# Lactic Acidosis Rates in Type 2 Diabetes

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**OBJECTIVE** — To provide a context for the interpretation of lactic acidosis risk among patients using metformin, we measured rates of lactic acidosis in patients with type 2 diabetes before metformin was approved for use in the U.S.

**RESEARCH DESIGN AND METHODS** — Using electronic databases of hospital discharge diagnoses and laboratory results maintained by a large, nonprofit health maintenance organization (HMO), we identified possible lactic acidosis events in three geographically and racially diverse populations with type 2 diabetes. We then reviewed hard-copy clinical records to confirm and describe each event and determine its likely cause(s).

**RESULTS** — From >41,000 person-years of experience, we found four confirmed, three possible, and three borderline cases of lactic acidosis. In each case, we identified at least one severe medical condition that could have caused the acidosis. The annual confirmed event rate is similar to published rates of metformin-associated lactic acidosis.

**CONCLUSIONS** — Lactic acidosis occurs regularly, although infrequently, among persons with type 2 diabetes, at rates similar to its occurrence among metformin users. The medical conditions with which both metformin-associated and naturally occurring lactic acidosis cooccur are also its potential causes. The observed association between metformin and lactic acidosis may be coincidental rather than causal. This possibility merits further study.

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Lactic acidosis is a life-threatening condition characterized by low arterial pH (<7.35) and elevated arterial lactate levels (>5.0 mEq/l). It is the most common metabolic acidosis in humans (1) and is usually a late-stage sequela of serious medical conditions such as sepsis, hypoxia, and cardiac failure (2–4). Lactic acidosis is also precipitated by phenformin, a biguanide formerly used to control hyperglycemia in type 2 diabetes. The sale of phenformin was suspended in the U.S. in 1977 because of unacceptably high rates of lactic acidosis. Metformin, a modified biguanide, has been widely used outside the U.S., with considerably fewer reported cases of lactic acidosis than were reported with phenformin. Concern about lactic acidosis, however, delayed the introduction of metformin in the U.S. until May 1995.

This concern about lactic acidosis has also led to recommendations that metformin not be used, or be used with caution, in persons with chronic conditions that can themselves cause lactic acidosis (e.g., significant cardiac and pulmonary disease) (5–9). These restrictions significantly reduce—by half, according to one study (10)—the number of persons who could benefit from metformin's availability.

Although the proportion of patients for whom the use of metformin is considered risky or contraindicated is high, lactic acidosis associated with metformin use is rare. The Food and Drug Administration (FDA) recently reported a rate of five cases per 100,000 persons who used metformin for some period, between May 1995 and 30 June 1996, its first year of availability in the U.S. (9). Population-based data from Sweden for the years 1987 through 1991 yielded an incidence of 2.4 cases per 100,000 person-years (11). Earlier data from France, Sweden, and Switzerland suggested rates of 1 to 15 cases per 100,000 person-years (11,12).

Virtually all reported cases of metformin-associated lactic acidosis have occurred in individuals with severe acute conditions that can themselves cause lactic acidosis (9,11–14). Whether the use of metformin was a cause or coincidence in these cases of lactic acidosis remains unclear. If metformin use or accumulation does not cause or exacerbate lactic acidosis, rates of lactic acidosis should be similar in treated and untreated groups. However, population-based rates of lactic acidosis have never been estimated for patients with type 2 diabetes who have not been exposed to metformin. Data on rates among metformin users have been obtained instead from case reports and from reporting systems for adverse drug events. It has thus been impossible to compare from the literature the rates of lactic acidosis associated with metformin use with rates not associated with metformin use. Fortunately, the delayed introduction of metformin in the U.S. provides an opportunity to study lactic acidosis rates among persons with diabetes before any treatment with metformin had begun.

