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Long-term use of Metformin and Vitamin B12 deficiency

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Abstract

There is well documented research surrounding the efficacy and utilization of metformin usage in patients with type II diabetes. It is a safe drug with minimal adverse side effects and has shown to have tremendous benefits for reducing A1C, aiding in weight loss, and improving sensitivity to insulin. This paper explores and reviews the research done surrounding possible implications of vitamin B12 deficiency, the challenges in distinguishing cause as its presentation can mimic peripheral neuropathy, and methods of screening and current guidelines. Future indications for research and important clinical pearls for clinicians providing care to these patients are included. The patient highlighted is of older age who is currently taking a combination oral hypoglycemic mediation that includes metformin. The importance of protecting and preventing permanent nerve damage is one of the main goals of monitoring for neuropathy, and vitamin B12 deficiency can mask this underlying process if diligence is not paid to proper and routine monitoring. The debate remains to how often, when, and what the best method for measuring vitamin B12 levels is.

Keywords: Metformin, vitamin B12 deficiency, diabetes

Background

Metformin has been around for a long time, with records demonstrating use at the time of Egyptian Pharaohs (Romero et al., 2017). It was approved by the Food and Drug Administration in 1995 for diabetes mellitus treatment in the United States; this was after Europe had been using it clinically and proved its safety and benefit for 20 years (Romero et al., 2017). However, while its introduction and use began as an antidiabetic agent, its treatment scope has expanded to prediabetes, gestational diabetes, and polycystic ovarian syndrome (Romero et al., 2017). Research has demonstrated clear health benefits for diabetic patients by mechanisms that decrease glucose absorption in the gastrointestinal tract, suppress glucose in both the liver and kidneys (Romero et al., 2017), increase glucose utilization in the peripheral tissues including the muscle and liver, lower lipids, aid in weight loss, and may even reduce all-cancer risk (McCulloch, 2018). It also may demonstrate cardiovascular protective benefits and be safe for that patient population (Cheng, C.S. Leung, C.P. Leung, & Wong, 2018).

With the overwhelming supporting evidence for the use of metformin and current recommendations of its utilization in diabetic patients, it's important for providers to also consider some of the potential adverse effects of its long-term use that are repeatedly noted in research, perhaps in some cases even only demonstrated by anecdote or observation. One of these adverse effects includes vitamin B12 deficiency, which occurs in up to 30% of patients on long-term metformin therapy (McCulloch, 2018). Peripheral neuropathy may develop as a result of this, and furthermore may even precede the development of megaloblastic anemia (McCulloch, 2018).

This report will investigate effects of vitamin B12 deficiency, the current guidelines surrounding vitamin B12 levels in patients taking metformin long-term, the benefits and

downfalls of doing so, and some recent evidence demonstrating a potential inaccuracy of serum vitamin B12 levels as a true indicator of deficiency. Clinically, what are the risks of not monitoring and checking vitamin B12 levels in this patient population? If the guidelines are not clear for clinical practice, how do providers navigate this to provide the best care for their patients? This literature review aims to address these questions.

Case Report

A 65-year-old male presents to the clinic for a 6-month follow-up regarding his diabetes. He currently has no complaints and states that he has been compliant in taking his medications. He isn't participating in regular exercise but works in his shop occasionally during the week. His weight has gone up, but he blames it on "in the winter it's too cold to do much." He is checking his blood sugars two to three times weekly, with varying results taken while fasting as well as pre and post prandial. He believes his morning fasting blood sugars range somewhere between 170-220.

His current medication list includes Glipizide 10 mg daily, Lisinopril 10 mg daily, Toprol XL 50 mg daily, Zocor 20 mg daily, Janumet 50-1000 BID, Aspirin 81 mg daily, and a Multivitamin daily. He has no known allergies. Past medical history includes obesity, hyperlipidemia, DM Type II, and actinic keratosis. Past surgical history includes cataracts, colon polyp removal, and carpal tunnel. He doesn't use tobacco products and drinks socially. He is due for pneumonia and tetanus vaccines as well as a colonoscopy screening.

Upon reviewing systems, the patient denied any headaches or blurred vision. He denies any changes in urination patterns and reports normal stool patterns. He describes no hypoglycemic episodes. He reports having no chest pain or shortness of breath with exertion.

