

Vitamin B12 deficiency in patients with type 2 diabetes mellitus using metformin and the associated factors

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نقص فيتامين ب12 عند مرضى السكري من النوع الثاني الذين يعالجون بالميتفورمين والعوامل المرتبطة به

الملخص:

الميتفورمين هو خط الدفاع الأول من العلاج الطبي لمرض السكري من النوع الثاني، لا تزال آلية الميتفورمين غير مفهومة بشكل كامل ولكن أثبتت الدراسات الحديثة وجود نقص في فيتامين ب12 في مرضى السكري الذين يعالجون بالميتفورمين. تهدف الدراسة الحالية إلى تقييم نقص فيتامين ب12 لمرضى السكري من النوع الثاني الذين يعالجون بالميتفورمين والعوامل المرتبطة به. شملت هذه الدراسة 60 مصاباً بداء السكري من النوع الثاني تم علاجهم بالميتفورمين لمدة عام على الأقل في مركز السكري والغدد الصماء مسلاتة- ليبيا من يوليو إلى سبتمبر 2023م. بلغ معدل انتشار نقص فيتامين ب12 بين مرضى السكري الذين تناولوا الميتفورمين (23.3%)، بينما (43.3%) من المرضى كانوا معرضين للقصور. الجدير بالذكر أن نسبة النقص والمرضى المهددين بالنقص مرتبطة بجرعة الميتفورمين فالمرضى الذين يتناولون جرعات الميتفورمين 850-1000 ملغ لديهم مستويات قليلة من فيتامين ب12.

الكلمات المفتاحية: داء السكري النوع الثاني - الميتفورمين - فيتامين ب12.

Abstract:

Metformin is the first line of medical therapy for type 2 diabetes, the mechanism of metformin remains as yet incompletely understood but recent studies have reported a decrease in vitamin B12 in patients treated with metformin. This study was aimed to assess the presence of vitamin B12 deficiency among metformin users and associated factors in patients with type 2 diabetes mellitus. This cross-sectional study involved 60 adult patients of type 2 diabetes treated with metformin for at least one year in Centre for Endocrinology and Diabetes in msallata-Libya, from July to September 2023. The prevalence of vitamin B12 deficiency was (23.3%) and the majority of the sample had borderline B12 levels (43.3%). The vitamin B12 deficiency and borderline levels were strongly associated with the dose of metformin. Patients taking doses of metformin 850-1000 mg had lower levels of vitamin B12. However, no significant difference was found between vitamin B12 deficiency and the age or gender.

Keywords: type 2 diabetes (T2DM) - Metformin - Vitamin B12.

Introduction:

Diabetes mellitus (DM) is a widely prevalent disease managed in primary health care, and its prevalence has increased significantly in the past decade. It is considered a serious public health concern due to the multiple comorbidities and complications, including retinopathy, nephropathy, peripheral neuropathy, cardiovascular diseases, and the necessity for lifelong management (WHO, 2018 and Kakkar, 2016).

Vitamin B12, is a vitamin which is important for several biological functions. It is a water-soluble vitamin principally obtained from animal proteins like meat and dairy

products (Langan and Goodbred, 2017). Vitamin B12 is an essential cofactor for converting homocysteine to methionine and for regenerating folate, leading to DNA synthesis and myelin sheath formation. Thus, enzymatic defects resulting from VitB12 deficiency lead to an accumulation of methylmalonic acid and homocysteine, which causes various hematological, gastrointestinal, and neuropsychiatric disorders (Singh and Tushar, 2016, Khan, 2019).

Metformin is an important drug used worldwide as a first-line treatment for type 2 diabetes mellitus (T2DM) as recommended by American and European diabetic associations (Zalak et al., 2018 and Miyan and Waris 2020). However, when used for prolonged periods, it may cause biochemical side effects such as lactic acidosis, diarrhea, nausea, vomiting, flatulence, and vitamin B12 deficiency (Singh and Tushar, 2016 and Out et al., 2018).

Several international studies have assessed vitamin B12 deficiency among type 2 diabetic patients using metformin. The prevalence of metabolically confirmed B12 deficiency in type 2 diabetic population on metformin was between 4% and 41% (Owhin et al., 2019). Several authors found the use of multivitamins and vitamin B12 supplement could be protective against developing vitamin B12 deficiency (AL saeed and Baraja, 2021 and Khan et al., 2017). Another study reported that longer duration of metformin use was strongly associated with vitamin B12 deficiency (Hasan et al., 2019 and Damio et al., 2016). In Libya, there are large number of cases of diabetes and its associated complications, but there is limited research regarding vitamin B12 deficiency related to the use of metformin. The aim of this study is to assess the presence of vitamin B12 deficiency among metformin users in patients with type 2 diabetes mellitus.