In this study, we calculate the rate of lactic acidosis in representative, diverse populations of U.S. residents with type 2 diabetes in whom metformin therapy had not yet been introduced. Our aim is to estimate the naturally occurring rate of lactic acidosis among people with diabetes and to allow comparison to the rates observed among metformin users. Similar rates might justify a reexamination of the assumption that metformin causes most of the cases of lactic acidosis associated with its use and of guidelines that now prevent access to metformin for many patients.

## RESEARCH DESIGN AND METHODS

### Study populations and research setting

Study subjects were members of three regions of Kaiser Permanente (KP), a large not-for-profit group-model health mainte-

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**Abbreviations:** FDA, Food and Drug Administration; HMO, health maintenance organization; KP, Kaiser Permanente.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

nance organization (HMO). The three regions studied were the Northwest (Oregon) region (KP-Northwest), the Hawaii region (KP-Hawaii), and the Georgia region (KP-Georgia). Only patients who were members of the health plan for 12 full months in the years 1993 or 1994, or both, were included. We identified patients with diabetes through the diabetes registries maintained in Oregon and Hawaii and through the creation of an ad hoc registry for Georgia.

The KP-Northwest diabetes registry was created in 1987. The HMO members included in this registry are defined as having diabetes if they received a pharmacy-dispensed antidiabetic drug, were discharged after 1986 from an acute care hospital with any listed diagnosis of diabetes, were identified as having diabetes by providers or diabetes educators, or (if identified only through the purchase of blood glucose–monitoring supplies) had their diagnosis confirmed by an endocrinologist's review of their medical record. In the present study, we presumed that KP-Northwest registrants had type 2 diabetes if they were newly diagnosed after the age of 45 years or if they were diagnosed at <46 years of age but had no insulin dispensed until at least 2 years after diagnosis.

Patients were included in the KP-Hawaii registry if they received an antidiabetic drug, had an inpatient discharge diagnosis of diabetes, or had an $HbA_{1c}$ test result >6.8% or a fasting glucose test result >160 mg/dl. We eliminated registrants with possible type 1 diabetes and gestational diabetes by restricting the study population to registrants who were ≥45 years of age. We created a KP-Georgia diabetes registry by using the KP-Northwest algorithm but not the data from educators or provider communications. To eliminate non–type 2 diabetes patients from the Georgia registry, we selected only subjects who were ≥45 years old at the beginning of the 1993 or 1994 study years.

Independent review of the KP-Northwest registry has shown it to be >99% sensitive and >99% specific for diagnosed diabetes for the years of this study. We estimate the KP-Georgia registry to be ~85% sensitive and >95% specific. The sensitivity and specificity of the KP-Hawaii registry are intermediate between the KP-Georgia and KP-Northwest registries.

### Identification and confirmation of lactic acidosis events

We used a two-stage strategy to find lactic acidosis events in each region, first identifying potential events and then examining these events in detail. We identified potential lactic acidosis events by searching management and clinical databases for at least one of the following indications:

- Any listed inpatient discharge diagnosis of acidosis, *International Statistical Classification of Diseases, 10th Revision (ICD-10)* code 276.2
- A serum lactate test result ≥2.2 mEq/l (inpatient or outpatient test)
- A serum $HCO_3$ test result ≤18 mEq/l in the presence of an anion gap [Na − (Cl + $HCO_3$)] ≥15 mEq/l (inpatient or outpatient test)

### Confirmation and classification of lactic acidosis

A physician in each region obtained hard-copy inpatient and outpatient medical records for each patient with a potential lactic acidosis event and used a formal abstraction form to review each event. The abstraction form elicited data to confirm a diagnosis of lactic acidosis and identify its proximal cause(s). We considered an event to be confirmed if a serum lactate test result >5.0 mEq/l was recorded (4). If a serum lactate measurement was not available, we considered an event to be possible lactic acidosis if all of the following criteria were met: evidence of an anion gap acidosis [Na − (Cl + $HCO_3$) >16 mEq/l], $HCO_3$ <18 mEq/l, no elevated serum or urine ketones (to exclude diabetic ketoacidosis), and no serum creatinine measurement >2.0 mg/dl (to exclude uremic acidosis). We defined cases as borderline lactic acidosis when the serum lactate measurement was between 2.2 and 5.0 mEq/l.

