Prevalence and Risk of Infection in Patients with Diabetes following Primary Total Knee Arthroplasty:
A Global Systematic Review and Meta-Analysis of 120,754 Knees

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Dissertation Submitted in Partial Fulfillment of The Requirements for The Degree of Master of Medicine

(ORTHOPAEDICS)

UNIVERSITI SAINS MALAYSIA

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My heartfelt thanks go to the following people for their contributions throughout the dissertation: My supervisor, Dr Shaifuzain Ab Rahman, lecturer and Consultant Orthopaedics Surgeon at HUSM, provided me with the opportunity and invaluable guidance throughout this research. Special thanks to my co-supervisor, Dr. Asiful Islam, lecturer in the Haematology department at HUSM, who is expert in systematic review and meta-analysis, for his advice and assistance in completing this paper.

I like to take this opportunity to thank my wonderful wife and children for their love, prayers, and concern throughout my journey. To my parents, for their unfailing love and patience. This journey will be difficult to complete without them.

Not to forget, many thanks to the editorial board of the Journal of Clinical Medicine for accepting my dissertation for publication in their prestigious journal.

Finally, I like to thank all of my lecturers and colleagues at the Department of Orthopedic of Universiti Sains Malaysia.

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LIST OF ABBREVIATIONS AND SYMBOLS

DM	Diabetes Mellitus
TKA	Total Knee Arthroplasty
PROSPERO	International Prospective Register of Systematic Reviews
CI	Confident interval
RR	Risk ratio
SSI	Surgical site infection
PJI	Periprosthetic join infection
SRMA	Systemic reviews and meta-analysis
M.A.A	Mohd Aliff bin Ahmad
S.A.R	Shaifuzain Ab Rahman
M.A.I	Md Asiful Islam
JBI	Joanna Briggs Institute
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
USA	United State of America
UK	United Kingdom

NR	Not reported
SD	Standard deviation
IQR	Inter quartile range

ABSTRAK

PENGENALAN

Diabetes mellitus (DM) ataupun diabetes (lebih dikenali sebagai kencing manis) adalah salah satu faktor yang dikenal pasti sebagai risiko jangkitan di kalangan pesakit yang menjalani pembedahan penukaran sendi lutut (TKA). Tujuan kajian ini adalah untuk menilai kelaziman dan risiko jangkitan di antara pesakit DM dan yang tidak menghidapi DM yang menjalani pembedahan penukaran sendi lutut (TKA) primer.

KAEDAH KAJIAN

PubMed, Scopus, Google Scholar, Web of Science, dan Science Direct adalah pengkalan data elektronik yang telah dimaanfaatkan sebagai sumber untuk mengidentifikasi kajian yang bersesuaian (kajian yang diterbitkan sehingga 21 April 2022) . Untuk membandingkan risiko jangkitan antara pesakit DM dan bukan DM, kelaziman, dan nisbah risiko (RR) dengan 95% selang keyakinan (CI) telah digunakan. Penyelidikan ini telah telah berdaftar dengan PROSPERO (CRD42021244391).

KEPUTUSAN

Seramai 119,244 pesakit daripada 18 kajian, dengan jumlah keseluruhan 120,754 spesimen lutut (25,798 DM dan 94,956 bukan DM) telah digunakan dalam penilaian ini. Kami mendapati risiko jangkitan di kalangan pesakit diabetes adalah 1.84 kali ganda lebih tinggi daripada pesakit bukan diabetes. Kelaziman jangkitan adalah lebih tinggi di kalangan pesakit diabetes (1.9%) berbanding pesakit bukan

diabetes (1.2%). Dalam analisis sub-kumpulan, risiko jangkitan di tempat pembedahan (SSI) dalam (deep SSI) adalah 1.96 kali lebih tinggi pada pesakit diabetes, tetapi tiada perbezaan yang ketara jika dibandingkan dengan SSI di kawasan permukaan luka (superficial SSI). Kelaziman SSI dalam adalah lebih tinggi di kalangan pesakit kencing manis (1.5%) berbanding bukan kencing manis (0.7%), tetapi kelaziman SSI di kawasan permukaan adalah lebih rendah di antara pesakit DM (1.4%) berbanding bukan DM (2.1%).

