REVIEW ARTICLE

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Lactic Acidosis Induced by Metformin
Incidence, Management and Prevention

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Contents

Abstract 727
1. The Incidence of Lactic Acidosis during Oral Antidiabetic Therapy 728
   1.1 The Incidence Reported in the Literature 728
   1.2 Limitations to the Accurate Assessment of Incidence 729
   1.3 The Incidence of What, Exactly? 730
2. Management 732
   2.1 The Conventional Scenario 732
   2.2 Comments on the Conventional Scenario 732
   2.3 What Are We Seeking to Manage? 733
3. Prevention 733
   3.1 The Conventional Contraindications 733
   3.2 Limitations of the Conventional Contraindications 734
   3.3 What Are We Seeking to Prevent? 736
4. Conclusions 737

Abstract

Lactic acidosis associated with metformin treatment is a rare but important adverse event, and unravelling the problem is critical. First, this potential event still influences treatment strategies in type 2 diabetes mellitus, particularly in the many patients at risk of kidney failure, in those presenting contraindications to metformin and in the elderly. Second, the relationship between metformin and lactic acidosis is complex, since use of the drug may be causal, co-responsible or coincidental. The present review is divided into three parts, dealing with the incidence, management and prevention of lactic acidosis occurring during metformin treatment. In terms of incidence, the objective of this article is to counter the conventional view of the link between metformin and lactic acidosis, according to which metformin-associated lactic acidosis is rare but is still associated with a high rate of mortality. In fact, the direct metformin-related mortality is close to zero and metformin may even be protective in cases of very severe lactic acidosis unrelated to the drug. Metformin has also inherited a negative class effect, since the early biguanide, phenformin, was associated with more frequent and sometimes fatal lactic acidosis. In the second part of this review, the objective is to identify the most efficient patient management methods based on our knowledge of how metformin acts on glucose/lactate metabolism and how lactic acidosis may occur (at the organ and cellular levels) during metformin treatment. The liver appears to be a key organ for both the antidiabetic effect of metformin and the development of

lactic acidosis; the latter is attributed to mitochondrial impairment and subsequent adenosine triphosphate depletion, acceleration of the glycolytic flux, increased glucose uptake and the generation of lactate, which effluxes into the circulation rather than being oxidized further. Haemodialysis should systematically be performed in severe forms of lactic acidosis, since it provides both symptomatic and aetiological treatment (by eliminating lactate and metformin). In the third part of the review (prevention), the objective is to examine the list of contraindications to metformin (primarily related to renal and cardiovascular function). Diabetes is above all a vascular disease and metformin is a vascular drug with antidiabetic properties. Given the importance of the liver in lactate clearance, we suggest focusing on the severity of and prognosis for liver disease; renal dysfunction is only a prerequisite for metformin accumulation, which may only be dangerous *per se* when associated with liver failure. Lastly, in view of metformin's impressive overall effectiveness profile, it would be paradoxical to deny the majority of patients with long-established diabetes access to metformin because of the high prevalence of contraindications. The implications of these contraindications are discussed.

Lactic acidosis induced by metformin is, relative to the very widespread use of the drug, a rare event. Why, then, should we pay much attention to this topic? In fact, unravelling this problem is critical. Despite the rarity of the event,[1,2] its possible occurrence still influences treatment strategies in type 2 diabetes mellitus – particularly in the many patients at risk of kidney failure, those presenting real or supposed contraindications to metformin and in the elderly. Under these circumstances, the choice between continuing metformin treatment and switching to other drugs is crucial. Another reason for paying attention to this topic is the complexity of the relationship between metformin and lactic acidosis, since use of the drug may be causal, co-responsible or coincidental.

This review examines the link between metformin and so-called 'metformin-associated lactic acidosis' (MALA), including discussion of the classical view of metformin's contraindications. The incidence, management and prevention of MALA are successively considered.

1. The Incidence of Lactic Acidosis during Oral Antidiabetic Therapy

1.1 The Incidence Reported in the Literature

Lactic acidosis is the most frequent cause of metabolic acidosis.[3] It is characterized by an increase in the anion gap (the blood concentration of sodium minus the concentrations of chloride and bicarbonate). The standard working definition is an arterial lactate concentration exceeding 5 mmol/L and pH ≤7.35.[4] Cases of lactic acidosis are conventionally classified as anaerobic (type A) or aerobic (type B). However, this distinction has become obsolete, since a restricted oxygen supply and metabolic factors often act simultaneously.[3,5,6]

Biguanides have a well defined effect on glucose/lactate metabolism, which actually contributes to their antidiabetic properties and is believed to result from the blockade of gluconeogenic precursors, such as lactate and alanine, to pyruvate. This effect is absent in all other classes of antidiabetic drugs.

