Applying high-quality medical care in everyday life requires making choices. Many factors come into play while making these choices, some of them based on evidence (when available), some on eminence (because I say so), or even on prejudice. It is striking to observe that metformin, a potentially very useful drug, has been withheld from a population that could benefit from its use based on prejudice induced by incorrect interpretation of the evidence and unjustifiable choices. It becomes even more remarkable when one observes that the evidence to support or refute this position is simply nonexistent, and a substantial portion of the population with chronic kidney disease (CKD) also has diabetes.

This article will attempt to justify the stance that, if applied correctly, the ugly duckling metformin has great potential in diabetic patients with chronic renal impairment. As an analogy, let us look at the following (fictitious) argument:

1. It is well known that the use of apozepam, a psychoactive drug, by drivers increases the risk for traffic accidents.
2. Several drivers involved in traffic accidents are being treated with citalopram, which is also a psychoactive drug.
3. The risk for a traffic accident increases during bad weather conditions.
4. Therefore, people who drive cars in bad weather should not be treated with apozepam.

Attentive readers already will have noticed several logical errors of reasoning in this argument. It does not follow that citalopram shares apozepam’s concentration-reducing properties just because it belongs to the same class of drugs. Citalopram is a commonly used drug, so one would at least demand a case-control study before associating its use with traffic accidents. Even if citalopram was shown to increase the risk of driving accidents, this would have to be weighed against its putative prophylactic effect on suicide.

The same argument seems, however, to have been applied uncritically to the use of metformin in situations where there is an increased risk of lactic acidosis (LA) (e.g., heart failure, liver cirrhosis, and CKD). This time, the argument goes as follows:

1. It is well known that phenformin causes LA.
2. Phenformin is a biguanide.
3. Metformin is a biguanide.
4. Several diabetic patients admitted with LA have been treated with metformin.
5. Metformin is particularly dangerous if patients are azotemic.
6. Therefore, azotemic patients with diabetes should not be treated with metformin.

It should be clear that there is something wrong with the logical sequence of this reasoning. In the following, we will try to dissect the argumentation to come to a more sensible conclusion.

**IN BRIEF**

Most guidelines advise against the use of metformin in uremia because of an enhanced risk for lactic acidosis (LA). However, there exists no firm theoretical or experimental evidence demonstrating a negative effect of metformin on p-lactate metabolism nor any epidemiological support for an increased risk of LA. Because metformin reduces cardiovascular events and mortality in type 2 diabetes, there is no justification for maintaining azotemia as a contraindication to metformin treatment.

**Assertions 1 and 2: “Phenformin, a biguanide, causes LA.”**

Biguanides are useful oral antidiabetic drugs. They increase insulin sensitivity, reduce glucose intestinal absorption, increase glucose uptake in cells, and reduce hepatic gluconeogenesis. Hypoglycemic episodes are relatively rare.

Phenformin, one of the earliest biguanides, was rapidly discovered to cause an increased incidence of LA (129/100,000 patient-years)\(^1\) a life-threatening condition with a mortality of 50%. The reason for this is that phenformin inhibits hepatic oxidative phosphorylation, resulting in a secondary increased lactate production by anaerobic pathways.
Phenformin is, therefore, no longer marketed.

**Assertion 3:** “Metformin is also a biguanide.”

Although metformin is also a biguanide, it inhibits hepatic gluconeogenesis by reducing hepatic lactate uptake but without altering intracellular (anaerobic) lactate production. In people with diabetes, basal lactate turnover and lactate oxidation, as well as total lactate turnover and lactate oxidation, during the insulin clamp were similar before and after metformin treatment. In addition, metformin has a weight-reducing effect.

Sixty patients with type 2 diabetes treated with phenformin were switched to metformin in equipotent doses in a cross-over study. P-lactate, which was consistently raised during phenformin treatment (28 mg/dl; normal 9–18 mg/dl) fell to 15 mg/dl during the 4 weeks after changing to metformin. In another study, physical exercise led to a rise in p-lactate from 18 to 50 mg/dl in untreated type 2 diabetic patients. The rise was significantly higher in patients treated with phenformin (22–68 mg/dl) whereas the change in p-lactate in metformin-treated patients was identical to that of the untreated patients. In a randomized, controlled trial lasting 29 weeks, DeFronzo and Goodman found no changes in lactate levels in patients treated with metformin.

