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## **Metformin (Glucophage)**

Metformin (brand name "Glucophage" or "Glucophage XR") is a drug that your doctor may have prescribed for you if you have polycystic ovary syndrome (PCOS). This drug Metformin is a drug that has been used to help control blood glucose levels in people with Type 2 Diabetes. Although Glucophage has been used in Europe for over 25 years, it was not available in the US until 1995. The FDA has approved metformin only for the treatment of Type 2 Diabetes. Consequently, some physicians don't have much clinical experience with Glucophage, or are reluctant to use it unless the patient has diabetes.

### **How does it work ?**

Metformin appears to work in three ways. First, it decreases the absorption of dietary carbohydrates through the intestines.

Second, it reduces the production of glucose by the liver. The liver uses the raw material in your food to create a reserve supply of blood sugar. When your body experiences stress, the liver releases the reserve glucose to supply your brain and muscles with an immediate source of energy to cope with the stress. Metformin suppresses the production of this reserve fuel.

Third, and perhaps most importantly, metformin increases the sensitivity of muscle cells to insulin. Insulin is the hormone that delivers glucose into your cells to be burned as fuel, or stored.

Women with PCOS, women who are overweight and some women with a genetic predisposition may have "insulin resistance", a condition where increased amounts of insulin are required in order to get blood glucose moved into cells, where it belongs. Metformin helps your body to transport glucose with relatively less insulin, thus lowering your insulin levels. Chronically high levels of either glucose or insulin in your blood contributes to obesity, heart disease, infertility, and certain cancers, as well as the development of diabetes.

### **Dosage**

Standard Metformin comes in 500 mg tablets.

The commonest side effect to Metformin is Gastro intestinal upset. ( diarrhoea)  
To minimize GI upset or diarrhea, it's recommended that you start with a low dosage and work your way up to the recommended dose. I normally suggest my patients start with

500 mg orally once a day, then if tolerated increase to one tablet twice a day – aiming for one tablet three times daily if tolerated.

### **Benefits of Metformin (Glucophage)**

#### LOWERING OF INSULIN, TESTOSTERONE, AND GLUCOSE LEVELS.

Studies indicate Metformin reduces insulin, testosterone and glucose levels -- which may reduce acne, hirsutism, abdominal obesity, amenorrhea and other symptoms.

#### PREVENTION OR DELAY OF ONSET OF DIABETES.

In women at risk for diabetes, Metformin may help to prevent diabetes.

#### RESTORATION OF NORMAL MENSTRUAL CYCLE.

In women with PCOS who are not having regular cycles ( women who are “anovulatory”) metformin may help regulate their cycles ( making them ovulatory) and thereby more fertile.

#### IMPROVED CHANCE OF PREGNANCY.

By restoring ovulation Metformin may help women with anovulatory infertility successfully conceive.

#### REDUCED RISK OF MISCARRIAGE.

Another aspect of PCOS-related infertility is the tendency for repeated miscarriages. A study from the Hospital de Clinicas Caracas in Venezuela looked at 65 women who received Metformin during their pregnancies vs. 31 who did not. The early pregnancy (first trimester) loss rate in the metformin group was 8.8% as compared to a 41.9% loss in the untreated group. Of those women who previously had miscarried, 11.1% of the metformin group miscarried again, while 58.3% of the untreated group again miscarried.

#### REDUCED RISK OF GESTATIONAL DIABETES.

Women at high risk for gestational diabetes may reduce that risk by taking metformin in pregnancy. Until recently there was some concern about the safety of Metformin in pregnancy, however there is increasing data supporting its safety in pregnancy – both for Mums and their babies.

## WEIGHT LOSS AND OTHER BENEFITS.

Metformin may contribute to weight loss in some patients. However, weight loss does not appear to be one of its primary benefits.

**Metformin may also be of some value improving success with in vitro fertilization, lowering cholesterol, and improving energy.**

### Side Effects of Metformin (Glucophage)

**MALAISE.** 10%- 25% of women who take Metformin just don't feel well. They experience a general malaise, fatigue and occasional achiness that lasts for varying lengths of time. Malaise a signal for the physician to closely monitor body systems affected by metformin, including liver, kidneys, and GI tract. A blood count should be taken from time to time, because metformin can induce B vitamin insufficiencies that can lead to a form of anemia.

