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Incidence of Vitamin B12 deficiency in metformin utilizers and it's relation to renal functions

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Abstract

Metformin is a widely used drug in the management of T2DM. To study the incidence of vitamin B12 deficiency in metformin elderly utilizers and its relation to renal functions. This prospective observational study was recruited from the outpatient clinic of the Department of Internal Medicine at Minia University hospital between August 2022 to November 2023 and included 100 patients with type 2 DM divided into two groups metformin (70 patients) and non-metformin users (30 patients as a control group). The metformin group was divided into subgroups according to GFR into three groups. First group (30 patients) with GFR more than 90 ml/min/1.73m. Second group (20 patients) with GFR 60-90ml/min/1.73m. Third group (20 patients) with GFR 45-60 ml/min/1.73m. There are statistically significant difference between the studied groups regarding GFR (p value<0.05) as all cases in non-metformin users had normal GFR >90 while in metformin users 43% had normal GFR, 28.5% had GFR 60-90 and the same had GFR<60. There are statistically significant difference between the different categories of GFR regarding vitamin B12 (p value<0.05). As in normal GFR level of Vitamin B12 was higher (298) than when GFR = (60-90) OR when GFR <60. The highest and lowest prevalence of VIT B12 deficiency was found among GFR categories <60 & GFR >90 respectively (65%& 10%). We can conclude that vitamin B12 deficiency in metformin elderly utilizers have risk to renal disease.

Keywords: GFR, metformin, vitB12.

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1. Introduction

Type 2 diabetes mellitus (T2DM) is the most common type of diabetes affecting 90%–95% of all people with diabetes. T2DM is a combination of insulin resistance (a condition in which the body fails to properly use insulin) and reduced secretion of insulin. Risk factors of this type include genetic factors, family history of diabetes, older age, obesity, and a sedentary lifestyle. Unhealthy dietary patterns and physical inactivity are the most common factors linked with DM. Metformin is a widely used drug in the management of T2DM [1, 2]. Most of the current international guidelines, including those of the American Diabetes Association and the Korean Diabetes Association, state that metformin should be the first-line oral therapy prescribed (if it is tolerated and not contraindicated) along with lifestyle modifications at initial diabetes diagnosis [3, 4]. The drug acts by reducing hepatic glucose production and improving peripheral insulin sensitivity. Moreover, it may have therapeutic potential in cardiovascular diseases and polycystic ovary disease [5]. Metformin is usually associated with mild side effects that include gastrointestinal symptoms, such as abdominal distress, nausea, and diarrhea. These side effects appear with the initiation of metformin and are associated with its dose and frequency [6]. Although the drug is well tolerated by most patients, its regimen is modifiable to address any adverse reactions. However, an important and underexposed side effect of metformin treatment is the reduction of serum vitamin B_{12} levels [7]. Vitamin B_{12} is an important water-soluble vitamin mainly found in animal foods, including meats, poultry, fish, eggs, and dairy products, and it plays a vital role in neurological function, optimal hematopoiesis, and DNA synthesis. Thus, clinical manifestations of vitamin B_{12} deficiency include megaloblastic anemia, gastrointestinal symptoms, and neurological dysfunction [8]. The association between vitamin B_{12} deficiency and metformin use has been reported in many studies, with the

first in the early 1970s [9]. Some studies suggested that an inverse relationship exists between the duration of metformin use and vitamin B_{12} levels, where they found that the prevalence of vitamin B_{12} deficiency ranges from 28% to 48% among patients on long-term treatment with metformin [10].

2. Materials and Methods

This prospective observational study was recruited from the outpatient clinic of the Department of Internal Medicine at Minia University hospital between August 2022 to November 2023 and included 100 patients with type 2 DM divided into two groups metformin (70 patients) and non-metformin users (30 patients as a control group). The metformin group was divided into subgroups according to GFR into three groups. First group (30 patients) with GFR more than 90 ml/min/1.73m. Second group (20 patients) with GFR 60-90ml/min/1.73m. Third group (20 patients) with GFR 45-60 ml/min/1.73m.

