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Francisco Manuel Pires Maia Figueira de Lemos

Terapias de substituição renal no tratamento de acidose láctica induzida pela metformina

Renal replacement therapies for metformin induced lactic acidosis

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NOME

Francisco Manuel Pires Maia Figueiras de Lemos

NÚMERO DE ESTUDANTE

201403341

E-MAIL

franciscolemos96@hotmail.com

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Renal replacement therapies for metformin induced lactic acidosis

ORIENTADOR

Luís Alexandre de Castilho Silva Cortinhas

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Dedicatória

Aos meus pais, pelo exemplo e inspiração que me dão todos os dias.

Renal replacement therapies for metformin induced lactic acidosis

Francisco Lemos[1], Luís Coentrão[2]

[1]Student at Faculdade de Medicina da Universidade do Porto, Porto, Portugal

[2]Nephrology Department, Centro Hospitalar Universitário de São João, Porto, Portugal

Abstract

Metformin is an oral hypoglicemic drug used as first line therapy in type 2 diabetes mellitus, a very common disease worldwide. It is well tolerated, safe and inexpensive, and it is not associated with some undesired adverse effects like weight gain or hypoglicemia. The most dangerous side effect associated with metformin use is lactic acidosis, a rare but life-threatening condition with a mortality rate up to 50%. Regarding treatment of metformin related lactic acidosis, initial approach consists on resuscitating the patient and assuring supportive measures. Then, extracorporeal treatments, such as renal replacement therapies, are considered very effective and their use is supported. However, renal replacement therapies have diferente modalities and choosing which modality to use, as well as its timing and duration, can be a very hard task as there are no irrefutable indications about this subject.

Keywords: acute kidney injury, dialysis, lactic acidosis, metformin, renal replacement therapy

1. Introduction

Metformin is an oral hypoglicemic drug used as first line therapy in type 2 diabetes mellitus, a very common disease worldwide, with a prevalence of 422 million people in 2016 (1-3). It is well tolerated, safe and inexpensive, and it is not associated with some undesired adverse effects like weight gain or hypoglicemia (4, 5). Its glucose-lowering effect is mainly achieved by its action in the liver, where it decreases hepatic gluconeogenesis (2, 5). It also improves insulin sensitivity, increasing peripheral glucose uptake and usage (2, 3). This drug also reduces cardiovascular disease and mortality, diabetes-related complications, diabetes-related deaths and all-cause mortality (3-6).

Metformin is absorbed in the small intestine and it does not experience hepatic metabolism, being excreted by the kidney through renal tubular secretion (3, 7).

When it comes to its adverse effects, gastrointestinal disturbances are the most common (7). The most dangerous side effect associated with metformin use is lactic acidosis, a rare but life-threatening condition with an incidence that can be as high as 47/100.000 patient-years, and a mortality up to 50% (1, 7-9). It can occur when metformin is prescribed with an improper dosage to patients with important risk factors, particularly chronic kidney disease (CKD) and in the context of acute kidney disease (AKI) (3, 5, 6, 10). These two conditions, especially AKI, lead to a rapid decrease in renal function, consequently reducing metformin clearance and promoting its accumulation in tissues, which contributes to an increase in lactate levels (1, 5, 6, 11). Metformin can also cause lactic acidosis through intentional overdose, without other comorbidities associated (1, 6). Thus, an early diagnosis and treatment are very important because of the high mortality associated with lactic acidosis related to metformin use, which can be even higher when there is a delay in either diagnosis or treatment (10). However, such delays can be inevitable as in an emergency context assessing metformin blood concentrations is not the most imperative thing to do and it is not always available at any time (11).

Regarding treatment of metformin-associated lactic acidosis (MALA), initial approach consists on resuscitating the patient and assuring supportive measures (10). Then, extracorporeal treatments, such as renal replacement therapies (RRT), are considered very effective and their use is supported as an adjuvant therapy. RRT grant concurrent metformin clearance and improvement of acidosis, as they are able to support compromised renal fuction (8, 10). They also allow electrolyte abnormalities correction and excess fluid and sodium elimination. Renal replacement therapies have diferente modalities and choosing which modality to use, as well as its timing and duration, can be a very hard task as there are no irrefutable indications about this subject (10).

