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Research Article

Vitamin B12 Deficiency Associated with Long-Term Use of Metformin

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Abstract

Type 2 diabetes is increasing in prevalence and has a significant impact on health care resources and causes a variety of health problems, some of which can affect the quality of life. The number of patients diagnosed with type 2 diabetes has increased steadily in recent years. There are many medicines available to treat diabetes and despite the development of many newer drugs, metformin continues to be widely used as a treatment option. The drug has proven itself over time and is still recommended as the first-line therapy. Metformin remains the most widely used oral antihyperglycemic (insulin-sensitizing) agent and is prescribed to more than 100 million people worldwide [1-3]. Metformin is generally well tolerated and effective in maintaining long-term glucose control. Possible side effects of metformin are gastrointestinal intolerance and the rare occurrence of lactic acidosis, which is more likely to occur in moderate to severe chronic kidney disease. However, in recent decades, several observational studies, systematic reviews, and meta-analyses have reported a connection between long-term metformin treatment and a biochemical vitamin B12 deficiency, including overt or borderline vitamin B12 deficiency. This article aims to prove Vitamin B12 deficiency associated with long-term metformin treatment for diabetes patients [4,5].

Keywords: Vitamin B12 Deficiency, Peripheral neuropathy, Megaloblastic anemia, Metformin, Diabetes mellitus

Introduction

Metformin works by reducing the amount of glucose produced by the liver and increasing the patient's sensitivity to insulin. The most prescribed drug used to treat people with type 2 diabetes can cause irreversible nerve damage in many patients. A recent study of two hospitals in the UK confirms a concern that the medical world has known for several years. Metformin causes vitamin B12 deficiency to varying degrees in approximately 10 percent of prescribed patients [5,6].

Vitamin B12 plays a crucial role in the development and function of the brain and nerve function. The biggest concern is that even a patient who maintains healthy blood sugar levels could suffer serious and permanent nerve damage. This is because vitamin B12 is essential for the formation and maintenance of the myelin sheath, a fatty substance that protects your central and peripheral nervous system. This diagnosis of peripheral neuropathy could be incorrectly attributed to the patient's blood sugar control rather than the side effects of the medications used to treat the patient's diabetes.

Once nerve damage is done it can no longer be repaired. However, after a basic blood test shows that you have a B12 deficiency, you can prevent further nerve damage by taking extra vitamin B12. Symptoms of B12 deficiency include diarrhea (which is also the most common side effect of metformin), constipation, exhaustion, loss of appetite, pale skin, sore tongue, and bleeding gums. The consequences of a vitamin B12 deficiency are permanent nerve damage, impaired brain function, memory loss, and temporary infertility in women. B12 deficiency is common in up to 15 percent of the US population in people without diabetes, according to the trusted source from the National Institutes of Health [7,8]. Although metformin may simply cause B12 malabsorption, there is no conclusive theory about why malabsorption is caused.

It should be emphasized that older people are at higher risk of developing a vitamin B12 deficiency. Other possible causes of megaloblastic anemia such as lack of intrinsic factor production, atrophic gastritis, or the use of H2 antagonists should always be considered as a possible cause of a B12 deficiency. Vegetarians (regardless of type), for example, tend to have a higher prevalence of B12 deficiency than non-vegetarians [9,10]. To clarify the cause of B12 deficiency, thorough testing and a complete medical history should be performed individually. It is noteworthy that the symptoms of peripheral neuropathy in DM2 are often attributed to long-term uncontrolled diabetes and are rarely seen because of a vitamin B12 deficiency.

Methods

Data Collection and Analysis

This study was a systematic review of publications in PubMed, Embase, Web of Science and Cochrane Library databases and the Cochrane Library. This study is a systemic review of publications in PubMed, Embase, Web of Science, and NCHI database comparing effects of long-term metformin use on Vitamin B12 levels and its effect on peripheral neuropathy and megaloblastic anemia. Databases were searched irrespective of the dates under the title "Metformin and its effects on Vitamin B12" and "Side-effects of Metformin". This study was a metanalysis of several eligible studies from public resources, thus informed content and approval were not necessary.