KESIMPULAN

Selaras dengan penyelidikan yang telah dijalankan sebelum ini, kami mendapati diabetes terbukti sebagai faktor risiko jangkitan di kalangan pesakit yang menjalani TKA primer. Walau bagaimanapun, risiko adalah jauh lebih rendah daripada data yang diterbitkan sebelum ini, menunjukkan bahawa faktor lain memainkan peranan yang lebih besar dalam jangkitan.

Keyword: diabetes; infection; periprosthetic joint infection; prevalence; risk; systematic review; total knee arthroplasty

ABSTRACT

INTRODUCTION

Diabetes mellitus (DM) is a known risk factor for infection following total joint arthroplasty. This study looked at the prevalence and risk of infection in diabetic and non-diabetic patients who had primary total knee arthroplasty (TKA).

METHODOLOGY

PubMed, Scopus, Google Scholar, Web of Science, and Science Direct electronic databases were searched for studies published up to 21 April 2022. To compare the risk of infection between diabetic and non-diabetic subjects, a pooled prevalence, and a risk ratio (RR) with 95% confidence intervals (CIs) were used. This research has been registered with PROSPERO (CRD42021244391).

RESULTS

There were 119,244 participants from 18 studies, with a total of 120,754 knees (25,798 diabetic and 94,956 non-diabetic). We discovered that the risks of infection in diabetic patients were 1.84 times significantly higher than in non-diabetic patients. Infection was more common in diabetic patients (1.9%) than in non-diabetic patients (1.2%). In a subgroup analysis, the risks of developing deep surgical site infection (SSI) were 1.96 times higher in diabetic patients, but no significant difference when compared in superficial SSI. Prevalence of deep SSI was higher in diabetic (1.5%) than in non-diabetic (0.7%), but the prevalence of superficial SSI was lower in diabetic (1.4%) than in non-diabetic (2.1%).

CONCLUSION

Consistent with previous research, we found diabetes is a risk factor for infection following primary TKA. However, the risk is much lower than previously published data, indicating that other factors play a larger role in infection.

Keyword: diabetes; infection; periprosthetic joint infection; prevalence; risk; systematic review; total knee arthroplasty

CHAPTER 1 – INTRODUCTION

1.1 INTRODUCTION

Total knee arthroplasty (TKA) has long been considered the most effective surgery for patients suffering from severe knee arthritis [1]. It is a major operation that is frequently used to relieve joint pain and improve joint mobility and function [2]. Though it is uncommon, postoperative infection is one of the most devastating and feared complications of TKA [3,4].

Diabetes mellitus (DM) is one of several risk factors for periprosthetic joint infection (PJI) following total joint arthroplasty [5]. It has been reported that more than half of those with diabetes have arthritis and may require a hip or knee replacement in the future [6,7]. With the increasing prevalence of diabetes worldwide, the number of diabetic patients requiring arthroplasty is expected to rise in the future [8]. Therefore, we believe that studies on risk infection in diabetics undergoing TKA will be extremely beneficial in preventing PJI

To the best of our knowledge, no recent systematic review and meta-analysis has been conducted comprehensively to investigate the prevalence and risk of infection in patients with diabetes following primary TKA, with the most recent known being in 2014 which was on the influence of DM on the post-operative outcome of elective primary TKA. Thus, author is keen to evaluate the recent overall prevalence of diabetes in patients who are to undergo elective primary TKR and the risk of post-operative infection.

1.2 OBJECTIVE

1. To study the outcome of primary total knee arthroplasty (TKA) among diabetic and non-diabetic patient by using systematic review and meta-analysis methodology.
2. To obtain the prevalence and estimating risk of infection in diabetic patient post primary total knee replacement
3. To obtain the prevalence and estimating risk of superficial SSI in diabetic patient post primary total knee replacement.
4. To obtain the prevalence and estimating risk of deep SSI in diabetic patient post primary total knee replacement.
5. To evaluate any difference between prevalence and comparing risk of superficial and deep SSI in diabetic patient post primary total knee replacement

CHAPTER 2 – STUDY PROTOCOL

2.0 METHODS

In accordance with the Preferred Reporting Items for Systematic Reviews and Meta analyses (PRISMA) guideline, we will conduct this systematic review and meta-analysis to assess the prevalence and risk of infection among diabetic patients compared to non-diabetic subjects who receive primary TKA [9].

