Renal Status Among Patients Using Metformin in a Primary Care Setting

LAURENCE KENNEDY, MD[1]
WILLIAM H. HERMAN, MD, MPH[2]
FOR THE GOAL A1C STUDY TEAM

Metformin use has been associated with lactic acidosis, a rare but potentially lethal condition characterized by elevated blood lactate levels (>5 mmol/l), an increased lactate-to-pyruvate ratio, and an increased anion gap (1). Most cases of metformin-associated lactic acidosis occur in patients with preexisting conditions (e.g., renal insufficiency, hepatic impairment, or heart failure) (2). When used as labeled, metformin may not increase the risk of lactic acidosis beyond what already exists with such conditions (3–5). However, despite evidence suggesting that the risk of lactic acidosis may be reduced if metformin is avoided in patients with renal impairment, and despite the ready availability of serum creatinine tests to assess renal function, inappropriate prescribing of metformin is a concern (2,3,6–9).

The randomized, open-label Glycemic Optimization with Algorithms and Labs At Po1nt of Care (GOAL A1C) study was designed to evaluate the impact of point-of-care versus laboratory testing of glycosylated hemoglobin (A1C) and monitored versus standard titration of insulin glargine on glycemic control in patients with type 2 diabetes inadequately controlled on oral agents. This study also provided an opportunity to assess appropriateness of metformin therapy based on serum creatinine levels at enrollment in a large, predominantly primary care population. This assessment forms the basis of the current report.

RESEARCH DESIGN AND METHODS

— Eligible subjects were ≥18 years of age, had type 2 diabetes for ≥1 year, were receiving oral antidiabetic agents for ≥2 months, and had inadequate glycemic control (A1C >7.0%). Peripheral venous blood samples were obtained at baseline to measure serum creatinine levels. In addition, physicians identified patients who they believed had clinically significant nephropathy. Metformin therapy was considered inappropriate if the baseline serum creatinine level was above U.S. Food and Drug Administration–approved prescribing guidelines (i.e., ≥1.5 mg/dl [≥133 μmol/l] for men or ≥1.4 mg/dl [≥124 μmol/l] for women). Such patients could participate in the study only if metformin was discontinued at enrollment. Baseline demographic characteristics of subjects taking versus not taking metformin, and of metformin-treated subjects with elevated versus nonelevated serum creatinine levels, were compared using ANOVA for continuous variables and the χ^2 test for categorical variables. The glomerular filtration rate (GFR) was estimated in patients using metformin with the abbreviated MDRD (Modification of Diet in Renal Disease) study equation (based on serum creatinine, patient age, race, and sex) (10).

RESULTS

— The majority of subjects were treated by primary care physicians (>75%) or other nonendocrinologists (14%). Subjects with known metformin treatment status and a baseline serum creatinine measurement were enrolled (n = 6,939). Of these, 4,838 (69.7%) were taking metformin. Subjects taking metformin were slightly younger than those not taking metformin (mean age 55.8 vs. 58.6 years, respectively; $P < 0.0001$) and more likely to be men (51.1 vs. 48.9%; $P = 0.0170$). Mean duration of diabetes (between 8 and 9 years) and BMI (34.0 kg/m^2) were similar between groups. Clinically significant nephropathy was less likely to be reported among subjects taking metformin than among those not taking metformin (4.4 vs. 8.1%, respectively; $P < 0.0001$).

Of the 4,838 patients receiving metformin, 219 (4.5%) had elevated baseline serum creatinine levels (3.7% of women and 6.6% of men). The median serum creatinine level in women using metformin was 0.8 mg/dl (range 0.4–5.0, interquartile range [IQR] 0.7–1.0) compared with 1.0 mg/dl (range 0.3–5.8, IQR 0.9–1.2) in men. Distribution plots show that elevated serum creatinine levels mostly clustered between 1.6 and 3.0 mg/dl (Fig. 1*A*). Subjects with elevated serum creatinine levels tended to be older (age 63.0 vs. 55.5 years, respectively; $P < 0.0001$), to be male (68.5 vs. 50.3%; $P < 0.0001$), to have a longer disease duration (10.0 vs. 8.5 years; $P = 0.0004$), and to have a greater prevalence of clinically significant nephropathy (8.3 vs. 4.2%; $P = 0.0037$). The groups did not differ with respect to BMI.

