

Original Article

Perioperative GLP1-RA management and risk of aspiration in patients with diabetes undergoing fast-track hip and knee arthroplasty

Luma Mahmoud Issa^{1, 2}, Henrik Kehlet^{2, 3}, Sten Madsbad⁴, Martin Lindberg-Larsen^{2, 5}, Claus Varnum^{2, 6}, Thomas Jakobsen^{2, 7}, Mikkel Rathsach Andersen^{2, 8}, Manuel Josef Bieder^{2, 9}, Søren Overgaard^{2, 10, 11}, Torben Bæk Hansen^{2, 12}, Kirill Gromov^{2, 13} & Christoffer Calov Jørgensen^{2, 14}

1) Department of Anaesthesia and Intensive Care, Copenhagen University Hospital – Hvidovre Hospital, 2) Center for Fast-track Hip and Knee Replacement, 3) Section of Surgical Pathophysiology, Copenhagen University Hospital – Rigshospitalet, 4) The Department of Endocrinology, Copenhagen University Hospital – Hvidovre Hospital, 5) Department of Orthopaedic Surgery and Traumatology, Odense University Hospital, Svendborg, 6) Department of Orthopaedic Surgery, Vejle Hospital, Lillebaelt Hospital, 7) Department of Orthopaedic Surgery, Aalborg University Hospital, 8) Department of Orthopaedic Surgery, Copenhagen University Hospital – Herlev and Gentofte Hospital, 9) Department of Orthopaedic Surgery, Copenhagen University Hospital – Næstved, Slagelse and Ringsted Hospitals, 10) Department of Orthopaedic Surgery and Traumatology, Copenhagen University Hospital – Bispebjerg Hospital, 11) Department of Clinical Medicine, University of Copenhagen, 12) University Clinic for Hand, Hip and Knee Surgery, Aarhus University Hospital – Hospital Unit West Jutland, 13) Department of Orthopaedic Surgery, Copenhagen University Hospital – Hvidovre Hospital, 14) Department of Anaesthesia, Copenhagen University Hospital – Hospital of Northern Zealand, Hillerød, Denmark

ABSTRACT

INTRODUCTION. Glucagon-like peptide-1 receptor agonists (GLP1-RAs) are increasingly used to manage type 2 diabetes (T2D) and obesity. Recently, concerns have been raised regarding perioperative GLP1-RA management due to delayed gastric emptying and the potential risk of pulmonary aspiration. However, since no prospective data are available on surgical patients, we aimed to investigate the risk of perioperative pulmonary aspiration in patients with T2D treated with a GLP1-RA undergoing fast-track hip and knee arthroplasty.

METHODS. This was a prospective observational study within a multicentre fast-track hip and knee replacement collaboration in patients with T2D with receiving GLP-1 RA. Detailed data were collected from 1 October 2022 to 1 April 2024, including perioperative GLP1-RA management, type of anaesthesia, complications and postoperative length of stay (LOS).

RESULTS. Among 426 patients with T2D, 19% had spinal anaesthesia without sedation, 53% had spinal anaesthesia with propofol sedation, and 26% had general anaesthesia. Data on perioperative management of GLP1-RAs were available in 93% of all patients, of whom 92% had continued their usual GLP1-RA regimen perioperatively, and the median LOS was one (IQR: 1-1) day. There were no cases with perioperative aspiration (0%; 95% confidence interval (CI): 0.0-0.9%) or LOS > 2 days (7%; 95% CI: 5-9%) potentially related to GLP1-RA-associated delayed gastric emptying.

CONCLUSION. Our results support reconsidering the arguments for prolonged withholding of GLP1-RA treatment before surgery and suggest that it may be safe to continue GLP1-RA treatment up to the day of surgery in these patients.

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About 10% of patients undergoing total hip arthroplasty (THA), total knee arthroplasty (TKA) and unicompartmental knee arthroplasty (UKA) in Denmark are diagnosed with type 2 diabetes (T2D) [1].

Glucagon-like peptide-1 receptor agonists (GLP1-RAs), used to treat T2D and obesity, stimulate glucose-dependent insulin secretion, suppress glucagon secretion and delay gastric emptying [2]. Due to the well-documented effects on blood glucose, weight loss [3] and prevention of cardiovascular events (such as acute myocardial infarction and stroke) without a heightened risk of hypoglycaemia [2], the use of GLP1-RAs is expected to increase rapidly. However, delay of gastric emptying has raised concerns about the risk of pulmonary aspiration, and perioperative management of GLP1-RAs is currently widely debated [4, 5].

