FULL PAPER

Evaluation of vitamin B12 and methylmalonic acid levels as markers with neuropathy in patients of type 2 diabetes mellitus

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Many case reports have previously emerged revealing that vitamin B12 deficiency can create an insidious neuropathy that, if left untreated, can lead to the poor glycemic control in patients with type 2 diabetic mellitus (T2DM). To evaluate vitamin B12 and methylmalonic acid levels as markers with neuropathy in patients with type 2 diabetes mellitus. This study included (100) volunteers aged (40-80) years, who were divided into three groups: (40) non-diabetic volunteers as a control group, (30) patients with type 2 diabetes without vitamin B12 treatment, (30) patients with type 2 diabetes within vitamin B12 treatment. A questionnaire was filled out by volunteers, which included age, body mass (BMI) and symptoms of neuropathy. Serum was taken for chemical tests and blood samples for HbA_{1C} analysis. Data analysis was performed statistically by descriptive statistics, one-way ANOVA, and Chi-square. Significant difference was selected at the statistical level ($P \leq 0.05$). There was a large statistically significant difference between the three groups of age, fasting blood sugar (FBS), HbA_{1C}, vitamin B12, and there was a no statistically significant difference between the three groups of body mass indexes (BMI) and methylmalonic acid (MMA) for patients of type 2 diabetes mellitus (T2DM). Further a difference was observed in the percentages of symptoms. The association was found between age and forget to speak symptom (p= 0.001), at the level of significance ($P \leq 0.05$). By studying the symptoms of neuropathy, it turned out that when type 2 diabetes mellitus (T2DM) develops, many complications appear, including neuropathy. Likewise, when performing a vitamin B12 level test, it is best to have a confirmatory test such as a methylmalonic acid (MMA) test to confirm changes in vitamin B12 levels. The study found that there is a relationship between age and symptoms of forgetting to speak as neuropathy symptoms.

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KEYWORDS

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Introduction

Diabetes mellitus (DM) is a global health issue which is becoming increasingly prevalent. In (2000), an estimated (171) million individuals were afflicted by DM globally; by (2011), that number had risen to more than (366) million, with the number anticipated to rise to more than (552) million by (2030) [1]. It is a multifactorial metabolic illness characterized by persistent hyperglycemia and other metabolic abnormalities caused by deficiencies in insulin synthesis, insulin action, or both [2]. There are three primary kinds of DM; type 1 diabetes mellitus (T1DM) or famous as Insulin dependent diabetes mellitus

(IDDM), type 2 diabetes mellitus (T2DM) or famous as noninsulin dependent diabetes mellitus (NIDDM), and gestational diabetes mellitus (GDM) [1-4].

Type 2 diabetes mellitus (T2DM) is a condition of the chronic metabolic whose incidence has been continuously growing across the world. T2DM is the most common kind of DM, accounting for at nearly (90%) of all instances of the disease. T2DM is intricately connected to the genetics and shifts to a Western lifestyle (high food and low physical activity) [3]. Insulin sensitivity is a symptom of T2DM, which is caused by insulin resistance, decreased insulin production, and eventual pancreatic beta cell (β-cell) loss. As a result, glucose transport into the liver and fat cells and muscle cells is reduced. Hyperglycemia is caused by decrease insulin levels and increased in insulin resistance. [4].

This illness can have serious and deadly consequences. Vascular problems can occur as a result of a vascular damage caused by a high glucose level, which can lead to abnormalities of the major and small blood vessels. Microvascular issues result in neuropathy, retinopathy, and other difficulties, whereas complications of major vascular result in complications of cardiovascular. Depression, impotence, dementia, and amputations of the lower limbs are all effects of chronic diabetes [1].

