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Research Article

Metformin Use is Associated with Lower Levels of Vitamin B12 in Obese Patients

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Abstract

Type 2 Diabetes Mellitus (DM2) is a chronic morbidity with worldwide high prevalence. Its treatment includes many therapies such as drugs and lifestyle changes. Bariatric surgery has been widely used for the treatment of severe obesity and has shown improvement in DM2 control. However, it has important nutritional complications such as iron, calcium, vitamin D and vitamin B12 malabsorption.

Vitamin B12 is found in animal derived foods and its deficiency is generally manifested by features of megaloblastic anemia with possible neurologic manifestations. Moreover, its deficiency also constitutes an important risk factor for cardiovascular diseases.

Metformin is the first line drug in the treatment of DM2 and its main side effects are gastrointestinal, such as nauseas and diarrhea. Besides, its use has been associated with vitamin B12 malabsorption and deficiency. Since it has positive impact on body weight, metformin is commonly used by patients in pre and post-operative of bariatric surgery.

This is a cross-sectional study based on medical record information that analyzed B12 serum levels and other variables in Obese patients with impaired glucose tolerance, in use or not of metformin, attended between 2010 and 2012 in a center specialized in clinical and surgical treatment of obesity.

Sixty six patients were included in the study. Twenty (30%) of them were in use of metformin and had lower vitamin B12 levels when compared to those who were not in use of this drug. Also, these levels were negatively correlated with metformin time of use and dosage. Thus, patients in use of metformin require special attention in both pre and post-operative of bariatric surgery regarding the deficiency of vitamin B12.

Introduction

Type 2 Diabetes Mellitus (DM2) is among the chronic morbidities whose prevalence's have increased in the past years, being Obesity is one of the major risk factor for its development. Its physiopathology is complex and involves multiples mechanisms. The treatment includes many therapies, such as lifestyle changes and many oral and parentheral medications [1,2]. Bariatric surgery has been widely used for the treatment of severe obesity and has shown improvement in DM2 control. However, it has important nutritional complications such as iron, calcium, vitamin D and vitamin B12 malabsorption [3,4].

Vitamin B12 is an important nutrient that is found in animal derived foods. Its deficiency may be asymptomatic for long periods of time, but it is generally manifested by features of megaloblastic anemia with possible neurologic manifestations, like polyneuropathy, myelopathy, dementia, optic neuropathy and others, which may become irreversible depending on the time of the vitamin deficiency [5]. Asthenia, glossitis, and paresthesias are frequent symptoms, with paraplegia and spasticity possible to occur in advanced stages. Moreover, vitamin B12 deficiency also constitutes an important risk factor for cardiovascular diseases [5,6].

Metformin is a biguanide derivate that, in addition of antihyperglycemic effects, shows improvement on body weight and serum lipids, thus being considered as the first line drug in the treatment of DM2. Metformin main side effects are gastrointestinal, such as nausea and diarrhea. Besides, its use has been associated with vitamin B12 malabsorption and deficiency, but the mechanism of this interaction is not clear yet. For being a low cost, widely studied and great efficacy medication (especially on obese and overweight patients) it is commonly used by patients that are candidates to bariatric surgery or by those that have already performed it, which may aggravate the deficiency of vitamin B12 [2,6,7,9]. So, this study focused on comparing the serum levels of vitamin B12 in overweight patients that were both partaking and not partaking in receiving metformin.

Methods

Cross-sectional study based on medical record information that analyzed Obese patients

Table 1: Clinical and demographic characteristics of the 66 patients studied.

Characteristics	Results
Age (years)*	42 (11)
Femalegender	44 (67%)
BMI (kg/m²)*	41 (5)
DM2	23 (35%)
High HbA_1C	30 (46%)
Medication use:	
Antihipertensives	29 (44%)
Metformin	20 (30%)
Other OADD†	8 (12%)
Insulin	5 (8%)
Levothyroxin	5 (8%)
LipidLoweringDrugs	6 (9%)
Oral Anticonceptives	5 (8%)
PPI ‡	2 (3%)

*Data expressed in mean (standard deviation); †oral antidiabetic drugs; ‡Proton-Pump Inhibitors

who attended centers that specialized in obesity treatment between the years 2010 and 2012. These patients experienced some type of altered glucose tolerance (diabetes, elevated fasting glucose and impaired glucose tolerance) and were included consecutively in the study. Patient inclusion criteria were serum vitamin B12 dosage performed by similar reference range methods, both using and not using metformin. Exclusion criteria were metformin usage period lower than 4 weeks or vitamin B12 supplementation in the six months prior to its dosage. Besides, patients with a medical history of previous gastrectomy of any kind or diagnosis of Chron´s disease, ulcerative colitis, and disorders of the terminal ileum or atrophic gastritis were also excluded from the study.