Inclusion criteria: ≥ 20 and ≤ 65 of age, T2D diagnosed as per the American Diabetes Association criteria, had not consumed any vitamin B12-containing supplement, and within the last 6 months.

Exclusion criteria: diagnosed with type 1 diabetes mellitus (T1D), who had secondary causes of diabetes, were newly diagnosed with T2D (< 3 months), who had received vitamin B12 supplementation or proton-pump inhibitors over the last 6 months, who had hypothyroidism, pernicious anemia, inflammatory bowel disease, and other causes of malabsorption, who had alcohol use disorder, and who had undergone surgical interventions including gastrectomy and colectomy.

2.1. Ethical Consideration

The data that was obtained from participants is confidential. The study participants will not be identified by name in any report or publication concerning this study. Before the participants were admitted in this study, the purpose and nature of the study, as well as the risk–benefit assessment was explained to them. An informed consent was obtained.

2.2. Statistical Analysis

All data were collected, tabulated, and statistically analyzed using SPSS 26 for windows (SPSS Inc., Chicago, IL, USA). Data were tested for normal distribution using the Shapiro Walk test. Qualitative data were represented as frequencies and relative percentages. Chi square test (χ^2) and Fisher exact was used to calculate difference between qualitative variables as indicated. Quantitative data were expressed as mean ± SD (Standard deviation) for parametric and median and range for non-parametric data. The Independent T test and Mann Whitney test were used to calculate difference between quantitative variables in two groups for parametric and non-parametric variables respectively. Kandel's tau and spearman Correlation analysis was done for relation between vitamin B12 and other variable. Univariate and multivariate regression analysis was done for determinant of Vitamin B 12 deficiency. All statistical comparisons were two tailed with significance Level of P-value ≤ 0.05 indicates significant, p <0.001 indicates highly significant difference while, P> 0.05 indicates non-significant difference.

3. Results and discussion

As shown in table 1; There are non-statistically significant difference between the studied groups regarding Age, sex, Duration of diabetes in years, BMI (kg/m^2) and BMI groups (p value >0.05). While there is statistically significant difference between the studied groups regarding diabetic peripheral neuropathy as 38% of metformin users had DPN compared to 16.7% of non-metformin users. As shown in table 2 there are statistically significant difference between the studied groups regarding creatinine level (p value<0.05), While There is non-statistically significant difference between the studied groups regarding FBG, HBA1C, CA, TSH and HB (p value >0.05). As shown in table 3; There are statistically significant difference between the studied groups regarding GFR (p value<0.05).as all cases in non-metformin users had normal GFR >90 while in metformin users 43% had normal GFR, 28.5% had GFR 60-90 and the same had GFR<60. As shown in table 4 there are statistically significant difference between the different categories of GFR regarding vitamin B12 (p value<0.05). As in normal GFR level of Vitamin B12 was higher (298) than when GFR = (60-90) OR when GFR <60. The highest and lowest prevalence of VIT B12 deficiency was found among GFR categories <60 & GFR >90 respectively (65%& 10%). The current study showed that there are non-statistically significant difference between the studied groups regarding Age, sex, Duration of diabetes in years, BMI (kg/m^2) and BMI groups (p value >0.05). While there are statistically significant differences between the studied groups regarding diabetic peripheral neuropathy as 38% of metformin users had DPN compared to 16.7% of non-metformin users. Our results supported with Almatrafi et al. [10] who aimed to estimate the prevalence of vitamin B_{12} deficiency in metformin-treated type 2 diabetic patients and its association with drug duration and dose with relation to B_{12} dietary intake. Their cross-sectional study was conducted with 206 patients with type 2 diabetic patients using metformin for 6 months or more and attending the diabetic clinics at Al-Noor Specialist Hospital in Holy Makkah. The authors reported that there was no significant difference between the studied groups (vitamin B_{12} deficiency or normal levels) regarding age, sex, duration of diabetes in years, BMI (kg/m^2) and BMI groups. In addition, Miyan & Waris [11] who aimed to assess the prevalence of vitamin B12 deficiency in people with type 2 diabetes mellitus (T2DM) on metformin and without metformin. Their prospective multicenter observational study. The authors reported that there was significant difference between the studied groups regarding age, and sex. Moreover, Alharbi et al. [12] who aimed to compare the prevalence of vitamin B12 deficiency and peripheral neuropathy between two groups of type 2 diabetes mellitus (T2DM) patients treated with or without metformin, and to determine factors associated with vitamin B12 deficiency therapy and dietary intake of vitamin B12.

