

IMPACT OF METFORMIN AND HIS RELATIONSHIP WITH HBA1C, FBG AND VITAMIN B12 IN MALES AND FEMALES DURING THE DIFFERENT AGE GROUPS IN THE HUMAN BODY

اثر الميتفورمين وعلاقته مع الهيموغلوبين السكري التراكمي وسكر الدم الصائم وفيتامين ب12 لدى الذكور والإناث في فئات عمرية مختلفة في جسم الإنسان

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Abstract

Metformin is an oral anti-diabetic drug that been used for decades However, long-term treatment with metformin has been shown to reduce vitamin B12 (vit B12) levels and causes unpleasant side effects. Studies on the influence of the duration and prevalence of vit B12 deficiency among type 2 diabetic people are lacking. **The aim** of this study is to investigate the impact of using metformin on the serum levels of vit B12 and glycated hemoglobin (HBA1C) among Libyan patients with type 2 diabetes, and evaluate the relationship between vit B12 deficiency and metformin

use. **The result** shown the highest rate was in the age group from 31 - 40 and the lowest rate was In the age group ≤ 20 , The arithmetic mean values of HBA1C, FBG are high in the patient group and the values of Vitamin B12 are low compared to people with low HBA1C, FBG and normal Vitamin B12 level (control group), This indicates that there is an inverse relationship between high HbA1c levels and Vitamin B12 levels in diabetic patients who use metformin treatment. however, there was no significant difference between the mean of HBA1C values in the patient group compared to the control group at Statistical level ($P < 0.05$). **Our recommend** are conduct a more in-depth study of metformin and levels of both cumulative blood glucose and vitamin B12 in the body, and the relationship of metformin to pancreatic hormones such as glucagon, insulin, and blood glucose levels. And to expanding the study of this aspect and obtaining more samples in a longer period of time. **In conclusion** the results of this study showed that the highest rate was in the age group from 30 - 40 and the lowest rate was In the age group from ≤ 20 , the HBA1C rate in the patient group was higher than the control group, However, there was no significant difference between the mean of HBA1C values in the patient group compared to the control group at Statistical level ($P < 0.05$).

Keywords: Metformin, HBA1C, FBG, vit B12, Human body.

المخلص

الميتفورمين دواء فموي مضاد للسكري، يُستخدم منذ عقود. ومع ذلك، فقد ثبت أن العلاج طويل الأمد بالميتفورمين يُخفض مستويات فيتامين ب12 ويُسبب آثارًا جانبية غير مرغوب فيها. لا توجد دراسات كافية حول تأثير نقص فيتامين ب12 على مدة وانتشاره لدى مرضى السكري من النوع الثاني. تهدف هذه الدراسة إلى دراسة تأثير استخدام الميتفورمين على مستويات فيتامين ب12 والهيموغلوبين السكري التراكمي (HBA1C) وسكر الدم الصائم في مصل الدم لدى المرضى الليبيين المصابين بداء السكري التراكمي من النوع الثاني، وتقييم العلاقة بين نقص فيتامين ب12 واستخدام الميتفورمين. أظهرت النتيجة أن أعلى معدل كان في الفئة العمرية من 31 إلى 40 عامًا وكان أقل معدل في الفئة العمرية ≥ 20 عامًا، وكانت القيم المتوسطة الحسابية لـ HBA1C و FBG مرتفعة في مجموعة المرضى وقيم فيتامين B12 منخفضة مقارنة بالأشخاص الذين يعانون من انخفاض HBA1C و FBG ومستوى طبيعي لفيتامين B12 (مجموعة التحكم)، وهذا يشير إلى وجود علاقة عكسية بين مستويات HbA1c المرتفعة ومستويات فيتامين B12 في مرضى السكري الذين يستخدمون علاج الميتفورمين. ومع ذلك، لم يكن هناك فرق كبير بين متوسط قيم HBA1C في مجموعة المرضى مقارنة بالمجموعة الضابطة على المستوى الإحصائي ($P < 0.05$). نوصي بإجراء دراسة أكثر تعمقًا للميتفورمين ومستويات كل من الجلوكوز التراكمي في الدم وفيتامين B12 في الجسم، وعلاقة الميتفورمين بهرمونات البنكرياس مثل الجلوكاجون والأنسولين ومستويات الجلوكوز في الدم. وتوسيع

