Alqalam Journal of Medical and Applied Sciences. 2025;8(1):189-197
https://doi.org/10.54361/ajmas.258130

Original article

The Association between Vitamin B12 Deficiency and Metformin Therapy in Libyan Diabetic Patients

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Abstract
Metformin is the first line treatment of diabetic hyperglycaemia. However, numerous studies have shown that long-term use of metformin can result in a vitamin B12 deficiency. In this study, we sought to assess the prevalence of vitamin B12 deficiency in diabetic patients taking metformin on a long-term basis as well as the association between vitamin B12 deficiency and diabetic neuropathy. Across sectional study was conducted on 143 Libyan diabetic patients attending endocrinology outpatient diabetic centre in Benghazi, who are on metformin for at least 6 months, and eligible to the inclusion criteria. Data on metformin intake and confounding variables were collected from questionnaires. Serum vitamin B12 levels were estimated, and vitamin B12 deficiency was defined as serum B12 less than 196pg/ml. Data analysis was performed using the statistical package for social sciences (SPSS) version 28. The study involved 143 patients, with a majority being women (50.3%) and men (49.7%). The mean duration of diabetes was 10.52 ± 7.260 years. The mean daily dose of metformin was 1435.42 ± 377.766 mg for females and 1495.77 ± 392.678 mg for males. The mean duration of metformin intake was 7.93 ± 5.859 years for females and 7.34 ± 5.780 years for males. The mean serum vitamin B12 level was 469.78 ± 233.477 pg/mL, with males having non-significantly higher levels than females. 59.2% of male patients had vitamin B12 levels ≤420 pg/mL, while 51.4% of female patients had levels ≤420 pg/mL. Nevertheless, no patient had a vitamin B12 deficit. No significant correlation was observed between serum vitamin B12 levels with metformin dose, duration of action, or patient characteristics. Despite the high prevalence of peripheral neuropathy (36.4%), there was no significant difference in B12 levels between patients with and without neuropathy.
Keywords. Diabetes, Metformin, Vitamin B12 Deficiency, Neuropathy.

Introduction

Worldwide, metformin is regarded as the first-choice oral medication for diabetic hyperglycaemia [1-3], since it effectively reduces insulin resistance, cardiovascular morbidity, and mortality [1-4]. Even though its well-established benefits, including cost-effectiveness and positive effects on body weight, there are unavoidable adverse effects, such as malabsorption of vitamin B12 [3-5]. Such findings have been documented and published consistently since Berchtold et al. originally suggested in 1969 that metformin may result in vitamin B12 deficiency by decreasing the gastrointestinal tract's absorption of vitamin B12 [2, 6].
Thereafter, several cross-sectional, retrospective, and longitudinal studies have further supported a possible clinical association between long-term use of metformin and vitamin B12 insufficiency in diabetic patients [1,2,5,7-10]. The risk of deficiency appears to be highest in individuals taking high doses of metformin (≥2000 mg/day) for extended periods, typically exceeding four years [7,8,11-13]. Previous studies indicate that between 6% and 30% of patients on long-term metformin therapy may develop vitamin B12 deficiency [2,3,14].
It is clinically relevant to diagnose vitamin B12 insufficiency since it may be associated with a variety of disorders, such as neuropathy, cognitive impairment, dementia, extrapyramidal symptoms, and megaloblastic anaemia [3]. Among these disorders, vitamin B12 insufficiency may only manifest clinically as peripheral neuropathy that may be erroneously diagnosed as diabetic neuropathy, without haematological abnormalities. Long-term metformin use, which is mediated by a vitamin B12 deficit, may increase the significant burden of peripheral neuropathy in diabetic patients [2,11,14]. Given the potential for long-term complications, early identification of vitamin B12 deficiency is crucial in these patients to prevent later neurological and haematological symptoms [8,11]. The current study sought to ascertain the prevalence of vitamin B12 deficiency among diabetic patients taking metformin who were monitored at an endocrinology outpatient diabetic centre in Benghazi.

