Metformin and other antidiabetic agents in renal failure patients

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This review mainly focuses on metformin, and considers oral antidiabetic therapy in kidney transplant patients and the potential benefits and risks of antidiabetic agents other than metformin in patients with chronic kidney disease (CKD). In view of the debate concerning lactic acidosis associated with metformin, this review tries to solve a paradox: metformin should be prescribed more widely because of its beneficial effects, but also less widely because of the increasing prevalence of contraindications to metformin, such as reduced renal function. Lactic acidosis appears either as part of a number of clinical syndromes (i.e., unrelated to metformin), induced by metformin (involving an analysis of the drug's pharmacokinetics and mechanisms of action), or associated with metformin (a more complex situation, as lactic acidosis in a metformin-treated patient is not necessarily accompanied by metformin accumulation, nor does metformin accumulation necessarily lead to lactic acidosis). A critical analysis of guidelines and literature data on metformin therapy in patients with CKD is presented. Following the present focus on metformin, new paradoxical issues can be drawn up, in particular: (i) metformin is rarely the sole cause of lactic acidosis; (ii) lactic acidosis in patients receiving metformin therapy is erroneously still considered a single medical entity, as several different scenarios can be defined, with contrasting prognoses. The prognosis for severe lactic acidosis seems even better in metformin-treated patients than in non-metformin users.

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This review of antidiabetic therapy mainly focuses on metformin in view of its first-line position in the treatment of type 2 diabetes mellitus patients and the debate concerning the drug's beneficial and potential harmful effects.[1] Although lactic acidosis associated with metformin is rare, it still influences today's treatment strategies because of the high proportion of patients presenting an established or suspected risk of contraindication, particularly in the context of renal failure. Moreover, the relationship between metformin and lactic acidosis is not a simple one in which accumulation of the drug inevitably leads to this adverse event.

This review mainly addresses solving a paradox: on one hand, metformin should be prescribed more widely because of its beneficial, pleiotropic effects[2] and on the other hand it should be prescribed less widely because of the high and increasing prevalence of contraindications to metformin. Indeed, there are more diabetic patients living longer with complications such as kidney disease. This review therefore consists of a critical examination of the fear of lactic acidosis in metformin therapy. As the use of metformin may coincide with, cause, or be co-responsible for lactic acidosis, (i) lactic acidosis in general (i.e., lactic acidosis that is unrelated to metformin), (ii) lactic acidosis induced by metformin, involving an analysis of the drug's pharmacokinetics and mechanisms of action, and (iii) an intermediate, more complex situation, called 'metformin-associated lactic acidosis' will successively be discussed. A critical analysis of guidelines and literature data on metformin therapy in patients with chronic kidney disease (CKD), the particular case of oral antidiabetic therapy in kidney transplant patients, and the potential benefits and risks of antidiabetic agents other than metformin in patients with CKD are also examined.

PART I. METFORMIN THERAPY AND THE FEAR OF LACTIC ACIDOSIS

I.A: Lactic acidosis (lactate levels > 5 mmol/l and serum pH < 7.35), unrelated to metformin

As described by Fitzgerald[3] and Robergs[4] recently, there are many myths about lactic acid. Perhaps the greatest of all is the notion that there is lactic acid in the human body. There

is not. Lactic acid is a weak acid dissociating in water, resulting in anion lactate and H^+. Under physiological circumstances the pH is much higher than the pKa (3.86) of that reaction, and hence almost all lactic acid in the body is dissociated and is present as lactate anion.

The potential confusion between lactate and exercise could be traced to the 1920s, when researchers showed that the exposure of frog legs to high levels of lactic acid (not lactate) interfered with the ability of the muscles to contract in response to electrical stimulation. Later, other research discovered that lactate was released through anaerobic glycolysis, or through the breakdown of glucose or glycogen molecules in the process of energy production deprived of oxygen. Researchers then derived that fatigue occurred at high exercise intensities because the cardiovascular system could no longer supply the muscles with enough oxygen to keep pace with muscular energy demands, resulting in increasing reliance on anaerobic glycolysis, and hence lactate buildup.[3]

At the time, biochemists (incorrectly) believed that lactate must be formed in the body by the removal of a proton from lactic acid. When protons accumulate in living tissues, these tissues become more acidic, and when muscles become too acidic they lose their ability to contract. However, this past research used to support the lactic acidosis 'problem' is entirely based on derived associations and evidence, such as the results from the frog experiment. There had not been any experimental research demonstrating a cause–effect relationship between the production of lactate and acidosis of the muscle tissue.[5]

The evidence began to unravel in 1977,[6] when South African biochemist Wieland Gevers showed that the production of lactate actually goes together with the consumption of a pair of protons, suggesting that lactate delays rather than induces muscular acidosis. In the reaction from 1 glucose to 2 lactate molecules, two ATPs are formed from $ADP + PO4 + H^+$. Hence, $2H^+$ are cleared in the glycolytic pathway. Much more recently, scientists have observed that, although protons do accumulate in the muscles during high-intensity exercise, increasing muscle acidity, these protons are produced through a reaction that should be viewed as a completely separate process from that which produces lactate.[6]

When oxygen supply is sufficiently available for the required muscular effort, cells in the body metabolize glucose to form water and carbon dioxide in a two-step process. First, glucose is broken down to pyruvate through glycolysis. Then, mitochondria oxidize the pyruvate into water and carbon dioxide by means of the Krebs cycle and oxidative phosphorylation. This second step requires oxygen. The net result is ATP, the energy carrier used by the cell to drive useful activity, such as muscle contraction. When the energy in ATP is used during cell work (ATP hydrolysis), protons are produced. The mitochondria normally incorporate these protons back into ATP, thus preventing buildup of protons and maintaining a neutral pH.

However, when oxygen supply is inadequate (hypoxia), the mitochondria are unable to continue ATP synthesis at a rate sufficient to supply the cell with the required ATP. In this situation, glycolysis is increased to provide additional ATP, and the excess pyruvate produced is converted into lactate and released from the cell into the bloodstream, where it may accumulate over time. Despite the fact that increased glycolysis, although much less efficiently, helps compensate for less ATP from oxidative phosphorylation, it cannot bind the protons resulting from ATP hydrolysis. Therefore, proton concentration increases and causes acidosis.

The process of lactate production by itself does not consume or produce protons but is chemically neutral and therefore cannot be the cause of acidosis. There is no cause link between lactate production and acidosis; instead, lactate production is a consequence of intracellular acidosis, slowing down the acidosis process with increasing levels of lactate. Lactate is a good marker for the metabolic condition of the cell; lactate does serve as a direct and indirect fuel for muscle contraction, and is one of the most important energy sources during intensive muscle activity.

Recently, Overgaard and Nielsen[7] have shown that high levels of lactate partially restore muscle cell function from a depolarized condition, a major cause of muscle fatigue at high exercise level.

Until very recently, lactate was vilified in the literature as the cause of acidosis, whereas it plays a 'mythical'/important role in the body's defense mechanisms against acidosis.

I.B: The pharmacokinetics and pharmacodynamics of metformin

Metformin has a dissociation constant of $\sim$11.5. Consequently, $>$99.9% of the molecules exist as cations at physiological pH; hence, rapid, passive diffusion into cells is unlikely. The drug is stable and not metabolized. The fractional oral bioavailability is 50–60%. After intravenous administration, the majority of metformin (80–100%) is eliminated unchanged in the urine (for a review, see ref. 8).