Table 1. Demographic data between the two studied groups.

Baseline characteristics (N=100)		Group A (metformin user) (n=70)	Group B (non-metformin user) (n=30)	P value
Age	Mean ± SD (Range)	43.5 ± 8.5 (21:60)	45.6 ± 8.5 29:60	0.27
Sex	Male Female	47(67.1%) 23(32.9%)	19(63.3%) 11(36.7%)	0.71
Duration of diabetes in years	Mean ± SD (Range)	4.8 ± 2.5 1:10	3.9± 1.2 2:8	0.08
BMI (kg/m^2)	Mean ± SD (Range)	25.5±2.8 18:31	25.8±2.9 20:32	0.81
BMI groups	Under weight Normal Over Obese	1(1.4%) 32(45.7%) 35(50%) 2(2.9%)	0 14(46.7%) 14(46.7%) 2(6.7%)	0.74
DPN	No Yes	43(61.4%) 27(38.6%)	25(83.3%) 5(16.7%)	0.03*

Table 2. Comparison between studied groups regarding lab data

Lab data		Group A (metformin user) (n=70)	Group B (non-metformin user) (n=30)	P value
Creatinine	Mean ± SD (Range)	2.1 ± 1.1 (0.3:4.2)	1.2 ± 0.25 0.08:1.8	0.001*
FBG	Mean ± SD (Range)	165 ± 24.3 120:199	159.7±25.8 120:200	0.33
HBA1C	Mean ± SD (Range)	7.9± 0.8 6.9:9.9	8.1±0.9 6.9:9.9	0.38
Ca	Mean ± SD (Range)	9.6±0.4 8.9:10.3	9.5±0.38 8.9:10.3	0.49
TSH	Mean ± SD (Range)	2.6± 1.1 0.3:4.8	2.3±0.9 0.5:4.3	0.18
HB	Mean ± SD (Range)	11.9±1.1 9.2:14.3	11.7±1.2 9.3:14	0.50

Table 3. Comparison between the two studied groups regarding GFR

GFR	Group A (metformin user) (n=70)	Group B (non-metformin user) (n=30)	P value
Normal GFR >90	30(43%)	30(100%)	<0.001*
GFR 60-90	20(28.5%)	0	
GFR 45-60	20(28.5%)	0	

Table 4. Relation between vitamin B12 level and GFR in metformin users group

Vitamin B 12		Metformin users (n=70)			P value
		Normal GFR >90	GFR= (60-90)	GFR= (45-60)	
Vitamin B12 level	**Mean ± SD (Range)**	298± 69 (167:410)	248± 76 117:398	181.2±100 88:391	<0.001*
Post hoc analysis		**P1=0.09 ,P2= 0.001* ,P3=0.03***			
Vit B12 groups	**Normal (>300 pg/ml)**	16(53.3%)	6(30%)	3(15%)	0.001*
	Borderline (200-300pg/ml)	11(36.7%)	8(40%)	4(20%)	
	Deficient (<200pg/ml)	3(10%)	6(30%)	13(65%)	
TOTAL		30(100%)	20(100%)	20(100%)	

