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Colloquium Vitae

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FOLIC ACID OR VITAMIN B12 DEFICIENCY AND USE OF METFORMIN

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Abstract
The very informative review published in this Journal by Teixeira MEG et al. called our attention in regarding the unclear relationship between the acid folic and/or vitamin B12 deficit during the use of metformin by patients with type 2 diabetes mellitus. The authors highlighted that metformin can reduce the levels of folic acid and vitamin B12, and the serum levels of these substances must be monitored to prevent adverse deficiency effects. Another concern is about the excess of folic acid supplementation, which can increase the adverse consequences of vitamin B12 deficiency, mainly neurologic disturbances. In this scenario, the aim of the following short comments on published data from 2024 is to emphasize the important inputs presented in the first manuscript of the reference list.
Keywords: acid folic, vitamin B12, vitamin B deficiency, metformin, type 2 diabetes mellitus, insulin resistance.

Dear Editor

The very informative review published in this Journal by Teixeira MEG, et al called our attention in regarding the unclear relationship between the acid folic and/or vitamin B12 deficit during the use of metformin (MET) to control type 2 diabetes mellitus (T2DM)[1]. As MET can reduce the levels of folic acid and vitamin B12, the serum determinations of these substances must be monitored to prevent the occurrence of their deficiency effect. One should estimate the real magnitude of these concerns, based on the global population with diagnosis of T2DM and on daily using MET as one of the best management options. Additional care is about the excess of folic acid supplementation, which can increase the adverse consequences of vitamin B12 deficiency, mainly the neurologic disturbances[1]. In this setting, the aim of the following short comments on published data in 2024 is to highlight the important inputs presented in the first manuscript of the reference list[2-9]. Worthy of note, the worldwide prevalence of T2DM is steadily increasing, and the prevalence of diabetes mellitus of 10.5% in 2021, is estimated to be 11.3% by 2030[9].

A literature review about the use of MET and vitamin B12 deficiency, performed from 2009 to 2021, found 21 articles confirming an association and four did not show this[2]. The estimated prevalence of this deficiency in diabetics using MET can be up to 93%; however, the pathophysiological mechanisms involved are not yet totally understood. Males had lower vitamin B12 levels, black people had a low prevalence of deficiency; while obesity, coronary disease, and polycystic ovary increased the risk of deficiency[2].

The estimated global number of diabetics by 2045 is at least 629 million patients, which increases the current concerns associated with the longstanding adverse drug reactions[2]. In a Saudi Arabian cross-sectional study among 388 diabetics, 49.5% were males, 84.5% of them utilizing MET, and approximately 73% were also utilizing the vitamin B12[3]. Almost 50% did not know why they needed to take the vitamin, while the younger aged patients had been advised about the favorable effect of vitamin B12 for all diabetics; the authors concluded that the healthcare providers should better inform all these patients[3]. From 2000 to 2020 4,203,020 patients taking MET and also underwent vitamin B12 level testing at any time after 1 month from initial medication were comparatively evaluated[4]. Of these, only 25% had the vitamin

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B12 levels tested, with the main differences occurring in 2000–2002 (39.6%) and 2018–2020 (20.1%); the decline in testing during these periods could have a negative role on the early detection of a harmful vitamin B12 deficiency.

The authors emphasized the routine monitoring of vitamin B12 use by the level testing[4]. The evaluation of 118 patients was distributed by two groups: 59 taking only MET, and 59 utilizing MET plus gliptin (35 used vildagliptin/MET and 24 used sitagliptin/MET; their demographic data, initial and 1-year follow-up blood parameters were analyzed[5]. Folic acid level decreased in the MET group but not in the MET/gliptin group; vitamin B12 and ferritin decreased in both groups, without differences between them; decreased fasting glycemia was more significant in the MET/gliptin group than in MET group[5]. After one year, patients using MET and MET/gliptin had low ferritin and vitamin B12, which must be monitored; ferritin levels can indicate if glycemic control was achieved[5]. Evaluation of data from 36,740 patients with T2DM showed that 16.9% used MET and had a mean age of 65.3 years; vitamin B12 deficiency was found in 7.5% of MET users and 6.3% of those not using MET; MET users had a 4.7% higher risk of the deficiency. Each additional year using MET increased in 5% the chance of vitamin B12 deficiency, and the use for 4 or more years resulted in 41% increased odds for this deficiency; the authors emphasize the long-term MET use and higher risk of B12 deficiency in T2DM[6].

A cross-sectional study from February to June 2023 among 156 patients with a mean age of 56.3 years, median DM duration of 4.8 years, median MET use duration of 48 months, had a median dose of MET of 1000 mg, and a vitamin B12 deficiency rate of 18.6%[7]. Folic acid deficiency was not detected in the participants; patients with vitamin B12 deficiency had a longer duration of DM and MET use, besides the higher MET dosage[7]. An 84-year-old man with T2DM who had frequent falls in the last 10 months and an acute-on-chronic subdural hematoma used MET 1700 mg/day for more than 25 years[8]. On admission, there was impaired vibratory sensation and proprioception in the feet, and positive Romberg test, and the plasmatic level of vitamin B12 was undetectable; neurological changes improved 1 week after treatment of hematoma and vitamin B12. The authors highlighted the need for periodic monitoring of vitamin B12 status in older patients on prolonged use of MET because of gait instability, with risk of frequent falls[8]. A novel narrative review included data about screening, diagnosing, and treating vitamin B12 deficiency among patients who underwent MET therapy to manage their T2DM[9]. The authors focused on diagnosis criteria for vitamin B12 deficiency and the use of biomarkers, besides therapeutic options for confirmed deficiency in patients using MET. The relationship between vitamin B12 deficiency and a prolonged use of MET is well established, but the involved mechanisms are incompletely known; this deficiency is higher in cases of T2DM treated with high doses of MET for long periods; or when associated with risk factors of the vitamin deficiency, as advanced age or antiacid use. There are also increased risks for peripheral neuropathy and anemia in these patients[9].

CONFLICT OF INTEREST DISCLOSURES: The authors have no conflicts of interest to disclaim.

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