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Evaluation of Vitamin B12 for Diabetic Kidney Disease in Iraqi Patients

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ABSTRACT: Objective: In the US and across the world, diabetic kidney disease (DKD) is the primary cause of both chronic kidney disease (CKD) and end-stage renal disease (ESRD), impacting over 40% of those with type 2 diabetes and 30% of those with type 1 diabetes. Diabetic kidney disease (DKD) is categorised as a macrovascular consequence of diabetes. Research indicates that vitamin B12 deficiency is associated with DKD, whereas elevated vitamin B12 levels may be detrimental for individuals with CKD due to impaired cyanide metabolism.

Material and Method: In a controlled study involving 45 volunteers aged 40 to 75 years, participants were assigned to three groups: controls, diabetics not receiving B12 supplements, and diabetics receiving B12 supplements.

Result: Significant associations were observed between group classification and fasting blood sugar (FBS), HbA1c, duration of type 2 diabetes mellitus (T2DM), vitamin B12 levels, and age. However, increasing B12 levels did not significantly influence kidney function.

Conclusion: This outcome may be attributed to the absence of pronounced kidney dysfunction in most participants, the relatively short duration of diabetes, and the limited sample size. Larger studies are required to clarify the relationship between vitamin B12 status and acute kidney complications.

INTRODUCTION

Vitamin B12, also referred to as cobalamin [1,4], is a water-soluble [4,5]. Is the combination of the intrinsic component found in gastric juice and the extrinsic component acquired from food consumption that allows for absorption in the small intestine [2,3]? It is a nutrient of vital importance to human health: it functions as an essential cofactor for the enzyme methionine synthase and takes part in a number of biological reactions, such as DNA synthesis and the beta-oxidation of fatty acids, methylation, mitochondrial metabolism, and erythropoiesis [1,5]. Animal products, such as meat and dairy, are the only dietary sources of vitamin B12 since microbes are the only ones capable of synthesizing it [5]. Researchers have found a prescription version of cobalamin called cyanocobalamin in liver extracts [3].

Diabetes mellitus (DM) is the predominant endocrine metabolic condition, characterised by elevated fasting or postprandial plasma glucose levels beyond the upper limits during an oral glucose tolerance test or random plasma assessments, as delineated by the diagnostic criteria for DM [8]. Exposure to these disorders results in numerous metabolic diseases characterised by hyperglycemia, and prolonged exposure promotes the production of free radicals and advanced glycation end products, which can cause injury to various organs including the heart, kidneys, eyes, neurones, and blood vessels. [9,10]. Additionally, these disorders predominantly impact tissues such as adipose tissue, skeletal musculature, and the liver as a result of insulin resistance [6]. T1DM, T2DM, gestational diabetes, and other less common types are all included in the classifications of diabetes mellitus [7,10_12]. T2DM is a widespread worldwide health concern that is steadily becoming more common [11].

DKD continues to be the leading cause of end-stage renal disease (ESRD) in the United States and in most other countries. In recent years, the spectrum of DKD has undergone evolution [13,14]. DKD is the main reason for CKD and ESRD. It is recognized as a macrovascular consequence of diabetes mellitus, affecting 40% of those with T2DM and 30% of those with T1DM. Clinically, DKD is characterized by persistent albuminuria, hypertension, and a gradual reduction in glomerular filtration rate (GFR). During the course of DKD, several biochemical and metabolic changes transpire. Previous literature has associated vitamin B12 deficiency with the development of chronic diabetic complications such as DKD. A further research conducted in North India revealed reduced levels of Vitamin B12 in individuals with DKD [14]. It is important to note that large dosages of B12 might be harmful to those who have chronic kidney disease (CKD). This is about how cyanide is broken down in the body, which doesn't work well in people with CKD since their glomerular filtration is lower. The most popular kind of vitamin B12 supplement, cyanocobalamin, is broken down into the active methylcobalamin and releases trace quantities of cyanide. Under normal conditions, cyanide and methylcobalamin combine to form cyanocobalamin. Reduced cyanide clearance in CKD patients prevents cyanocobalamin from changing into its active form, which reduces its ability to lower Hcy levels. Moreover, excessive cyanocobalamin supplementation may liberate cyanide ions that are insufficiently eliminated, hence exacerbating difficulties in individuals with CKD [1]. Consequently, this study was undertaken to ascertain the dosage of therapeutic vitamin B12 supplementation and its impact on DKD.

