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QUESTION 28: What is the most accurate marker for assessing glycemic control that best predicts surgical site infection/periprosthetic joint infection (SSI/PJI)?

RECOMMENDATION: While there is evidence showing an association between elevated glycated haemoglobin (HbA1c) and fasting blood glucose and increased risk for subsequent SSI/PJI, this association is not strong. Recent findings suggest that fructosamine in the preoperative period and glucose variability in the immediate postoperative period may provide greater prediction of SSI or PJI.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 76%, Disagree: 8%, Abstain: 16% (Super Majority, Strong Consensus)

RATIONALE

Diabetes mellitus (DM) patients are predisposed to a host of complications following total joint arthroplasty (TJA) [1–3], with SSI and PJI being perhaps the most dreaded [4]. Glycemic control throughout the perioperative period has been a focus of many recent studies, since it could serve as a modifiable risk factor and targeting it holds the potential to reduce SSI/PJI rates following TJA [5–9]. However, the proper marker for assessing glycemic control in the perioperative period remains unknown. Studies into the subject have produced conflicting results due to diversity in the marker used for assessment, timing of assessment and different cutoff values used for stratifying patients.

Traditional markers for assessing glycemic control can crudely be divided into long-term (HbA1c) and short-term (glucose levels) in the preoperative and postoperative period. A recent meta-analysis of ten studies suggested that elevated HbA1c levels were not significantly associated with a higher risk of SSI/PJI after TJA (pooled odds ratio (OR): 1.49, 95% confidence interval (CI): 0.94 to 2.37, p = 0.09) However, this was most likely due to the low threshold (7%) chosen to define inadequate control in the majority of the studies, with accumulating evidence to support the utility of preoperative HbA1c levels above 7.5 to 8.0% as a predictor for PJI. Similar to HbA1c, the prognostic value of perioperative hyperglycemia remains unclear [10,11]. Studies supporting the association between perioperative hyperglycemia and PJI were underpowered and did not take into account other confounders [9,12]. In those studies that did include important confounders, the association was markedly attenuated [5–9,12–14].

We conducted a systematic review and found ten studies examining the association between glycemic control and PJI. Of those, six examined HbA1c solely [10,11,15–18], one looked at perioperative control alone [12] and three assessed both [5,6,8]. Similar to the meta-analysis mentioned above, the results of our review suggest that higher HbA1c levels are not clearly associated with higher PJI rates, possibly due to inaccurate cutoffs to define inadequate glycemic control. We also found that hyperglycemia in the perioperative period appears to have some association with PJI; however, this relationship is complex and is not well-characterized by the studies reviewed given their varied design.

The uncertainty of the independent role perioperative HbA1c or hyperglycemia have on PJI raises the question of whether these are the most appropriate markers for assessing glycemic control. The focus on fluctuation of glucose around the mean has gained popularity in recent years and has been studied extensively [19–21]. Both in vivo and in vitro studies attribute the negative effects of these fluctuations to the activation of pro-inflammatory proteins and excessive oxidative stress [22]. Short-term fluctuations in glucose levels may have a larger effect on inflammatory cytokine levels than continuous hyperglycemia that may impair host defense from infection [23,24]. Lately, fructosamine (in the preoperative period) and glucose variability (in the postoperative period), which are medium and short term markers for glycemic control, respectively, were shown to correlate strongly with the risk for PJI in both diabetics and unknown-diabetics who seemed to be adequately-controlled based on traditional markers [25].

Fructosamine measures the level of glycated serum proteins and reflects the average glucose levels over a 14- to 21-day time period [26]. It better detects fluctuation and rapid variations of glucose and may detect short term hyperglycemic events better than HbA1c. In a recent study, fructosamine above 292 mmol/L had a better association with SSI and PJI compared to HbA1c when 7% was used as a threshold for inadequate control. One of the immense advantages of fructosamine, compared to HbA1c, is the shorter half-life of the glycated proteins that may reflect the effect of treatment within a week or 2 as opposed to glycated hemoglobin that could take up to 120 days.

In conclusion, our systematic review of the literature on the subject could not detect the most accurate marker for assessing perioperative glycemic control and further research in this area, with consistent study design, is required to answer this question. Based on recent findings, we conclude that fructosamine can serve as an alternative to HbA1c in the setting of preoperative glycemic assessment. Further research to solidify its utility and specify and exact threshold level indicative of inadequate glycemic control should be conducted. With improvement in technology, non-invasive continuous glucose monitoring devices could become more readily available. Future studies should evaluate the role of continuous glucose monitoring in the perioperative period to reduce glucose variability.

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