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Serum Vitamin B12 Level in Type 2 Diabetes Patients on Metformin Therapy

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Abstract

Background and Objective: Type 2 diabetes mellitus is a common non-communicable disease all over the world. Metformin is an effective treatment option for diabetic patients. However, this option is frequently accompanied by vitamin B_{12} deficiency. Therefore, we aimed to measure the prevalence of serum vitamin B12 deficiency in type 2 diabetic patients and recognize risk factors related to vitamin B_{12} deficiency.

Methods: This study was a retrospective cross-sectional study implemented in Layla Qasim Diabetic Center in Erbil city-Kurdistan region/Iraq through six months from 1st of October 2023 to 31st of March 2024 on a sample of 100 type 2 diabetic patients. We investigated and analyzed patients' data. The vitamin B_{12} deficiency was diagnosed regarding the center laboratory cutoff value of less than 191 pg/ml.

Results: The mean serum B_{12} level of type 2 diabetic patients was (421.9 pg/ml); 21% had low serum B_{12} levels. A significant association was observed between good glycemic control (i.e. HbA1c of less than 7.0%)[1] of type 2 diabetic patients and low serum B_{12} level (p-value=0.04). No significant relationships existed between serum B_{12} levels and other type 2 diabetic patients' characteristics ($p>0.05$).

Conclusions: The prevalence of serum vitamin B_{12} deficiency among type 2 diabetic patients on metformin is within the acceptable range (i.e. serum vitamin B12 between 191-663 pg/ml). The strict glycemic control by high doses of metformin therapy for type 2 diabetic patients commonly leads to serum vitamin B_{12} deficiency.

Keywords: Glycemic control, Metformin, Type 2 diabetes mellitus, Vitamin B_{12}

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Introduction

Type 2 diabetes mellitus is a chronic metabolic disease manifested by increased blood glucose levels related to inadequate insulin secretion and/or insulin resistance. It is a common public health problem all over the world.[1] Globally, the prevalence of type 2 diabetes mellitus was (10.5%) by 2021, and is expected to reach (11.3%) by 2030 and (12.2%) by 2040.[2] The type 2 diabetes mellitus is affecting multiple human systems such as renal, nervous, and cardiovascular systems leading to different co-morbidities, high cost and poor quality of life.[3] Additionally, type 2 diabetes mellitus is responsible for 15% of earlier death with a marked reduction in life expectancy.[4] In Iraq, the prevalence of type 2 diabetes mellitus represented approximately 8.5-13.9% of the population.[5] In the Iraqi Kurdistan region, type 2 diabetes mellitus is highly complicated by hyperlipidemia, hypertension, chronic heart diseases, nephropathy, and neuropathy.[6] The treatment goal of type 2 diabetes mellitus is achieved by controlling glycemic status to delay or prevent diabetic complications. Nevertheless, strict glycemic control is impossible without anti-diabetic agents.[7] Metformin (Biguanide derivative) is the first treatment described for type 2 diabetes mellitus patients by different guidelines. Metformin approved its efficacy in lowering the blood glucose level of patients with type 2 diabetes mellitus.[8] Currently, metformin is used in different diseases other than diabetes like some cancers, cardiovascular diseases, hepatic dysfunction, increased body mass index, neurological disorders, and renopathy.[9] Different authors revealed the efficacy of metformin monotherapy or combination therapy with other anti-diabetics in treating type 2 diabetes mellitus.[10] Metformin's mechanism of action depends on inhibiting mitochondrial complex I and decreasing adenosine triphosphate production which activates cellular adenosine 5′-monophosphate-activated protein kinase and regulating cellular metabolism.[11] It also helps in improving insulin sensitivity and fasting insulin levels.[12] Despite these advantages, numerous disadvantages of metformin were reported such as beta cell failure, insulin resistance, lactic acidosis, etc.[13] Gastrointestinal disturbances are the common adverse effects of metformin; while vitamin B_{12} deficiency is the commonly neglected adverse effect of metformin.[14,15] Vitamin B_{12} deficiency is either asymptomatic or clinically manifested megaloblastic anemia, sometimes accompanied by neurological adverse effects.[16] Different kinds of literature reported the relation between low serum vitamin B_{12} levels and metformin use by type 2 diabetic patients.[17] Prevalence of serum vitamin B_{12} deficiency among type 2 diabetic patients on metformin might reach (93%).[18] Moreover, many authors related peripheral neuropathy in type 2 diabetic patients to the effect of serum vitamin B_{12} deficiency.[19] It was found that the prevalence of serum vitamin B_{12} deficiency among type 2 diabetic patients was higher than the general population.[20] Generally, vitamin B_{12} deficiency might be related to gastroparesis in type 2 diabetic patients.[21] For that, routinely monitoring serum vitamin B_{12}in type 2 diabetic patients on metformin therapy is highly recommended.[22] Some authors revealed that metformin use the duration affected the prevalence of serum vitamin B_{12} deficiency in addition to the effect of metformin use and peripheral neuropathy.[23] This study aimed to measure the prevalence of serum vitamin B12 deficiency in type 2 diabetic patients and recognize risk factors related to vitamin B_{12} deficiency.