Inclusion Criteria

The inclusion criteria were increased fasting glucose, glucose intolerance, and overweight / obesity. The analytical population included participants with available stored samples. B12 levels were determined after 5 years.

Exclusion Criteria

Studies were excluded if the studies had incomplete data or if the study cannot be statically analyzed. Studies were also excluded on the basis if they were letters or comments. Also, literature that included the same population demographics was excluded. Only the literation which had complete results and include various demographics of the population were included.

Statistical Analysis

All information was removed from the articles' content, tables, and considers and entered along with an electronic spreadsheet for examination. For constant results, mean net contrasts (benchmark to-treatment change in treatment bunch mirrors change in charge gathering) were utilized as essential results. For clear-cut results, chances proportions were utilized to analyze the treatment impact. To evaluate distribution inclination, channel plots were built for every result. No noteworthy distribution predisposition was identified for any investigation result utilizing either measurable strategy. Furthermore, affectability examinations were directed by barring each investigation thusly, to assess its relative impact on the pooled evaluation [11-14] (Figure 1).

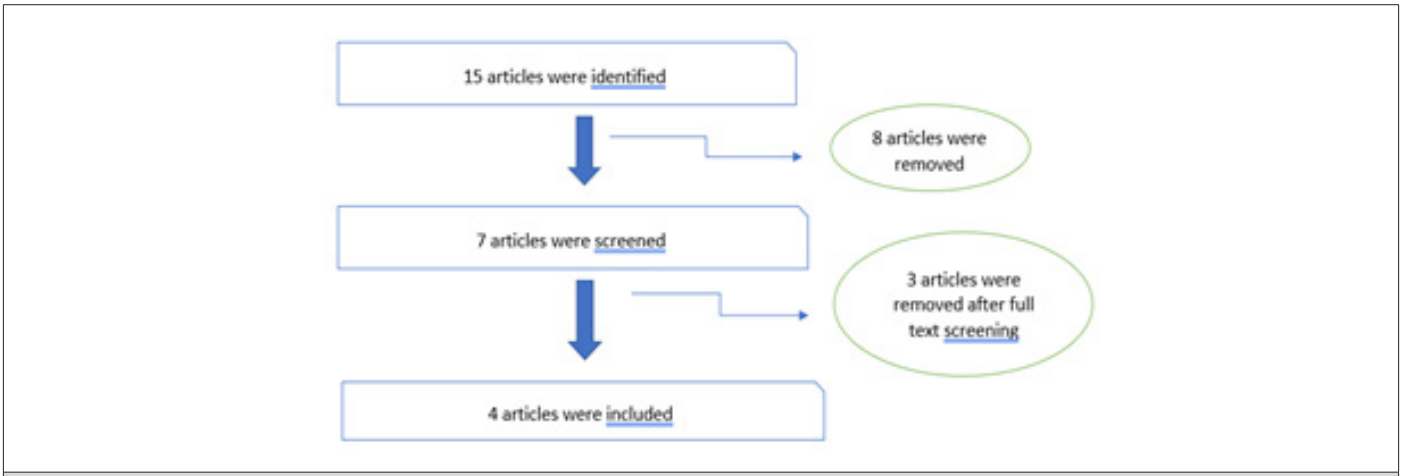

Figure 1: Identifying Different Research Papers of The Field and Differentiating the Necessary Papers.

Results

Metformin is widely used to treat type 2 Diabetes Mellitus (DM). One of the main side effects of long-term metformin therapy is vitamin B12 malabsorption, which can lead to megaloblastic anemia and peripheral neuropathy. Therefore, an annual serum vitamin B12 level or serum Methylmalonic Acid (MMA) / serum homocysteine level should be tested if metformin has been taken for more than four to five years at an average dose of> 1 g per day even if there are no hematological or neurological abnormalities. However, as the incidence of type 2 DM increases, so does the cost of measuring vitamin B12 levels annually. Given the cost factor of annual screening, vitamin B12 supplementation appears to be a more cost-effective approach than annual screening for routine

prophylaxis. Routine vitamin supplements available on the market may contain lower amounts of B12 and therefore do not have much therapeutic benefit in treating B12 deficiency due to metformin. Therefore, it is necessary to look for higher doses of around 500-2000μg / day.

