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Glycated Hemoglobin and the Risk of Sternal Wound Infection after Adult Cardiac Surgery: A Systematic Review and Meta-analysis

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Glycated hemoglobin (HbA1c) is the end-product of non-enzymatic glycosylation of hemoglobin and its increased level is a marker of poor glycemic control.¹ Advanced glycation end-products are responsible for impairment of immunity,¹ which in turn significantly increases the infection risk in diabetics.² Increased HbA1c has also been shown to increase the risk of mortality, myocardial infarction and stroke after cardiac surgery,³ whereas its impact on the occurrence of sternal wound infection is less clear (SWI). This issue has been investigated in the present meta-analysis.

MATERIAL AND METHODS

The protocol of this study was registered in the PROSPERO registry (CRD42018090160). PubMed, Scopus and Google Scholar were searched on August 20, 2018 without date and language restriction. Search criteria included the following terms: "HbA1c", "glycated hemoglobin", "glycosylated hemoglobin", "hemoglobin A1c", "wound" and "surgical site infection". Reference lists of pertinent articles were also reviewed. Observational studies evaluating the impact of preoperative HbA1c levels on the occurrence of SWI after any adult cardiac surgery procedure were considered for this analysis. Population, Intervention, Comparator, Outcomes, and Study design (PICOS) of this analysis and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist are summarized in Supplementary Tables 1 and 2. Abstracts and full-text articles were independently reviewed and data collected by two investigators (F.B., S.G.). Discrepancies were resolved through consensus. The QUADAS-2 risk of bias tool⁴ was used to assess the methodological quality of the included studies. The exposure of interest was increased preoperative levels of HbA1c as reported in the included studies. The primary outcome was deep SWI/mediastinitis and secondary outcome was any superficial or deep SWI. The definition criteria of SWI were expected to vary between studies and were kept as originally defined in the retrieved articles.

Statistical analysis was performed using STATA v. 15.1 statistical software (StataCorp, 4905 Lakeway Drive College Station, Texas 77845 USA9). Outcomes are reported as pooled proportions with 95% confidence intervals (CI). Since the included studies evaluated the accuracy of preoperative HbA1c to predict postoperative SWI using different cutoff values, diagnostic test meta-analysis was

performed to estimate the diagnostic odds ratio (DOR). Furthermore, the outcomes of two-arm analyses employing HbA1c ranging from 6% to 7% were pooled with the random-effects method leading to computations of risk ratios (RR) with 95% CI. Sensitivity analysis for different HbA1c cutoff values, elective procedures and in diabetics were performed. I^2 statistic was used to estimate the heterogeneity of the studies, with $I^2 > 40\%$ as a threshold for significant heterogeneity. Publication bias was assessed by inspecting funnel plot asymmetry. $P < 0.05$ was set for statistical significance.

RESULTS

Of the 311 records identified, 14 studies fulfilled the inclusion criteria and were included in this analysis (Suppl. Fig. 1). Their characteristics are summarized in Table 1 and Supplementary Figure 2. Diagnostic test meta-analysis including studies evaluating baseline HbA1c cut-off values ranging from 6 to 7% DCCT units (42 to 53 mmol/mol IFCC units) showed that the DOR for deep SWI was 3.02 (95% CI 2.10-4.35), with a sensitivity of 66.5% and a specificity of 60.3% (Fig. 1). The DOR for any SWI was 2.81 (95% CI 2.02-3.93), with a sensitivity of 64.7% and a specificity of 60.6%.

Binary meta-analysis confirmed that baseline HbA1c cut-off values ranging from 6 to 7% increased the risk for deep SWI (pooled incidence 2.7% vs. 0.8%, RR 3.01, 95% CI 2.32-3.90, $I^2 0\%$) (Fig. 1, Suppl. Fig. 3). Six studies included only diabetics and their pooled RR for deep SWI was 2.94 (1.59-5.45, $I^2 0\%$). Nine studies evaluated a HbA1c cutoff value of 7% and their RR for deep SWI was 3.22 (95% CI 2.38-4.37, $I^2 0\%$). The RR for any SWI was 2.92 (95% CI 2.42-3.53, $I^2 0\%$). Two studies (4,5) reported on adjusted estimated of continuous HbA1c levels for deep SWI and their pooled RR was 1.33 (95% CI 1.19-1.46, $I^2 0\%$).

DISCUSSION

Diabetes is a risk factor for surgical site infection⁵ and this pooled analysis showed that such a risk is substantially increased when glycemia is poorly controlled as shown by HbA1c levels over 6-7%. These findings are clinically relevant because HbA1c may allow a stratification of the risk of SWI and may guide preventative strategies to reduce the risk of such a severe complication. However, the

included studies might be affected by significant clinical heterogeneity in the use and harvesting technique of internal mammary arteries, antibiotic prophylaxis and wound care. Future studies should evaluate whether postponing surgery for optimization of the glycemic control can reduce the risk of SWI in patients with increased levels of HbA1c.

CENTRAL MESSAGE

Elevated glycated hemoglobin (HbA1c) is associated with increased risk of sternal wound infection and should be routinely measured before cardiac surgery, at least in patients with known diabetes.