Biguanides are synthesized from two guanidine molecules. The drug class comprises buformin, metformin and phenformin and was introduced into diabetes treatment in the 1950s. All biguanides are strong bases and are essentially 100% protonated at physiological pH. Their 2-dimensional structures suggest close similarities between members of this class.[7] The slight differences do, however, lead to profound differences in the behaviour of these molecules in solution and then in terms of their pharmacokinetics and metabolism.[8-11] Although buformin and especially

phenformin were initially widely used in the clinic, their close association with fatal lactic acidosis resulted in their withdrawal from the market in most countries.[12]

This great concern about lactic acidosis delayed the US market introduction of metformin until May 1995. Following marketing authorization of the drug, the US FDA requested a post-marketing safety surveillance study with broad inclusion criteria to facilitate recruitment of patients who were representative of the country's type 2 diabetes population. In this 1-year prospective trial, none of the 7227 patients receiving metformin experienced lactic acidosis and plasma lactate levels did not vary significantly according to the antidiabetic therapy.[13]

In a Cochrane meta-analysis, Salpeter et al.[14] identified all comparative trials and observational cohort studies published between January 1959 and October 2009 in which metformin had been used for at least 1 month. From a total of 347 studies (about two-thirds of which were randomized, controlled trials, with the remainder as observational studies) lasting from 3 months up to more than 10 years and with 70 490 patient-years of metformin exposure, the authors did not identify a single case of lactic acidosis. By using Poisson statistics, the estimated hypothetical upper 95% confidence limit for the true incidence of lactic acidosis was 4.3 cases per 100 000 patient-years in the metformin group and 5.4 per 100 000 patient-years in the non-metformin group. It is noteworthy that this analysis did not find a significant effect of metformin on plasma lactate levels when compared with other drugs. Bolen et al.[15] also compared all the antidiabetic agents with one another. They also concluded as to the lack of a relevant risk for lactic acidosis in metformin recipients compared with subjects taking other oral antidiabetic agents. Bodmer et al.[16] also compared metformin with other diabetes drugs in a large population, but in a different manner, by using data from the UK-based General Practice Research Database rather than from clinical trials. In a population of 50 048 type 2 diabetic patients, they found that the risk of lactic acidosis in metformin users was very low (six cases) and no greater than in users of other oral antidiabetic agents (a crude incidence rate of 3.3 cases per 100 000 person-years in metformin users versus 4.8 cases per 100 000 person-years in sulphonylurea users).

The above-mentioned rates do not differ from the rate of lactic acidosis before metformin was approved for use in the US. Indeed, by using electronic databases of hospital discharge diagnoses and laboratory results from over 41 000 person-years of exposure in three diverse US populations with type 2 diabetes, Brown et al.[17] observed 9.7 confirmed lactic acidosis events per 100 000 person-years.

1.2 Limitations to the Accurate Assessment of Incidence

Logically, health problems are first considered from an epidemiological viewpoint, so that the problem with every disease or event relates to both its nature and its extent. However, what is the best way to count this type of event? One strategy involves maintaining a systematic record from prospective trials. This approach has the advantage of comparing metformin with placebo but can also be criticized in several respects. First, the assessment of a rare event requires the evaluation of a very large group. Second, published trials may produce biased results; it is probable that the proportion of participants at low risk for acidosis (as a result of better observance of the contraindications for metformin therapy) is greater in clinical trials than in clinical practice. In contrast, retrospective datasets better reflect 'real-life' use of the drug. Consequently, the fact that no cases of lactic acidosis were observed in trials does not rule out the possibility of metformin accumulation and subsequent lactic acidosis in the general population of patients with diabetes, in whom contraindications may not be respected, e.g. when acute organ failures occur or in cases of metformin overdose.

Alongside epidemiological data, case reports also provide evidence. However, in their review of 216 publications, Bolen et al.[15] stated that "the evidence for metformin-associated lactic acidosis stems mainly from about 300 case reports" but did not consider case reports in their review because

they "pose problems in determining causality" and provide no clear denominator for risk estimation. Furthermore, the extensive review by Salpeter et al.[14] evaluated studies in which metformin treatment had been implemented for at least 1 month; consequently, a potential effect of metformin introduction on the induction of lactic acidosis would not have been fully taken into account.

