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Major article

Diabetes mellitus is associated with increased risk of surgical site infections: A meta-analysis of prospective cohort studies

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Background and Objective: Observational studies have suggested an association between diabetes mellitus and the risk of surgical site infections (SSIs), but the results remain inconclusive. We conducted a meta-analysis of prospective cohort studies to elucidate the relationship between diabetes mellitus and SSIs.

Methods: We searched PubMed, Embase, and Web of Science databases and reviewed the reference lists of the retrieved articles to identify relevant studies. Associations were tested in subgroups representing different patient characteristics and study quality criteria. The random-effect model was used to calculate the overall relative risk (RR).

Results: Fourteen prospective cohort studies (N = 91,094 participants) were included in this meta-analysis, and the pooled crude RR was 2.02 (95% confidence interval, 1.68-2.43) with significant between-study heterogeneity observed (I^2 = 56.50%). Significant association was also detected after we derived adjusted RRs for studies not reporting the adjusted RRs and calculated the combined adjusted RR of the 14 studies (RR, 1.69; 95% confidence interval, 1.33-2.13). Results were consistent and statistically significant in all subgroups. Stratified analyses found the number of confounders adjusted for, sample size, and method of diabetes case ascertainment might be the potential sources of heterogeneity. Sensitivity analysis further demonstrated the robustness of the result.

Conclusions: This meta-analysis suggests diabetes mellitus is significantly associated with increased risk of SSIs. Future studies are encouraged to reveal the mechanisms underlying this association.

Surgical site infections (SSIs) are the most common nosocomial infection among patients undergoing surgery.[1] Data from the Centers for Disease Control and Prevention (CDC) and National Nosocomial Infections Surveillance (NNIS) system showed that SSIs accounted for 14% to 16% of such infections among hospitalized patients and 38% among surgical patients.[1,2] Similarly, European data suggest that the incidence of SSIs might be as high as 30% depending on the procedure, the surveillance criteria used, and the quality of data collected.[3] SSIs result in an excess cost of more than $1.6 billion in hospital charges alone and prolong hospital stays by more than 5 days per episode.[4,5] More importantly, patients who developed such infections were 60% more likely to spend time in an intensive care unit and twice as likely to die.[6]

It is well known that patients with diabetes are predisposed to bacterial infections, including SSIs.[7] And a number of primary studies have evaluated the association of diabetes and the risk of SSIs, suggesting that diabetes could be a risk factor for SSIs. There is, however, a question of whether patients with diabetes are at an increased risk for SSIs, and to our knowledge the quality and the clinical features of these existing studies have not been systematically assessed. We therefore performed a meta-analysis to systematically assess the association between diabetes and risk of SSIs based on prospective cohort studies.

METHODS

Literature search

We conducted this meta-analysis in accordance with the Meta-Analysis of Observational Studies in Epidemiology guidelines.[8] We searched PubMed, Embase, and Web of Science databases up to

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December 23, 2014, by using the following search terms: *diabetes mellitus, impaired glucose tolerance*, *impaired fasting glucose*, *glucose metabolism disorders*, or *insulin resistance* in combination with *surgical site infections*. Reference lists of the retrieved articles were also reviewed. We did not contact authors of the identified studies for additional information.

Study selection

Two reviewers (YZ and SW) identified eligible articles independently by performing an initial screen of the titles and abstracts, and then reading the full articles. Studies were included if they met the following criteria: had a prospective cohort study design; the exposure was diabetes mellitus and the outcome was SSI with reported estimates of the odds ratio (OR) or relative risk (RR) or hazard ratio (HR) and its 95% confidence interval (CI) or reported data to calculate them; and if the same population was studied in more than 1 study, we only included the 1 with more complete design or larger sample size.

Data extraction and quality assessment

Data extraction was completed by 2 authors (YZ and QZ) independently using a predesigned data extraction form. Information was recorded as follows: last name of the first author, publication year, study location, surgery type, methods of defining SSI, the number of participants, SSI incidence, method of diagnosing diabetes, length of follow-up, crude or adjusted RR (RRa) with the corresponding 95% CI, and adjusted variables.

Two authors (XB and SW) conducted the quality assessment using a 9-star system based on the Newcastle-Ottawa scale.[9] Articles scoring 0 to 3, 4 to 6, and 7 to 9 were considered low, moderate, and high quality, respectively. Any dispute was resolved by discussing with a third author (YZ).