Metformin is eliminated both rapidly and actively by the kidney. The mean renal clearance in subjects with normal renal function was reported as $510\,ml \pm 130\,ml/min$,[8] suggesting tubular secretion following glomerular filtration. A study in obese and non-obese diabetic patients showed that the apparent clearance rate for metformin was influenced by the lean body weight.[9] By pooling data from studies performed in patients with varying degrees of CKD, Graham *et al.*[8] found a significant inverse and close correlation between renal clearance of metformin and kidney function.

Quoting a half-life ($t_{1/2}$) for elimination is difficult, as the drug's plasma concentration–time curves follow a bi-exponential or even tri-exponential model.[8] The terminal $t_{1/2}$ is $\sim$20 h. Such a high value indicates the existence of a deep compartment for metformin. After oral administration of a 1.5 g dose of metformin, the peak plasma concentration is reached after $\sim$3 h.

Given that metformin is essentially present as a cation *in vivo*, its transfer across the cell membrane must be carrier-mediated. Organic cation transporters (OCTs) and the

plasma membrane monoamine transporter (PMAT) are polyspecific transporters for small, hydrophilic organic cations and enable uptake of metformin by the gut (mostly via PMAT, but also via OCT1 and OCT3), the liver (via OCT1 and possibly OCT3), and the kidney (via OCT1, OCT2, and PMAT). OCT1 is abundantly expressed in the liver and, to a lesser degree, in the kidney, where it is localized in the basolateral membrane. Metformin, however, is a much better substrate for renal OCT2 than for hepatic OCT1.[10] The multidrug and toxin extrusion 1 and 2 (MATE1 and MATE2K) proteins are located in the luminal membrane of the kidney and liver and mediate the elimination of metformin into the bile and the urine.

Genetic variations modulate metformin's pharmacodynamics and pharmacokinetics (for a review, see refs 11,12). The impact of genetic variations on intestinal absorption appears to be low, whereas they have a significant effect on hepatic handling of metformin and on therapeutic response to metformin in glucose tolerance tests.[13,14]

The impact of these polymorphisms has been confirmed in patients taking 1 g of metformin twice daily over a 24-month period.[15] Strikingly, an 80-fold interindividual variation in trough steady-state plasma concentrations of metformin was documented. Interestingly, metformin plasma concentrations and metformin's impact on HbA1c were both correlated to the number of reduced function alleles in OCT. Genome-wide association studies reveal that other candidate genes may be involved in the therapeutic response to metformin.[16,17]

These genetic factors are also responsible for modulation of drug–drug interactions that affect metformin's pharmacokinetics (implying, for instance, the inhibitory effect of the H2 blocker, proton pump inhibitors, and the antidiabetic compounds repaglinide and rosiglitazone)[18,19] and also influence hepatic OCT1 and OCT3 expression.[20]

Knowledge of tissue metformin levels is needed to correctly interpret data from cell-based and animal experiments. Metformin is concentrated for some hours in particular tissues, such as the gut and, to a lesser extent, in the liver and kidney.[21] A relatively new approach is the measurement of levels in erythrocytes. After a single oral dose of metformin, due to a terminal $t_{1/2}$ about sixfold higher in erythrocytes compared with plasma, concentrations in plasma and erythrocytes cross each other $\sim$13 h after the plasma peak (Table 1). Metformin would have disappeared from plasma 24 hours after the oral intake, whereas it would remain detectable in erythrocytes for up to 48 h.[22]

Table 1 | Kinetic parameters (mean ± s.e.m.) for metformin in plasma and erythrocytes in six healthy subjects after a single oral dose of 0.85 g (from Robert *et al.*[22])

	Plasma	Erythrocytes	*P*-value
Time of maximal concentration (h)	3.0 ± 0.3	4.7 ± 0.5	NS (0.068)
Maximal concentration (mg/l)	1.7 ± 0.1	0.3 ± 0.0	0.028
Elimination half-life (h)	2.7 ± 0.2	23.4 ± 1.9	≪0.001
Area under the curve (mg · h/l)	8.9 ± 0.4	7.5 ± 1.5	NS
Distribution volume (l)	146 ± 11	—	—

I.C: Metformin's mechanism of action

Although metformin's action on glucose metabolism is not fully understood, it is nevertheless accepted that metformin mainly acts as an insulin sensitizer and reduces hepatic glucose output from gluconeogenesis.[23] Metformin also has a variety of other effects on different tissues (Table 2). In brief, metformin counteracts the determinants of the imbalance between glucose production and glucose utilization, with the noticeable exception of pancreatic β-cell failure.

Metformin's pleiotropic actions have been associated with the activation of AMP-activated protein kinase (AMPK).[24] AMPK can be viewed indeed as a key 'fuel gauge' that protects cells under energy-restricted conditions. It is activated by an increase in the AMP/ATP ratio and thus by an imbalance between ATP production and consumption. This activation requires phosphorylation by upstream kinases (STK11/LKB1). Further studies have shown that metformin activates the LKB1/AMPK pathway secondarily to its effect on the mitochondria through time-dependent, self-limiting inhibition of the mitochondrial respiratory chain complex 1 in liver and other tissues. This complex is the sole entry point for NADH, which promotes the maintenance of the mitochondrial proton gradient required for ATP production (it should be borne in mind that gluconeogenesis is a costly process).[25] Metformin's maximum inhibitory effect on complex 1 activity is $\sim$30%.[25] The partial, reversible inhibition of complex 1 activity leads to a reduction in the cell's energy content and thus activation of AMPK. However, Foretz *et al.*[26–28] recently reported that

Table 2 | Anti-hyperglycemic effects of metformin and the corresponding mechanisms

Tissue	Effects	Mechanism(s)
Intestine	Increase in glucose utilization.	Conversion of glucose into lactate in the splanchnic bed.
	Activation of the incretin axis.	Modulation of several components of the incretin axis.
Liver	Inhibition of gluconeogenesis and (to a lower extent) glycogenolysis.	Decrease in substrate availability.
		Decrease in hepatic energy state (through inhibition of fatty acid oxidation and direct inhibition of oxidative phosphorylation).
		Antagonism of glucagon.
Insulin-dependent peripheral tissues (muscle, adipose tissue)	Increased insulin-mediated glucose uptake.	Enhanced insulin receptor expression and tyrosine kinase activity.
	Decreased release of free fatty acids from adipose tissue.	
Non insulin-dependent peripheral tissues	Enhanced glucose disposal.	Stimulation of non-insulin-dependent glucose transport.

