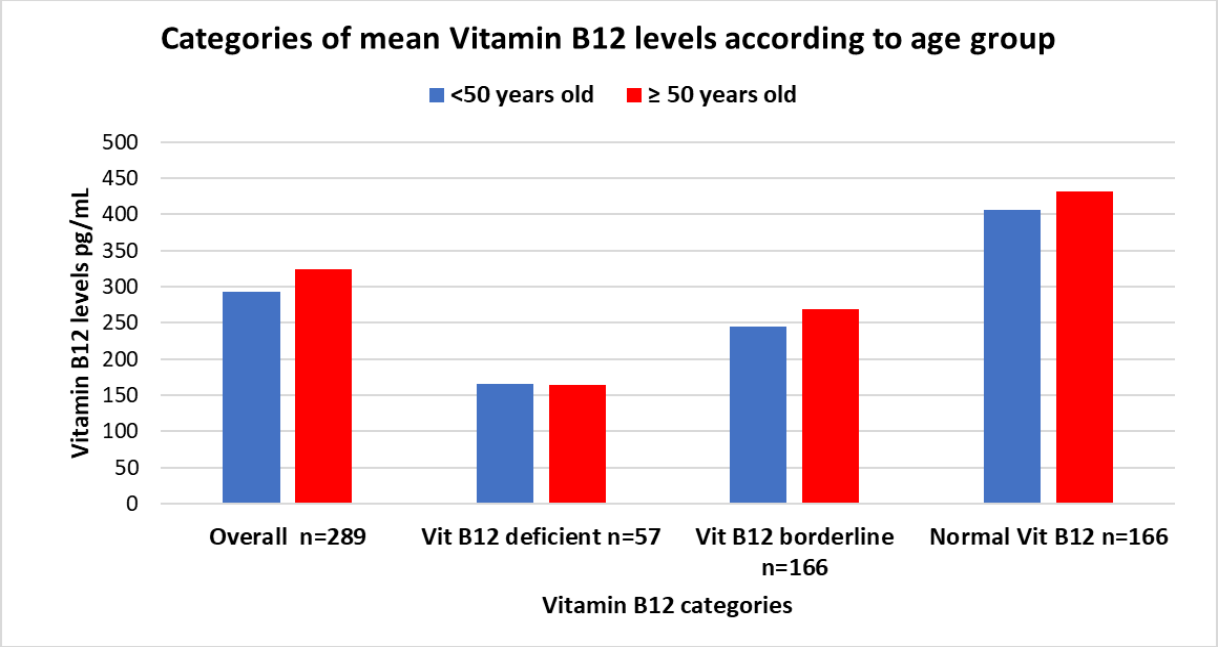



**Figure 3** Categories of mean Vitamin B12 levels according to age group




## Conclusion

In summary, we found 19.72% prevalence of Vitamin B12 deficiency among patients seen at the family medicine clinics with 40.14% of our patients in the borderline Vitamin B12 status. Contrary to other previous studies, we found that females are more at risk for Vitamin B12 deficiency in this region. This study suggests the importance of measuring the Vitamin B12 levels of women especially and improve their Vitamin B12 status.

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