



Diabetes in focus



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Metformin's Link to Vitamin B12 Deficiency

Contributed by: Saranya Venkatachalam, 3rd Year PharmD. Candidate

Metformin is the first-line treatment for patients with Type 2 Diabetes due to its low cost, low incidence of hypoglycemia, low rate of drug-drug interactions because of renal excretion, and improvement of cardiovascular morbidity and mortality. However, recent studies have shown that metformin modulation of calcium-dependent membrane channels can reduce vitamin B12 levels. Because B12-intrinsic factor complex uptake is calcium dependent, metformin can hinder vitamin B-12 absorption by the intestines.¹ Vitamin B-12 is essential for maintaining the health of red blood cells and nerve cells, and a lack of B-12 can lead to a wide array of symptoms such as anemia, fatigue, cognitive changes, and nerve damage.

Signs of B-12 Deficiency

Tingling	Mood changes
Difficulty Walking	Memory loss
Weakness/Fatigue	Bruising

Studies indicate that metformin use for a course of 4 years leads to an average of 20% reduction in B-12 levels.² Patients taking metformin were 12% more likely to suffer from B-12 insufficiency and 7.2% more likely to experience B-12 deficiency ($p < 0.001$). Insufficient vitamin B-12 levels were also correlated with increasing levels of homocysteine, a cardiotoxic amino acid.² In a recent study, chronic metformin use led to a vitamin B12 deficiency in 30% of the people. Further, more than 75% of people with low B12 also had peripheral neuropathy. Peripheral neuropathy is often misdiagnosed as diabetic neuropathy and the root cause (i.e., vitamin B12 deficiency) is not treated. This can lead to further nerve damage and cognitive impairment.³ While a direct relationship cannot yet be verified, ADA strongly recommends that all patients on metformin take supplemental vitamin B-12 or calcium to reduce the chances of nerve damage. Furthermore, studies also indicate that

10% of people on long-term metformin develop B12 related megaloblastic anemia.⁴

Metformin is a chronic medication, and the B-12 deficiency can worsen with time. Therefore, regular assessments of B-12 during long-term metformin treatment should be considered, and physicians should routinely screen patients for neuropathy and megaloblastic anemia. For prophylactic measures, a vitamin B12 supplement can be taken along with the medication. Adults need an average of 2.4 mcg of B12 daily. Elevated serum homocysteine and urinary methylmalonic acid (MMA) levels are also indicative of B12 deficiency. Recommending that patients who take metformin eat foods rich in B12 or take a daily multivitamin containing 100% of the daily value for vitamin B12 will be beneficial for patients and is a valuable counseling tip for pharmacists.⁵

Foods Rich in Vitamin B-12

Seafood	Cheese
Beef	Eggs

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Could A Spoonful of Cinnamon Help Lower Blood Glucose?

Contributed by: Shelley Strickland, 2013 Doctor of Pharmacy Candidate

Scenario: A patient walks into your pharmacy and tells you that her most recent A_{1c} was 7%. She read on WebMD that supplementing with cinnamon could help lower her blood glucose. She fills all her diabetic medications at your pharmacy, and she wants to know your opinion about if this is a good option for her.

There are many different species of cinnamon, but two of the most common types include ceylon cinnamon (*Cinnamomum verum*) and cassia cinnamon (*Cinnamomum aromaticum*). Ceylon is most commonly used in baking cinnamon rolls, muffins, and other food items; however, most studies investigating the efficacy of cinnamon in diabetes uses cassia cinnamon, and only cassia has been shown to affect blood glucose in humans. Most *in vitro* and *in vivo* studies suggest that cinnamon's mechanism of action involves activating glycogen synthesis and enhancing glucose uptake by increasing the activity of the insulin receptor. The effects of cinnamon were studied on 60 type 2 diabetic patients.¹ This randomized placebo controlled trial evaluated the reduction in mean fasting blood glucose at cinnamon doses of 1 g, 3 g, and 6 g.¹ Cinnamon reduced serum glucose 18-29% (results were not dose dependent), suggesting that this natural product was a useful supplement in combination with standard therapy, but since this publication, new evidence has emerged blurring the value that cinnamon supplementation plays in diabetes management. In 2007, an article in *Diabetes Care* evaluating 72 type 1 diabetic patients treated with cinnamon or placebo for 90 days determined that there were no significant differences in the change in A_{1c} between the two groups.² The next year the journal published a meta-analysis that included five randomized controlled trials with 282 type 1 and type 2 diabetic patients.³ All studies used cinnamon cassia, and doses ranged from 1 g to 6 g. The researchers concluded that there were no significant changes in A_{1c} or fasting blood glucose between the cinnamon and placebo groups. Analysis of type 1 and type 2 diabetics separately did not alter the outcome. Other recent studies have replicated these incon-

