

Should Metformin Be Used in Patients with Kidney Disease? March 29, 2012

Background

In 2009, the American Diabetes Association (ADA) recommended initiation of metformin in combination with lifestyle changes for type 2 diabetes mellitus (T2DM) at the time of diagnosis.¹ This was based on the level of glycemic control achieved, little association with weight gain or hypoglycemia, generally low level of adverse effects, high level of acceptance, and relatively low cost of the drug. The ADA continues to recommend metformin as first-line therapy, unless contraindicated, in the most recent update of their guidelines.² Prescribers are advised to initiate metformin at a dose of 500 mg daily and titrate up to the maximum tolerated dose or 2000 mg (immediate or extended-release) per day.³ Of note, although the manufacturer asserts a maximum dosage of 2550 mg per day for the immediate-release formulation, little clinical benefit has been demonstrated at doses exceeding 2000 mg per day. A second oral antidiabetic agent is recommended only if metformin monotherapy at the maximum tolerated dose is not effective in achieving or maintaining the goal A1C over 3 to 6 months.² Additionally, the ADA recommends initiation of metformin for prevention of T2DM in patients with impaired glucose tolerance, impaired fasting glucose, or an A1C of 5.7 to 6.4%, particularly those with a body mass index >35 kg/m² or under 60 years of age, and in women with a history of gestational diabetes mellitus.

The National Institute for Health and Clinical Excellence (NICE), an organization based in the United Kingdom, recently issued an update of their guidelines on the management of type 2 diabetes.⁴ The NICE also recommends metformin as a first-line therapy in patients whose blood glucose is inadequately controlled with lifestyle modifications. Additionally, they recommend reviewing the dose of metformin if serum creatinine (Scr) levels exceed 130 μ mol/L (1.5 mg/dL) or the estimated glomerular filtration rate (eGFR) falls below 45 mL/min/1.73 m² and discontinuing metformin if Scr levels exceed 150 μ mol/L (1.7 mg/dL) or the eGFR falls below 30 mL/min/1.73 m². The NICE advocates prescribing metformin with caution in patients who are at risk for acute renal dysfunction.

Contraindications to metformin use include renal impairment, defined by the manufacturer as Scr levels exceeding 1.4 mg/dL in females and 1.5 mg/dL in males or abnormal creatinine clearance, as well as metabolic acidosis.³ It has been proposed that usage of metformin in patients with renal impairment may lead to an increased risk of lactic acidosis due to decreased renal clearance of the drug. Lactic acidosis is a rare metabolic adverse event with a documented incidence of 0.03 cases per 1000 patient-years, but it is potentially fatal in up to 50% of cases. Per the manufacturer, the risk of lactic acidosis increases with degree of renal function impairment and patient age, and the risk may be significantly reduced through regular monitoring of renal function and use of the minimum effective dose.

Literature Evaluation

While there are concerns for an increased risk of lactic acidosis in patients with renal impairment, there is no evidence from which a causal relationship can be established.⁵ Per Lalau,⁶ the idea of a threshold Scr for continuation or cessation of metformin therapy is undesirable as it suggests that metformin should be either given at the usual dose or “not at all.” This may lead to underutilization of metformin in patients who could significantly benefit from therapy. Lalau also suggests that the threshold is inappropriate as metformin-associated lactic acidosis has been shown to occur more often in patients with acute kidney failure, as opposed to chronic kidney failure.

In a review of contraindications to metformin, Holstein and Stumvoll state that lactic acidosis is a non-specific consequence of a variety of disorders, characterized by serum pH <7.25 and elevated lactate levels (>5 mmol/L).⁷ They note that data from some prospective studies and a meta-analysis suggest that metformin may be used safely in patients with chronic renal impairment. Moreover, they assert based on several studies performed in the U.S. and abroad that the incidence of lactic acidosis was comparable in patients with T2DM without metformin therapy and those in patients receiving metformin (9.7 vs. 5 to 9 cases per 100,000 patient-years, respectively). This observation casts some doubt onto whether metformin use itself plays a causal role in the development of lactic acidosis.