Patients and Methods:

This is a prospective study conducted on 60 (30 males and 30 females) patients with Type 2 diabetic (T2DM) coming to Centre for Endocrinology and Diabetes in msallata-Libya, from July to September 2023. The inclusion criteria for this study were: participant had to be a type 2 diabetic patient between the ages of 25 and 90 years; taking an oral antidiabetic medication, including metformin (average daily dose and duration of use). Vitamin B12 concentration measured by using Vitamin B12 kit (MINDRAY CL-900I). The reference value indicating vitamin B12 deficiency was < 180 pg/mL, a value between 180 and 399 pg/mL was considered for borderline deficiency, and a value above 400 pg/mL was considered normal. Data analysis was performed with Statistical Package for Social Sciences (SPSS) version 19. Continuous variables were presented as mean \pm standard deviation (SD). $P < 0.05$ was considered statistically significant.

Results:

Prevalence of vitamin B12 deficiency:

Vitamin B12 levels were normal in 20 patients (33.3%). Borderline deficiency was seen in 26 (43.3%) patients while absolute deficiency was seen in 14 (23.3%) patients (Fig. 1).

Association between vitamin B12 levels and gender and age:

As shown in Table1, the gender distribution in normal group was male (25%) and female was (75%) while in group Borderline deficiency was male (61.5%) compared to female (38.5%). In deficiency group the present in male more than female (64.3%, 35.7%) respectively. The majority of vitamin B12 deficiency were found aged 45-64 years (50%), while the majority Borderline deficiency found in two groups aged 45-64 years

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and 65-90 years (42.3%). The statistically no association of vitamin B12 deficiency with gender and age.

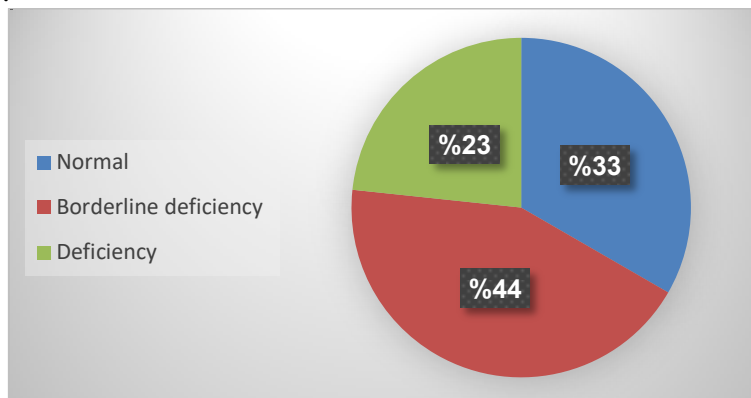


Figure 1: showed percent of vit, B12 between patients with Type 2 diabetic.

Table1: Characteristics and demographic data of diabetic patients on metformin.

Characteristics	Groups	Normal of vit,B12	borderline deficiency of vit,B12	Deficiency of vit,B12
Gender	Male	25%	61.5%	64.3%
	Female	75%	38.5%	35.7%
Age	24-44 years	5%	15.4%	14.3%
	25-64 years	50%	42.3%	50%
	65-90 years	45%	42.3%	35.7%

Association between vitamin B12 levels and does of metformin:

Metformin daily dose showed the most significant baseline association with B12 deficiency. The group that was taking 850-1000mg metformin had higher proportions of vitamin B12 deficiency levels (57.1%) and borderline deficiency (61.5%), compared to (42%) for deficiency group and (38%) for borderline deficiency group in the group that was taking 500-800mg , which was statistically significant ($p=0.038$), as showed Figure (2).

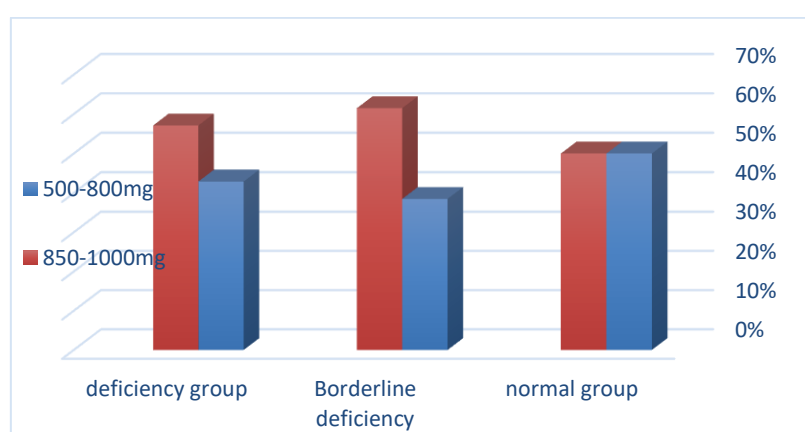


Figure 2: Association between vitamin B12 levels and does of metformin.