The aim of this review is to talk about lactic acidosis related with metformin use and to focus particularly on the different modalities of renal replacement therapies used to treat it, approaching their different advantages and disadvantages, along with trying to help decide when and which modality can be the most appropriate choice in a specific patient with this very severe condition.

2. Metformin

As said before, metformin is a biguanide used in the treatment of type 2 diabetes mellitus as the drug of choice for first-line therapy (2, 3, 7). It is one of the most used antidiabetic medicine in clinical practice, as type 2 diabetes mellitus is increasing at frightening rates worldwide, especially in the USA and Europe (2, 4). Metformin boosts glucose peripheral utilization and reduces hepatic gluconeogenesis, making it a suitable drug to use in diabetes mellitus. Besides that, it also reduces the incidence of cardiovascular events and mortality and overall mortality (2, 3, 5, 12). Metformin also has other properties and specificities which will be discussed further.

2.1 Pharmacocynetics

Metformin is a small molecule with a molecular weight of 165 Da (7, 10, 13). After oral consumption, metformin is mainly absorbed in the small intestine with a bioavailability of 50-60% (3, 6, 13). Also, 20-30% of the drug dose ingested orally can be found in faeces (14). It is an hydrophilic molecule with low lipid solubility and virtually no protein binding (7, 10). Metformin has a high volume of distribution (63 to 276 L) (3, 15). This is explained by the drug accumulation in the deep or distributional compartment, more precisely in the peripheral tissues and erythrocytes. Metformin's plasma half-life is 2.7 h (erythrocyte half-life is 23.4 h) and its mean terminal whole blood half-life is about 20 h (6, 10, 11). However, Kajbaf et al. reported erythrocyte and plasma half-lives of meformin of 43.4 h and 51.9 h, respectively, in a study with 12 patients with metformin accumulation, 11 of whom were treated with dyalisis in the context of lactic acidosis and severe renal failure. They were also able to detect metformin in both plasma and erythrocytes up to 13 days after admission. These findings support the premise of metformin redistribution into the deep compartments (11). Therefore, metformin concentration in erythrocytes can be a reliable indicator of metformin accumulation or removal from the deep compartment (9, 11). Metformin does not go through metabolization in the liver and it is eliminated by the kidney through glomerular filtration and renal tubular secretion (3, 7, 10, 15). It has a clearance of 450-500 mL/min, about 3.7

to 5 times the clearance of creatinine (6, 13). 90% of the dosage consumed orally will be removed intact in the kidney by the mechanisms explained above in about 12 h (9, 13, 15). Consequently, metformin clearance will be reduced proportionally to the depression of renal function (6, 7, 10). Thus, metformin can accumulate in the tissues when there is a decrease in renal function in the context of CKD and AKI, leading to lactic acidosis (3, 11). Hence, renal failure is a risk factor for metformin accumulation (15). Lastly, metformin elimination can be limited because of its large volume of distribution, as its allocation from the deep compartment back to plasma is not as quick as its renal clearance (6, 10). This will have repercussions in the treatment of metformin induced lactic acidosis by renal replacement therapies, as it will be explained afterwards.

2.2 Mechanisms of action, Molecular effects and benefits

Metformin is na antihyperglicemic drug used to treat type 2 diabetes mellitus (6, 10). It is a secure and cheap medication, which is associated with a good day-time glucose pattern control, lower incidences of cardiovascular disease, cardiovascular death, diabetes-associated complications, diabetes-associated death and overall mortality, and it also shows favorable effects on plasma lipid profile and adipose mass regulation (2-5). Unlike other hypoglicemic drugs used to treat diabetes mellitus, metformin does not show any relation with both weight gain and increased risk of hypoglicemia, as it does not enhance insulin production and release to the blood (2, 5). This drug also has some benefits in clinical contexts other than diabetes mellitus, demonstrating favorable effects in non-alcoholic steatohepatitis, polycystic ovarian syndrome and precocious puberty (2, 4, 7). Lastly, it is associated with lower risk of cancer and it has other pleiotropic effects like enhancement of fibrinolysis, increased endothelial function and inhibition of oxidative stress and glycation. These last pleiotropic effects provide vascular protection, which might help explain the lower cardiovascular mortality associated with metformin use (5, 6).

