Metformin-Associated Lactic Acidosis Undergoing Renal Replacement Therapy in Intensive Care Units: A Five-Million Population-Based Study in the North-West of Italy

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Keywords

Metformin · Acute kidney injury · Renal replacement therapy · Lactic acidosis · Intensive care units · Epidemiology · Survival

Abstract

Background: Metformin-associated lactic acidosis (MALA) is a severe complication of drug administration with significant morbidity and mortality. So far no study in large population areas have examined the incidence, clinical profile and

outcome of acute kidney injury (AKI)-MALA patients admitted in intensive care units (ICUs) and treated by renal replacement therapy (MALA-RRT). **Methods:** Retrospective analysis over a 6-year period (2010–2015) in Piedmont and Aosta Valley regions (5,305,940 inhabitants, 141,174 diabetics treated with metformin) of all MALA-RRT cases. **Results:** One hundred and seventeen cases of AKI-MALA-RRT were observed (12.04/100,000 metformin treated diabetics, 1.45% of all RRT-ICU patients). Survival rate was 78.3%. The average duration of RRT was 4.0 days at mean dialysis effluent of 977 mL/kg/day. At admission most patients were dehydrated, and experienced shock and oliguria. **Conclusion:** Our data showed that MALA-RRT is a common complication, needing more prevention. Adopted policy of early, extended, continuous and high efficiency dialysis could contribute to an observed high survival rate.

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Introduction

Metformin, an old drug known for more than 45 years, is the first-line treatment for type 2 diabetes mellitus in the world [1]. Metformin reduces the risk of mortality and morbidity in diabetic population [2] and decreases insulin resistance [3].

Generally speaking, metformin is considered a safe drug, with some limitations. Due to increased risk of lactic acidosis, metformin is contraindicated in patients with organ dysfunction such as congestive heart failure, renal, or hepatic insufficiency, and in very elderly patients [4]. Since metformin prescriptions have been progressively increasing over time, the reported cases of metformin-associated lactic acidosis (MALA) have become not so uncommon, and are associated with significant morbidity and mortality [5–7]. Estimated incidence of MALA is reported to range from 1 to 47 cases per 100,000 patient/year [5–9], with a mortality rate as high as 50% [10, 11].

As regards therapy, extracorporeal removal of metformin is a crucial part of MALA treatment, and it is recommended as adjunctive therapy [11]. As reported for phenformin-induced lactic acidosis more than 15 years ago [12], apart from drug removal, continuous renal replacement therapy (RRT) can support impaired kidney function. RRT corrects significant electrolyte disturbances and severe metabolic acidosis [13–15]. It allows removal of fluid and sodium overload due to a large amount of bicarbonate needed to correct acidemia [15–17].

However, the true incidence of MALA patients admitted in intensive care unit (ICU) and treated by RRT (RRT-MALA) is unknown. Moreover, so far no study among large population areas has examined the incidence, clinical profile, and outcome of these patients.

In Piedmont and Aosta Valley (North-West of Italy, with a population of 5.4 million inhabitants), consultant nephrologists of the 20 Nephrology and Dialysis Centers provide, or largely support, all RRT treatments in ICUs [18].

This study, focusing on the diabetic population of 141,174 subjects treated with metformin, was aimed to retrospectively evaluate the incidence of RRT-MALA patients over a 6-year period. In addition, we examined the patients' risk factors, clinical profile, and outcome.

Methods

Data Sources

In North-West of Italy, the “GRuppo Acuti del Nord Ovest” (GRANO, the network of consultant nephrologists of the 20 Nephrology and Dialysis Centers located in Piedmont and Aosta Valley regions) deals with RRT treatments in ICUs [18].

As standard practice, in every Dialysis Center, a consultant nephrologist is specifically dedicated to Critical Care Nephrology, and for each RRT session done in ICUs, a dedicated dialysis schedule was prescribed and filled in by nephrology nurses [18]. The Nephrology and Dialysis Centers were located in area-hospitals in which 14 Diabetes Centers were also present. Each of them is responsible for a specific area and its inhabitants. Together they provide diabetes care for the population of Piedmont and Aosta Valley (5,298,000 inhabitants, year 2012).