Moreover, the correct assessment of incidence requires that under- and over-reporting are taken into account. There is the possibility of under-reporting, as all cases of lactic acidosis are not necessarily declared. Conversely, lactic acidosis may be over-reported if the imputability of metformin is overestimated. In fact, the rate of event reporting depends partly on whether or not the event is considered as truly harmful. By way of an example, the reporting rate for hypoglycaemia occurrence during sulphonylurea treatment is certainly very low because this kind of event may simply be viewed as resulting from the potent therapeutic effect – as a consequence of the drug's virtue, in other words. Metformin may be considered differently, i.e. capable of inducing lactic acidosis as a truly adverse, collateral effect. Strictly speaking, however, the development of hyperlactataemia during metformin accumulation is also the direct consequence of the magnification of its therapeutic effect, as the drug's antihyperglycaemic action is partly due to its facilitation of the conversion of glucose into lactate.

It could be argued that metformin has inherited a negative class effect, since the early biguanide phenformin was indeed associated with more frequent, severe and even fatal lactic acidosis.[18] It must be borne in mind that even though phenformin and metformin belong to the same family, they are structurally distinct and have markedly different effects on metabolism and the vascular system[3,6,10] and in terms of adverse effects. MALA is not the same as (and occurs much less frequently than) phenformin-induced lactic acidosis.

1.3 The Incidence of What, Exactly?

When seeking to correctly assess the incidence of MALA, one cannot accurately count the overall number of occurrences (i.e. regarding MALA as a single clinical entity), as the nature of the MALA must be taken into account. In reality, MALA is an equivocal concept, since metformin may be either a cause of lactic acidosis or merely a coincidental factor; lactic acidosis in a patient taking metformin is not necessarily MALA. Accordingly, knowledge of the blood metformin concentration from case reports is critical when evaluating metformin's imputability in the incident (after having first checked that the criteria of lactic acidosis are met; surprisingly, this is not always performed in case reports).[19]

Our group has reported on the importance of measuring plasma metformin concentrations.[19-23] We illustrated this point by reporting the case of a 62-year-old patient who developed anuria (serum creatinine level of 4 mg/dL [350 μmol/L]) and lactic acidosis (blood lactate 16.3 mmol/L, pH 7.09).[20] As metformin therapy had not been withdrawn, a high plasma metformin concentration would have been expected and would have prompted the conclusion that lactic acidosis occurred as a result of drug accumulation. In fact, the plasma metformin concentration (0.4 mg/L) was well within the therapeutic range (0.6 ± 0.5 mg/L) due to the recent occurrence of kidney failure following cardiogenic shock.

However, measuring plasma metformin concentrations only provides retrospective information, since a metformin assay[24] is not readily available (especially in an emergency context). This is illustrated by another literature case report featuring very severe lactic acidosis (pH 6.38, with recovery).[25] When searching for the cause, the authors incriminated metformin as "toxicology later confirmed the presence of almost twice the therapeutic plasma concentration of metformin," i.e. 3.4 mg/L. Could that have meant that the metformin assay was requested rapidly but that the result was given with some delay? Or that the assay had been performed 'later'? In the first case, the responsibility of metformin can be ruled out, as the drug concentration was only slightly elevated with regard to the severity of the lactic acidosis (given that concentrations of metformin 70 times higher have been observed in our clinic). In the second case, how high was the real metformin

concentration peak and so how strong was the link between metformin and the development of lactic acidosis?

Given that it is generally impossible to rapidly obtain data on plasma metformin accumulation, measurement of the metformin concentration in erythrocytes may be very useful – at least for retrospective analysis. Our group was the first to delineate the clinical implications of this type of measurement.[26,27] Metformin may indeed accumulate in erythrocytes, which may reflect the deep compartment for the drug. The slow decline in erythrocyte metformin concentration may therefore contribute to retrospective diagnosis of metformin accumulation.

If the metformin concentration cannot be determined in either plasma or erythrocytes, it is at least possible to estimate the risk of metformin accumulation and its extent by considering the patient's renal function, the change over time in this parameter, the metformin dosage and the time of the last metformin administration. However, this requires careful analysis of the patient's case history, as metformin accumulation may be either a precipitating factor (e.g. metformin overdose or acute kidney failure in the absence of metformin discontinuation) or an underlying factor (e.g. chronic kidney failure). Likewise, organ failure may be either a precipitating factor (e.g. myocardial infarction) or an underlying condition (e.g. liver failure).

The problem, however, is even more complicated than that. Even though determination of a low metformin blood concentration can exonerate metformin, the opposite is not necessarily true: high plasma metformin concentrations are not necessarily accompanied by hyperlactataemia.[23] This means that lactic acidosis may occur because of metformin accumulation in the absence of overt pathologies (e.g. organ failure, sepsis and haemorrhage); an underlying impairment in the cellular energy metabolic cascade may nevertheless be required to either favour the development of lactic acidosis in some patients or, conversely, prevent it in others.