Metformin’s glucose-lowering effect is achieved through suppression of hepatic gluconeogenesis and enhancement of peripheral cellular glucose intake and consumption, particularly in the muscles. This last effect is caused by a better insulin sensitivity related to metformin ingestion (2-4, 6). It can also decrease blood glucose levels by other mechanisms like an enhanced glucose utilization in the gut and a reduced fatty-acid

oxidation (13). As explained above, metformin's most important gluocose-lowering action occurs in the liver. Metformin supresses the mitochondrial respiratory chain complex I, which will further result in a reduced production of cellular ATP (1, 2, 7). Consequently, AMP/ATP and ADP/ATP proportions will rise, resulting in a stimulation of AMP-activated protein kinase (AMPK), which will motivate a diminution in the transcription of genes involved in gluconeogenic pathways (2). In addition, hepatic gluconeogenesis is a process that requires cellular energy (ATP), which will explain its inhibition after metformin administration (7). Metformin also inhibits mitochondrial glycerophosphate dehydrogenase, leading to a reduction in the mitochondrial redox state and an increase in the cytosolic redox state (1, 6, 10). This will contribute to a decrease in lactate and other gluconeogenic substrates utilization and thus leading to an inhibition of gluconeogenesis (1, 2, 4). Another hypoglicemic effect performed by metformin occurs in the intestine, where it will stimulate glucagon-like peptide 1 (GLP-1) release and interact with the intestinal microbiome. GLP-1 will supress pancreatic glucagon secretion and enhance glucose-dependent insulin release, leading to a better glycemic control. Moreover, GLP-1 reduces hunger and, consequently, food ingestion by slowing stomach voidance, which helps in the management of postpandrial glycemia. Lastly, metformin also interacts with gut microbiome, which may also help in the reduction of blood glucose concentrations (2). Through all mechanisms mentioned above, metformin leads to a decrease of 20-30% in postpandrial blood glucose levels (4).

However, these mechanisms may also result in some adverse effects and in the development of serious clinical conditions, as it will be subsequently discussed.

2.3 Adverse effects, Precautions and Contraindications

Metformin's most frequent side effects include gastrointestinal abnormalities such as nausea, vomiting, diarrhea, bloating, reduction of appetite and metallic taste and they occur in roughly 20% of patients treated with metformin (7, 16). However, the most concerning potential adverse effect related to metformin use is lactic acidosis, an uncommon but very dangerous condition (1, 10, 16). Metformin supresses mitochondrial alpha-glycerophosphate dehydrogenase enzyme and the mitochondrial respiratory chain complex I (1, 10). This will cause a switch in the cytosolic redox state from an aerobic state to a more anaerobic state, leading to a decline in cellular ATP levels (1, 7, 10, 16).

Consequently, gluconeogenesis, an energy expending mechanism, will be compromised resulting in the acummulation of gluconeogenic precursors including alanine, pyruvate and, most importantly, lactate (3, 7, 9). Metformin can also increase lactate levels through other processes, which will be discussed further. As metformin's excretion occurs mainly in the kidney, a reduction in its renal clearance, which can occur in the context of AKI or CKD, can lead to its accumulation (3, 5, 10). Thus, lactate levels may also rise and increase the risk of developing lactic acidosis. Besides renal function, there are other clinical conditions associated with an increased risk of lactic acidosis such as congestive heart failure, liver insufficiency, lung disease, alcohol excess, sepsis, shock, volume depletion, former development of lactic acidosis and in advanced age subjects. These conditions are associated with reduced metformin clearance and increased risk of AKI. Therefore, the conditions mentioned earlier are contraindications and rejection criteria for metformin usage (3, 6, 8, 9). Concerning renal function, metformin can be used in patients with eGFRs <60 ml/min/1.73m^2 and in patients with eGFRs <45 ml/min/1.73m^2, provided it is used with caution and with a dose readjustment. However, it is contraindicated when eGFRs is as low as <30 ml/min/1.73m^2 (3, 6). Lastly, in patients with CKD, AKI can occur with subsequent metformin accumulation in certain contexts such as treatment with angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, non-steroidal anti-inflammatory drugs (NSAIDs) and diuretics (5, 12). AKI can also be caused through exposure to intravenous nephrotoxic radiographic contrast substances and by significant dehydration related to significant volume depletion (3). In conclusion, the cincumstances referenced above should be taken seriously in patients using metformin and it could be recommended to stop the drug or reduce its dosage depending on the situation.