Vital signs are as follows: blood pressure 138/80, pulse 72, respirations 18. Current weight is 122 kg (269 lb) and BMI is 36.5. Labs are listed in the table below:

Creatinine Urine	30.00 - 259.00 mg/dL	101.82
Microalbumin mg/L	mg/L	22.17
Microalbumin/Creatinine Ratio	0 - 30 mg/g	22
Hgb A1C	4%-5.6%	9.5 Abnormally high
Cholesterol	0 - 200 mg/dL	133
Triglyceride	30 - 150 mg/dL	167 Abnormally high

HDL	40 - 60 mg/dL	39 Abnormally low
LDL	0 - 129 mg/dL	61
Fasting	Yes, No, Unknown	Yes
Glucose	70-100 mg/dL	324 Abnormally high
BUN	7 - 18 mg/dL	16
Creatinine	0.70 - 1.30 mg/dL	0.92
BUN/Creatinine Ratio	15.0 - 20.0	17.4
Sodium	136 - 145 meq/L	139
Potassium	3.5 - 5.1 meq/L	4.3
Chloride	98 - 107 meq/L	102
CO2	21 - 32 meq/L	28
Anion Gap with K	6 - 20 meq/L	13
Calcium	8.5 - 10.1 mg/dL	9
Protein Total	6.4 - 8.2 g/dL	7.8
Albumin	3.5 - 5.0 g/dL	4.7
Alkaline Phosphatase	46 - 116 U/L	84
AST - SGOT	15 - 37 U/L	19
ALT - SGPT	12 - 78 U/L	30
Bilirubin Total	0.2 - 1.0 mg/dL	1.1 Abnormally high

There are several lab values here of concern. One of the most obvious is the hemoglobin A1C, which has gone from 8.1 (6 months ago) to 9.6 today. The blood sugar control in inadequate, so stepping up therapy is essential at this point. It is important to also focus on weight management by means of healthy diet and consistent exercise. A diabetic educator referral would be indicated at this point. He will need help revamping his diet as well as learning how to inject insulin, which is a medication that would be started at this point.

The other lab result of concern is the lipid panel. Although the LDL level is normal, the triglycerides are elevated. This patient is currently taking a low-intensity statin. According to the American Diabetes Association (2018), patients who are between the ages of 40 and 75 with diabetes who do not have a history of atherosclerotic disease should be taking a moderate intensity statin along with lifestyle interventions.

Physical exam revealed no significant concerning findings. Heart sounds were regular with no murmur auscultated. Lung sounds were clear, and effort was unlabored. The patient had normal microfilament sensation per foot exam and had adequate perfusion and sensation to lower extremities.

Current UptoDate guidelines (2019) recommend follow up specific to this patient that includes a routine diabetic clinic visit in 3 months, as A1C measures are not where they need to be, and we are adjusting the medication regimen. We may also see this patient back in a few weeks, as the Lisinopril dosage would be increased to get better blood pressure control, further aiming to prevent complications such as diabetic retinopathy, neuropathy, and cardiovascular complications (McCullough, 2019). Other labs are up to date. Close monitoring is essential until overall management is achieved.

Literature Review

Mechanisms and Monitoring

The research behind long-term use of metformin and B12 deficiency has been well documented (Hansen et al., 2018; Langan & Goodbred, 2017; Pawlak, 2017; Out, Koov, Lehert, Schalkwijk, & Stehouwer, 2018; Rodríguez-Gutiérrez, 2017), though controversial at times (Rodríguez-Gutiérrez, 2017). However, the current recommended guidelines for providers does not provide clear-cut indications for monitoring and treatment for this population (Rodríguez-Gutiérrez, 2017). There has also been some investigation that has shown serum vitamin B12 to be an insufficient test to reveal true vitamin B12 deficiency (Out et al., 2018). A look at current research concludes that providers need to have an awareness of this potential adverse effect and use their best clinical judgement to appropriately screen and treat these patients when deemed necessary. Complications that occur because of vitamin B12 deficiency can be very serious and lead to a poorer quality of life.