It is known that diabetes per se disposes to hyperlactemia. Cusi et al. found a concentration of lactate of 9 mg/dl in untreated type 2 diabetic patients, which was double the level of a healthy control group. The patients were thereafter randomized to metformin or placebo for 15 weeks. There were no changes in p-lactate, lactate metabolism, or lactate oxidation in either group. It was concluded that metformin had no effect on lactate metabolism or gluconeogenesis from lactate in either the resting state or during insulin stimulation. A review of all reported cases of biguanide-associated LA between 1959 and 1977 counted 330 cases; of these, 281 were associated with phenformin, 30 with buformin, and 12 with metformin. Sixty-five percent of the reported cases had additional risk factors for LA. The association between LA and metformin, if higher than baseline, is certainly much weaker than that for phenformin.

**Assertion 4:** “Diabetic patients who are treated with metformin develop lactate acidosis.”

Lactate is produced when pyruvate metabolism is inhibited (e.g., during diabetes or starvation) but also when pyruvate synthesis is increased (e.g., during insulin treatment). Lactate production in diabetic muscle is increased both at rest and during physical exercise. Diabetes in itself thus increases the risk of LA.

A study from three states in the United States (Hawaii, Oregon, and Georgia) during the period 1993–1994 when biguanides were unavailable in the area, identified seven cases (four certain and three possible) of LA in type 2 diabetic patients observed for 41,426 patient-years. All cases were related to severe acute illness. The calculated rate of 10–17/100,000 patient-years can thus be regarded as the natural rate of LA in unselected type 2 diabetic patients.

Aguilar et al. investigated the incidence of nonketotic acidosis among 609 acute admissions of type 2 diabetic patients. The incidence was 2.9% among patients being treated with sulfonylureas, 4.8% among insulin-treated patients, and 0% among metformin-treated patients. The authors concluded that metformin was not associated with an increased risk of LA, the main cause of which was acute illness.

Bodmer et al. found that the incidence of LA during sulfonylurea treatment was higher than for metformin. Furthermore, the risk of hypoglycemia was three times higher, and it has been pointed out that the risk of death from sulfonylurea-associated hypoglycemia is at least as high as that of metformin-associated LA.

Lalau et al. analyzed metformin levels in 14 patients admitted with LA. There was no relationship between metformin and LA levels. Neither the severity of the clinical picture nor the degree of metformin accumulation predicted survival; rather, the prognosis was dependent on the severity of the associated pathological conditions. This seems logical because metformin inhibits hepatic uptake of (external) lactate but does not alter intrahepatic lactate metabolism, so an external source of LA (e.g., profound shock) must be available.

These and other studies concerning the epidemiology of metformin-associated LA are shown in Table 1. Salpeter et al. investigated all controlled investigations comparing metformin with other treatments or placebo between 1959 and 2002. A total of 194 studies reported no cases of LA during either 38,893 patient-years in the metformin group or 30,109 patient-years in the control group. There was no significant difference in p-lactate between the two groups, nor where there changes in p-lactate during the studies. The investigation was repeated in 2010 with identical results, this time with 347 controlled studies (70,490 patient-years in the metformin group and 55,451 patient-years in the control group). The true incidence was calculated to be < 4.3/100,000 patient-years.
There is, of course, the potential explanation that the reported rate of LA in association with metformin is so low because high-risk patients are no longer being treated with metformin. However, contraindications are very often ignored in general practice; 51–73% of metformin-treated patients have at least one contraindication, and 19% have renal insufficiency. In the meta-analysis by Salpeter et al., renal insufficiency was not a reason for exclusion in 44% of studies.

Assertion 5: “Metformin is particularly dangerous in renal insufficiency.” LA rises when tissue perfusion or tissue oxygenation is reduced and will therefore be common during grand mal attacks, heart failure, pulmonary hypoxia, hypovolemic shock, and sepsis. Lactate is metabolized in the liver, so cirrhosis and hepatic insufficiency can also contribute to LA. A reduction in intracellular hepatic pH (e.g., during phenformin treatment) changes the liver to a lactate-producing organ.

Lactate is metabolized in the kidney, but only to a small extent. Renal lactate excretion is increased during LA; preexisting LA will thus be exacerbated with co-existent uremia. Metformin is renally excreted. A putative causal role for metformin could therefore be metformin intoxication. However, a study of 20 cases of metformin-associated LA revealed that only seven patients had increased levels of metformin in the blood, with the rest having either normal or reduced levels.