Data about demographics of the 14 Diabetes Center areas (population, number of diabetic patients, type of diabetes, diabetes onset, number of drug-treated, and metformin-treated patients) were taken from the official report of Regione Piemonte “Registro Diabete Piemonte” [19].

The RRT treatment data collected by GRANO were referred to the population of each of the 14 Diabetes Center areas.

Collection of Data

The data recorded include demographic information, drug prescription before admission, comorbidities, clinical profile during ICUs stay, and major outcomes. The response rate was 20/20 centers.

Five main areas of clinical practice were investigated:

1. Number of RRT-MALA treated patients, presence of comorbidities (sepsis, chronic renal failure [CRF], chronic respiratory disease, chronic liver failure, neoplastic disease), risk factors (daily metformin amount, other drugs such as sartans/angiotensin-converting enzyme inhibitors [ACEi], diuretics, nonsteroidal anti-inflammatory drugs or exposition to iodine media), dehydration and gastrointestinal (GE) symptoms, and value of preadmission creatinine (the last known value, e.g., the last diabetologic control, or a reported value over the last 6 months);

2. Values of creatinine, pH, and lactate, the presence of oliguria, shock, norepinephrine infusion, and mechanical ventilation at the start of RRT;

Fig. 1. Study flowchart. In 2012, the population of North-west of Italy was 5,298,000, of whom 282,973 were diabetics (5.46%). Metformin-treated patients were 141,174, and 17 cases of RRT-MALA were observed.

3. RRT duration (CRRT, PIRRT, or standard dialysis) and type (convective-mixed or diffusive), prescribed dialysis dose, percentage of predilution, and applied anticoagulation;

4. Outcome of patients (ICU survival, withdrawal from dialysis or preexisting CRF worsening).

All data sheets were completed with aggregated data year after year. Since the study was retrospective, not all comprehensive data could be retrieved from clinical documentation.

The study was in adherence with the Declaration of Helsinki. No ethical approval was required for this study.

RRT Procedure

RRT was performed in ICUs following the indications of the GRANO nephrologist. All RRT sessions were performed with monitor Prismaflex (Gambro Hospal, Lund, Sweden) equipped with a high permeability AN69 filter (ST150, or filters of the same series), or with monitor Multifiltrate (Fresenius Medical Care, Bad Homburg, Germany) equipped with a high permeability polysulfone filter (AV1000 or filter of the same series, Fresenius Medical Care).

Commercially available bicarbonate-containing bags were used for exchange/infusion fluids during all sessions (Baxter, Fresenius Medical Care).

Dialysis sessions were delivered in the continuous, prolonged (>6 h) or standard (<6 h) hemofiltration, hemodiafiltration, or hemodialysis. The length of the sessions, the prescribed dialysis dose, and the net fluid removal were done in accordance with patient clinical needs, as long as best practice recommendations were adhered to [20].

Most patients received unfractionated heparin for extracorporeal circuit anticoagulation, whereas a minor part did not.

Statistical Analysis

Anonymized and aggregated data were treated in a confidential manner and analyzed.

Values were expressed as mean. Descriptive statistics was performed with software Statistica (Statistica 10.1, StatSoft Inc., Tulsa, OK, USA).

Results

Epidemiology of RRT-MALA Patients

In 2012, the “Registro Diabete Piemonte” reported a population of 5.3 million of inhabitants, and 231,024 drugs-treated diabetics (4.36%), of whom 61.1% were metformin-treated (Fig. 1).

From 2010 to 2015, 117 cases of MALA-RRT were observed, with an average incidence of 19.5 cases/year. Of 117 RRT-MALA patients, 92 survived (78.3%; Table 1).

In 2012, there were 17 cases of RRT-MALA patients, indicating an incidence of 12.04/100,000 metformin-treated diabetics (Fig. 1). These 17 patients represented 1.45% of all RRT-treated patients in ICUs in 2012 (Fig. 1).

With regard to distribution in the 14 different diabetic areas, the incidence of RRT-MALA cases varied from 4.7 to 80.9 cases/100,000 metformin-treated diabetics/year (Fig. 2).