The protocol of this study was registered with International Prospective Register of Systematic Reviews (PROSPERO) database, registration number: CRD42021244391.

2.1. Data Sources and Searches

PubMed, Scopus, Google Scholar, Web of Science, and Science Direct electronic databases will be searched to identified studies published from inception to April 2022.

We will look over the reference lists of the included studies for other potential studies that could be included in the SRMA. EndNote X8 software will be used to manage and screen out duplicate studies.

2.2. Eligibility Criteria

We will consider observational studies as eligible studies. Preprints were not considered and only published studies reporting data of interest were considered eligible. Review papers, case studies, comments, and perspectives will be excluded from the study. Data from news reports and press releases, as well as data gathered from websites and databases, were not taken into account. Studies published in languages other than English will be included, with Google Translate going to be used to translate them. We will be cautious about studies from the same authors or facilities, but if the study population was distinct, the study was included.

2.3. Inclusion and Exclusion Criteria

Patients with diabetes who had a primary TKA will be included in the study and compared with non-diabetic subjects. Research involving (1) revision total knee replacement, (2) original knee replacement with evidence of prior infection, and (3) animal studies are excluded. At the same time, we also going to exclude data obtained from insurance companies and from hospital billing.

2.4. Study Selection

Articles of interest will be reviewed based on title and abstract, then full text by two authors (M.A.A. and S.A.R.) separately to find suitable studies. Disagreements over inclusion will be aired and a consensus will be reached by discussion among the authors.

2.5. Data Extraction

Data extraction will be done by M.A.A. and cross-checked independently by two authors (M.A.I. and S.A.R.). When duplicate data were discovered, the study with the smaller sample size or incomplete data will be discarded. We will take the following data from each eligible study and entered it into a pre-set Excel spreadsheet: the first author's last name; the participants' region (country); the data collecting period; the total number of TKA patients; the total number of knees examined; age; type of infection and the study design.

2.6. Quality Assessment

The quality of included studies will be assessed independently by two authors (M.A.A. and S.A.R.) using the Joanna Briggs Institute (JBI) critical appraisal tools [10]. Further, the results of the quality assessment will be checked by another author (M.A.I.). Studies will be categorised as "high risk of bias" (low quality), "moderate risk of bias" (moderate quality) or "low risk of bias" (high quality) when the overall score was <50%, 50–70% or >70%, respectively [11,12].

2.7. Data Analyses

The pooled prevalence and 95% confidence intervals (CIs) of infection in diabetes patients will calculate using a random-effects model. The risk ratio (RR) with 95% confidence intervals (CIs) was used to compare the risk of infection between diabetic and non-diabetic subjects. In addition, the pooled prevalence of infection with the corresponding 95% CI will be calculated for both diabetic and non-diabetic subjects.

To examine publication bias, funnel plots displaying prevalence estimates versus sample variance will be created, and the asymmetry of the funnel plot was confirmed using Egger's test when a minimum of 10 studies were available. Heterogeneity between studies will be assessed using the I2 statistic (I2 > 75% indicating substantial heterogeneity) in addition to using Cochran's Q test to identify the significance of heterogeneity. Galbraith plots will be constructed to identify the sources of heterogeneity. Subgroup analysis will be done by analysing the risk and prevalence of deep surgical site infection and superficial infection. Sensitivity analyses will be performed by (A) leave-one-out method, (B) excluding the outlier studies, (C) excluding small studies (n < 500 for RR estimation and n < 100 for prevalence estimation) and (D) excluding low- and moderate-quality studies. All the analyses and plots will be generated by using metaprop codes in meta (version 4.11–0) and metafor (version 2.4–0) packages of R (version 3.6.3) in RStudio (version 1.2.5033) and RevMan (version 5.3) software [13,14].