Methods

This study used cross-sectional observational data. The study was explained to diabetes mellitus patients who visited endocrinology outpatient diabetic centre in Benghazi. The study included patients who were willing to participate and were between the ages of (23 years -69 years). Every patient gave his or her

***Received**: 03-12-2024 - **Accepted**: 25-01-2024 - **Published**: 02-02-2025*

informed permission. We maintained the confidentiality of all the information that the participants submitted. Furthermore, the data collection tool excluded any information that could be used to identify study participants.

Patients were included in the study if they had been taking metformin at least 1000 mg per day for more than 6 months. Additionally, patients receiving other anti-diabetic medications than metformin were included. Patients who had a history of anemia of any kind, renal insufficiency, prior gastric surgery, thyroid illness, malabsorption syndrome, patients using vitamin supplements—particularly B12, or proton pump inhibitors, or who were vegetarians based on past records or history. Pregnant women were excluded. A serious medical condition such as sepsis, a serious infection, cancer, liver cirrhosis, heart failure also disqualified a patient. Out of 300 diabetes patients who were interviewed during the research period, only 143 adult patients, met the inclusion criteria and agreed to participate. They were subsequently assessed by a comprehensive evaluation of medical records and laboratory testing.

Data on the participants' initial demographics was gathered. There were three categories for smoking habits: non-smokers, ex-smokers, and current smokers. Personal and medical history, such as age, gender, length of diabetes, type of anti-diabetic medication taken by the patients, dose, and duration, were among the information gathered. In addition, the blood groups of the participants were recorded, and they were asked about previous medical history or manifestation of peripheral neuropathy.

Vitamin B12 levels were measured. In this study, biochemical vitamin B12 deficiency was defined as serum B12 <300 pg/mL. Based on this distinction, patients were categorized as B12-deficient or normal, and the clinical characteristics of the 2 groups were compared.

Data were recorded, stored and prepared for analysis. All statistical analysis were performed using, the statistical package for social sciences (SPSS) version 28 for the purpose of data processing. We used arithmetic mean and standard deviation (SD) for qualitative variables. Inferential statistical analysis is used to make chi square test for inference differences between the two qualitative variables. Quantitative variables are transformed into descriptive variables for testing chi-square. A test for correlation between two quantitative variables was conducted using the correlation coefficient. P values less than 0.05 were regarded as significant. When presenting the data we used the frequency table, and diagrammatic (par chart) for qualitative variables.

Results

This study included 143 patients in total, 72 of whom were women (50.3%) and 71 of whom were men (49.7%). The average age of the male and female participants was 57.11 ± 7.988 and 54.67 ± 9.418 years, respectively. The mean duration of diabetes among female participants was 10.31 ± 6.872 years, compared to 10.74 ± 7.677 years in male participants. All patients had diabetes for an average of 10.52 ± 7.260 years. The mean daily dose of metformin was 1435.42 ± 377.766 mg for females and 1495.77 ± 392.678 mg for males, resulting in an overall mean daily dose of 1465.38 ± 385.075 mg. The maximum daily dose recorded was 2700 mg, with a range of 1000–2700 mg. Daily dose of metformin among metformin treated diabetic patients, and clinical characteristic of study participants at different daily dose of metformin are shown in Figure 1 and table 1 respectively.

The mean duration of metformin intake was 7.93 ± 5.859 years for females and 7.34 ± 5.780 years for males, leading to a combined mean duration of 7.64 ± 5.807 years across all patients. All patients in this study were adherent to their regular daily metformin therapy as prescribed. Duration of metformin intake among metformin treated diabetic patients are shown in Figure 2.

The mean serum vitamin B12 level in the patient pool was 469.78 ± 233.477 pg/mL. Males exhibited non-significantly higher vitamin B12 levels than females (474.49 ± 253.977 vs. 465.13 ± 213.033 pg/ml, P = 0.812). A recent negative history of multivitamin or vitamin B complex intake was reported. Stratifying the data revealed that 59.2% of male patients (42 patients) had vitamin B12 levels ≤420 pg/mL, with a mean level of 334.27 ± 49.04 pg/mL. In contrast, 51.4% of female patients (37 patients) had vitamin B12 levels ≤420 pg/mL, with a mean level of 314.85 ± 58.16 pg/mL. Collectively, this indicates that 55.2% of metformin-treated diabetic patients were within the lowest range of vitamin B12, irrespective of metformin dosage. In this patient pool, 5 male patient and 3 female patients had B12 level above than normal (≥866 pg/ml), however none of the patients had vitamin B12 deficiency (serum B12 levels <197 pg/mL). Serum levels of vitamin B12 among metformin treated diabetic patients are shown in Figure 3.

