Incidence of Lactic Acidosis in Patients With Type 2 Diabetes With and Without Renal Impairment Treated With Metformin: A Retrospective Cohort Study

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OBJECTIVE

To determine whether the use of metformin in type 2 diabetic patients with various kidney functions is associated with an increased risk of lactic acidosis (LA).

RESEARCH DESIGN AND METHODS

This study was a retrospective analysis of U.K. patient records from the Clinical Practice Research Datalink database from 1 January 2007 to 31 December 2012. Inclusion criteria were *1*) diagnosis of type 2 diabetes before 1 January 2007, *2*) treatment with metformin, and *3*) at least one assessment of renal function between 2007 and 2012. Renal function was assessed by glomerular filtration rate and categorized as normal (N), mildly reduced (Mi), moderately reduced (Mo), or severely reduced (Se) function. The outcome of the study was LA.

RESULTS

A total of 77,601 patients treated with metformin for type 2 diabetes were identified. There were 35 LA events (10.37 [95% CI 7.22–14.42] per 100,000 patient-years) of which none were fatal and 23 were linked to a comorbidity. No significant difference in the incidence of LA was observed across N, Mi, Mo and Se renal function groups (7.6 [0.9–27.5], 4.6 [2.00–9.15], 17 [10.89–25.79], and 39 [4.72–140.89] cases per 100,000 patient-years, respectively).

CONCLUSIONS

The overall LA incidence rate for patients on metformin in this study was within the range of rates reported in the literature for patients with type 2 diabetes, and no significant difference was observed among patients with N, Mi, Mo, and Se function.

Metformin is a widely used antihyperglycemic agent recommended by both the American Diabetes Association and the European Association for the Study of Diabetes as the first-line type 2 diabetes treatment in all patients receiving a new diagnosis, regardless of age (1). It enhances the sensitivity of both hepatic and peripheral tissues to insulin. In addition, metformin improves glycemic control and the oxidative disposal of glucose and lactate in the body, without altering

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muscle lactate metabolism, plasma lactate concentration, or plasma lactate turnover (2). Metformin is eliminated primarily unchanged by the kidneys by both filtration and active tubular secretion (3). Renal clearance of metformin decreases in proportion to decreasing renal function, which can be measured by the estimated glomerular filtration rate (GFR). One of the most important known risk factors for elevated metformin concentration is the inability to clear the drug efficiently due to renal impairment (4). The relationship between metformin clearance and estimated GFR indicates that the maximum dosage of metformin should be decreased in line with impaired renal function. All diabetic patients, especially those with chronic kidney disease (CKD), may be at risk for more rapid decline in their renal function, and 10–40% of those with type 2 diabetes eventually experience kidney failure (3,5).

Lactic acidosis (LA) is a rare event, with an estimated incidence of 4.3 cases per 100,000 person-years in metformin users (6,7). LA is caused by the buildup of lactic acid in the bloodstream. It is characterized by an arterial lactate level $\geq$5 mmol/L and a blood pH $\leq$7.35, and occurs when oxygen levels in the body drop (hypoxia). The occurrence of LA in type 2 diabetes is of great concern because the mortality rate of LA can be as high as 50% (8).

There is a significant divergence in opinion about whether metformin is associated with LA, mainly because a prior biguanide-phenformin was removed from the market as a result of a strong association with LA. Although, no case of LA was recorded in the clinical trials of metformin, which included >70,000 patient-years of exposure to metformin treatment (7,9,10), a secondary analysis of >41,000 person-years in type 2 diabetes showed that the incidence of LA in diabetic patients not exposed to metformin was between 9.7 and 16.7 per 100,000 person-years (11). Previous studies of metformin tolerability demonstrated safe therapeutic use of metformin in patients with no renal risk factors (12), but no real-life evidence has supported its safe use in patients with various levels of renal impairment. The objective of this study was to determine whether the use of metformin is associated with an increased risk of LA in patients with normal and mildly, moderately, or even severely reduced kidney function in a real-world setting.

RESEARCH DESIGN AND METHODS

Study Design and Data Source

This study was performed through the Clinical Practice Research Datalink (CPRD) database. CPRD is the British National Health Service observational data and interventional research service and is the primary data source of patients in the U.K. Its roots were established in 1987, and the database now contains data collected from general practitioners from 545 practices around the U.K., accounting for 13 million total patients, 5.2 million of whom are currently active. This translated into 68 million patient-years of data in December 2012.

