BMJ Open

Protocol for a prospective multicentre cohort study to address the question whether diabetes and its management is still a risk factor in fast-track joint arthroplasty

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To cite: Issa LM, Kehlet H, Madsbad S, *et al*. Protocol for a prospective multicentre cohort study to address the question whether diabetes and its management is still a risk factor in fast-track joint arthroplasty. *BMJ Open* 2024;**14**:e080232. doi:10.1136/bmjopen-2023-080232

► Prepublication history for this paper is available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2023-080232).

Received 24 September 2023
Accepted 09 April 2024

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ABSTRACT

Introduction Perioperative glycaemic control is important. However, the complexity of guidelines for perioperative diabetes management is complicated due to different and novel antihyperglycaemic medications, limited procedure-specific data and lack of data from implemented fast-track regimens which otherwise are known to reduce morbidity and glucose homeostasis disturbances. Consequently, outcome in patients with diabetes mellitus (DM) after surgery and the influence of perioperative diabetes management on postoperative recovery remains poorly understood.

Methods and analysis A prospective observational multicentre study involving 8 arthroplasty centres across Denmark with a documented implemented fast-track programme (median length of hospitalisation (LOS) 1 day). We will collect detailed perioperative data including preoperative haemoglobin A1c and antidiabetic treatment in 1400 unselected consecutive patients with DM undergoing hip and knee arthroplasty from September 2022 to December 2025, enrolled after consent. Follow-up duration is 90 days after surgery. The primary outcome is the proportion of patients with DM with LOS >4 days and 90-day readmission rate after fast-track total hip arthroplasty (THA), total knee arthroplasty (TKA) and unicompartmental knee arthroplasty (UKA). The secondary outcome is the association between perioperative diabetes treatment and LOS >2 days, 90-day readmission rate, other patient demographics and Comprehensive Complication Index for patients with DM after THA/TKA/UKA in a fast-track regimen.

Ethics and dissemination The study will follow the principles of the Declaration of Helsinki and ICH-Good Clinical Practice guideline. Ethical approval was not necessary as this is a non-interventional observational study on current practice. The trial is registered in the Region of Southern Denmark and on ClinicalTrials.gov. The main results and all substudies of this trial will be published in peer-reviewed international medical journals.

Trial registration number NCT05613439.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This will be the first large prospective and procedure-specific observational multicentre study on perioperative diabetes treatment and 90 days outcome within a well-implemented fast-track regimen in joint arthroplasty from eight large public hospitals across Denmark.
⇒ We will collect detailed data on perioperative diabetes treatment, in a homogenous surgical group, accepting 99% follow-up.
⇒ Data on adherence to local guidelines will be registered in order to analyse the influence of differences in perioperative diabetes treatment on overall outcome after fast-track joint arthroplasty in patients with diabetes.
⇒ The study examines associations between perioperative diabetes treatment and outcome, but due to the observational study design causality cannot be assessed.

INTRODUCTION

People with diabetes mellitus (DM) are traditionally considered 'high-risk' surgical patients. Previous research has established a link between uncontrolled diabetes and hyperglycaemia and an increased risk of postoperative complications and prolonged hospitalisation.[1 2] Consequently, numerous studies have suggested benefits of strict glycaemic control during the perioperative period.[3] However, existing literature concerning perioperative diabetes treatment is characterised by inconsistent definitions of DM and glycaemic control, making it difficult to analyse data across studies.[2 4] Furthermore, the lack of procedure-specific and general high-grade evidence is reflected in the complicated and heterogeneous guidelines

both nationally and internationally.[5 6] Consequently, the optimal perioperative diabetes management and blood-glucose control remains debatable.[7 8]

The clinical care problem regarding perioperative management of patients with diabetes has been further complicated by novel antihyperglycaemic agents (glucagone-like-peptide-1 receptor agonists (GLP-1 RA) and sodium-glucose cotransporter-2 inhibitors (SGLT2i)), which have different sites of action and risk profiles further complicating management recommendations.[5]

