not mention thiamine deficiency as an important cause of lactic acidosis.

In 2004, Klein et al. described thiamine deficiency as a cause of fatal metabolic acidosis.[1] Their patients were Thai workers who lived in Israel and ate polished rice. Since then, we have also treated several patients with thiamine deficiency that has caused life-threatening lactic acidosis. These patients were either workers from the Far East or malnourished persons with alcoholism.

Thiamine deficiency can be responsible for a number of serious medical problems, none more so than lactic acidosis. Thiamine is a cofactor in the normal functioning of pyruvate dehydrogenase, and with its deficiency, lactate accumulates, causing lactic acidosis.[2] Fortunately, early therapy with intravenous thiamine is lifesaving.[3]

Thiamine deficiency should also be considered in infants who are receiving parenteral nutrition without adequate thiamine supplements.[4]

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: Kalantar-Zadeh et al. describe a 54-year-old woman with metformin accumulation, acute renal failure, pancreatitis, and lactic acidosis. The authors use an approach that is based on the following formula for the expected respiratory response in metabolic acidosis: 1.1 Δ (serum bicarbonate level) = Δ partial pressure of carbon dioxide (pCO_2).[1] This formula is misleading and not advocated in major textbooks. In this patient, the pH was 6.62, the pCO_2 was 18 mm Hg, and the serum bicarbonate level was below 2 mmol per liter. Despite a life-threatening low pH, the authors conclude that the patient had a "remarkable and effective compensatory hyperventilation." With the use of Winters' formula,[2] the expected pCO_2 would be 11 mm Hg (1.5 × the serum bicarbonate level + 8 mm Hg), and because the pCO_2 was 18 mm Hg, the extremely low pH was due to additional respiratory acidosis, perhaps because of the decreased sensorium or exhaustion.

The exceptionally high anion gap (the sodium level minus the chloride level minus the serum bicarbonate level) of 61 mmol per liter was multifactorial. Dehydration increased the sodium concentration. Renal failure and lactic acidosis decreased the bicarbonate level. The decreased chloride level maintained electroneutrality after the disproportionate increase in the phosphorous level to 19.3 mg per deciliter (6.2 mmol per liter) because of lactic acidosis.[3,4]

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TO THE EDITOR: We would like to emphasize three peculiarities of metformin-induced lactic acidosis. First, hypoglycemia is not the rule, possibly because metformin primarily inhibits the endogenous overproduction of glucose, with a minor effect on peripheral consumption.[1] Second, venous hyperoxia is common, since mitochondrial respiration is globally inhibited.[2-4] As a consequence, oxygen extraction decreases and venous oxygen content increases. Third, the outcome is usually favorable.[2,4]

We have reviewed the data sheets of 17 patients (13 women and 4 men; mean [±SD] age, 68±8 years) with metformin intoxication (mean serum drug level, 52±26 μg per milliliter) and lactic acidosis (mean arterial pH, 7.03±0.18, and mean lactate level, 18±9 mmol per liter) in whom central or mixed venous blood oxygen-saturation levels were monitored.[2,4] The initial mean blood glucose level was 117±84 mg per deciliter (6.5±4.7 mmol per liter) (only 6 patients had a

glucose level of <80 mg per deciliter [<4.4 mmol per liter]) and the mean venous oxygen saturation was 80±10% (normal value, 65 to 70%). Three patients (18%) died in the hospital.

In line with these findings, the patient presented in the case had an initial blood glucose level of 116 mg per deciliter (6.4 mmol per liter), venous partial pressure of oxygen of 73 mm Hg, and a good clinical course.

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THE DISCUSSANT REPLIES: Consistent with the comments by Goldman and Shtaynberg, methanol or ethylene glycol toxicity cannot be ruled out exclusively on the basis of a narrow osmolal gap. After initial exposure to these alcohols, the osmolal gap may decrease over time as parent alcohol is converted into other metabolites and hydrogen ions, leading to changes in the anion gap. This patient's multiple-organ involvement, lactic acidosis, and negative toxicologic screening make such alcohol toxicities less likely. Whereas fomepizole is usually well tolerated, data to support its use are inconclusive.[1]

Korzets et al. are correct that thiamine deficiency can lead to lactic acidosis.[2] The gastrointestinal thiamine-deficiency syndrome, known as "gastrointestinal beriberi" and manifested by nausea, vomiting, and severe abdominal pain prompting laparotomy, has been reported[3] and could have been considered as a potential differential diagnosis for this patient. Nevertheless, her gastrointestinal symptoms were probably from pancreatitis resulting from metformin toxicity.

As stated in the Case Record, on respiratory compensation of metabolic acidosis for each 10 mmol per liter decrease from normal in the serum bicarbonate level, a compensatory decrease in the arterial pCO_2 of at least 12 mm Hg is expected. The decrease in pCO_2 of 1.2 mm Hg for each millimole-per-liter reduction in the serum bicarbonate level begins within minutes. Berend asserts that the use of this approach is misleading and suggests that the traditional Winters' equations should be used. Whereas these different formulas usually yield similar results, there are no convincing comparative studies of which formula is more accurate. Nevertheless, the delta approach, recommended in contemporary medical literature, is useful in other acid–base disorders. For instance, in metabolic alkalosis with adequate respiratory compensation, for each millimole-per-liter increase in the serum bicarbonate level, pCO_2 should increase by 0.7 mm Hg. In severe metabolic acidosis, there is a limit to the maximum respiratory compensation; for example, if the serum bicarbonate level is below 5 mmol per liter, the pCO_2 rarely, if ever, goes below a range of 10 to 15 mm Hg.[4] As stated in the Case Record, a part of the anion gap is probably related to severe hyperphosphatemia.

The statement by Protti and Gattinoni that hypoglycemia is not the rule in metformin overdoses is accurate. It is possible that the patient's venous oxygen content was not low because of mitochondrial respiration block caused by very high metformin exposure or because of severe acidosis itself.[5] Whereas this patient had a favorable outcome, metformin overdose should still be considered a potentially lethal event.

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