clusive results.⁴ In 109 type 2 diabetics randomized to cinnamon or placebo, cinnamon lowered A_{1c} by 0.83% (95% CI, 0.46-1.20). Another recent meta-analysis evaluating 577 type 1 and type 2 diabetics showed conflicting results and insufficient evidence to support the supplementation of cinnamon for glucose management.⁵ Currently, the American Diabetes Association (ADA) position on the use of cinnamon in diabetes mellitus states that current studies do not validate the use in this disease state. The organization concluded that cinnamon does not replace the standard therapy of "medication, a healthy diet, and exercise" for diabetic patients. According to Micromedex, cinnamon only interacts with tetracycline antibiotics by reducing their efficacy. Cinnamon has limited side effects, but the most common include dizziness, nausea, vomiting, and abdominal cramps. The product is safe for most patients unless there is a documented sensitivity to the agent. Based on this information, what do you tell your patient about this product? Do you recommend she use this supplement along with her current therapy? Key points to include in your answer might be the lack of conclusive evidence at this point in time, the ADA's position statement, a recommendation to consult an endocrinologist if the patient is looking to further intensify their diabetic therapy, and finally a reminder to always include vitamins and natural supplements in conversations with healthcare professionals about medications a patient takes.

Bonus Question: When making recommendations on natural supplements, what is one quality assurance to instruct your patients to look for when choosing a product?

Answer: United States Pharmacopeia (USP) label on bottle.

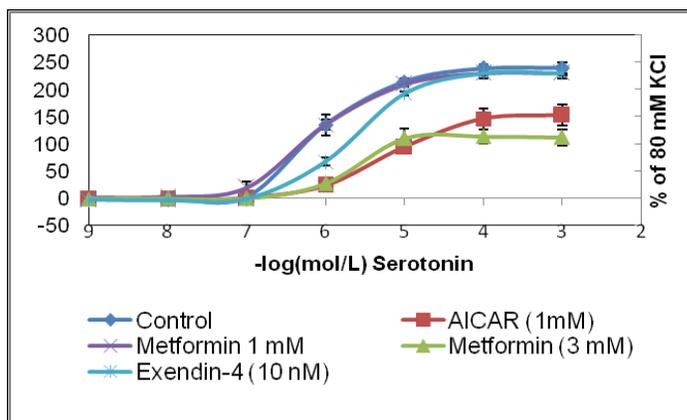
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Vascular Protective Effects of Metformin

Contributed by: Paul Hansen, 4th year PharmD Candidate

Metformin is the only oral anti-hyperglycemic that has been shown to reduce overall mortality. This study was designed to assess the vasoprotective effects of metformin by evaluating its inhibition of vascular contraction in response to serotonin, which is released during vascular injury. Rodent aorta samples were denuded of their endothelial lining by passing a small tube through each vessel. The vessel was then cut into rings, mounted onto a myograph, and placed into a physiologic, oxygenated buffer. Samples were treated with potassium chloride to assess viability, then acetylcholine to evaluate removal of the endothelium. Finally serotonin, metformin, and 5-amino-1- β -D-ribofuranosyl-imidazole-4-carboxamide (AICAR) were added in varying concentrations depending on the treatment groups to record the force of contraction. At 3 mM concentrations, metformin showed statistically significant inhibition of serotonin induced contraction with a p value <0.05. Furthermore, this inhibition was represented by not only an increased EC₅₀, but also a reduced overall maximal response. The 3 mM metformin group was statistically equivalent to the 1 mM AICAR group.¹ Metformin showed inhibitory effects on serotonin-induced contraction, indicating it



may have a stabilizing effect on vascular smooth muscle cells. This stabilizing effect could partially contribute to the reduction in mortality associated with metformin use.²

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1. Paul Hansen, Pharm. D. Candidate, Rajkumar Pyla, M.D., Ph.D., Lakshman
2. Segar, Ph.D. Metformin treatment and washout attenuate serotonin-induced contractility in endothelium-denuded aorta. Poster presentation at ACCP. Hollywood, FL. October 2012.