In this study, no statistically significant correlation was observed among serum vitamin B12 levels with regard to the metformin dose (P=0.977) or its duration of action (P=0.913). likewise, there were no significant associations of the vitamin B12 level with patient characteristics such as gender, P = 0.812; age, P = 0.548; or duration of diabetes, P = 0.364 as indicated in table 2. Additionally, there was no statistically significant trend in mean variations of vitamin B12 level among different blood groups in diabetic patients treated with metformin (p = 0.056), as indicated in table 3.

Received: *03-12-2024* - ***Accepted***: *25-01-2024* - ***Published***: *02-02-2025*

Although all study participants were on metformin, several were also undergoing multi-drug therapy. In particular, 59 patients (41.2%) were using insulin, 14 patients (9.7%) were on sitagliptin, and 30 patients (20.9%) were taking sulfonylureas. Nonetheless, there was no significant difference in serum B12 levels between individuals on metformin alone and those taking it in combination with insulin (P = 0.783), sulfonylureas (P = 0.353), or sitagliptin (P = 0.725), as shown in table 4.

There was no statistically significant difference in B12 levels between patients with and without peripheral neuropathy (p = 0.541), despite the high prevalence of peripheral neuropathy in this study (36.4%). Patients with neuropathy had mean blood B12 levels of 485.657± 234.2741 pg/ml, while those without neuropathy had mean levels of 460.708 ± 233.8309 pg/ml. The elevated rate of neuropathy may be attributed to long-term inadequate diabetes management, which has been present for 11.8269 ± 7.36904 years.