Statistical analysis

The RRs were used as the common measure of association across studies. Because HR was broadly equivalent to RR,[10,11] HRs were directly considered as RRs. The ORs were transformed into RRs using the formula $RR = OR/[(1\text{-}Po) + (Po \times OR)]$ where Po is the incidence of the outcome of interest in the nonexposed group,[12] and the Miettinen test-based approach was used to calculate the variance of lnRR (variance lnRR = variance lnOR × [lnRR/lnOR]).[13] This method of transformation has some limitations and can underestimate the variance of the RRs derived from the ORs,[14,15] so we performed a sensitivity analysis that excluded the studies in which this transformation was performed. For the studies only reporting unadjusted RR (RRu), we derived the RRa estimates using the formula RRa = RRu/U where U was estimated via the external data that was similar to the study under review, and the variance of lnRRa was calculated via the equation $\sqrt{Vu + SE}$ where Vu was an estimate of the variance of lnU, and SE the estimated standard error for the unadjusted estimate lnRRu.[16] Between-study heterogeneity was assessed using the Cochrane *Q* statistic (significance level at $P < .10$) and the I^2 statistic.[17,18] The random-effect model was applied to calculate pooled RR among studies if $P < .10$ and I^2 <50%.[19] Sensitivity analysis was executed by excluding 1 study in turn to detect the influence of individual study on the overall result. We also performed stratified analyses according to the study quality and clinical characteristics. The effect of publication bias on the summary estimates was assessed by the Harbord bias indicator.[20] Funnel plots were also performed to evaluate potential publication bias using the standard error.[21] All analyses were conducted using STATA version 12.0 (StataCorp, College Station, Tex).

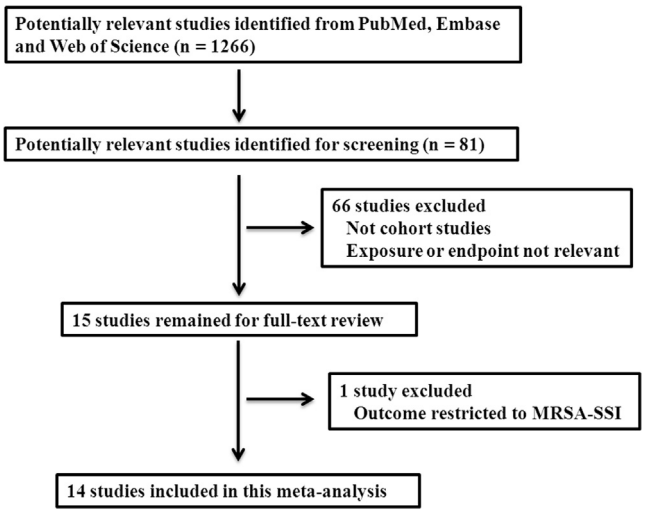

Fig 1. Flow chart of study selection. *MRSA-SSI*, methiciliin-resistant surgical site infection.

A *P* value <.05 was considered significant, except where otherwise specified.

RESULTS

Literature search

The search strategy retrieved 1,266 unique studies. Of these, 1,185 studies were excluded after the first screening based on abstracts or titles, leaving 81 articles for full-text review. After assessing the full-text of the 81 potentially relevant articles, 67 articles were excluded for the reasons listed in Figure 1, leaving 14 studies[22-35] included for the final analyses.

Study characteristics

Characteristics of the 14 included studies are shown in Table 1. All were prospective cohort studies with 3 conducted in Asia, 10 in Europe or the United States, and 1 in Brazil. The population size per study ranged from 195 to 56,216, with a total of 91,094 participants involved. All studies reported the incidence of SSI as an outcome of interest, ranging from 0.72% to 17.0%.

SSIs were defined according to criteria of the CDC/NNIS in 10 studies, to criteria of the National Surgical Quality Improvement Program in 1 study, and this informaiton was not mentioned in the 3 remaining studies. Diabetes status was ascertained by screening medical records in 4 studies, was reported by infection control professionals (ICPs) in 3 studies, and was determined by other methods (database, semistructured interviews, and long-term chronic management) in 7 studies. The length of follow-up ranged from 15 days to at least 1 year; the follow-up duration was given for only 9 studies.

The quality of the studies as assessed using the Newcastle-Ottawa scale is shown in Table 2. Twelve studies were of high quality (ie, score of 7, 8, or 9) whereas the other 2 were of moderate quality (ie, 1 study scored 6 and 1 study scored 5). The areas that scored poorest were in the methods of ascertaining the SSI status (outcome) and determining if the follow-up was long enough for outcomes to occur (outcome). The representativeness of the cohorts to the population and the comparability of the cohorts scored above 90%.

Crude RRs (ORs and HRs) were reported in all studies, whereas RRas (ORs or HRs) could be determined for only 7 studies (Table S1). Adjustment for potential confounding factors differed across studies, and the common adjusted factors were age, gender, and tobacco use.