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REVIEW

Metformin: effective and safe in renal disease?

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Abstract There is good evidence supporting more extensive use of metformin in type 2 diabetes, in reducing morbidity and mortality. The evidence for a real problem from metformin-induced lactic acidosis is weak, and the risks of alternative agents are often overlooked. We have examined the available data regarding metformin that might cause concern in patients with kidney disease, and find it to be extremely limited. There is no good data on which to offer guidance, but it seems likely that metformin can be used in patients with GFR 60–90 ml/min but at reduced dose at lower levels of GFR, and can probably be safely used at GFRs from 30–60 ml/min but with the same caution as with any renally excreted drug. The risks (often overlooked) and benefits of alternative hypoglycaemic agents should be considered carefully. The overall evidence that metformin causes major harm is poor.

Keywords Metformin · Renal impairment · Lactic acidosis · Chronic kidney disease · Diabetes mellitus

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Abbreviations

DM	Diabetes mellitus
eGFR	Estimated glomerular filtration rate
CKD	Chronic kidney disease
MALA	Metformin-associated lactic acidosis
MILA	Metformin-induced lactic acidosis
MULA	Metformin-unrelated lactic acidosis
FDA	Foods and Drugs Administration
BNF	British National Formulary

Introduction

Metformin is a well-established drug for the treatment of type 2 diabetes mellitus. There are more than 40 million patient years of experience over almost half a century [1]. Evidence suggests metformin reduces mortality and morbidity in type 2 diabetes. It possesses a cardioprotective property that is independent of its hypoglycaemic effect, and not exhibited by sulphonylureas or insulin [2]. Prescription has often been limited, however, by concern that accumulation may be associated with lactic acidosis. Metformin is excreted unchanged by the kidney, thus as glomerular filtration rate (GFR) falls the theoretical risk of lactic acidosis rises [3]. However, the most recent Cochrane review has once again found the risk to be minimal [4].

Both diabetes and chronic kidney diseases predispose to accelerate cardiovascular disease [5].

However, as advancing renal disease increases the already high cardiovascular risk from diabetes, the only hypoglycaemic agent with independent cardioprotective features becomes relatively contraindicated. Despite the common clinical conundrum of a patient with diabetic nephropathy on metformin with a decreasing GFR, there is no universally accepted point when the potential risk of lactic acidosis outweighs the cardiovascular and metabolic benefits of metformin. The main reason for a lack of clear guidance is a lack of any studies of metformin in renal impairment. Simultaneously, there is a surplus of case reports quick to blame life-threatening episodes of lactic acidosis on the drug [6]. However, these case reports are unreliable and there is now a weight of evidence to suggest metformin is a safe drug in most circumstances.

Evidence for the benefit of metformin

Metformin acts to improve peripheral and liver sensitivity to insulin. In combination with acarbose, it is one of only two hypoglycaemic agents to demonstrate a protective effect on macrovascular complications of diabetes independent of glycaemic control [2, 7]. In monotherapy, metformin not only improves glycaemic control, but also weight, lipid profile and diastolic blood pressure when compared to diet alone. A Cochrane meta-analysis has provided significant evidence for the use of metformin, especially in the obese. All-cause mortality in obese patients treated on intensive glycaemic regimes with metformin compared to intensive control with sulphonylureas or insulin monotherapy was significantly reduced. There was also a significant reduction in incidence of myocardial infarction in the overweight on intensive therapy with metformin therapy when compared to conventional therapy. None of the current monotherapy regimes show better results than metformin [8].

More recently, a systematic review of diabetic patients with heart failure has demonstrated a greater reduction in mortality and hospital admissions is associated with metformin than with any of the other anti-diabetic drugs [9].

It has been postulated that because of their higher baseline risk of cardiovascular disease, the absolute magnitude of the benefit of metformin may actually increase in patients with diabetes for longer than 10 years and in those with renal impairment [1].