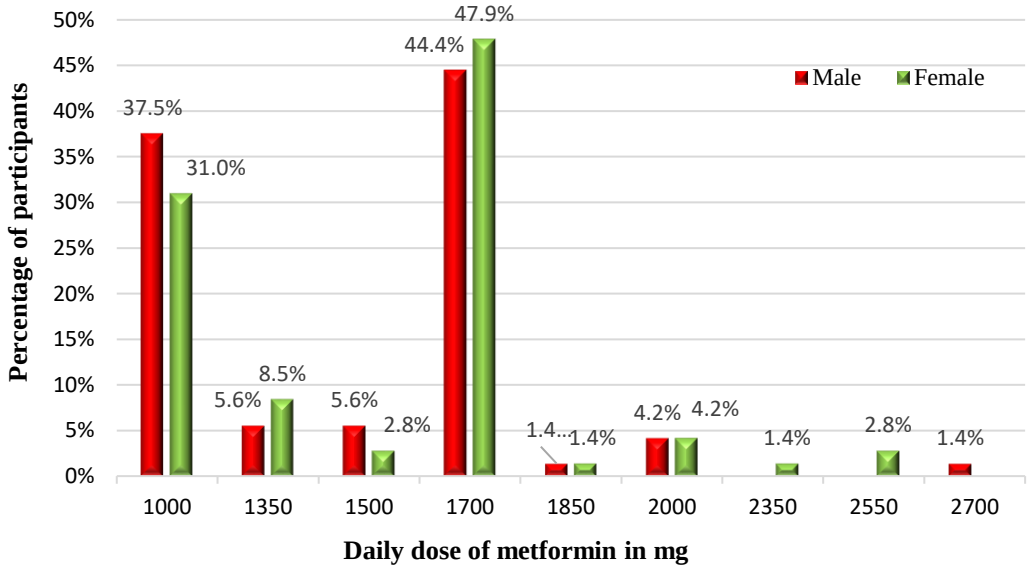

Figure 1. Percentage of patients on different daily doses of metformin in mg

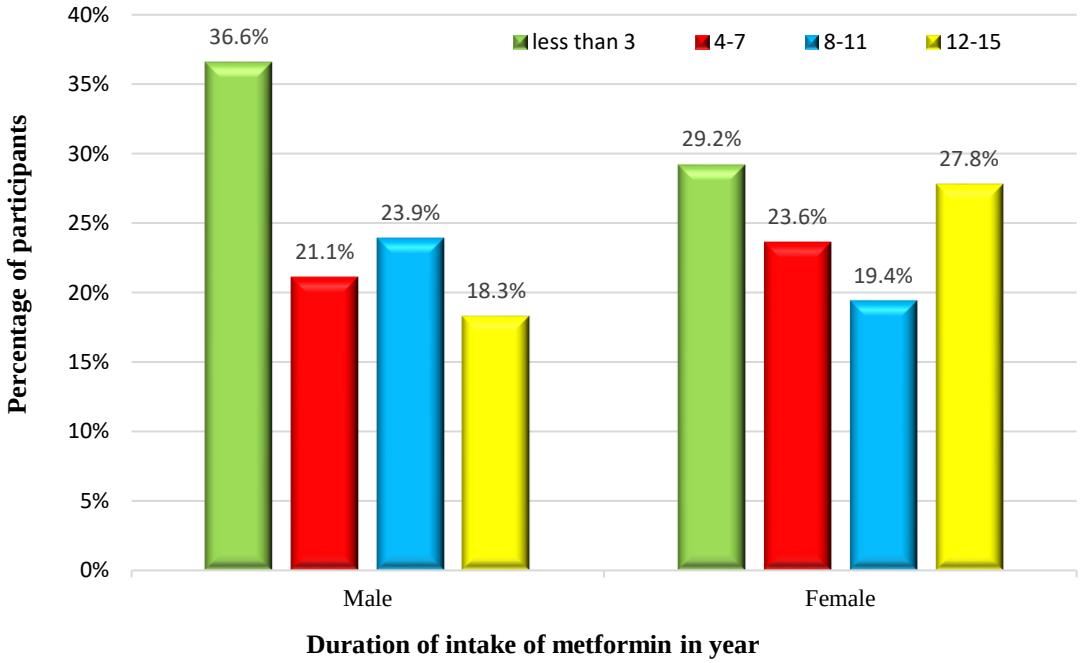

Figure 2. Duration of metformin intake for all participants

Received*: 03-12-2024 -* ***Accepted****: 25-01-2025 -* ***Published****: 02-02-2025*

