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Prevalence of Vitamin B_{12} Deficiency in Patients with type 2 Diabetes Mellitus on Metformin

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Abstract

Background: Type 2 diabetes mellitus (T_2DM) is a common public health problem in metabolism. Metformin is the oral hypoglycemic agent used as a first line together with life style modification in type 2 diabetes patients worldwide. Continuous metformin therapy increases the risk of vitamin B12 insufficiency, and its medical consequences in T_2DM patients.

Objective: To detect the prevalence of serum vitamin B_{12} deficiency in T_2DM who has been treated with metformin in Erbil Province.

Patients and Methods: The study involved 200 cases (100 patients and 100 controls) that met the study's basic criteria. A completed questionnaire, and a blood test for serum vitamin B_{12} levels were performed. A deficiency of vitamin B_{12} is defined as <160 pg/mL in serum vitamin B_{12}.

Results: Deficiency of serum vitamin B12 was found in 48% of patients (n=48), while HbA1c levels had no impact on this finding. In T_2DM level of serum vitamin B_{12} that has been on metformin at a dose of ≤ 1 gm/ day shows a significant difference with those patients with no history of metformin use.

Conclusion: Low levels of serum vitamin B_{12} came as a result of the overdosing of metformin for long period of treatment.

Keywords: Type 2 diabetes mellitus, , metformin, serum vitamin B_{12} deficiency

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Introduction

Diabetes mellitus is a term used to describe a group of metabolic diseases that all have a hyperglycemic phenotype[1]. A complicated combination between heredity and environmental factors results in several clinically different kinds of diabetes mellitus. Reduced insulin secretion, decreased glucose utilization, and increased glucose production are all factors that contribute to hyperglycemia[2]. Several oral hypoglycemic medications are used to treat type 2 diabetes mellitus.

Metformin is the first-line oral hypoglycaemic medication because of its low cost, high efficacy, and weight-loss benefits. It is also often used as a dietary modification [2, 3]. Metformin mainly affects the liver by reducing the release of glucose and then increasing the intake of glucose in the peripheral tissues, especially muscles [4]. Metformin inhibits vitamin B_{12} absorption

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via changing intestinal motility, causing bacterial overgrowth, and changing the vitamin B_{12}-IF complex. The likelihood of developing metformin-induced vitamin B_{12} insufficiency is influenced by the patient's age, metformin dosage, and treatment duration [5]. Metformin's side effects include nausea, upset stomach, lactic acidosis, and reduced absorption of vitamin B_{12} [6].

Vitamin B_{12}, also known as cyanocobalamin, is a critical component found in animal diets. It is a necessary cofactor in the creation of deoxyribonucleic acid (DNA) and metabolic processes [5].

Vitamin B_{12} is essential for brain, and neurological system function, as well as the creation of red blood cells. Peripheral neuropathy can be brought on by T_2DM patients who are vitamin B_{12} deficient [7]. B_{12} deficiency is common in patients taking long-term metformin therapy, with rates ranging from 5.8% to 30%.[8] Metformin prevents vitamin B_{12} absorption in the small intestine (ileum) [9], and it causes block of calcium-dependent channels in the ileum [4, 10].

Many metformin users suffer from vitamin B_{12} insufficiency[7], which is frequently ignored and rarely checked, resulting in paraesthesias and anemia that are mistakenly attributed to underlying DM by physicians and hence never addressed [11]. Vitamin B_{12} is essential for the conversion of homocysteine (Hcy) to methionine, and a deficiency can lead to high homocysteinemia, which has been associated with macrovascular issues and may aggravate peripheral neuropathy in T_2DM patients [1]. Deficiency of vitamin B_{12} usually appears in the form of haematological and neurological symptoms. Without a haematologic presentation, neurological symptoms may be the only sign of a deficiency [12, 13]. On the other hand, neurological manifestations come before hematological alterations [4].

In Iraq, there are large numbers of diabetes and its consequences; there is little study on vitamin B_{12} deficiency associated with the use of metformin [14, 15]. As a first step in identifying vitamin B_{12} deficiency in T_2DM patients, a serum vitamin B_{12} level should be determined. It is usually indicated by concentrations of less than 200pg/mL [16, 17].

