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van de Laar, Inge

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# Chapter 4

## Metformin Associated Lactic Acidosis: Incidence and clinical correlation with metformin serum concentration measurements

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Inge RF van Berlo – van de Laar
Cornelis G Vermeij
Cornelius J Doorenbos

# Abstract


## Background

The reported incidence of metformin associated lactic acidosis (MALA) in type 2 diabetes mellitus (DM) is 3 to 9 cases per 100,000 patient-years. In clinical practice, 22-94% of patients using metformin have contraindications to metformin, so the incidence of MALA may be higher than reported.

## Objectives

To estimate the incidence of MALA in type 2 DM patients by means of metformin serum concentration measurements and investigate the correlation of metformin serum concentration with the clinical outcome of MALA.

## Methods

MALA cases were identified by reviewing the medical records of patients with metformin serum concentrations measured between January 2000 and October 2008. MALA was defined as arterial pH <7.35 and lactate concentration >5.0 mmol/l in patients using metformin. Renal failure was defined as serum creatinine >132 µmol/l (men) and >124 µmol/l (women). The incidence of MALA was calculated from the number of cases and the at risk population. The correlation coefficient between the metformin and lactate concentration was calculated by linear regression. The relationship between metformin serum concentration, lactate concentration and outcome was examined by calculating the mean metformin and lactate concentration in patients who survived and those who died. The Student's t-test was used to compare groups.

## Results

In 29 patients metformin serum concentration was measured, 16 had MALA. 11 of the 16 MALA cases (69%) had risk factors for lactic acidosis in their medical history, 13 cases (81%) had renal failure on admission. The incidence of MALA was estimated at 47 per 100,000 patient-years, this is 5 to 16 times higher than previously reported. This may be explained by the use of metformin in the presence of risk factors for lactic acidosis. Survivors had a higher metformin serum concentration (18.9 mg/l) than non-survivors (2.9 mg/l, p=0.006) which can be explained by less severe underlying disease in patients who survived MALA, rather than an effect of metformin itself.

## Conclusion

The incidence of MALA estimated from metformin serum concentration measurements in type 2 DM patients is 5 to 16 times higher than reported in literature. MALA is probably caused by the frequent use of metformin in the presence of risk factors for lactic acidosis. Metformin serum concentration measurements may aid in the timely diagnosis and therapy of MALA. The outcome of MALA is determined by the severity of the underlying disease, rather than by metformin itself.

# Introduction

Metformin is a frequently used drug in the management of type 2 diabetes mellitus (DM). The UKPDS has shown that metformin use was associated with a lower mortality from cardiovascular diseases and all cause mortality than sulfonylureas or insulin in type 2 DM patients.[1] However, metformin has been associated with the risk of developing lactic acidosis.[2-4] Renal impairment, liver failure, heart failure and pulmonary disease increase the risk of lactic acidosis and are contraindications to metformin use. In clinical practice, metformin is used despite the presence of contraindications in 22-94% of the patients.[5-10] In literature, there is doubt whether metformin itself causes lactic acidosis in DM patients.[11-13] A Cochrane review found no increased risk of lactic acidosis for metformin compared with other antidiabetic drugs.[14] Estimates of the incidence of MALA range from 3 to 9 per 100,000 patient-years.[2-4, 15-17] In view of the frequent use of metformin in the presence of risk factors for lactic acidosis, the incidence of MALA may be higher than previously reported. Metformin serum concentrations often have not been measured in studies on MALA. Measurement of the metformin serum concentration may aid in the identification of MALA cases and estimation of the incidence of MALA. Furthermore, metformin serum concentration measurements may elucidate the correlation between metformin accumulation and clinical outcome. The aim of this study was to estimate the incidence of MALA in type 2 DM patients by means of metformin serum concentration measurements and investigate the correlation of metformin serum concentrations with the clinical outcome of MALA.



# Methods

The laboratory data of the Deventer Hospital were searched for patients with measured metformin serum concentrations in the period February 2000 to October 2008. The medical records of the selected patients were reviewed for data on age, sex, metformin dose, risk factors for lactic acidosis in the medical history and on admission, previous and admission creatinine concentration and MDRD estimated GFR, admission diagnosis, arterial pH, plasma lactate concentration, metformin serum concentration, treatment and outcome (30 days after admission). Renal failure was defined as creatinine concentration >132 μmol/l in men and >124 μmol/l in women (based on the FDA recommendation for metformin use). Impaired liver function was defined as serum ALAT concentration >3 times the upper limit of normal (40 U/l). MALA was defined as an arterial pH <7.35 and plasma lactate concentration >5.0 mmol/l. In the selected MALA cases, the correlation coefficient between metformin serum concentration and plasma lactate concentration was calculated. Linear regression analysis was applied to determine significance. The relationship between metformin serum concentration, lactate concentration and outcome was examined by

calculating the mean metformin serum concentration and lactate concentration in patients who survived and those who died. The Student's t-test was used to compare groups. A p-value <0.05 was considered statistically significant. The incidence of MALA was calculated from the number of cases and the number of patients using metformin in the observation period of the study. This calculation was based upon metformin prescription and DM prevalence data from 53 general practices in the hospital referral area, covering 91% of the population.