2.2 CONTRIBUTIONS OF AUTHORS

Conceptualization

Shaifuzain Ab Rahman and Md Asiful Islam

Methodology

Md Asiful Islam and Mohd Aliff Ahmad

Software,

Md Asiful Islam and Mohd Aliff Ahmad

Validation,

Shaifuzain Ab Rahman and Md Asiful Islam

Formal analysis

Md Asiful Islam and Mohd Aliff Ahmad

Investigation

Shaifuzain Ab Rahman**,** Md Asiful Islam and Mohd Aliff Ahmad

Resources

Shaifuzain Ab Rahman and Md Asiful Islam

Data curation

Md Asiful Islam and Mohd Aliff Ahmad

Writing—original draft preparation

Mohd Aliff Ahmad

Writing—review and editing

Shaifuzain Ab Rahman and Md Asiful Islam

Visualization

Shaifuzain Ab Rahman and Mohd Aliff Ahmad

Supervision

Shaifuzain Ab Rahman and Md Asiful Islam

Project administration

Shaifuzain Ab Rahman

Funding acquisition

Shaifuzain Ab Rahman

2.3 APPENDIX

2.3.1 Search strategy

Table S1. Search strategies

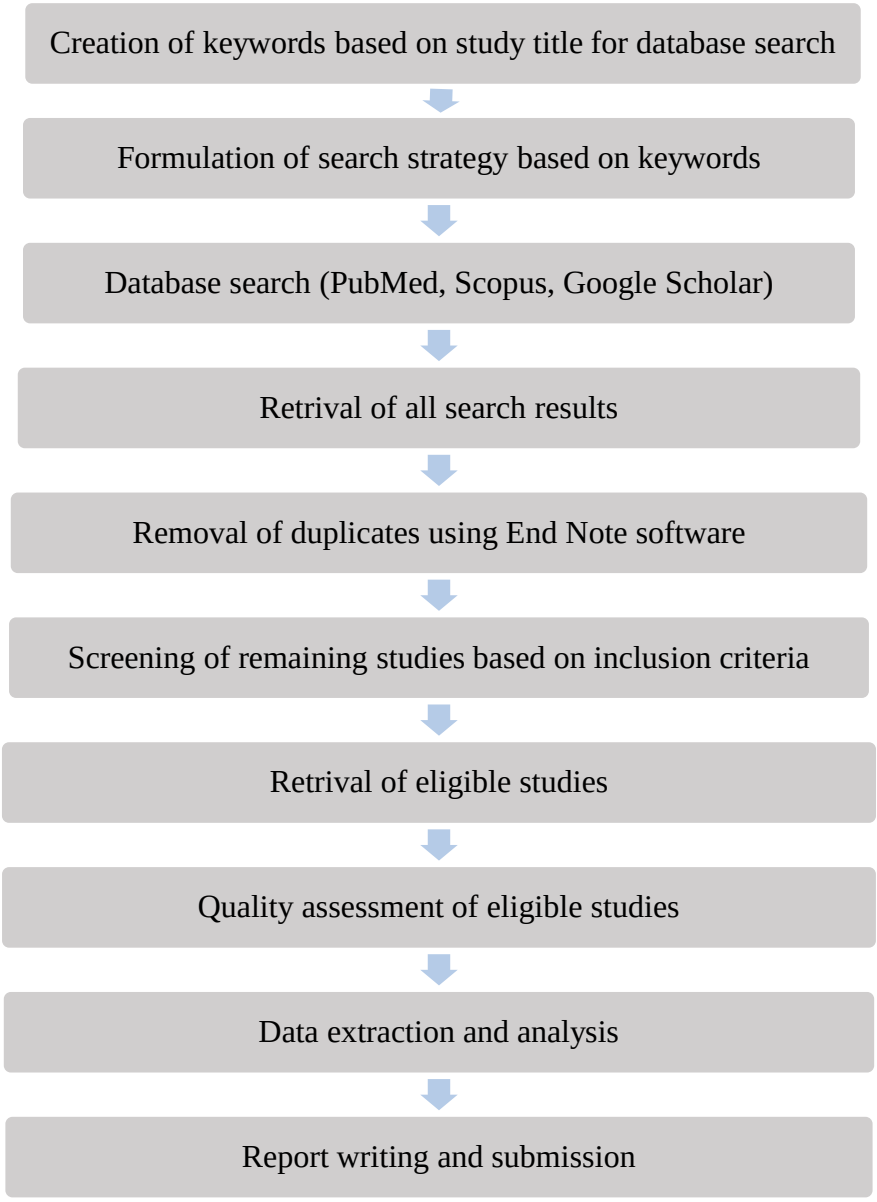
Databases	Search strategies
PubMed	(knee replacement[Title/Abstract] OR knee replacements[Title/Abstract] OR knee arthroplasty[Title/Abstract] OR knee arthroplasties[Title/Abstract] OR TKA[Title/Abstract] OR TKR[Title/Abstract]) AND (Diabetic[Title/Abstract] OR Diabetics[Title/Abstract] OR diabetes[Title/Abstract])
Scopus	TITLE-ABS("knee replacement" OR "knee replacements" OR "knee arthroplasty" OR "knee arthroplasties" OR TKA OR TKR) AND TITLE-ABS(Diabetic OR Diabetics OR diabetes)
Web of Science	TI=("knee replacement" OR "knee replacements" OR "knee art hroplasty" OR "knee arthroplasties" OR TKA OR TKR) AND TI=(Diabetic OR Diabetics OR diabetes) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI Timespan=All years*
ScienceDirect	Title, abstract, keywords: ("knee replacement" OR "knee replacements" OR "knee arthroplasty" OR "knee arthroplasties" OR TKA OR TKR) AND (Diabetic OR Diabetics OR diabetes)
Google Scholar	allintitle:("knee replacement" OR "knee replacements" OR "knee arthroplasty" OR "knee arthroplasties" OR TKA OR TKR) (Diabetic OR Diabetics OR diabetes)