Patients & methods

The current study was a retrospective cross-sectional study implemented in Layla Qasim Diabetic Center in Erbil city-Kurdistan

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region/Iraq through six months from 1st of October 2023 to 31st of March 2024. Inclusion criteria were patients with type 2 diabetes mellitus who were either on metformin alone or metformin plus other oral hypoglycemic agents. Exclusion criteria were pernicious anemia, alcohol, gastrectomy, gastric bypass surgery, pancreatic diseases, malabsorption syndromes, surgery involving the small intestine, human immunodeficiency viral infection, patients on proton pump inhibitors and any other drugs that impair B_{12} absorption, missing and incomplete records of patients. This study was ethically approved by the ethics committee of the Kurdistan Higher Council of Medical Specialist-Internal Medicine taking into consideration the confidentiality of data. A sample of one hundred types-2 diabetic patients on metformin was enrolled. The data of type 2 diabetic patients were collected retrospectively by the researcher by reviewing their saved records in the diabetic center and filling in a prepared questionnaire designed by the researchers. The informed consent questionnaire contained general characteristics of patients (like age, gender, diabetes mellitus duration, daily metformin dosage, and duration of metformin intake), investigations findings (such as HbA1c level, serum vitamin B_{12} level, and serum creatinine level), and other characteristics of type 2 diabetic patients (co-morbidities and other anti-diabetic drugs). Diabetes mellitus (DM) was diagnosed previously by other physicians in the diabetic center according to American diabetes association criteria for the diagnosis of diabetes.[1] Researcher recorded the vitamin B12 deficiency concerning center laboratory cutoff value of less than 191 pg/ml. All investigations were implemented in the diabetic center laboratory and other private medical laboratories. The collected data were entered and interpreted statistically by SPSS program26. Suitable statistical tests (Chi-square and Fisher's exact tests) for categorical variables. The p-value of ≤ 0.05 was regarded as significant.

Results

This study included one hundred types-2 diabetic patients on metformin therapy with a mean age of (55.8 years), ranging from 13 years to 61 years; 40% of type-2 diabetic patients were 50-59 years old. Female type 2 diabetic patients were more than males (71% vs. 29%). The mean duration of diabetes mellitus disease was (8.6 years); 47% had a disease duration of 5-10 years. The mean daily metformin dosage was (1628.8 mg); 68% of patients were on more than 1000 mg of metformin. The mean duration of metformin use was (7 years); 44% of patients had a duration of 5-10 years, Table (1).

Table (1): General characteristics of type 2 diabetic patients.