Few studies have been published evaluating the safety of metformin in patients with mild renal impairment. Connolly and Kesson conducted a case-control study of the adverse effects associated with metformin use in patients with T2DM and either normal or elevated Scr (>120 mcmmol/L or 1.4 mg/dL).⁸ They identified a total of 17 patients with elevated Scr and 24 controls (age-matched, normal Scr) who had been taking metformin for ≥ 6 months. The primary endpoint was the difference in plasma lactate levels between groups, using lactate levels from age-matched healthy volunteers as a reference. The mean age among groups was similar (60.7 vs. 66.5 years, normal vs. elevated Scr; p=non-significant [NS]), as well as the metformin doses (1846 mg vs. 1717 mg, normal vs. elevated Scr; p=NS) and duration of diabetes (6.5 ± 5.3 years vs. 10.6 ± 8.2 years, normal vs. elevated Scr; p=NS). The mean Scr was 101.7 mcmmol/L (1.2 mg/dL) in the normal group vs. 132.2 mcmmol/L (1.5 mg/dL) in the elevated group (p<0.00001). Baseline use of metformin was significantly longer in patients with elevated Scr compared to those with normal Scr (3.0 ± 2.9 years vs. 6.3 ± 5.4 years; p<0.02). However, there was no significant difference observed among groups in the plasma lactate levels (2.64 vs. 2.3 vs. 1.7 mmol/L; normal vs. elevated Scr vs. reference value; p=NS for normal vs. elevated Scr). Connolly and Kesson concluded that while plasma lactate levels were elevated in patients with diabetes vs. healthy volunteers, there was no association between the mild renal impairment and elevated lactate levels.

Rachmani et al performed a prospective cohort study in which they sought to evaluate the safety of continued use of metformin in patients who had been taking metformin and developed a contraindication.⁹ They included patients aged 40 to 75 years with an Scr of 132 to 220 mcmmol/L (1.5 to 2.5 mg/dL) and chronic heart failure, abnormal liver function, chronic obstructive pulmonary disease, and/or acute coronary syndromes. A total of 393 patients were randomized to either stop metformin (n=198) or continue therapy (n=195) and were followed for 4 years. Of note, all patients included had an elevated Scr. Primary endpoints included differences between groups in lactic acid and various micro/macrovascular complications. In the group who discontinued

metformin, lactic acid levels increased from 1.50 to 1.63 mmol/L ($p < 0.01$). Similarly, lactic acid levels increased in the group continuing metformin, from 1.50 to 1.66 mmol/L ($p < 0.01$); however, the difference between groups was not statistically significant. The Scr values increased in both groups, as well, from 161 to 186 $\mu\text{mol/L}$ (1.8 to 2.1 mg/dL) in the group that discontinued therapy and 163 to 179 $\mu\text{mol/L}$ (1.8 to 2.0 mg/dL) in the group that continued therapy. However, the difference between groups was also not significant and, despite the elevated Scr, none of the patients continuing metformin therapy developed lactic acidosis. No statistically significant differences were observed in the number of cardiovascular events or cardiovascular mortality between groups. The authors concluded that metformin may be relatively safe in patients with mild renal impairment, and possibly in patients with other current contraindications to metformin.

More recently, Lim et al conducted a cross-sectional study of patients with diabetes who had been taking metformin for ≥ 1 month, comparing fasting plasma lactate levels in those with normal renal function and those with renal impairment.¹⁰ A total of 97 patients were included and stratified by total daily metformin dose and GFR. For the latter analysis, patients were categorized according to GFR levels of < 60 ($n = 39$), 60 to 90 ($n = 34$), and > 90 mL/min/1.73 m² ($n = 24$). The mean fasting plasma lactate levels were 1.7, 1.8, and 1.8 mmol/L, respectively ($p = 0.757$). When further categorized according to total daily metformin dose, no statistically significant differences were observed in the fasting plasma lactate levels. The authors concluded that there was no association between level of renal impairment and fasting plasma lactate levels in these patients.