In summary, the incidence of MALA should not be considered in isolation (since it is not a single clinical entity) but according to each kind of triggering situation: (i) a severe disease not associated with metformin accumulation; (ii) metformin accumulation not associated with any pathology; and (iii) the coexistence of severe disease and metformin accumulation. How, then, can one check that the case reports in the literature have been correctly categorized and that the incidence has been correctly assessed when most lack conclusive data? In particular, how can one draw solid conclusions when metformin blood concentration data are missing? When the metformin concentration is only moderately elevated? Or when major accumulation is not necessarily accompanied by lactic acidosis? And when might kidney failure in fact be secondary to a shock syndrome and thus not the cause of metformin accumulation? When the shock syndrome is not necessarily the consequence of MALA or if the lactic acidosis is not severe enough to provoke haemodynamic disturbances and multi-organ failure? Or when the clinical data are too scarce to rule out predisposing factors other than metformin accumulation? This explains why the interobserver agreement was extremely low in an expert panel study of whether metformin was the most important causative factor in several cases of lactic acidosis.[28] Nevertheless, the work at least showed that metformin was not necessarily responsible in some of the cases.

This discussion is not speculative, since the typology described here influences the clinical outcome and thus patient management and disease prevention. In summary, the prognosis (i) of lactic acidosis *unrelated* to metformin is still that of a serious and frequently life-threatening condition; (ii) is excellent in isolated metformin-*induced* lactic acidosis (in which the drug can be withdrawn); and (iii) is intermediate in so-called 'metformin-*associated* lactic acidosis' (in which other factors such as patient factors and concomitant medication may also play a part in determining the prognosis), depending upon the severity of the underlying condition, the presence of precipitating factors and, perhaps, the degree of metformin accumulation (which could even exert a protective effect, as is discussed in section 3.2).[22]

2. Management

2.1 The Conventional Scenario

In addition to supportive care, the elimination of the 'offending' medication with renal function replacement therapies (i.e. haemodialysis and continuous haemofiltration) is typically recommended with a view to restoring blood volume, enhancing renal blood flow, correcting metabolic acidosis (as a very low pH may compromise myocardial function) and removing lactate and metformin.

2.2 Comments on the Conventional Scenario

The supposition that haemodialysis is the most efficient method (providing both symptomatic and aetiological treatment by eliminating lactate and metformin) implies that both lactate and metformin are considered to be toxic substances.

In fact, lactate *per se* is not an acidogenic substance, the excess protons generated by hydrolysis of adenosine triphosphate (ATP) during anaerobic glycolysis titrating endogenous buffers which are regenerated by lactate metabolism.

Furthermore, lactate can be viewed as an energy substrate rather than as a toxic substance.[29] Lactate substitutes directly for glucose as a metabolic substrate through entry via pyruvate into the tricarboxylic acid cycle and can be used as a gluconeogenic substrate, oxidized or transaminated into alanine. It has been consistently shown that intravenous lactate infusion prevents cerebral dysfunction during hypoglycaemia both in healthy volunteers[30-33] and in diabetic subjects.[34] In one study from our group the median lactate level in metformin-treated patients with lactic acidosis was twice as high as in patients not treated with metformin.[22] Hence, for a given lactate level, the higher the degree of metformin accumulation, the higher the hyperlactataemic effect of metformin. This equates to a greater protective effect via lactate production, less lactate release from damaged tissues and, ultimately, a better prognosis. In other words, when hyperlactataemia is synonymous with adverse outcomes it is because the underlying cause is problematic (except in cases of liver failure, as discussed in section 3.2).

Let us now consider how metformin acts on glucose/lactate metabolism and how lactic acidosis may occur during metformin treatment. Several mechanisms of action for the antidiabetic effect of metformin have been proposed. These are mainly related to a decrease in hepatic glucose production, an increase in peripheral glucose disposal, a reduction in intestinal glucose production and a possible reduction in lipolysis in adipocytes.[35,36] The main mechanism is likely to be the reduction in hepatic glucose production, although increased glucose turnover in the splanchnic bed is probably also an important factor. Metformin increases the rate of anaerobic metabolism of glucose within the splanchnic bed;[37,38] the excess lactate passes directly into the liver, where it is metabolized and the rate of gluconeogenesis from lactate falls.[39] The cellular mechanisms of action have yet to be determined. The mitochondrion is a key factor,[40] but not the only one, since metformin also normalizes glucose uptake and storage in mitochondrion-lacking erythrocytes. Furthermore, metformin has been shown to inhibit mitochondrial respiration via complex I[41] and to activate adenosine monophosphate-activated protein kinase (AMPK).[42] This results in an increase in oxidative phosphorylation, glycolysis and mitochondrial fatty acid β-oxidation. However, whether this activation of AMPK is direct and/or indirect via inhibition of complex I remains to be determined. Recent experiments with primary cultures of hepatocytes from AMPK catalytic subunit (AMPKα1α2) knockout mice have suggested that metformin inhibits gluconeogenesis through an AMPK-independent mechanism via a decrease in intracellular-dependent ATP levels.[43]