Patients and Methods

Design of the research

From April to August 2021, diabetes patients who visited the Layla Qasim diabetic center, Hawler teaching hospital, and Rizgary teaching hospital as outpatients were studied in this cross-sectional study. A total of 200 cases (100 patients and 100 controls) were targeted for the study. The samples gwere gathered after taking a short history from each patient. At the time of the vitamin B_{12} measurement, information about age, gender, weight, height, diabetes mellitus as a medical condition, and metformin (a medication used to treat it; dosage and frequency of administration daily) were gathered. Our patients were split into two groups: 100 cases of diabetes patients who took metformin (Glucophage, 1000 mg tab, Merck Company) and other hypoglycemic drugs, and 100 cases of control patients.

Data collection

Four milliliters of venous blood were obtained using a full aseptic procedure following fasting overnight. Two milliliters of blood were distributed into EDTA tubes,

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with the remaining two milliliters going into gel separator tubes. The sample in the EDTA tube was used to determine glycated hemoglobin (HbA1c) using a Cobas c 311 automated analyzer and complete blood counts (CBC) using a Mythic 18 automated analyzer. To get the serum, the gel separator tubes were placed in a centrifuge and spun at 3000 rpm for 5 minutes. Cobas e 411 was used to calculate serum vitamin B_{12} levels (1). A pathologist then checked the results. The levels of serum vitamin B_{12} less than 160pg/mL were considered deficient, whereas values of more than 160-220pg/mL and >220 were considered borderline and normal serum vitamin B_{12}, respectively (17). The biodata, serum hemoglobin level, time of diabetes onset, metformin dosage, and duration of metformin use were all included in each patient's profile. The work sheet was created, and all of the information was saved. The study was approved by the Kurdistan Board of Medical Specialties.

Statistical Analysis

On an excel sheet, all the information has been entered. Appropriate statistical analysis will be employed in order to analyze all data during the final analysis in order to provide an observer survey by Chi-square and ordinary one-way ANOVA. A P-value of less than 0.05 was considered statistically significant. The prism (graph pad (6.1)) was used in all of the analyses.

Results

The important comparisons of characteristics between cases and controls with and without deficiency of vitamin B_{12} are shown in Table (1). 100 patients with type 2 diabetes mellitus (30 males and 70 females) were recruited for the study, and 100 control cases (48 males and 52 females) were also included. There is a significant difference between patients and case control in serum vitamin B_{12} deficiency ($p<0.005$). The highest rate of serum vitamin B_{12} deficiency was found in females (34 cases) as compared with normal serum vitamin B_{12} (7 cases) in male diabetic cases. There is a non-significant difference between them. The demographic data was used to determine age, weight, and body mass index (BMI) characteristics linked to serum vitamin B_{12} deficiency as shown in Table (2).

Table (1): Level of serum vitamin B_{12} according to the gender from patients and control cases

Serum Vitamin B_{12} level	Diabetic Case				Control		
	No. of Patients	Gender		P Value	No. of control	Gender	
		Male	Female			Male	Female
<160 (B_{12} deficiency)	48	14 (14%)	34 (34%)	0.932	1	0	1(1%)
160-220 (Border Line)	31	9 (9%)	22 (22%)		8	2 (2%)	6 (6%)
>220 (Normal Vitamin B_{12})	21	7 (7%)	14 (14%)		91	46 (46%)	45 (45%)
Total	100	30	70		100	48	52

* P value=0.0001

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Table (2): Serum vitamin B_{12} level according age, weight and BMI

Serum Vitamin B_{12} level	Total Patients	Age	weight	BMI	P Value
		Mean±S.D	Mean±S.D	Mean±S.D	
<160 (B12 deficiency)	48	52.96±7.82	83.54±10.9	30.41±4.422	0.1611
160-220(Border Line)	31	51.74±9.903	75.97±16.04	28.26±5.413	
>220(Normal Vitamin B_{12})	21	56.43±9.086	77.24±11.29	28.27±4.547	

Figure (1) showed that the level of serum vitamin B_{12} is unrelated to fasting blood sugar and glycosylated hemoglobin (HbA1c). In the borderline of serum vitamin B_{12} levels, according to T_2DM, FBS and HbA1c were found to be (256.5±133.6) and (8.083±2.274), respectively.