Finally, patients undergoing primary total hip arthroplasty, total knee arthroplasty and unicompartmental knee arthroplasty (THA/TKA/UKA) in a fast-track enhanced recovery regimen have fewer complications and reduced hospital stay.[9] The benefits of a standardised fast-track approach are well-documented[10] and result in faster recovery, reduced medical complications and with less impact on glucose homeostasis,[11] although there is very limited procedure-specific fast-track data in patients with DM.[4 12] A previous prospective study in 36 762 patients undergoing THA/TKA in a fast-track regimen (2010–2017), found that patients with diabetes (n=3452) had increased risk of longer LOS and that patients with insulin-treated diabetes (n=837) had a slightly increased risk of complications compared with non-insulin-treated patients with diabetes and patients without diabetes.[12] The study found no increased risk of postoperative infections or readmissions but highlighted the need for further research concerning postoperative complications differentiated by type of antihyperglycaemic treatment.[12] Since then median LOS has decreased to 1 day[9] as the fast-track protocols have been continually refined. Although fast-track surgery has reduced postoperative complications, several issues in relation to perioperative diabetes treatment and association with postoperative outcome remains unexplored. The fast-track regimen together with a homogeneous surgical group, makes it a perfect setup to elucidate the specific role of DM per se and perioperative DM management on outcome.

During the last decade, the Lundbeck Foundation Centre for fast-track hip and knee arthroplasty has published >150 studies, demonstrating improved outcome (http://www.fthk.dk). More recently, a subsequent follow-up Danish multicentre collaboration has been established (https://fast-track.health/) focusing on increased use of outpatient THA, TKA and UKA[13] and high-risk patients including patients with DM within an improved care protocol.[9] The prevalence of patients with DM undergoing THA/TKA/UKA in the present collaborating centres is about 10%.[12]

In this study, we wish to investigate clinical challenges in perioperative diabetes management and the association with outcome after surgery in these potential 'high-risk' patients, thus providing much-needed information on what and how to optimise the postoperative course for surgical patients with DM within an established fast-track protocol. Such detailed analyses do not exist in the literature.

In the present established multicentre collaboration, we will prospectively examine LOS, Comprehensive Complication Index (CCI)[14] and 90-day readmission rate in patients with DM undergoing THA, TKA and UKA in a fully implemented fast-track regimen with detailed data on perioperative diabetes treatment (table 1) and comorbidities to provide an improved basis for future guideline development.

OBJECTIVES

We will address following research questions:

1. Is there a further reduction in proportion of patients with LOS >4 days and 90-day readmission rate after THA/TKA/UKA in a fast-track regimen for patients with DM compared with those reported from the collaboration previously?[12]
2. Is there any clinically relevant association with the different aspects of perioperative diabetes treatment and LOS >2 days, 90-day readmission rate or CCI?[14]
3. How does perioperative GLP-1 RA and SGLT2i treatment influence outcome after THA/TKA/UKA in a fast-track regimen in patients with DM?
4. Does adherence to local perioperative diabetes guidelines influence postoperative outcomes?
5. Is discharge on the same day after THA/TKA/UKA in a fast-track regimen feasible and safe in patients with diabetes?

Table 1 Perioperative diabetes treatment data registered in the trial

Preoperative	Intraoperative	Postoperative
Haemoglobin A1c (<30 days prior to surgery) Type of antihyperglycaemic medication Pausation of antihyperglycaemic medication prior to surgery Preoperative glucocorticoid dose and type	Time of surgery Use of glucose/insulin/(potassium) infusion or other antihyperglycaemic agents	Insulin regimen used while in hospital Time for reuptake of usual antihyperglycaemic medication Last measured blood glucose before discharge (maximum 8 hours)

Box 1 Key points for fast-track protocol for patients undergoing primary knee arthroplasty or hip arthroplasty[9 13]

⇒ Multimodal opioid-sparing analgesia (local infiltration analgesia for total knee arthroplasty/unicompartmental knee arthroplasty, non-steroidal anti-inflammatory drug/cyclooxygenase-2 inhibitors, paracetamol, high-dose glucocorticoid)
⇒ Intended early mobilisation (<6 hours postoperatively)
⇒ In-hospital only thromboprophylaxis when length of stay <5 days
⇒ Tranexamic acid during surgery
⇒ Spinal anaesthesia preferred over general anaesthesia
⇒ Discharge to own home based on well-defined functional criteria
⇒ Intended hospital stay 0–1 day

METHOD

Design and organisation: prospective observational study in a well-established multicentre fast-track collaboration. The Center for Fast-track Hip and Knee Replacement consists of eight public hospital arthroplasty centres across Denmark covering approximately 40% of all THA/TKA/UKA in Denmark (https://fast-track.health/).[13] All centres adhere to the same fast-track protocol where median LOS in 2018 was 1 day.[13] The fast-track protocol includes preferred spinal anaesthesia, multimodal opioid-sparing analgesia including perioperative high-dose glucocorticoid, avoidance of tourniquet and bladder catheterisation, early mobilisation and discharge to own home based on functional discharge criteria. Postoperative thromboprophylaxis is given 6–8 hours after surgery and used only during hospitalisation when LOS is 5 days or less. Key points for the fast-track protocol are listed in box 1.[9 13]

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Settings and participants

Consecutive patients (about 7000/year) scheduled for THA/TKA/UKA at the eight participating centres will be included in a database after informed consent. The participating centres contribute about 40%–50% of the annual procedures in Denmark and all centres have a main responsible surgeon and 1.5 dedicated research staff (nurses and physiotherapists) to secure a uniform standardised setup.