دراسة هذا الجانب والحصول على المزيد من العينات في فترة زمنية أطول. وفي الختام أظهرت نتائج هذه الدراسة أن أعلى معدل كان في الفئة العمرية من 30 - 40 وأقل معدل كان في الفئة العمرية من ≥ 20 ، وكان معدل الهيموغلوبين السكري HBA1C في مجموعة المرضى أعلى من مجموعة الضبط (مجموعة التحكم)، ومع ذلك لم يكن هناك فرق معنوي كبير بين متوسط قيم الهيموغلوبين السكري التراكمي (HBA1C) في مجموعة المرضى مقارنة بمجموعة الضبط عند المستوى الإحصائي ($P < 0.05$).

الكلمات المفتاحية : الميتفورمين, الهيموغلوبين السكري التراكمي, سكر الدم الصائم, فيتامين ب 12, جسم الانسان.

Introduction

Metformin is a drug used together with diet to lower high blood sugar levels in patients with type 2 diabetes mellitus (T2DM). Some studies have shown the metformin in some diabetic patients has long-term effects on vitamin B12 levels whether metformin is used alone or in combination with glibenclamide or in combination with mild. Some reports indicate that a deficiency in the level of vitamin B12 is accompanied by some nerve and blood disorders. Many other studies also indicate the importance of metformin in reducing blood sugar levels. This study was conducted on many patients to determine and determine the effect of metformin on vitamin B12, blood sugar levels, and cumulative blood sugar levels.

Problem statement:

Metformin-induced vitamin B12 deficiency can cause or exacerbate homeostatic and autonomic neuropathy and cardiomyopathy in a diabetic patient.

This is why it was necessary to conduct many studies to clarify all questions about the relationship between metformin and vitamin B12.

Objectives of study:

- This study aimed to determine the prevalence of vitamin B12 deficiency.
- To compare the benefits and harms of metformin and insulin versus insulin alone of patients with type 2 diabetes.

Materials and methods:

This work was carried out in three laboratories namely Al-Jouri laboratories, Al-Mukhtar laboratory, and Al-Ruya laboratory. 80 samples were targeted and divided into 40 healthy samples and 40 diseased samples for comparison. Their ages ranged from ≤ 20 to 85 years due to diabetes to study the effect of metformin treatment on vitamin B12 in the period from May to September 2024. After blood samples are taken from the patient, they are sent to the biochemistry laboratory.

Study area

This study was tried in the city of Tripoli, and targeted the Al-Jouri laboratories, Al-Mukhtar laboratory, and Al-Ruya laboratory

Time Limits

This study lasted for a period of five months, May to Sep. 2024, during which data were collected.

Materials and tools used:

In the biochemistry laboratory, a fully automatic Cobas e411 machine was used to monitor and analyze vitamin B12. 3 milliliters of blood were collected from each patient into a clot activator tube. Blood serum was used to analyze the level of vitamin B12. A sodium citrate tube was also used, and then the serum was obtained using a centrifuge at 3000 rpm for 5 minutes. The test was performed using an Integra 400 Plus device. To measure FBG and HBA1C levels. The normal range for vitamin B12 is (200-1100 pg/ml), the normal range for blood sugar is (95-120 mg/dL), and the normal range for HBA1C is (4.4-6.4%).

Fully automated Cobas e411 machine:

Electrochemical luminescence (ECL) technology is a method that generates electrochemical radiation in the form of light emission by an electrochemical reaction in solution resulting in the formation of an antigen-antibody complex; It is intended to identify quantitative and qualitative in vitro tests for a wide range of applications including markers of anemia, bone, cardiac, oncology, critical care, fertility hormones, maternity care, and infectious diseases.