Although the mechanisms are not well understood (Farland et al., 2015; Hansen et al., 2018; Pawlak, 2017; Wong et al., 2018), patients with type 2 diabetes who take metformin are more prone to developing vitamin B12 deficiency (Ahmed, Muntingh & Rheeder, 2017; Hansen et al., 2018; Pawlak, 2017; Wong et al., 2018). This may be due to metformin's interference of calcium metabolism in the intestine (Wong et al., 2018). This affects the vitamin B12 intrinsic factor complex as it is calcium dependent (Pawlak, 2017; Wong et al., 2018). Presse (2016) agreed that calcium supplementation could be an effective modifier in the relationship between gastric acid inhibitors and vitamin B12 deficiency, and that the deficiency is less likely among those, who while taking gastric acid inhibitors, also took calcium supplements. Consequently, these factors may result in the vitamin B12 deficiency as the vitamin is malabsorbed (Out et al., 2018; Pawlak, 2017; Wong et al., 2018) Hansen et al., (2018) also added that the addition of

PPI's may exacerbate the deficiency by inhibiting the release of peptin and lowering acidity in the stomach, which in turn decreases the ability of the body to absorb the protein bound vitamin B12. This may point to further evidence of malabsorption being the main player in the mechanism of action.

In older populations, prevalence of vitamin B12 deficiency has shown to be as high as 53.2% in those who are diabetic and taking metformin compared to those that do not (Wong et al., 2018). Older patients not taking metformin can have vitamin B12 deficiencies that exceed 30% (Campbell, 2018). How do we determine age-related changes against medication and other factors that may contribute to this? What defines long term use? The liver stores of vitamin B12 in humans are impressive and can sometimes delay clinical symptoms for up to 10 years after deficiency onset (Langan & Goodbred, 2017). The studies reviewed aren't conclusive about what defines long-term use duration; some elude to long-term use as being several years while other studies reveal absorption issues as early as 4 months (Zdilla, 2015).

Complications

Peripheral neuropathy is one of the most common complications of type 2 diabetes mellitus (Ahmed et al., 2017), and may result in part because of a vitamin B12 deficiency (Ahmed et al., 2017). The neuropathy of diabetes may be hard to distinguish from the neuropathy that presents from a deficiency of vitamin B12 and is often wrongly or misdiagnosed as such (Ahmed et al., 2017; Farland et al., 2015; Out et al., 2018; Rodríguez-Gutiérrez, 2017; Wong et al., 2018). Permanent nerve damage cannot be reversed if this is not caught in a timely manner (Farland et al., 2015; Out et al., 2018; Wong et al., 2018). These symptoms range from parasthesias, loss of cutaneous sensation, muscle weakness, abnormal reflexes, urinary and

bowel incontinence and loss of vision, among others (Zdilla, 2015). These permanent changes can be seen and reflected on imaging scans (Zdilla, 2015).

Studies surrounding vitamin B12 related neuropathy are also inconclusive and difficult to make a case for (Ahmed et al., 2017; Out et al., 2018), as metformin may have neuroprotective effects by its ability to lower blood glucose (Campbell, 2018; Out et al., 2018) and abolish pain induced by activation of sensory neurons (Ahmed et al., 2017). In many cases, neuropathy may be the only clinical manifestation of vitamin B12 deficiency, and hematologic presentation may be absent (Ahmed et al., 2017). Research is difficult to obtain to determine the true relationship between metformin use and worsening peripheral neuropathy because of the deceptive and indirect nature of how neuropathy presents clinically (Ahmed et al., 2017).

Screening

There are currently conflicting recommendations regarding routine screening of vitamin B12 deficiency when considering the discontinuation of metformin. According to the American Diabetes Association, periodic measurement of vitamin B12 levels should be considered in those who are taking metformin, with special attention in those who also have anemia or peripheral neuropathy (Standards of Medical Care in Diabetes, 2019). Some sources reported that screening vitamin B12 levels for average-risk adults is not currently recommended (Langan & Goodbred, 2017; Rodríguez-Gutiérrez, 2017), while others recommended reassessing metformin use for high risk populations (Langan & Goodbred, 2017). These high-risk populations use include those using the drug for more than 4 months (Langan & Goodbred, 2017). Another source recommended annual vitamin B12 screening for anyone on metformin; this is based on the Glucophage package insert (Farland et al., 2015). Langan & Goodbred (2017) further recommended routine screening for patients with gastric or small intestine resections,

inflammatory bowel disease, use of PPI's or H2 blockers for more than 12 months, those who consider themselves to be vegan, and the older adult population (those older than 75 years).

It is evident that a specific time and frequency to screen for vitamin B12 deficiency in patients taking metformin has not been established. However, the consensus could be assumed that anytime a clinical manifestation is suspected, diagnostic testing should be considered; perhaps screening could even be warranted without clinical manifestations (Out et al., 2018). Sources indicate a vitamin B12 level of less than 150 pg per mL diagnostic for a deficient level (Langan & Goodbred, 2017; Out et al., 2018). Caution in false high levels is indicated in patients with alcoholism, liver disease or altered hepatic clearance (Langan & Goodbred, 2017).