Vitamin B12 called cobalamin (Cbl) [5], it is one of the necessary and useful vitamins for the body, which has the ability to dissolve in water [5-9] and it has a major role in deoxyribonucleic acid (DNA) synthesis and has an assistant role in the metabolism of fats and amino acid metabolism [5,9-11]. It can be noted the ambiguity in the deficiency of vitamin B12 in older people, where symptoms begin to appear in them after (3-6) years of stopping their bodies of absorbing vitamin B12, the symptoms begin to appear in a simple way which can be expected due to aging [12]. The deficiency of vitamin B12 caused the emergence of several symptoms, including

severe anemia, different types of cancer [6], the total vascular diseases [10], osteoporosis, and neuropathy [5-12]. Vitamin B12 has essential roles in all ages for brain function, protection against advanced disorders of the central nervous system (CNS), dementia, and mood disorders which occur for the elderly [13].

Methylmalonic Acid (MMA), it is a dicarboxylic acid which is basically a byproduct from propionate metabolism. Adenosylcobalamin (AdoCbl) is a cofactor of methylmalonyl-CoA mutase (MUT) which responsible for creating succinyl-CoA from methylmalonyl-CoA. The overabundance of succinyl-CoA turns into MMA. Therefore, the MMA concentration in serum reflects the utilization and availability of AdoCbl via the mitochondria. MMA will accumulate when methylmalonyl coenzyme is not changed to succinate, since this transformation is a vitamin B12 dependent method. Therefore, the measurements of the MMA plasma level been suggested as a functional indicator for Cbl cases into animals, a high MMA concentration level indicates to deficiency of vitamin B12, and this persists of days even next to taking supplementation [14-15].

Vitamin B12 has an essential function into the functioning of the CNS and so the peripheral nervous system (PNS) for humans at all ages. Therefore, the peripheral neuropathy can be considered as one of the classic undiagnosed complications which is an indicative of vitamin B12 deficiency. The clinical and electrophysiological characteristics which appear in people with neuropathy when taking vitamin B12 therapy have not been well elucidated so far [16].

The international association for the study of pain (IASP) has recognized that neuropathic pain is due to a disease or lesion that enters or affects the somatosensory nervous system [17]. The peripheral pathogens take the first place for neuropathic pain, including (cancer, diabetes, chronic alcohol consumption, traumatic nerve injuries, and infection of

herpes zoster), central pathogens (spinal cord injuries, multiple sclerosis, and cerebrovascular accidents), and there are mixed pain causes [17].

This study aim was to determine the strength of the relationship between vitamin B12 and MMA levels with symptoms of neuropathy in patients of type 2 diabetes (T2DM). Because T2DM patients are at risk for vitamin B12 deficiency and neuropathy after several years of infection determining the link between symptoms and vitamin B12 deficiency with neuropathy in the diagnosis is important.

Material and methods

Subjects and Sampling of Population

This study was conducted at Ibn Al-Nafis Hospital during the period (October 2020-March 2021). The study included 100 volunteers between the ages of 40-80 years and they were divided into three groups as follows: Forty non-diabetic subjects were taken as a control sample, thirty volunteers with diabetes who not treated with a supplement of vitamin B_{12} with and without symptoms of neuropathy were taken as a patient sample, and thirty subjects with diabetes who treated with a supplement of vitamin B_{12}, with or without symptoms of neuropathy were taken as a patient sample. A questionnaire was filled up by patients personally based on the previous studies, which included several inquiries, including age and body mass indexes (BMI), they were questioned the appearance of symptoms of neuropathy, including forgetfulness, not remembering a speech, foot pain, tingling in the feet, eye problems, and other symptoms.

Fasting blood samples were collected at between (9:00 AM - 12:30 PM) when the two groups (controls and patients) were in a state of fasting for at least (8) hours. (7 mL) of venous blood was taken from the patient and divided. The blood sample (4.5 mL) was placed in a tube (gel tube), left at room

temperature for (30 minutes), and separated inside a centrifuge (10 minutes) at a speed of (100.62 g). The serum for chemical tests was taken directly as follows: FBS by spectrophotometer assay, the vitamin B_{12} by AIA-Immunoassay, and MMA by LC-MS assay. The blood sample (1 mL) was isolated and placed in a tube having the anti-coagulant, ethylene diamine tetra acetic acid (EDTA). Tubes were carefully stirred to mix the blood with EDTA for direct HbA_{1c} analysis by HPLC assay.