Study Population

The study included patients with records from 1 January 2007 through 31 December 2012. Eligibility was defined as any valid database record at least 180 days before the index date. The index date was defined as the date that the patient began his or her most recent metformin treatment. Patients were grouped by metformin monotherapy and combination metformin therapy with other oral antidiabetes drugs (metformin combo). The censor date was defined as the earliest date of an LA event, death, or end of study period (31 December 2012). If a patient started treatment before 2007, he or she was given an index date of 1 January 2007. Study inclusion criteria were type 2 diabetes diagnosis before the start of the study, continuous database registration from 1 January 2007 until the censor date, metformin treatment, and a CKD or serum creatinine test assessment. The population was categorized into one of four mutually exclusive groups according to the latest known value in the study period: normal kidney function (CKD stage 1 diagnosis or GFR >90 mL/min/1.73 m^2), mildly impaired kidney function (CKD stage 2 diagnosis or GFR >60 or $\leq$90 mL/min/1.73 m^2), moderately impaired kidney function (CKD stage 3 diagnosis or GFR >30 or $\leq$60 mL/min/1.73 m^2), and severely impaired kidney function (CKD stage 4 or stage 5, end-stage renal disease, or GFR $\leq$30 mL/min/1.73 m^2).

Outcomes of Interest

The primary end point of the study was the incidence rate of LA in metformin-treated patients with type 2 diabetes by CKD stage. Events were captured using ICD-9 code 276.2. An LA event was defined as fatal if death occurred within 14 days (i.e., no more record of further diagnosis, procedure, prescription for >14 days after the event, was considered a proxy of LA-related death). The secondary end point was the proportion of patients with normal or mildly, moderately, and severely impaired renal function. In addition, we analyzed potential proximal causes of LA.

Data Analysis

Descriptive statistics, including patient numbers and proportions, were performed for the entire cohort and stratified by age, sex, level of kidney impairment, and treatment group. Exposure was calculated from the index date to the end of the study, date of an event, or database cutoff date. Incidence rates for patients with various levels of kidney impairment were compared. The 95% CIs were calculated for the upper and lower limits of the incidence rates. Fisher exact tests were used to calculate differences in incidence rates and incidence rate ratios by level of kidney impairment. Exploratory statistical comparisons of LA incidence were performed across renal function groups, with normal kidney function as a reference.

RESULTS

Patient Characteristics

The study population included 77,601 patients, accounting for a total exposure of 337,590 patient-years. Within this group, 6,038 (7.8%) patients had normal kidney function, 38,836 (50%) mild kidney impairment, 31,278 (40.3%) moderate kidney impairment, and 1,449 (1.9%) severe kidney impairment. Patient demographics, stratified by kidney function, are presented in Table 1. The majority of patients were at least 65 years old on their index date (55.2%). Although the majority of study subjects were male (57.1%), female subjects made up a larger portion of the population with moderately and severely reduced kidney function (51.8% and 57.5%, respectively). Metformin combination treatment was the most common

Table 1—Patient demographics and treatment according to the level of kidney function

Demographic	All patients	Normal	Mildly reduced	Moderately reduced	Severely reduced
Cohort	77,601 (100)	6,038 (100)	38,836 (100)	31,278 (100)	1,449 (100)
Age on index date					
18–34 years	419 (0.5)	210 (3.5)	196 (0.5)	10 (0.0)	3 (0.2)
35–44 years	3,134 (4.1)	946 (15.7)	1,973 (5.1)	208 (0.7)	7 (0.5)
45–54 years	10,498 (13.5)	1,923 (31.8)	7,109 (18.3)	1,405 (4.5)	61 (4.2)
55–64 years	20,726 (26.7)	1,762 (29.2)	12,934 (33.3)	5,839 (18.7)	191 (13.2)
65–74 years	24,136 (31.1)	883 (14.6)	11,250 (29.0)	11,599 (37.1)	404 (27.9)
75+ years	18,688 (24.1)	314 (5.2)	5,374 (13.8)	12,217 (39.1)	783 (54.0)
Sex					
Male	44,307 (57.1)	4,188 (69.4)	24,426 (62.9)	15,077 (48.2)	616 (42.5)
Female	33,294 (42.9)	1,850 (30.6)	14,410 (37.1)	16,201 (51.8)	833 (57.5)
Metformin dose					
100 mg	276 (0.4)	19 (0.3)	110 (0.3)	138 (0.4)	9 (0.6)
500 mg	59,449 (76.6)	4,469 (74.0)	29,485 (75.9)	24,382 (78.0)	1,113 (76.8)
750 mg	862 (1.1)	63 (1.0)	448 (1.2)	343 (1.1)	8 (0.6)
850 mg	11,707 (15.1)	984 (16.3)	5,975 (15.4)	4,533 (14.5)	215 (14.8)
1,000 mg	4,869 (6.3)	479 (7.9)	2,691 (6.9)	1,651 (5.3)	48 (3.3)
Unknown	438 (0.6)	24 (0.4)	127 (0.3)	231 (0.7)	56 (3.9)
Type of treatment					
Metformin solo	36,058 (46.5)	2,632 (43.6)	17,693 (45.6)	15,082 (48.2)	651 (44.9)
With insulin	10,298 (13.3)	842 (14.0)	4,832 (12.4)	4,386 (14.0)	238 (16.4)
Without insulin	25,760 (33.2)	1,790 (29.6)	12,861 (33.2)	10,696 (34.2)	413 (28.5)
Metformin combo	41,543 (53.5)	3,406 (56.4)	21,143 (54.4)	16,196 (51.8)	798 (55.1)
With insulin	5,195 (6.7)	465 (7.7)	2,537 (6.5)	2,066 (6.6)	127 (8.8)
Without insulin	36,348 (46.8)	2,941 (48.7)	18,606 (47.9)	14,130 (45.2)	671 (46.3)