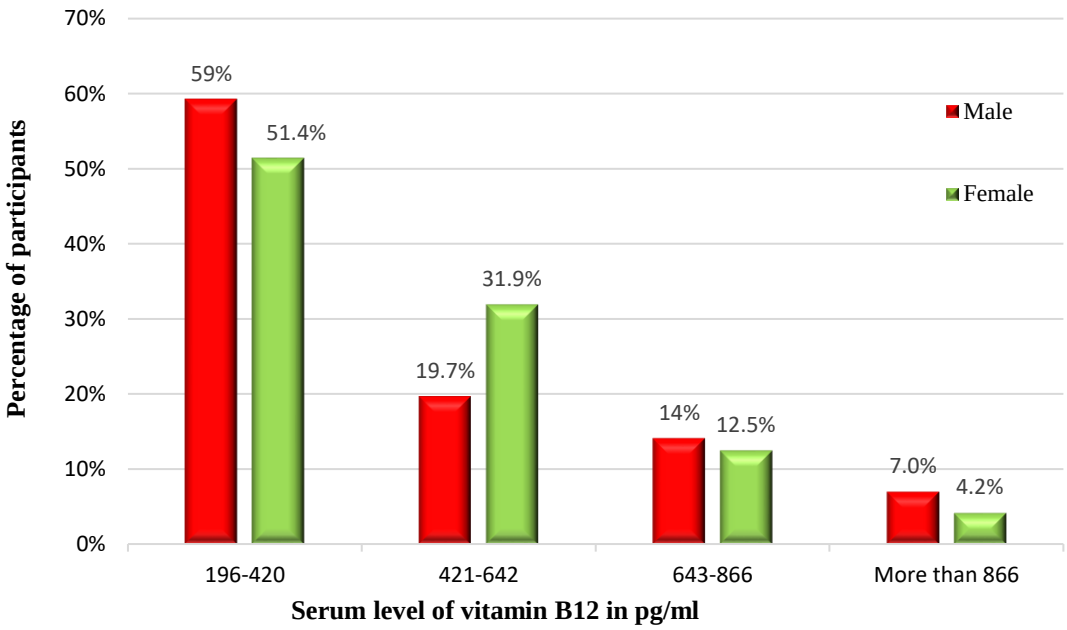

Figure 3. Serum level of vitamin B12 in pg/ml among all metformin treated diabetic patients

Table 1. Clinical characteristics of the study population.

Metformin dose		Duration of intake/years	Duration of diabetes/years	Vitamin B12
1000	N	49	49	49
	Mean	6.91	8.614	1.612
	Std. Deviation	5.658	6.339	0.786
1350	N	10	10	10
	Mean	5.15	8.350	1.900
	Std. Deviation	6.174	7.188	1.287
1500	N	6	6	6
	Mean	8.33	9.000	1.333
	Std. Deviation	6.022	5.404	0.516
1700	N	66	66	66
	Mean	8.18	12.109	1.758
	Std. Deviation	5.667	7.416	0.962
1850	N	2	2	2
	Mean	7.50	7.500	3.000
	Std. Deviation	3.536	3.536	1.414
2000	N	6	6	6
	Mean	8.75	14.333	1.333
	Std. Deviation	6.970	11.219	0.516
2350	N	1	1	1
	Mean	5.00	5.000	2.000
	Std. Deviation	0	0	0
2550	N	2	2	2
	Mean	18.00	18.000	1.000
	Std. Deviation	5.657	5.657	0.000
2700	N	1	1	1
	Mean	4.00	4.000	2.000
	Std. Deviation	0	0	0
Total	N	143	143	143
	Mean	7.64	10.523	1.692
	Std. Deviation	5.807	7.260	0.906

Received*: 03-12-2024 -* ***Accepted****: 25-01-2024 -* ***Published****: 02-02-2025*

Table 2. Comparison of clinical characteristics between female and male metformin treated diabetic participants

Variables	Gender	N	Mean	Std. Deviation	T	P Value
Duration of diabetes/years	Female	72	10.3111	6.87208	-0.35	0.726
	Male	71	10.738	7.67678		
Metformin dose	Female	72	1435.42	377.766	-0.937	0.35
	Male	71	1495.77	392.678		
Duration of intake/years	Female	72	7.9292	5.85863	0.602	0.548
	Male	71	7.3437	5.77988		
Vitamin B12	Female	72	465.132	213.0329	-0.239	0.812
	Male	71	474.494	253.9767		

Table 3. Number and percentage of the metformin treated diabetic patients on various treatment regimens

Drugs		Vitamin B12				x^2	P. value
		196-420	421-642	643-866	>866		
Metformin & Sulfonylurea	N	17	10	3	0	3.263	0.353
	%	21.5%	27.0%	15.8%	0.0%		
Metformin & Sitagliptin	N	6	4	3	1	1.316	0.725
	%	7.6%	10.8%	15.8%	12.5%		
Metformin & Insulin	N	33	16	6	4	1.075	0.783
	%	42.3%	43.2%	31.6%	50.0%		

Table 4. The serum vitamin B12 level among different blood groups

Blood Group	N	Vitamin B12		F	Sig.
		Mean	Std. Deviation		
A-	4	376.743	80.0634	2.12	0.056
A+	36	407.354	148.3015		
AB+	8	442.794	183.9634		
B-	6	413.842	132.5464		
B+	18	415.616	162.0844		
O-	9	644.967	364.0071		
O+	43	532.959	301.5153		
Total	124	470.969	240.9102		

Discussion

Several studies have investigated the relationship between metformin use and vitamin B12 status among diabetic patients. In this regard, Fatima et al. [15] undertook a systematic review of different studies and concluded that though in some long-term metformin therapies, patients have shown to have lower serum levels of vitamin B12, in most, it was not found in all populations. Vitamin B12 deficiency was found in 17.5% of the patients with type 2 diabetes treated with metformin.