MATERIALS AND METHODS

A controlled study was conducted on a number of volunteers; the study sample collection period was from 1-3-2024 to 1-5-2024. The study included 45 volunteers, aged between (40_75) years, samples were collected from outpatient clinics after ensuring that they were granted a clinic opening license by the Iraqi Ministry of Health.

The appropriate sampling method was adopted during the selection of cases. People who didn't want to give blood samples were not required to. Mothers who were pregnant or breastfeeding were not included. The study sample was divided into three groups: a control sample, a sample of volunteers with diabetes who were not treated with vitamin B12 supplements as a patient sample, and the last group of volunteers with diabetes who were treated with vitamin B12 supplements as a patient sample as well.

After collecting detailed demographic characteristics of all participants (age, gender, duration of diabetes, weight, height), and then conducting a clinical examination. Weight was calculated with a standardized weighing machine measuring in kilograms; while height was measured with a wall-mounted length ruler. Then we calculated the body mass index (BMI) in units of kg/m^2 , where kg represents weight in kilograms, and m^2 means height in square meters.

Then, venous blood samples were collected from all volunteers using a needle used in laboratory withdrawal under sterile conditions and sent to the Biochemistry Department of the Medical Laboratory to measure each of the fasting blood sugar (FBS), vitamin B12, B.urea, S.Creatinine, Serum uric acid (S.uric acid) in serum and glycated hemoglobin (HbA_{1c} %) analysis in whole blood.

Spectrophotometry technique at wavelength [500-510 nm] was used to measure the levels of each of the FBS, B.urea, S.Creatinine and S.uric acid, and the principle of HPLC was used to perform the HbA_{1c} %, and AIA-Immunoassay technique was used to perform the vitamin B12 test.

The normal reference ranges for all tests were adopted as mentioned in Table (1):

Table 1 The normal reference ranges for all tests

The Tests	Normal Reference Ranges
Body Mass Index [BMI]	Underweight: - Below 18.5 Normal: 18.5 – 24.9 Overweight: 25.0 – 29.9 Obese: 30.0 and above Obese class I: 30.00 - 34.99 Obese class II: 35.00 - 39.99 Obese class III: ≥ 40.00 [15,16]
Fasting Blood Sugar [FBS]	Normal: 70 - 100 mg/dL Prediabetes: 100 - 125 mg/dL Hypoglycemia: ≥ 126 mg/dL [17]
Glycated Hemoglobin [HbA _{1c} %]	Normal: ≤ 6.0 % Prediabetes: 6.0 % - 6.4 % Hypoglycemia: ≥ 6.5 % [18]
Vitamin B12	160_ 950 pg/mL or 118_ 701 pmol/L [19]
Blood Urea (B.urea)	15 _ 40 mg/dL [20]
Serum Creatinine (S.Creatinine)	For men: 0.7_1.3 mg/dL or 61.9 _ 114.9 μ mol/L For women: 0.6 _ 1.1 mg/dL or 53_ 97.2 μ mol/L [21]
Serum Uric Acid (S.Uric Acid)	For men: 3.5 _ 7.2 mg/dL For women: 2.6 _ 6.0 mg/dL [22]

Subsequently, SPSS v26, was used to statistically contrast the groups' biochemical and clinical data, analyze the data, and obtain the findings. Descriptive statistics were employed to calculate the mean and standard error (SE). Since the variables follow a normal distribution, one-way analysis of variance was employed to examine the differences among groups. Correlation analysis was employed to assess the extent of the association between the biochemical assays. The statistical difference was deemed statistically significant at a threshold of ($P \leq 0.05$).

RESULTS

This study included 45 volunteers and they were divided into three groups as follows: 15 volunteers without diabetes were taken as a control sample, and 15 people with T2DM and without vitamin B12 treatment were taken as patient group 1. In addition, 15 volunteers with T2DM and within vitamin B12 treatment were taken as patient group 2. For the demographic distribution (Gender, Age, the Duration of T2DM, and Body Mass Index (BMI)) of the results presented in Table 2 and Figure1, one-way ANOVA analysis of variance statistic was used to determine the distribution of the studied groups.

