The Paradox of Hyperglycemia and Surgical Outcomes in Patients with and without Diabetes

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To the Editor:

PATIENTS WITHOUT DIABETES MELLITUS who have peri-operative hyperglycemia have worse surgical outcomes than those with diabetes mellitus at similar levels of hyperglycemia, a paradox that has yet to be explained [1–4]. Several hypotheses have been proposed including the underuse of insulin, greater sensitivity to the deleterious effects of hyperglycemia, and higher levels of inflammation at similar levels of hyperglycemia for those without diabetes mellitus. To test this last hypothesis, we examined the relation between peri-operative hyperglycemia and systemic surgery-induced inflammation in patients with and without diabetes mellitus who have hyperglycemia.

We performed a prospective observational study of patients undergoing infra-inguinal bypass surgery at the VA Puget Sound Health Care System (2007 to 2015). The blood concentrations of C-reactive protein (CRP) and interleukin-6 (IL-6) were determined from platelet-free plasma using multiplex assays (EMD Millipore, Billerica MA). Peri-operative glucose levels were obtained from clinical laboratory and calibrated point-of-care glucose tests. Among patients with hyperglycemia (glucose >140 mg/dL) we compared CRP and IL-6 between patients with and without diabetes mellitus, focusing on the difference between pre-operative and

peak post-operative measures. Medians and interquartile ranges were reported and measures of central tendency were compared using the Mann-Whitney test.

Of the 88 patients studied, 97% were males, their mean age was 64 years, 45% (n=40) had diabetes mellitus, and 94% (n=83) had a history of smoking. Sixty-eight percent experienced peri-operative hyperglycemia, including 42% (n=20) of patients without diabetes mellitus and 100% of patients with diabetes mellitus. The median pre-operative, day of surgery, and post-operative day one glucose values were 152, 150, and 168 mg/dL and 106, 117, and 121 mg/dL for patients with and without diabetes mellitus, respectively. The pre- and post-operative levels of the markers of inflammation were no different in those with hyperglycemia (n=60), whether they had diabetes mellitus or not (Fig. 1). Similarly, when we examined the increase in post-operative inflammation in response to surgery (post-operative peak minus pre-operative value), those with hyperglycemia showed a similar increase, regardless of their diabetic status.

We found that when patients experience hyperglycemia, the inflammatory response to surgical stress (as measured by CRP and IL-6) was similar for patients with and without diabetes mellitus. The paradoxical association between worse surgical outcomes and hyperglycemia among those without

FIG. 1. Median inflammatory marker levels among patients with hyperglycemia. Inflammatory marker levels pre- and post-operatively among those with peri-operative hyperglycemia. No difference was observed between those with and without diabetes. Error bars show interquartile range. CRP=C-reactive protein; IL-6=interleukin 6; POD1=postoperative day one.

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diabetes mellitus is not explained by differences in inflammatory response. Patients without diabetes mellitus who exhibit peri-operative hyperglycemia may be more prone to complications because of differences in their clinical management, or their hyperglycemia may be a manifestation of other clinical factors responsible for the worse outcomes. Alternatively, the inflammatory response could differ in some aspect not reflected by CRP and IL-6.

These findings may be limited because this was a small study in a predominantly male population. However, our data fail to support the hypothesis that inflammation is a driving force behind the association of hyperglycemia and worse surgical outcomes among patients without diabetes mellitus. Further studies are warranted to investigate underlying mechanisms to explain this paradox, including the role of stress hormones and the possibility of suboptimal glucose monitoring and treatment in patients without known diabetes mellitus.

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