2.3.2 Data collection sheet

Major characteristics of the included studies

Study ID	Country	Data collection period	Total number of knees (diabetic)	Total number of study participants (diabetic)	Age of the patients (years) [mean ± SD / median (IQR) / range]	Type of infection	Study design

2.3.3 Flow chart



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2.4 Ethical exemption letter

Jawatankuasa Etika
Penyelidikan Manusia USM (JEPeM)

Human Research Ethics Committee USM (HREC)

Universiti Sains Malaysia
Kampus Kesihatan
16150 Kubang Kerian, Kelantan. Malaysia.
Tel. : +609 - 767 3000/2354/2362
Fax. : + 609 - 767 2351
Email : jepem@usm.my
Laman Web : www.jepem.kk.usm.my
www.usm.my

7th October 2021

Dr. Mohd Aliff Ahmad
Department of Orthopaedics
School of Medical Sciences
Universiti Sains Malaysia
16150 Kubang Kerian, Kelantan.

JEPeM Code : USM/JEPeM/21090614
Protocol Title: Prevalence and Risk of Infection in Patient with Diabetes Following Primary Total Knee Arthroplasty: A Systematic Review and Meta-Analysis.

Dear Dr.,

We wish to inform you that the Jawatankuasa Etika Penyelidikan (Manusia), JEPeM USM has reviewed your study protocol entitled, "**Prevalence and Risk of Infection in Patient with Diabetes Following Primary Total Knee Arthroplasty: A Systematic Review and Meta-Analysis**".

Upon review of study protocol, the committee decided that this project can be exempted from ethical review. Should you require any additional information, kindly please contact JEPeM USM Secretariat at 09-7672354/2352 and email at bazlan@usm.my/ctfatihah@usm.my.

Thank you.