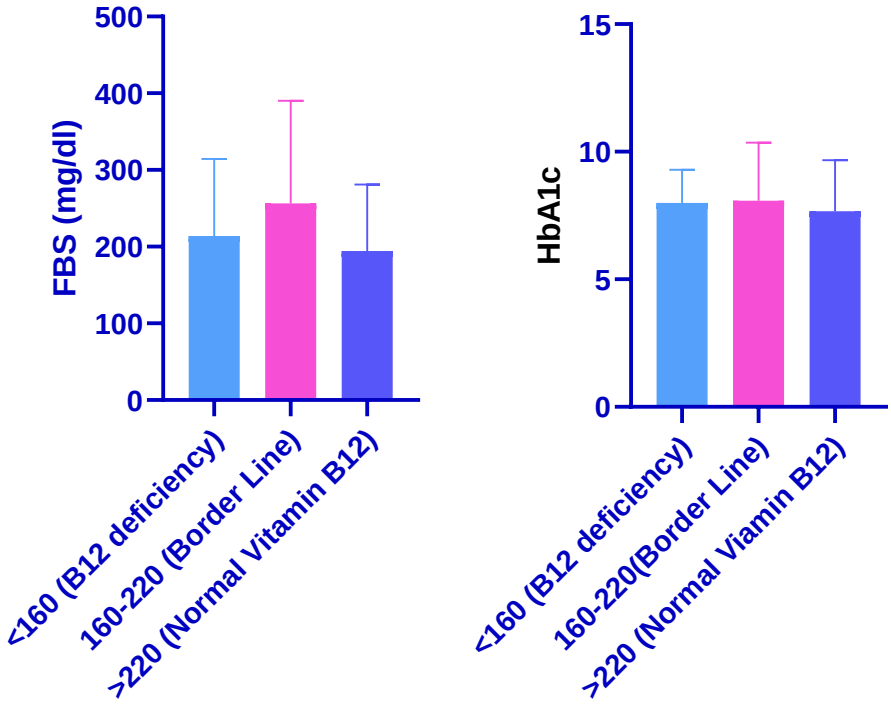

Figure (1): Level of Vitamin B_{12} in Serum according Fasting blood Sugar (FBS) and HbA1c

Table (3): Level of Serum Vitamin B_{12} according Fasting blood Sugar (FBS) and HbA1c

Serum Vitamin B_{12} level	FBS Mean±S.D	HbA1c Mean±S.D
<160 (B_{12} deficiency)	213.9±100.6	7.998±1.292
160-220(Border Line)	256.5±133.6	8.083±2.274
>220(Normal Vitamin B_{12})	194.5±86.52	7.671±1.991

Figure (2) shows the haematological parameters in T2DM patients with a level of serum vitamin B_{12} which aimed to establish the blood marker most responsive to changes in vitamin B_{12} concentration. Statistically, there is no significant difference between Hb, MCV, and MCH with serum vitamin B_{12} levels.

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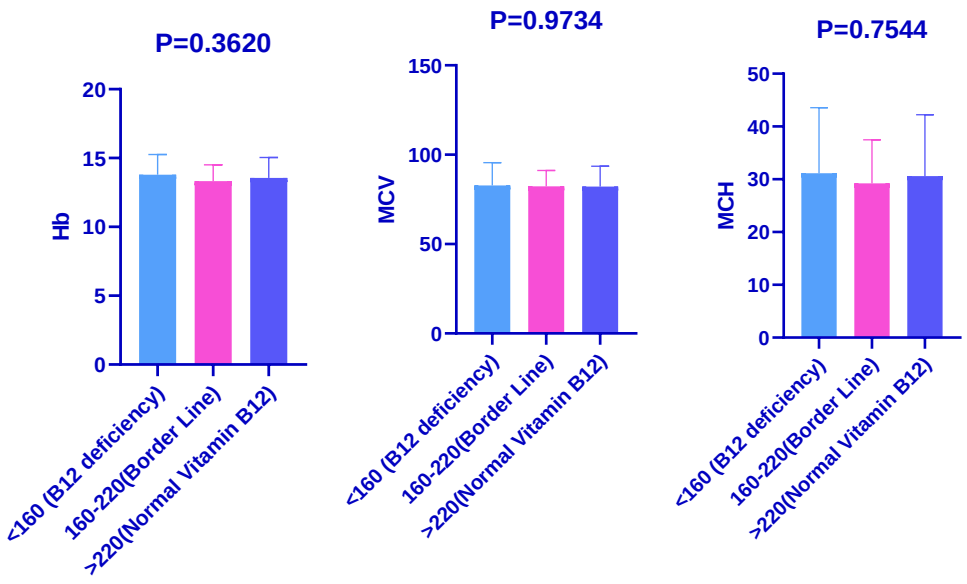