Exclusion criteria: The patients who have contracted the emerging coronavirus (Covid-19) or who have recovered from it for a period of no less than six months, patients with diabetes with types other than T2DM, patients over 80 years, and those who do not know the names of the special treatments taken for DM and vitamin B12 deficiency.

Statistical analysis

The SPSS (statistical package for social sciences, version 26) program was used to analyze the data. The descriptive statistics were utilized to know the mean, the standard error (SE), range, and percentages of the obtained results. Because the variables had a normal distribution, a one-way ANOVA was utilized to analyze the differences between the groups. Chi-square was utilized to limit the strength of the relationship between biochemical tests with symptoms. The statistical significant difference was chosen at ($P \leq 0.05$).

Results

This study included (100) volunteers between the ages of 40-80 years and they were divided into three groups as follows: 40 non-diabetic volunteers were taken as a control sample, (30) subjects as type 2 diabetes mellitus (T2DM), and without the vitamin B12 treatment volunteers were taken as a patient group 1. In addition, (30) type 2 diabetes mellitus (T2DM) and within the vitamin B12

treatment volunteers were taken as a patient group 2. For the demographic distribution and biochemical test, the results which are provided in Table 1, the one-way ANOVA statistic was employed to determine the examined groups' distribution.

The mean age results of the control group were depicted in Table 1 were calculated as a mean±SE of (49.625±1.375) years. For patients with T2DM without the vitamin B12 treatment group, the mean±SE for them was (57.200±1.413 a) years. As with T2DM within the vitamin B12 treatment group, the mean±SE for them was (58.833±1.721b) years. At the level of significance (P ≤ 0.05), a strong statistically significant difference (P = 0.000) was found between the three groups and a significant difference was indicated between the control group and patients with T2DM without the vitamin B12 treatment group, and further they indicated that there were significant differences between the control group and patients with T2DM within the vitamin B12 treatment group.

For BMI results of the control group were indicated in Table 1, a mean±SE of (29.161±0.589). For patients with T2DM without the vitamin B12 treatment group, the mean±SE for them was (28.333±0.845). As patients with T2DM within the vitamin B_{12} treatment group, the mean±SE for them was (29.017±0.849). At the level of significance (P ≤ 0.05), a no statistically significant difference (P= 710) was found among the three groups. For FBS results of the control group were demonstrated in Table 1 a mean±SE of (109.458±1.742). For patients with T2DM without the vitamin B12 treatment group, the mean±SE for them was (205.987±9.296 a). As patients with T2DM within the vitamin B_{12} treatment group, the mean±SE for them was (195.590±11.387 b). For HbA$_{1C}$ results of the control group were presented in Table 1 as a mean±SE of (5.490±0.067). For patients with T2DM without the vitamin B12 treatment group, the mean±SE for them was (8.750±0.332 a). As patients with T2DM

within the vitamin B_{12} treatment group, the mean±SE for them was (8.497±0.393 b). At the level of significance (P ≤ 0.05), a strong statistically significant difference (P= 0.000) was found between the three groups and a significant difference was indicated between the control group and patients with T2DM without the vitamin B_{12} treatment group, and they indicated that there were significant differences between the control group and patients with T2DM within the vitamin B_{12} treatment group of FBS and HbA$_{1C}$.

Vitamin B12 results of the control group were revealed in Table 1 a mean±SE of (401.700±36.455). For patients with T2DM without the vitamin B_{12} treatment group, the mean±SE for them was (539.867±71.139 a). As patients with T2DM without the vitamin B_{12} treatment group, the mean±SE for them was (660.862±66.471 b). At the level of significance (P ≤ 0.05), a strong statistically significant difference (P= 0.000) was found between the three groups and a significant difference was indicated between the control group and patients with T2DM without the vitamin B_{12} treatment group and they indicated a significant difference between the control group and patients with T2DM without the vitamin B_{12} treatment group and indicated that there was a significant difference between the control group and patients with T2DM in the vitamin B_{12} treatment group.

For MMA results of the control group were reported in Table 1 as a mean±SE of (0.389±0.045). For patients with T2DM without the vitamin B_{12} treatment group, the mean±SE for them was (0.441±0.059). As patients with T2DM within the vitamin B_{12} treatment group, the mean±SE for them was (0.432±0.054). At the level of significance (P ≤ 0.05), no statistically significant difference (P= 735) was found between the three groups.