TOD²AY's Recommended Diabetes Therapy in Pediatrics

Contributed by: Andrea Sikora, 4th year PharmD candidate

TOD²AY stands for Treatment Options for Type 2 Diabetes in Adolescents & Youth.¹ The study was a randomized clinical trial to compare the efficacy and safety of three interventions: metformin, metformin plus rosiglitazone, and metformin plus an intensive lifestyle program incorporating nutrition, physical activity, and behavior modification.¹ While generally accepted that metformin is the first line agent in type 2 diabetes treatment, little data exist to guide therapy upon treatment failure. Further, little data existed on how many patients were failing metformin therapy. While the use of rosiglitazone, given its severely restricted status, may seem an unlikely choice, the black box warning surrounding rosiglitazone describes an increased risk of heart failure secondary to edema. Because the study population was aged 10-17 years old, the risk of rosiglitazone-induced heart failure is quite low. The primary outcome of this study was time to treatment failure and percentage of treatment failure. Overall, 45.6% of the study population reached

treatment failure within one year.² Metformin monotherapy had a 51.7% treatment failure, and the metformin + rosiglitazone treatment group had significantly less treatment failure with 38.6% ($p=0.006$).² The metformin-lifestyle group showed no difference as compared to metformin alone. These findings are significant because it shows that 1 in 2 youth will require combination therapy to reach an appropriate A_{1c}. For pharmacists, this study points towards the necessity of a more aggressive treatment plan in type 2 diabetes in the pediatric population. If at 1 year of metformin therapy, a patient is not well-controlled, additional therapy with a second agent should most likely be recommended.

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Pharmacist Role in Diabetic Foot Infection Management

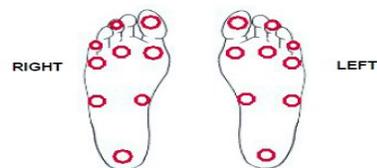
Contributed by: Beth Ensley, 4th year Pharm.D. candidate, Sarah Evans, 4th year Pharm.D. candidate, and Eunice Kim, 4th year Pharm.D. candidate

Pharmacists play a pivotal role in the management of diabetic foot infections (DFIs), a frequent and potentially devastating complication of diabetes. For community pharmacists, providing information to diabetic patients about the appropriate management of diabetes through medication, diet, and exercise, and stressing the importance of proper foot care can prevent many of these infections. The community pharmacist can triage and refer patients to the appropriate healthcare provider if necessary. Referral is warranted if there are any a) purulent secretions or b) two or more signs of inflammation, such as erythema, warmth or induration. If a patient must be hospitalized due to a severe infection or concerns of noncompliance, the hospital pharmacist can further assist in the management of the patient's care by deciding when antimicrobial therapy is necessary and what agent(s) to select. The Infectious Diseases Society of America (IDSA) recommends using antibiotics only in patients with clinical signs of an infection. This prevents overutilization of antibiotics and decreases the risk of unnecessary side effects and resistance. If the wound is infected, however, antibiotic therapy should be combined with wound care

since most mild-moderate infections are caused by Gram-positive cocci, agents that target these organisms are usually sufficient. For more severe infections, broad-spectrum antibiotics should be initiated while cultures are pending. Coverage for *Pseudomonas aeruginosa* is usually not required unless there are compelling reasons why a patient may be at risk for this organism, such as recent hospitalization or antibiotic use, or residence in a long-term care facility. Once cultures have returned, the pharmacist can assist in narrowing coverage for the susceptible organisms and ensuring an appropriate route and duration of therapy. Patients should receive oral therapy for 1-2 weeks for mild infections and parenteral therapy for 2-3 weeks for more severe infections. Conversion to oral antibiotics during treatment is often possible, and opportunities for these "IV to PO" switches should be continually monitored by pharmacists. Upon discharge, both the community and hospital pharmacist can play a vital role in counseling the patient on medication side effects and importance of compliance. Diabetes disease state education on foot examinations and appropriate footwear can also ensure future complications are less likely to occur. Thus, the role of the pharmacist in managing DFIs can not only save money by selecting the appropriate therapy, but can also restore quality of life to diabetic patients and prevent countless unnecessary amputations.