3. Lactic acidosis

Metformin's most dangerous potential adverse effect and the main concern related to its use is the possibility of lactic acidosis, a type of metabolic acidosis (1, 16). It is a rare but very serious condition, with na incidence that can be as high as 47/100.000 patient-years and a mortality rate up to 50% (3, 7-9, 17, 18). Lactic acidosis related with metformin use can happen in the context of metformin accumulation associated with CKD or AKI due to concurrent comorbidities such as those described above, but it can

also occur as a result of an acute metformin overdose or intoxication in patients without concomitant illnesses (1, 3, 4, 17, 19). Mechanisms and other particularities concerning lactic acidosis related with metformin will be discussed further.

3.1 Pathophysiology and risk factors

Metformin stimulates the production of lactate from glucose in the gut through anaerobic glycoysis (3, 6). It also inhibits mitochondrial respiratory complex I, causing a change in the cellular redox state, supressing oxidative metabolism and leading to a more anaerobic state (1, 3, 6, 16). Consequently, hepatic gluconeogenesis will be restrained causing an accumulation of neogluconeogenic precursors like alanine, pyruvate and, most importantly, lactate (2, 3, 6, 9). Metformin still supresses mitochondrial glycerophosphate dehydrogenase, which also contributes to the mitochondrial redox state shift (1, 6, 16). All these effects are responsible for the reduction of hepatic gluconeogenesis and oxidation of lactate to pyruvate, anaerobic glycolysis and consequent accumulation of lactate (3, 16). Since metformin is mainly excreted unchanged in the kidney, when renal function is impaired, like in AKI, there will be an accumulation of the drug with further increase in lactate serum concentrations, resulting in lactic acidosis (5, 6, 15-17). Thus, lactic acidosis associated with metformin accumulation is defined by a triad of AKI, increased serum metformin concentrations and lactic acidosis (7). Metformin-associated lactic acidosis (MALA) occurs in certain contexts that predetermine renal impairment and organ hypoxia such as advanced age, CKD, obstructive nephropathy, gastrointestinal disturbances like vomiting, diarrhea and bleeding leading to volume depletion, infection, sepsis, liver disease, pancreatitis, cardiopulmonar disease, hemorrhage, rhabdomyolysis, alcohol abuse, contrast and chemotherapy agents and lastly medications commonly used in diabetic patients such as diuretics, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and nonsteroidal anti-inflammatory drugs (1, 3, 5, 16, 20). All these contexts, when overlooked, can lead to AKI and consequent lactic acidosis in patients treated with metformin (13). However, lactic acidosis related with metformin use can occur by acute metformin overdose in patients without any comorbidities, as reported by Lacher et al. (14). Ellis and Iliescu also reported a metformin-asscociated lactic acidosis precipitated by AKI in a patient with type 2 diabetes without prior CKD or other absolute contraindications to metformin use (21).

3.2 Types of lactic acidosis

There are three mechanisms responsible for lactic acid accumulation: reduced clearance, excessive production or a mix of the two (22). Type A lactic acidosis is defined by lactic acid accumulation caused by excessive production in the context of poor tissue oxigenation and it can occur due to sepsis, hypotension, mesenteric ischemia, cardiac failure, cardiopulmonary arrest, seizures or strenuous exercice (22, 23). In these contexts, cellular metabolism will shift from aerobic to anaerobic leading to lactate overproduction (22). On the other hand, type B lactic acidosis consists of increased lactate concentrations in the absence of tissue ischemia and compromised oxigenation (22, 23). Type B lactic acidosis can further be branched in other three subgroups. The B1 subtype is related to an underlying disease state such as chronic liver disease or diabetes mellitus. The B2 subtype includes metabolic states provoked by toxins such as salicylates, alcohol or biguanides, like metformin. Finally, subtype B3 is caused by congenital metabolism flaws like pyruvate oxidase enzyme abnormalities or type I glycogen storage disease (23). Lastly, type D lactic acidosis occurs in patients with surgical short gut syndrome. In these patients, as glucose is not properly absorbed, it reaches the colon where it is converted by the intestinal flora to D-lactic acid (22). Thus, metformin related lactic acidosis can be put in the B2 lactic acidosis subtype group.

