Association of Metformin Use with Vitamin B12 Deficiency in Iraqi Patients with Type II Diabetes Mellitus

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Abstract

Objective: To evaluate the association of metformin use with vitamin B12 deficiency in Iraqi patients with type II diabetes mellitus.

Methods: This is a prospective study conducted among the diabetic patients coming to the outpatient clinic at Al-Zahraa teaching hospital in Al-Kut and Al-Baghdad teaching hospital in the medical city of Baghdad from October to December 2018, the samples taken randomly after taking a short history from each patient. Data concerning age, medical disease including diabetes mellitus, and medications including metformin (average daily dose and duration of use) at the time of vitamin B12 measurement were collected. Our patients were classified into 2 groups: diabetic patients taking metformin, diabetic patients not taking metformin. The statistical analysis was done using the SPSS 23 statistical package to analyze the data. The two groups were compared by Paired Samples t-test. Data are presented as the number, percentage, mean value, and standard deviation. The p-value < 0.05 was taken as significant.

Results: Vitamin B12 level in diabetic patients who have been on metformin for ≤ 1 year at a dose of ≤ 1 gm/day showed a significant difference with those patients with no history of metformin use.

Conclusion: Low levels of vitamin B12 are related to a longer period and a higher dose of metformin use.

Keywords: *"Metformin, Type 2 diabetes mellitus, Vitamin B12".*

Introduction

Metformin is mostly prescribed as a primary line glucose-lowering medical therapy for the diabetic patient's type II due to the great clinical effectuality and low risk of hypoglycaemia [(1)]. Additionally, metformin demonstrates vessel safety and probable vessel advantages [(2, 3)]. However, the employment of metformin will increase the danger of vitamin B12 deficiency with prevalence varies between 5.8% and 33% in studies [(4)]. Mechanism of metformin-induced vitamin B12 deficiency is unclear; however, the alternation of calcium-dependent membrane operates in terminal ileum looks to be a presently additional accepted rationalization. As nutrition B12-intrinsic factor complex uptake by the ileal cell surface receptor is calcium dependent [(5)]. Metformin interferes intestinal calcium metabolism [(6)]. which in turn impairs the delivery of vitamin B12 to an ileal cell, leading to vitamin B12 malabsorption. This interfering effect could be reversed with calcium supplementation [(7)].

Vitamin B12 deficiency predisposes patients to hyperhomocysteinemia that is related to enhanced cardiovascular risk[(8)]. Furthermore, peripheral neuropathy of diabetes could also be indistinguishable from pathology resultant from vitamin B12 deficiency and will cause permanent nerve damage if correction of deficiency is not prompt[(9)]. Furthermore, vitamin B12 deficiency is related to cognitive impairment and depression, which may impede the ability of self-care and independence. These may increase the burden of medicine intake for the resultant medical conditions and complicate the medical management. Taken along,

metformin-related vitamin B12 deficiency might counteract the potential advantage of metformin in the long run. Thus, detection in time with correction is warranted [10].

Elderly people are at risk of vitamin B12 deficiency due to the enhanced prevalence of pernicious anaemia and high prevalence of gastric atrophy that successively impairs the release of vitamin B12 from food protein for absorption [11]. The prevalence varies between 5% and 40% within the older among studies [12].

In this study, we tend to evaluate the association between metformin use and vitamin B12 deficiency in one hundred twenty Iraqi diabetic patients with type II diabetes mellitus of that 50% taking metformin and the other 50% not taking metformin.

Patients and Methods

This is a prospective study conducted among diabetic patients coming to the outpatient clinic of Al-Zahraa teaching hospital in Al-Kut and Al-Baghdad teaching hospital in the medical city of Baghdad from October to December 2018, the samples taken randomly after taking a short history from each patient. Data concerning age, medical disease including diabetes mellitus, and medications including metformin (average daily dose and duration of use) at the time of vitamin B12 measurement were collected. Our patients were classified into 2 groups: diabetic patients taking metformin (Glucophage 1000 mg tab, Merck company), diabetic patients not taking metformin. Serum vitamin B12 concentration measured by using Vitamin B12 kit (ALA_PACK B12 is designed for VITRO diagnostic Use only for the quantitative measurement of Vit. B12 in human serum 00 TOSOH ALA system analyser) and immunoassay method by AIA-2000 Automated Immunoassay Analyzer. Vitamin B12 deficiency was diagnosed if the serum vitamin B12 concentration was < 173 Pg /ml [13].