Data are *n* (%).

therapy among all treated patients (53.5%). The most widely prescribed dose was 500 mg (76.6%). The most frequent comorbidities were hypertension (45%), hypertensive disease (31%), ischemic heart disease (12%), angina pectoris (14%), and obesity (13%). All proportions were compatible with a type 2 diabetic population and were correlated with renal function (Table 2).

LA Patient Characteristics

There were 35 LA events in the study population (Table 3). The majority of patients with an LA event were at least 65 years old on their index date (62.1%). The LA population was split nearly evenly by sex (18 male, 19 female). Of the 23 cases with moderately reduced kidney function, 16 had a condition that could have placed them at an increased risk for LA independent of metformin use (e.g., acute kidney failure, ischemic heart disease, heart failure). In the eight patients with LA and mildly reduced kidney function, three had conditions outside CKD that put them at risk for LA.

LA was more frequently reported in patients treated with combination therapy than with metformin alone (20 of 35). The 500 mg metformin dose was the most commonly prescribed dose in 78.4%. The mean known duration of diabetes for all LA patients was 107 months. None of the LA events recorded were fatal. The average time to LA event from the start of metformin treatment was 32 months.

Table 2—Comorbidities by renal function level in the study population

	Normal	Mildly reduced	Moderately reduced	Severely reduced	All patients
Hypertension	33	41	52	47	45
Hypertensive disease	20	28	38	44	31
Angina pectoris	7	11	18	22	14
Ischemic heart disease	5	9	16	22	12
Obesity	17	13	12	13	13

Data are %.

Incidence Rate of LA by CKD

The incidence rates of LA stratified by kidney function are shown in Table 3. The overall incidence of LA in patients receiving metformin was 10.37 per 100,000 patient-years (95% CI 7.22–14.42). No significant difference in the incidence of LA was observed across normal, mild, moderate, and severe renal function groups (7.6 [0.9–27.5], 4.6 [2.00–9.15], 17 [10.89–25.79], and 39 [4.72–140.89] cases per 100,000 patient-years, respectively). The incidence rate ratios for metformin-treated patients with severely, moderately, and mildly reduced kidney function compared with patients with normal kidney function were 5.26 (P = 0.12), 2.27 (P = 0.41), and 0.61 (P = 0.63), respectively (Table 4).

CONCLUSIONS

To our knowledge, this was the first large-scale study (77,601 patients) to evaluate the incidence of LA by renal function in patients receiving metformin

Table 3—Incidence rates of LA in metformin-treated patients stratified by CKD stage

Subgroup	Patients	LA events	Person-years	Incidence rate per 1,000 person-years (95% CI)
All patients	77,601	35	337,590.2	10.37 (7.22–14.42)
Kidney function				
Normal	6,038	2	26,266.0	7.61 (0.92–27.51)
Mildly reduced	38,836	8	172,354.4	4.64 (2.00–9.15)
Moderately reduced	31,278	23	133,841.8	17.18 (10.89–25.79)
Severely reduced	1,449	2	5,127.9	39.00 (4.72–140.89)

in an observational setting. The prevalence of metformin treatment in the source data set was similar to values previously reported (13–15). This study also featured a patient-level data segment that allowed for evaluating the potential proximal causes for LA.