Chi-square statistic has been used to identify the most prominent symptoms of neuropathy in two groups of patients. A difference was observed in the percentages of

symptoms, some of which appeared in high percentages such as (slow movement, difficulty in getting up, sitting down, and forgetting to speak while talking and eye-vision problems), some symptoms which appeared in medium percentages such as (difficulty in learning new information) and some of them appeared in percentages less than the average (50%) such as (amnesia, tremors, shaking of the limbs, and Insomnia) and some of them appeared in weak or very weak percentages such as (forgetting about property locations, slowness, and hesitation during speech, muscle stiffness, and limitation of movement and forget to speak), as demonstrated in Table 2.

Pearson Chi-square statistic has been used to identify the association between nominal and interval variables at up with ($P \leq 0.05$) levels; the result was presented in the Table (3). The relationship was found between age and forgetting to speak symptom (p= 0.001), at the level of significance ($P \leq 0.05$). As for the rest the association was not found between nominal and interval variables at the level of significance ($P \leq 0.05$).

TABLE 1 Distribution of the study groups according to the demographic and biochemical tests

Parameters	Control	Group 1	Group 2	P-value
Age (year) (Mean±SE)	49.625±1.375	57.200±1.41 a	58.833±1.72 b	0.000**
BMI (Kg/m^2) (Mean±SE)	29.161±0.589	28.333±0.845	29.017±0.849	0.710
FBS (mg/dL) (Mean±SE)	109.458±1.742	205.987±9.296 a	195.590±11.38 b	0.000**
HbA$_{1C}$ % (Mean±SE)	5.490±0.067	8.750±0.332 a	8.497±0.393 b	0.000**
Vitamin B$_{12}$ (pg/mL) (Mean±SE)	401.70±36.455	539.867±71.14 a	660.86±66.471 b	0.006**
MMA (µmol/L) (Mean±SE)	0.389±0.045	0.441±0.059	0.432±0.054	0.735

Note: Means with a different letter are significantly different at p ≤ 0.05 level; *: Significant at p ≤ 0.05 level; **: Highly Significant at p ≤ 0.01 level; Group 1: Patients with T2DM without the vitamin B12 treatment; Group 2: Patients with T2DM within the vitamin B12 treatment; a: Indicate a significant difference between control and Group 1; b: Indicate a significant difference between control and Group 2; BMI: Body Mass Index; FBS: Fasting Blood Sugar; HbA$_{1C}$: Glycated Hemoglobin; MMA: Methylmalonic Acid.

TABLE 2 The most prominent symptoms of neuropathy in patient groups

Groups Symptoms		Total	Group 1	Group 2
Amnesia	(+)%	45.0	50.0	40.0
	(—)%	55.0	50.0	60.0
Forgetting about property locations	(+)%	28.3	30.0	26.7
	(—)%	71.7	70.0	73.3
Forgetting to speak while talking	(+)%	60.0	53.3	66.7
	(—)%	40.0	46.7	33.3
Forgetting to speak	(+)%	6.7	0.00	13.3
	(—)%	93.3	100	86.7
Tremors and shaking the limbs	(+)%	35.0	30.0	40.0
	(—)%	65.0	70.0	60.0
Slow movement and difficulty in getting up and sitting down	(+)%	91.7	83.3	100
	(—)%	8.3	16.7	0.00
Muscle stiffness and limitation of movement	(+)%	15.0	10	20.0
	(—)%	85.0	90.0	80.0
Eye- vision problems	(+)%	60.0	53.3	66.7

	(—)%	40.0	46.7	33.3
Slowness and hesitation during speech	(+)%	25.0	30.0	20.0
	(—)%	75.0	70.0	80.0
Difficulty in learning new information	(+)%	50.0	53.3	46.7
	(—)%	50.0	46.7	53.3
Insomnia	(+)%	41.7	43.3	40.0
	(—)%	58.3	56.7	60.0

Note: Group 1: Patients with T2DM without the vitamin B12 treatment; Group 2: Patients with T2DM within the vitamin B12 treatment.