In any case, simple dose reduction to obtain correct serum metformin levels would be sufficient to avoid intoxication. It is not the drug, but rather the way the drug is used, that makes it poisonous. The great majority of cases of metformin-associated LA occur in connection with acute illness in diabetic patients where cardiac, hepatic, pulmonary, or renal function are compromised. There are always at least two disposing factors present in these instances. It is therefore reasonable to assume that metformin is just a “bystander.”

Assertion 6: “Azotemic patients should not be treated with metformin.” The discussion about the relevant contraindications to metformin would be academic if metformin were just one of many oral antidiabetic agents. Metformin has, however, the singular capacity to reduce mortality in overweight type 2 diabetic patients. The U.K. Prospective Diabetes Study randomized 753 adipose type 2 diabetic patients to metformin or placebo. After 10 years, the relative risk reduction in the metformin group was 39% for myocardial infarction (P = 0.01) and 36% for death (P = 0.01). Follow-up was continued.

| **Tabel 1. Epidemiology of Lactic Acidosis** |
|-------------------------------|----------------|----------------|-------------|----------------|----------------|----------------|----------------|----------------|----------------|
| **Author** | **Location** | **Treatment** | **Year** | **Cases (n)** | **Patient-Years (n)** | **Incidence Per 100,000 Patient-Years** |
| Brown⁹³ | United States | No biguanides | 1993–1994 | 4(7) | 41,426 | 9.7 (16.9) |
| Bergman¹ | Sweden | Metformin | 1975–1977 | 2(3) | 20,548 | 9.7 (14.6) |
| Wilholm²⁰ | Sweden | Metformin | 1977–1991 | 18 | 249,400 | 7.2 |
| Stang³¹ | Canada | Metformin | 1980–1995 | 2 | 22,296 | 8.9 |
| Misbin³² | United States | Metformin | 1995–1996 | 47 | Approx. 1,000,000 | 4.7 |
| Bodmer⁴⁵ | United States | Metformin Sulfonylurea | 1994–2006 | 5 | 50,048 | 3.3 (4.8) |
| Aguilar¹⁴ | Mexico | Metformin Sulfonylurea | 1987–1990 | | | 0.0* (2.9*) |
| Salpeter¹⁸ | World | Metformin | 1959–2002 | 0 | 36,893 | 0.0 |

*Data in parentheses indicate possible cases included. *Per 100 acute admissions.
for an additional 10 years. At this point, the risk reductions were 2% for diabetes-related complications (P = 0.01), 33% for myocardial infarction (P = 0.005), and 27% for death (P = 0.002).

Approximately 10% of the patients had avoided each of these complications after 20 years, corresponding to a rate of 500 saved lives per 100,000 patient-years. Even if there were a risk of metformin-associated LA of 10-fold the alleged order, it would be fully acceptable compared to the probable advantage.

A decision to introduce metformin as standard treatment in CKD would not be without precedent; there are areas in India where insulin is unavailable for economic reasons, and metformin is standard treatment for CKD stages 3 and 4 (glomerular filtration rate [GFR] of 15–60 ml/min). A series of more than 1,000 such patients without any cases of LA has been reported. The Dutch guidelines now permit the use of metformin in CKD stage 3 (GFR of 30–60 ml/min).

The only caveat we would like to point out is the use of contrast media in patients on metformin. Although it is unclear whether there is a real need to stop metformin 48 hours before contrast media administration, it is hard to find any harm in this practice, and it has to be admitted that the risk of further decline of renal function, and thus the potential for metformin accumulation, does exist.

Conclusion
It is apparent from the above that there is little, if any, theoretical justification for the claims that metformin contributes to the incidence of LA and that epidemiological evidence is lacking. If there is any impact, it is probably rather low.

Metformin has a proven benefit on outcome in the treatment of patients with type 2 diabetes, and no alternative agent with a better profile exists. There is no reason to suppose that metformin’s highly beneficial effects on nonazotemic, overweight type 2 diabetic patients should not extend to azotemic patients. In contrast, because uremia predisposes to insulin resistance, this patient group could potentially benefit most from this treatment.

Because metformin is excreted renally, the therapeutic dose will be lower in CKD. There is no case for maintaining azotemia as a contraindication to metformin treatment when it is used wisely. What we do need is a randomized trial, or at least a well-performed registry, so we can perform a case-control study on this important topic. Our ugly duckling can turn into a white swan if we make the correct choices.

REFERENCES


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