3.3 MALA vs MILA

Metformin-associated lactic acidosis is characterized as a lactic acidosis that occurs in a patient that regularly uses metformin but also has concomitant diseases related to an increased risk of lactic acidosis (4). Thus, MALA occurs when acute or chronic clinical contexts coincide with improper metformin usage, often in the context of renal failure (6, 15). As renal function declines, the capability of the kidney to remove lactate is compromised and consequently lactate accumulates leading to more renal damage (8, 16). Hence, MALA is caused by an aggravation of prior comoborbities that can lead to lactic acidosis aside from metformin but without disregarding metformin enrollment (1, 4). On the other hand metformin-induced lactic acidosis (MILA) consists of cases where metformin single-handedly can cause lactic acidosis in patients without any comorbidities (1). A French multicenter study by Corchia et al. (n=173) compared, among other parameters, patients with MILA and MALA. They concluded that, concerning median

arterial pH and lactate blood levels, there was no signifficant difference. However, the death rate was more than three times higher in the MALA patients (26%) compared to the MILA patients (7%). Additionally, MILA subgroup patients had significantly higher baseline plasma creatinine levels and less schock frequency. Also, in dialysed patients, dialysis duration was two times higher in the MALA subgroup. Lastly, metformin concentrations were not correlated with lactate levels and pH in MALA, unlike in MILA. These findings may be due to the fact that MALA is caused by risk factors other than metformin, therefore MALA patients may have concomitant comorbidities that influence their clinical condition (1).

3.4 Clinical presentation and Diagnosis

Lactic acidosis can be defined as a metabolic acidosis with a pH below 7.35 and a lactate concentration above 5 mmol/L (4, 7, 9). However, lactate concentrations greater than 2 mmol/L might be enough to meet inclusion criteria when it comes to studying metformin related lactic acidosis (1). Regarding signs and symptoms, MALA can present with gastrointestinal disorders such as nausea, vomiting, anorexia, diarrhea and epigastric pain, renal failure with oliguria, tachypnea, tachycardia, hypotension, hypovolemia, dehydration, myalgias, arrhythmia, hypoglycemia, cardiac arrest, mental state changes and coma (7, 16, 17, 20, 23). Myocardial ischemia, although very rare, has also been reported (23). Typical clinical presentation of MALA includes a diabetic patient with chronic CKD, metformin usage, gastrointestinal disorders, severe metabolic acidosis with hyperlactacidemia and AKI with oliguria due to hypovolemic shock (6). Nevertheless, MALA signs and symptoms are highly non-specific which might cause a delay in diagnosis (20, 23). In a case series of MALA by Angioi et al. (4) lactic acidosis was only diagnosed after a mean of six days after the beginning of manifestations. However, symptoms may prevail up to fourteen days until MALA is diagnosed, as shown in another case series by Ditchwald et al. (17).

It is important to rule out other possible diagnosis when dealing with MALA. For instance, MALA clinical presentation might simulate an acute abdomen due to ischemia or perforation with abdominal sepsis (6, 17). Drugs that may be implicated in lactic acidosis such as zidovudine, linezolide and salicylates need to be checked (6). Methanol and ethylene glicol can also cause metabolic acidosis but lactate levels are usually normal

because their acidosis is caused by generation of different acids. Diabetic ketoacidosis and uremia might as well be excluded as they are also associated with not elevated lactate levels. Cyanide and iron poisoning, although associated with elevated lactate levels, have a more abrupt clinical presentation compared with MALA. Intoxication by carbon monoxide can also generate lactic acidosis but mental state changes like lethargy or coma are more dominant when it comes to clinical presentation. Finally, lactic acidosis can also be induced by sympathomimetic agents like cocaine and amphetamines (22).

This huge variety of metabolic acidosis ethiologies make it very important to properly approach each case in order to make a correct diagnosis and start appropriate and early treatment.