Evidence for the danger of metformin

Metformin is a well-tolerated and safe drug. It does not cause hypoglycaemia and its main side effect is gastrointestinal disturbances, which occurs in up to 20% of patients [10–12]. Phenformin, another biguanide, however is not safe. Both these biguanides were widely prescribed in the 1960s. Phenformin is metabolised by the liver, where it accumulates, causing unacceptable rates (60/100,000 patient years) of lactic acidosis [13]. It was withdrawn in 1977. Metformin is excreted unchanged by the kidney and has a much lower propensity to cause lactic acidosis. However, after the withdrawal of phenformin, no biguanides were available in the US for 18 years. In 1995, metformin was re-licensed for sale in the US after continued satisfactory use in Europe for almost 30 years [14]. On the re-introduction into the US, fear of a surge in incidence of lactic acidosis was augmented by the strong FDA warnings contained in the drug's packaging and by calls for a registry of all treated patients [15]. Perhaps predictably, a flourish of reports implicating metformin in cases of lactic acidosis was subsequently published [6]. However, unlike phenformin, metformin does not raise fasting lactate levels and does not accumulate in the liver [4]. Phenformin's liver accumulation causes a fall in hepatocellular pH. An acidotic intracellular environment inhibits further lactate liver uptake resulting in increasing circulating lactic acid. Metformin in contrast is rapidly excreted unchanged by the kidney, and thus only begins to accumulate when the GFR falls. Pharmacokinetic studies have demonstrated that this is only significant when the GFR is less than 50–60 ml/min [16]. It is thus unlikely for metformin accumulation and thus the risk of lactic acidosis to occur in patients with reasonable and stable renal function.

Importantly of course patient with diabetes carry a high risk of lactic acidosis in the absence of drug therapy. This is in part because predisposing conditions for lactate accumulation are more commonplace in diabetics. These include cardiac and pulmonary diseases causing hypoxia, which increases lactate production, and liver dysfunction that reduces the rate

of lactate clearance. Patients with diabetes may also be intrinsically more 'lactogenic'. Animal models have demonstrated altered liver lactate processing in diabetes. In patients with ketoacidosis who have not received biguanides, elevated lactate levels are also found [12]. Before the re-introduction of metformin in the US, one study used a database of type 2 diabetes to examine over 41,000 person years. The incidence of lactic acidosis in diabetic patients not exposed to metformin was between 9.7 and 16.7 per 100,000 person years [14]. Lactic acidosis in diabetes is thus not unusual.

Metformin overdose does still, however, highlight metformin's intrinsic ability to cause lactic acidosis when taken in very large doses. Chan et al. [12] described a non-diabetic woman who had taken an unquantified amount of metformin resulting in a lactate of 33 mmol/l and bicarbonate of 4.4 mmol/l. A second case of overdose of 55 g of metformin with 1 g of glibenclamide resulted in a pH of 6.79 and serum bicarbonate of 1.8 mmol/l [15]. The probable mechanism of the metformin toxicity is high plasma metformin concentration eventually halting liver gluconeogenesis and thus lactate catabolism. Metformin overdose, however, is rare and the majority of hospital lactic acidosis is not caused by metformin accumulation but instead by tissue hypoxia.

Reports of metformin-associated lactic acidosis between May 1995 and January 2000 (50% from the US) have been critically analysed. Lalau et al. reviewed 26 cases. Only 4 (15%) of these reports actually measured a metformin level to attempt to prove metformin accumulation and thus its causal role in the acidosis. In three of these cases, plasma levels of metformin were normal. In fact, in only 12 reports (46%) did the patients have preceding reduced renal function that could actually account for the supposition that metformin had accumulated. Lalau et al. thus divided the cases reports into three categories: metformin-induced lactic acidosis (MILA), metformin-associated lactic acidosis (MALA), where metformin may have contributed to a multi-factorial aetiology and metformin-unrelated lactic acidosis (MULA) where metformin had no role. Forty-six percent of the case reports were MILA, 8% of the cases were MALA and 23% were MULA. Fifteen percent of the cases did not meet diagnostic criteria for lactic acidosis (pH < 7.35 and lactate >5 mmol/l) and Lalau et al. were uncertain in the remaining 8% of the cases [6]. Importantly mortality in the MILA group was only 8%, compared to 75% in MALA and MULA, and in the patients that had metformin levels measured, the level of accumulation did not correlate to mortality or lactate concentrations. Mortality was instead predicted by the severity of the underlying hypoxia. It is thus suggested that MILA is in fact a separate entity to MALA or MULA carrying a significantly lower mortality, and that metformin does not appear to have a central role in fatal lactic acidoses. Indeed, metformin may often be a simple innocent bystander, implicated due to prejudice from its guilty predecessor [18, 19].

