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Ask the PHARMACIST

Metformin and Vitamin B12 Deficiency

By James S. Scozzari, RPh

Q: I am a 72-year-old woman currently taking metformin for diabetes. My diabetes is well controlled with this medication, but I heard from a friend that metformin can cause a deficiency of vitamin B12. Can you tell me if this is true, and if so, what I can do about it? I do not want to stop taking this medication.

A: Many patients who are taking metformin, as well as quite a number of their physicians, are not aware that a deficiency of vitamin B12 (cobalamin) is a potential side effect of the drug. Studies have found that 10-30% of patients taking metformin experience below-normal levels of serum B12; these individuals previously had normal serum B12 levels.¹

So your friend is right, and you do have reason to be concerned. However, it is possible to avoid this problem and to safely continue taking metformin by adding daily supplements of vitamin B12 and calcium. Metformin has also been found to interfere with calcium metabolism, which can affect B12 absorption, so calcium supplements are also recommended for metformin patients.

UNDERSTANDING DIABETES

About 20% of North Americans over the age of 65 have type 2 diabetes, which too often becomes a chronic, progressive, and irreversible disease. An even greater percentage of American adults suffer from metabolic syndrome or pre-diabetes, which may cause more arterial disease than type 2 diabetes, since so many aging people are affected. The causes of type 2 diabetes (as well as metabolic syndrome) include genetics and normal aging, as well as environmental factors such as obesity, poor diet, and a sedentary lifestyle.

Patients with type 2 diabetes initially suffer from "insulin resistance," which means that the body's cells do not respond appropriately when insulin is present. The body responds initially by overproducing insulin (hyperinsulinemia) to drive more glucose into the cells. As the disease progresses, the insulin-producing beta cells of the pancreas become dysfunctional, and the type 2 diabetic may become dependent on drugs that stimulate insulin production, or require exogenously administered insulin to keep excess blood glucose under some degree of control.

Symptoms of type 2 diabetes may include fatigue, extreme thirst, blurred vision, and skin infections. In its early stages, type 2 diabetes can be treated through changes in diet, exercise, and weight loss, especially in obese patients. In many cases, these initial efforts can substantially restore insulin sensitivity.

However, if these efforts are not successful, the next step is treatment with anti-diabetic oral agents, such as metformin and/or one of the newer classes of anti-diabetic medications such as Januvia® (sitagliptin), which functions to speed the insulin response to food, decrease glucagon-mediated glucose postprandial (after-meal) output in the liver, and reduce fasting blood glucose levels. If these anti-diabetic oral agents fail or stop helping, the next step is to add insulin therapy.

METFORMIN

Metformin, an oral medication used by patients with type 2 diabetes who do not require daily injections of insulin, is sold under the brand names Glucophage®, Fortamet®, Riomet®, Glumetza™, and Glucophage® XR. It is also available as a low-cost generic.

Metformin mimics the effects of calorie restriction, the most scientifically documented way to slow aging and extend life span in animals. Metformin works by helping to remove excess glucose from the blood, slowing down the release of additional glucose (from glycogen) from the liver, and reducing excess insulin levels. The drug functions by decreasing intestinal absorption of glucose and improving insulin sensitivity, thereby increasing peripheral glucose uptake and utilization.



The most significant calorie-restriction-mimicking effect of metformin, however, is that it produces some of the favorable gene expression changes observed in response to radically reduced food intake. Metformin may also mimic the physiologic effects of decreased calorie intake by modifying certain metabolic and stress response pathways. In most cases, metformin does not produce hypoglycemia (abnormally low blood glucose). Although most people do well on metformin, it is important to be aware of the possibility of certain side effects, which may include vitamin B12 deficiency.

METFORMIN AND VITAMIN B12 DEFICIENCY

In recent years, a number of studies have concluded that metformin can cause a vitamin B12 deficiency in some patients, although the precise mechanism by which this occurs remains unknown.