3.5 Prognosis

As previously stated, MALA is a very serious and potentially life-threatening condition with a mortality rate up to 50% (8, 9). However, in a case series (n=6) by Ditchwald et al. (17) only one out of six MALA patients died, although another experienced everlasting neurological sequelae. Another case series (n=28) by Angioi et al. (4) showed an early mortality rate of 21.4%. Besides that, 14.8% of the surviving patients could not restore to their prior kidney function. Also, they did not find any correlation between clinical or laboratory parameters and death, which might suggest that MALA can be lethal regardless of patients concurrent illness. On the other hand, a retrospective case series (n=66) by Vecchio et al. (7) states, in accordance with the previous case series, that there is no correlation between metformin or lactate concentrations and mortality. However, they propose that mortality may be conditioned by the patients concomitant comorbidities. Mortality rate was 26%. Also, in a case series by Nguyen and Concepcion (n=12), the only difference found between survivors and deceased was their age, with younger patients having a predictably lower mortality rate than more elderly patients. Mortality rate was 25% (18). A case series (n=16) by Moioli et al. (3) also showed a lower mortality (31%) than the classic 50%. However, death rate was mainly defined by the magnitude of acidemia, unlike in other case series. Similarly, in a retrospective study by Corchia et al. (1), lactate levels were also correlated with death but only when above 5 mmol/L. Gastrointestinal disorders like nausea and vomiting, renin-angiotensin-aldosteron system (RAAS) inhibitors and shock were too signifiantly

related with mortality whereas neither metformin nor lactate concentrations were associated with death. Finally, an Italian study (n=117) by Mariano et al. (8) and a case series by Wen Y.K. (16) also showed lower metformin related lactic acidosis mortality rates than the 50% often stated: 21.4 and 10%, respectively.

This shows that MALA mortality rates may be lower than classically described when appropriate treatment is given. Besides that, prognosis factors can variate between different case series and retrospective studies. Thus, more studies are needed to better define prognosis factors of MALA and their influence in each case.

4. Renal replacement therapies and other modalities of treatment

4.1 Initial approach

MALA inicial management banks on emergency resuscitation, supportive measures like hydration, intubation and vasopressor agents, antibiotics in case of infection and bicarbonate administration (10, 16, 20, 22). Resuscitation measures in lactic acidosis aim to keep central venous pressure (CVP) above 8 mmHg, central venous oxygen saturation ($ScvO_2$) above 70% and correction of lactate levels back to normal (3). Intubation and vasopressor agents might be very important in the management of lactic acidosis. Intubation can be used to enhance tissue oxygenation, while vasopressor agents may be helpful in cases of persistent hypotension (22). Activated charcoal may also be used in order to limit metformin absorption (15).

4.2 Bicarbonate infusion

Sodium bicarbonate administration might as well be adopted. However, its usage is not unanimous. Handicaps to its use include excess sodium load resulting in hypernatremia, potassium and calcium levels disorders, rebound metabolic alkalosis, reflex vasodilation, left deviation of the oxyhaemoglobin dissociation curve, volume overload and increased plasma osmolarity (3, 14, 23). Besides that, sodium bicarbonate stimulates carbon dyoxide (CO_2) production from H_2CO_3. Sodium bicarbonate also promotes intracellular CO_2 inflow when this molecule is not adequatly eliminated leading

to a decrease in intracellular pH. This will result in a decrease of ionized calcium intracellular levels, which will affect myoardial contratility (3, 23). However, bicarbonate therapy might be helpful in certain contexts such as in severely ill patients, pH lower than 7.1 and in order to keep HCO_3^- levels not lower than 8-10 mmol/L (20, 23).

4.3 Renal replacement therapies

Renal replacement therapies (RRTs) are one of the main keystones concerning metformin related lactic acidosis treatment, as they allow not only metformin removal from plasma but also correction of the metabolic acidosis (6, 10, 17). RRT may also correct the fluid overload and hypernatremia that can occur after bicarbonate infusions (8).

Indications for RRT include pH less than 7.0, lactate levels above 20 mmol/L, shock, failure of previous therapeutic effortsand mental state changes (1, 4, 6). Its use may also be considered in patients with importante comorbidities (8, 18). In a french multicenter study by Corchia et al. (1), RRT usage was not statistically different between survivors and deceased. However, the use of RRT was significantly related with higher baseline plasma creatinine levels, hyperlactacidemia, hypernatremia and shock, which indicates that dialysis was more likely commenced in more critically ill patients. This demonstrates the potential benefits of RRT in cases of metformin related lactic acidosis. Besides that, the use of a bicarbonate dialysate might be very benefitial as it allows metformin removal and acidosis correction without the need of bicabornate infusion and its associated risks (14, 20).