### Statistical methods

Event rates were estimated as the ratio of events to total patient-years of response. We calculated 95% CIs using the normal approximation to the binomial (15).

## RESULTS

### Identification of members

In total, we obtained 41,426 person-years of data for patients with type 2 diabetes. In the Northwest region, the age of the study population was 63.6 ± 12.4 years (mean ± SD), and men represented 50.5% of this group. In Georgia, the subjects were aged 55.4 ± 8.6 years, and 54.6% of the subjects were men. In Hawaii, the subjects were aged 63.6 ± 10.8 years, and 52.5% of the subjects were men.

The Georgia subjects were younger and slightly more likely to be male than the Oregon and Hawaii subjects. Although data describing ethnicity at the individual level were not available, it is known that African-Americans represent ~40% of the Georgia population. The Hawaii population is known to comprise mostly people of Japanese, native Hawaiian, Philippine, and Pacific Island descent. The Oregon population is ~85% non-Hispanic white.

### Rates of lactic acidosis events

Frequencies of confirmed, possible, and borderline cases of lactic acidosis are displayed in Table 1. Overall, we confirmed four lactic acidosis events among 75 cases identified for medical records review, yielding a confirmed event rate of 9.7/100,000 person-years of exposure (95% CI, 0.2–19.1) Three other events, for which serum lactate measurements were not available, met criteria for anion gap acidosis without evidence of ketoacidosis or uremic acidosis. One or more of these may have been a true lactic acidosis event. Including these three events would increase the lactic acidosis rate to 16.9/100,000 person-years (4.4–29.4). In addition, we observed three borderline cases.

### Details of events

Table 2 provides a clinical summary of each confirmed, possible, and borderline case. We were able to identify a proximal medical cause in each case. Hypotension, sepsis, and congestive heart failure were the most common proximal causes. Three of the four confirmed cases ended in death. The three possible and three borderline cases were discharged alive.

**CONCLUSIONS** — Investigating a period that preceded the introduction of metformin, we used electronic data screening, followed by chart review, to observe a rate of 9.7 confirmed lactic acidosis events per 100,000 person-years in a diverse U.S. population of patients with type 2 diabetes. This rate increased to 16.9 events per 100,000 person-years when nonketoacidotic or nonuremic gap acidoses, without lactate measurements, were included.

Our estimate of 9.7–16.9 events per 100,000 person-years is indistinguishable from rates observed among metformin users based on country-wide reporting systems for adverse drug events in the U.S. (9) and Sweden (11). In the U.S. in 1995–1996, the

Table 1—*Frequency of lactic acidosis*

| | Mean age (years) | Person-years reviewed | Events reviewed | Identified lactic acidosis events | | |
|---|---|---|---|---|---|---|
| | | | | Confirmed | Possible | Borderline |
| KP-Northwest | | | | | | |
| 1993 | 63.5 ± 12.4 | 10,983 | 10 | 0 | 0 | 0 |
| 1994 | 63.7 ± 12.3 | 10,667 | 9 | 2 | 1 | 0 |
| KP-Georgia | | | | | | |
| 1993 | 55.2 ± 8.5 | 3,803 | 6 | 2 | — | 2 |
| 1994 | 55.6 ± 8.7 | 4,027 | 12 | 1 | — | 1 |
| KP-Hawaii | | | | | | |
| 1993 | — | 4,710 | 13 | 2 | 1 | 0 |
| 1994 | — | 7,236 | 25 | 3 | 1 | 0 |
| Total | | | | | | |
| 1993 | 62.6 ± 10.8 | 19,506 | 29 | 4 | 1 | 2 |
| 1994 | 64.3 ± 10.9 | 21,930 | 46 | 6 | 2 | 1 |
| Overall | — | 41,436 | 75 | 4 | 3 | 3 |
| Rate per 100,000 person-years | — | — | — | 9.7 | 7.2 | 7.2 |
| 95% CI | — | — | — | 0.2 to −19.1 | −1.0 to 15.4 | −1.0 to 15.4 |

Data are means ± SD or *n*.