**GI DISTURBANCE.** About one third of women on metformin experience gastrointestinal disturbances, including nausea, occasional vomiting and loose, more frequent bowel movements, or diarrhea. This problem occurs more often after meals rich in fats or sugars. The symptoms lessen over time, so if you can tolerate the GI upset for a few weeks, it may go away. Some women have found it helps to start with a very low dose and gradually increase it.

**VITAMIN B12 MALABSORPTION.** Of patients who take this drug, 10%-30% show evidence of reduced vitamin B12 absorption. A substance formed in the stomach called "intrinsic factor" combines with B12 so that it can be transferred into the blood. Metformin interferes with the ability of your cells to absorb this intrinsic factor-vitamin B12 complex.

Over the long term, vitamin B12 insufficiency is a significant health risk. B12 is essential to the proper growth and function of every cell in your body. It's required for synthesis of DNA and for many crucial biochemical functions. There is also a link between B12 insufficiency and cardiovascular disease.

At least one study raises the concern that even if metformin is withdrawn, the vitamin B12 malabsorption may continue in some people. The apparent cause is continued problems with availability of intrinsic factor, which is required for B12 absorption.

It is therefore suggested that you make sure you are taking adequate Vitamin B12 and folic acid. Taking extra Calcium may improve Vitamin B12 absorption.

(<http://ods.od.nih.gov/factsheets/vitaminb12>)

**ELEVATED HOMOCYSTEINE.** People who take Metformin tend to have higher homocysteine levels. Women with PCOS also tend to have elevated homocysteine. Homocysteine is an amino acid in the blood. A normal amount is OK. But an elevated level means that your metabolic processes are not working properly. Elevated homocysteine is associated with increased health risks which may include coronary artery disease, heart attack, chronic fatigue, fibromyalgia, and blood clots. Vitamin B12, along with vitamin B6 and folic acid (another B vitamin), is responsible for metabolizing homocysteine into less potentially harmful substances. Therefore, when metformin reduces absorption of vitamin B12, you lose one of the nutrients needed to reduce homocysteine and thus reduce your risk of cardiovascular disease.

#### **ELEVATED HOMOCYSTEINE & PREGNANCY COMPLICATIONS.**

Pre-eclampsia is a complication of pregnancy characterized by increasing blood pressure and edema. If left untreated, pre-eclampsia can lead to eclampsia, a serious condition that puts you and your baby at risk.

Elevated homocysteine levels may increase risk of pre eclampsia and recurrent pregnancy losses.

**If you are taking Metformin – it is recommended that you pay attention to your diet to make sure you are getting enough Vitamin B12 – and that you discuss with Dr.Hudson having your B12 levels checked annually.**

**PREGNANCY WARNING.** Many women use metformin in their pursuit of a successful pregnancy.

Although studies suggest that it is safe in pregnancy – it is recommended that when pregnant you discuss whether to continue taking it or not with your physician.

**ANEMIA.** By preventing optimal absorption of vitamins B12 and folic acid, metformin could induce or contribute to megaloblastic anemia. Megaloblastic anemia occurs when your bone marrow doesn't have enough B vitamins to manufacture red blood cells. Your bone marrow then releases immature and dysfunctional red blood cells into circulation.

Although anemia is not common among people taking metformin, it remains a risk for those whose B12 and folic acid levels were already low when metformin therapy was started.

**LIVER OR KIDNEY PROBLEMS.** If you have liver or kidney problems of any kind, metformin could pose a problem, because it alters liver function and is excreted through the kidneys. A healthy liver and kidneys will improve your outcome with metformin. Liver and kidney function should be assessed before starting metformin and rechecked at least once a year while taking it. A blood chemistry screen and a complete blood count will tell your physician how well your system is doing with this drug.

**MULTIPLE MEDICATIONS.** You may be at risk for health problems or symptoms if you take metformin in addition to other medications. The more drugs you take, and the

higher the dosage, the greater the probability there will be some kind of interaction between the drugs or some unexpected effect from the combined drugs. The effect of combined drugs also depends on the state of your health, your genetic uniqueness, and your diet and lifestyle. Always consult with your doctor if you add or change any medication, or if you develop any symptoms.

**HAIR LOSS.** Metformin may contribute to male pattern hair loss at the temples and top of head. Although there's nothing in the medical literature to support this linkage, some women have reported that hair loss was made worse by metformin.