Figure (2): Level of Serum Vitamin B_{12} according Hemoglobin concentrations (Hb), Mean Corpuscular Volume (MCV) and Mean Corpuscular Hemoglobin (MCH)

Based on levels of serum vitamin B_{12}, all patients were separated into three groups during the duration of type $_2$ diabetic patients and metformin therapy, as indicated in Figure (3). Statistically, there is a significant difference between both groups ($p < 0.001$).

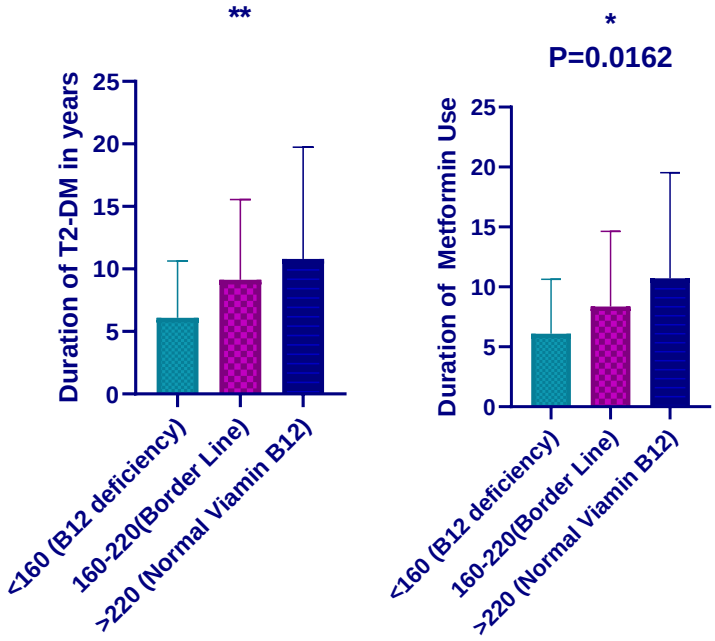

Figure (3): Level of Serum Vitamin B_{12} in Relation to Various Factors (T_2DM Duration and Metformin Usage time)

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Deficiency of vitamin B_{12} (<160 pg/mL) was higher significantly (p=0.0161) in users of metformin 37 (37%), as compared with other medication (glimepride tablets and insulin) 11 (11%), while normal vitamin B_{12} (>220 pg/mL) was higher in users of metformin 11 cases, as compared with other medication users 10 cases Table (4). Patients who used more than 1000 mg of metformin per day had a lower level of serum vitamin B_{12} than those who took less than 1000mg per day. According to Table (5), there is statistically a significant correlation between the dose of metformin and the range of serum vitamin B_{12} levels in our study.

Table (4): Serum Level of Vitamin B_{12} according Metformin and other Medication (glimepride tablets and insulin)

Level of Serum Vitamin B_{12}	Total Patients	Metformin (n= 75)	other O.H (n=25)	P value
<160 (B_{12} deficiency)	48 (48%)	37 (37%)	11 (11%)	0.0161
160-220 (Border Line)	31 (31%)	27 (27%)	4 (4%)	
220 (Normal Vitamin B_{12})	21 (21%)	11 (11%)	10 (10%)	

