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Colloquium Vitae

DEFICIÊNCIA DE ÁCIDO FÓLICO EM PACIENTES QUE USAM CLORIDRATO DE METFORMINA: UMA REVISÃO NARRATIVA

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RESUMO

Este artigo reúne, apresenta e discute estudos sobre a relação entre os níveis plasmáticos de ácido fólico e o uso de cloridrato de metformina (MET). Esta é uma revisão narrativa com a seguinte questão norteadora: Pacientes em uso de MET apresentam deficiência de ácido fólico? A busca na literatura foi realizada utilizando as bases de dados Pubmed, Scielo, LILACS e Science Direct. Foram encontrados 9.930 artigos, com um total de cinco selecionados para responder à questão norteadora. Em conclusão, o uso de MET pode reduzir os níveis séricos de ácido fólico, no qual se apresentam como um evento adverso causado pelo uso do medicamento. Por este ser um medicamento amplamente utilizado, é de suma importância que haja monitoramento dos níveis séricos de ácido fólico dos pacientes pelos profissionais de saúde, a fim de evitar que atinjam os níveis de deficiência.

Palavras-chave: folato, metilfolato, biguanidas, diabetes mellitus tipo 2, anemia megaloblástica.

FOLIC ACID DEFICIENCY IN PATIENTS WHO USE METFORMIN HYDROCHLORIDE: A NARRATIVE REVIEW

ABSTRACT

This paper presents a review that brings together, presents, and discusses studies on the relationship between plasma folic acid levels and metformin hydrochloride (MET) use. This is a narrative review, with the following guiding question: Do patients using MET have folic acid deficiency? The literature search was conducted using Pubmed, Scielo, LILACS, and Science Direct as databases. 9930 articles were found, with a total of five selected to answer the guiding question. In conclusion, the use of MET can reduce serum levels of folic acid, in which they present themselves as an adverse event caused by the use of the drug. Because MET is a widely used drug, it is of paramount importance that there is monitoring of the serum levels of folic acid of patients by health professionals, in order to prevent them from reaching the levels of deficiency.

Keywords: folate, methylfolate, biguanides, type 2 diabetes mellitus, megaloblastic anemia.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic disease caused by a metabolic disorder. Hyperglycemia and glycosuria are a consequence of insufficient production and/or inability of insulin to exert its metabolic effects. It is known that this syndrome evolves in a severe, slow and progressive way and can cause acute and chronic complications. Despite not having a cure, there is treatment, through changes in lifestyle and, when necessary, the use of medication. Currently, T2DM diagnosis occurs more in adults, but it is growing more and more in children and adolescents due to increased levels of obesity, physical inactivity, and poor diet[1,2].

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Metformin hydrochloride (MET) is the first-line drug and the most used worldwide for the treatment of T2DM. This antihyperglycemic agent, belonging to the biguanide class, has been used safely for 60 years[3,4]. MET aims to reduce blood glucose levels by reducing intestinal glucose absorption, increasing peripheral glucose uptake by tissues at the muscle level, increasing insulin sensitivity, and also inhibiting gluconeogenesis[5–7]. MET is also widely used in T2DM because it reduces appetite and abdominal circumference and because it allows the combination with drugs from other hypoglycemic classes, such as sulfonylureas, glitazones and insulin[8].

One of the most common adverse events of this drug is gastrointestinal disturbances such as diarrhea, vomiting, nausea, flatulence, abdominal pain, abdominal swelling, constipation, and dyspepsia[3,9–11]. Another effect of MET use is related to the decrease in serum levels of vitamin B12 and folic acid, and to the increase in homocysteine (Hcy) concentration[12]. The reason for these changes is not yet fully elucidated in the scientific literature, but there are possible mechanisms to which they are linked.