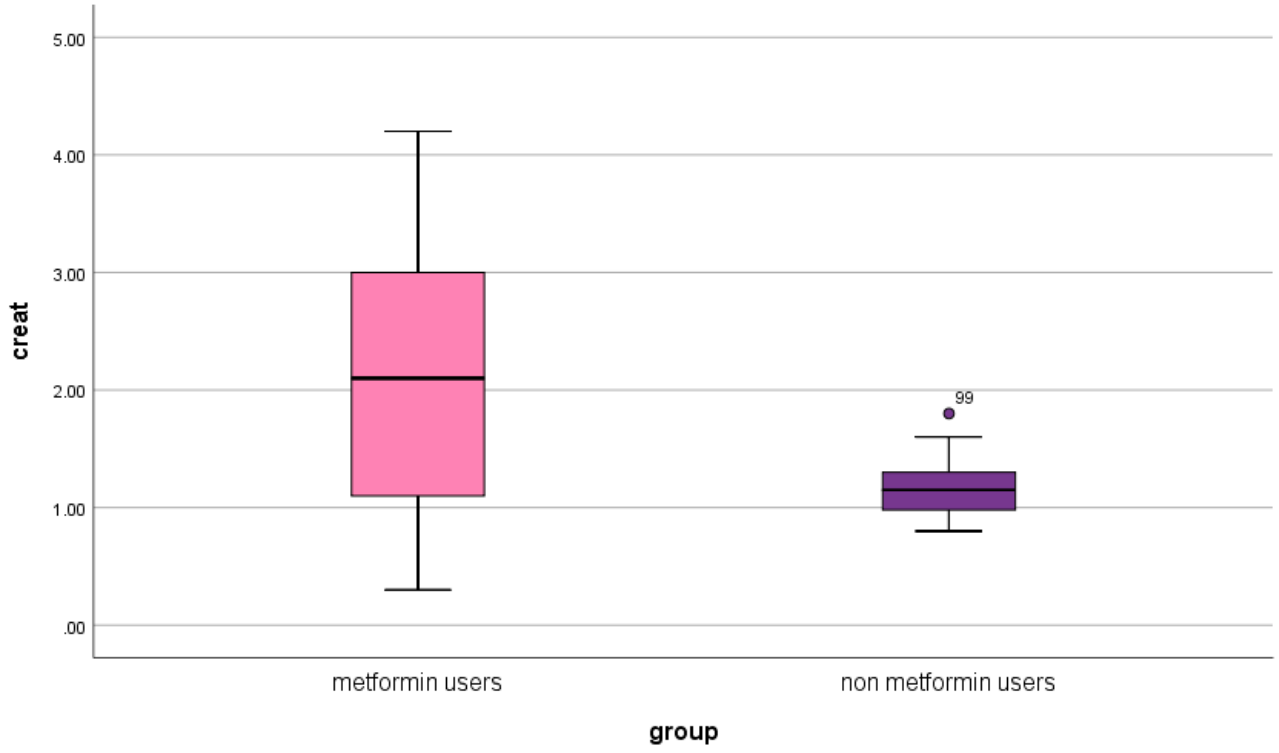

Figure 1. Box plot for creatinine level between two studied groups

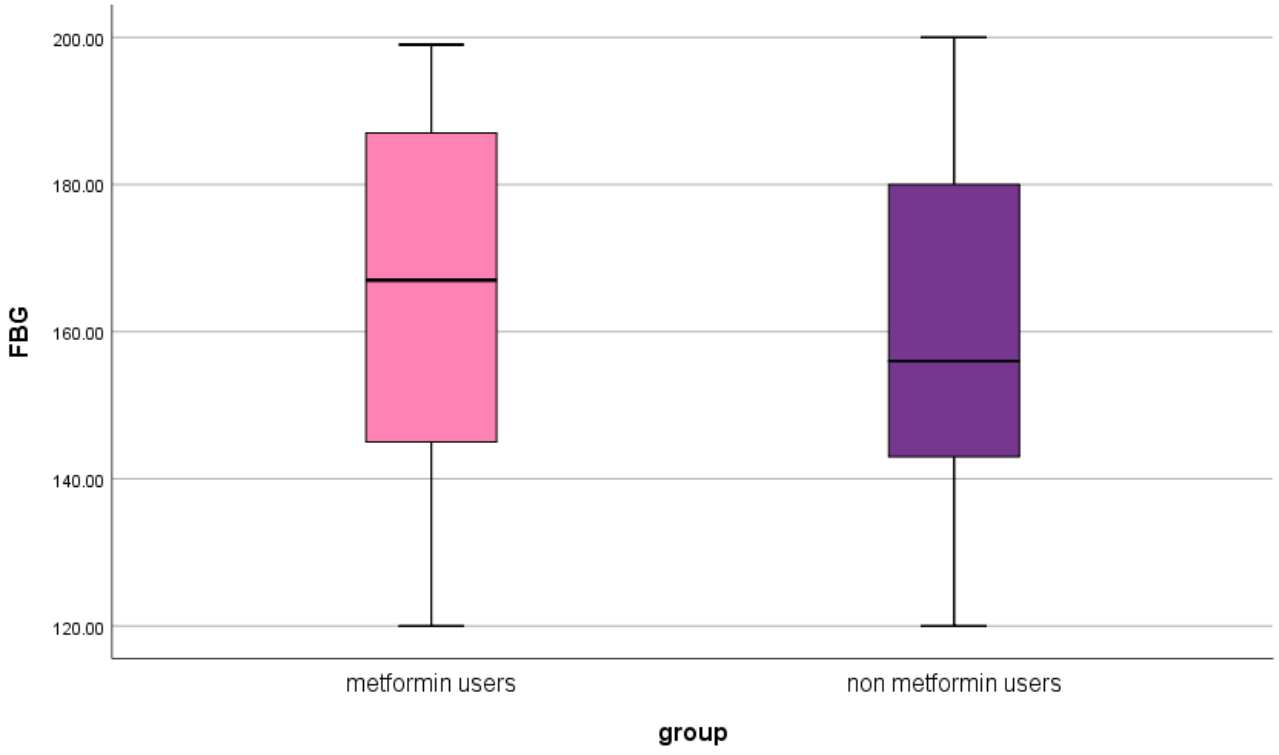

Figure 2. Box plot for FBG level between two studied groups

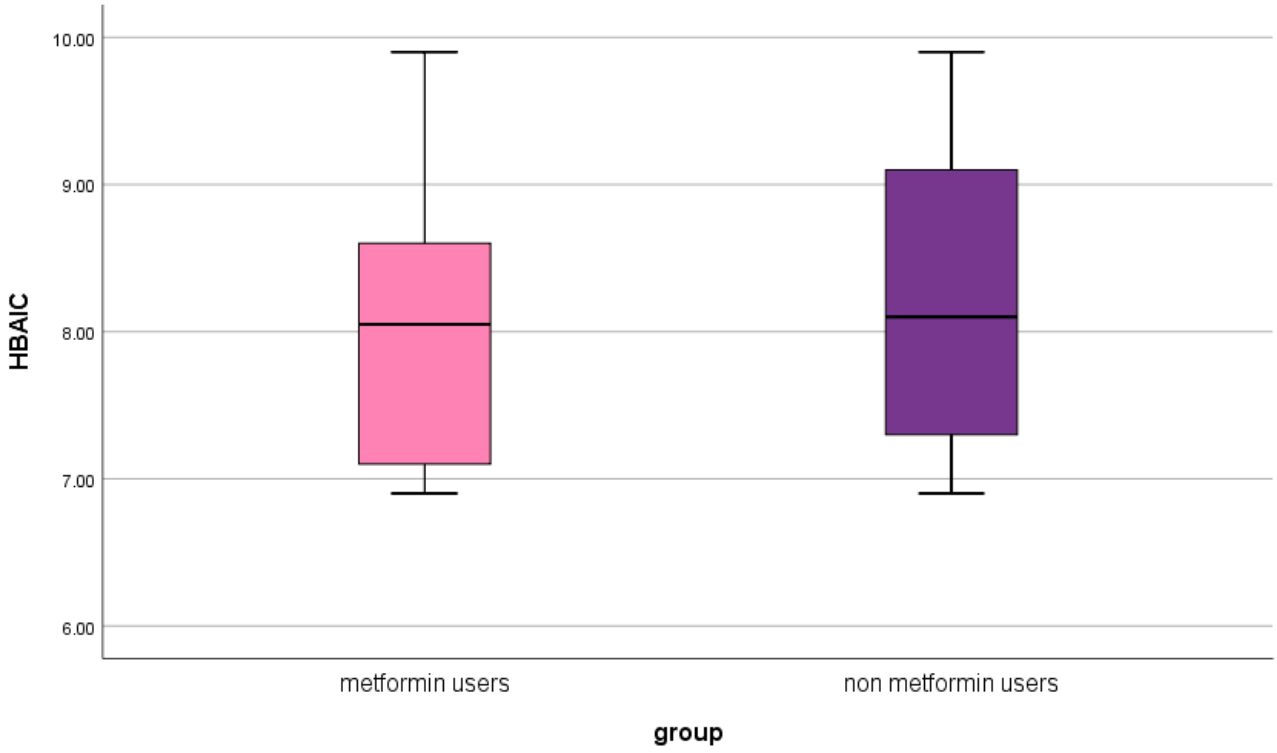