Fig. 2. Mean incidence of RRT-MALA patients (cases/year/100,000 metformin-treated diabetics) from 2010 to 2015. RRT-MALA patients were stratified by the referring 14 Diabetes Center Areas.

The trend of RRT-MALA incidence showed a constant increase of cases from 2010 to 2015, without any substantial difference on the survival rate (Fig. 3).

Basal Clinical Characteristics of RRT-MALA Patients

Mean age and duration of diabetes of 117 RRT-MALA patients were 71.6 and 9.5 years respectively (Table 1). Among the chronic organ failure comorbidities, only CRF was relevant, and it was reported in one third of patients. Basal creatinine before admission was 107.3 $\mu\text{mol/L}$ (Table 1).

Other than metformin (mean daily taken amount of 1.6 g), most of the patients took sartans/ACEi and/or diuretics.

Clinical Profile and Characteristics of RRT Sessions

At admission, most of the patients presented signs of dehydration, had experienced GE losses, were shocked and oliguric, and one fourth of cases had a diagnosis of sepsis (Table 2). During ICU stay, 47.4% of patients needed mechanical ventilation and 71.4% needed hemodynamic support by norepinephrin (Table 2).

At RRT start, all patients were uremic with severe acidosis and increased lactatemia (mean creatinine, pH, and lactates were, respectively, 598.8 $\mu\text{mol/L}$, 7.04, and 12.0 mmol/L; Table 3). The time interval between the entry into ICU and RRT start was 3.2 h, with an average duration of RRT of 4.0 days. In most cases, the sessions were continuous, prolonged, and at high volume (mean dialysis effluent of 977 mL/kg/day; Table 3). Unfractionated

Table 1. Demographic characteristics and comorbidities of 117 RRT-MALA patients

	Values	Number of valid patients
<i>Demographic data</i>		
Patients (F/M), n (%)	76/41 (64.9)	117
ICU survival (survived/dead), n (%)	92/25 (78.6)	117
Age, years, mean	71.6	97
Duration of diabetes, years, mean	9.52	54
Metformin dosage, mg/day, mean	1,585.7	63
<i>Other drugs, n (%)</i>		
ACEi/sartans	55/24 (69.6)	79
Diuretics	30/47 (38.9)	77
Nonsteroidal anti-inflammatory drugs	3/73 (3.9)	76
Contrast iodine	4/74 (5.1)	78
Creatinine pre-admission, $\mu\text{mol/L}$, mean	107.3	91
<i>Comorbidities, n (%)</i>		
Chronic nephropathy (yes/no)	35/64 (35.4)	99
Chronic liver disease (yes/no)	8/83 (8.8)	91
Chronic respiratory disease (yes/no)	12/69 (14.8)	81
Neoplastic disease (yes/no)	2/89 (2.2)	91

heparin was the most common anticoagulant used (81.5% of sessions), whereas the remaining sessions were carried out without any anticoagulant (Table 3).

Outcome of Patients

In terms of the renal function, mean creatinine at discharge was 147.6 $\mu\text{mol/L}$, and 96.7% of survived patients were off dialysis at discharge (3 out of 92 patients needed

Fig. 3. Mean incidence and survival of RRT-MALA patients from 2010 to 2015. RRT-MALA patients were stratified by year.

Table 2. Clinical characteristics of the RRT-MALA patients at admission in ICU and at discharge

	Values	Number of valid patients
<i>At admission, n (%)</i>		
Dehydration symptoms (yes/no)	66/16 (80.5)	82
Gastrointestinal symptoms (yes/no)	61/17 (78.2)	78
Oligoanuria (yes/no)	95/10 (90.5)	105
Shock (yes/no)	69/28 (71.1)	97
Sepsis (yes/no)	24/72 (25.0)	96
Mechanical ventilation (yes/no)	45/50 (47.4)	95
Norepinephrin (yes/no)	68/27 (71.6)	95
<i>Outcome</i>		
Creatinine at discharge, $\mu\text{mol/L}$, mean	147.6	55
Withdrawal from dialysis (yes/no), n (%)	89/3 (96.7)	92
Creatinine/CRF worsening (yes/no), n (%)	32/44 (42.1)	76