Data and Statistical analysis:

Data were presented as percentages using Microsoft excel (2015), t-test was conducted statistically on the data for this research at a value ($P < 0.05$).

Results:

This study obtained samples from different age during the last five months from May to Sep 2024. This study included 80 samples (40 healthy and 40 diseased), 47 samples (59%) were females and 33 (41%) were males. We found that from 40 samples of patients the percentage of women is greater than that of men as shown in the (Figure 1, Figure 2) The result of this study was as follows:

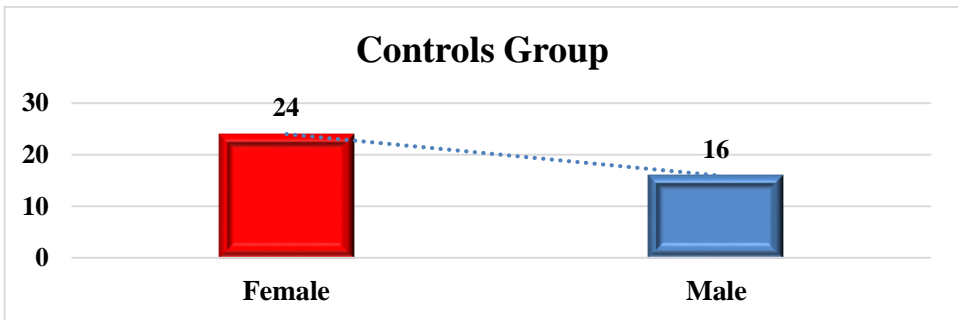


Figure (1): Comparison between Male and Female percentages in healthy people (Control Group).

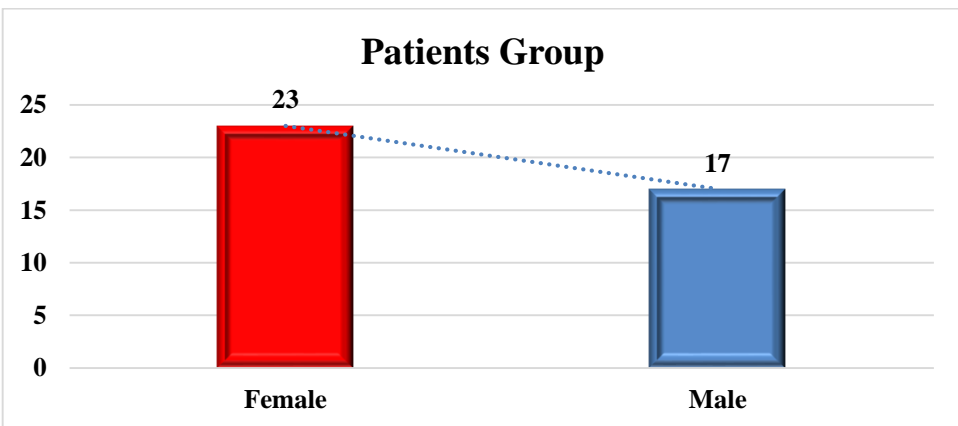


Figure (2): Comparison between Male and Female percentages in sick people

(Patients Group)

Table 1: the distribution of age in the study population: -

Ages	Frequency	Percent%
≤ 20	3	3.75%
21-30	9	11.25%
31-40	16	20%
41-50	14	17.50%
51-60	13	16.25%
61-70	13	16.25%
71-85	12	15%
Total	80	100%

The previous table shows that cases from 31 to 40 years old had a higher rate of 20%, while cases from ≤ 20 % years had a lower rate of only 3.75%. (Table1, Figure 2).