### Drug analysis

Metformin serum concentrations were determined by means of a high-performance liquid chromatography (HPLC) assay with UV detection. The HPLC analysis used a Chromspher Biomatrix column (particle size 5 µm, 150x4.6 mm) and a mobile phase consisting of acetonitril and phosphate-buffer solution with a pH of 5.0 in a ratio of 35:65. UV detection was set to 235 nm. Metformin was extracted from serum by protein precipitation with acetonitril.

## Results

29 patients with measured metformin serum concentration were identified in the hospital pharmacy laboratory database. Two patients were excluded, because they were treated in other hospitals. Ten patients were excluded because lactate was <5.0 mmol/l, one patient was excluded because the pH was exactly 7.35. This resulted in 16 patients fulfilling the criteria of MALA. Table 1 summarizes the demographic and laboratory data of the selected MALA cases. Arterial pH was 7.10±0.16 (mean±SD, range 6.77-7.33), lactate was 13.8±5.3 mmol/l (5.8-23.2) and metformin serum concentration was 13.9±14.9 mg/l (0.4-44.0). Creatinine was 178±174 µmol/l (64-731) and MDRD estimated GFR was 44±26 ml/min/1.73 $m^2$ (5-98) before admission and 477±333 µmol/l (86-1039) and 20±20 ml/min/1.73 $m^2$ (3-56) on admission. Seven patients (44%) had renal failure before admission and 13 patients (81%) had renal failure on admission. 11 Patients (69%) had risk factors for lactic acidosis in their medical history. The risk factors, admission diagnosis, treatment and outcome (30 days after admission) are summarized in table 2. Five out of the 16 patients with MALA died (mortality rate 31%).

**Table 1 Demographic and laboratory data of patients with MALA**

| Patient | Gender | Age (yr) | pH | Lactate (mmol/l) | Metformin (mg/l) | Metformin dose (mg/day) | Creatinine history (umol/l) | MDRD (ml/min/ 1.73m²) | Creatinine admission (umol/l) | MDRD (ml/min/1.73m²) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | F | 67 | 7.05 | 19.0 | 2.9 | 1000 | 448 | 8 | 478 | 8 |
| 2 | F | 66 | 7.12 | 13.5 | 19.4 | 2550 | 236 | 18 | 640 | 6 |
| 3 | F | 75 | 7.03 | 16.5 | 5.0 | 1500 | 105 | 44 | 266 | 15 |
| 4 | F | 75 | 7.22 | 5.8 | 32.0 | 1700 | 159 | 27 | 813 | 4 |
| 5 | F | 88 | 7.30 | 11.0 | 2.3 | 850 | 94 | 49 | 126 | 35 |
| 6 | F | 78 | 6.85 | 10.2 | 4.0 | 2550 | 94 | 50 | 547 | 7 |
| 7 | M | 83 | 7.33 | 9.3 | 2.4 | 1700 | 67 | 98 | 158 | 37 |
| 8 | F | 72 | 7.16 | 14.0 | 2.3 | 2550 | 113 | 41 | 140 | 32 |
| 9 | M | 58 | 6.77 | 23.0 | 38.0 | 2550 | 114 | 57 | 1039 | 4 |
| 10 | F | 72 | 7.15 | 14.5 | 20.0 | 1700 | 731 | 5 | 814 | 4 |
| 11 | F | 77 | 7.18 | 11.1 | 25.4 | 1500 | 144 | 31 | 960 | 3 |
| 12 | F | 68 | 7.07 | 9.9 | 22.0 | 2550 | 126 | 37 | 706 | 5 |
| 13 | F | 78 | 6.94 | 20.3 | 44.0 | 1500 | 150 | 29 | 612 | 6 |
| 14 | M | 64 | 7.18 | 12.7 | 0.4 | 1700 | 82 | 82 | 123 | 51 |
| 15 | M | 70 | 6.95 | 23.2 | 0.7 | 1000 | 124 | 50 | 125 | 50 |
| 16 | F | 73 | 7.31 | 6.7 | 1.2 | 1000 | 64 | 79 | 86 | 56 |
| Average | | 73 | 7.10 | 13.8 | 13.9 | 1744 | 178 | 44 | 477 | 20 |
| Standard deviation | | 7.4 | 0.16 | 5.3 | 14.9 | 627 | 174 | 26 | 333 | 20 |
| Minimum | | 58 | 6.77 | 5.8 | 0.4 | 850 | 64 | 5 | 86 | 3 |
| Maximum | | 88 | 7.33 | 23.2 | 44.0 | 2550 | 731 | 98 | 1039 | 56 |