Inclusion and exclusion criteria

All patients included in the fast-track collaboration (https://fast-track.health/)[13] scheduled for surgery from 1 October 22 will be screened for eligibility according to inclusion and exclusion criteria.

Inclusion criteria

- Diagnosed with DM.
- An active prescription of antihyperglycaemic treatment including metformin, sulfonylureas, dipeptidyl peptidase-4 inhibitors, GLP-1 RA, SGLT2i, long-acting or short-acting insulin and mixed insulin.

Exclusion criteria

- Dietary regulated diabetes with no active prescribed antihyperglycaemic treatment.

An active prescription on an antihyperglycaemic prescribed for weight loss only, without any other active antihyperglycaemic prescriptions.

Data collection

All data are collected in an established Research Electronic Data Capture database in collaboration with the Open Patient Data Explorative Network in Odense University Hospital. Patients will be enrolled in the database in different periods in the centres from September 2022 until December 2025. There will be interim reports on the subtopics after every 400th patient with DM. Data will be used to address and overcome possible clinical and organisational issues.

The data collection includes patient-reported data from questionnaires, online or on paper, with help from the research staff, along with data extraction from electronic medical records with backup from physicians if needed.[13] All data are collected by research staff in a systematic way both preoperatively and postoperatively. Data contain demographics, comorbidity, frailty scale, preoperative blood tests, CCI, LOS after surgery and 90-day readmissions, including cause and length of stay (LOS). Additionally, all patients with DM treated with at least one antihyperglycaemic drug prior to surgery will have preoperative haemoglobin A1c (taken <30 days prior to surgery), type of prescribed antihyperglycaemic medication and types of antihyperglycaemic drugs given during hospitalisation collected from their record files. Data on preoperative antihyperglycaemic medication cessation on the day of surgery and resumption postsurgery will be collected daily while in hospital.

To ensure a uniform working method across centres, joint knowledge-sharing meetings are held several times a year.

Outcome

The primary outcome is the proportion of patients with DM with LOS >4 days and the 90-day readmission rate after current fast-track THA/TKA/UKA with a median LOS of 1 day[9] compared with our previous fast-track studies where median LOS was 2–3 days.[12]

The secondary outcomes are the association between perioperative diabetes treatment and LOS >2 days, the reasons for 90-day readmission, CCI and the role of other patient demographics for patients with DM after THA/TKA/UKA in a fast-track regimen.

Data presentation, power calculation and statistics

There is sparse procedure-specific data in patients with diabetes having THA, TKA or UKA within a fully

implemented fast-track setting. However, our previous study found about 10% of patients with diabetes had LOS >4 days.[12] Based on published data showing a continued decline in LOS >4 days from 10% in 2010 to 5% in 2018,[9] we assume that the continued improvements in the fast-track protocol have reduced the number of patients with diabetes requiring a LOS of >4 days to 7% in 2022. Consequently, 920 patients will be needed to confirm this hypothesis using a 'difference from constant' power analysis with a power of 0.9 and a level of 0.05 significance.[15] Similarly, 10% of patients with diabetes had readmissions within 90 days in our previous study,[12] and overall 90-day readmission rates were about 8% in 2018[9] and 1347 patients with diabetes are required for confirming a reduction in readmission rate to 7.5% with a power of 0.9 and a level of significance of 0.05.[15] Loss to follow-up was not considered an issue as current data from the database demonstrated a withdrawal of consent in <0.5%. Based on these assumptions, we decided that the present study will include at least 1400 patients with DM to assure sufficient power.

Data will be analysed using descriptive statistics and adjusted analysis will be performed using multivariate regression when appropriate.

Data statement

Data are available on request to the corresponding author according to Danish law (patient privacy).