TABLE 3 The association between nominal variables and interval variables

Parameters / Symptoms	Age(year)	BMI (kg/m2)	FBS (mg/dL)	HbA$_1$c%	Vitamin B12 (pg/mL)	MMA (Mmol/L)
Amnesia	0.225	0.439	0.617	0.708	0.402	0.750
Forgetting about property locations	0.115	0.381	0.248	0.201	0.495	0.660
Forgetting to speak while talking	0.215	0.443	0.465	0.350	0.478	0.487
Forgetting to speak	0.001	0.591	0.115	0.117	0.402	0.770
Tremors and shaking the limbs	0.473	0.452	0.462	0.322	0.402	0.346
Slow movement and difficulty getting up and sitting down	0.618	0.299	0.844	0.673	0.402	0.315
Muscle stiffness and limitation of movement	0.338	0.434	0.463	0.661	0.402	0.749
Eye-vision problems	0.450	0.299	0.286	0.298	0.402	0.608
Slowness and hesitation during speech	0.101	0.487	0.455	0.646	0.504	0.583
Difficulty in learning new information	0.544	0.513	0.611	0.641	0.475	0.402
Insomnia	0.267	0.367	0.515	0.473	0.402	0.766

Note: *: Significant at $p \leq 0.05$ level; **: Highly Significant at $p \leq 0.01$ level; BMI: Body Mass Index; FBS: Fasting Blood Sugar; HbA$_1$c: Glycated Hemoglobin; MMA: Methylmalonic Acid.

Discussion

Type 2 diabetes mellitus (T2DM) was once thought to be a condition which only affected the elderly. T2DM is still more common in people in late middle age and older. In the United States of America (USA) in 2018, the highest estimated incidence of diagnosed primary DM was among adults aged 45-64 years. This value was lower among the individuals under the age of 45 years, as well as those over the age of 64 years [18]. When compared to T2DM which starts in the middle age or later, the individuals with advanced T2DM have a higher risk of renal and neurological problems, as well as a higher death rate. The age of 40 years produces the largest excess mortality [19]. T2DM is on the rise globally, with no indications of slowing down. The fast increasing burden in low-income nations is a troubling result. The non-modifiable risk factors, as such as age and family history, might be one cause [20]. This study is consistent with one that did not observe any significant associations between DN severity and BMI, or the centimeters number beyond the usual waist circumference independent of the other risk factors [21].

Besides, this study is consistent with what was stated in one of the studies, in which mean of FBS was high significantly. And other study was stated that there was significant difference into mean of FBS in patients with T2DM as compared to the control group in Indian population. Increased intracellular glucose causes drives mitochondrial and induced oxidative stress, likewise the

synthesis of advanced glycation of end products, causing changes in endothelial cell control of vascular wall homeostasis [22]. HbA_{1c} does not always need fasting prior to testing, as with FBS, and specimens can be taken at any time of day. HbA_{1c} correctly depicts glycemia over a longer length of time than FBS [23-25]. Raising the blood glucose level in the groups of the patients leads to the growth and progression of diabetic neuropathy. One study confirms the strong association which is found between hyperglycemia and diabetic neuropathy (micro and macrovascular complications) and it is in agreement with other relevant studies [25-27]. In one studies, the results revealed a relationship between self-care behaviors, HbA_{1c}, and FBS levels of T2DM patients into Binjai City, with the better self-care behavior resulting in more regulated levels of HbA_{1c} of DM patients. Because HbA_{1c} is the strongest indicator of future complications, it is preferable to the FBS test. The higher the value of HbA_{1c}, the greater the risk of complications for the patient [28].

Vitamin B_{12} deficiency is clinically significant because it can lead to the bone marrow failure, also demyelinating nerve illness, both of which are reversible. The patients may mistakenly think they have diabetic neuropathy (DN) when they have neurologic damage that manifests as principle neuropathy (PN). The long-term use of DM medications is linked to low vitamin B12 levels, according to accumulating evidence, and results from both interventional and observational studies have corroborated this association. Vitamin B_{12} testing should be done on a regular basis in patients of DM, those with PN especially, according to new American diabetes association (ADA) guidelines [29-31].