Table (5): Characteristics of Level Serum Vitamin B_{12} based on Metformin Dose

Serum Vitamin B_{12} level	Total	>1000mg/day (%)	<1000mg/day (%)	P value
<160 (B_{12} deficiency)	37	35 (46.67%)	2 (2.67%)	0.0009
160-220 (Border Line)	27	15 (20%)	12 (16%)	
220 (Normal Vitamin B_{12})	11	7 (9.33%)	4 (5.33%)	
Total	75	57 (76%)	18 (24%)	

Discussion

Out of 100 diabetic patients, the highest rate of serum vitamin B_{12} deficiency was found in females (70 cases) as compared with males (30 cases). These agreed with Yakubu *et al.*, [10] and Krishnan *et al*., [18], who revealed that the lowest rate was found in males at 59 (30.1%) and 79 (38.5%) as compared to 137 (69.1%) and 126 (61.5%) females, respectively [10, 18]. When compared to male diabetic patients' normal serum vitamin B_{12} levels (7%) in Table (1), female diabetic patients had the highest rate of vitamin B_{12} deficiency (34%). This agrees with Jeetendra *et al*., [16], who have shown that, in patients with T_2-DM, the level of serum vitamin B_{12} should be used as an initial screening technique for diagnosing deficiency of vitamin B_{12} [16]. Deficiency of vitamin B_{12} is usually indicated by concentrations of less than 200 pg/ml, but concentrations greater than 220 pg/mL indicate the absence of vitamin B_{12} deficiency. As well, Khan *et al*., [17] explain that the levels of vitamin B12 in the blood ranged from 122 to 2034pg/mL.[17]. Furthermore, concurrent intake of metformin, which lowers stomach acidity and plays a key role in vitamin B_{12} deficiency, and the parietal cells produce stomach acid, which is necessary for the absorption of vitamin B_{12} from dietary sources, causes the parietal cells to produce less acid [15, 19].

Patients' demographic data was used to detect potential vitamin B_{12} deficiency-related factors (age, weight, and BMI). There is no significant difference between levels of serum vitamin B_{12} with these factors. These

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agreed with Owhin *et al*., [2] and Krishnan *et al*., [18], which showed that, there was no significant relationship between age, sex, weight, height, and level of serum vitamin B_{12} insufficiency. In numerous observational studies, serum vitamin B_{12} insufficiency was found in 5.8% of T_2DM patients over 50 who received metformin for a median of 5 years, compared to 2.4% of T_2DM patients who did not receive the drug [1, 4, 10, 19]. Figure (1) showed that the level of serum vitamin B_{12} is unrelated to fasting blood sugar and glycosylated hemoglobin (HbA1c). Based on T_2DM, FBS and HbA1c were discovered (256.5±133.6) and (8.083±2.274), respectively in the border line of serum vitamin B_{12} Table (3). Keep in mind that HbA1c values are linked to blood glucose levels[20]. In our results, we discovered that HbA1c levels were not associated with vitamin B12 as compared with Zhao *et al.*, and Ko *et al*., [21, 22]. Metformin-induced vitamin B_{12} insufficiency in T_2DM patients has been associated with changes in small intestine motility, bacterial flora, competitive inhibition, sluggish vitamin B_{12} absorption, and alterations in intrinsic-factor levels. According to Carrizzo *et al*., [23] and Lata *et al*., [24], glycosylated hemoglobin levels in patients prescribed with metformin reduced mean HbA1c levels by 1.1%, and a comparison between low dose and high dose metformin. HbA1c levels were 0.3% lower with high dose therapy [23, 24]. The haematological parameters in T2DM patients with a level of serum vitamin B_{12} are shown in Figure (2). Alternatively, a deficiency of vitamin B_{12}, as measured by the level of serum vitamin B_{12}, had no effect on the hematological parameters. Previously, similar findings have been reported [25]. However, total level of serum vitamin B_{12} may not adequately reflect the body's Vitamin B12 status; therefore biochemical shortage may not always equate to clinical deficiency [10]. Changes in small intestine motility and increased bacterial overgrowth have been linked to metformin-induced B_{12} deficiency, as has metformin's interference with calcium-dependent intrinsic factor release [26]. The elevated incidence of anaemia in this group could be due to a number of reasons. One possible explanation is that our patients are older, as the prevalence of anemia has been found to be higher in older age groups. Our findings revealed that metformin therapy had a considerable impact on vitamin B_{12} levels in T_2DM patients [11, 27, 28].could indicate a dietary shortage or be the result of metformin use. As well, metformin duration was the most consistent risk factor for vitamin B12 deficiency [9, 13, 16]. According to mainstream recommendations, metformin is the first medicine of choice for T_2-DM. When there are contraindications to its usage or patients can't take it due to bad effects, physicians have a choice of additional classes of drugs to treat hyperglycemia linked with T_2DM. Each type of agent has its own set of advantages and risks. When choosing another to metformin, there are a number of factors such as overall efficacy in lowering HbA1c, adverse effect profile, cost, and patient preference. The number of factors that influence the decision-making process is often difficult to determine, and no single specific agent is ideal [29, 30]. On the other hand, Table (5) shows that patients who took more than 1000 mg of metformin per day had a lower level of