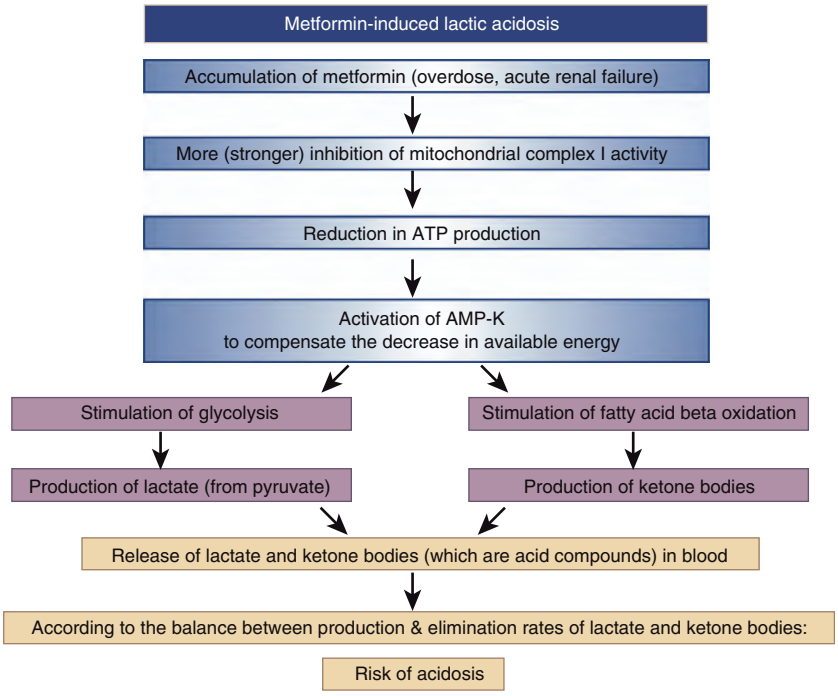

Figure 1 | An overview of the mechanisms of metformin-induced lactic acidosis.

metformin inhibits hepatic gluconeogenesis through a decrease in the energy charge and that this occurs independently of the LKB1/AMPK pathway.

Very recently, Miller[29] suggested a novel mechanism through which metformin reduces hepatic glucose output via antagonism of glucagon and decreased production of cyclic AMP. The relationship between molecular characteristics of this drug and its biological effects remains to be established. As a cationic compound, metformin binds to protein negative charges and may easily insert into the phospholipid bilayer. It may therefore be hypothesized that metformin behaves as a membrane fluidizer.[30] Pleiotropic actions of metformin implicate membrane-related events, including, at the cell level, a stimulation of insulin receptor tyrosine kinase activity and an amelioration of the increased membrane stiffness and, at the mitochondrion level, a depression of the respiratory chain at complex I. Interestingly, (i) a reduction in membrane fluidity may contribute to the development of diabetic complications and (ii) metformin's action on the respiratory chain, besides its antihyperglycemic effect, is associated with an inhibitory effect on reactive oxygen species production[31] and a prevention of hyperglycemia- and ischemia/reperfusion-induced cell death through a mitochondrial permeability transition-dependent process.[32]

Such effects may explain the association between pre-admission metformin use with decreased 30-day mortality among intensive care patients with type 2 diabetes (the adjusted HRs were 0.80 (95% CI: 0.69, 0.94) for metformin monotherapy users and 0.83 (0.71, 0.95) for metformin combination therapy users, compared non-users).[33]

Noticeably, the pleiotropic effects of metformin (e.g., in cardiovascular disease, hepatic steatosis, cancer, inflammation, and polycystic ovary syndrome) also include a protective effect on diabetic nephropathy.[34,35] It has also been shown that metformin is associated with a significant reduction in the incidence of diabetes itself.[36]

I.D: Metformin-induced lactic acidosis

Metformin is linked to lactate metabolism in different ways. In addition to inhibition of lactate conversion through gluconeogenesis and augmentation of lactate production in insulin-dependent tissues, it augments lactate production by accelerating glycolysis in response to mitochondrial impairment and by activating anaerobic metabolism of glucose in the intestine. This does not result in a significant increase in plasma lactate at usual therapeutic levels because of the conversion of lactate back to glucose in the liver (via the Cori cycle). In contrast, high therapeutic metformin levels provoked a reduction in lactate uptake by the liver.[37] Metformin accumulation may therefore combine hyperproduction of lactate from the intestine and other organs and reduced lactate clearance by the liver. This may ultimately generate hyperlactatemia or even lactic acidosis, which has been referred to as 'metformin-induced lactic acidosis' (Figure 1).

Metformin may accumulate because of defective elimination or excessive intake. In fact, overdose should be considered the only cause of 'pure' metformin-induced lactic acidosis. 'Metformin-induced lactic acidosis' is, however, exceptional, as isolated metformin overdoses are rare. In a review on metformin overdoses, Dell'Aglio *et al.*[38] cited our reports but omitted available information on mutidrug

intoxication in 11 of our 13 cases.[39] Nevertheless, overdose is a good model for understanding how metformin can generate hyperlactatemia. The liver has a key role in this phenomenon. Indeed, using OCT1$^{-/-}$ mice and metformin overdose, it was shown that blood lactate levels increased significantly in wild-type mice and only slightly in OCT1$^{-/-}$ mice. There was a significant reduction in metformin level in the liver in the latter, whereas the plasma and muscle levels of metformin were similar in both groups.[40] Experiments in MATE1$^{-/-}$ mice reinforce the central role of the liver.[41]

Using a battery of tests developed to reveal drug-induced mitochondrial impairment, Dykens *et al.*[42] concluded that cells compensate for reductions in mitochondrial function by accelerating the glycolytic flux; hence, lactate is released into the circulation rather than being oxidized. When testing the hypothesis in which inhibition of mitochondrial respiration is responsible for hyperlactatemia, Protti *et al.*[43] observed a 30–60% reduction in overall oxygen consumption in animals[44] and humans with metformin overdose, despite normal or even elevated systemic delivery of oxygen. Such a large reduction could hardly be explained by inhibition of hepatic respiration alone. Indeed, metformin overdose alters mitochondrial activity in many cell types.[45]

The link between metformin accumulation and hyperlactatemia, and that between hyperlactatemia and lactic acidosis, remains to be determined. Indeed, not all patients with an isolated metformin overdose necessarily develop lactic acidosis, or even significant hyperlactatemia.[46] In fact, metformin would tend to protect against lactic acidosis, as the drug's inhibition of the respiratory chain should be self-limiting. As the matrix concentration of the drug increases, progressive inhibition of the respiratory chain would lead to a drop in membrane potential, which would prevent further accumulation of the drug.

The fact that the very low metformin uptake in immortalized cell lines can be dramatically enhanced by transfection of OCT1 cDNAs[10,47] suggests that metformin concentration and the exposure time to metformin reflect the interindividual variability in the tissue/cell abundance of transporters and ultimately determine the balance between lactate production and lactate clearance. In some cases, however, the magnitude of the efflux of lactate in the bloodstream, which is the anionic form of lactic acid, may override the body's ability to utilize protons, hence converting hyperlactatemia into lactic acidosis (Figure 1).

I.E: Metformin-associated lactic acidosis (MALA)

There are major pitfalls in many of the epidemiological studies related to MALA (for a review, see ref. 48): (i) clinical trials comparing metformin with placebo produce biased data, as a result of better monitoring and the exclusion of contraindications; (ii) even though retrospective data sets and case reports of MALA probably better reflect 'real-life' metformin use than do clinical trials, the frequency and quality of reporting lactic acidosis in metformin-treated patients are very poor;[49,50] (iii) the link between metformin and lactic acidosis is generally analyzed in terms of frequency, without assessment of the putative link between the drug and lactic acidosis. This explains why the intraobserver agreement on the causal role of metformin was extremely low even within an expert panel.[51]

It is possible to estimate the risk and extent of metformin accumulation by evaluating the following parameters: (i) the patient's renal function and its change over time; (ii) the prescribed dosage of metformin, (iii) the patient's compliance, and (iv) the time of last metformin administration. The best way for obtaining meaningful information is evidently to assay blood levels of metformin, and of erythrocyte levels in particular (Table 3). However, the broad range of observed metformin plasma and erythrocyte concentrations and the continuous distribution of values[52,53] make it impossible to set a formal 'danger threshold' for metformin accumulation.