Overview of Providing a Sensory Exam:

1. When conducting a sensory exam, the patient should not watch while the examiner applies the monofilament.
2. Try the monofilament on the patient's hand so they know what to expect
3. Test the nine sites as indicated on the image to the left
4. Press the monofilament to the skin's surface and apply sufficient force to cause the monofilament to bend. This process should last 1-2 seconds.
5. Do not apply the monofilament on an ulcer site, callus, or scar and do not slide the filament across the skin
6. Press the monofilament to the skin twice with each time saying to the patient "time one" and "time two" so that the patient can identify which time they were touched
7. Randomize the sequence of applying the filament throughout the exam



Diabetes and OTC Products

Contributed by: Uvette Lou, 4th year PharmD candidate

One of the community pharmacist's most important jobs is answering patient questions about over-the-counter (OTC) products. Diabetics often have questions regarding the effects of OTCs on their medications and their blood glucose, and a pharmacist should consider at least three factors when counseling a patient: blood-sugar raising capacity of the medication, the patient's comorbid conditions, and possible drug interactions. An easy thing to consider when recommending products is the sugar and alcohol content. Decongestant and/or antihistamine syrups such as Robitussin® or NyQuil® are examples of products with sugar and alcohol as part of the normal formulation, which can cause an increase in blood sugar. However, alternative sugar-free and alcohol-free products are available and are often marketed towards diabetics. Another alternative is for the patient to take tablet or capsule forms of these medications, which do not contain any ingredients that could raise blood sugar. During allergy season, patients often ask about the effects of decongestants and antihistamines on their blood sugar. Over-the-counter decongestants such as phenylephrine and pseudoephedrine do increase blood glucose levels. Topical decongestants like oxymetazoline, however, have a lesser effect on blood sugar than systemic agents. For patients wondering if diphenhydramine will affect their glucose levels, antihistamines have not been shown to increase blood sugar. During winter months, patients interested in antitussives, expectorants, and analgesics will be relieved to know that dextromethorphan, guaifenesin, acetaminophen, and ibuprofen have not been shown to raise blood sugar. Aspirin has been shown to lower blood sugar in several clinical trials, but only in doses well above the recommended over-the-counter dose. Patients taking niacin should be aware that niacin (even in over-the-counter doses) can increase blood sugar as well. The antagonistic effect of niacin and the patient's other blood sugar-lowering medications can cause raise blood sugar. Patients during any period of illness should monitor their blood sugar closely, regardless of whether or not they are taking over-the-counter medications. Sickness can cause both hypo- and hyperglycemia even without the added effect of medications. Since diabetic patients often have comorbid conditions, pharmacists should take extra time to consider other drug-disease interactions. For example, patients with concurrent hypertension should avoid decongestants and non-steroidal anti-inflammatories (NSAIDs). Patients with renal failure should avoid NSAIDs. Patients with liver failure should avoid acetaminophen. Finally, pharmacists should scan the patient's prescription profile and ensure that no dangerous drug interactions are possible, and if a drug interaction exists, that the patient knows how to handle any potential problems. Common drug interactions between prescription and OTC medications are listed in the table below.

OTC	Prescription	Interaction	Action
Salicylates	Insulin Glipizide Glyburide	Aspirin lowers blood sugar. Additive blood sugar lowering	Monitor blood sugar closely. Educate patient on signs of hypoglycemia.
H2RAs* Antacids PPIs**	Glipizide Glyburide	Gastric pH-lowering agents increase absorption of sulfonylureas with possible hypoglycemia	Monitor blood sugar. Educate patient on signs of hypoglycemia. Take sulfonylurea 2 hours before or 6 hours after antacid. Antacids only.
Niacin	Any blood-sugar lowering agent	Niacin increases blood sugar. Antagonistic effect.	Monitor blood sugar.

*Histamine-2 receptor antagonists **PPIs: Proton pump inhibitors

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SDC Club Highlights

- SDC participated in two health fairs in October: Dawgtoberfest in Athens, GA and Barney's Health Fair in Augusta, GA.
- The first pediatric diabetes support group "Sweeties" was held at Barney's Pharmacy in October.
- SDC participated in the Junior Diabetes Research Foundation walk in Augusta, GA raising money and awareness.
- SDC was the subject of a student poster presented at ASHP Midyear in Las Vegas.



Pictured Right: Lauren Willis, class of 2014, promoting the Sweeties support group at the JDRF walk on November 3rd.