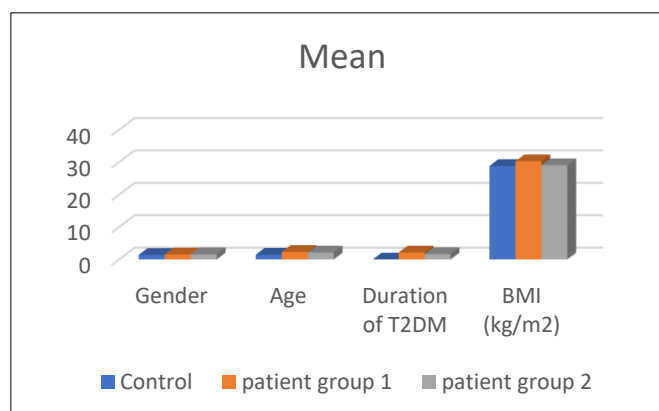
Table 2 The demographic distribution and three groups

Demographics	Control	Patient Group 1	Patient Group 2	P-Value
Gender (M or F) (Mean$\pm$SE)	1.40 $\pm$ 0.131	1.60 $\pm$ 0.131	1.53 $\pm$ 0.133	0.555
Age (Y) (Mean$\pm$SE)	1.467 $\pm$ 0.236 a b	2.133 $\pm$ 0.236 a	2.333 $\pm$ 0.232 b	0.032*
Duration of T2DM (Y) (Mean$\pm$SE)	0.000 $\pm$ 0.000 a b	1.667 $\pm$ 0.211 a	2.133 $\pm$ 0.215 b	0.000**

BMI (Kg/m²) (Mean±SE)	28.826±1.008	29.055±1.330	30.288±1.354	0.672
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Not: - Means denoted by various letters are significantly different at the $p \leq 0.05$ level; *: Significant at the $p \leq 0.05$ level; **: Highly significant at the $p \leq 0.01$ level; a: Indicates a significant difference between Control and Group 1; b: Indicates a significant difference between Control and Group 2. M: Male; F: Female; SE: Standard Error; Y: Year; T2DM: Type 2 Diabetes Mellitus.

Figure 1 The demographic distribution (Mean) and three groups



The gender mean $\pm$ SE of the control group was 1.40 ± 0.131 , for-patient group 1 was 1.60 ± 0.131 , and for-patient group 2 was 1.53 ± 0.133 , which was not statistically significant. As for the mean age $\pm$ SE, the results were statistically significant, as it was 1.467 ± 0.236 a b for the control group, 2.133 ± 0.236 a for-patient group 1, and 2.333 ± 0.232 b for-patient group 2. As for the duration of T2DM, the results were highly statistically significant, as the results of the control group for the mean $\pm$ SE were 0.000 ± 0.000 a b for-patient group 1, 1.667 ± 0.211 a for-patient group 2, and 2.133 ± 0.215 b. The results of the mean $\pm$ SE for the BMI for the control group were 28.826 ± 1.008 , for-patient group 1 was 29.055 ± 1.330 , and 30.288 ± 1.354 for-patient group 2. The results were not statistically significant.

As for the results of the parameters FBS and HbA1c%, they are presented in Table 3 and illustrated in Figure 2.

Table 3 The parameters (FBS, HbA1c%) and three groups

Parameters	Control	Patient Group 1	Patient Group 2	P-Value
FBS mg/dL (Mean±SE)	110.040±2.622 a b	206.827±14.379 a	231.060±15.445 b	0.000**
HbA1c % (Mean±SE)	5.480±0.097 a b	8.720±0.495 a	9.700±0.540 b	0.000**

Not: - Means denoted by various letters are significantly different at the $p \leq 0.05$ level; *: Significant at the $p \leq 0.05$ level; **: Highly significant at the $p \leq 0.01$ level; a: Demonstrate a substantial difference between Control and Group 1; b: Demonstrate a significant difference between Control and Group 2; SE: Standard Error; FBS: Fasting Blood Sugar; HbA1c %: Glycated Hemoglobin Percentage.