Characters: 197

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risk of surgical site infection: a systematic review and meta-analysis. *Infect Control Hosp Epidemiol.* 2016;37:88-99.

Table 1. Characteristics and data of the included studies.

| Author | Year | Country | Study design | Study period | No. of patients | CABG (%) | Diabetics (%) | Postop. glycemic control | HbA1c cutoff |
|-------------|------|-----------|--------------|--------------|-----------------|----------|---------------|--|--------------|
| Alserius | 2008 | Sweden | P | 2002-2004 | 605 | 100 | 100 | NS | ≥7% |
| Finger | 2017 | USA | R | 2014 | 531 | 100 | 34 | In ICU range 5.5-7.9 mmol/l, in ward NS | >7% |
| Fohl | 2013 | USA | R | 2005-2009 | 616 | 100 | 100 | Range 5.3-7.8 mmol/l | ≥7% |
| Gumus | 2013 | Turkey | R | 2010-2012 | 510 | 74 | 40 | Range 6.7-7.8 mmol/l | ≥6% |
| Göksedef | 2010 | Turkey | P | 2007-2008 | 150 | 100 | NS | NS | >7% |
| Halkos | 2008 | USA | R | 2002-2007 | 5199 | 100 | 34 | In ICU range 4.4-6.3 mmol/l, in ward <8.3 mmol/l | ≥7% |
| Narayan | 2017 | India | R | 2011-2014 | 4678 | 51 | NS | <8.3 mmol/l | ≥6.5% |
| Nicolini | 2018 | Europe | P | 2015-2016 | 2606 | 92 | 36 | NS | ≥7% |
| Ramadan | 2018 | Egypt | P | 2013-2015 | 80 | 100 | 100 | <8.3 mmol/l | >7% |
| Santos | 2015 | Argentina | P | NS | 96 | 100 | 100 | In ICU <6.7 mmol/l, in ward <8.3 mmol/l | >7% |
| Sato | 2010 | Canada | P | 2008-2009 | 130 | 60 | 100 | Range 4.0-8.0 mmol/l | ≥6.5% |
| Subramaniam | 2014 | USA | P | 2008-2011 | 1461 | 100 | 38 | Range 5.0-6.7 mmol/l | ≥6.5% |
| Tarazi | 2017 | Egypt | R | 2014-2016 | 101 | 100 | NS | NS | >7% |
| Tsuruta | 2011 | Japan | P | 2002-2007 | 306 | 100 | 100 | NS | ≥6.5% |

R: retrospective study; P: prospective study; NS: not stated.

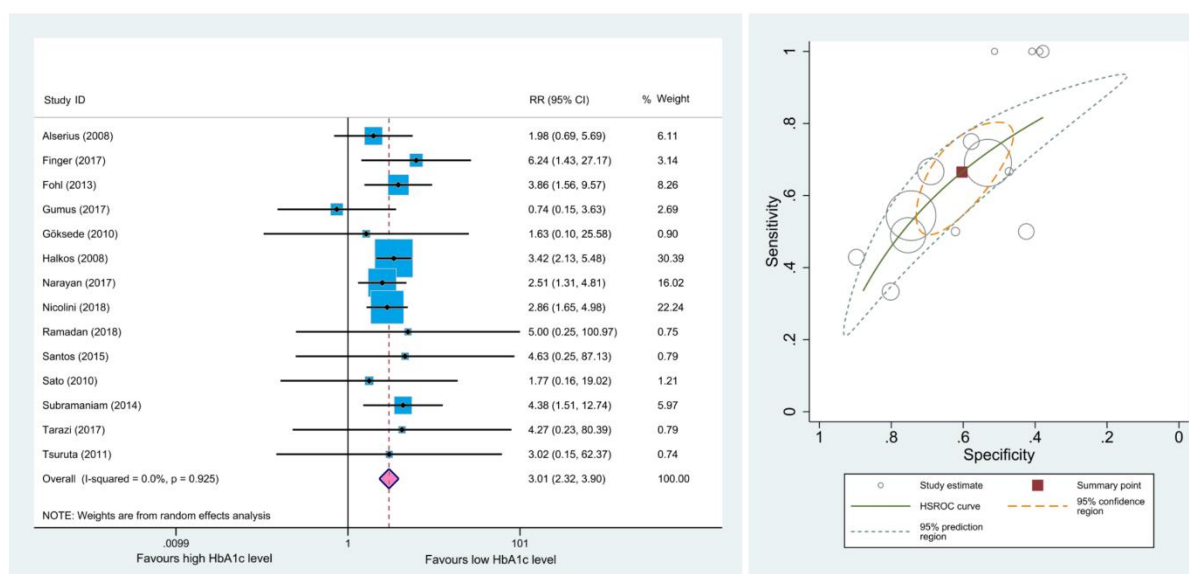


Figure legends

Central picture. HbA1c and risk of deep sternal wound infection after adult cardiac surgery.

Figure 1. Forest plot and hierarchical summary receiver operating characteristic plot of the impact of baseline glycated hemoglobin (HbA1c) ranging from 6% to 7% on the occurrence of deep sternal wound infection after adult cardiac surgery. ID, identification; RR, risk ratio; CI, confidence interval; HSROC, hierarchical summary receiver operating characteristic.