**Table 2 Risk factors, admission diagnosis, treatment and outcome of patients with MALA**

| Patient | Risk factors | Admission diagnosis | Treatment | Outcome |
|---|---|---|---|---|
| 1 | CRF | Hemorrhagic shock, liver failure | HD | Death |
| 2 | CRF | Dehydration by vomiting, acute renal failure | HD | Survival |
| 3 | - | Myocardial infarction, liver failure, acute renal failure | CVVHDF | Death |
| 4 | CRF, heart failure | Myocardial infarction, shock, acute renal failure | CVVHDF | Survival |
| 5 | Heart failure, COPD | Pneumonia, dehydration, liver failure | No dialysis | Survival |
| 6 | Heart failure | Dehydration, bradycardia, shock, acute renal failure, | No dialysis | Death |
| 7 | - | Myocardial infarction, shock, acute renal failure, liver failure | No dialysis | Survival |
| 8 | CRF | Myocardial infarction, shock, acute renal failure, liver failure | HD | Death |
| 9 | – | Dehydration, acute renal failure | HD | Survival |
| 10 | CRF | Metformin overdose | HD, CVVH | Survival |
| 11 | CRF | Dehydration by diarrhea, acute renal failure | HD | Survival |
| 12 | CRF | Dehydration, acute renal failure | HD | Survival |
| 13 | CRF, COPD | Dehydration by fever and diarrhea, acute renal failure | CVVH | Survival |
| 14 | Heart failure, COPD | Cardiogenic shock, liver failure, acute renal failure | No dialysis | Death |
| 15 | Alcohol abuses | Myocardial infarction, heart failure, acute renal failure | HD, CVVHDF | Survival |
| 16 | - | Anaphylactic shock | No dialysis | Survival |

CRF chronic renal failure

HD haemodialysis

CVVH continuous venovenous haemofiltration

CVVHDF continuous venovenous haemodiafiltration

## Incidence of MALA

The study period of observation was 8.7 years. In 2000 the hospital referral area had 160,357 and in 2008 180,226 inhabitants, so the average population in the study period was 171,483. In 2008 the studied 53 general practices in the hospital referral area had 156,458 registered patients, 7,619 of which had DM. As 90% of DM patients have type 2, we estimated there were 6,857 type 2 DM patients in the 53 general practices, yielding a type 2 DM prevalence of 4,38% of the population. In the hospital referral area this resulted in an estimated 7,515 type 2 DM patients in the study period. Analysis of the prescription data of the 53 general practices showed that 3,599 patients, this is 52% of the type 2 DM patients used metformin. Extrapolation of this prescription rate to the hospital area population indicates that there were 3,944 patients at risk of developing MALA each year. In the 8.7 year study period there were 34,316 patient-years at risk. With 16 MALA cases, the incidence of MALA was 16 per 34,316 patient-years, or 47 per 100,000 patient-years.



## Correlation between metformin serum concentration, lactate and outcome

The correlation coefficient between metformin serum concentration and lactate concentration in patients with MALA was 0.19 (p=0.47). In survivors, the mean metformin serum concentration was significantly higher (18.9 mg/l) than in non-survivors (2.9 mg/l, p=0.006, figure 1). The mean metformin dosage was 1,691 mg/day in survivors and 1,860 mg/day in non-survivors. There was no significant difference between the mean plasma lactate concentration in survivors (13.5±6.2 mmol/l) and non-survivors (14.5±3.4 mmol/l, p=0.68).

