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FOR DEBATE

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# Contraindications can damage your health—is metformin a case in point?

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**Abstract** Metformin is an effective anti-hyperglycaemic and cardioprotective agent, but a long list of contraindications precludes millions of patients with type 2 diabetes from using it. This is largely due to the historical experience of lactic acidosis with phenformin, despite the fact that metformin does not predispose to this when compared with other therapies. Contraindications such as old age, renal impairment and cardiac insufficiency are increasingly disregarded in clinical practice, yet there is no evidence that the incidence of lactic acidosis has changed. Metformin has been shown to improve metabolic control without causing lactic acidosis in elderly patients with multiple comorbidities, including explicit contraindications, and its use in patients with type 2 diabetes over the age of 70 with mild renal impairment did not produce a clinically relevant increase in plasma lactate. There is no correlation between levels of metformin and lactate in patients with lactic acidosis, and its prognosis is mainly related to the causal hypoxic underlying disease and comorbidities. These findings raise doubts about the pathogenetic significance of metformin in lactic acidosis. We propose that advanced age per se, mild renal impairment and compensated heart failure can no longer be upheld as contraindications for metformin. A clear re-definition of contraindications to metformin will enable more physicians to prescribe within guidelines.

**Keywords** Contraindications · Lactacidosis · Metformin

**Abbreviations** AMPK: AMP-activated protein kinase · MALA: metformin-associated lactic acidosis · NYHA: New York Heart Association · UKPDS: UK Prospective Diabetes Study

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## Introduction

Since publication of the results of the UK Prospective Diabetes Study (UKPDS) in 1998, metformin has become the most widely prescribed oral agent for the treatment of diabetes. This study showed a 36% reduction in all-cause mortality, a 42% reduction in diabetes-related mortality and a 32% reduction in diabetes-related endpoints [1]. Metformin can also be combined synergistically with other oral agents. When added to insulin therapy, 20–30% less insulin is required and body weight is reduced [2]. Furthermore, as monotherapy it does not cause hypoglycaemia [3]. Metformin can therefore be regarded as drug of first choice for patients with type 2 diabetes, and has recently been approved for use in affected children and adolescents. Metformin reduces cardiovascular morbidity and mortality, and a recent population-based study suggests that it may also offer protection from certain cancers [4].

Two factors limit the use of metformin. The first is that some patients do not tolerate it well, and the second is that traditional contraindications limit its use [5–9]. Although such contraindications are frequently overlooked in clinical practice, an increased incidence of serious side-effects—particularly lactic acidosis—has not been observed [10–14]. This raises the question whether the contraindications, as currently outlined, deprive many patients with type 2 diabetes of the benefits of metformin. We will therefore examine the scientific basis for the traditional contraindications of metformin and the potential consequences of relaxing them.

## Mechanism of action and pharmacokinetics of metformin

The antihyperglycaemic action of metformin is based on suppression of endogenous glucose production in patients

with type 2 diabetes, in particular excessive gluconeogenesis. The improved insulin-stimulated glucose uptake seen with its use is probably secondary to reduced hyperglycaemia [15]. At the molecular level, activation of AMP-activated protein kinase (AMPK) seems to be of critical importance [16]. In addition, metformin has beneficial effects on body weight, lipids and NEFAs, fibrinolysis, endothelial dysfunction and blood pressure [1, 3, 17].

In contrast to the earlier biguanides phenformin and buformin (which have a half-life of 7–12 h), metformin (which has a half-life of 1.5–5 h) is less lipophilic, does not accumulate in the liver and is eliminated unchanged by glomerular filtration and tubular secretion [3, 18]. Both phenformin and metformin inhibit gluconeogenesis (mostly from lactate). However, while phenformin increases lactate turnover and suppresses lactate oxidation [19], with metformin the lactate that cannot be metabolised via gluconeogenesis can still be eliminated by a compensatory increase in lactate oxidation [15].