By adopting the above reasoning, it is ultimately possible to distinguish three clinically relevant scenarios for lactic acidosis occurring in patients treated with metformin:

1. Metformin-unrelated lactic acidosis, when metformin is not detectable in the blood;
2. Metformin-induced lactic acidosis (rare), when causal factors other than marked metformin accumulation (such as cardiovascular failure, sepsis, hemorrhage, hepatic failure, and pulmonary failure[54]) are absent;
3. Metformin-associated lactic acidosis (less rare), with detectable metformin and the presence of other disease conditions (listed above) to varying extents.

However, this analysis requires further refinement (Figure 2). Indeed the imputability of metformin as the trigger agent in the so-called MALA is difficult to assess as metformin accumulation, even major, does not necessarily lead to lactic acidosis.[46] Furthermore, MALA is often misclassified. We should indeed distinguish 'true' MALA in which metformin accumulation and systemic medical conditions bear the responsibility of lactic acidosis, at varying degrees, from lactic acidosis without metformin accumulation (strictly speaking, the latter should be renamed 'lactic acidosis associated with metformin therapy') (Figure 2).

Such a discussion is not only of theoretical interest but also has an impact on the patient's prognosis, which does not depend on the extent of metformin accumulation. Indeed, the unexpectedly high rate of survival in patients with severe MALA suggests that metformin may have beneficial effects in lactic acidosis caused by systemic medical conditions.[55] The sole negative prognosis was liver failure, which is not surprising given the liver's importance in lactate clearance.[54,56,57]

I.F: Metformin therapy and renal failure

The criteria for metformin withdrawal in three international guidelines, 31 national guidelines, and 20 literature-based recommendations were analyzed.[58] These criteria were (i) mainly qualitative ('kidney failure') in guidelines issued in the most populated countries, (ii) mainly quantitative in the most scientifically productive countries (with, in all cases, a

Table 3 | Advantages and limitations of measuring the metformin concentration in blood in metformin-associated lactic acidosis

Advantages	Limitations
Differentiation between (i) true, excessive metformin acquisition in cells (such as erythrocytes) and (ii) a plasma peak after a recent metformin intake.	Unavailability of the measurement of metformin (both in plasma and in erythrocytes).
Assessment of the risk, extent or duration of metformin accumulation.	Inability to define a blood metformin concentration as a threshold for metformin accumulation.
Assessment of a patient's compliance with metformin therapy.	High blood metformin concentrations are not necessarily linked to hyperlactatemia or lactic acidosis.
Help for distinguishing between metformin-unrelated, metformin-induced and metformin-associated lactic acidosis.	Does not provide information on factors predisposing to and/or triggering hyperlactatemia (other than metformin accumulation).
Retrospective establishment of a link between metformin use and the development of lactic acidosis (especially in an emergency context, when a metformin assay is not the top priority).	Measurement of the metformin concentration with a long time lag and/or lack of information of when the blood samples were collected (particularly for plasma samples).
Detection of metformin accumulation in special cases of metformin accumulation that is unrelated to kidney disease (i.e., intestinal occlusion)[53]	Measurement of metformin concentration after treatments that may affect its value (i.e., dialysis and vasoactive drugs).
Monitoring of the elimination of accumulated metformin.	

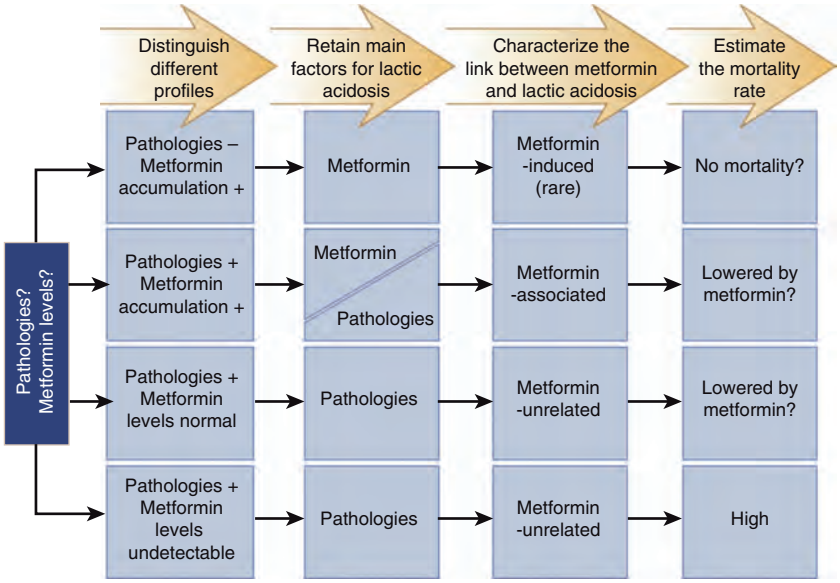

Figure 2 | Lactic acidosis occurring in patients treated with metformin: toward a global approach.

suggested threshold—mostly based on serum creatinine values—for withdrawing metformin), and (iii) quantitative in all but one of the literature proposals (with indication of a CKD threshold for withdrawal and/or adjustment of the metformin dose). Although there was a good degree of consensus on serum creatinine thresholds (generally $\geqslant 1.5$ mg/dl in male patients and $\geqslant 1.4$ mg/dl in female patients), the eGFR thresholds varied from 60 ml/min per 1.73 m^2 to stage 5 CKD. The latter is a less restrictive position than that provided by the manufacturer in the package insert.

On the basis of this review, it is surprising that official guidelines still reason in terms of thresholds for withdrawal of metformin rather than adjustment of the metformin dose to suit the patient's renal status. Moreover, none of the official guidelines takes into account the instability of kidney function over time as a criterion.

A debate over the beneficial and harmful effects of metformin should include a critical analysis of current guidelines most frequently applied to patients with renal impairment.[59] Some authors consider the latter as exaggerated[60,61] and even suggest that metformin is safe in stable severe CKD.[62] This position was supported by the observed efficacy and safety of metformin in a 4-year study of a large cohort of patients at varying CKD stages.[63] Compared with other oral antidiabetic agents and insulin, metformin was associated with lower all-cause mortality and a lower risk for cardiovascular disease, acidosis, and serious infection (one of the study's end points). These beneficial effects were consistently found in patients with eGFR values ranging from 45 to 60 ml/min per 1.73 m^2. The study's results are also in line with those of an observational study of almost 20,000 patients with diabetes and established cardiovascular disease or with three atherothrombotic risk factors (i.e., patients who could be considered as particularly vulnerable to metformin).[64] Relative to other antidiabetic treatments, metformin significantly lowers the risk of all-cause mortality

after nearly 2 years. The recent observation that chronic metformin treatment augments myocardial resistance in an animal model of ischemia–reperfusion constitutes further evidence of a protective cardiovascular effect.[65]

Given the critical importance of antidiabetic therapies and the fact that metformin has been available for over 50 years, it is surprising to note that the scientific literature comprises only two clinical studies on metformin therapy in CKD patients (from the same group):

1. A retrospective study featured data on metformin dose, erythrocyte metformin level, and eGFR from 240 metformin-treated CKD stage 1–5 patients[66] (68.5% of whom had an eGFR <60 ml/min per 1.73 m^2). The proportions of CKD stages 2, 3, and 4 patients with a metformin level above the 95th percentile (for the total study population as a whole) were low (1.7%, 3.3%, and 10.5%, respectively), when compared with stage 1 patients (the low number of CKD stage 5 patients ($n=6$) prevented such a calculation in this particular group). Importantly, the metformin dose had been pragmatically reduced (by up to two-thirds) in CKD patients. This indicates that many physicians did not comply with a standard contraindication for metformin and rather preferred to adjust the metformin dose to match the patient's renal status.