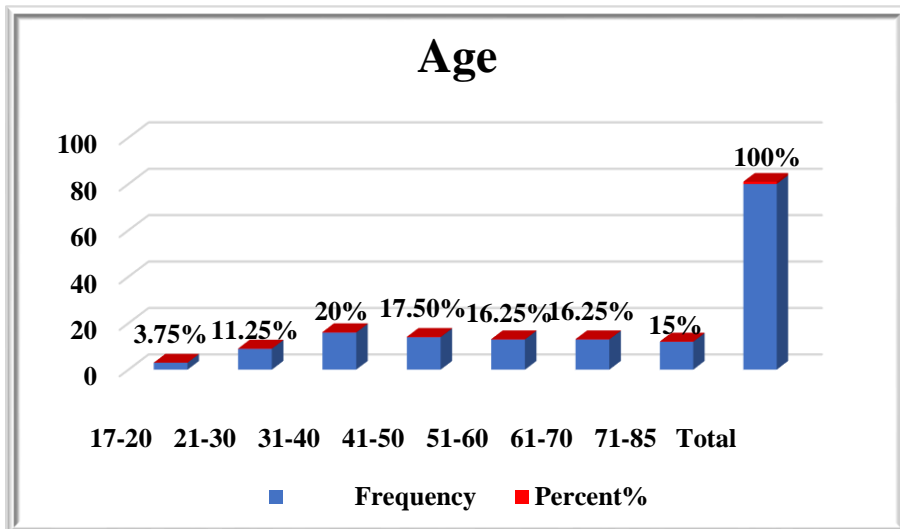


Figure (3): the distribution of age in the study population

Table 2: Statement of the number of samples, average, minimum, maximum, and standard deviation in the study samples.

Characteristic		N	Minimum	Maximum	Mean	Std.deviation
Control	HBA1C	40	4.5	6.6	5.04475	0.732995
	FBG	40	74	115	88.9675	11.9327
	Vitamin B12	40	293	701	503.035	97.63957
Patients	HBA1C	40	6.7	13.9	8.1525	1.782535
	FBG	40	126	503	274.8525	112.687
	Vitamin B12	40	123	300	214.975	67.78567

The arithmetic mean values of HBA1C, FBG are high in the patient group and the values of Vitamin B12 are low compared to people with low HBA1C, FBG and normal Vitamin B12 level (control group). This indicates that there is an inverse relationship between high HBA1C levels and Vitamin B12 levels in diabetic patients who use metformin treatment. As for HBA1C and FBG, the relationship was positive, as there was an increase in HBA1C and a rise in FBG in the patient group. The control group had lower levels of HBA1C and higher levels of Vitamin B12 as shown in the (Table 2).

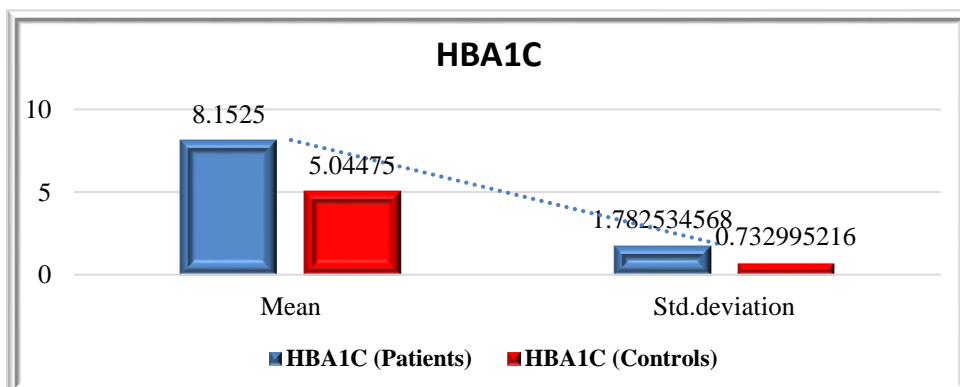


Figure (4): Correlation between HBA1C levels in samples.