The GFR calculation revealed that, among patients using metformin, 17.7% of females and 13.4% of males had an estimated GFR ≤60 ml · min^{-1} · 1.73 m^{-2} (Fig. 1*B*). The median GFR in women was 79 ml · min^{-1} · 1.73 m^{-2} (range 11–192, IQR 66–95) compared with 81 ml · min^{-1} · 1.73 m^{-2} (range 10–357, IQR 69–94) in men.

From the [1]Division of Endocrinology, Department of Medicine, Shands Hospital at the University of Florida, Gainesville, Florida; and the [2]Michigan Diabetes Research and Training Center, University of Michigan, Ann Arbor, Michigan.

Address correspondence and reprint requests to Laurence Kennedy, MD, Professor and Chief, Division of Endocrinology, Department of Medicine, Shands Hospital at the University of Florida, Gainesville, FL 32610. E-mail: kenneal@medicine.ufl.edu.

Received for publication 21 December 2004 and accepted 27 December 2004.

Abbreviations: GFR, glomerular filtration rate; IQR, interquartile range.

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

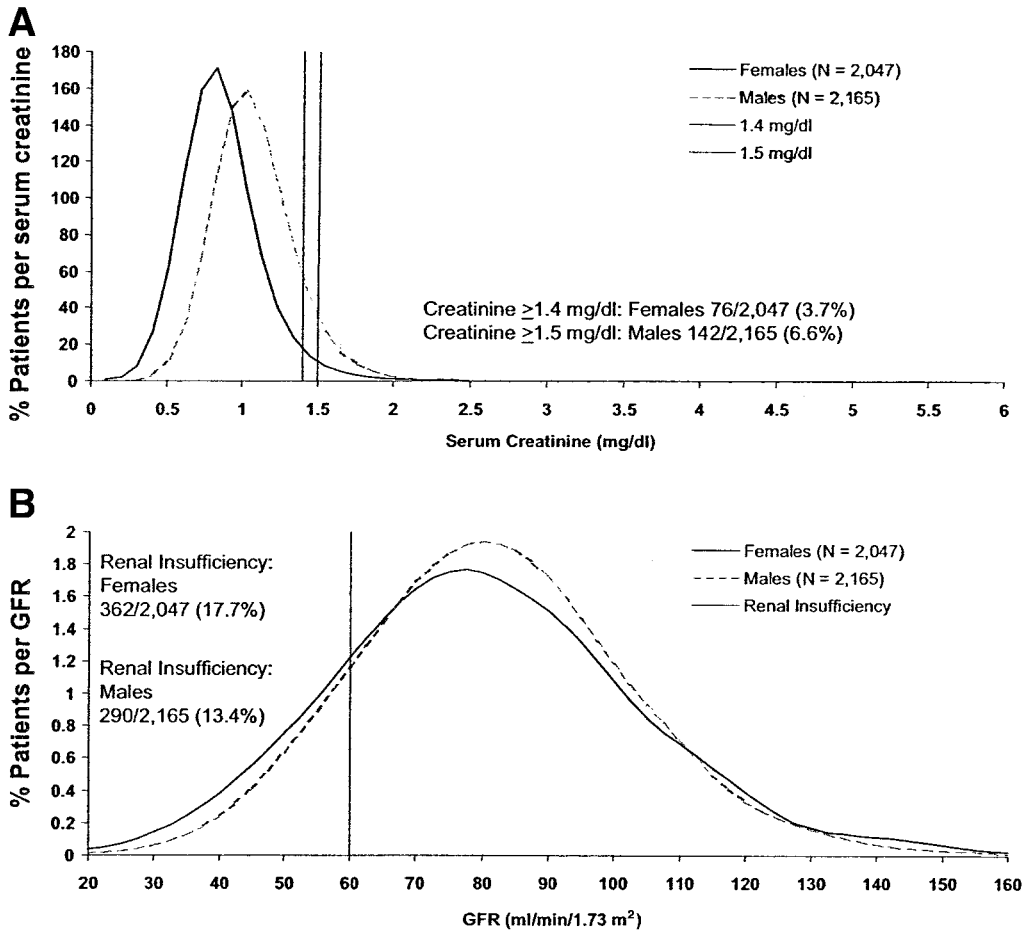

Figure 1—*Renal function in patients using metformin.* A: *Distribution of serum creatinine levels according to sex.* B: *Distribution of GFR according to sex.*

