

## **Does an increase in metformin dosage lead to an increased risk of lactic acidosis?**

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Lactic acidosis is a well-documented side effect of metformin, occurring rarely but potentially fatal in up to 50% of cases, and it is thought to occur due to decreased renal clearance of the drug.<sup>1</sup> 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.<sup>2</sup> (Of note, other risk factors that have been proposed in the literature include concurrent liver disease, alcohol abuse, heart failure, and a history of lactic acidosis). Although this suggests that lactic acidosis may be a dose-related side effect, the literature concerning this is conflicting. The reports that describe a potential dose-related effect of metformin are toxicologic, involving patients who have overdosed on metformin. For example, Al-Makadma and Riad describe the development of lactic acidosis in a patient who had ingested 40-45 g of metformin in a suicide attempt.<sup>3</sup> They allude to other, similar cases detailing metformin-associated lactic acidosis with metformin overdoses ranging from 25 g to 100 g.

With regard to therapeutic doses, few studies have been published addressing the possibility of lactic acidosis as a dose-related side effect of metformin. Lim et al conducted a cross-sectional study of Asian patients with type 2 diabetes mellitus (T2DM) with or without renal impairment, assessing for an association between fasting plasma lactate levels, total daily dose of metformin, and glomerular filtration rate (GFR).<sup>4</sup> There were 97 patients in their study with a mean age of 58.8 years; the mean fasting plasma lactate level was 1.8 mmol/L. (Of note, the manufacturer defines lactic acidosis as plasma lactate >5 mmol/L and decreased blood pH).<sup>2</sup> The mean fasting plasma lactate levels for patients taking metformin ≤1000 mg/d, 1001-2000 mg/d, and >2000 mg/d were 1.7 mmol/L, 1.6 mmol/L, and 2.1 mmol/L, respectively (p=0.119).<sup>4</sup> The levels for patients with GFR <60, 60-90, and >90 ml/min/1.73m<sup>2</sup> were 1.7 mmol/L, 1.8 mmol/L, and 1.8 mmol/L, respectively (p=0.757). The authors determined that there was no significant correlation between total daily metformin dose, GFR, and plasma lactate levels in these patients.

In a similar study, Van Berlo-van de Laar et al investigated the incidence and correlation of lactic acidosis with metformin serum concentrations.<sup>5</sup> A total of 16 cases of metformin-associated lactic acidosis (defined as arterial pH<7.35 and lactate>5 mmol/L) were identified, 11 of which had risk factors for lactic acidosis in their medical history (e.g., heart failure, COPD), and 13 with renal failure. Metformin doses ranged from 850 to 2550 mg/d, and serum concentrations from 0.4 to 44 mg/L. Interestingly, the patients who survived the metformin-associated lactic acidosis had a higher metformin serum concentration compared to those who did not survive (18.9 mg/L vs. 2.9 mg/L, p=0.006). Based on these results, the authors determined that the incidence and outcome of lactic acidosis is dependent on severity of the underlying disease, rather than the level of metformin. While serum metformin levels are not routinely drawn nor recommended in clinical practice, it may be suggested that they are correlated with metformin dose.

In summary, at this time, evidence for metformin-associated lactic acidosis as a dose-related side effect is available in the toxicology literature. However, literature supporting lactic acidosis as a dose-related effect at therapeutic doses was not found.

References:

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