2. A proposal for dose adjustment was based on a single prospective study of elderly CKD patients on a 2-month course of metformin.[67] Mean plasma metformin concentrations remained within the therapeutic range (i.e., <1.65 mg/l) when subjects were given either 1700 mg per day of metformin for creatinine clearances above 60 ml/min (i.e., CKD 2) or 850 mg per day for clearances between 30 and 60 ml/min (CKD 3). The difference in plasma metformin concentration between the two dosage groups was not statistically significant.

We hope that it will soon be possible to establish whether or not it is clinically feasible to continue metformin therapy in CKD, even in severe cases. In an ongoing study, patients in all CKD stages undergo 3- or 4-week-long blocks of metformin treatment at an increasing dosage level, each of which is followed by a 1-week washout period (i.e., 500 mg per day for a week, followed by 1-week washout; 1000 mg per day for a week, followed by 1-week washout; and 2000 mg per day for a week, followed by 1-week washout). Furthermore, stage 1 CKD patients go on to complete a final block of treatment with 3000 mg per day for a week. At the end of each week of treatment, plasma and erythrocyte metformin levels are assayed and checked for compliance with the recommended therapeutic window. Venous lactate is also assayed in CKD stage 3–5 patients.

PART II. RENAL TRANSPLANTATION

New-onset diabetes after kidney transplantation (NODAT) is an important medical complication,[68,69] but evidence with regard to the efficacy of anti-glycemic agents post transplantation is limited. A nonrandomized pilot study in 15 kidney allograft recipients with NODAT utilizing sitagliptin (dipeptidyl peptidase-4 inhibitor) demonstrated an improvement in insulin secretion via an incretin effect with no safety concerns.[70] Turk *et al.*[71] compared repaglinide (short-acting meglitinide) with rosiglitazone (insulin-sensitizing thiazolidinedione) in a nonrandomized observational trial and observed equivalent efficacy and tolerable side effect profile between the two groups. Pietruck *et al.*[72] reported their experience with rosiglitazone in 22 renal transplant recipients with NODAT and observed improved glycemic control in 16 patients. More recently, Werzowa *et al.*[73] have demonstrated the efficacy of both vildagliptin (dipeptidyl peptidase-4 inhibitor) and pioglitazone (thiazolidinedione) versus placebo in a randomized controlled trial at improving postprandial hyperglycemia in renal allograft recipients diagnosed with impaired glucose tolerance 6 months post transplantation.

NODAT Consensus guidelines from 2003 do not recommend metformin as the first-line anti-glycemic agent in a post-transplantation setting due to perceived safety concerns.[74] Theoretically, it has many advantages that should promote it as the agent of choice post transplantation,[75] but post-transplantation evidence is limited to a single retrospective report.[76] This study compared metformin with thiazolidinediones in 24 renal transplant recipients with NODAT or preexisting diabetes mellitus and demonstrated safety but non-superiority. Lack of evidence has fuelled ongoing debate regarding the safety of metformin in the complicated transplantation milieu and polypharmacy of kidney transplant recipients.[77,78]

Preventing NODAT is more important than management. Emerging evidence suggests that pancreatic beta cell dysfunction is the primary insult in the pathophysiology of NODAT,[79,80] suggesting that attenuating beta cell stress post kidney transplantation may be beneficial. Hecking and colleagues have reported the benefit of early basal insulin post kidney transplantation in a randomized controlled trial (73% lower odds of NODAT development at 1 year post transplant compared with standard-of-care management).[81] In the context of immediate postoperative hyperglycemia (and dynamic changes in allograft function), insulin therapy is the most appropriate glucose-lowering therapy for both safety and efficacy. Metformin therapy could be safely considered for treatment of early NODAT onset after this early postoperative period, with stable allograft function (eGFR >30 ml/min), using graded dosages as outlined in Table 4. However, in the context of acute allograft dysfunction (e.g., cellular and/or antibody-mediated rejection), cessation of metformin would be advised because of dynamic changes in allograft function and the risk of potentiating metformin-related side effects.

In the long term it remains unclear which class of anti-glycemic agent is superior because of the absence of comparative head-to-head randomized controlled trials with important clinical end points, a shortcoming that must be overcome with collaboration between multiple centers in large, adequately powered clinical trials.[82]

PART III. ANTIDIABETIC AGENTS OTHER THAN METFORMIN

In the presence of contraindications or intolerance to metformin or when metformin alone does not result in optimal control, other antidiabetic medications are necessary.

Replacing metformin with other classes is, however, not a neutral choice, considering the huge advantages of metformin (see above and in ref. 83).

Many studies show increased cardiovascular risk and mortality with different insulin secretagogues compared with metformin.[84–86]

Metformin compared with sulfonylureas may offer renoprotective effects that are independent of its known beneficial effects on weight, blood pressure, and glycemic control.[87]

In addition, recent observational data suggest that, when compared with sulphonylureas and insulin, metformin is associated with a reduced risk of developing solid organ cancer.[88] None of the other current oral monotherapy regimens show better results than metformin.[89]

Unlike metformin, insulin secretagogues (sulfonylureas or glitinides), and insulin itself, cause weight gain, but above all cause hypoglycemia. The risk of hypoglycemia with sulfonylurea is reported to be increased by 4–9% when compared with treatment with other oral hypoglycemic agents. Severe hypoglycemic episodes with sulfonylurea are estimated to occur at a rate of >2400 per 100,000 patient-years. Other risk factors for hypoglycemia include advanced age, combination therapy, and comorbid conditions, especially CKDs.[90]

In CKD, renal gluconeogenesis is impaired and the clearance of insulin and many other hypoglycemic agents is delayed, thus increasing the risk of hypoglycemia.[91]

Thiazolidinediones reduce insulin resistance but cause weight gain and fluid retention and can exacerbate congestive heart failure or trigger its onset. Further, a 2011 report from the FDA links long-term pioglitazone use with bladder cancer.[92]

In Table 4, adapted from Inzucchi *et al.*[93] and Arnouts *et al.*,[94] we summarize the dose adjustments by CKD stage for drugs used to treat hyperglycemia.

Dose recommendations were based on the literature, package inserts, and expert opinion.

Below, we will briefly discuss the impact of renal insufficiency on the different classes of antidiabetic drugs, other than the biguanide, metformin.

III.A: Sulfonylureas

Agents in this class stimulate insulin secretion from the islet beta cell by binding to the sulfonylurea receptor 1 of the adenosine triphosphate-dependent potassium channel, resulting in closure of these channels, depolarization of the β-cell membrane, calcium influx, and, subsequently, insulin release.

The main risk is hypoglycemia. Therefore, low starting doses and slow titration are required.

