



Vitamin B12 deficiency in diabetic subjects taking metformin: A cross sectional study in a Lebanese cohort

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ABSTRACT

Metformin is the only biguanide derivative used to treat type 2 diabetes mellitus (T2D). Several studies documented that its use contributes to vitamin B12 deficiency in 10–30% of diabetics. The incidence of deficiency varies among populations and studies reported. There has been no reports documenting this incidence in the Middle East and Lebanon.

The objectives of this study were to establish the incidence of vitamin B12 in our population, to investigate and characterize any specific associations between taking metformin and vitamin B12 deficiency to establish clear recommendations based on this data.

During the first 6 months of 2015, we conducted a cross sectional study on 200 Lebanese individuals. The cohort consisted of subjects with an established diagnosis of T2D and who have been on metformin for at least three months. The patients were subjected to a questionnaire, medical record review, and vitamin B12 level measurement.

Thirty three percent of the subjects were found to have borderline values of the serum vitamin B12 (148–220 pg/dl) while 22.5% had a clear, deficiency (levels less than 148 pg/dl). We found a highly significant inverse correlation between the dose and duration of metformin treatment and the serum levels of vitamin B12. Furthermore, both borderline and low levels of vitamin B12 were associated with the presence of different neuropathies and macrocytic anemia in a dose dependent manner.

Based on our results, we strongly recommend the routine screening of subjects with T2D on metformin for vitamin B12 deficiency due to its high prevalence and the significant clinical effects it may result in. Furthermore, we recommend, based on our data, to start treating those subjects once a borderline or low level is detected.

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1. Introduction

T2D is the most common endocrine disorder in the world [1]. Metformin (1,1-dimethylbiguanide hydrochloride) is the only biguanide available and the recommended first line treatment for T2D [2,3]. Metformin is being used as monotherapy or in combination with other medications. In addition, lifestyle counseling, weight loss and exercise are usually recommended to every diabetic person. Metformin is probably one of the most commonly used medication on the planet given the incidence of T2D reaching

5–10% of the population depending on the cohort studied. It has a long-standing evidence base for efficacy and safety, is inexpensive, and has been shown to reduce the risk of cardiovascular events [3]. Its most common side effects include gastrointestinal upset and lactic acidosis. However, the associated vitamin B12 deficiency is less known and not routinely tested for by clinicians [4].

Diabetic neuropathy is one of the most dreaded complications of diabetes affecting about half of the T2D subjects and may manifest as sensory, motor, and/or autonomic dysfunction [5]. Its main impact is quality-of-life alteration with tingling, numbness, reduced or heightened sensations to pain, cramps, muscle weakness, imbalance, bowel and bladder irregularities, sexual dysfunctions, orthostatic maladjustments, and mono or focal neuropathies [5]. Peripheral neuropathy inflicts almost half of diabetic subjects. It is a risk factor for leg ulcers, infections, fractures, amputations, and

Abbreviations: fl, femtoliter; HAS, Haute Autorité de Santé; MCV, Mean Corpuscular Volume; T2D, Type 2 Diabetes.

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major life altering and productivity changes, and progressive utilization of health care [6]. In the United States, Gordois et al. estimated the annual cost of the neuropathy to be 4.6 to 13.7 billion dollars, about one third the costs related to diabetes [7].

Vitamin B12 also called cobalamin, is a water-soluble vitamin with a key role in the normal functioning of the central and peripheral nervous systems, hematopoiesis, and the DNA synthesis of every cell [8]. Its deficiency causes megaloblastic anemia, peripheral neuropathy that could be indistinguishable from the diabetic neuropathy even by nerve conduction studies. Memory and cognitive impairments could also result from B12 deficiency [9,10]. Malabsorption of vitamin B12 in diabetic patients treated with metformin was first noted in 1969 [11]. Subsequent studies revealed a prevalence of vitamin B12 deficiency in the range of 10–30% of diabetic patients using metformin. The mechanisms are thought to be related to slowing of the bowel transit time resulting in bacterial overgrowth and interference of the Biguanide with the absorption of vitamin B12 [12–15].

The neuropathy associated with B12 deficiency usually precedes the megaloblastic anemia. Although the associated anemia is reversible, the neuropathy may not be completely reversible in certain patients. Recommendations for periodic testing of vitamin B12 in metformin-treated patients, have recently been made by the American Diabetes Association (ADA) especially in those with peripheral neuropathy [2,16].

To our Knowledge, this is the first study to investigate the vitamin B12 deficiency in a Lebanese cohort and to take into consideration the dose, duration and correlate it with the symptoms of peripheral neuropathy and the presence of the megaloblastic anemia.