Variable	No.	%
Age mean ± SD (55.8±10 years)		
<40 years	5	5.0
40-49 years	23	23.0
50-59 years	40	40.0
≥60 years	32	32.0
Gender		
Male	29	29.0
Female	71	71.0
Duration of Diabetes mean ± SD (8.6±6.4 years)		
<5 years	26	26.0
5-10 years	47	47.0
>10 years	27	27.0
Daily Metformin dosage mean ± SD (1628.8±500.7		
<1000 mg	8	8.0
1000 mg	24	24.0
>1000 mg	68	68.0
Duration of Metformin intake mean ± SD (7±6		
<5 years	39	39.0
5-10 years	44	44.0
>10 years	17	17.0
Total	100	100.0

The mean HbA1c level of type 2 diabetic patients was (8%); 66% had poor glycemic control (i.e. HbA1c more than 7%). The

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mean serum B_{12} level of type 2 diabetic patients was (421.9 pg/ml); 21% had low serum B_{12} levels. The mean serum creatinine level of type 2 diabetic patients was (0.84); 14% had high serum creatinine levels, Table (2).

Table (2): Investigations findings of type 2 diabetic patients.

Variable	No.	%
HbA1c level mean ± SD (8±1.8 %)		
<7%	34	34.0
≥7%	66	66.0
Serum B_{12} level mean ± SD (421.9±400.5 pg/ml)		
Normal	79	79.0
Low	21	21.0
Serum Creatinine mean ± SD (0.84±0.7 mg/dl)		
Normal	86	86.0
High	14	14.0
Total	100	100.0

Common clinical co-morbidities of type 2 diabetic patients were dyslipidemia (36%), hypertension & dyslipidemia (24%), hypertension (16%), etc. The common other anti-diabetic drugs used by type 2 diabetic patients were Glimepride (28%), Sitagliptin (18%), Pioglitazone (14%), etc., Table (3).

Table (3): Other characteristics of patients.

Variable	No.	%
Co-morbidities		
None	19	19.0
HT	16	16.0
Dyslipidemia	36	36.0
HT & dyslipidemia	24	24.0
Thyroid nodule	1	1.0
IHD	1	1.0
HF & dyslipidemia	3	3.0
Other Anti-diabetic drugs		
None	37	37.0
Sitagliptin	18	18.0
Pioglitazon	14	14.0
Glimepride	28	28.0
Insulin	3	3.0
Total	100	100.0

There were no significant relationships between serum B_{12} levels and type 2 diabetic patients' general characteristics ($p>0.05$), Table (4).

Table (4): Distribution of patients' general characteristics according to serum B12 level.

Variable	Serum B_{12} level				P
	Normal		Low		
	No.	%	No.	%	
Age					0.9 NS
<40 years	4	5.1	1	4.8	
40-49	19	24.1	4	19.0	
50-59	32	40.5	8	38.1	
≥60 years	24	30.4	8	38.1	
Gender					0.09 NS
Male	26	32.9	3	14.3	
Female	53	67.1	18	85.7	
Duration of Diabetes					0.3 NS
<5 years	18	22.8	8	38.1	
5-10 years	39	49.4	8	38.1	
>10 years	22	27.8	5	23.8	
Daily Metformin dosage					0.6 NS
<1000 mg	7	8.9	1	4.8	
1000 mg	20	25.3	4	19.0	
>1000 mg	52	65.8	16	76.2	
Duration of Metformin intake					0.8 NS
<5 years	30	38.0	9	42.9	
5-10 years	35	44.3	9	42.9	
>10 years	14	17.7	3	14.3	

S=Significant, NS=Not significant.

A significant association was observed between good glycemic control of type 2 diabetic patients and low serum B_{12} levels ($p=0.04$). There were no significant relationships between serum B_{12} levels and other type 2 diabetic patients' characteristics ($p>0.05$), Table (5).

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Table (5): Distribution of investigation findings and other features according to serum B12 level.