The first-generation sulfonylureas—chlorpropamide, acetohexamide, tolbutamide, and tolazamide—are almost exclusively excreted by the kidneys and are therefore contraindicated in cases of severe renal failure.[94]

Glibenclamide is converted in the liver to three major metabolites, one of which (4-hydroxyglibenclamide) has $\sim$15% of the potency of glibenclamide. This metabolite accumulates in patients with renal failure and likely contributes to an increased risk for hypoglycemia with glibenclamide in patients with renal failure.[95]

Glimepiride is hepatically metabolized with two major metabolites, one of which has some pharmacologic activity. Glimepiride does not accumulate in patients with reduced GFR, but urinary excretion of its metabolites is reduced. Prolonged hypoglycemia has been reported in patients with reduced GFR.[96,97]

The metabolism of gliclazide occurs in the liver, resulting in at least eight metabolites, none of which has any recorded hypoglycemic activity. The renal clearance of unchanged total gliclazide is low (0.5 ml/min) because of the high protein binding with $<1\%$ found in the urine, hence increasing the possibility of using the drug in patients with renal failure.[98,99]

Glipizide undergoes near-complete hepatic biotransformation to inactive metabolites, and its half-life is unaffected by kidney function, making dose adjustments in patients with reduced GFR unnecessary.[100]

Gliquidone is extensively metabolized in the liver via hydroxylation and demethylation to largely inactive metabolites. These metabolic processes are maintained in patients with hepatic insufficiency. Ninety-five percent of the gliquidone dose is excreted as metabolites via bile in the feces. Less than 5% of the gliquidone dose is eliminated through the renal route.[101,102]

III.B: Nonsulfonylurea insulin secretagogues (glinides)

Glinides also stimulate insulin secretion from the pancreatic beta islet cells by binding to adenosine triphosphate-dependent potassium channels but at a different site. In contrast with sulfonylureas, they have a very short half-life and duration of action (3–4 h) and therefore are administered shortly before meals. Glinides have modest glycemic efficacy and lack clinical outcome data.

Repaglinide is almost completely converted to inactive metabolites in the liver, and $<10\%$ is excreted by the kidneys. There is no increased risk for hypoglycemia in patients with CKD.[103–105]

Nateglinide is hepatically metabolized, with renal excretion of active metabolites. Appproximately 15% of the drug is excreted unchanged in the urine; the remainder is metabolized by the liver to weakly active metabolites and conjugates that are excreted through the urine (80%) and feces (20%). In advanced CKD, there is accumulation of an active metabolite of nateglinide, which may increase the risk for hypoglycemia.[106,107]

III.C: Insulin

Insulin is the most effective therapy for patients with diabetes. The need for subcutaneous injections, concern for weight gain, and occurrence of hypoglycemia, however, create a lot of resistance to its use.

Table 4 | Summary of antihyperglycemic agents with dosing adjustments by CKD stage

Class	Mechanism of action	Cellular mechanisms	Drug/name	Metabolism/ Elimination	Usual dose (mg)	Use in CKD stage 3	Use in CKD stage 4	Use in CKD stage 5/dialysis	Advantages	Disadvantages	Cost
Biguanides	Decrease hepatic glucose production; increase insulin sensitivity	Activates AMP-kinase	Metformin	Filtered and secreted unchanged in urine	500–2550	CKD3A: 2×850 mg CKD3B: 1×850 mg Contraindicated*	Contraindicated	Contraindicated	•Extensive experience •No weight gain •No hypoglycemia •Likely ↓CVD events (UKPDS)	•Gastrointestinal side effects: diarrhea, abdominal cramping •Lactic acidosis risk (rare) •Vitamin B_{12} deficiency •Multiple contraindications: CKD, hypoxia, dehydration, shock, liver failure.	Low
Sulfonylureas	Stimulate pancreatic insulin secretion from the pancreas	Closes K_{ATP} channels on β-cell plasma membranes	Glyburide/ glibenclamide	100% Liver metabolism to weakly active metabolites excreted in urine (50%) and bile/feces (50%)	2.5–15	Avoid	Avoid	Avoid	•Extensive experience •↓Microvascular risk (UKPDS)	•Hypoglycemia •Weight gain? •Blunts myocardial ischemic preconditioning •Low durability	Low
			Glipizide	90% Liver metabolism to inactive metabolites excreted in urine/feces; 10% excreted unchanged in urine/feces	2.5–10	No dose adjustment necessary	No dose adjustment necessary	No dose adjustment necessary			
			Glimepiride	100% Liver metabolism to weakly active and inactive metabolites excreted in urine (60%) and feces (40%)	1-6	Initiate at low dose	Initiate at low dose	Avoid			
			Gliclazide	99% Liver metabolism to 8 inactive metabolites excreted in urine (80%) and bile (20%)	30–120 unidiamicron 80–240 gliclazide	No dose adjustment necessary	No dose adjustment necessary	No dose adjustment necessary			
			Gliquidone	95% Liver metabolism to inactive metabolites excreted in bile	30–90	No dose adjustment necessary	No dose adjustment necessary	No dose adjustment necessary			
Glitinides	Stimulate pancreatic insulin secretion from the pancreas	Closes K_{ATP} channels on β-cell plasma membranes	Repaglinide	100% Liver metabolism to inactive metabolites excreted in urine (10%) and feces (90%)	0,2–12	No dose adjustment necessary	No dose adjustment necessary	No dose adjustment necessary	•↓Postprandial glucose excursions •Dosing flexibility	•Hypoglycemia •Weight gain •? Blunts myocardial ischemic preconditioning •Frequent dosing schedule	High
			Nateglinide	85% Liver metabolism to weakly active metabolites excreted in urine (83%) and feces (10%); 15% excreted unchanged in urine	60–360	Initiate at low dose	Initiate at low dose	Avoid			
Insulins	Activate insulin receptors	-↑Glucose disposal -↓Hepatic glucose production	Human NPH Human Regular Lispro Aspart Glulisine Glargine Detemir Premixed (several types)	Metabolism through proteolytic degradation by liver and kidney	Variable	No advised dose adjustment; Adjust dose based on glycemic monitoring	No advised dose adjustment; Adjust dose based on glycemic monitoring	No advised dose adjustment; Adjust dose based on glycemic monitoring	- Universally effective - Theoretically unlimited efficacy -↓Microvascular risk (UKPDS)	- Hypoglycemia - Weight gain -? Mitogenic effects - Injectable - Training requirements - 'Stigma' (for patients)	Variable

Table 4 | (Continued)