Metformin is an organic cation that is transported into the liver via the polyspecific organic cation transporter 1 (OCT1, encoded by the gene *Slc22a1*).[44] A study with OCT1 knock-out mice has demonstrated that this transporter is required for metformin transport into the liver and eliciting the drug's metabolic effects.[45] Wang et al.[46] looked at whether OCT1 was involved in not only the therapeutic effect of metformin but also MALA and whether the liver was a key organ in the development of lactic acidosis. When mice

were given metformin 150 mg/h/kg intravenously for 3.5 hours, the blood lactate concentration increased significantly in wild-type mice but only slightly in OCT1 knock-out mice. The plasma metformin concentration profile was similar in both types, suggesting that the liver is indeed the key organ responsible for lactic acidosis. Dykens et al.[47] evaluated metformin in a battery of tests developed to reveal induction of mitochondrial impairment (e.g. the viability of HepG2 cells in galactose and respiration by isolated mitochondria). They concluded that biguanide-induced lactic acidosis may be attributed to mitochondrial impairment and subsequent ATP depletion, acceleration of the glycolytic flux, increased glucose uptake and generation of lactate, which finally effluxes into the circulation rather than being oxidized further. A high concentration of metformin (2 mmol/L) was needed to inhibit respiration, indicating that bioaccumulation into mitochondria is required. This is also supported by other experiments.[48,49] Due to their positively charged guanidium group, which is responsible for cellular uptake, biguanides may accumulate in the mitochondrial matrix 100-fold more than in the plasma (as a function of the Nernst equation), via an uptake mechanism. Some molecules may become even more concentrated in the mitochondrion, depending on the cell's bioenergetic status and the compound's physicochemical characteristics. This ultimately results in major respiratory inhibition. Consequently, and even though metformin appears to be easily dialyzable,[50] total metformin removal by dialysis is difficult to achieve because of this intracellular binding (as well as the large volume of distribution). Dialysis therapy should therefore be extended: an example of spontaneous metformin elimination from blood (i.e. in a patient not treated with dialysis) is given in figure 1.

In summary, true metformin-induced lactic acidosis results from a combination of anaerobic stimulation of lactate production by intestinal cells with defective lactate elimination by the liver, via metformin accumulation due to kidney failure,[52] liver failure[22] or overdosing.[53] It remains to be seen whether such metabolic effects are harmful or not. Although this point is discussed in the Prevention section (section 3), it is important to note here that the action on the respiratory chain complex does indeed have a cytoprotective effect.

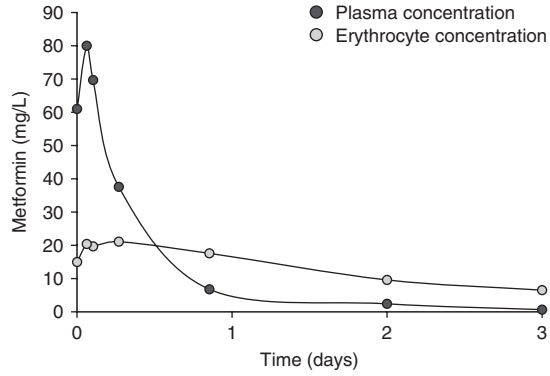

Fig. 1. An example of the time-course of spontaneous metformin elimination from blood in a patient with metformin accumulation but not treated with dialysis. Therapeutic levels of metformin are 0.5 ± 0.4 mg/L in plasma and 0.8 ± 0.4 mg/L in erythrocytes (reproduced from Lalau and Masmoudi,[51] with permission. © 2005, Springer Berlin/Heidelberg).

2.3 What Are We Seeking to Manage?

With a view to suggesting appropriate means of treatment, the above findings prompt us to focus therapeutic efforts on normalizing the acid-base imbalance – particularly by optimizing ventilation to compensate for metabolic acidosis and treating the triggering factors for lactic acidosis. This discussion is indeed facilitated by the fact that patients with significant metformin accumulation necessarily have severe renal failure (except in the case of intestinal occlusion):[21] dialysis should therefore be considered for the rapid correction of blood pH, volume and osmolarity, and the elimination of lactate and metformin. Nevertheless, the fact that lactate and metformin can be removed by dialysis does not mean that they are necessarily toxic.