"WAWASAN KEMAKMURAN BERSAMA 2030"

"BERKHIDMAT UNTUK NEGARA"

Sincerely,

ASSOC. PROF. DR. AZLAN HUSIN
Chairperson
Jawatankuasa Etika Penyelidikan (Manusia) JEPeM
Universiti Sains Malaysia

JEPeM
JAWATANKUASA ETIKA PENYELIDIKAN MANUSIA

2.4 PROSPERO

PROSPERO
International prospective register of systematic reviews

NHS
National Institute for Health Research

UNIVERSITY of York
Centre for Reviews and Dissemination

Systematic review

1. * Review title.

Give the title of the review in English

Prevalence and risk of infection in patient with diabetes following primary total knee arthroplasty: a systematic review and meta-analysis

2. Original language title.

For reviews in languages other than English, give the title in the original language. This will be displayed with the English language title.

3. * Anticipated or actual start date.

Give the date the systematic review started or is expected to start.

23/03/2021

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.

30/07/2021

5. * Stage of review at time of this submission.

Tick the boxes to show which review tasks have been started and which have been completed. Update this field each time any amendments are made to a published record.

Reviews that have started data extraction (at the time of initial submission) are not eligible for inclusion in PROSPERO. If there is later evidence that incorrect status and/or completion date has been supplied, the published PROSPERO record will be marked as retracted.

This field uses answers to initial screening questions. It cannot be edited until after registration.

The review has not yet started: No

Review stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Provide any other relevant information about the stage of the review here.
Preliminary searches

Preliminary searches

6. * Named contact.

The named contact is the guarantor for the accuracy of the information in the register record. This may be any member of the review team.

MOHD ALIFF BIN AHMAD

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

Dr Aliff

7. * Named contact email.

Give the electronic email address of the named contact.

drmohdaliff@gmail.com

8. Named contact address

Give the full institutional/organisational postal address for the named contact.

Orthopaedic Department,

Kampus Kesihatan,

Universiti Sains Malaysia,

16150 Kubang Kerian

Kota Bharu, Kelantan, Malaysia.

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

+60133722174

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

Universiti Sains Malaysia

Organisation web address:

https://www.usm.my/

11. * Review team members and their organisational affiliations.

Give the personal details and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong. **NOTE: email and country now MUST be entered for each person, unless you are amending a published record.**

Dr MOHD ALIFF AHMAD. Universiti Sains Malaysia
Dr SHAIFUZAIN AB RAHMAN. UNIVERSITI SAINS MALAYSIA
Dr MD ASIFUL ISLAM. UNIVERSITI SAINS MALAYSIA

12. * Funding sources/sponsors.

Details of the individuals, organizations, groups, companies or other legal entities who have funded or sponsored the review.

None

Grant number(s)

State the funder, grant or award number and the date of award

13. * Conflicts of interest.

List actual or perceived conflicts of interest (financial or academic).

None

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members. **NOTE: email and country must be completed for each person, unless you are amending a published record.**

15. * Review question.

State the review question(s) clearly and precisely. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS or similar where relevant.

What is the risk and prevalence of infection in diabetic patients following primary total knee arthroplasty?

16. * Searches.

State the sources that will be searched (e.g. Medline). Give the search dates, and any restrictions (e.g. language or publication date). Do NOT enter the full search strategy (it may be provided as a link or

attachment below.)

PubMed, Scopus, Web of Science, ScienceDirect, Google Scholar

No restriction in language and year

Searches will be re-run prior to the final analysis

17. URL to search strategy.

Upload a file with your search strategy, or an example of a search strategy for a specific database, (including the keywords) in pdf or word format. In doing so you are consenting to the file being made publicly accessible. Or provide a URL or link to the strategy. Do NOT provide links to your search **results**.

https://www.crd.york.ac.uk/PROSPEROFILES/244391_STRATEGY_20210322.pdf

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Yes I give permission for this file to be made publicly available

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied in your systematic review.

Diabetes mellitus is a disorder in which the body does not produce enough or respond normally to insulin, causing blood sugar (glucose) levels to be abnormally high infection in total knee arthroplasty is the presence of acute inflammation based on histopathologic examination of periprosthetic tissue at the time of surgical debridement or prosthesis removal

19. * Participants/population.

