Assessment of Vitamin B12 Deficiency Caused by Metformin in Type II Diabetic Patients

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

Original Research Article

ABSTRACT

Metformin use over time reduces vitamin B12 levels, according to several studies, and its clinical manifestation can be mistaken as diabetic peripheral neuropathy. In order to investigate vitamin-B12 deficiency in type II diabetic patients with long-term metformin treatment, a link between vitamin B12 and peripheral neuropathy, and to evaluate the quality of life in (T2DM) patients, the current study was done. At Sree Balaji Medical College and Hospital's outpatient and inpatient departments, a prospective observational case-control research was done. The study included 35 healthy volunteers (controls) and 35 Type 2 diabetes patients who had been on metformin for more than six months (cases). Patients' venous blood samples were collected in K2 EDTA vacutainers and centrifuged at 1500 rpm for 10 minutes, settled plasma was transferred into cryo-vials, and parameters such as Vitamin-B12, HbA1c, and CBP were estimated and this is used to conduct the statistical analysis. The prevalence of blood vitamin B12 deficiency and borderline deficiency in T2DM patients is 20.5 percent, while the mean HbA1C values in our study T2DM subjects are 9.07 percent, indicating either poor diabetes control or poor metformin drug compliance. Vitamin B12 insufficiency was found in 83 percent of T2DM patients who had been using metformin for 1 to 10 years. The reliability test was used to assess their quality of life, and the results revealed that the study participants' quality of life was poor.

Keywords: Vitamin B12; T2DM; metformin; peripheral neuropathy.

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1. INTRODUCTION

Metformin is the most widely prescribed oral hypoglycaemic medication among type 2 diabetes patients, especially those who are overweight and have normal renal function. It is the most frequently used anti-hyperglycemic medicine that is used as first-line treatment for individuals with type 2 diabetes mellitus, according to numerous guidelines [1,2].

Vitamin B12 is an essential nutrient for good health, since it aids in the proper functioning of the brain, neurological system, and red blood cell development. Vitamin B12 deficiency, in addition to anaemia, may exacerbate the severity of peripheral neuropathy in T2DM patients. Furthermore, because vitamin B12 is involved in the most important pathway of homocysteine (Hcy) metabolism, a deficiency in the vitamin would result in higher Hcy levels in the blood, which is closely connected to cardiovascular illness in people with T2DM and PCOS. Nutritional inadequacy, stomach mucosal injury, pernicious anaemia, and medications like Proton Pump Inhibitors (PPIs) and metformin may all cause vitamin B12 shortage [1,3-5].

Vitamin B12 deficiency has been found in 10-30% of patients taking metformin for longer periods of time and at greater doses, according to several research. Patients with type 2 diabetes, particularly those on long-term metformin medication, should have their vitamin B12 levels checked. Changes in mental status, megaloblastic anaemia, and neurological impairment are all signs of vitamin B12 insufficiency. Diabetic neuropathy can also present with symptoms such as paresthesias, numbness, and tingling in the hands and feet, which can lead to a mix-up between vitamin B12 deficiency and diabetic peripheral neuropathy diagnosis [2]. Thus, early discovery of vitamin B12 deficiency could slow the progression of neurological damage, and if misdiagnosed as diabetic neuropathy, this vitamin B12 shortage could lead to permanent neurological impairment [6-8].

The study's goal was to see if long-term Metformin use causes Vitamin B12 shortage in Type II diabetic patients, as well as to assess their quality of life. The goals are to compare the levels of vitamin B12 in diabetic patients to those in the control group, to investigate the link between vitamin B12 and peripheral neuropathy.

2. MATERIALS AND METHODS

In the planned case-control study, 35 patients with type 2 diabetes mellitus (T2DM) and 35 healthy volunteers ranging in age from 30 to 80 years old were enlisted. All of the T2DM patients were on metformin and had been for at least six months.

2.1 Criteria for Inclusion

Patients with type 2 diabetes who are above 37 years old and have been taking Metformin for more than 6 months are included in this study.

Non-diabetics were used as controls (age and sex matched).

2.2 Criteria for Exclusion

This study did not include patients with Pernicious Anemia, recently diagnosed T2DM, pregnant women, Type-I Diabetes, vegetarians, IBD, Gastrectomy, Colectomy, or Hypothyroidism. Patients who had recently taken vitamin B12 medicine, either orally or intramuscularly, were also excluded.

2.3 Sample Collection and Storage

2 ml of venous blood was obtained from each person recruited in the study after an overnight fast of roughly 6–8 hours, and the separated serum was preserved in cryo-vial tubes. The samples were centrifuged for 10 minutes at 1500 rpm to obtain serum samples, which were maintained at -80 C until the vitamin B12 level was determined. Serum vitamin B12 and HbA1c levels are measured.

2.4 Statistical Analysis

Chi-square cross tabulation was used to compare serum B12 levels to metformin years of use. A Scatter plot was used to evaluate the NTSS-6 scores with vitamin B12 levels in all metformin-treated T2DM patients. SPSS was used for all of the statistical analysis (version 25.0).

3. RESULTS

Table 1 shows the clinical characteristics of the study population. In T2DM patients, the prevalence of blood vitamin B12 insufficiency is 20.5 percent, compared to 8.82 percent in age-matched controls. The mean HbA1C values in our study T2DM individuals are 9.09 percent, as shown in Table 1, indicating either poor diabetes control despite high metformin dosages or a lack of compliance.