According to Kim et al[13], the decrease in vitamin B12 levels in this situation is related to the reduction of its absorption in the gastrointestinal tract. The studies by Pawlak and Rusher[14] and Butola et al[15] report that the mechanism that induces B12 deficiency in patients using MET occurs due to the drug affecting the membrane receptors of the calcium-dependent ileal cells required for intrinsic factor uptake. Increased Hcy is related to vitamin B12 deficiency and folic acid[12]. In vitamin B12 deficiency, the development of megaloblastic anemia is frequent and the increase in Hcy is a catalyst for the progression of vascular disease[15].

Also, the reduction of folic acid may be associated with the reduction of vitamin B12, since B12 acts in the metabolization process to obtain the active form of folic acid[12]. According to Olgun, MET reduces the absorption of folic acid and can affect some types of bacteria that produce folic acid, leading to an imbalance of the intestinal microbiota[3].

The classic symptom of folic acid deficiency is megaloblastic anemia, which may also be associated with increased Hcy, increasing the risk of cardiovascular and cerebrovascular diseases. Low levels of folic acid are also related to various types of cancer, such as colorectal, breast and prostate, as folic acid acts on DNA synthesis and, when at low levels, it can induce its breakdown by incorrect incorporation of uracil into DNA or also induce its hypomethylation, leading to carcinogenesis[16].

The worldwide prevalence of patients with T2DM is high and tends to increase[1,17]. Consequently, the use of MET becomes increasingly frequent because it is a first-choice drug[4]. In this context, it is necessary to observe the evidence on the use of MET and folic acid deficiency. Therefore, this paper presents a narrative review that brings together, presents, and discusses studies on the relationship between plasma levels of folic acid and patients using MET.

METHODS

This narrative review includes the elaboration steps described by Nazareth, Kalil and Kalil[18], with the following guiding question: Do patients using MET have folic acid deficiency?

In order to reduce biases in this qualitative study, the literature search was conducted by two people at the same time, M.E.G.T. and M.A.S., in September 2022, using the following scientific databases: Pubmed, Scielo, LILACS, and Science Direct. The descriptors used were: “metformin” and “folic acid”, the Boolean operators “AND” and “OR” were used. In the databases for the “acid folic” descriptor, the Boolean operator “OR” was used, also including the keywords “methylfolate” and “folic acid deficiency”, as an alternative for searches for this descriptor.

Original articles and published case reports, with clinical results, were included covering the period from 1997 to 2010. Review articles, theses and dissertations, news, book chapters, abstracts published in conference proceedings, and scientific journals, as well as duplicate articles were excluded.

RESULTS

A total of 9930 articles were found in the databases, with a total of five (n= 5) selected to answer the guiding question. Figure 1 describes the steps taken to select the articles. The results found, after selecting the articles, are shown in Table 1.

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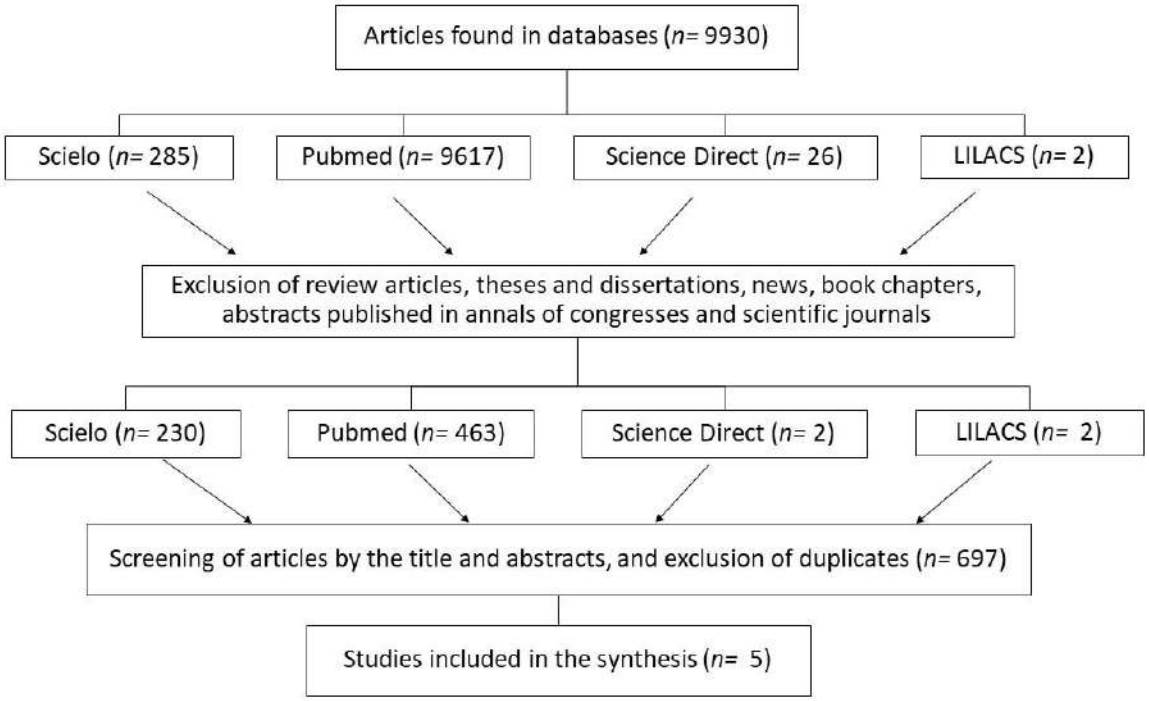