Discussion

Metformin has been the most prescribed drug for the treatment of type 2 Diabetes Mellitus (DM2) since its introduction in Europe in the mid-1950s and in the US in 1995. All guidelines, including the European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA), focus on metformin as a first-line treatment option along with lifestyle interventions to control hyperglycemia in patients with DM2. Beyond glycemic control, Metformin has positive effects on lipid metabolism, inflammation, and oxidative stress. In addition, metformin can promote weight loss and has been shown to reduce the risk of myocardial infarction and all-cause mortality in obese patients newly diagnosed with DM2. Several studies have also shown an association between the use of metformin and a reduced risk of cancer in patients with DM2 [11,12].

The main side effects of metformin include gastrointestinal disorders such as diarrhea and vomiting used with caution in heart failure patients. However, if the eGFR falls below 45 ml/min, renal function should be monitored and if the eGFR falls below 30 ml/min, treatment should be discontinued. Recently, many studies have also linked the long-term use of metformin to biochemical vitamin B12 deficiency and anemia. Vitamin B12 plays an important role in red blood cell formation, nerve cell physiology, and megaloblastic anemia in peripheral homocysteine metabolism. neuropathy and cardiovascular disease.

Several studies have shown that vitamin B12 deficiency is related to both the dose and the duration of metformin. Metformin is believed to interfere with B12 uptake from the terminal ileum. A relevant study has shown that metformin-induced B12 malabsorption is calcium-dependent and can be reversed by increasing calcium intake19. An estimated more than 150 million people with T2D are taking metformin worldwide. Therefore, symptoms related to vitamin B12 deficiency are expected to be very common in such a large population. However, after studies on metformin treatment and vitamin B12 deficiency, clinically associated symptoms and complications are observed rarely.

A relevant study of megaloblastic anemia (during a mean screening period of 11.8 years) showed that 9% of the patients treated with metformin developed symptoms of the disease. There are very few cases of metformin associated B12 megaloblastic anemia in the literature. The first case of megaloblastic anemia due to long-term use of metformin was reported in the early 1980s but was unable to prove a cause-and-effect relationship. In this case, cyanocobalamin treatment increased hemoglobin levels and decreased the average volume of red blood cells. One study presented a case of megaloblastic anemia due to vitamin B12 deficiency, which led to a total gastrectomy inpatient with DM2 after the introduction of metformin therapy [13,14].

It should be emphasized that the elderly is at higher risk of developing vitamin B12 deficiency. Other possible causes of megaloblastic anemia should always be considered, such as lack of intrinsic factor production, atrophic gastritis, or the use of H2 antagonists. The daily diet must also be considered. be seen as a possible cause of a B12 deficiency. Vegetarians (regardless of type), for example, tend to have a higher prevalence of B12 deficiency than non-vegetarians. To clarify the cause of B12 deficiency, thorough testing and a complete medical history should be performed individually.

It should be noted that symptoms of peripheral neuropathy are often attributed to long-term uncontrolled diabetes in DM2 and are rarely seen because of vitamin B12 deficiency and have been shown to have symptomatic peripheral neuropathy taking metformin-reduced vitamin B12. More severe levels and symptoms compared to similar patients who were not exposed to metformin. Although there are currently no published guidelines for the detection and control of vitamin B12 in DM2, patients who received long-term treatment with metformin when other risk factors are present. Monitoring the B12 level would also be helpful with at least an annual B12 supplement. Most likely, vitamin B12 supplementation should be considered in elderly patients with T2D who are receiving long-term treatment with high doses of metformin, especially if they have other risk factors.

Conclusion

Metformin therapy is associated with an increased risk of biochemical B12 deficiency and megaloblastic anemia. People with type 2 diabetes taking metformin should have their vitamin B12 levels tested at least once a year. More clinical studies are needed to understand the mechanisms involved in the relationship between metformin therapy and vitamin B12 deficiency, and the need for additional vitamin B12 supplementation in populations with T2DM.

Acknowledgement

None.

Conflict of Interest

None.

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