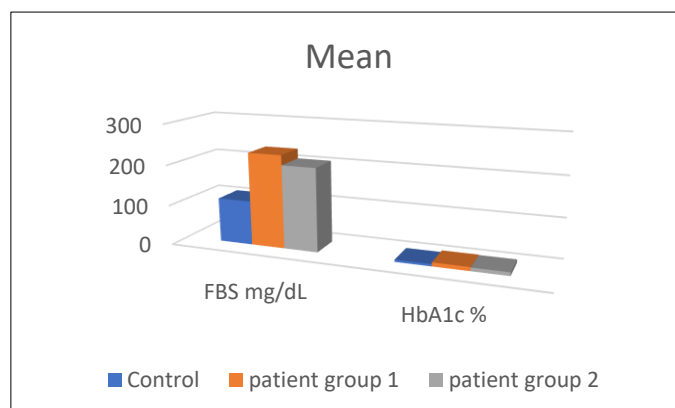


Figure 2 The parameters (FBS, HbA1c) and three groups

The mean $\pm$ SE of the FBS test for the control group was 110.040 ± 2.622 a b, for-patient group 1 it was 206.827 ± 14.379 a, and for-patient group 2 it was 231.060 ± 15.445 b. The results were highly statistically significant, and the same was true for the HbA1c% test. The results of the control group were 5.480 ± 0.097 a b, and the results of patient group 1 were 8.720 ± 0.495 a, followed by the results of patient group 2 which were 9.700 ± 0.540 b.

After conducting vitamin B12 tests, we obtained the results of the mean $\pm$ SE for the three groups: the control group, the patient group 1, and the patient group 2, as follows: 514.867 ± 79.024 b, 434.133 ± 72.998 c, 907.933 ± 125.925 b c. The results were highly statistically significant, as shown in Table 4 and Figure 3.

Table 4 The vitamin B12 and three groups

Parameters	Control	Patient Group 1	Patient Group 2	P-Value
Vitamin B12 (pg/mL) (Mean $\pm$ SE)	514.867 ± 79.024 b	434.133 ± 72.998 c	907.933 ± 125.925 b c	0.002**

Not: - Means denoted by distinct letters are significantly different at the $p \leq 0.05$ level; *: Significant at the $p \leq 0.05$ level; **: Highly significant at the $p \leq 0.01$ level; a: Indicates a significant difference between Control and Group 1; b: Indicates a significant difference between Control and Group 2; Standard Error.

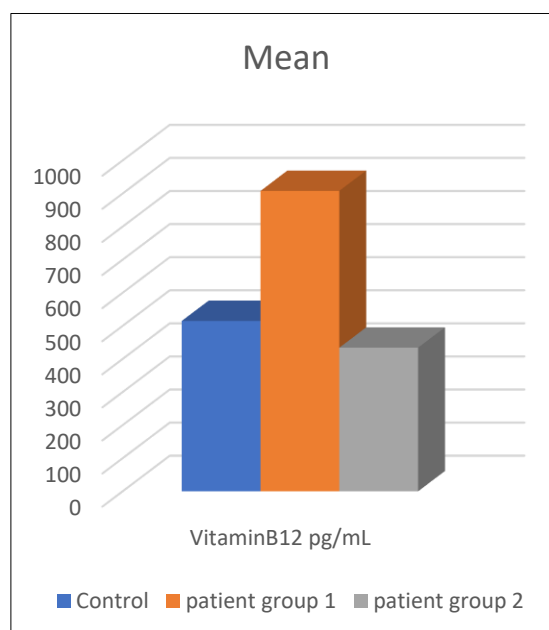


Figure 3 The vitamin B12 and three groups

As for the kidney function tests (B.urea, S.Creatinine and S.uric acid), the results of the mean $\pm$ SE for the three groups, the control group, patient group 1, and patient group 2, were as shown in Table 5 and Figure 4. The results of B.urea were as mentioned in the groups sequence (28.813 $\pm$ 1.865, 37.260 $\pm$ 5.933, 40.280 $\pm$ 3.606) and as for the results of S.Creatinine they were (0.893 $\pm$ 0.072, 0.999 $\pm$ 0.126, 1.147 $\pm$ 0.092) and the results of S.uric acid were (4.767 $\pm$ 0.331, 5.073 $\pm$ 0.672, 5.173 $\pm$ 0.432) and all the results were not statistically significant.