Figure 1. Flowchart selection of articles used in this narrative review.

Table 1. Characteristics of the included studies.

Authors/ Country	Characteristics of the patient	Duration of study	Results found	Markers
Carlsen et al/ Norway[19]	Under treatment with MET	12-40 weeks	Hcy levels increased, whereas serum levels of vitamin B12 and folic acid decreased when compared to the control group. Absolute levels of folic acid in the MET group and control group increased after 12 and 40 weeks	Serum folate
Wulffelé et al/ Netherlands[20]	Individuals with T2DM treated with MET and insulin	16 weeks	4 % increase in Hcy and a decrease in folic acid and vitamin B12 compared to placebo	Serum folate
Carlsen et al/ Norway[21]	Pregnant or non-pregnant women with polycystic ovary syndrome (PCOS)	16 weeks	In non-pregnant women with PCOS, there was no change in Hcy levels, and vitamin B12 and folic acid levels decreased. In pregnant women with PCOS, there was no change in Hcy, vitamin B12, or folic acid levels	Serum folate
Sahin et al/ Turkey[22]	Individuals with newly diagnosed T2DM being treated with MET and rosiglitazone	6 weeks	Decrease in folic acid and vitamin B12 concentrations and increase in Hcy levels. In the control group there was no change	Serum folate
Jager et al/ UK[23]	T2DM patients receiving treatment with MET and insulin	4, 17, 30, 43, and 52 months	Mean decrease in vitamin B12 concentration and folic acid concentration, and a 5 % increase in Hcy concentration	-

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DISCUSSION

In general, the selected studies showed a relationship between the use of MET and the decrease in the serum levels of folic acid, however it was not possible to associate this alteration with any mechanism. It is important to emphasize that this clinical condition is present both in patients with T2DM who use only this oral antihyperglycemic agent and in patients who use MET combined with insulin[20,23]. Despite the satisfactory results, some limitations were observed, such as: dietary monitoring, age difference between the placebo group and the group treated with MET, vitamin B12 supplementation and folic acid, and the lack of use of more specific indicators for the diagnosis.

In the studies by Carlsen et al[21], shown in Table 1, MET was used in the treatment of polycystic ovary syndrome (PCOS). This is an endocrine syndrome whose main consequence is anovulation. The most common clinical manifestations are: infertility, hirsutism, amenorrhea, and obesity. The relationship between PCOS and hyperinsulinism and insulin resistance is also observed. Therefore, the use of MET for the treatment of this syndrome considerably reduces body mass index and fasting insulin levels, thus improving insulin sensitivity, hyperandrogenism, the menstrual cycle, and ovulation[24].

