



## **Metformin: What, Me Worry?**

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The anti-diabetic drug metformin (marketed as Glucophage™ in the U.S.) has had a somewhat checkered past. People have known about its sugar reducing capabilities for a long time, and a plant called “goat’s bane” that makes a metformin-like molecule may have been used in medieval times as a treatment for diabetes.

Other biguanide compounds (as the class of drugs that includes metformin is called) were used in Europe in the 1930’s, but for unclear reasons fell out of favor. Metformin was “rediscovered” in the 1950’s in the United Kingdom in particular, and has remained on the market there since that time, enjoying significant popularity as an oral therapy for type 2 diabetes.

In the United States, metformin was ignored. Instead, a related compound called phenformin was licensed and sold. It proved to be a poor choice, as a significant number of patients developed a severe derangement of their blood chemistry called lactic acidosis, half of who died of the complication. Phenformin was withdrawn from the U.S. market, and for years sulfonylureas were the only oral anti-diabetic agent available in this country. Metformin was, unfortunately, painted with the same brush as phenformin, and there was little enthusiasm for using it here because it was assumed it would suffer from the same propensity to cause lactic acidosis.

Nonetheless, metformin continued to be used in Europe, and studies in the 1980’s showed that it works by improving insulin resistance rather than by increasing insulin secretion (as sulfonylureas do). This makes it a particularly attractive drug for type 2 diabetes, which is characterized by severe insulin resistance. Encouraged by the decades-long safety record of metformin in Europe, the U.S. FDA finally approved it for use here as well, and it hit the market in 1997. Since that time, metformin has become the most widely prescribed oral anti-diabetic agent in this country.

Why did it become so popular so fast? A few reasons, actually. First, for a few years it was the only insulin-sensitizing drug available, which is particularly important for type 2 diabetes (thiazolidinedione drugs like rosiglitazone and pioglitazone are also insulin sensitizers, and have since become available as well).

Second, unlike other anti-diabetic medications like sulfonylureas, thiazolidinediones, and insulin itself, metformin is not associated with weight gain. It may, in fact, have a mild weight-reducing (or at least weight-stabilizing) effect. This makes it ideal for patients with obesity, an all too common situation among folks with type 2 diabetes.

Finally, metformin became immensely popular because it works well. Reductions in hemoglobin A1c are at least as good among metformin users as among users of other anti-diabetic drugs, and important longitudinal studies like the UKPDS have suggested that metformin might be even more effective than other agents for obese patients with diabetes.

The fly in the ointment for metformin, however, is that it’s never completely shaken the taint of association with its evil twin, phenformin. Because of the fear of lactic

acidosis, metformin carries a huge warning label that discusses the issue, and physicians are explicitly cautioned not to use the drug in patients who have secondary conditions that might predispose them to lactic acidosis, such as renal insufficiency, liver problems, heart failure, and advanced age. The number of patients who are thus "ineligible" for metformin is quite large, and may include up to 50% of those who might otherwise benefit from the medication.

Furthermore, patients who take metformin are often switched to other medications (or worse, simply left untreated) when they are admitted to the hospital for any reason, because of the fear that hospital-based factors (such as IV contrast dyes, other medications, and bleeding) might temporarily increase the risk of lactic acidosis.

Studies have shown that lactic acidosis does occur in metformin users, at a rate of around 2-9 cases per 100,000 person-years. This is an extremely low risk, but would be reason enough for all the warnings and concern if the problem were truly due to the metformin. And here's where the connection gets a little sticky. Lactic acidosis occurs when tissues become "hypoperfused," which means they do not get enough oxygen-containing blood flow, as in heart failure.

Lactic acidosis can also occur when the lactate molecule, which is made by all tissues at low levels even in healthy people, builds up in the blood because it cannot be excreted by the liver or kidney. As it turns out, liver, kidney, and heart disease is not all that uncommon in patients with diabetes. Furthermore, metabolic adaptations to diabetes per se may also increase lactate production. One might therefore expect that diabetes, even in the absence of metformin, should be associated with lactic acidosis. In fact, that's exactly what's been shown. Lactic acidosis appears in diabetic patients at around 9-10 cases per 100,000 person-years, *even in patients who do not take metformin.*

A new study has just been published which sheds even more doubt on the whole metformin-lactic acidosis connection. This study is a "meta-analysis," which means it's a study of other studies, rather than a direct look at a new group of patients. The authors compiled 194 papers that looked at metformin use in type 2 diabetes, and found no examples of either fatal or non-fatal lactic acidosis in a cumulative 37,000 patient-years. The authors were able to put a statistical upper bound on the risk of lactic acidosis in diabetes at 8 cases per 100,000 person-years, which is not different from that seen in patients who don't take metformin.

Now, this sort of study has significant limitations, but it clearly suggests that metformin might be a less problematic therapy than originally anticipated. Interestingly, many of the studies they analyzed had quite a few patients with at least one of the contraindications to metformin mentioned above.

This implies that (1) the guidelines for avoidance of metformin are not being rigorously adhered to in the real world, and (2) despite the presence of such patients, there were still no cases of lactic acidosis seen.

Because it is unclear just how many of the patients had heart, liver, or kidney disease, one cannot start agitating for the repeal of those contraindications.

It does point to the need for further analysis, however, that takes into account the baseline rate of lactic acidosis in patients with type 2 diabetes, and it opens the door

just a little for the thousands of patients who are not currently able to use metformin in their glucose control programs.

**Reference:**

*Archives of Internal Medicine* 163:2594 (2003)

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