FDA received approximately five reports of metformin-associated lactic acidosis per 100,000 mostly part-year users (9). The 1987–1991 Swedish rate was 2.4/100,000 person-years (11). Earlier data from Sweden showed rates of 10/100,000 person-years between 1981 and 1987, and 15/100,000 person-years in 1977–1981 (11).

Our results probably underestimate the pre-metformin lactic acidosis rate because lactic acidosis is not always noted in medical records or confirmed by laboratory testing. The condition is often presumptive (not requiring a test), and the need for rapid action may preclude testing. In addition, we used conservative criteria to establish confirmed cases.

Uncertainties are inevitable when researchers undertake comparisons across countries, time periods, and methods of ascertainment. Just as we undoubtedly undercounted lactic acidosis events before the introduction of metformin, reporting systems for adverse drug events may miss such occurrences, despite the fact that reporting fatal and serious drug reactions has been "compulsory" in Sweden since 1975 (11) and is compulsory in the U.S. for pharmaceutical firms (but not for pharmacists or clinicians). On the other hand, clinicians may be more alert for lactic acidosis in patients who have used metformin and may be more likely to obtain a diagnostic serum lactate measurement.

It is also possible that our pre-metformin rates are comparatively elevated because clinicians avoid prescribing metformin to patients in high-risk diabetic subgroups, whereas our population included all patients with type 2 diabetes. Increasing therapeutic selectiveness may explain why Swedish event rates in late 1970s and early 1980s are higher than more recent rates in Sweden and the U.S. Our pre-metformin rates, however, are similar to the earlier Swedish rates.

The similarity of lactic acidosis rates in populations with and without access to metformin suggests the possibility that lactic acidosis among metformin users is related more to their underlying medical conditions than to their use of metformin. Virtually all reported cases of metformin-associated lactic acidosis have occurred in persons with severe acute conditions that themselves cause lactic acidosis (9,11–14), such as serious hepatic disease, which increases risk by blocking lactate metabolism (5,7,13), and conditions causing hypotension, which increase serum lactate and acidify the blood (16,17).

Of the initial 47 cases of metformin-associated lactic acidosis reported to the FDA after metformin was introduced in the U.S. in 1995, 64% involved patients with preexisting cardiac disease (9). If metformin-associated lactic acidosis occurred in healthy patients, the causative role of metformin in lactic acidosis would be easy to establish. Because these events occur in persons already at high risk for lactic acidosis, coincidence is harder to rule out.

The fact that metformin accumulates to a high level in many persons with metformin-associated lactic acidosis is often considered to be evidence for metformin's causative role. Renal impairment is important because metformin is eliminated from the body primarily through renal tubular secretion (18–21). (Unlike phenformin, metformin is not extracted by the liver, nor is it metabolized [22–25].) Renal insufficiency therefore leads to drug accumulation when metformin is not withdrawn. Of the 20 deaths initially reported to the FDA, 80% were of patients with significant renal impairment (creatinine >1.5 mg/dl) (9). However, renal insufficiency independently leads to lactate accumulation when renal capacity for oxidative removal of lactate is compromised (5,6,26–29). Therefore, the accumulation of metformin may also be coincidence.

The possibility of a coincidental relationship is supported by a study by Lalau et al. (30) of 14 patients who experienced lactic acidosis while receiving long-term treatment with metformin. As in other studies, all subjects had severe intercurrent illness that could explain the development of lactic acidosis independent of metformin use. Ten patients had marked accumulations of metformin (usually because of failure to withdraw metformin as renal function deteriorated), but metformin accumulation was not predictive of mortality. Only one subject with metformin accumulation died, and end-stage hepatic failure was the cause of death (30).