Different modalities of RRT can be used depending on the patient condition. In hemodynamically unstable patients, continuous RRT modalities may be the best choice whereas standard intermittent hemodialysis (IHD) can be considered as first option in more stable patients as it allows metformin removal and acidosis correction more efficiently (6, 10, 16, 18). A case series (n=12) of metformin-induced lactic acidosis by Nguyen H.L. and Concepcion L. (18) found no difference between traditional hemodialysis (70% of patients) and continous veno-venous hemodialysis (30%), a CRRT modality. As mentioned earlier, metformin does not bind to plasma proteins and has a high distribution volume intarcellularly, which makes a rebound in metformin and lactate serum levels very likely to happen after a session of conventional hemodialysis (6, 17).

This rebound phenomenon is mentioned in several metformin related lactic acidosis case reports after patients underwent conventional hemodialysis (9, 14, 15). Thus, this two-compartment figure of metformin distribution results as expected in a biphasic metformin elimination model, which makes prolonged RRT modalities more suitable for this kind of lactic acidosis since metformin can be continuously eliminated while it is transfered from the intracellular to the extracellular domain (8, 15, 17). Therefore, CRRT utility may not be restricted to cases of hemodynamic instability. Mujtaba et al. (13) successfully applied continuous veno-venous hemodiafiltration (CVVHDF), a CRRT modality, without verifying the presence of rebound. Ditchwald et al. (17) used CRRT in six MALA patients and all but one took less than 24 hours for their lactate concentrations to hit zero. Moioli et al. (3) treated sixteen MALA patients, thirteen of whom with RRT and, among those treated with RRT, 77% were treated with CRRT with an overall mortality of 31%. Mariano et al. (8) treated 117 MALA patients with RRT with a mortality rate of 21.45%. Another acceptable alternative would be to start treatment with conventional hemodialysis until correction of acid-base abnormalities and then switch to a CRRT modality to continue treatment (15).

It has been suggested that a quick and agressive therapeutic approach could lead to better outcomes as shown by the 10% mortality rate achieved by Wen Y.K. in a case series (16). However, Vecchio et al. (7) found no difference between survivors and non-survivors regarding time to start dialysis after hospital arrival.

In critical patients with AKI, sustained low-efficiency dialysis (SLED) has been suggested as a RRT modality that can combine features of both IHD and CRRT as it is not only capable of granting a better hemodynamic stability compared with IHD but also a more efficient drug removal compared with CRRT (6, 10). Angioi et al. (4) treated 28 patients with SLED with a mortality rate of 21.4%. They decided to use SLED in all patients with lactic acidosis using metformin regardless of their clinical condition. However, a second dialysis treatment was needed for lactate levels to reach values below 5 mmol/L. Greco et al. (10) treated 10 patients with SLED with a mortality of 20% and a median percentage of metformin levels reduction of 78.5%. Although, they verified a little rebound in metformin concentrations which they predicted it could be corrected with one aditional SLED session. Regolisti et al. (6) also noticed a modest rebound in metformin levels after treating a patient with SLED. Besides that, SLED might be a very good option to treat lactic acidosis related with metformin use. However, clinical

background concerning SLED use is minimal and SLED may also not be available in many centres, which creates the need to find plausible alternatives (6, 10).

5. Conclusion

Metformin related lactic acidosis is a very serious and conceivably deadly condition that can occur in the context of intoxication with very high quantities of this drug (MILA) or in type 2 DM patients prescribed with therapeutic dosage in the context of acute or chronic illness that can diminish its clearance, such as AKI or CKD (MALA) (1, 6).

When it comes to MALA, it is important to consider that metformin is mostly used by an elderly population where comorbidities such as heart failure or CKD are very frequent and require a strict surveillance (5, 12). Thus, metformin withdrawal should be considered in patients who are at risk of developing AKI or other conditions that might impair metformin clearance (3, 16, 20).

Metformin-related lactic acidosis is characterized by a triad of metformin usage, serious lactic acidosis and kidney failure (17). It should be considered when these features are present in patients with a prescription for metformin and a history of gastrointestinal symptoms days before hospital arrival (7).

Regarding approach to this condition, supportive measures of the cardiorespiratory systems and RRT in order to correct the acid-base disorder and metformin levels are the main cornerstones (12, 16, 17). Regarding RRT, it should be started when certain conditions are met as discussed above. It is also important to pay attention to a likely rebound phenomenon in the metformin and lactate levels during or between dialysis sessions.

In conclusion, more importante than to treat metformin-related lactic acidosis patients is to identify patients at risk in order to preclude the occurence of this severe and life-threatening condition (16, 17, 19).