Results

In this study a review of (120) Type 2 D.M patients, (60) with metformin treatment and (60) without metformin treatment which examined by measuring Vitamin B12 levels (Pg/ mL) as follows:

"The statistical analysis was done using the SPSS 23 statistical package. The two groups were compared by paired samples t-test". Data are presented as the number, percentage, mean value, and standard deviation. The p-value < 0.05 was taken as significant.

Mean age (years) among the type 2 diabetes (on metformin treatment) 47.80 ± 7.213 and 52.20 ± 8.578 among the type 2 diabetes without metformin use, significant difference, P < 0.05. while the gender distribution in both groups was male (18, 30.0%) and female was (42, 70.0%) respectively, the statistically non-significant difference was P > 0.05. Duration of diabetes lasted more than a year among patients on metformin and without metformin treatment. The mean Vitamin B12 levels Pg/ mL in patients on metformin were 311.80 ± 141.124 and in patients without metformin were 399.60 ± 146.333, the difference was statistically significant, P < 0.05. About the range of Vitamin B12 levels in patients represented as percentage frequencies which are less than 173 Pg/ mL were (6, 10.0%) on metformin treatment and without metformin treatment respectively. Within the normal range of vitamin B12 (173-700 Pg/ mL) were (54, 90%) on both groups respectively. The difference was statistically non-significant, P > 0.05, (Table 1).

Table-1: Clinical characteristics of study group

Parameters	Patients on Metformin	Patients without Metformin	P value
Age (years) mean (SD)	47.80 ± 7.213	52.20 ± 8.578	.006
Male n (%))	18 (30.0)	18 (30.0)	1.000
Females (n (%))	42 (70.0)	42 (70.0)	

Cont... Table-1: Clinical characteristics of study group

Vit.B12 levels Pg/ mL (mean (SD))	311.80 ± 141.124	399.60 ± 146.333	.001
Range of Vit.B12, deficiency (n (%))	6 (10.0)	6 (10.0)	1.000
Range of Vit. B12, normal (n (%))	54 (90)	54 (90)	
Total	60	60	

· Paired samples t-test, · N = number,· S.D = standard deviation,· P- Value < 0.05 significant.

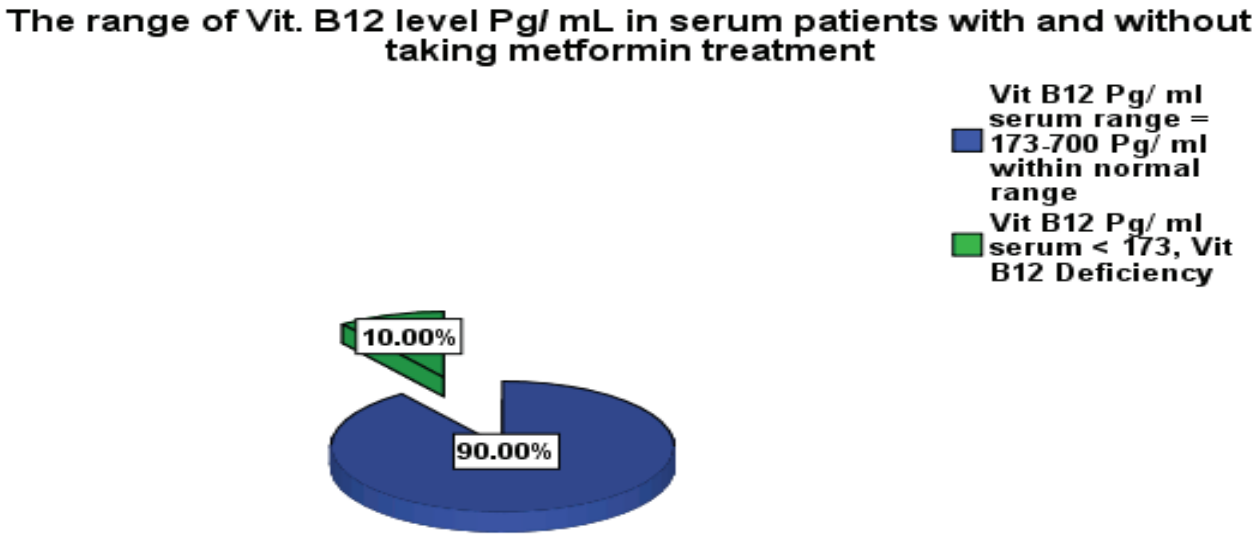

Figure-1: Serum Vitamin B12 range (Pg/ mL) in all patient groups.