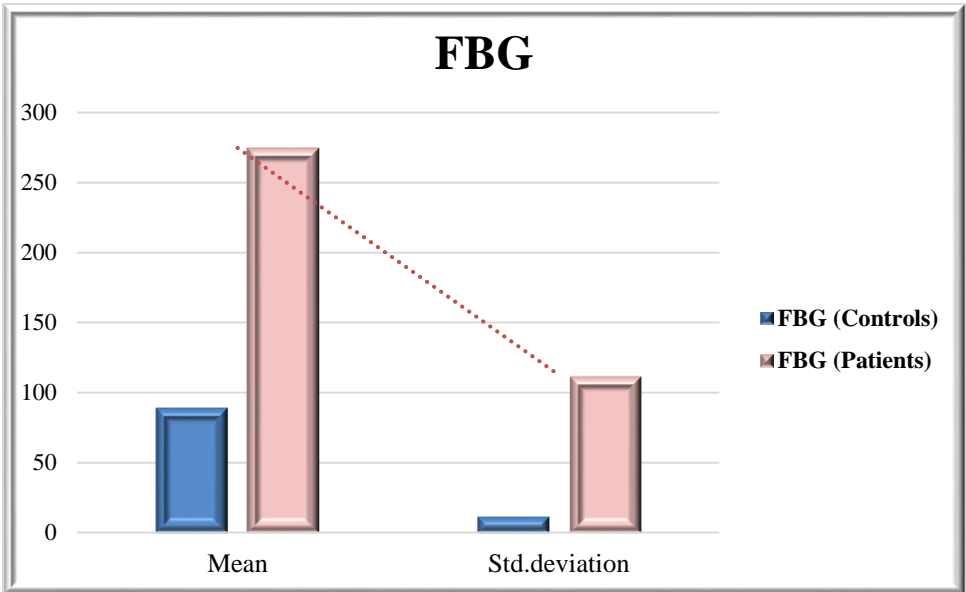


Figure (5): Correlation between FBG levels in samples.

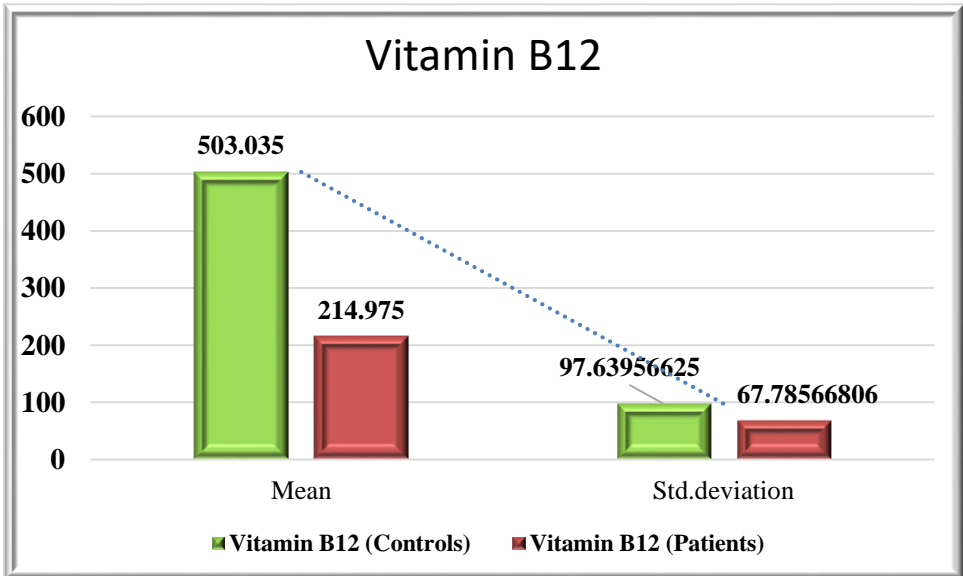


Figure (6): Correlation between Vitamin B12 levels in samples

Table (3): showing standard deviation, mean, T-test, and P- value.