Table 3. Biochemical data, dialytic parameters, and outcome for RRT-MALA patients in ICUs

	Values	Number of valid patients
<i>At RRT start</i>		
Creatinine, $\mu\text{mol/L}$, mean	598.8	96
pH (arterial blood), mean	7.04	77
Lactate, mmol/L , mean	12.0	70
Time interval before RRT start, h, mean	3.2	88
<i>RRT clinical data and parameters</i>		
Duration of RRT, days, mean	3.9	96
Dialysis dose, mL/kg/day , mean	977.7	58
Predilution, % of infusion, mean	31.8	49
Heparin anticoagulant, n (%)	84/19 (81.5)	103
HF or HDF techniques (yes/no), n (%)	91/18 (83.4)	109
CRRT or PIRRT modalities (yes/no), n (%)	87/22 (79.8)	109

chronic dialysis). However, more than 40% of patients had a worsening of the preadmission creatinine values, either normal or increased due to a preexisting CRF (Table 2).

Discussion

In a homogeneous area of 5.3 million of inhabitants, 6 years follow-up from 2010 to 2015 showed that the mean incidence of MALA patients treated by RRT in ICUs was as high as 13.8 cases/year/100,000 metformin-treated diabetics. However, the survival rate of these old patients, with a mean age of 71.6, reached to about 80%, a value better than those previously estimated [11, 14, 21, 22].

As a matter of fact, data regarding the effective incidence of RRT and survival in the setting of MALA patients are limited, mostly relying on a single center, small observational studies, or other extrapolated data [11, 14, 21, 22]. To our knowledge, data collected from the nephrologist network GRANO constitute the largest detailed epidemiologic study on RRT-MALA patients, as it covers all ICU needs of RRT in such a large population [18]. The phenomenon observed (117 RRT-MALA patients over 6 years) likely represents the trend in the diabetic population in Italy.

The incidence of 13.8 cases/year/100,000 metformin-treated diabetics is one of the highest previously reported [5, 9, 11, 23–26]. However, this discrepancy could be due to the different methods and target of the study (data base screening, definition of lactic acidosis, and definition of MALA as patients undergoing RRT in ICU), or due to the different health policies implemented at that time. Metformin use has increased over the years, due to its low cost and the discovered additional benefits to glycemic control [1–3]. Even if we do not have data supporting a more popular use of metformin between 2010 and 2015 in Piedmont and Aosta' Valley, we could assume that the increased number of RRT-MALA every year simply reflected an increased risk of MALA in an ageing population (Fig. 3).

The incidence of RRT-MALA stratified by Diabetes Center area ranged from 6.1 to 80.9 cases/year. However, the small absolute number of cases/years, as well as a heterogeneity on case reports could explain the high rate of variability among Center areas. Regarding the high incidence of RRT-MALA by one center (Aosta' Diabetes Center; Fig. 2), it may reflect first a higher rate of associated comorbidities in the 14 RRT-MALA patients (6 were with septic shock, 4 with chronic liver disease, and 1 with

advanced neoplastic disease). And second, the diabetological center might have had a different attitude to metformin use (more than 70% among all drug-treated diabetics were on metformin).

Among comorbidities chronic nephropathy was present in one third (Table 1) of the RRT-MALA patients. Recently, a large-scale, nationally representative, population-based study demonstrated that metformin prescription was not uncommon in diabetics with CKD stage 3, and that this prescription was not significantly associated with the risk of severe acidosis [27]. Even if the prescribed mean metformin dosage was as low as 1.6 g/die, we cannot rule out the role played by the reduced renal clearance coupled with gastrointestinal losses and dehydration (very common conditions at admission). In fact, abdominal disturbances and drug interference (ACEi/sartans and diuretics) favored a hemodynamics of underlying volume depletion and reduced renal perfusion.

At admission, all RRT-MALA patients had AKI, and 90.5% of the cases had oliguric AKI. It is known that MALA can occur as a consequence of a discrepancy between increased lactate generation and metformin liver and kidney clearance. Beyond reduction of metformin clearance, AKI could be pathogenetic in MALA onset, since it impairs renal cortex utilization of lactate as metformin does [11]. In effect, as extracellular pH falls, the ability of the kidney to remove lactate is enhanced, and it is sufficient to compensate for approximately one half of the concomitant fall in liver lactate extraction capacity. When AKI complicates MALA, the role of the kidney as a lactate-consuming organ is severely impaired, and MALA derangements can accelerate [28].