Figure 3. Box plot for HBA1C between two studied groups

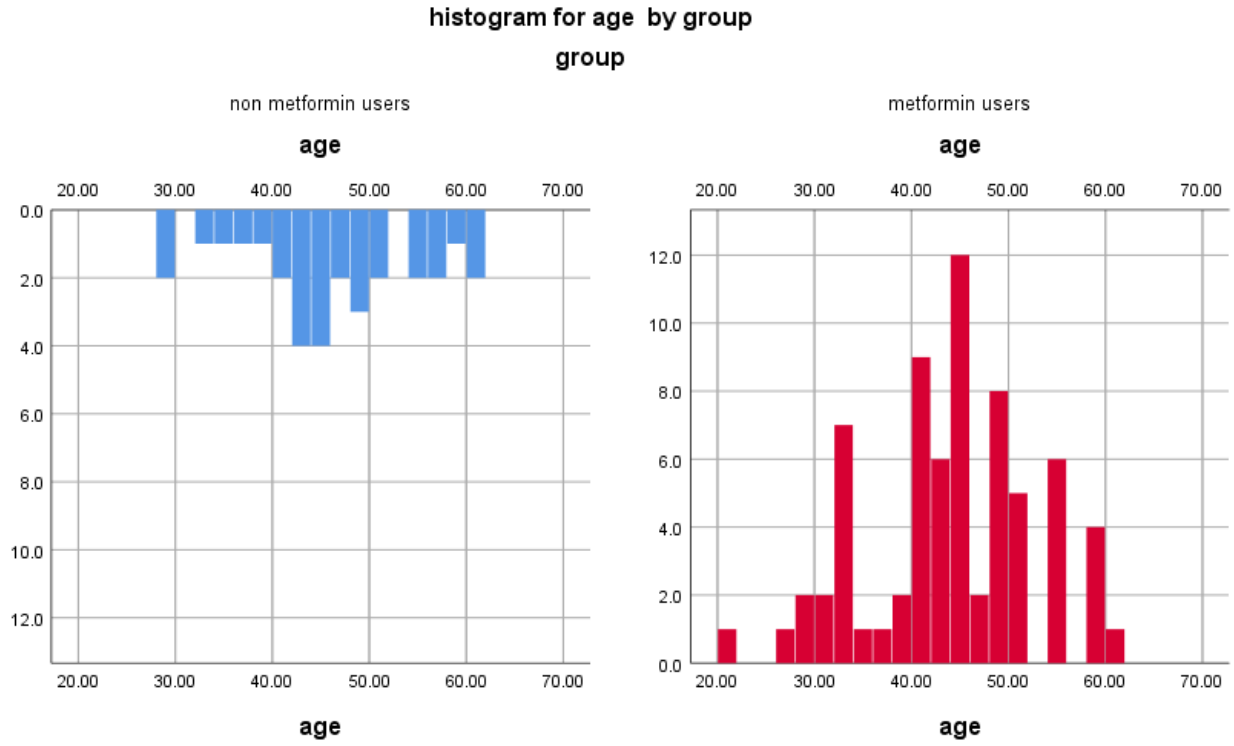

Figure 4. Histogram show age distribution between 2 groups

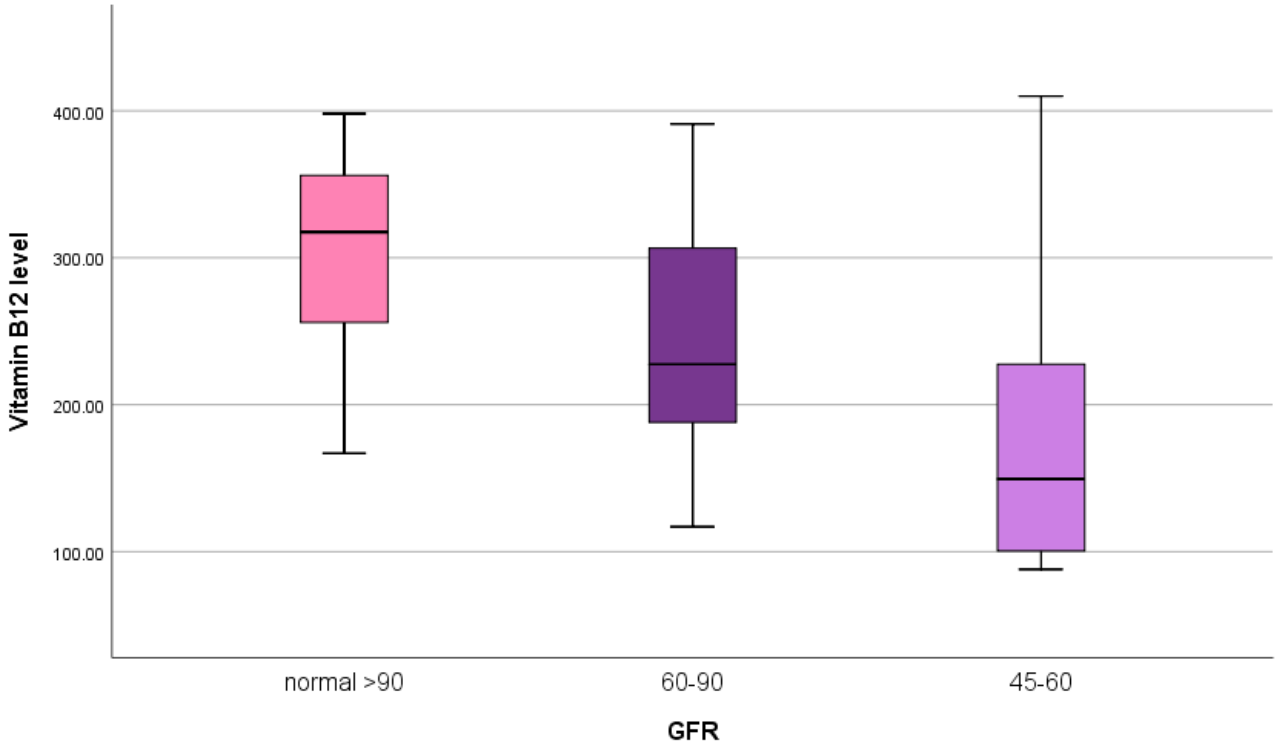

Figure 5. Box plot for vitamin B 12 level between different categories of GFR

Type 2 diabetes mellitus (T2DM) is the most common type of diabetes affecting 90%–95% of all people with diabetes. T2DM presents from a combination of insulin resistance (a condition in which the body fails to properly use insulin) and reduced secretion of insulin [6]**.**

Risk factors of this type include genetic factors, family history of diabetes, older age, obesity, and a sedentary lifestyle. Unhealthy dietary patterns and physical inactivity are the most common factors linked with DM. Metformin is a widely used drug in the management of T2DM [11].