Association between vitamin B12 levels and duration therapy by metformin:

Duration of therapy by metformin less than 10 years show higher proportions of deficiency vitamin B12 levels in deficiency group (71.4%) compared to borderline deficiency group (65.4%), while in patients has therapy by metformin more than 10 years show higher proportions of deficiency vitamin B12 in borderline deficiency group (34.6%) compared to deficiency group (28.6%). The association was statistically significant ($p=0.038$), as showed Figure (3).

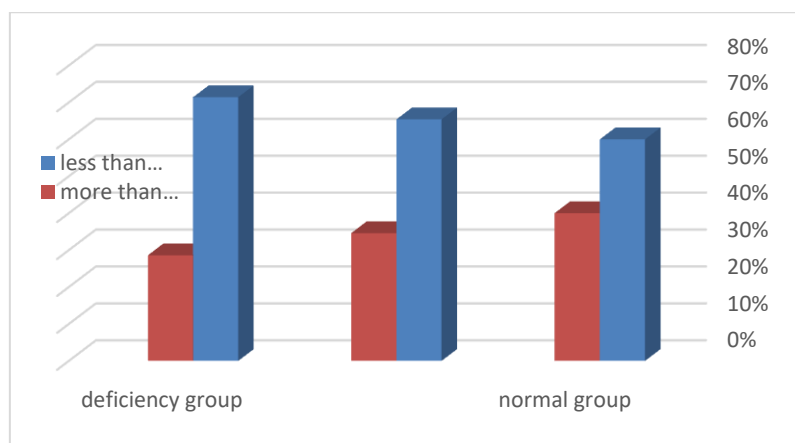


Fig. 3: Association between vitamin B12 levels and duration of therapy by metformin.

Discussion:

In the current study, the prevalence of vitamin B12 deficiency about 23.3% in diabetic patients taking metformin. This finding is similar to study carried out in Libya and Qatar where the prevalence was 20.67% and 30.7% respectively (Sulaiman *et al.*, 2023 and Khan *et al.*, 2021). However, this study is in contrast to a study conducted in Pakistan and Saudi Arabia, at 4% and 9.4%, respectively (Miyan and Waris 2020 and Alharbi *et al.*, 2018). Possible reasons for the variations in vitamin B12 levels globally are the cutoff levels used in the studies, diverse cultural and religious beliefs, as well as dietary habits, which play a significant role in vitamin B12 levels. The majority (43.3%) of the sample in this study had borderline B12 levels. My results are more or less similar to several previous studies in Brazil (36.8%) and India (34.1%) (Nervo *et al.*, 2011 and Arundhati *et al.*, 2018). But this is low than what was reported (66.1%) by the study in Saudi Arabia (AL saeed and Baraja, 2021). Patients with borderline deficiency need additional evaluation to identify the group who are vitamin B12 deficient.

The vitamin B12 deficiency and borderline levels were strongly associated with the dose of metformin and duration of metformin therapy. Patients taking higher doses of metformin, 850-1000mg, had lower levels of vitamin B12. These results are consistent with several studies where the metformin dose was the strongest predictor of vitamin B12 deficiency (Ko *et al.*, 2014, Saqer *et al.*, 2018 and Akinlade *et al.*, 2015). Studies by (Nervo *et al.*, 2011 and Damiao *et al.*, 2016) reported no significant association between the concentration of vitamin B12 and the dose or the duration of intake of metformin. A few previous studies have demonstrated that the decrease in serum B12 levels occurs within 3-4 months after the commencement of metformin treatment (Wulffele *et al.*, 2003). However, according to most reports, vitamin B12 deficiency occurs only after 5-10 years of metformin usage (Wile *et al.*, 2010). This delay in the appearance of B12

deficiency may be due to the significant hepatic stores of this vitamin (Ruscin *et al.*, 2002). In addition, the current study did not find a correlation between age or gender and vitamin B12 deficiency which is similar to previous studies (Kamrul-Hasa *et al.*, 2016 and Arundhati *et al.*, 2018).

Conclusions:

This study showed a high prevalence of VitB12 deficiency in metformin-treated patients with T2DM. A daily dose of metformin more than 1000 mg and duration of therapy were independent risk factors for metformin-associated VitB12 deficiency in Patients with T2DM.

Recommendations:

- 1-Physicians must screen diabetics on metformin therapy for underlying B12 deficiency.
- 2-Take dietary supplements with vitamin B12 to avoid the severe deficiency of vitamin B12 levels due to metformin treatment.

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