Table 5 The kidney function tests and three groups

Parameters	Control	Patient Group 1	Patient Group 2	P-Value
B.urea (mg/dL) (Mean $\pm$ SE)	28.813 $\pm$ 1.865	37.260 $\pm$ 5.933	40.280 $\pm$ 3.606	0.141
S.Creatinine (mg/dL) (Mean $\pm$ SE)	0.893 $\pm$ 0.072	0.999 $\pm$ 0.126	1.147 $\pm$ 0.092	0.204
S Uric Acid (mg/dL) (Mean $\pm$ SE)	4.767 $\pm$ 0.331	5.073 $\pm$ 0.672	5.173 $\pm$ 0.432	0.836

Not: - Means with a different letter are significant different at $p \leq 0.05$ level; *: Significant at $p \leq 0.05$ level; **: Highly Significant at $p \leq 0.01$ level; SE: Stander Error.

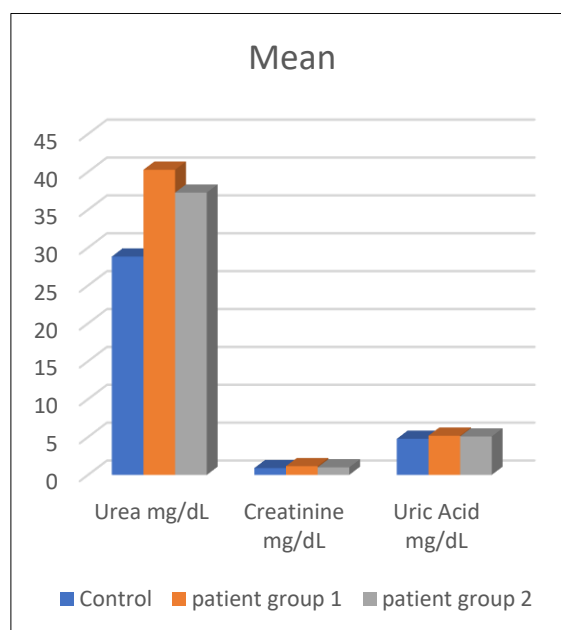


Figure 4 The kidney function tests and three groups

The Pearson correlation was utilized to measure the linear correlation between three groups, the result was presented in the table 6.

Table 6 The Pearson correlation results between three groups

Correlation		Group	Gander	Age	Duration of T2DM	BMI (kg/m2)	FBS mg/dL	HbA1c %	Vitamin B12 pg/mL	Urea mg/dL	Creatinin e mg/dL	Uric Acid mg/dL
Group	r	1	0.109	0.371*	0.775**	0.127	0.710**	0.715**	0.388**	0.288	0.269	0.088
	p		0.476	0.012	0.000	0.404	0.000	0.000	0.008	0.055	0.074	0.563
Gander	r		1	0.024	0.074	0.004	0.199	0.175	0.016	-0.030	-0.300*	-0.277
	p			0.877	0.630	0.979	0.191	0.251	0.918	0.846	0.046	0.065

Age	r			1	0.399**	0.068	0.236	0.226	0.289	0.085	0.019	0.026
	p				0.007	0.656	0.118	0.136	0.055	0.580	0.902	0.865
Duration of T2DM	r				1	-0.133	0.724**	0.723**	0.199	0.103	0.098	0.109
	p					0.385	0.000	0.000	0.189	0.501	0.520	0.475
BMI (kg/m ²)	r					1	0.027	0.051	-0.092	0.273	0.231	0.314*
	p						0.863	0.739	0.547	0.069	0.127	0.036
FBS mg/dL	r						1	0.996**	0.243	0.093	0.012	0.097
	p							0.000	0.107	0.545	0.939	0.526
HbA1c %	r							1	0.246	0.101	0.016	0.074
	p								0.103	0.509	0.919	0.629
Vitamin B12 pg/mL	r								1	0.132	0.147	0.073
	p									0.388	0.336	0.632
Urea mg/dL	r									1	0.697**	0.795**
	p										0.000	0.000
Creatinine mg/dL	r										1	0.775**
	p											0.000
Uric Acid mg/dL	r											1
	p											
*Correlation is significant at the 0.05 level.												
**Correlation is significant at the 0.01 level.												