CONCLUSIONS — We report that 1 of 22 (4.5%) patients treated with metformin in general practice had serum creatinine levels exceeding predefined safety limits. This is consistent with the literature (7–9). The fact that subjects with elevated serum creatinine levels tended to be older and to have a longer duration of diabetes is not surprising, as both of these factors are associated with the development of renal impairment. Increased prevalence in men may be due to sex-specific differences in muscle mass. Because most participants in the GOAL A1C study were taking oral antidiabetic agents for several years preceding study entry, the available data do not allow assessment of whether serum creatinine levels were measured and taken into consideration at the time metformin was originally prescribed.

At least three scenarios can be proposed to explain the use of metformin in patients with elevated serum creatinine levels: *1*) levels are not appropriately or consistently assessed, 2) levels are normal at the time of the initial prescription and subsequent elevations go unrecognized, or 3) physicians judge that benefits of therapy outweigh potential risks.

Because serum creatinine can overestimate renal function, particularly in older or obese patients (11,12), GFR was calculated (10). Based on GFR, the proportion of patients taking metformin who are actually renally impaired may be larger than would be determined by using serum creatinine. Regardless of patients' current or prior metformin use, these data question the practice of relying solely on serum creatinine for evaluation of renal function in diabetic patients. While the benefit of metformin use in patients with contraindications may be debated, it is clear that metformin can accumulate in the setting of renal impairment, and thus unmonitored use is of concern (3). Further research is needed to determine whether periodic testing of serum creatinine levels or 24-h creatinine clearance measurements should be mandatory for patients receiving metformin.

References

1. Glucophage/Glucophage XR [package insert]. Princeton, NJ, Bristol-Myers Squibb, 2004
2. Misbin RI, Green L, Stadel BV, Gueriguian JL, Gubbi A, Fleming GA: Lactic acidosis in patients with diabetes treated with metformin. *N Engl J Med* 338:265–266, 1998
3. Misbin RI: The phantom of lactic acidosis due to metformin in patients with diabetes. *Diabetes Care* 27:1791–1793, 2004
4. Stacpoole PW: Metformin and lactic acidosis: guilt by association? *Diabetes Care* 21:1587–1588, 1998
5. Emslie-Smith AM, Boyle DI, Evans JM, Sullivan F, Morris AD, for the DARTS/MEMO Collaboration: Contraindications to metformin therapy in patients with type 2 diabetes: a population-based study of adherence to prescribing guidelines. *Diabet Med* 18:483–488, 2001
6. Howlett HC, Bailey CJ: A risk-benefit assessment of metformin in type 2 diabetes mellitus. *Drug Safety* 20:489–503, 1999
7. Horlen C, Malone R, Bryant B, Dennis B, Carey T, Pignone M, Rothman R: Frequency of inappropriate metformin

prescriptions. *JAMA* 287:2504–2505, 2002
8. Sulkin TV, Bosman D, Krentz AJ: Contraindications to metformin therapy in patients with NIDDM. *Diabetes Care* 20: 925–928, 1997
9. Calabrese AT, Coley KC, DaPos SV, Swanson D, Rao RH: Evaluation of prescribing practices: risk of lactic acidosis with metformin therapy. *Arch Intern Med* 162: 434–437, 2002
10. National Kidney Foundation: National Kidney Foundation Kidney Disease Outcomes Quality Initiative. Available from http://www.kidney.org/professionals/doqi/kdoqi/p5_lab_g4.htm. Accessed 13 December 2004
11. Ishida K, Ishida H, Narita M, Sairenchi T, Saito Y, Fukutomi H, Takahashi H, Yamagata K, Koyama A: Factors affecting renal function in 119,985 adults over three years. *Q J Med* 94:541–550, 2001
12. Salazar DE, Corcoran GB: Predicting creatinine clearance and renal drug clearance in obese patients from estimated fat-free body mass. *Am J Med* 84:1053–1060, 1988