In surveillance studies based on adverse drug reporting, many of the cases of MILA probably represent MALA or even MULA. The UK Medicines and Healthcare Regulatory Agency (MHRA) have received 77 suspected adverse drug reaction reports of lactic acidosis associated with metformin use via the Yellow Card Scheme, over a 10-year-period from 1st May 1996 until 30th April 2006 [Commision on Human Medicines (CHM)/MHRA, personal communication]. It is not clear in how many million patient years of metformin use these occurred, nor whether these were metformin associated, induced or unrelated.

The safety of metformin has been confirmed by large meta-analysis. Two hundred and six prospective trials from 1966 to August 2005 incorporating 47,846 patient years on metformin and 38,221 patient years off metformin were analysed. About 28,244 of the patient years on metformin were in studies that included patients with serum creatinine >1.5 mg/dl (>132 μmol/l). In these studies, no cases of lactic acidosis occurred. By using a 95% confidence interval Poisson distribution, an upper limit for the incidence of lactic acidosis was predicted at 6.3/100,000 patient years for the metformin group and 7.8/100,000 for the non-metformin group [4]. Thus the incidence of lactic acidosis is not different in diabetic patients taking and not taking metformin, including those with mild to moderate renal impairment. Furthermore it confirms that MILA is indeed a rare entity. The authors concluded that there was no association between metformin and lactic acidosis if prescribed under the study conditions.

For comparison, how does this risk of lactic acidosis in diabetics compare to the risk of severe hypoglycaemia in type 2 diabetics? Especially since this is more likely with declining renal function. A retrospective cohort of study of 33,048 person years

of insulin or sulphonylurea use found an incidence of severe hypoglycaemia (BM < 2.8 mmol/l) of 2.76 and 1.23/100 patient years respectively [20]. In the UKPDS study the rates of major hypoglycaemic episodes per year were 0.7/100 patient years with conventional treatment, 1/100 patient years with chlorpropamide, 1.4/100 patient years with glibenclamide, and 1.8/100 patient years with insulin [21]. There was an increased risk of this complication with advancing age, and an increased risk is well recognised in patients with deteriorating renal function. Outside the controlled conditions of a randomised trial, mortality from severe hypoglycaemia is between 4.3 and 9% [22, 23]. Metformin in comparison does not cause hypoglycaemia even in non-diabetic subjects [10, 11].

Mortality associated with lactic acidosis is often quoted as 50%, but as we have seen this is mostly related to the underlying cause of tissue hypoxia and not metformin per se, and in Lalau's case report analysis there was only 8% mortality in MILA [6, 24]. Due to the relative infrequency of lactic acidosis, the absolute number of deaths it causes is small compared to severe hypoglycaemia. Table 1 illustrates the relative safety of metformin compared to the serious complications of the alternative treatments in type 2 diabetes. It is noteworthy that even when using mortality rate figures that are biased in favour of insulin and the sulphonylureas, the calculated resultant mortality rate that can be attributed to hypoglycaemia remains an order of magnitude higher than the mortality from MALA. Substituting Lalau's mortality rate for MILA (8%), and therefore excluding those patients in which metformin is unlikely to be of any relevance, would reduce the predicted mortality by an order of magnitude again.