The use of MET is strongly related to folic acid deficiency, mainly due to the decrease in vitamin B12, however this correlation requires further clarification. The results presented in Table 1 can exemplify this association, since in the five selected studies, a reduction in folic acid was observed simultaneously with a reduction in vitamin B12. When compared with the placebo group, individuals on MET treatment showed a greater reduction in folic acid levels[19–23].

According to the World Health Organization, when serum folate concentrations are below 3 ng/mL (6.8 nmol/L), it is characterized as a deficiency[25]. In order to reduce this situation, several countries have fortified foods with this macronutrient. In Brazil, this began in 2004 through RDC No. 344 of December 13, 2002, which was updated to RDC No. 150 of April 13, 2017, which establishes that wheat and corn flour must be fortified with 140 to 220 µg of folic acid and 4 to 9 mg of iron for each 100 g of flour. The Recommended Dietary Intake, Estimated Mean Requirement and Tolerable Upper Intake Limit indices for folate vary according to the age group of patients. Supplementation requires monitoring, as excess folic acid can potentiate the effects of vitamin B12 deficiency[26].

Despite all its benefits, MET has adverse events such as gastrointestinal disorders (most common) and changes in serum levels of folic acid, vitamin B12, and Hcy[12]. According to Carlsen et al[19], after 12 weeks of treatment with MET, serum levels of vitamin B12 and folic acid decreased by 13.4 % and 2.0 %, respectively, and subsequently (40 weeks), these levels were reduced by 17.7 % and 8.0 %. Data found by Jager et al[23], demonstrate that after treatment with MET there was an increase in the concentration of Hcy of 5 %. Folic acid is part of the vitamin B complex, found in foods such as beef liver, vegetables, meats, and fruits, being essential for the synthesis of nucleotides. Its deficiency has megaloblastic anemia as its main symptom[16,27].

Megaloblastic anemia is characterized by macrocytosis caused by a dysfunction in cellular DNA metabolism. This dysfunction impairs cell division, as it decreases the cell's ability to synthesize DNA, so the growth of the nucleus becomes much slower than the cytoplasm. This can be due to a deficiency of folic acid or vitamin B12, as well as the use of drugs that affect their metabolism, such as, for example, antineoplastic agents, gemcitabine and cytarabine, and the immunosuppressant, azathioprine. In addition, megaloblastocytosis can also result from interferences in the synthesis of purines (adenine and guanine), pyrimidines (cytosine, uridine and thymidine), or protein (haptocorrin)[27].

The diagnosis is made by observing typical morphological alterations in the blood count and myelogram, in addition to measuring serum levels of cobalamin, folate and/or erythrocytes, measuring urinary methylmalonate (increased in vitamin B12 deficiency), and measuring Hcy. Megaloblastic anemia caused by vitamin B12 deficiency has polymorphic symptoms, ranging from mild to very severe conditions[27,28].

It is very important to define the cause of megaloblastic anemia: vitamin B12 deficiency or folic acid. It is known that if the patient has a deficit in folic acid, vitamin B12 supplementation can improve the clinical picture. In contrast, if the patient has vitamin B12 deficiency and is supplemented with folic acid, there will be hematological improvement, but with the possibility of the neurological condition worsening. The differential diagnosis is based on specific tests of methylmalonic acid and Hcy, since vitamin B12 acts in the transformation of methylmalonic acid into succinyl-CoA and folic acid in the conversion of Hcy into methionine[28].

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Folate deficiency is considered when serum levels are below 4 ng/mL. Folate levels can be measured from red blood cells (erythrocyte folate) or from serum (serum folate). Erythrocyte folate is not influenced by drugs or food, but is reduced in the presence of severe vitamin B12 deficiency, making the differential diagnosis of megaloblastic anemia difficult. Measurement of serum folate is not a determining factor to guide the treatment of megaloblastic anemia, as it may present false-positive or false-negative results[28].