Most of the current international guidelines, including those of the American Diabetes Association and the Korean Diabetes Association, state that metformin should be the first-line oral therapy prescribed (if it is tolerated and not contraindicated) along with lifestyle modifications at initial diabetes diagnosis [12].

The drug acts by reducing hepatic glucose production and improving peripheral insulin sensitivity. Moreover, it may have therapeutic potential in cardiovascular diseases and polycystic ovary diseases. Metformin is usually associated with mild side effects that include gastrointestinal symptoms, such as abdominal distress, nausea, and diarrhea. These side effects appear with the initiation of metformin and are associated with its dose and frequency. Although the drug is well tolerated by most patients, its regimen is modifiable to address any adverse reactions. However, an important and underexposed side effect of metformin treatment is the reduction of serum vitamin B_{12} levels [10]

Vitamin B_{12} is an important water-soluble vitamin mainly found in animal foods, including meats, poultry, fish, eggs, and dairy products, and it plays a vital role in neurological function, optimal hematopoiesis, and DNA synthesis. Thus, clinical manifestations of vitamin B_{12} deficiency include megaloblastic anemia, gastrointestinal symptoms, and neurological dysfunction [7]

The present prospective observational study conducted on 100 patients with type 2 DM divided into two groups metformin (70 patients) and non-metformin users (30 patients as a control group). The metformin group was divided into subgroups according to GFR into three groups:
First group (30 patients) with GFR more than 90 ml/min/1.73m
Second group (20 patients) with GFR 60-90ml/min/1.73m and
Third group (20 patients) with GFR 45-60 ml/min/1.73m

The present study aimed to study incidence of vit b12 deficiency in metformin elderly utilizers and its relation to renal functions.

In the present analysis the mean age of the participants was 43.5± 8.5, and more than two thirds of participants were male. There is non-statistically significant difference between the studied groups regarding Age, sex, Duration of diabetes in years, BMI (kg/m2) and BMI groups (p value >0.05). While There is statistically significant difference between the studied groups regarding diabetic peripheral neuropathy as 38% of metformin user had DPN compared to 16.7% of non-metformin users.

There is statistically significant difference between the studied groups regarding vitamin B12 level (p value<0.05)

as mean vit B12 was much less in metformin user (250) than non-metformin user (330). Also, prevalence of vitamin B 12 deficiency in metformin user was 31% which was higher than in non-metformin user (16.5%)

In agreement, **[5]** a prospective study conducted on 150 diabetic patients divided into 2 groups Metformin treated (group I): included 75 patients administered metformin for the previous 6 months or more and non-metformin treated (group II): included 75 patients who weren't administered metformin for the previous 6 months (but administered other oral hypoglycemic drugs). The two groups were similar in age, sex and BMI. Also, there was no important difference between both groups regarding differences in the disease severity, the duration of diabetes, and duration of diabetic PN (P = 0.9 and 0.82 respectively. the incidence of DPN was higher in metformin group than non-metformin (50% VS 26%) respectively. It was explained as Metformin-treated diabetics (MTD) showed a decrease in cobalamin, a rise in homocysteine, and methylmalonic acid, leading to accentuated diabetic peripheral neuropathy (DPN).

4. Conclusions

Regarding our results, we found that there is statistically significant difference between the studied groups regarding vitamin B12 level as mean vitamin B12 was much less in metformin user (250) than non-metformin user (330). In addition, prevalence of vitamin B 12 deficiency in metformin user was 31%, which was higher than in non-metformin user (16.5%). We can have concluded that vitamin B12 deficiency in metformin elderly utilizers have risk to renal disease. Further prospective studies are needed with larger scales for confirming our results.

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