The cohort study conducted by Bauman et al., [16], demonstrated that even in patients with long-term administration of metformin, its effect on reducing serum vitamin B12 levels has been very minor. The same authors indicated that only a limited proportion of the studied participants eventually had a clinically significant deficiency of vitamin B12 that might justify supplementary or interventional measures. The result of this study is consistent with our results, which showed no significant association between metformin intake and vitamin B12 deficiency in diabetic patients.

On the other hand, several research studies have shown that vitamin B12 concentrations are significantly lower in patients taking metformin than those not on this drug [10]. They found that about 8.6% of patients treated with metformin presented B12 levels <197 pg/mL. Because of these results, there is enough justification for the monitoring of vitamin B12 levels in diabetic patients undergoing metformin therapy

Metabolism changes that occur as one ages, further affects the absorption and use of these nutrients. This is because decreased production of stomach acid and shifting in gut microbiome composition create an environment that already makes the nutrients more susceptible to deficiency among the elderly [17]. To therefore attribute such a low level of vitamin B12 on metformin treatment without considering all these

Received*: 03-12-2024 -* ***Accepted****: 25-01-2024 -* ***Published****: 02-02-2025*

variables, is misleading. In addition, elderly people are usually at a higher risk of deficiency because of poor dietary habits. Moreover, longer duration of diabetes might signify other comorbidities within a patient, which may give rise to impaired nutrient absorption. However, unpredictably, our research results indicated that there was no notable correlation between serum vitamin B12 levels and age (P = 0.548),_participants with higher age group did not show any significant reduction in vitamin B12 level.

Our Results provide a statistically insignificant association between the dose of metformin and serum vitamin B12 levels, supported by a p-value of (0.97). This suggests that an increase in the dose of metformin does not leads to a corresponding decline in serum B12 in patients.

In this respect, the systematic review done by Fatima et al., [15] examined a certain number of studies and drew a conclusion that while the use of metformin was indeed associated with somewhat lower serum vitamin B12 levels, higher doses were not consistently related to a higher risk of deficiency. Such results, therefore, depict that, in fact, factors other than dose could be important determinants for vitamin B12 status in metformin-treated patients.

It has also been indicated that the long-term users of metformin had lower serum levels of vitamin B12 compared to the subjects in the non-metformin user group; simultaneously, however, a very remarkable reduction is not observed every time a dosage level increases, which would imply thereby that while there may be an association generally between use and reduced vitamin B12, mere dosage does not come into play for its determination [2].

The B12 lowering is dose-dependent, with higher doses, such as ≥1500 mg/day, more significantly lowering B12 levels [18]. The prevalence of vitamin B12 deficiency with metformin use is of moderate frequency.

Our results indicated that, the length of time taking metformin did not significantly correlate with the categories of vitamin B12 levels (P = 0.913). Meaning that there is no association between the duration of intake and serum level of vitamin B12. In this regard, a study by Kim et al. [2] was specifically designed to assess the association of metformin duration with serum vitamin B12 concentration in diabetic patients. This study did not find any significant association between the duration of metformin therapy and serum levels of vitamin B12. This would further suggest that, although monitoring should be considered and performed to avoid deficiency-especially in higher-risk groups like elderly patients, it does not clearly appear to result directly from the metformin therapy itself. It has been showed that with each additional year on metformin, there is a 5% increased risk for vitamin B12 deficiency [19]. This points out the fact that other than monitoring of vitamin B12, its supplementation in patients on chronic metformin is also necessary. In addition, long-term therapy with metformin was more associated with an increased risk for deficiency of vitamin B12. Patients treated with metformin for over four years had significantly lower serum levels of vitamin B12 compared to other patients who were on the medication for shorter duration [15].