ETHICS AND DISSEMINATION PLAN

According to Danish law, ethical approval was not necessary since surgical and perioperative treatment will follow usual practice without any changes (https://researchethics.dk/information-for-researchers/overview-of-mandatory-reporting). Permission to collect, store and process data was approved by the Region of Southern Denmark (Journal No 22/39454) and the study is registered on ClinicalTrials.gov (NCT05613439). Patients give consent regarding completion of questionnaires and data extraction from medical records.

The main results will be prepared for publication in internationally peer-reviewed journals with Luma Mahmoud Issa as first author. Other authorships include Professor in Endocrinology Sten Madsbad and members of the steering committee from the multicentre collaboration (https://fast-track.health/)[13] according to the rules of the Vancouver group (International Committee of Medical Journal Editors) for the fulfilment of co-authorship. All manuscripts derived from the trial will be published by the same author group in internationally peer-reviewed journals. All authors will be mentioned by name and affiliation.

Future perspective

New technologies have been developed regarding automatic continuous glucose monitoring equipment[16 17] but further studies are required before possible clinical implementation. Finally, although future care of surgical patients with DM may be simplified with the introduction of automatic monitoring and treatment equipment (the closed-loop system), there is currently very limited perioperative data available[18] and again without specific procedure data and consideration of a well-implemented fast-track programme. Consequently, an in-depth understanding of DM and the perioperative treatment is required in relation to introducing new technology.

The findings of this study will contribute with detailed novel data on perioperative diabetes treatment in THA/TKA/UKA in fast-track surgery, related to outcome. Improving perioperative care for patients with DM might lead to shorter LOS, higher rate of same day surgery, fewer readmissions and thereby an overall safer treatment for patients with DM undergoing THA/TKA/UKA in a fast-track regimen. The results will be valuable for similar developments in other procedures.

Economy and funding statement

The initiative to start the study was taken by Professor Henrik Kehlet and the study is financially supported by a grant from the Novo Nordisk Foundation (grant number NNF21SA0073760), which is given to the Center for Fast-Track Hip and Knee Replacement managed by Professor Henrik Kehlet, Rigshospitalet and Thomas Jakobsen, Aalborg Hospital.

Expenses in connection with the study relate to the remuneration of the investigator responsible for the trial, project nurses and database administration. PhD student Luma Mahmoud Issa is remunerated by a grant from the Novo Nordisk Foundation for the present study and has no financial benefit from the study.

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Contributors Devised the project, contributed to study design and developed protocols for data collection and analysis: LMI, CCJ, SM, HK. Contributed to conception and design, and acquired data: ML-L, CV, TJ, MRA, MJB, SO, TBH, KG. Drafted the article: LMI, CCJ, SM, HK. Revised the article critically for important intellectual content: ML-L, CV, TJ, MRA, MJB, SO, TBH, KG. Gave final approval of the version to be published: all authors. All authors met the ICMJE criteria for authorship and agreed to be accountable for the integrity and veracity of this protocol and the data collected and analysed thereafter.

Funding This study was funded by Novo Nordisk Foundation (NNF21SA0073760).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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Correction: *Protocol for a prospective multicentre cohort study to address the question whether diabetes and its management is still a risk factor in fast-track joint arthroplasty*

Issa LM, Kehlet H, Madsbad S *et al*. Protocol for a prospective multicentre cohort study to address the question whether diabetes and its management is still a risk factor in fast-track joint arthroplasty. *BMJ Open* 2024;14:e080232. doi: 10.1136/bmjopen-2023–080232

Author has identified two errors that need to be corrected for clarity and accuracy:

1) The manuscript currently states:

"All patients included in the fast-track collaboration (https://fast-track.health) scheduled for surgery from 1 October 23 will be screened for eligibility according to inclusion and exclusion criteria."

It should correctly state:

"All patients included in the fast-track collaboration (https://fast-track.health) scheduled for surgery from 1 October 22 will be screened for eligibility according to inclusion and exclusion criteria."

2) Incorrect Reference (Reference 1)

The current reference is:

"Aghamelu O, Buggy P, Smith G, *et al*. Serum Netosis expression and recurrence risk after regional or volatile anaesthesia during breast cancer surgery: A pilot, prospective, randomised single-blind clinical trial. *Acta Anaesthesiol Scand* 2021;65:e044394:313–9."

The correct reference is:

Buggy DJ, Nolan R, Coburn M, *et al*. Protocol for a prospective, international cohort study on the Management and Outcomes of Perioperative Care among European Diabetic Patients (MOPED). *BMJ Open*. 2021;11:e044394.

BMJ Open 2025;**15**:e080232corr1. doi:10.1136/bmjopen-2023-080232corr1