3. Prevention

3.1 The Conventional Contraindications

The contraindications and precautions for metformin use given by the manufacturer in the package insert[54] include renal impairment, the

risk of metformin accumulation and conditions that may be associated with or promote hypoxia (e.g. heart failure, tissue hypoxia, respiratory failure) or defective lactate clearance (alcohol abuse and liver failure). Notably, the guidelines in some countries differ and are more restrictive, which indicates a well entrenched fear of lactic acidosis.[55]

3.2 Limitations of the Conventional Contraindications

Since diabetes is above all a vascular disease, and given that the diabetic population is aging globally,[56] the list of contraindications (including the warning 'may cause tissue hypoxia') is rather daunting. If one also considers the fact that these contraindications are often disregarded (in up to 94% of cases, according to the observational studies reviewed in Tahrani et al.[57]), the occurrence of true metformin-induced lactic acidosis would be expected to be rather frequent. In fact, it is rare,[1,2] and mortality due to metformin accumulation is even questionable. Indeed, what ultimately matters is not the occurrence of a metabolic disorder *per se* but rather whether the latter is life-threatening or not.

To date, there is still no clear evidence that lactic acidosis solely induced by metformin causes mortality. In contrast, there is growing clinical evidence demonstrating rapid recovery survival in MALA, despite massive metformin ingestion (as much as 63 g),[58] hypoglycaemia (due to combined intoxications) that is severe enough to result in prolonged coma in the elderly,[51] circulatory failure as severe as shock,[20,22] an APACHE (Acute Physiology and Chronic Health Evaluation)[59] score as high as 30 or more,[60] body temperature as low as 29°C,[25] a pH as low as 6.38[25] and an arterial lactate concentration as high as 40 mmol/L.[61] In sepsis, a dose of metformin that mimics accumulation in an experimental model does not aggravate the mortality rate.[62] In hamsters submitted to severe haemorrhagic shock, the survival rate in the metformin-treated group was almost 100% (vs zero in the placebo group).[63]

Such an unexpectedly favourable outcome under very severe conditions leads to the challenging and provocative hypothesis that metformin may even be protective. This would not be so surprising, given the pleiotropic protective effects of metformin on metabolism and the macro- and microvasculature (as described in table I). It is noteworthy that most of these vascular effects are unrelated to the metformin dose[74] and are even independent of the antihyperglycaemic effect. Metformin has even been presented as a vascular drug with antidiabetic properties.[64] By way of an example, metformin reduced the myocardial infarct size in an *in vivo* murine model of myocardial ischaemia-reperfusion injury at a dose as low as 0.25 mg/kg intraperitoneally.[75]

In other words, it is possible to present MALA in the literature as still being associated with a high rate of mortality. The mortality of 22 of 49 patients in our experience[22] appears in a poor light. In fact, rather than expressing mortality as a mean, a distinction should be made between lactic acidosis unrelated to metformin where mortality is likely to be much higher (at least in the 1970s, studies reported that the overall mortality

Table I. Metformin as a vascular drug: from proposed mechanisms of vascular protection to clinical benefits[64-66]

Anti-ischaemic effects: reduced cardiometabolic risk factors reduced atherosclerosis improved fibrinolysis/thrombolysis reduced infarct size Improved microcirculation: improved arterial vasomotion reduced permeability preserved glycocalyx improved erythrocyte deformability Improved endothelial function Neutralized advanced glycation end-products Antioxidant effects	Main clinical consequences: improved peripheral arterial disease[67] reduced myocardial infarction[68] reduced coronary restenosis[69] reduced myocardial re-infarction[70] improved outcome in heart failure[71-73] unexpected survival in severe lactic acidosis with shock syndrome[20,22] reduced all-cause mortality in large populations[68]

for lactate levels >5 mmol/L was around 80%)[76,77] and lactic acidosis induced by metformin where there is a doubt that this may cause mortality.