Even though we did not measure metformin levels, we can postulate that in dehydrated patients, metformin physiologically cleared by kidney can accumulate [29–32]. In these cases, the risk of lactic acidosis increased when metformin administration was associated with ACEi/sartans or diuretics [30, 32]. The observed high incidence of RRT-MALA leads to the conclusion that patients need more prevention. Patients should be warned about metformin, ACEi/sartans, and diuretics discontinuation when they experience GE loss, or all conditions of reduced urine output.

The Extracorporeal Treatments in Poisoning Workgroup recommends RRT in severe metformin intoxication defined as patients with lactate concentrations >20 mmol/L or pH ≤7.0, or with failure of standard supportive measures. However, it also suggests that in the presence of comorbid conditions, the timely access to RRT would be useful [11]. All RRT-MALA patients were ure-

mic, and most of them were oliguric. Therefore, they all had a potential condition for metformin accumulation. And beyond uremic indication, RRT was very important to remove toxic levels of metformin in order to break down the vicious cycle of MALA.

Generally speaking, the adopted dialysis policy of nephrologists network GRANO consisted of an early start of dialysis, at high intensity dose with a continuous (or prolonged) modality. Several reasons supported this adopted dialysis policy. First, metformin is a low-molecular-weight drug, with a dialysis membrane sieving coefficient near the unit. The amount removed, proportional to the exchanged fluid, could be consistent with high-volume dialysis. Second, even if metformin can be easily removed by convection and/or diffusion, its volume of distribution within a 2-compartment model implied that a continuous (or prolonged) treatment was more effective for its extracorporeal clearance [12–14]. Third, an initial correction of acidosis needed a large infusion of bicarbonates. As shown in phenformin-induced lactic acidosis where CRRT brought benefits without any appreciable elimination of drug [12], CRRT could impact survival simply by correcting the net positive sodium balance, fluid overload, and hypernatremia. Lastly, treatment with RRT in continuous modality was preferable, as it was tailored to suit the unstable hemodynamic conditions of our patients, a majority of whom were under shock and under norepinephrin support.

Interestingly, the ICU survival rate of 117 RRT-MALA patients was 78.6%, the highest reported in wide clinical records of MALA [11, 14, 21, 22, 33]. With more recent data, Doeniyas-Barak found an overall survival rate of 43.2% in 44 admitted ICU patients with severe shock. Of these, 17 underwent RRT with a survival rate of 41.2% [34]. In terms of factors impacting survival, previous data suggested that RRT dose and modality could influence the outcome. Higher mortality rates were observed when low-efficiency techniques were applied [13, 17]. On the other hand, the use of high-flux/high-efficiency dialyzers, the maximization of blood and effluent flow rates, or additional catheters and extracorporeal circuits could increase lactate and metformin removal, and may be even increase survival rates [35–37]. Even if we suppose that an early, intensive, and extended dialysis may have specific benefits for our patients, we could not provide a clear demonstration of this fact.

Several limitations to the present study need to be mentioned. Our study is retrospective with all inherent drawbacks. Several patients experienced sepsis or shock, and the role of metformin in inducing the degree of lactic

acidosis could not be clearly defined since these conditions may per se be associated with hyperlactatemia. Moreover, the retrieval of data was not complete and we missed out on the metformin dosage. The lack of information on metformin dosage did not allow us to confirm the certainty of diagnosis and to quantify the severity of the metformin intoxication.

In conclusion, our data demonstrated that in a large part of Italy, the incidence of RRT-MALA among metformin-treated diabetics was high, and more preventive

measures should be implemented. Survival rate in RRT-MALA patients was unexpectedly high, reaching up to 80%. Adopted dialysis policy of early, extended, continuous, and high efficiency RRT could have contributed to the reported positive results.

Disclosure Statement

The authors declare no conflicts of interest, and no sponsorship or funding arrangements related to their research.

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