Class	Mechanism of action	Cellular mechanisms	Drug/name	Metabolism/ Elimination	Usual dose (mg)	Use in CKD stage 3	Use in CKD stage 4	Use in CKD stage 5/dialysis	Advantages	Disadvantages	Cost
DPP—IV inhibitors	Inhibit DPP-4, which inactivate endogenous incretins	Inhibit DPP-4 activity, increasing postprandial active incretin (GLP-1, GIP) concentrations Insulin secretion (gluc-dependent) and glucagon secretion (gluc-dependent)	Sitagliptin	Excreted mostly unchanged in urine (87%) and feces (13%)	100	50 mg	25 mg	25 mg	•No hypoglycemia •Well tolerated	•Generally modest HbA_{1c} efficacy •Urticaria/angioedema •? Pancreatitis	High
			Vildagliptin	Only 25% of the drug is excreted by the kidneys. Main route of elimination is metabolism	2×50	50 mg	50 mg	50 mg			
			Saxagliptin	Renal excretion as parent drug (12-29% of dose) or as half potent metabolite (21-52% of dose)	5	2,5 mg	2,5 mg	2,5 mg			
			Linagliptin	Liver metabolism to inactive metabolites; >85% excreted in bile; 5% of dose is cleared in urine	5	5 mg	5 mg	5 mg			
Incretin mimetics	Bind to GLP-1 receptors in pancreatic β-cell and promote glucose-dependent insulin secretion; decrease glucagon secretion and gastric emptying	Activate GLP-1 receptors	Exenatide	Kidney metabolism proteolytic degradation; excretion in urine	2×5 to 2×10 μg	2×5 μg	Not recommended	Not recommended	•No hypoglycemia •Weight reduction •? Potential for improved β-cell mass/function •? Cardiovascular protective actions	•Gastrointestinal side effects (nausea/vomiting) •? Acute pancreatitis •C-cell hyperplasia/medullary thyroid tumors in animals •Injectable •Training requirements	High
			Liraglutine	Fully metabolized within the body through endogenous enzymes, DPP-IV and NEP	0.6-1.8	No dose adjustment necessary but limited experience	No dose adjustment necessary, but no experience	No dose adjustment necessary, but no experience			
Thiazolidinediones	Improve insulin sensitivity; ligand for PPAR-γ-receptor	Activate the nuclear transcription factor PPAR-γ	Pioglitazone	Extensive liver metabolism; active metabolites; excreted in urine (15%) and feces (85%)	15-45	No dose adjustment necessary	No dose adjustment necessary	No dose adjustment necessary	•No hypoglycemia •Durability •↑HDL-C •↓Triglycerides (pioglitazone) •?↓CVD events (ProACTIVE, pioglitazone)	•Weight gain •Edema/heart failure •Bone fractures •?↑Bladder cancer (pioglitazone)	High
α-Glucosidaseinhibitors	Block α-glucosidase in brush borders of small intestine, delay absorption of carbohydrates	Inhibit intestinal α-glucosidase	Acarbose	Nearly 100% GI tract metabolism	75–300	Avoid	Avoid	Avoid	•No hypoglycemia •↓Postprandial glucose excursions •?↓CVD events (STOP-NIDDM) •Non-systemic effects	•Generally modest HbA_{1C} efficacy •Gastrointestinal side effects (flatulence, diarrhea) •Frequent dosing schedule	Moderate
			Miglitol	No metabolism; absorbed systemically and excreted unchanged in urine (95%)	75–300	Avoid	Avoid	Avoid			

Avoid: only use if no alternative and then cautiously; Contraindicated: do not use; Not recommended: no data, possibly safe.
CKD 3A: 45-59 ml/min; CKD 3B: 30–44 ml/min.
UKPDS: United Kingdom Prospective Diabetes Study; STOP-NIDDM: Study to Prevent Non-Insulin Dependent Diabetes Mellitus; Pro-ACTIVE: Prospective Pioglitazone Clinical Trial in Macrovascular Events.
*Issue of prescribing metformin to patients with CKD3 is currently controversial. A pharmacokinetic study (EudraCT nr 2012-001207-20) dealing with that issue will be available at the end of 2014.

As renal failure progresses, peritubular insulin uptake increases. This compensates for the decline in degradation of filtered insulin. However, once the GFR drops below 20 ml/min, the kidneys clear markedly less insulin, an effect enhanced by a decrease in the hepatic metabolism of insulin that occurs in uremia. Especially after the start of dialysis, insulin-treated diabetic patients require less insulin as peripheral insulin resistance improves with the initiation of dialysis.[91,108]

With decreased clearance and catabolism of insulin, the metabolic effects of both short- and longer-acting insulin preparations persist longer and the potential for symptomatic hypoglycemia increases.

Regular human insulin shows a higher maximal concentration and longer half-life in severe renal failure, whereas rapid-acting analogues maintain similar maximum concentrations and half-lives. The latter are less likely to cause hypoglycemia. Hence, rapid-acting insulin analogues are preferred to regular human insulin in patients with CKD. Similarly, long-acting insulin analogues are also preferred to NPH insulins.[109,110] Dose adaptations of insulin are not, however, based on kidney function but are guided by glycemic measurements.

III.D: Incretin-based insulin secretagogues

Incretin hormones, such as GLP-1, are released after meals and serve to stimulate pancreatic insulin secretion, temper glucagon release, slow down gastric emptying, and suppress appetite centrally in the hypothalamus.

The incretin effect is the augmentation of glucose-stimulated insulin secretion by intestinally derived peptides, which are released in the presence of glucose or nutrients in the gut. This incretin pathway is attenuated in patients with type 2 diabetes. The incretin effect is composed primarily of two peptides: glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1).

The incretin effect can be increased by blocking the inactivating enzyme dipeptidyl peptidase IV (DPP4) or by using incretin mimetics (GLP-1 analogues), which are not inactivated by endogenous DPP4.

Advantages of these drugs include a very low risk for hypoglycemia and lack of weight gain. DPP-4 inhibition with saxagliptin and alogliptin did not increase or decrease the rate of ischemic events, though the follow-up period was not very long in these studies (the median follow-up was, respectively, 2.1 years and 18 months) and the rate of hospitalization for heart failure was increased with saxagliptin.[111,112]

DPP4 inhibitors

Sitagliptin is an oral, once-daily DPP4 inhibitor that is primarily cleared by the kidneys. In normal, healthy subjects, 75–80% of the drug is excreted unchanged in the urine. Excretion is thought to be via active secretion and glomerular filtration.

Relative to subjects with normal or mildly impaired renal function, patients with moderate renal insufficiency (CrCl 30–60 ml/min), severe renal insufficiency (CrCl <30 ml/min, not on dialysis), or end-stage renal disease on dialysis have $\sim$2.3-fold, 3.8-fold, or 4.5-fold higher plasma sitagliptin exposures, respectively, with Cmax increased 1.4-fold to 1.8-fold. Compared with values in subjects with normal renal function (12.1 h), the terminal half-life values of sitagliptin in those with mild, moderate, and severe renal impairment and in those with end-stage renal disease were raised to 16.1, 19.1, 22.5, and 28.4 h, respectively.[113,114]

Vildagliptin is an oral twice-daily DPP-4 inhibitor at the therapeutic dose of 2×50 mg. The major circulating components in the plasma are unchanged drug and a main metabolite (M20.7) that is not biologically active. Elimination of vildagliptin mainly involves renal excretion of unchanged parent drug (23%) and cyano group hydrolysis with little CYP involvement.

In patients with mild, moderate, and severe renal impairment, and in end-stage renal disease patients on hemodialysis, systemic exposure to vildagliptin was increased (Cmax 8–66%; AUC 32–135%) compared with that in subjects with normal renal function.

Exposure to vildagliptin increases only ±2-fold in patients with severe renal insufficiency relative to healthy volunteers with little change in Cmax.[115,116]

Saxagliptin is a DPP-4 inhibitor usually administered once daily at the therapeutic dose of 5 mg. Although the overall half-life is short, metabolism of saxagliptin (mainly by CYP3A4/5) produces an active metabolite (5-hydroxy-saxagliptin) that keeps 50% of the hypoglycemic power of the primary drug. An estimated 75% (saxagliptine, 5-hydroxy-saxagliptin and other minor hydroxylated inactive metabolites combined) of the administered dose is eliminated via the renal route and recovered in urine.