However, diagnosing vitamin B_{12} deficiency might be tricky. According to reports, high vitamin B_{12} levels in blood can be accompanied with indications of deficiency, with functional deficiency due to tissue

absorption deficiencies and vitamin B_{12} activity at the cellular level being implicated. As a result, even if blood vitamin B_{12} levels are high, the functional deficiency of vitamin B_{12} can develop. As a result, a more sensitive screening test is required. One test makes the use of metabolites which build up as a result of vitamin B_{12} deficiency. In conjunction with folic acid, vitamin B_{12} is involved in the conversion of MMA to succinyl-CoA and homocysteine (Hcy) to methionine (Met). In comparison to serum vitamin B_{12} level alone, serum vitamin B_{12} levels in conjunction with MMA levels has been revealed to be helpful in identifying vitamin B_{12} deficiency [30,32]. Vitamin B_{12} is a cofactor that promotes the conversion of methyl malonyl-CoA to succinyl-CoA in the crucial enzymatic pathway to vitamin B_{12}; in the presence of deficiency of vitamin B_{12}, this conversion pathway is decreased, and serum MMA rises [33].

Furthermore, studies have linked low vitamin B_{12} levels to worsening DN in diabetic individuals using DM medicines. Some experts believe that neuropathy is caused in part by a lack of vitamin B_{12}, which might be caused by high amounts of Hcy and MMA, both of which can neurons damage. Not surprisingly, the use of DM medications can negatively affect vitamin B_{12} levels [34].

Many cases of deficiency of vitamin B_{12} are ignored or even misdiagnosed in clinical practice. The illness spectrum of individuals with vitamin B_{12} deficiency was described, with the diagnosis based on low levels of serum vitamin B_{12}, high biomarkers such as MMA and/or Hcy, or improvement of clinical symptoms following the administration with parenteral vitamin B12 treatment [35].

A distinction should be made between vitamin B_{12} deficiency neuropathy and DN. The incidence of symptoms linked to vitamin B12 deficiency, on the other hand, has not been explored. In general, to confirm diabetic neuropathy electromyography (EMG) or nerve conduction tests should be performed, that are not performed because they are not

performed routinely. These studies should be conducted for the perfect evaluation and diagnosis of neuropathic pain into patients with deficiency of vitamin B_{12}.

It is possible that the reason for the lack of appearance of vitamin B_{12} deficiency is that the majority of patients have not had T2DM for more than five years, or the diet they eat contains animal sources, or it is possible that race has a role in not showing up of vitamin deficiency B_{12}, or it is possible that the color of the skin for people with brown skin has a role in the lack of ease infection of the vitamin B_{12} deficiency.

The strength of this study is the examination of vitamin B_{12} levels and MMA levels in patients with T2DM because it gives a clearer picture of the results of vitamin levels, the study of symptoms which appear when suffering from neuropathy in T2DM patients to distinguish between DN and neuropathy caused by the vitamin deficiency, and examining the strength correlation between the studied symptoms and the demographic and biochemical tests which were conducted to clarify what influences them.

In conclusion, it was concluded that age is a factor influencing the incidence of type 2 diabetes mellitus (T2DM). By studying the symptoms of neuropathy, it became obvious that when type 2 diabetes mellitus (T2DM) develops, many complications appear, including neuropathy. Furthermore, it is preferable when performing a vitamin B_{12} level test to performing test one of the confirmed parameters such as test of Methylmalonic acid (MMA) to confirm a possible deficiency or increase of vitamin B_{12} levels. The relationship was found between age and symptom of forgetting to speak, and thus it is one symptoms of neuropathy.

Conclusion

By studying the symptoms of neuropathy, it turned out that when type 2 diabetes mellitus (T2DM) develops, many complications appear, including neuropathy. Also, when performing a vitamin B_{12} level test, it is best to have a confirmatory test such as a methylmalonic acid (MMA) test to confirm changes in vitamin B_{12} levels. The study found that there is an association between age and symptoms of forgetting to speak as neuropathy symptoms.

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