The process of absorption of vitamin B12 begins after the digestion of proteins of animal origin, captured by transcobalamin I (TC I) – R protein produced in saliva and the stomach – and degraded by pancreatic proteases. Consequently, the vitamin B12 molecule is transferred to a gastric intrinsic factor, forming a complex in the mucosa that must be resistant to the proteolytic enzymes of the intestinal lumen. This complex binds to specific receptors on the epithelial cells of the terminal ileum, where this vitamin is absorbed and bound to a plasma transporter, being released into the circulation[29]. It takes two to three hours for absorption to occur in the terminal ileum[12]. Subsequently, vitamin B12 adheres to transcobalamin II, making it bioavailable and subsequently distributed[12,29]. Alterations in the said absorption process can lead to vitamin B12 deficiency[28].

According to studies by Pawlak and Rusher[14] and Butola et al[15], the mechanism that induces B12 deficiency in patients using MET is linked to the fact that the drug affects calcium-dependent ileal cell membrane receptors, necessary for the uptake of intrinsic factor. Thus, there is a reduction in the release of vitamin B12 into the circulation, which in the long term will lead to its deficiency.

According to Butola et al[12] the serum level of vitamin B12 is directly related to the serum level of folic acid, since B12 acts as a methylfolate donor, helping in the transformation of methyltetrahydrofolate – the circulating form of folate - to tetrahydrofolate, which is the active form of folic acid, which is present in the synthesis of nucleotides and DNA. In this way, when there is a deficit of vitamin B12, a reduction in folate will consequently occur. Thus, the previously exposed mechanism and the studies shown in Table 1, which demonstrate that folic acid deficiency in the groups treated with MET are possibly associated with vitamin B12 deficiency, is validated.

It is noteworthy that the deficiency of this vitamin in patients treated with MET can induce peripheral neuropathy, cognitive impairment, and subacute bone degeneration[30]. Gupta et al[31] suggested that diabetic patients using hypoglycemic agents should be evaluated by electrophysiological tests even in the absence of signs and symptoms of neuropathy. Furthermore, in cases of deficiency, alternative routes of administration should also be considered, such as the parenteral or sublingual route, due to the impairment of enteral mechanisms by the action of MET[32].

It is known that the use of MET has as adverse events the presence of diarrhea and abdominal discomfort. This fact may be related to its accumulation in the intestine due to its rapid release and low permeability, promoting changes in the intestinal microbiota. This effect can be compared with the use of antimicrobials. MET can accumulate in the intestine, exerting a toxic action on folic acid -producing bacteria. This action also affects other folic acid -dependent species, causing potentially virulent strains to develop in the intestinal lumen, leading to the emergence of gastrointestinal adverse events[3,33,34]. There are reports that the use of MET is associated with an increase in the useful life of *Caenorhabditis elegans*, which decreases folic acid and the production of methionine by the bacteria as it is their food source[3].

According to studies by Gargari et al[35], folate supplementation with folic acid (5 mg/day) for eight weeks in patients with T2DM using MET, led to a significant increase in serum levels of vitamin B12 and folate, in addition to a decrease in Hcy. This fact may explain Carlsen's results in 2007[21], as shown in Table 1, where pregnant women did not present alterations in the levels of vitamin B12, folic acid, and Hcy. As they were pregnant, this group received folic acid supplementation, since it can prevent the occurrence of defects in the neural tubes in the fetus[21,35].

In conclusion, in view of the bibliographic survey carried out, it could be seen that the use of the drug MET can reduce the serum levels of folic acid and vitamin B12, which are presented as an adverse event caused by the use of the drug. However, there is still a shortage of studies that directly assess the serum levels of folic acid in patients using MET. Thus, it is suggested to carry out a clinical study to exclusively monitor folic acid levels in patients using MET in order to investigate possible associated mechanisms. As it is a widely used drug, it is extremely important to monitor patients' folic acid serum levels, as well as vitamin B12, in order to avoid levels of deficiency that indicate the need for

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supplementation. Finally, it is suggested that the relationship between folic acid supplementation and the decrease in gastrointestinal disorders resulting from the use of MET be also evaluated.

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