Regarding the effect of metformin therapy on the changes in the levels of vitamin B12, Kahn et al. [20] conducted research into the gender differences in response. No significant difference concerning the incidence of B12 deficiency among males and females on long-term metformin use was observed. This fact further supports that any potential change in B12 status due to metformin affects or does not affect both genders. This finding supports our results which indicated that the incidence of vitamin B12 deficiency in males and females receiving long-term metformin therapy did not differ significantly (P = 0.812). This finding could be interpreted as suggesting that any alteration in vitamin B12 status brought on by metformin use is probably going to have an equal impact on men and women. Given the lack of sex-specific responses.

Different results were concluded in other previous studies, which stated that there is a gender difference regarding vitamin B12 level. For instance, male patients showed lower levels of vitamin B 12 compared to females [21]. This finding is supported by other study which concluded that higher metformin doses and male sex are associated with lower vitamin B12 levels in diabetic patients [14]. However, an opposite finding was concluded, Metformin use in diabetic patients is associated with a higher rate of vitamin B12 deficiency in females compared to males [22].

Dosage and duration are risk factors related to the action of metformin on vitamin B12 levels in patients with diabetes; longer durations suggest a higher probability of developing vitamin B12 deficiency. Vitamin B12 levels were lower in male patients than in female patients, and vitamin B12 deficiency was less common in patients of Black race taking metformin [21].

Considering the influence of antidiabetic drugs on serum level of vitamin 12, we compared people on metformin alone and those taking multidrug including sulfonylurea, insulin and sitagliptin. According to our results there was no significant difference in serum B12 levels between sulfonylurea and metformin (P = 0.353), insulin plus metformin (P = 0.783), or sitagliptin and metformin (p = 0.725) compared to those on metformin alone. Our results support other studies, for example, studies have examined the impact of more than one class of antidiabetic medication, including metformin, on vitamin B12 levels. Compared to metformin, sulfonylureas, DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT2 inhibitors generally did not significantly change the status of vitamin B12 [23]. Further, a study conducted on diabetic patients on both metformin and insulin therapy, showed that vitamin B12 status was not different from the group that

Received: *03-12-2024* - ***Accepted***: *25-01-2024* - ***Published***: *02-02-2025*

were not on metformin. This perhaps indicates that insulin therapy may have a protective effect on vitamin B12 status when on metformin [24].

In patients with type 2 diabetes, metformin use has also been linked to vitamin B12 deficiency and clinical neuropathy. It has been showed that exposed subjects had significantly lower serum B12 concentrations and higher neuropathy scores than unexposed subjects [25]. Crucially, a higher incidence of clinical neuropathy is also linked to long-term metformin use [26]. Long-term (>5 years) and high-dose metformin (>1g/day) has been associated with neuropathy and B12 insufficiency [27].

However, our study indicated that the neuropathy is not associated with vitamin b12 deficiency in diabetic patients who are on metformin, suggesting poor glycaemic control. It has been concluded that, this stronger associations with peripheral neuropathy are related to poor glycaemic control and female gender rather than vitamin B12 deficiency [28]. Vitamin B12 deficiency was recorded to be relatively prevalent among metformin-treated diabetic patients. Nonetheless, the investigators did not report any major associations between peripheral neuropathy and the development of vitamin B12 deficiency [29].

The association between blood group types and vitamin B12 levels in diabetic patients on metformin has not been thoroughly examined in many studies. Our results indicated no significant differences was observed in the mean vitamin B12 levels among variable blood groups in diabetes patients treated with metformin, (P = 0.056). It has been discovered that vitamin B12 levels differed between blood groups, but it did not specifically address those with diabetes or those using metformin [30]. According to a different study people with a particular blood type may react differently to diets high in vitamin B12 in terms of metabolism. For these findings, a great deal more research is required in the context of metformin use and diabetic control [31].

When discussing the impact of metformin on vitamin B12 levels, it has to be put into perspective with regard to variability among patients. Genetic background, eating habits, medications taken concomitantly, and general health status can influence individual metabolic disposal of both metformin and vitamin B12. Thus, although some patients may show declines in vitamin B12 levels as a consequence of extended metformin administration, it does not, however, imply an overall effect which universally includes all diabetic patients. Future studies with larger sample sizes across all dosage categories are necessary to better understand this relationship and its clinical implications.