Table 1. The study population's clinical characteristics

Variables	Total	Cases	Controls
No. of Participants	70	35	35
Age	44.8±12.6	51.35 ± 10.09	35.58±14.26
Sex (%)			
Female	34 (49.1)	16 (48.1)	16 (48.1)
Male	36 (52.9)	18 (53.9)	18 (53.9)
HbA1c	9.09 ±2.69%	9.09 ±2.69%	-
Vitamin-B12 pg/ml	345 ± 153.3	353.1±178.2	350.6±143.49
Vitamin-B12 deficiency (<200 pg/ml)	12(18.1)	8 (21.5%)	4 (9.02%)

Table 2. Years of metformin use and vitamin B12 levels in cases

Metformin use in years	Vitamin-B$_{12}$ (pg/ml)					
	< 200	200 – 300	300 – 400	400 – 500	>500	Total
>6 months	0	1	0	2	0	3
1 – 10	5	5	8	3	4	25
11 – 20	2	1	0	1	1	5
21 – 30	0	1	0	0	1	2
Total	35					

Table 2 shows that 82 percent of T2DM patients who took metformin for 1 to 10 years developed vitamin B12 insufficiency. A substantial link exists between vitamin B12 insufficiency and peripheral neuropathy at this level (200 pg/ml).

4. DISSCUSSION

When compared to age-matched non-diabetic study controls, the prevalence of vitamin-B12 insufficiency in T2DM patients using metformin was 20.5 percent in the current study. In a study involving 196 T2DM patients, De Jager et al. found a 9.9% prevalence of vitamin-B12 insufficiency and 4.3 mean metformin years of use [9]. The study by Hermann et al. found an 8 percent prevalence rate with an average of 5.2 years of metformin use [10]. According to Reinstatler et al., the study comprised 575 metformin-treated individuals, resulting in a 5.8% prevalence rate with a mean metformin use of 5 years [11]. Beulens et al. studied 550 people and found that 28.1 percent of them had metformin insufficiency after taking it for an average of 5.3 years, with holotranscobalamin deficiency occurring in 3.9 percent of the patients [12]. A 0.042 drop in cobalamin concentrations was associated with a 1 mg/day increase in daily metformin intake. The Sun-Hye ko et al., study found that 9.5 percent of metformin-treated type 2 diabetic patients (n = 76) had vitamin B12 deficiency, with a mean vitamin B12 level of 662.5 246.7 pg/mL [13].

Our data demonstrated a clear relationship between metformin dosage and duration, as well as vitamin B12 deficiency, and T2DM patients' NTSS scores and QOL. The current study was carried out at Sree Balaji Medical College and Hospital's in India on 35 metformin-treated patients with a mean age of 54.3 years and a mean duration of metformin treatment of 2.83 years. After excluding renally compromised patients, the prevalence rate was found to be 20.5 percent.

5. CONCLUSION

When compared to control people, the prevalence of vitamin B12 deficiency and borderline deficiency in T2DM patients was shown to be substantial. The reliability test was used to assess their quality of life, and the results revealed that the study participants' quality of life was poor. In T2DM patients on long-term metformin, a peripheral smear can be performed to detect macrocytic anaemia, followed by biochemical analysis on a frequent basis, taking into account the cost of regular vitamin-B12 screening.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and
preserved by the author(s).

COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

1. Liu Q, Li S, Quan H, Li J. Vitamin B_{12} Status in Metformin Treated Patients: Systematic Review. PLoS ONE. 2014;9:e100379.

2. Jeetendra S, Tushar B. Metformin Use and Vitamin B_{12} Deficiency in Patients with Type-2 Diabetes Mellitus. 2016;3:67–70.

3. Yajnik C, Deshpande S, Lubree H, et al. Vitamin B_{12} Deficiency and Hyperhomocysteinemia in Rural and Urban Indians. JAPI. 2006;54:775–82.

4. Shobhaa V, Tareya S, Singh R, et al. Vitamin B_{12} deficiency & levels of metabolites in an apparently normal urban south Indian elderly population. Indian J Med Res. 2011;134:432-9.

5. Akinlade KS, Agbebaku SO, Rahamon SK, Balogun WO. Vitamin B12 Levels in Patients with Type 2 Diabetes Mellitus on Metformin. Annals of Ibadan Postgraduate Medicine. 2015;13:79–83.

6. Ting RZ, Szeto CC, Chan MH, Ma KK, Chow KM. Risk factors of vitamin B -12 deficiency in patients receiving metformin. Arch Intern Med. 2006;166:1975.

7. Trikkalinou A, Papazafiropoulou A, Melidonis A. Type 2 diabetes and quality of life. World J Diabetes Contents Monthly. 2017;8:120–71.

8. Stanetić K, Savić1 S, Račić2 M. The quality of life of patients with type 2 diabetes mellitus. Оригинални Радови. 2012;18:70–7.

9. de Jager J, Kooy A, Lehert P, et al. Long-term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: Randomised placebo- controlled trial. BMJ. 2010;340: c2181.

10. Sparre Hermann L, Nilsson BO, Wettre S. Vitamin B12 status of patients treated with metformin: A cross- sectional cohort study. The British Journal of Diabetes & Vascular Disease. 2004;4:401-406.

11. Reinstatler L, Qi YP, Williamson RS, et al. Association of biochemical B_{12} deficiency with metformin therapy and vitamin B_{12} supplements: The National Health and Nutrition Examination Survey, 1999-2006. Diabetes Care. 2012;35:327-333.

12. Beulens JW, Hart HE, Kuijs R, et al. Influence of duration and dose of metformin on cobalamin deficiency in type 2 diabetes patients using metformin. Acta Diabetol. 2015;52:47-53.

13. 13. Ko S, Ko S, Ahn Y, Song K, Han K, Park Y, et al. Association of Vitamin B 12 Deficiency and Metformin Use in Patients with Type 2 Diabetes. Issn. 2014;29:965–72.