Whether or not serum vitamin B12 levels are a true indicator of levels in the body is a controversial subject (Out et al., 2018). Measurement of serum methylmalonic acid (MMA) should be a consideration and utilized to confirm a true vitamin B12 deficiency in those who may be high risk, asymptomatic, with low-normal results on a serum vitamin B12 test (Langan & Goodbred, 2017; Out et al., 2018). MMA is a much more direct measure of vitamin B12 and its physiological function (Farland et al., 2015; Langan & Goodbred, 2017; Pawlak, 2017; Rodríguez-Gutiérrez, 2017).

Serum MMA levels will rise when vitamin B12 levels are low, which can give a more accurate picture for clinicians (Out et al., 2018). The continual use of metformin over time has a progressive effect and continues to increase MMA levels, which further reduces vitamin B12 levels (Out et al., 2018). Vitamin B12 is a major player in the conversion of methylmalonic acid to succinyl coenzyme A, which is important in neurological function in the body (Ahmed et al., 2017; Langan & Goodbred, 2017; Pawlak, 2017;). Pawlak (2017) also discussed holotranscobalamin II homocysteine (HoloTC) levels as being a better measure of vitamin B12

status; it is the carrier of vitamin B12 into cells and has a short-half life. This measure can reveal early deficiency of active vitamin B12 (Pawlak, 2017).

Another potential issue in diagnostic measuring is that in cases of high glucose concentration (most diabetics), vitamin B12 may be caught in plasma which would show a false high level, while the patient might actually have a deficiency (Pawlak, 2017). Pawlak theorized that metformin only has an impact on the vitamin B12 levels that are circulating in the body, and that it doesn't affect intracellular levels (2017). Obviously, more research is needed to establish solid and accurate methods of measurement if we are to best move forward with the best treatment plans for patients.

Treatment

Intramuscular injections of cyanocobalamin or oral vitamin B12 are the current recommended treatment for deficiency (Pawlak, 2017), with the British Society for Hematology recommending every other day injections for up to three weeks for those who are experiencing neurological deficits (Langan & Goodbred, 2017). Neurological symptom progression such as nerve damage can possibly be stopped by supplementation of vitamin B12 (Farland et al., 2015) To maintain adequate vitamin B12 levels in diabetic patients taking metformin, a dose of 25ug/day or higher may be warranted, with those who use other medications that affect gastric acidity potentially needing up to 250 ug/day to maintain therapeutic levels (Pawlak, 2017). Langan & Goodbred (2017) claimed that serum methylmalonic acid levels do not improve with oral vitamin B12 supplementation, though this hasn't been studied thoroughly. If indeed methylmalonic acid levels are a better indicator of vitamin B12 levels in the body, one must consider route of replacement.

Regardless of the uncertainties and differing conclusions about which route and dosage of vitamin B12 supplementation is superior, clinicians must be diligent about prescribing adequate replacement in those patients in which it is reasonable and appropriate. Prophylactic vitamin B12 supplementation is not discussed in this literature review nor was it noted in any of the articles as a consideration, though future studies may or may not explore that as a possible treatment adjunct for those with type II diabetes.

Learning Points

The focus and evaluation gathered from this literature synthesis is that there remains to be inconclusive evidence on the best diagnostic screening and frequency of vitamin B12 deficiency in long-term users of metformin. It is currently unclear because the signs and symptoms of diabetic neuropathy and vitamin B12 deficiency can manifest the same. We also haven't established a gold standard of laboratory testing that would give us our best indicator of vitamin B12 status within the body. Until further guidelines are established, clinicians need to be aware of the ability to screen and treat when it is clinically indicated. We want to prevent complications that are irreversible and provide our patients with the best quality of life possible. In summary:

- Vitamin B12 deficiency is a serious clinical consideration for patients who have been taking metformin long-term
- Diabetic neuropathy manifestations can be masked due to the overlapping similar symptoms of vitamin B12 deficiency
- It is reasonable for clinicians to screen vitamin B12 levels on a routine basis and treat with supplemental vitamin B12 based on clinical judgement so to avoid complications of deficiency

- More research is needed to establish accurate vitamin B12 deficiency diagnostic and screening guidelines

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