2. Material and methods

We carried out this cross sectional study during the first half of 2015 on 200 Lebanese subjects diagnosed with T2D and taking metformin for at least three months prior to the study. The study was approved by the Ethics Committee of the Department of Human Nutrition and Dietetics, Faculty of Agricultural and Food Sciences at the Holy Spirit University in Lebanon. All participants gave their informed consent to collect their data and publish it.

The exclusion criteria included subjects known to be B12 deficient or receiving any form of B12 supplementation. Subjects were also excluded if they had celiac disease, chronic atrophic gastritis, pernicious anemia, chronic pancreatitis, any neurologic condition like MS, ALS, or others, those who had bariatric surgery, resection of any part of the intestines, cancer, blood transfusions during the last 3 months, any gastrointestinal disease like crohn's disease or gastritis, liver disease, thyroid disease, excessive alcohol intake (>1/day for women, and >2 per day for men) were all excluded.

Subjects taking any of the following medications during the past 3 months were also excluded: proton pump inhibitors, H2 receptor antagonists, antibiotics, neomycin, colchicine, aminosalicilic acid, B12 or calcium supplements.

Two hundred T2D subjects being treated with metformin for at least three months were randomly selected from four different diabetes clinics. Their ages ranged between 18 and 90 years.

The medical record of each patient was reviewed and a questionnaire was adopted to assess their lifestyle, diet, alcohol use, exercise, and any neurologic symptoms including peripheral autonomic, sensory and motor symptoms.

In parallel, the subjects had a battery of laboratory tests covering the vitamin B12 levels, Complete blood counts, liver and renal function tests. Additional tests were left to the discretion of their treating physician.

For the vitamin B12, we adopted the cut point levels

recommended by Snow in 1999 [17] as follows:

- Normal B12 > 221 pmol/L: Vitamin B12 deficiency is unlikely (i.e., probability of 1–5%).
- Borderline: B12 between 148 and 221 pmol/L: Vitamin B12 deficiency possible.
- B12 deficiency: B12 < 148 pmol/L: consistent with vitamin B12 deficiency (specificity of 95–100%).

Anemia was defined as Hb < 130 g/l for men and <120 g/l for women based on the WHO guidelines [9]. The reference value of the Mean Corpuscular Volume (MCV) is 80–100 fl. Macrocytosis is defined as an MCV level higher than 100 fl [18].

2.1. Statistical analysis

The Statistical Package for the Social Sciences (SPSS) Version 21.0 was used for data entry and data analysis. The confidence interval was set at 95% and significance considered at $p < .05$. Descriptive statistics were performed on the data of age, sex, dose of metformin, the duration of use, the body mass index, the serum levels of vitamin B12 and its difference according to age, neurological symptoms (the presence of at least one symptom), hemoglobin, and the MCV levels. The correlation between the levels of vitamin B12 and the dose of metformin were assessed according to the bivariate correlation. A T-test for independent groups was used to assess the relationship between the levels of vitamin B12 and the duration of the use of metformin. A One way Anova-test was performed to investigate the relationship between serum vitamin B12 and the presence of at least one neurologic symptom. Finally a Chi-2 test was used to demonstrate the association between serum vitamin B12 levels, anemia, and macrocytosis.

3. Results

Two hundred subjects were enrolled on this cross sectional study. Thirty three percent of the subjects were found to have serum vitamin B12 levels in the borderline range while 22.5% had a deficiency; a total of 55.3% of the cohort (Fig. 1). The serum vitamin B12 levels decreased as the dose of metformin increased in a linear way and this inverse correlation was highly significant ($p = 0$) (Fig. 2).

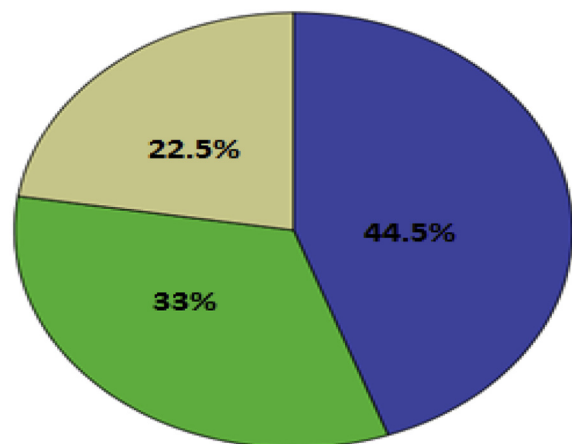


Fig. 1. Distribution of normal B12 levels (>212 pg/l in blue), Borderline levels in green (148–212 pg/l) and low levels in grey (<148 pg/l). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

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