Campbell reviewed the world literature until December 1982 when long-acting sulphonylureas were more widely prescribed, but intensive glycaemic control was not. He revealed 843 cases of sulphonylurea-induced hypoglycaemia with a mortality of 9% (76 patients). There were 42 potential cases of MALA with 18 deaths. A comparative mortality risk was obtained from the Swedish Adverse Drug Reactions Advisory Committee (SADRAC) where there was accurate information regarding MALA and glibenclamide-associated hypoglycaemia. The calculated mortality risk for MALA and glibenclamide-associated hypoglycaemia showed no significant differences with values of 2.4 and 3.3 per 100,000 patient years, respectively [23].

Finally, systematic review of diabetic patients with heart failure (traditionally a relative contraindication to metformin therapy) has demonstrated metformin to be the only anti-diabetic drug not associated with harm. Metformin was associated with a significant decrease in hospital admissions and mortality in monotherapy or in conjunction with thiazolodinediones compared to other anti-diabetic agents (hazard ratio 0.86). Thiazolidinediones alone were associated with increased hospital admission. Whilst data on sulphonylureas was conflicting, data on insulin in three from four studies suggested an increase in mortality [9].

In summary, it seems that lactic acidosis caused by metformin has been over-emphasised. The incidence of lactic acidosis in diabetes is unaltered regardless of metformin prescription. False allegations in case reports of lactic acidosis, however, have usefully demonstrated the comparatively low mortality with MILA. Metformin has also endured an unrepresentatively large area of journal space for a relatively infrequent complication by an innocent bystander, compared to the much commoner problem of hypoglycaemia with other hypoglycaemic agents. The absolute mortality rate from MALA and MILA compared to severe hypoglycaemia is at least comparable and acceptable.

Table 1 Predicted absolute number of deaths caused by the life-threatening complications of metformin and sulphonylureas

	Metformin-associated lactic acidosis	Sulphonylurea-induced hypoglycaemia	Insulin-induced hypoglycaemia
Incidence of lactic acidosis or severe hypoglycaemia in type 2 DM (number per 100,000 patient years)	6.3 [4]	1,000 [2]	1,800 [2]
Mortality (percentage; most pessimistic available figure)	50% [22]	4.3% [21]	4.3% [21]
Predicted absolute no. of deaths (number per 100,000 pt years)	3	43	77.4

Metformin's pharmacokinetics

Sambol et al. [17] performed studies on metformin pharmacokinetics in 1995 and demonstrated that metformin clearance was not different in normal and diabetic individuals with the same creatinine clearance. Metformin clearance was reduced when creatinine clearance fell below 60 ml/min, and reduced further at clearances <50 ml/min, and with increasing age (over 70) even with unchanged renal function [3].

Metformin prescription practices

Evidence suggests metformin use is safe in patients with normal renal function and mild renal impairment. Is there evidence for its safety in more severe renal impairment? Prescription data suggests that metformin prescribing often does not follow the restrictive prescription guidelines in current circulation. It is not clear if this is a result of deliberate and rational consideration of the available evidence, or clinical error. A Pittsburgh study showed 62% of in patients on metformin had a "contraindication" to its use, of which 14% had renal impairment [25]. A study of almost 350,000 Scottish patients with diabetes, of whom a quarter were receiving metformin, found 25% had contraindications to metformin use. Prescription of metformin in renal impairment [creatinine >1.7 mg/dl (>150 μmol/l)] accounted for a further quarter of these cases. Despite this, during 4,600 patient years of treatment, there was only one episode of lactic acidosis in a patient with acute renal failure and myocardial infarction, and of course this degree of hypercreatinaemia may represent very severe renal impairment if GFR had been measured [26].

Thus metformin is an efficacious drug in type 2 diabetes and it is not associated with an increased incidence of lactic acidosis even when prescribed outside current guidelines, and in patients with significant renal disease. Metformin use is at least as safe as hypoglycaemic agents.