Several inconclusive studies attempted to assess the association among metformin, its dose, and LA (16–18). In the current study, the overall incidence rate of LA was 10.37 per 100,000 person-years, which is in the range of the incidence rates of LA found in the literature (3.0–16.7 per 100,000 person-years) (11,19–22) for both metformin- and nonmetformin-treated patients.

Of the 23 patients with LA and moderately reduced kidney function, 16 had either acute kidney failure, ischemic heart disease, heart failure, or other proximal conditions independent of metformin use. An analysis without these patients showed an incidence rate for patients with moderately reduced kidney function (without a proximal cause of LA) of 5.23 per 100,000 patient-years (compared with 17 per 100,000 patient-years in the original analysis). In the eight LA patients who had mildly reduced renal function, three had other potential proximal causes for LA. The incidence rate for LA excluding patients with proximal causes was 2.90 per 100,000 person-years (compared with 4.64 per 100,000 patients-years in the original analysis). For comparison, the study by Brown et al. (11), which aimed to estimate the incidence of LA in type 2 diabetic patients before metformin came to the market, placed the risk of LA between 9.7 and 16.7 per 100,000 person-years.

In the present study, the incidence rate of LA in patients receiving metformin as monotherapy was lower than that in patients receiving metformin combination therapy, as previously reported by Bodmer et al. (23). Of the 35 metformin patients with LA, 20 were concomitantly taking other oral antidiabetic drugs. Patients on metformin combination therapy were taking sulfonylureas, with gliclazide and glimepiride being the most common. Metformin and sulfonylurea combination therapy has been shown to be more effective than either therapy alone for glycemic control (24). Some studies suggested that the risk of LA associated with sulfonylurea monotherapy is higher than for metformin monotherapy (23,25). To document the respective risk of LA by treatment, demographics, comedications, and comorbidities, another study design comparing patients with similar characteristics but different treatment schemes would be helpful, but it was not the objective of the current study, which was intended to be descriptive. Matching patients would have resulted in less-representative populations and a potential underestimation of the number of LA cases. More research is needed to accurately document the respective risks of LA induced by other treatments.

Table 4—Comparison of IRRs among LA incidence rates with respect to normal kidney function group

Comparison group	IRR	IRR_L	IRR_U	Fisher exact two-sided *P* value
Normal kidney function	1	1	1	1
Mildly reduced kidney function	0.61	0.12	5.26	0.63
Moderately reduced kidney function	2.27	0.56	20.00	0.41
Severely reduced kidney function	5.26	0.37	71.43	0.12

IRR, incidence rate ratio; IRR_L, lower bound of the incidence rate ratio; IRR_U, upper bound of the incidence rate ratio.

The study has several limitations. Inherent to the observational study design, several confounders may have played a role in the results, namely age, health status, disease severity, comorbidities, and concomitant medications. Patients taking metformin may have been prescribed metformin well before the beginning of the study period; therefore, the duration of therapy may be underestimated. Other limitations include a potential selection bias of patients based on the availability of data on their renal function. Because the CPRD database contains information on prescribed rather than dispensed medications, an underestimation of treatment exposure is possible, although no differential bias related to renal function would be anticipated. Finally, immortal time bias resulting from the fact that included patients were required to be free of death or LA in the 180 days before the observation period might have led to a biased subpopulation of patients with better characteristics compared with the general population (because they were basically all survivors during the run-in period). Although one cannot completely rule out this bias, it should be of marginal impact on the main findings from this study. Indeed, diabetes is a slowly progressing disease. Immortal time bias would have more of an impact in studies on diseases that can rapidly lead to acute conditions, such as chronic obstructive pulmonary disease, asthma, and acute myocardial infarction (26). Additionally, all subjects were exposed to the same drug, so the possibility for a differential outcome related to drug or comparator is nonexistent, and comorbidities in the run-in period were representative of a general population with type 2 diabetes.

In conclusion, this study focused on the risk of LA in metformin-treated type 2 diabetic patients with various levels of kidney function in a large-scale electronic medical records database from the U.K. The majority of metformin-treated patients (92.2%) also had some level of renal impairment. With 35 events in >330,000

patient-years (incidence rate, 10.37 per 100,000 patient-years), LA was rare. The differences in incidence rates between metformin patients with normal kidney function and metformin patients with impaired kidney function were not significant. There were no fatal cases. More research is needed to understand the exact etiology of LA in patients with type 2 diabetes.

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