**LACTIC ACIDOSIS.** About 3 of every 100,000 people who take metformin will develop a medical emergency called "lactic acidosis". Lactic acid is a metabolic byproduct that can become toxic if it builds up faster than it is neutralized. Lactic acidosis is most likely to occur in people who with diabetes, kidney or liver disease, multiple medications, dehydration, or severe chronic stress.

Lactic acidosis can gradually build up. **Symptoms to watch for include a need to breathe deeply and more rapidly, a slow, irregular pulse, a feeling of weakness, muscle pain, sleepiness, and a sense of feeling very sick. Treatment requires intravenous administration of sodium bicarbonate. Contact your doctor or go immediately to a hospital emergency room if you have these symptoms.**

**Common sense prevails – if you are not feeling well on ANY medication. Do NOT continue to take it – contact your physician.**

**BILE ABNORMALITIES.** Bile is produced by the liver, stored in the gallbladder, and secreted into the intestines in order to absorb fats into the bloodstream. One possible reason for the GI problems is that metformin reduces normal reabsorption of bile from the intestines back into the bloodstream, which causes elevated bile salt concentrations in the colon. Most studies suggest that colonic bile salts cause free radical damage to DNA and may contribute to colon cancer.

In addition, bile acids may stimulate cells in the colon to produce leukotriene B4 (LTB4), a highly inflammatory substance. LTB4 would be a contributor to any intestinal inflammatory condition.) Byproducts of bacterial action on bile salts may lead to intestinal cell damage and absorption of "foreign" molecules such as food or bacteria particles into the bloodstream, possibly causing allergies and other immune responses. Moreover, many PCOS women have switched to a high-protein diet. If that protein consists of beef and other meats, bile acid concentration in the intestines is increased.

A diet high in meats is also linked to a higher risk of colon cancer.

**CONSULT WITH YOUR PHYSICIAN TO MINIMIZE RISK.** Your physician should always do a thorough medical history and metabolic assessment before putting you on metformin. You should be re-checked at least once a year for as long as you take this drug. Make sure to ask your physician what the unique benefits and risks of metformin will be for you.

## **What to Do if You Are Taking Metformin (Glucophage)**

**IMPROVE YOUR DIET** AND INCREASE EXERCISE. If you improve your diet and increase your level of exercise, you may be able to reduce or eventually eliminate your Metformin therapy.

Many studies have shown that reducing weight and increasing exercise improves ovulation rates and reduces male hormone levels. There's no question that healthy diet, exercise and lifestyle habits will significantly improve PCOS-related health problems, as well as reduce the risk of diabetes and cardiovascular disease.

**CONSIDER SPECIAL NUTRIENT THERAPY.** There are herbs, vitamins and minerals, and other specialty natural foods and supplements that have effects similar to Metformin. These nutrients have an excellent safety record and are a valuable complement to regular exercise and healthy diet.

As a first step, we suggest you protect yourself from the potential malabsorption and loss of B vitamins that are needed to control homocysteine and to keep you healthy by taking a high-quality B-complex vitamin.

Blood sugar levels, insulin resistance, and male hormone levels can be favorably influenced by chromium, vitamin E, certain [fish oils](#), magnesium, CoQ10, zinc, conjugated linoleic acid (CLA), [biotin](#), certain amino acids, and soluble fiber from particular plants.

An important potential alternative to metformin is [d-chiro-inositol](#). A form of the B vitamin inositol, d-chiro-inositol increases the action of insulin in women with polycystic ovary syndrome. It improves ovulatory function and decreases male hormones, triglycerides and blood pressure.

D-chiro-inositol is fairly hard to find and extremely expensive. Fortunately, [d-pinitol](#), a derivative of d-chiro-inositol, is easily available at a lower price.

While on Metformin, you should seriously consider taking a [high-quality multiple vitamin & mineral supplement](#) as well as extra calcium, magnesium and vitamin D.

Specific details about special nutrient therapy are beyond the scope of this article, but we hope to go into more detail in future newsletters.

## **Conclusion**

Metformin may have some significant benefits for you. However like all medications there are risks and benefits. These need to be evaluated.

There are also recent studies suggesting that Metformin may also have some beneficial effects on: Fibroids, endometriosis, IVF success rates.

Please remember that:

Healthy diet and lifestyle are essential – and that there is no magic medication as a suitable alternative.

Dr. Stephen Hudson