Unsurprisingly, the mechanisms of action of metformin are also pleiotropic at the cellular level. Due to its action on the respiratory-chain complex, metformin activates both glycolysis and fatty acid β-oxidation and has a cytoprotective effect via the diminution of oxidative stress and repression of the mitochondrial permeability transition.[78] The production of reactive oxygen species induced by a reverse-electron flux is slowed by metformin.[78] In cultured micro- and macrovascular endothelial cells, therapeutic concentrations of metformin inhibit the permeability transition pore and prevent the apoptosis usually induced by either a direct oxidizing agent or hyperglycaemia.[79] All these various vascular effects are in sharp contrast to those seen with phenformin, which has been shown to decrease cardiac output and to increase left ventricular end pressure.[80]

Defining the patient populations who are contraindicated for metformin mainly refers to renal and cardiovascular function. Hence, safety considerations must understandably take into account the relationship between renal function, plasma metformin concentrations and the adverse event rate in patients presenting with coronary or heart disease. With regard to renal function, it is important to bear in mind that metformin normally clears 4–5 times more quickly than creatinine does (for a review see Scheen[81]); due to this high clearance rate, unmodified metformin is rapidly excreted by the kidneys (with an estimated half-life of 1.5–4.9 hours). About 90% of the ingested dose is eliminated in the urine within 12 hours. Consequently (and with the exception of cases of intoxication and intestinal occlusion),[82] plasma metformin concentrations well above the therapeutic range imply both defective metformin elimination and ill-advised continuation of metformin therapy (i.e. despite the presence of contraindications).

In view of this rapid, comprehensive elimination, the conventional recommendation of withdrawing metformin prior to (for example) radiography with iodinated contrast agents is not justified. In fact, stopping metformin in a context of potential renal impairment is counter-intuitive, as the very real risk of 'rebound hyperglycaemia' may actually precipitate the impairment of renal function via dehydration. A much more pragmatic approach is needed.

Contraindications or precautions have traditionally been based on serum creatinine measurements (for a review see Holstein and Stumvoll[55]). With a view to better defining patients still indicated for metformin administration, some authors have suggested assessing the implications of replacing the current serum creatinine threshold of >150 μmol/L with a criterion based on various levels of estimated glomerular filtration rate (eGFR, determined using the abbreviated Modified Diet in Renal Disease equation[83]). In a study of 11 297 patients taking metformin in accordance with the current guideline, 82.0% had at least stage 2 renal impairment (eGFR <90 mL/min/1.73 m^2) and 25.5% had at least stage 3 impairment (eGFR <60 mL/min/1.73 m^2).[84] The authors found that an eGFR threshold of ≥36 mL/min/1.73 m^2 would have had a neutral effect on the number of patients eligible for metformin therapy and would have enabled continuation with creatinine concentrations of up to 179 μmol/L. Another large study performed along the same lines suggested an eGFR cut-off value of <30 mL/min/1.73 m^2 as an absolute contraindication to metformin use.[85]

We contest the idea of defining a threshold (whether based on serum creatinine or eGFR) for continuing or stopping metformin therapy because it amounts to stating 'either the usual dose or not at all'. Given that metformin is usually cleared rapidly, the renal impairment has to be very severe if it is to lead to significant metformin accumulation. When it is possible to perform regular blood metformin assays, we believe that it is possible to continue the therapy as long as the dosage is adjusted to match the state of renal impairment. Indeed, in patients aged 74 ± 1.5 years, we have shown that plasma metformin concentrations remained within expected values when subjects were given 1700 mg/day of metformin for creatinine clearances above 60 mL/min or 850 mg/day for clearances between 30 and 60 mL/min. There was no statistically significant difference in metformin concentration between

the two dosage groups.[86] Moreover, prophylactic measures relative to renal function are mainly used as a guide for initiating metformin treatment, whereas lactic acidosis due to metformin occurs more often in acute kidney failure. In the largest series of metformin-treated patients with lactic acidosis yet reported, acute kidney failure appeared to be about three times more frequent than chronic kidney failure.[22]

Turning now to cardiovascular status, the United Kingdom Prospective Diabetes Study (UKPDS) is well known for its demonstration that treatment with metformin in patients with newly diagnosed type 2 diabetes was associated with marked reductions in myocardial infarction, diabetes-related death, any diabetes-related endpoint and all-cause mortality.[68] However, one limitation of this trial was that it defined the benefits of metformin in subjects with a rather low risk of cardiovascular events.

In a 4-year follow-up study of 393 patients with contraindications to metformin (266 with coronary heart disease and 94 with heart failure) randomized to either continue or discontinue metformin, the two groups did not differ significantly in terms of cardiovascular events and cardiovascular and overall mortality.[87] To date, no other prospective trial has evaluated metformin in patients with established cardiovascular disease. Some retrospective and prospective epidemiological and cohort studies do, however, provide evidence for a cardioprotective effect of metformin treatment both in large populations receiving standard care[88] and in patients with coronary artery disease or heart failure (generally with sulphonylureas as a comparator)[71-73] [also reviewed in Chan and Davidons[65]]. The study by Masoudi et al.[72] is important in several respects: the large size of the population (n = 16 417), a fragile population (older diabetic patients discharged from hospital with a principal diagnosis of heart failure), the method employed (a multivariable analysis), the patient outcomes (death, readmission for all causes or readmission for heart failure) and, lastly, its results (with favourable patient outcomes and no increase in the rate of admission for metabolic acidosis, despite the vulnerability of the population).