When moderate renal impairment is present, the AUCs of saxagliptin and its active metabolite are 1.4- and 2.9-fold higher, becoming 2.1- and 4.5-fold higher in the presence of severe renal impairment (eGFR <30 ml/min). Therefore, in order to achieve and keep plasma levels similar to those in patients with normal renal function, the starting dose should be halved to 2.5 mg/daily in CKD stage 3-5D. Saxagliptin can be taken after dialysis as a single 4-h dialysis session removes 23% of the dose.[116,117]

Linagliptin is a DPP-4 inhibitor administered at the therapeutic dose of 5 mg once daily. The half-life is long and drug metabolism produces several inactive metabolites. Almost 85% of the dose undergoes fecal excretion via the entero-hepatic system, whereas renal excretion accounts for 5% of the dose. As renal excretion is a minor elimination pathway of linagliptin at therapeutic dose levels (<1% of unchanged linagliptin appears in urine), no dose adjustments are required in the presence of impaired renal function.[118–121]

Incretin mimetics

Exenatide reaches peak concentrations within 2 h of subcutaneous administration and undergoes minimal systemic metabolism. The kidney is the primary organ responsible for

clearance and degradation of exenatide into small, biologically inactive peptide fragments, with a half life of 2.5 h in patients with normal renal function. The elimination half-life increases to 3.2 h in patients with moderately reduced GFR (31–60 ml/min) and up to 6 h in patients with GFR < 30 ml/min or end-stage renal disease, which is associated with an increase in AUC with potentially toxic blood levels detected.

Exenatide is contraindicated in patients undergoing hemodialysis or in patients who have a GFR < 30 ml/min.[122–124]

Liraglutide has a high degree of sequence identity (97%) to human GLP-1.[125] Binding to serum albumin (>99%) results in no or very limited renal extraction. Liraglutide is fully metabolized within the body through the widely distributed endogenous enzymes DPP-IV and NEP. The cleavage sites of liraglutide are similar to those reported for GLP-1, but the degradation is much slower for liraglutide. The half-life is ~13 h after subcutaneous injection, with plasma peak levels after 8–12 h.

Liraglutide is not recommended in people with a creatinine clearance <60 ml/min because of the lack of clinical trial experience. Pharmacokinetic and pharmacodynamic studies, however, have demonstrated no significant effect in terms of product accumulation down to a creatinine clearance of ⩽15 ml/min. Reduced GFR does not alter its metabolism or excretion.[126,127]

III.E: Thiazolidinediones (glitazones)

Only one glitazone, pioglitazone, is left on the market since troglitazone (hepatotoxicity) and rosiglitazone (enhanced myocardial infarction) were removed.

Pioglitazone ameliorates insulin action in insulin target tissues through binding to peroxisome proliferator-activated receptor gamma (nuclear transcription factors involved in glucose and lipid homeostasis). Pioglitazone decreases insulin resistance, enhances peripheral disposal of glucose, and has some effect on hepatic production of glucose.

Pioglitazone has an elimination half-life of about 3–7 h and has six hepatic metabolites, of which three are active. There is, however, no accumulation of the parent drug or the major metabolites in the setting of renal insufficiency.[128]

Important side effects of glitazones, especially in the setting of CKD, include fluid retention with edema and even congestive heart failure (CHF).

Pioglitazone should be used with great caution in patients with increased risk for CHF and is contraindicated in patients with NYHA Class III and IV heart failure. More recently, an increased risk for bladder cancer was reported for pioglitazone.[92]

III.F: Alpha-glucosidase inhibitors

By inhibiting alpha-glucosidases a delay is caused in the absorption of glucose from starch and sucrose, attenuating postprandial glucose increases.

Acarbose is only minimally absorbed from the gastrointestinal tract, where it is largely broken down by intestinal flora and intestinal enzymes into at least 13 metabolites, at least one of which has some biological activity. Some of the metabolites are partially absorbed, although <2% of a dose of acarbose and the active metabolites appears in the urine. In patients with reduced renal function, the plasma levels of the drug and its metabolites can increase several-fold, but the clinical significance of this is not known. Information about the long-term use of acarbose in patients with reduced kidney function is sparse, and consequently its use in patients with later stage 3 and stages 4 and 5 CKD is not recommended.[129]

Miglitol has greater systemic absorption than acarbose, has minimal protein binding, and is not metabolized. However, it does undergo renal excretion and accumulates in patients with impaired kidney function. Miglitol is not recommended for patients with impaired kidney function.[130]

III.G: SGLT2-inhibitors (sodiumglucose co-transport inhibitors)

Sodiumglucose cotransporter 2 (SGLT2) inhibitors are a new class of antidiabetic drugs with a novel mechanism of action. They reduce renal glucose reabsorption in the proximal convoluted tubule, leading to increased urinary glucose excretion and this without inducing insulin secretion, hypoglycemia, or weight gain.[131]

The selective inhibitors canaglifozin and dapagliflozin, derived from phlorizin, block selectively the SGLT2, which is a high-capacity, low-affinity transporter expressed chiefly in the proximal tubulus, where it is responsible for 90% of the filtered glucose reabsorption.[131]

Cardiometabolic benefits include a reduction in systolic blood pressure, reduction in triglycerides, and weight loss of up to 3 kg. The major side effect, occurring in about 5–10% of patients, is genital mycotic infections (balanitis in men and vulvovaginal candidiasis in women).[132]

Canagliflozin is 99% protein-bound and has a half-life of 10–13 h. The drug is metabolized primarily into two inactive metabolites by uridine diphosphate glucuronosyl transferase (UGT) enzymes: UGT 1A9 and UGT 2B4 via glucuronidation. Canagliflozin is eliminated largely unchanged in the feces (41.5%) and as metabolites in the urine (30.5%). Less than 1% of the dose is eliminated in the urine as unchanged parent compound.[133]

The recommended starting dose of canagliflozin is 100 mg once daily before the first meal. The dose can be increased to 300 mg once daily if GFR exceeds 60 ml/min. A maximum dose of 100 mg daily should be used in those with a eGFR between 45 and 60 ml/min. Therapy should not be used if eGFR is below 45 ml/min.[133]

Dapagliflozin is also a once daily oral, selective, and reversible inhibitor of SGLT2. It is rapidly absorbed with an oral bioavailability of almost 80% and with a mean plasma half-life of 12.9 h. It is extensively metabolized by UGT1A9 in the liver and kidneys to give inactive dapagliflozin 3-O-glucuronide. About 60% of a dapagliflozin dose is recovered in urine as this metabolite and <2% of a dose is recovered in urine as parent drug.

The recommended dose is 5–10 mg once daily.[134]

Because the rate of urinary glucose excretion is proportional to the GFR (as well as to the blood glucose concentration), the effect of SGLT2 inhibitors is less in subjects with CKD. In CKD3 with eGFR 45–60 ml/min HgA1c reductions of only 0.3–0.4% are seen, <45 ml/min almost no reduction in HgA1c is seen.[135] Hence there is no indication to use these drugs below a eGFR of 45 ml/min.

CONCLUSION

Metformin should itself be no longer considered a paradox. After more than half a century of experience, clinical studies continue to shed new light on the multiple beneficial effects of this drug. In addition, it will probably be clinically feasible in the near future to continue metformin therapy in cases of severe CKD.

A carefully performed clinical pharmacokinetic study in patients with moderate or severe renal failure is necessary to establish the way in which metformin is to be used in these patients.

DISCLOSURE

All the authors declared no competing interests.

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