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serum vitamin B_{12} than those who took less than 1000 mg, as similar results have been discovered [1, 16, 30]. Although the specific mechanism of deficiency of vitamin B_{12} caused by a high dose of metformin is still unknown, in patients using high doses of metformin, we observed a stronger reduction of vitamin B_{12} absorption, which could lead to a rapid depletion of the liver's vitamin B_{12} storage [28].

Conclusions

Based on our current studies, we conclude that vitamin B_{12} is unrelated to gender, age, weight, or height. The HbA1c test provides accurate results and can be a useful tool in determining diabetes diagnosis, although it is unrelated to the level of serum vitamin B_{12}. Vitamin B_{12} deficiency is most common in patients with T_2DM who have been using metformin for a longer period of time and who are taking higher doses of metformin are taking higher doses of metformin.

Recommendations

Our data suggest the need for routine vitamin B_{12} monitoring in patients with type-2 diabetes, especially in metformin users with an average dose of over 1,000 mg per day.

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Ethical clearance: Ethical approval for this study was issued by the ethical committee of the Kurdistan higher counsel of medical specialist .

Conflict of interest: Nil

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تحديد انتشارنقص فيتامين B_{12} في مرضى السكري (النوع الثاني) اللذين يعالجون بالعقار ميتفورمين

ته لارمحمد رقيب حسام الدين [١] ، د. رنان قرداغ بولص [٢] ، د.نوشيروان صادق محمد [٣]

الملخص

خلفية الدراسة: يعتبر مرض السكري من النوع الثاني مشكلة صحية عامة شائعة في عملية التمثيل الغذائي. يزيد العلاج المستمر بالميتفورمين من مخاطر نقص فيتامين B_{12} وعواقبه الطبية على مرضى السكري من النوع الثاني.
اهداف الدراسة: للكشف عن انتشار نقص فيتامين B_{12} في الدم في مرضى السكري من النوع الثاني الذين تم علاجهم بالميتفورمين أو بدونه.
المرضى والطرائق: اشتملت الدراسة على ٢٠٠ حالة (١٠٠ مريض و ١٠٠ مجموعة ضابطة) استوفت المعايير الأساسية للدراسة. تم إجراء استبيان كامل وقياس لمستوى فيتامين B_{12} في الدم. يُعرَّف نقص فيتامين ب ١٢ بأنه <١٦٠ جزء من الغرام / مل في مصل الدم.
النتائج: تم التعرف على نقص فيتامين B_{12} في مصل الدم في ٤٨٪ من المرضى (العدد = ٤٨) ، بينما لم يكن لمستويات HbA1c أي تأثير على مستوى فيتامين B_{12} في المصل للمرضى المعالجين بالميتفورمين بجرعة ١ غم / يوم ، أظهر فرقًا كبيرًا مع هؤلاء المرضى الذين ليس لديهم تاريخ من استخدام الميتفورمين.
الاستنتاجات: يرتبط المستوى المنخفض من فيتامين B_{12} في مصل الدم بأستخدام دواء الميتفورمين لفترات اطول وجرعة اعلى.

الكلمات المفتاحية: مرض السكري نمط-٢ ، ميتفورمين عوز فيتامين ب ١٢ في المصل

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