Variable	Serum B_{12} level				P
	Normal		Low		
	No.	%	No.	%	
HbA1c level					0.04 S
<7%	23	29.1	11	52.4	
≥7%	56	70.9	10	47.6	
Serum Creatinine					0.4 NS
Normal	69	87.3	17	81.0	
High	10	12.7	4	19.0	
Co-morbidities					0.8 NS
None	15	19.0	4	19.0	
HT	11	13.9	5	23.8	
Dyslipidemia	30	38.0	6	28.6	
HT &	19	24.1	5	23.8	
Thyroid	1	1.3	0	-	
IHD	1	1.3	0	-	
HF &	2	2.5	1	4.8	
Other Antidiabetic drugs					0.2 NS
None	25	31.6	12	57.1	
Sitagliptin	15	19.0	3	14.3	
Pioglitazon	12	15.2	2	9.5	
Glimepride	24	30.4	4	19.0	
Insulin	3	3.8	0	-	

S=Significant, NS=Not significant.

Discussion

Assessing serum vitamin B_{12} levels among type 2 diabetic patients on metformin is essential in the prevention of peripheral neuropathy and earlier treatment of vitamin B_{12} deficiency.[24] In the present study, the mean serum B_{12} level of type 2 diabetic patients was (421.9 pg/ml) and the prevalence of serum vitamin B_{12} deficiency was (21%). This serum vitamin B_{12} deficiency prevalence among type 2 diabetic patients is close to the prevalence of (24.6%) reported by the Abubakr et al. cross-sectional studies.[25] However, our study serum vitamin B_{12} deficiency prevalence in type 2 diabetes mellitus is lower than the results of recent Iraqi studies which reported serum vitamin B_{12} deficiency prevalence of (48% and 39.5%, respectively).[26, 27] These differences might be attributed to differences in glycemic control, DM duration and diagnostic techniques between studies in addition to differences in sample size and study methodology. Our study's prevalence of serum vitamin B_{12} deficiency among type 2 diabetic patients on metformin is close to the results of Damião et al. cross-sectional studies (22.5%).[28] On the other hand, the current study's prevalence is higher than the results of the Almatrafi et al. cross-sectional studies which found that the prevalence of serum vitamin B_{12} deficiency among type 2 diabetic patients on metformin was (17.5%).[29] These discrepancies may be related to variances in DM characteristics and vitamin B_{12} levels between populations of different countries. The present study showed that common clinical co-morbidities of type 2 diabetic patients were dyslipidemia and hypertension. This finding coincides with the results of the Ali et al. study.[6] In our research, the common other anti-diabetic drugs used by type 2 diabetic patients were Glimepride (28%), Sitagliptin (18%), Pioglitazone (14%), etc. These findings agree with reports of Artasensi et al review study.[30] The current study found a significant association (p-value of 0.04) between good glycemic control of type 2 diabetic patients on metformin therapy and low serum B_{12} levels. This finding parallels the Alhaji meta-analysis study results, which revealed that high metformin doses' strict glycemic control leads to severe vitamin B_{12} deficiency among type 2 diabetic patients.[31] Li et al stated that vitamin B_{12} level was correlated with glycemic changes in type 2 diabetic patients, which might be useful in

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predicting the glycemic status of patients on metformin therapy. [32]

Limitations

The study's main limitation is the modest sample size, which we attribute to a lack of computerized data collection and difficulty following up with the selected patients. These limitations restricted the ability to determine the real causality of the study's findings.

Conclusions

The prevalence of serum vitamin B_{12} deficiency among type 2 diabetic patients on metformin is within a justifiable range. The strict glycemic control by high doses of metformin therapy for type 2 diabetic patients commonly leads to serum vitamin B_{12} deficiency. It's recommended patients frequently monitor glycemic status and physicians for reasonable doses of metformin in treating type 2 diabetes mellitus. Furthermore, we suggest periodic measurement of serum vitamin B12 levels to avoid serious complications.

Conflicts of interest

The authors recorded no conflict of interest.

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