A 2006 study reported in *Archives of Internal Medicine* found “an increased risk of vitamin B12 deficiency associated with current dose and duration of metformin use,” and advised screening and prevention strategies for metformin-treated patients.² In 2004, a study reported in the *British Journal of Diabetes and Vascular Disease* found that patients exposed to metformin had significantly lower serum B12 concentrations than those who did not use the medication,³ while a 2006 study in *Age and Ageing* found that in patients taking metformin, the drug was not always the cause of B12 deficiency, but that the clinician must be aware of the possibility of metformin-related B12 deficiency in older patients with diabetes, and should test accordingly.⁴

Although the exact cause of vitamin B12 deficiency with metformin use remains unknown, one possible factor is interference with B12 absorption created by the B12-intrinsic factor complex. However, this can be reversed quickly with vitamin B12 supplementation (or with discontinuing the use of metformin). Metformin may interfere with calcium metabolism; this may indirectly reduce vitamin B12 absorption, since vitamin B12 absorption requires calcium. Researchers also found that using calcium supplements (1,200 mg/day) helped limit metformin’s effect on vitamin B12 absorption in a group of individuals.¹ In addition, certain individuals who use metformin may have an inadequate intake or absorption of vitamin B12; these two causes are often linked to vitamin B12 deficiency in patients on metformin. It has also been suggested that metformin can induce food-cobalamin malabsorption.⁵

VITAMIN B12

Vitamin B12 plays an important role in DNA synthesis and neurological function, and aids the formation of red blood cells. It may protect us from fatigue, cardio-vascular disease, Alzheimer’s disease, depression, and mood swings. For diabetics, B12 helps to restore normal nerve transmission, counteracts the “pins and needles” tingling that often goes with the disease, and assists in keeping homocysteine levels low, thereby preventing cardiovascular disease. Some good dietary sources of B12 include clams, liver, salmon, beef, and fortified breakfast cereals.⁶ Since vitamin B12 primarily occurs in animal products, vegetarians must be particularly diligent in consuming enough B12.

It is a good idea to become familiar with the symptoms of vitamin B12 deficiency, which include: depression; weakness; fatigue; lightheadedness; a pale appearance; a sore, red tongue; bleeding gums; nausea; decreased appetite; weight loss; diarrhea or constipation; headaches; memory loss; or nervousness. Remember that if you are taking metformin and experience one or more of these symptoms, it does not necessarily mean you have a B12 deficiency, so it is important that you work with your doctor to find out the cause(s) of your symptoms.

You should also be aware that some of the symptoms of B12 deficiency, such as memory loss and nervous system disorders, are frequently misattributed to the aging process; doctors may not readily connect these or other symptoms with nutrient deficiencies induced by medications such as metformin.⁷

Finally, long-term vitamin B12 deficiency can cause cognitive impairment that can not always be reversed, so it is very important that you begin supplementation without delay.

PRACTICAL RECOMMENDATIONS

Because of the potential problems that can arise due to below-normal levels of both vitamin B12 and calcium, the following are strongly recommended for everyone taking metformin on a regular basis:

- A daily supplement of 1000 mcg of vitamin B12.
- A daily supplement of 1,000 to 1,200 mg of calcium.
- An annual or semi-annual blood test to check your B12 levels, which you may want to discuss with your doctor.⁸

In addition:

- Remember to always take metformin with or after meals.
- If you are taking the extended release type of metformin (Glucophage® XR, Fortamet®, Glumetza®), always swallow the tablet whole and never chew it, since chewing breaks down the coating of the extended release form, and the medication will not be effective.
- Your doctor will instruct you to temporarily stop taking metformin if you have surgery or any medical procedure that involves the use of injectable contrast dyes.

CONCLUSION

Many prescription drugs can cause a deficiency in one or more nutrients. Unfortunately, patients and physicians are usually unaware of this fact, and often fail to recognize that resulting health problems are a direct result of easy-to-remedy vitamin deficiencies.

Taking vitamin B12 and calcium supplements as a preventive measure is beneficial for everyone taking metformin. Do not hesitate to begin taking these supplements on a daily basis to avoid any possible future complications with your health. If you have any other concerns about metformin, consult your physician or pharmacist.

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