	Mean	Std.deviation	T-Test	P-Value
HBA1C (Control, Patient)	6.598625	2.0685589	1.9908471	0.05
FBG (Control, Patient)	181.91	122.82816	1.6646246	0.02
Vitamin B12 (Control, Patient)	359.005	167.27822	1.6646246	0.03

To evaluate whether there was a potential difference between these values, the mean values between the non-diabetic control group and the diabetic patient group were compared statistically using an independent t-test. The results showed that HBA1C, FBG Vitamin B12 values were statistically significantly higher in the patient group compared to the diabetic group ($P < 0.05$). Which leads us to accept the hypothesis that there are statistically significant differences between people with diabetes and those who do not suffer from diabetes. However, there was no statistically significant difference between the mean HBA1C values in the patient group compared to the control group ($P < 0.05$).

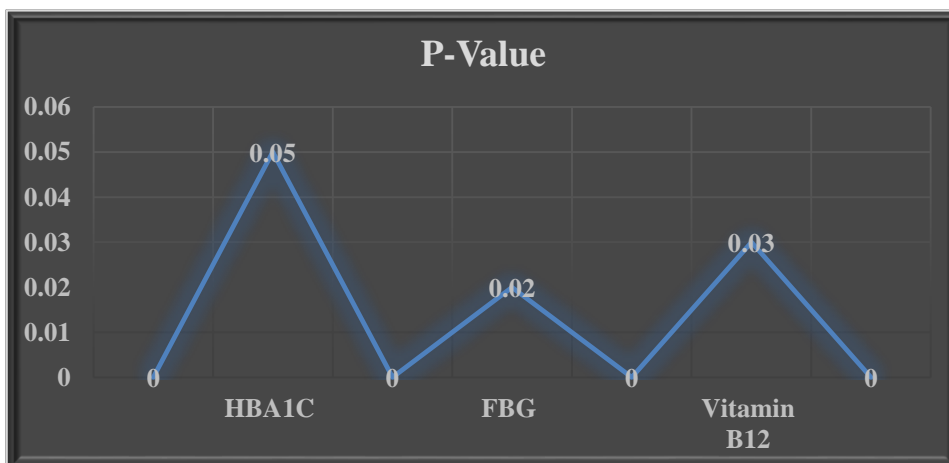


Figure (7): Correlation between HBA1C, FBG and Vitamin B12 level in samples.

Discussion

Metformin is a drug used together with diet to lower high blood sugar levels in patients with type 2 diabetes mellitus (T2DM). Metformin is usually the first medication given by the physician for patients with T2DM. Unfortunately, it has been reported that metformin is considered a risk factor for vit B12 deficiency in diabetes patients, American Diabetes Association. (2018). Sahar et al (2025) conducted the study on Impact of Metformin Therapy on Vitamin B12 Levels in Patients With Type 2 Diabetes Mellitus, The metformin significantly decreased vitamin B12 serum levels by 443.56 pg/mL versus the control group of 541.33 pg/mL ($p = 0.003$). The prevalence of patients with vitamin B12 deficiency under the metformin treatment was 23.84%. There was no significant difference in correlation between serum vitamin B12 levels and both doses of metformin and the duration of diabetes mellitus This is entirely consistent with the present study. Vitamin B12, also known as cobalamin, is a water-soluble vitamin that plays an essential role in DNA synthesis, optimal blood formation, and neurological function. Although this vitamin is present in many foods, Vitamin B12 deficiency is relatively common. This is usually due to poor dietary intake, malabsorption, or certain medical conditions, Fritz et al (2019). The deficiency of vit B12 can cause physical, neurological and psychological symptoms and is typically characteristic of hematology and neurocognitive dysfunction Oh and Brown (2003). Such as symptoms can develop slowly and can get worse over time until adversely affects health, causing anemia and neuropathy. Interestingly, metformin medicine can cause serum vit B12 deficiency.. It acts primarily by decreasing glucose synthesis in the liver and improving your body's sensitivity to insulin therefore make your body uses insulin more effectively. Despite metformin being an old medicine, it is still a good choice and the best for the treatment of type 2 diabetes Singh and Tushar (2016). HbA1c reverses previous average blood glucose levels from 8 to 12 weeks an HbA1c of more than 6.5% is recommended for the diagnosis of diabetes.HbA1c testing plays a key role in the management of diabetes, American Diabetes Association (2016). Guidelines on HbA1c testing frequency and treatment modifications aim at supporting the achievement of glycemic targets. However, low adherence to these recommendations among