Even though precautions for metformin use are principally related to renal and cardiovascular function, it is surprising (given the importance of the liver in lactate clearance)[89] that little attention is given to liver failure in general and cirrhosis in particular; these are the sole exceptions to the rule in terms of a good prognosis in MALA. In our experience of MALA, liver failure was the second most predominant feature of organ failure, with mortality in 8 of 12 patients (mortality was 5 of 15 in patients with cardiovascular failure).[22] Interestingly, the only biochemical parameter associated with a fatal outcome in two other series[65,89] was the initial prothrombin time (which averaged 23% in non-survivors and 82% in survivors in the study by Seidowsky et al.[90]). Consequently, we suggest focusing on the severity of and prognosis for liver disease and cirrhosis in particular (according to the Child-Pugh classification,[91] for example), rather than trying to define a GFR threshold for initiating or maintaining metformin therapy. Lastly, renal dysfunction is only a prerequisite for metformin accumulation, which is only dangerous *per se* when associated with liver failure.

In short, kidney failure in patients on metformin calls for prompt precautions to be taken (such as adjusting the metformin dosage to the renal status), whereas severe liver failure must be considered as the true, absolute contraindication. Fortunately, hepatic impairment was observed in only 4% of the patients in a study of the frequency of contraindications to metformin.[92]

3.3 What Are We Seeking to Prevent?

Clearly, what we should prevent when prescribing metformin is the induction of lactic acidosis and, more precisely, when the latter may be truly life-threatening (because of either the severity of the acidosis itself or the occurrence of severe liver failure, i.e. in very rare situations).

Indeed, the risk of lactic acidosis corresponds to a few cases per 100 000 patient-years, whereas the reduction in all-cause mortality in patients on metformin is in the percentage range. Interestingly, a review of population-based studies of retrospective samples (totalling around 2500

patients who frequently disregarded the precautions or even contraindications for metformin use) found that only one case of lactic acidosis was noted and, furthermore, was not related to metformin (intercurrent myocardial infarction).[93]

Lastly, a simple but necessary preventive procedure is to inform and warn patients (and, in the elderly, their relatives) of the risk and symptoms of lactic acidosis, the risk factors for developing it and the need to stop treatment when risk factors are present and, especially, when the symptoms occur. Special attention should be paid to situations and medications that may induce acute kidney failure, i.e. dehydration, infection, intravenous administration of iodinated contrast agents, and the use of ACE inhibitors or NSAIDs.

There are now demands in the literature to redefine the contraindications for metformin.[55,87,94,95] This debate is of particular and growing importance, as the current contraindications of metformin exclude its use in a large proportion of potential beneficiaries (for a review see Holstein and Stumvoll[55]) – a proportion that is likely to grow in view of the aging, more fragile population.

The problem of lactic acidosis in metformin therapy relates to a class effect, as phenformin and buformin initially caused frequent, severe and even fatal events. In fact, it is a 'psychological effect', as underlined by Stades et al.:[28] ''once a serious side-effect has entered general medical opinion, it is very difficult to deny it.'' Hence, qualifying metformin as a 'friend' capable of becoming an 'enemy' is not necessarily appropriate.[96]

Metformin is inexpensive and has weight-neutral efficacy.[97] It exerts impressive preventive effects: prevention of diabetes, micro- and macrovascular complications, major events in patients with heart failure, apoptotic neuron death,[98] cancer,[99] osteopenia[100] and even mortality in lactic acidosis not related to metformin. Its replacement by other drugs may be associated with severe adverse events (hypoglycaemia with sulphonylureas or insulin,[101] weight gain with thiazolidinediones and insulin,[102] cardiac events[103] and bone loss[104] with thiazolidinediones and even an increased incidence of cancer with sulphonylureas[105] and insulin[106]).

4. Conclusions

Lactic acidosis associated with metformin treatment is a rare but important adverse event, and represents a problem that requires critical examination. The relationship between metformin and lactic acidosis is a complex one. Given the established efficacy of metformin, it would be paradoxical to deny the majority of patients with long-established diabetes access to metformin because of the high number of contraindications to this drug, when the same pharmacological mechanisms that relate to lactic acidosis would probably result in protective benefits to these patients.

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