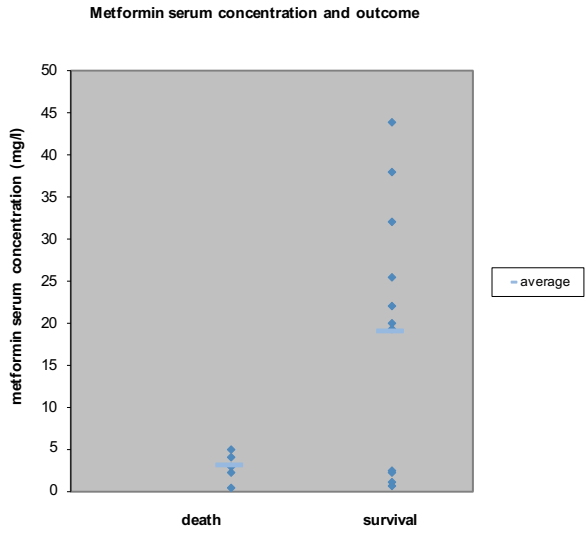


**Figure 1 Metformin serum concentration and outcome**

## Discussion

The incidence of metformin associated lactic acidosis (MALA) assessed by metformin serum concentrations in our study was 47 cases per 100,000 patient-years. This is 5 to 16 times higher than the incidence of 3 to 9 per 100,000 patient-years reported in previous studies.[2-4, 15-17] We used the same criteria for the diagnosis of MALA: arterial pH below 7.35 and lactate concentration above 5.0 mmol/l in patients using metformin. In our study, identification of MALA cases was based on metformin serum concentration measurements confirming the use of metformin in the patients with MALA. The incidence of MALA in our study was accurately calculated from the DM prevalence and metformin prescription data of 53 general practices covering 91% of the hospital referral area. Emslie-Smith et al.[8] found one MALA case in 4,600 patient-years (22 in 100,000 patient years). Nyirenda et al.[18] found 10 cases and an incidence of 30 per 100,000 patient-years. In the Fremantle Diabetes Study, the incidence of lactic acidosis was 57 per 100,000 patient-years in patients using metformin.[19] These studies and the present study demonstrate that the incidence of MALA is higher than previously reported. In studies reporting a low incidence of MALA, patients on metformin who developed lactic acidosis may not have been labeled as MALA cases, because concominant risk factors for lactic acidosis or comorbid conditions were held responsible for the lactic acidosis.[3,4,16,17] Similarly, in our study 69% of the MALA cases had at least one risk factor for lactic acidosis before admission and 81% of the patients had renal failure, a major potential risk factor for MALA, on admission. The frequent presence of risk factors for lactic acidosis in MALA cases raises the question to what extent metformin contributes to the development of lactic acidosis.[13] Findings against metformin as the only cause of lactic acidosis in type 2 DM are published data that the incidence of lactic acidosis in type 2 DM patients using metformin is not higher than with other oral antidiabetic agents or than before the introduction of metformin.[14,15,17,19,20] In our study, we found no significant correlation between the metformin serum concentration and the lactate concentration, which is in agreement with a previous reported study.[21] On the other hand, the numerous cases of metformin accumulation due to overdose or acute renal failure demonstrate that metformin can cause lactic acidosis in the absence of pre-existing risk factors for lactic acidosis or comorbid conditions.[22-30] Also in our study, six of the 16 patients had lactic acidosis due to metformin accumulation caused by renal failure (mean creatinine 795±175 µmol/l, MDRD GFR 4.7±1.2 ml/min/1.73 $m^2$) without cardiac or liver disease. These patients had a mean lactate concentration of 15.4±5.2 mmol/l and mean metformin serum concentration of 28.1±10.4 mg/l. Treatment consisted of rehydration and/or renal replacement therapy, resulting in survival in all six patients. The other 10 patients had more severe illnesses such as cardiogenic shock or

liver failure, but less severe renal failure (mean creatinine 286±245 μmol/l, MDRD GFR 30±20 ml/min/1.73 $m^2$), and therefore lower metformin concentrations (mean 5.3±9.5 mg/l). Their lactate levels were similarly elevated (mean 12.7±5.5 mmol/l), but this was probably caused by circulatory failure rather than by metformin. The severity of the underlying condition may have resulted in the high mortality rate in this group (five out of 10 patients). Apparently, the extent to which metformin contributes to lactic acidosis depends on the underlying disease. The difference in underlying disease also explains why metformin serum concentrations were much higher in survivors (18.9 mg/l) than non-survivors (2.9 mg/l), as previously described by Lalau.[21,31] It has been hypothesized that the higher metformin serum concentrations in survivors may reflect a beneficial effect of metformin in type 2 DM patients.[21] As the underlying diseases were different in survivors and non-survivors, this cannot be concluded from our study. An alternative explanation for the lack of correlation of the metformin serum concentration with lactate and the inverse relation with outcome may be that the metformin serum concentration does not reflect metformin's tissue effects. Metformin is regarded as an intracellular toxin, which may accumulate in erythrocytes and tissues, notably the mucosa of the human intestine.[32] On the other hand, the correlation between plasma and erythrocyte metformin concentrations was found to be high, so metformin serum concentration measurements do may adequately reflect its tissue effects.[33]



## Conclusion

The incidence of MALA estimated from metformin serum concentration measurements in type 2 DM patients is 5 to 16 times higher than reported in the literature. MALA is probably caused by the frequent use of metformin in the presence of risk factors for lactic acidosis. Metformin serum concentration measurements may aid in the timely diagnosis and therapy of MALA. The outcome of MALA is determined by the underlying disease, rather than by metformin itself.

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