While there are few studies investigating the safety of metformin use in patients with mild renal impairment, the available data, in conjunction with the presence of conflicting data regarding the causality of metformin use alone and lactic acidosis, suggest that this therapy may be appropriate.⁵⁻¹⁰ Limitations to current studies include the small number of patients involved and their demographics, length of metformin treatment and follow-up methods, as well as differences in estimates of renal function and definitions of renal impairment.⁸⁻¹⁰ The appropriateness and accuracy of parameters such as Scr for measurement of renal function and frequency of monitoring should be evaluated.

Clinical Implications

It may be recommended that prescribers consider the individual patient's renal function in concert with other factors that may predispose the patient to the development of lactic acidosis when choosing to initiate or continue metformin therapy. Consideration of the nature of renal dysfunction is also warranted, as the development of lactic acidosis has been shown to occur more often in acute rather than chronic renal failure.

Of note, metformin-associated lactic acidosis is characterized generally by elevated plasma metformin levels (> 5 mcg/mL) in the setting of decreased serum pH and elevated lactate levels and may be accompanied by abdominal pain, nausea, vomiting, malaise, myalgia, and dizziness.^{3,11} More severe symptoms include confusion, hypothermia, respiratory insufficiency and hypotension. Patients and care-givers should be instructed to notify their healthcare providers should these symptoms arise. Metformin-associated lactic

acidosis may be managed through hemodialysis, which will filter metformin at a clearance of up to 170 mL/min, and general supportive measures.³

As recommended in the NICE guidelines, prescribers should consider refraining from metformin therapy in patients with Scr levels exceeding 1.7 mg/dL or an eGFR below 30 mL/min/1.73 m².⁴ While metformin should not be used in patients with acute kidney failure or severe kidney dysfunction, mild renal impairment alone may be insufficient cause to discontinue or avoid metformin use. Metformin use in the setting of stable chronic kidney disease may be both safe and effective.

References:

1. Nathan DM, Buse JB, Davidson MB, et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2009;32(1):193-203.
2. American Diabetes Association. Standards of medical care in diabetes – 2012. *Diabetes Care*. 2012;35(Suppl 1):S11-S63.
3. Glucophage and Glucophage XR [package insert]. Princeton, NJ: Bristol-Myers Squibb; 2009.
4. National Institute for Health and Clinical Excellence. Type 2 diabetes: the management of type 2 diabetes – an update of NICE clinical guidelines E, F, G, and H. Available at: <http://www.nice.org.uk/nicemedia/pdf/CG66NICEGuideline.pdf>. Accessed February 14, 2012.
5. Philbrick AM, Ernst ME, McDanel DL, Ross MB, Moores KG. Metformin use in renal dysfunction: is a serum creatinine threshold appropriate? *Am J Health Syst Pharm*. 2009;66(22):2017-2023.
6. Lalau JD. Lactic acidosis induced by metformin: incidence, management, and prevention. *Drug Saf*. 2010;33(9):727-740.
7. Holstein A, Stumvoll M. Contraindications can damage your health – is metformin a case in point? *Diabetologia*. 2005;48(12):2454-2459.
8. Connolly V, Kesson CM. Metformin treatment in NIDDM patients with mild renal impairment. *Postgrad Med J*. 1996;72(848):352-354.
9. Rachmani R, Slavachevski I, Levi Z, Zadok B, Kedar Y, Ravid M. Metformin in patients with type 2 diabetes mellitus: reconsideration of traditional contraindications. *Eur J Intern Med*. 2002;13(7):428-433.
10. Lim VC, Sum CF, Chan ES, Yeoh LY, Lee YM, Lim SC. Lactate levels in Asian patients with type 2 diabetes mellitus on metformin and its association with dose of metformin and renal function. *Int J Clin Pract*. 2007;61(11):1829-1833.
11. Bosse GM. Antidiabetics and hypoglycemics. In: Flomenbaum N, Goldfrank L, Hoffman R, et al. *Goldfrank's Toxicologic Emergencies*. 8th ed. New York, NY: McGraw-Hill;2006:759-760.