Specify the participants or populations being studied in the review. The preferred format includes details of both inclusion and exclusion criteria.

Any diabetic patient post primary total knee arthroplasty with infection post operatively

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the interventions or the exposures to be reviewed. The preferred format includes details of both inclusion and exclusion criteria.

Inclusion criteria, patient with diabetes who underwent primary total knee arthoplasty experiencing post operative infection

Exclusion criteria, secondary knee replacement, primary knee replacement with evidence of previous knee infection,

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the intervention/exposure will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

For estimating the risk, only case-control studies will be considered and in this part, controls will be the non-diabetic patient who underwent primary total knee arthoplasty experiencing post operative infection.

However, for the prevalence estimating part, there will be no control group.

22. * Types of study to be included.

Give details of the study designs (e.g. RCT) that are eligible for inclusion in the review. The preferred format includes both inclusion and exclusion criteria. If there are no restrictions on the types of study, this should be stated.

We will include observational studies (including cohort, case–control and cross sectional studies) for the assessment of infection

23. Context.

Give summary details of the setting or other relevant characteristics, which help define the inclusion or exclusion criteria.

Patients with diabetes who underwent primary total knee arthroplasty with evidence of prevalence of infection infection,

24. * Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

Post operative infection prevalence and risk in patient underwent primary total knee arthroplasty

Measures of effect

Please specify the effect measure(s) for you main outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

Prevalence and risk ratio

25. * Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state 'None' or 'Not applicable' as appropriate to the review

None

Measures of effect

Please specify the effect measure(s) for you additional outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

26. * Data extraction (selection and coding).

Describe how studies will be selected for inclusion. State what data will be extracted or obtained. State how this will be done and recorded.

Study selection

Two reviewers applying eligibility criteria and selecting studies for inclusion in the systematic review

Two people will independently screen records and will be blinded to each other's' decisions.

Any disagreements between individual judgements will be discussed and any further dispute will be consulted among the review authors

Data extraction

Data that will be extracted from study documents, including information about study design and methodology, participant demographics and baseline characteristics and numbers of events effect. Two people will independently extract data and another person check the extracted data. Recording data is via excel spreadsheet. Disagreements between individual judgements will be resolved by discussion and consensus

27. * Risk of bias (quality) assessment.

State which characteristics of the studies will be assessed and/or any formal risk of bias/quality assessment tools that will be used.

Disagreements between individual judgements will be resolved by discussion and consensus.

28. * Strategy for data synthesis.

Describe the methods you plan to use to synthesise data. This **must not be generic text** but should be **specific to your review** and describe how the proposed approach will be applied to your data. If meta-analysis is planned, describe the models to be used, methods to explore statistical heterogeneity, and software package to be used.

This systematic review and meta-analysis will be used to synthesise existing data of infection in patients with diabetes following total knee replacement to calculate the prevalence with a 95% confidence interval (CI). Random-effects models will be used and measures of heterogeneity will be presented with p-values in a forest plot. All the analyses will be performed by using the metafor and meta packages of R and RStudio software by using metaprop codes

29. * Analysis of subgroups or subsets.

State any planned investigation of 'subgroups'. Be clear and specific about which type of study or participant will be included in each group or covariate investigated. State the planned analytic approach.

Subgroup' analysis will be including the level of HbA1c of the patient prior to operative intervention in addition based on age, sex and location of the participants

30. * Type and method of review.

Select the type of review, review method and health area from the lists below.

Type of review

Cost effectiveness
No

Diagnostic
No

Epidemiologic
Yes

Individual patient data (IPD) meta-analysis
No

Intervention

No

Living systematic review
No

Meta-analysis
Yes

Methodology
No

Narrative synthesis
No

Network meta-analysis
No

Pre-clinical
No

Prevention
Yes

Prognostic
Yes

Prospective meta-analysis (PMA)
No

Review of reviews
No

Service delivery
No

Synthesis of qualitative studies
No

Systematic review
Yes

Other
No

Health area of the review

Alcohol/substance misuse/abuse
No

Blood and immune system
No

Cancer
No

Cardiovascular
No

Care of the elderly
No

Child health
No