Our results show that before the introduction of metformin, lactic acidosis was a rare but regularly occurring event among

**Table 2—*Details of lactic acidosis events***

| Type of lactic acidosis event | Serum lactate | Patient | Region | Sex | Age (years) | Race | Bicarb (mEq) | Anion gap | pH | Survival status | Other medications | Proximal cause | Other relevant medical conditions |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Confirmed (serum lactate >5.0 mEq/l) | 11.1 | 1 | Northwest | M | 48 | White | 17 | 8 | 7.15 | Dead | Atenolol, verapamil, Lopid, erythromycin | CHF | Cardiomyopathy, hypertension |
| | 13.4 | 2 | Hawaii | M | 72 | White | 14 | 21 | 7.09 | Alive | Digoxin, Lasix, Zestril, Isordil, Norvasc, sulfonylurea | Hypotension, pacemaker malfunction with symptomatic bradycardia | Peripheral vascular disease, ischemic cardiomyopathy, chronic renal insufficiency, intermittent atrial fibrillation |
| | 13.7 | 3 | Hawaii | M | 76 | White/ Hawaiian | 13 | 23 | 7.35 | Dead | Calan SR, Tagamet, sulfonylurea, insulin | Sepsis, CHF, hypotension | Colon cancer, hypertension, arrhythmia, dementia |
| | 23.7 | 4 | Hawaii | F | 62 | Chinese | 8 | 33 | 7.05 | Dead | Sulfonylurea, digoxin, spironolactone, verapamil, Calan, Carafate, Premarin | Sepsis, hypotension | Chronic hepatitis B with cirrhosis, cholelithiasis, paroxysmal atrial fibrillation, hemosiderosis, hyper-triglyceridemia |
| Possible (serum lactate unknown) | — | 5 | Georgia | F | 48 | African-American | 15 | >16 | Unknown | Alive | Insulin | Sepsis, hypotension, urinary infection | — |
| | — | 6 | Georgia | F | 58 | African-American | 8 | >16 | 7.18 | Alive | None | Sepsis | Hypertension, goiter |
| | — | 7 | Georgia | M | 54 | White | 12 | >16 | Unknown | Alive | Inderal, folic acid | Alcoholic ketoacidosis | Hypertension, gastroesophageal reflux disease, peptic ulcer disease, alcoholism |
| Borderline (serum lactate 2.2–5.0 mEq/l) | 3.0 | 8 | Hawaii | F | 64 | White/ Hawaiian | 16 | 16 | 7.21 | Alive | Aspirin, sulfonylurea, Procardia, lisinopril, Lopressor, Isordil, Lopid, Zoloft | CHF | Coronary artery disease, hypertension, renal insufficiency |
| | 3.3 | 9 | Hawaii | M | 65 | Japanese | 14 | 19 | 7.18 | Alive | Sulfonylurea | Hypotension, hypovolemia, mild diabetic ketoacidosis | Smoker |
| | 4.6 | 10 | Northwest | F | 71 | White | 8 | 19 | 7.17 | Alive | Tagamet, Pro-Banthine, amitriptyline | Alcohol/Motrin overdose, renal failure, hypotension | — |

Bicarb, bicarbonate; CHF, congestive heart failure.

patients with type 2 diabetes. As reports of lactic acidosis increase in the U.S. with the growing use of metformin, it would be a mistake to assume automatically that these cases are caused by metformin. To obtain a more precise comparison of event rates with and without exposure to metformin, research should be done to compare rates of lactic acidosis before and after metformin was introduced in the U.S. In our registry, the perceived risk of lactic acidosis currently limits access to metformin among many of the registrants who *1*) are receiving treatment with other oral agents but have poor glycemic control and are reluctant to start injecting insulin, *2*) are ineffective insulin users, or *3*) are prone to or fearful of hypoglycemia. Such patients would benefit significantly from further research that broadened their access to metformin.

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