Discussion

In this study groups, the vitamin B12 range (Pg/ mL) in the serum of all patient groups as in table (1) and figure (1) were (173-700) with high frequency and percent (54, 90 %), with low frequency and percent (6, 10 %), the non-significant difference in these groups (P > 0.05). The prevalence of vitamin B12 levels among diabetic patients taking metformin in this study and those not taking metformin is significant P = 0.001. Our results are non-concordance with previous studies [14].

This non-concordance may be due to many reasons; the relatively small number of metformin users in this study, low dosage of metformin with a short period of treatment, low awareness of our patients concerning the disease, short history period of sampling collection about patient information, and accurate dose of metformin usage, most of our patients taking multivitamin supplements which contain vitamin B12 and finally not all patients are elderly with minimum age/ year 40 year and maximum age/ year 60 year [4].

Although our results not in concordance with previous studies, the fact of metformin usage still present that metformin not only exacerbates the risk of developing vitamin B12 deficiency but also magnify the severity of vitamin B12 deficiency among the elderly patients [15]. Most of our patients using multivitamin supplements due to the knowledge of our physicians that multiple comorbidities and the chronic disease state of the elderly diabetic patients are detrimental to nutritional status in the body and may increase the body's vitamin requirements. Furthermore, medications, in addition to metformin, prescribed for comorbidities, such as proton pump inhibitor or H2-blocker and phenytoin, can interfere or reduce vitamin B12 absorption and metabolism. Gastrointestinal intolerance resulting from metformin use may exacerbate poor dietary intake and further compromise the vitamin status [15].

The risk of developing vitamin B12 deficiency in metformin users is related to the dose and duration of metformin use, which is the most consistent risk factor found in previous studies [16]. Which is not shown in this study because of the many reasons mentioned above. There are even graded increase in risk with the higher dose and longer duration of metformin use demonstrated [17]. Due to the relatively small number of samples included in this study; the graded increase in risk with longer duration was not obvious.

The deficiency of vitamin B12 in the serum of type II diabetes mellitus is explained as in [16]. The risk of developing metformin-associated vitamin B12 deficiency is greatly influenced by the patient's characteristics such as age, health status, metformin dose, and length of use [15].

One Chinese study was done showing the effect of metformin treatment on vitamin B12 levels for periods ranging from more than three years of treatment [18]. The decrease in vitamin B12 absorption and levels following metformin use generally starts as early because of the fourth month [19]. Clinically severe options of vitamin B12 deficiency manifest by 5–10 years due to the big body stores within the liver principally that don't seem to be quickly depleted [20]. The planned mechanisms to elucidate metformin-induced vitamin B12 deficiency among patients with type II diabetes mellitus comprise alterations in little small intestine motility that stimulates microorganism overgrowth and important vitamin B 12 deficiency, impaired absorption of vitamin B12, change in intrinsic factor (IF) levels, and interaction with the endocytic receptor [21]. "Metformin has additionally been shown to inhibit the calcium-dependent absorption of the vitamin B12-IF complex at the terminal small intestine. This restrictive result is reversed with calcium supplementation" [21]. To avert vitamin b12 deficiency particularly among adult type 2 diabetic patients on the future use of metformin, it is plausible to adopt an easy and efficient supplementation and approach to diabetes care. A 1000 μg dose of vitamin b12 given annually would be enough to fill again the body's vitamin b12 stores among this class of patients [22]. While high or very high levels of vitamin B12 in this study represented as (5% of a total percent) with more than 700 pg/ mL are due to liver disease especially with uncontrolled patient type II diabetes mellitus without treatment. A larger sample of metformin users and a prospective study would allow the strength of association between the dose and duration of metformin and vitamin B12 deficiency to be shown in detail and for a suggestion of timeframe for screening.

Conclusion

In this short-term study, patients with type 2 diabetes showed significant reductions in vitamin B12 levels in the blood with metformin at a high dose of more than 1 gram daily and for a long period of more than a year. It is therefore very important to measure the levels of vitamin B12 in the blood of patients with type 2 diabetes to be needed to take dietary supplements with vitamin B12 to avoid the severe deficiency of vitamin B12 levels due to metformin treatment.

Recommendation

Physicians should acknowledge this necessary reality and screen diabetics on metformin treatment for underlying vitamin B12 deficiency, particularly those presenting with neuropathic symptoms. Additional studies are needed to judge the result of vitamin B12

replacements in these patients towards reducing vitamin B12 deficiency and associated symptoms.

Financial Disclosure: There is no financial disclosure.

Conflict of Interest: None to declare.

Ethical Clearance: All experimental protocols were approved under the Al-Yarmouk university college and all experiments were carried out in accordance with approved guidelines.

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