The variables studied were: age in years, gender, body mass index (BMI in kg/m²), time of diabetes diagnosis in months, daily dose and time of use of metformin, and use of other medications. Laboratory variables studied were serum vitamin B12 levels, red blood cells Mean Corpuscular Volume (MCV), glycated hemoglobin (HbA_1C), serum foliate levels, TSH and free thyroxin (FT4). Vitamin B12 was analyzed as a continuous variable. The other laboratory variables were categorized as high, normal or low, also according to the reference range of the laboratory method performed.

The Statistical Package for Social Science (SPSS Inc., Chicago, IL, USA, and Release 16.0.2, 2008) was used for statistical analysis. Quantitative variables were expressed by mean and Standard Deviation (SD) or Median (Md) plus Interquartile Range (IQR) and were compared by Student t test or the Mann–Whitney. Qualitative variables were expressed as relative frequency and were compared using the Fisher exact test. Spearman correlation test was used to verify the correlation between vitamin B12 serum levels and time of use and daily dose of metformin. Values of p lower than 0.05 were considered statistically significant.

The study was approved by the Research Ethics Committee of the local institution by the protocol number 096/2011.

Results

Of the 66 patients included in the study, 67% were females. The demographics and clinical characteristics of these patients are shown in (Table 1). Among the patients studied, 23 (35%) were diabetic and 43 (65%) had high fasting blood glucose. The time of diabetes varied from 1 to 192 months and 50% of the patients had diagnosis of diabetes for more than 30 months. Twenty (30%) of the patients were in use of metformin and 46 (70%) were not. The time of use ranged from 3 to 120 months with a median of 27 (13 – 44). Daily dose of metformin varied from 500 to 2,550 mg, being the median value 1,000 (850 – 1,500) mg. Of the patients studied, no one had low folate serum levels and only one (1.5%) had high MCV. Five (8%) patients were in use of levothyroxin, but no one had clinical hypothyroidism.

When comparing the groups according to the use of metformin, it was evident that the group in use of this medication was older and had lower vitamin B12 levels. There was no difference between the two groups regarding the use of other drugs, except for antihypertensive, which were more often used by the patients in the metformin group (Table 2).

Vitamin B12 serum levels showed negative and statistically significant correlation with metformin time of use (r_s= -0,322; p=0,008) and daily dosage (r_s= -0,308; p=0,012).

Discussion

The present study showed evidence that patients in use of metformin had lower levels of vitamin B12 than those not in uses of this drug. Plus, the serum levels of this vitamin were also negatively correlated with time of use and dosage of metformin, with statistical significance.

Medical literature has presented studies that consistently evidence the association between the use of metformin and higher risk for vitamin B12 deficiency [4,6,7,9]. A Brazilian research [7] that studied 144 diabetic patients that were over a year in use of metformin found low and possibly low vitamin B12 serum levels in respectively 6,9% and 36,8% of these individuals. Although the above mentioned association is already well described, no studies have been performed with a population of exclusively overweight/obese patients yet.

Table 2: Characteristics of the 66 patients according to the use of metformin.