## Current contraindications of metformin

Table 1 shows the contraindications of metformin as given by manufacturers [5], British guidelines [6, 7], the German Diabetes Association [8] and experts [9]. These are not perfectly congruent (creatinine clearance <60 ml/min in the package insert [5] vs <90 ml/min as an expert statement [9], or a serum creatinine of >106 μmol/l in a German guideline [8] vs 133 mg/dl in British guidelines [6, 7]) and are sometimes not well defined (e.g. advanced age). Special precautions have been added to cover clinical circumstances such as the use of i.v. contrast media. The rationale behind the list of contraindications is twofold: the potential accumulation of metformin in renal insufficiency and the development of lactic acidosis, the most feared side-effect of metformin. Conditions that can result in increased lactate production or decreased lactate elimination have therefore been emphasised. Lactate production is increased as a result of severe tissue hypoxia (e.g. myocardial insufficiency, respiratory insufficiency) and lactate elimination is decreased in conditions associated with liver dysfunction (e.g. alcohol abuse).

## Metformin and lactic acidosis: association vs causality

Generally speaking, lactic acidosis is a non-specific end-stage consequence of a variety of serious disorders characterised by tissue hypoxia, particularly conditions such as septicaemia, renal or hepatic failure. It is characterised by the presence of metabolic acidosis (pH<7.25) and elevated lactate levels (>5.0 mmol/l) [20].

The incidence of phenformin-associated lactic acidosis was reported to be 40–64 cases per 100,000 patient-years [21], and lactic acidosis has also been reported in patients treated with metformin. These patients were mostly elderly and had multiple comorbidities, including advanced renal failure, hepatic failure, heart failure, myocardial infarction and septicaemia [22–24]. The mortality of cases

**Table 1** Current contraindications and precautions to the use of metformin

| Contraindication | Manufacturers (Package insert), 2005 [5] | German Diabetes Association, 2003 [8] | British National Formulary, 2005 [6] | UK national clinical guidelines, 2002 [7] | Howlett and Bailey, 1999 [9] |
|---|---|---|---|---|---|
| Impaired renal function | Creatinine clearance <60 ml/min | Serum creatinine >107 μmol/l | Serum creatinine >133 μmol/l | Serum creatinine >133 μmol/l | Creatinine clearance <90 ml/min |
| Heart failure | yes | yes | yes | not stated | yes |
| (Advanced) cardiovascular disease | not stated | not stated | not stated | not stated | yes |
| Respiratory failure | yes | yes | yes | not stated | yes |
| Severe liver disorders | yes | yes | yes | not stated | yes |
| Tissue hypoxia | yes | yes | yes | not stated | yes |
| Acute and chronic alcohol abuse | yes | yes | not stated | not stated | yes |
| Advanced age | not stated | yes | not stated | not stated | not stated |
| Before i.v. contrast medium administration | yes | yes | yes | not stated | not stated |
| Perioperatively | not stated | yes | yes | not stated | not stated |
| Hypocaloric diets (<1,000 kcal) | not stated | yes | not stated | not stated | not stated |
| Wasting diseases | not stated | yes | not stated | not stated | not stated |
| Pregnancy, lactation | yes | not stated | yes | not stated | yes |
| Diabetic ketoacidosis, diabetic precoma | yes | not stated | yes | not stated | yes |

of metformin-associated lactic acidosis published before 1996 was 40–50% [23].

The key question is whether the occurrence (or severity) of lactic acidosis was causally related to metformin treatment, or whether these were simply critically ill patients who happened to be receiving metformin and would have developed lactic acidosis anyway. The question of causality could only be examined in controlled studies, which, for obvious reasons, are not possible. Thus, no conclusive answer is possible.

## Serum concentration of lactate and metformin

Most studies of patients with type 2 diabetes, including those over 70 years of age and those with mild renal failure, have shown that metformin treatment is not associated with significantly increased plasma lactate levels, as compared with other forms of treatment [17, 25–28]. In some, however, a non-significant trend was seen [17, 28] or post-meal lactate peaks were increased [25]. In a community-based cohort of patients with type 2 diabetes, plasma lactate concentrations were higher in metformin-treated patients than in those who did not receive the drug (1.86 vs 1.58 mmol/l, $p<0.001$) [29]. It is important to point out that patients with contraindications were excluded from many studies examining the effects of metformin on plasma lactate, and this clearly limits the conclusions that can be drawn for this subgroup.

Notwithstanding, neither serum lactate concentrations nor the prognosis of lactic acidosis appear to be determined by the serum concentration of metformin, but rather by the severity of the underlying hypoxic disease and comorbidities [24, 30, 31]. This indicates that neither lactate nor metformin levels can predict the risk of lactic acidosis in a given patient, and is compatible with the hypothesis that metformin does not play a causative role.