Current guidelines/recommendations

Despite the frequency of diabetic nephropathy and the wide prescription of metformin, there is no universally agreed guideline on when to stop metformin in renal impairment, and no good evidence base. The British National Formulary (BNF) currently warns doctors not to use metformin with even "mild renal impairment", but then defines mild renal impairment as a GFR of 20–50 ml/min [10]. Jones et al. in 2003 arbitrarily suggested a serum creatinine absolute cut-off point of 1.7 mg/dl (150 μmol/l), and caution in the elderly. [27] The Canadian Pharmacists Association suggested that metformin is contraindicated in males with a creatinine ≥1.5 mg/dl (≥136 μmol/l) and women with a creatinine ≥1.4 mg/dl (≥124 μmol/l). Caution was also advised in advancing age (>80) unless creatinine clearance was not reduced. McCormack et al. [1] acknowledged the problem with using serum creatinine alone as a cut-off point. They instead recommended the use of the creatinine clearance and basing their advice on pharmacokinetic principles they recommended reducing the maximum dose of metformin by 50% when the creatinine clearance falls below 60 ml/min. There was no level of creatinine clearance at which they contraindicated metformin completely [1]. In 2003 Nisbet et al. also offered a set of guidelines utilising the creatinine clearance calculated by the Cockcroft–Gault equation. They proposed an absolute cut-off GFR of 30 ml/min, below which metformin should be discontinued; and using metformin with extreme caution in patients with a creatinine clearance in the range 30–50 ml/min. They also included commonly accepted recommendations on stopping metformin when these patients become acutely unwell and for 48 h after receiving radioopaque contrast, until renal function is proven to be unchanged [24].

These limits are all equally arbitrary, and the increasingly widespread use of eGFR via the MDRD calculation has re-enforced the appreciation of the variation in GFR compared to serum creatinine measures. Furthermore, the introduction of eGFR reporting has complicated drug prescribing somewhat. eGFR is reported as a figure normalised for body surface area (ml/min/1.73 m^2), while most historic studies have utilised creatinine clearance or Cockroft–Gault estimations which are absolute figures. Whether this will make a significant difference in practice remains to be seen, although in theory the differences between these various figures can be large.

Recommendations

The major risk factor in diabetes for lactic acidosis is tissue hypoxia. The risk from metformin is very low. The risk of serious complications from alternative hypoglycaemic agents is higher, and metformin has significant benefits compared to these alternatives. There is also no high level evidence to formulate absolute dosing guidelines.

Given the widespread use of the MDRD eGFR it is likely to be useful in guiding prescribing, and allow early recognition of renal insufficiency, although in patients at the extremes of age and body weight it may be very unreliable. We would recommend continuing to use metformin in patient with mild renal impairment (stage 1–2 CKD; GFR 60–90 ml/min) and also in moderate (stage 3 CKD; 30–60 ml/min) renal impairment, but with some caution. Since metformin clearance is reduced by up to a third when GFR falls between 90 and 60 ml/min and in the elderly (over 70 years old), we would suggest reducing the starting and maximum dose of metformin by a half in these groups [17]. Once GFR falls below 60 ml/min, metformin dosing should be halved again, but can most probably be used safely. One concern is clearly that renal function may be declining and that worsening renal function is overlooked. Thus renal function should be checked regularly. The point at which metformin should be absolutely contraindicated is unclear. As GFR falls from 60 towards 30 ml/min (stage 3 CKD) the balance of risk and benefit should be closely weighed, but in most patients there is no good evidence on which to substitute metformin for an alternative. Similarly the evidence for major harm from metformin even at GFR below 30 is poor, however, these patients may also be more at risk for tissue hypoxia inducing lactic acidosis (e.g. from sepsis, ischaemic limbs, etc.) and it may be that the presence of metformin in this circumstance is detrimental, and hence this may be a point at which alternatives should be instituted.

Other sensible approaches to preventing lactate accumulation should also be employed. In acute and chronic conditions that predispose to hypoxia or an acute deterioration in renal function (e.g. myocardial infarction, sepsis, shock, surgery) metformin should be stopped, and in individuals undergoing contrast imaging studies lest they develop an acute decline in renal function. Metformin is contraindicated in liver dysfunction, alcoholism and pregnancy.

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