Considering the results of Table 6, at the significance level of $P \leq 0.05$, a high positive correlation was found between the groups and each of Duration of T2DM, FBS, HbA1c, Vitamin B12 and the results were as follows: 0.775, 0.710, 0.715, 0.388. Also, a high positive correlation was found between age and Duration of T2DM and it was 0.399. Also, between Duration of T2DM and FBS, HbA1c and the results appeared respectively 0.724 and 0.723. In addition to the high positive correlation between FBS and HbA1c which is 0.996. The last results that appeared with a high positive correlation were between kidney functions urea with creatinine and uric acid and creatinine and uric acid and the results were respectively 0.697, 0.795, 0.775. There were positive correlations between group type and age and between BMI and uric acid, with results of 0.371, 0.314. While there was a negative correlation between gender and creatinine -0.300.

DISCUSSION

Diabetes significantly contributes to global morbidity and death, and despite extensive knowledge and several treatment choices, it remains challenging to manage well. It has been demonstrated that diabetes is associated with disturbances in vitamin B12 metabolic processes. A deficiency of vitamin B12 has been recognized as a contributing factor in the advancement of diabetes. Numerous research have been undertaken in recent years to investigate the correlation between diabetes, nephropathy, and vitamin B12 insufficiency [9]. This study investigates the relationship between vitamin B12 levels in diabetic people, including those with and without renal illness.

This study investigated the amount of vitamin B12 supplements taken and their effects on diabetic kidney disease patients in a sample of Iraqi society. It concluded that there is an association between aging and diabetes, which results in complications such as heart disease, memory loss, kidney disease, and others. Chronic kidney disease (CKD) resulting from type 2 diabetes is the primary factor exacerbating the CKD burden over recent decades, and it is the sole aetiology of CKD that exhibited a notable rise in disability-adjusted life years (DALYs), increasing by 9.5% (95% uncertainty interval [UI] 4.3-13.7) from 1990 to 2017. This phenomenon may be partially attributed to the rising incidence of diabetes linked to demographic ageing, urbanisation, industrialisation, dietary shifts, obesity epidemics, and reduced physical activity levels. Nonetheless, the worldwide significance of chronic kidney disease (CKD) resulting from type 2 diabetes has not been well acknowledged [24_26]. A separate research revealed that all assessed rates of chronic type 2 diabetes escalated with age, indicating the cumulative impact of age-associated risk factors. The ageing response rate among type 1 diabetic patients has risen globally, with sex hormones significantly influencing the progression of diabetes and renal problems [27].

This research identified a statistically significant correlation between fasting blood sugar levels and the duration of type 2 diabetes mellitus. According to a study, the association's strength lies in the fact that one of the most prevalent and serious long-term sequelae of diabetes mellitus (DM) is diabetic kidney disease (DKD), which is characterised as chronic kidney disease (CKD) in individuals with DM. Approximately 20–50% of those with type 2 diabetes mellitus may ultimately develop diabetic kidney disease. Diabetic kidney disease (DKD) is the leading cause of chronic kidney disease (CKD) and end-stage renal disease worldwide, accounting for 50% of cases. Moreover, DKD results in elevated rates of cardiovascular morbidity and death, and diminishes patients' health-related quality of life [28].

Our study also found a statistically significant relationship between FBS, HbA1c and DKD, as they are among the most important tests used to detect DM or know the blood sugar levels in the body, as these tests are used in the diagnosis and management of diabetic patients, so it would be scientific and logical to measure HbA1c and FBS together, and many studies have addressed this axis [29]. A separate research shown that the prompt recognition of impending problems, such as nephropathy in diabetic individuals, may significantly reduce the prevalence of the condition. FBS and HbA1c levels in diabetic individuals may considerably forecast renal function deterioration prior to changes in blood creatinine levels. Consistent monitoring of HbA1c levels and adjusting the treatment approach appropriately may postpone the onset of diabetic nephropathy [30].