## Incidence of lactic acidosis in metformin-treated patients

In the UKPDS and other controlled studies with meticulous adherence to standard contraindications, no cases of lactic acidosis on metformin were recorded [1, 17, 28]. In the Comparative Outcomes Study of Metformin Intervention vs Conventional (COSMIC) approach study, the therapeutic safety of metformin was studied in more than 7,200 patients treated with metformin vs a control group of 1,505 patients with type 2 diabetes receiving other established treatments. The frequency of lactic acidosis, death and hospitalisation did not differ significantly between the two groups [28].

From 1987 to 1991, population-based data from Sweden showed an incidence of 2.4 cases of metformin-associated lactic acidosis per 100,000 patient-years [32]. In 1995, 1 year after metformin had become available in the USA, the retrospectively estimated incidence was 5.0 per 100,000

**Table 2** Adherence to metformin contraindications as shown by population-based studies and retrospective samples

| Authors/ Time period | Number of patients | Country/ Region | Frequency of all contraindications and risks (%) | Frequency of renal impairment (%) | Frequency of liver disorders (%) | Frequency of heart failure (%) | Frequency of CHD including myocardial infarction (%) | Number of cases of lactic acidosis |
|---|---|---|---|---|---|---|---|---|
| Sulkin et al. [10] 3 months | 89 | England Southampton | 54 | 2 | 2 | 2 | 22 | 0 |
| Holstein et al. [11] 3.5 years | 308 | Germany Lippe | 74 | 19 | 1.3 | 25 | 51 | 0 |
| Emslie-Smith et al. [12] 3 years | 1,847 | Scotland Tayside | 24.5 | 4.8 | 2.8 | 25.2 | 3.5 | 1 |
| Horlen et al. [13] 9 months | 100 | USA North Carolina | 22 | 5 | Not stated | 14 | Not stated | 0 |
| Calabrese et al. [14] 6 months | 204 | USA Pittsburgh | 62 | 12 | Not stated | Not stated | Not stated | 0 |
| Kennedy and Herman [36] | 4,838 | USA | Not stated | 4.5 | Not stated | Not stated | Not stated | Not stated |
| Rakovac et al. [37] 5 years | 4,401 | Austria | 18.9 | 3.1 | Not stated | 13.6 | Not stated | Not stated |

patient-years, with restrictive prescribing presumably still the norm [22]. The incidence reported for a Canadian region was 9 per 100,000 patient-years [21]. The clinical data were, however, incomplete in many of these studies as serum lactate or metformin concentrations were not available. In patients with type 2 diabetes without metformin therapy, the incidence of lactic acidosis, as verified by measurement of elevated lactate levels, was 9.7 per 100,000 patient-years [33], which is comparable to the incidence of lactic acidosis in metformin-treated patients [21, 34].

A recent meta-analysis of 194 prospective comparative trials and cohort studies—an update of a former Cochrane review—revealed no cases of lactic acidosis in 18,689 metformin-treated individuals with type 2 diabetes (36,893 patient-years) or in the 38,003 individuals (30,109 patient-years) in the non-metformin group [34]. Using Poisson statistics with 95% confidence intervals, the authors found an incidence of 8.1 cases of lactic acidosis per 100,000 patient-years in metformin-treated patients as compared with 9.9 per 100,000 patient-years in the control group. Of the studies included in this meta-analysis, 16% included patients aged over 65 years and 44% included patients with renal insufficiency (creatinine >133 μmol/l) and metformin therapy. However, the exact percentage of patients with renal failure could not be established. Taken together, the available evidence indicates that the incidence of lactic acidosis in type 2 diabetic patients treated with metformin is similar to that in patients who do not receive metformin treatment.

## Disregard of metformin contraindications and incidence of lactic acidosis

Representative prescribing figures from the USA (Medicare 2000–2001) showed that 24.6% of patients with type 2 diabetes who were discharged from hospital on metformin had heart failure [34]. Moreover, both retrospective population-based studies [12] and studies in selected cohorts [10, 11, 13, 14, 35, 36] showed that the currently proclaimed contraindications and precautions for metformin therapy are frequently disregarded (Table 2). Interestingly, among the ~2,500 patients followed in these studies only one case of lactic acidosis was reported, and even this one case could not be causally attributed to metformin since it was associated with intercurrent myocardial infarction and renal failure [12].