adult patients with type 2 diabetes has been reported. Even when no clear explanation has been found as to why this is the case, the rapid availability of HbA1c testing results has been shown to facilitate diabetes management. In response to this, HbA1c testing at the point-of-care is currently increasing. T2DM is the most common type of diabetes affecting 90 to 95% of all people with diabetes. T2DM presents a combination of insulin resistance (a condition in which the body fails to properly use insulin) and reduced secretion of insulin, Tripathi and Srivastava (2006) . This type of diabetes is a prevalent global health problem and is on the rise, particularly in middle and low income countries, Cho et al (2018). It is one of four priority non-communicable diseases (NCDs) targeted for action worldwide, WHO (2021). Unexpectedly, the longer use of metformin can result in many unwanted side effects. For example, it leads to malabsorption of vit B12, thus increasing the risk of developing vit B12 deficiency Bauman et al (2000) and Ting et al (2006) Furthermore, the most common gastrointestinal side effects associated with metformin are diarrhea, heartburn, and nausea, followed by abdominal pain, bloating, and regurgitation , Nathan et al (2006) . In general, these side effects appear soon after the start of metformin treatment and disappear immediately after stopping, Miyan and Waris (2021). So both diabetic patients using metformin had lower levels of vitamin B12 than controls when they compared newly diagnosed religious patients with healthy .controls The decrease in vitamin B12 levels depends on time and dose, as the greatest risk of vitamin B12 deficiency is associated with long-term use and high doses, Tomkin et al 1971. The current study showed that The arithmetic mean values of HBA1C, FBG are high in the patient group and the values of Vitamin B12 are low compared to people with low HBA1C, FBG and normal Vitamin B12 level (control group). This indicates that there is an inverse relationship between high HbA1c levels and Vitamin B12 levels in diabetic patients who use metformin treatment. As for HBA1C and FBG, the relationship was positive, as there was an increase in HbA1c and a rise in FBG in the patient group. The control group had lower levels of HBA1C and higher levels of Vitamin B12 . on the other hand, Sayedali et al (2023) conducted the study titled Association between metformin and vitamin B12 deficiency in patients with type 2 diabetes there result showed that increasing

evidence of vitamin B12 deficiency among metformin-treated diabetic patients. Many studies have reported that vitamin B12 deficiency is related to the malabsorption of vitamin B12 among metformin-treated T2DM patients. Vitamin B12 deficiency may have a very bad complication for the T2DM patient, this is completely consistent with the results of the current study, as we noted previously in the results chapter.

Martono et al (2016) carried out the study on Predictors of HbA1c levels in patients initiating metformin, the cohort included 6050 patients initiating metformin. Baseline HbA1c at target consistently predicted better HbA1c outcomes. Longer diabetes duration and lower total cholesterol level at baseline were predictors for higher HbA1c levels at 6 months. At 18 months, cholesterol level was not a predictor. Longer diabetes duration was also associated with not achieving the target HbA1c at follow-up. The association for longer diabetes duration was especially seen in patients starting on low dose treatment. No consistent associations were found for comorbidity and comedication, this study is fully consistent with t This study is fully consistent with the current study.

Conclusion

In conclusion, It is clearly evident that metformin has a clear effect on the rate of blood glucose levels by reducing the rate of absorption in the small intestines. It also leads to a deficiency in the rate of vitamin B12. the results of this study showed that the highest rate was in the age group from 30 - 40 and the lowest rate was In the age group from ≤ 20 , the HBA1C rate in the patient group was higher than the control group, However, there was no significant difference between the mean of HBA1C values in the patient group compared to the control group at Statistical level ($P < 0.05$).

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