This study noted a highly significant relationship between vitamin B12 and the classified groups, indicating an improvement in vitamin B12 levels in diabetic patients taking vitamin B12 supplements, as we notice an increase in its absorption and an increase in its levels in the body, as vitamin B12 is a water-soluble vitamin, and it is one of the vitamins that are important for normal cell functions as well as the growth and development of the human body. As a result, vitamin deficiency may cause serious health problems. It has been reported that vitamins play important roles in the diagnosis of CKD. High blood homocysteine (hHcy) levels were very common and closely associated with deterioration of kidney function in patients with CKD. While vitamins B9 and B12 regulate the metabolism of homocysteine (Hcy) and reduce the chances of developing CKD by 83% [31]. Another study noted that despite the normal total vitamin B12. Consequently, functional vitamin B12 insufficiency may arise in individuals with chronic kidney disease (CKD) due to heightened excretion of transcobalamin II (TC2), a key intestinal transport protein for vitamin B12, reduced reabsorption of TC2 in the proximal tubule, and diminished cellular uptake of TC2. Elevated amounts of vitamin B12 may be detrimental to patients with chronic kidney disease (CKD). This pertains to cyanide metabolism, which is impaired in persons with chronic kidney disease owing to diminished glomerular filtration. Cyanocobalamin, the predominant form of vitamin B12 supplementation, is converted to the active methylcobalamin, leading to the production of trace quantities of cyanide. In typical conditions, methylcobalamin interacts with cyanide and transforms it into cyanocobalamin. In individuals with chronic kidney disease (CKD), impaired cyanide clearance hinders the conversion of cyanocobalamin to its active form, rendering supplementation in this form less efficient in lowering homocysteine (Hcy) levels. Moreover, excessive cyanocobalamin supplementation might generate cyanide ions that are not eliminated, thereby exacerbating difficulties in people with chronic kidney disease, such as uremic neuropathy. A research derived from another investigation analysed the efficacy of folic acid and vitamin B12 in lowering homocysteine levels in vascular disease (HOPE-2) and concluded that high-dose vitamin B12 supplementation had no impact on renal impairment. Nevertheless, the average blood vitamin B12 level in the supplement group remained within the normal range. The research indicated that the average blood vitamin B12 concentration in the acute kidney injury (AKI) cohort was 2000 pg/ml, suggesting a correlation between vitamin B12 toxicity and the onset of renal damage. While the mechanism behind acute renal failure in diabetic kidneys is not

fully understood, several studies indicate that these kidneys exhibit inadequate restoration of renal perfusion after ischaemia. Nonetheless, other research has shown that heightened proximal tubular cell mortality and postponed reperfusion in the cortex may be contributing factors to renal reperfusion damage resulting from ischaemia in diabetic kidneys [32].

Our research has many limitations. Initially, despite the equilibrium between the diabetic group receiving no vitamin B12 treatment and the diabetic group receiving vitamin B12 supplementation, potential concealed biases may exist owing to the retroactive nature of the research design. The mechanism linking high blood vitamin B12 to acute renal damage in diabetes individuals is yet unidentified. Vitamin B12 is associated with systemic inflammation; nevertheless, further study is necessary to clarify the specific processes by which vitamin B12 affects kidney injury. Further research on vitamin B12 toxicity in the renal system is necessary. This investigation was performed at a single centre. Future multicenter studies with substantial sample sizes should be undertaken to reduce possible biases and confounding variables.

CONCLUSION

To our knowledge, diabetic patients who were taking vitamin B12 supplements and those who were not taking vitamin B12 supplements were evaluated in patients with diabetic kidney disease, where an improvement in vitamin B12 levels was observed, although there was no clear effect on kidney function. This has several explanations, including that most of the volunteers did not have clear kidney dysfunction, and the second explanation is that the period of diabetes was not such that the complications that appeared on the volunteers were severe. The last explanation is that high and low vitamin B12 levels that lead to acute kidney problems are under study and require a larger and more comprehensive study sample. Despite the emergence of clear and high evidence in the study about the relationship between diabetes and advancing age, the period of infection, and the complications that appear and their development, one of these complications is diabetic kidney disease and the emergence of a strong relationship between kidney function tests and the evidence they provide about the onset of kidney injuries.

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