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Conflict of interest

The authors declare that they have no conflict of interest or disclosure.

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ANEXOS

Normas da revista

Portuguese Journal of Nephrology & Hypertension

ISSN 2183-1289

The journal is indexed in Thompson Reuter's SciELO Citation Index

Instructions to Authors

AIMS AND SCOPE

The *Portuguese Journal of Nephrology and Hypertension* is the official organ of the Portuguese Society of Nephrology and is published quarterly. Supplementary issues are also published including selected themes, at the discretion of the Editor-in-Chief, as well as abstracts of the annual congresses of the Society. The Journal is peer-reviewed and is indexed in Thompson Reuter's SciELO Citation Index, with free online access in our website http://www.spnefro.pt/RPNH.

The Journal publishes articles on clinical or laboratory topics of relevance to nephrology, dialysis, transplantation and hypertension. Papers relating to basic immunology, physiology, genetics and epidemiology are accepted when kidney-related. Manuscripts must be submitted in English to the Editor-in-Chief. Only previously unpublished work should be submitted. The Editor-in-Chief has complete editorial freedom.

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REVIEW AND PUBLICATION SPEED

All submissions will be subject to an immediate editorial screening process by the Editor-in-Chief after which they will normally be sent to two or three reviewers. The Editor-in-Chief will make every effort to reach a decision on all submitted papers within 8 weeks of receipt. Papers will normally be published in the next issue to go to press after their acceptance. Papers that do not meet the scientific standards of the Journal may be declined by the Editor-in-Chief without further review.

CONTENT TYPES

The Portuguese Journal of Nephrology and Hypertension publishes: 1) Editorials; 2) Review Articles; 3) Original Articles; 4) Case Reports; 5) Letters to the Editor; 6) Nephropathology Quiz; 7) Perspective; 8) Comments.

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Editorials are usually invited, but authors may propose a paper for the Editor-in-Chief's consideration. They may have up to 2000 words and a maximum of 2 tables or figures. A maximum of 5 references is generally recommended.

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Review articles should provide novel insights and comprehensive analyses of topics on Nephrology, and interpretation of the published literature. They are usually commissioned by the Editors. However, unsolicited reviews will be considered. These articles may have up to 5000 words and an abstract of up to 300 words. The use of 3 tables or figures is acceptable. A maximum of 70 references is generally recommended.

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An original article must focus on relevant clinical investigation or basic research, and is limited to 4000 words

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Case Reports

Original and succinct description structured in Introduction, Case Report and Discussion. They should not exceed 2500 words (including an abstract up to 300 words) and should not include more than 4 tables or figures. A maximum of 30 references is generally recommended.

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Letters must contain information related to an article published in the Journal or may concern a topic of current interest in Nephrology. Letters (maximum of 3 authors) are limited to 500 words and 1 table or figure. A maximum of 5 references is generally recommended.

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Perspective articles are brief, accessible pieces covering a wide variety of timely topics of relevance to health care and medicine. They are nearly always solicited, although unsolicited articles may occasionally be considered. Perspective articles are limited to 1000 to 1200 words and may include one figure or table. A maximum of 8 references is generally recommended.

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Should the manuscript be accepted for publication the authors will be asked to give signed consent for publication in a letter which must contain the statement that “the results presented in this paper have not been published previously, in whole or in part, except in abstract form”.

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References must be numbered consecutively in the order in which they are cited in the text. Each reference should give the name and initials of all authors unless they are more than six, when only the first three should be given followed by et al. Authors’ names should be followed by the title of the article, journal abbreviations according to

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Examples

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Dis 2014;63(4):656-666

2. *Books*:
Morris Peter, Knechtle Stuart. Kidney Transplantation - Principles and Practice. 7th Edition. Saunders, 2014:72

3. *Website*:
Substitutive Renal Therapy of Chronic Renal Disease in Portugal.
Available at http:www.spnefro.pt/comissoes_Gabinete_registo_2013/registo_2013.
Accessed October 6, 2013.

4. *Published Meeting Abstract*:
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Efficacy of preventing hemodialysis catheter infections with citrate lock (Encontro Renal abstract SE001). Port J Nephrol Hypert 2011; 25(1):56

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When reporting experiments on human subjects, it is mandatory to indicate whether the procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975 (revised in 2015) and, in the case of renal transplant, the Declaration of Istanbul.

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