An Israeli study [27] investigated 393 patients with type 2 diabetes and multiple comorbidities and explicit contraindications to metformin, particularly, chronic renal insufficiency (serum creatinine 130–220 μmol/l), coronary heart disease ($n$=266), chronic heart failure (New York Heart Association [NYHA] stage III or IV) ($n$=94), liver disease ($n$=51) and chronic obstructive lung disease ($n$=91). These patients were randomly assigned to continued metformin or no further treatment. After 4 years, the patients who had continued to take metformin had significantly lower body mass indices and $HbA_1c$ values, and more favourable lipid profiles than the control group; no cases of lactic acidosis were recorded. Progression of renal insufficiency, patient-oriented endpoints and all-cause mortality did not differ significantly between the two groups.

## Suggested modifications of metformin contraindications

Most patients with type 2 diabetes are over 65 years of age. There is no evidence that old age should in itself be a reason to withhold metformin. It is important to point out, however, that 'hard' contraindications are far more likely to emerge in the elderly [11] than in the young, and these should therefore be regularly monitored.

Metformin is undoubtedly contraindicated in patients with severe renal impairment. Evidence from meta-analyses [34] and prospective studies does however suggest that metformin can be used safely in chronic renal insufficiency with a creatinine of up to 133 μmol/l [26, 27]. It must be borne in mind, however, that serum creatinine generally overestimates renal function, particularly in the elderly and in the obese with reduced muscle mass. Therefore, calculation of the creatinine clearance according to the method of Cockroft-Gault [38] or estimation of the GFR [39] is to be preferred. An estimated GFR as low as 40 ml/min may be acceptable to continue metformin.

Stable heart failure of NYHA stages I and II that is effectively controlled by diuretics and ACE inhibitors can no longer be upheld as a contraindication. In fact, there is evidence suggesting that metformin can be safely taken by patients with more severe heart failure [27]. However, the drug must be withdrawn immediately in the event of acute myocardial infarction or other intercurrent diseases with generalised hypoxia and hypoperfusion, as such disorders can themselves cause lactic acidosis.

The recommendation to discontinue metformin 2 days before X-ray examinations with intravenous contrast media or surgical procedures under general anaesthesia is not supported by any studies, and in practice leads to unnecessary interruption of glycaemic control. In view of its low lipophilicity and short plasma half-life [3] it should be safe to withdraw metformin the evening before the intervention in patients with normal renal function. Metformin therapy can be resumed 2 days after the procedure following verification of normal renal function.

## Conclusion

Although the risk of lactic acidosis on metformin is 10–20 times lower than that on phenformin [21, 33] and does not differ from the risk in patients not taking the drug, this agent still carries the historic burden of its predecessors. It is even doubtful whether metformin plays a causal role in the pathogenesis of lactic acidosis at all. It cannot be disputed that conscientious adherence to current prescribing guidelines protects patients from serious adverse events. On the other hand, the currently stated contraindications of metformin deprive many typical patients with type 2 dia-

betes of the benefits of this drug. Moreover, the decision to withdraw metformin is not a neutral one, since suggested alternative therapies such as thiazolidinediones or sulfonylureas [6, 40] predispose to weight gain, and have other disadvantages such as heart failure (thiazolidinediones) and hypoglycaemia (sulfonylureas).

We believe that standard contraindications to the use of metformin should be relaxed, and that the benefits of reducing the number of patients excluded from using it would by far outweigh the potential risks. We propose removal of the following contraindications from the list: (1) old age; (2) chronic renal insufficiency (as long as GFR >40 ml/min); (3) chronic heart failure (NYHA stages I and II); and (4) discontinuation of metformin therapy 2 days before surgery and i.v. contrast medium administration. A clear re-definition of metformin contraindications will enable more physicians to prescribe within the guidelines, which in times of fear of litigation is an important issue. The main effect of revising these contraindications and precautions will be to bring the official guidelines into harmony with day-to-day clinical practice.

**Duality of interest** A. Holstein has received honoraria from Merck/Germany for speaking engagements. M. Stumvoll is not aware of any duality of interest.

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