Conclusion

In conclusion, there is currently a complicated link between vitamin B12 levels and metformin treatment in diabetic individuals. Some studies suggest minimal to no effect from metformin, while others show a modest decrease in B12 levels. Age, dosage, and personal health state are other significant factors. It is recommended that vitamin B12 levels be regularly checked, particularly for high-risk individuals. Better general health for those on metformin can be supported by early detection and knowledge of certain deficits.

Conflict of interest

We declare no conflict of interest

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Received*: 03-12-2024 -* ***Accepted****: 25-01-2024 -* ***Published****: 02-02-2025*

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ملخص الدراسة

الميتفورمين هو العلاج الأول لفرط سكر الدم لدى مرضى السكري. ومع ذلك، أظهرت العديد من الدراسات أن الاستخدام طويل الأمد للميتفورمين يمكن أن يؤدي إلى نقص في فيتامين ب12. في هذه الدراسة، سعينا لتقييم انتشار نقص فيتامين ب12 لدى مرضى السكري الذين يتناولون الميتفورمين على أساس طويل الأمد، بالإضافة إلى العلاقة بين نقص فيتامين ب12 واعتلال الأعصاب السكري. تم إجراء دراسة مقطعية على 143 مريضًا ليبيًا مصابًا بالسكري يترددون على مركز السكري الخارجي لأمراض الغدد الصماء في بنغازي، والذين يتناولون الميتفورمين لمدة لا تقل عن 6 أشهر، ويستوفون معايير الإدراج. تم جمع بيانات حول تناول الميتفورمين والمتغيرات المؤثرة من الاستبيانات. تم تقدير مستوى فيتامين ب12 في المصل، وتم تعريف نقص فيتامين ب12 بأنه مستوى أقل من 196 بيكوغرام/مل.تم إجراء تحليل البيانات باستخدام الحزمة SPSS الاصدار 28 . تمثل النساء (50.3%) والرجال (49.7%). كان متوسط مدة الإصابة بالسكري 10.52 ± 7.260 سنوات. كان متوسط الجرعة اليومية من الميتفورمين 1435.42 ± 377.766 ملغ للإناث و1495.77 ± 392.678 ملغ للذكور. كان متوسط مدة تناول الميتفورمين 7.93 ± 5.859 سنوات للإناث و7.34 ± 5.780 سنوات للذكور. كان متوسط مستوى فيتامين ب12 في المصل 469.78 ± 233.477 بيكوغرام/مل، مع وجود مستويات أعلى غير ذات دلالة إحصائية

Received*: 03-12-2024 -* ***Accepted****: 25-01-2024 -* ***Published****: 02-02-2025*

لدى الذكور مقارنة بالإناث. كانت نسبة 59.2% من المرضى الذكور لديهم مستويات فيتامين ب12 ≥420 بيكوغرام/مل، بينما كانت النسبة لدى الإناث 51.4% لديهم مستويات ≥420 بيكوغرام/مل. ومع ذلك، لم يكن هناك أي مريض يعاني من عجز في فيتامين ب12. لم يتم ملاحظة أي ارتباط ذو دلالة إحصائية بين مستويات فيتامين ب12 في المصل مع جرعة الميتفورمين أو مدة العمل أو خصائص المرضى الأخرى. على الرغم من الانتشار العالي للاعتلال العصبي المحيطي (36.4%)، لم يكن هناك فرق ذو دلالة إحصائية بين مستويات فيتامين ب12 في المصل مع جرعة الميتفورمين أو مدة العمل أو خصائص المرضى الأخرى. على الرغم من الانتشار العالي للاعتلال العصبي المحيطي (36.4%)، لم يكن هناك فرق ذو دلالة إحصائية بين مستويات B12 لدى المرضى الذين يعانون من اعتلال الأعصاب والذين لا يعانون منه B12 .لدى المرضى الذين يعانون من اعتلال الأعصاب والذين لا يعانون منه.

Received*: 03-12-2024 -* ***Accepted****: 25-01-2024 -* ***Published****: 02-02-2025*