Variables	Metformin		p
	Yes 20 (30%)	No 46 (70%)	
Age (years)*	49(10)	41(8)	0,035
BMI (Kg/m²)*	41(5)	41(4)	0,942
High serumfolate*	15%	9%	1,000
Vitamin B12 (pg/mL)†	358 (268 - 437)	441 (342 - 557)	0,013
Proton-Pump Inhibitors	_	2 (4%)	1,000
Oral Anticonceptives	_	5 (11%)	0,312
Levothyroxin	2 (10%)	3 (6%)	0,635
Antihipertensives	14 (70%)	15 (33%)	0,005
LipidLoweringDrugs	4 (20%)	2 (4%)	0,063

*Data expressed in mean (standard deviation); †Data expressed in median and interquartile range

Jolien de Jager et al. [9] have done a multicenter, randomized, placebo-controlled study with 277 diabetic patients that were divided into two groups: a test group with 131 individuals in use of insulin and metformin with a mean daily dosage of 2050 mg, and a control group composed by 146 diabetics in use of insulin and placebo. At the end of a 52 month period of patient-following, the study revealed that the group in use of metformin had vitamin B12 serum levels 19% lower than those in the control group (insulin and placebo).

Daryl J. Wile and Cory Toth [6] also demonstrated that, besides mean vitamin B12 levels are lower in patients in use of metformin, the cumulative dosage of the drug was inversely correlated with serum vitamin B12. Elizabeth Kos et al. [4] analyzed the relation between metformin use and not only vitamin B12, but also serum vitamin D. They did find evidence of lower vitamin B12 levels in patients in metformin use; however, the use of metformin had no association with altered vitamin D levels in this study.

The mechanisms by which metformin seem to influence vitamin B12 levels are still controversial and unclear. Alterations in intestinal bacterial growth, Intrinsic Factor (IF) levels and inhibitory/inactivate competition with vitamin B12 absorption have been postulated as possible causes [6]. It has been shown the existence of a damaging effect of the biguanide over the ileum calcium-dependent membrane, which mediates the absorption of the cobalamin-IF complex. Thus, this could be a mechanism that leads to cobalamin lower levels in metformin use.

Serum vitamin B12 dosage is most often utilized exam to diagnose vitamin B12 deficiency in today's world. This more spread use is, in part, due to the exam´s dispensability and low cost. However, there are several limitations concerning its sensitivity and specificity [5]. The influence of binding proteins in the plasma as well as the use of oral contraceptives, low folate levels and illnesses such as multiple myeloma may erroneously indicate vitamin B12 deficiency. Meanwhile, many other conditions such as hepatic, renal and myeloproliferative disorders may mimetize falsely normal or high vitamin B12 levels [4,5].

The literature varies when it comes to the reference values that should be used diagnose vitamin B12 deficiency and the limits for this diagnose have become wider. Generally, it is defined by low (<200pg/mL) or very low (<100pg/mL) serum levels, with or without clinical symptoms. Values between 200 and 350pg/mL are usually characterized as low-normal [4,5]. Many laboratorial tests have been suggested to help diagnosing vitamin B12 deficiency, between them serum holo-transcobalamin (holo-TC), as an early deficiency marker [5], methylmalonic acid (MMA) and homocystein (Hcy). MMA and Hcy have been shown to be very sensitive markers in vitamin B12 deficiency [4-6,9]. Still, Hcy may be elevated in many situations, such as folate deficiency, levodopa use and familial hyperhomocysteinemia. Thus, vitamin B12 deficiency is only one among many features that may increase Hcy levels. On the other hand, increased MMA levels have been demonstrated to be more specific of vitamin B12 deficiency, although they may also be high in other disorders, as renal failure [4,5].

The present study has limitations. The fact that the data used was extracted from medical records and that the patients had performed their tests in different laboratories could influence the inclusion patient's inclusion in the study. Also, the population here analyzed is formed by exclusively obese patients, which might be associated with a higher food intake and, subsequently, a higher vitamin B12 intake. As mentioned above, laboratorial dosage of MMA and Hcy may be valuable instruments to help diagnose vitamin B12 deficiency. However, these tests were not available in medical records since they are not routinely solicited. Besides, the cross-sectional design of the study itself can´t establish a cause-effect relation and forward cohort studies are necessary to reinforce the evidence of the association here reported.

Conclusion

In this study, Metformin use was associated with lower serum levels of vitamin B12. The literature shows that this vitamin deficiency is common in patients in the post operative of bariatric surgery, and, if not treated, may lead to severe hemathologic and neurologic problems. Thus, patients in use of this medication require special attention in both pre and post-operative of bariatric surgery regarding the deficiency of this vitamin.

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