Recent studies examined the relationship between semaglutide and GLP1-RAs use and residual gastric content (RGC) in patients undergoing gastric endoscopy. RGC was defined as any solid contents or fluids of > 0.8 ml/kg body weight and any solids in the stomach, respectively. Both studies found increased RGC in patients treated with semaglutide and GLP1-RAs [6, 7]. Furthermore, case reports have described solid foods in the stomach of patients treated with GLP1-RA during gastric endoscopy, despite a > 6-hour fasting period [8, 9]. Consequently, the American Society of Anesthesiologists has published a consensus-based guidance on perioperative management of GLP1-RAs, recommending holding daily doses of once-daily GLP1-RAs on the day of surgery and of once weekly dosing one week prior to surgery, ensuring at least one-week cessation of long-acting GLP1-RAs [10]. However, the American guidelines have not been adopted by any other country [11] and have been questioned due to a lack of evidence and clinical studies [4, 12]. For example, the Danish Society of Anaesthesia and Intensive Care did not find sufficient evidence to support a regular guideline but published a consensus paper on considerations and precautions before anaesthesia in these patients. The consensus paper suggests continuing usual treatment with weekly administered GLP1-RAs and pausing once-daily administered GLP1-RAs on the day of surgery [13]. Finally, the American Society for Metabolic and Bariatric Surgery recently proposed a statement on the perioperative use of GLP1-RAs, suggesting a multi-society clinical practice approach. They clarified that the statement serves as guidance rather than an evidence-based guideline, further emphasising the need for safety studies within the area [14].

As no surgical procedure-specific data is available, we aimed to prospectively investigate the incidence of perioperative aspiration in patients with T2D being treated with GLP-1 RAs undergoing fast-track hip and knee arthroplasty [15].

Methods

This prospective observational study was conducted within a well-established multicentre fast-track collaboration, adhering to a standardised fast-track protocol [15]. All reporting was performed according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Setting

The Center for Fast-track Hip and Knee Replacement collaboration consist of eight public hospitals in Denmark, covering approximately 40% of all national THA/TKA/UKA. Each centre has a main responsible surgeon and dedicated research staff members (nurses and physiotherapists) to ensure a uniform setup. All patients operated in the fast-track protocol receive standardised multimodal opioid-sparing analgesia, including local infiltration analgesia for TKA/UKA, non-steroidal anti-inflammatory drug (NSAID)/cyclooxygenase (COX)-2 inhibitors, paracetamol and high-dose glucocorticoid [15] along with postoperative nausea and vomiting prophylaxis including ondansetron. Participants were instructed to pause daily doses of short-acting GLP1-RAs on the day of surgery and continue long-acting GLP1-RAs before surgery according to established clinical practice.

Study population

All patients eligible for inclusion in the fast-track and scheduled for surgery from 1 October 2022 to 1 April 2024 underwent screening according to the inclusion criteria.

Inclusion criteria

The inclusion criteria were diabetes mellitus type 2 and an active prescription of antihyperglycaemic treatment, including a GLP-1 RA.

Data collection

All data were collected in an established REDCap database in collaboration with the Open Patient data Explorative Network at Odense University Hospital. Written informed consent was achieved through dedicated research staff. Data collection included patient-reported information collected via questionnaires, either online or on paper, with assistance from research staff and data extraction from electronic medical records. Data contained demographics, comorbidity, pre-operative blood tests and length of stay (LOS) after surgery, defined as an overnight stay.

Furthermore, for all patients with T2D, preoperative HbA_{1c} levels and antihyperglycaemic drugs administered during hospitalisation were documented. Information regarding the cessation of preoperative antihyperglycaemic medication on the day of surgery and its resumption after surgery was collected daily during hospitalisation [15].

The type of anaesthesia was either spinal anaesthesia, spinal anaesthesia with propofol sedation or general anaesthesia (total intravenous anaesthesia (TIVA); propofol and an opioid). Data on perioperative complications (pulmonary aspiration) and LOS were collected from medical records. The patients' electronic health-records were reviewed to identify cases with a LOS > 2 days potentially caused by GLP1-RA-associated delayed gastric emptying to ensure no cases of pulmonary aspiration were overlooked.

Outcome

The primary outcome was the incidence of perioperative aspiration based on information from the anaesthesia record or reason for hospitalisation > 2 days after surgery from the electronic health-care records of patients with T2D who were treated with GLP-1Ras while undergoing fast-track hip and knee arthroplasty.

The secondary outcome was the proportion of patients with LOS > 2 days related to GLP1-RA-associated delayed gastric emptying according to the electronic health care records in patients with T2D treated with GLP1-RAs undergoing fast-track hip and knee arthroplasty.

Statistics

Data were analysed using descriptive statistics. We report categorical data as frequencies and percentages with 95% confidence intervals (CI). Continuous data are reported as median (interquartile range (IQR)) or mean (\pm standard deviation). For statistical analysis, RStudio (version 2023.06.0) and vassarstats.net (95% CI for proportions) were used.

Data sharing statement

Anonymised data are available upon reasonable request to the corresponding author according to Danish law (patient privacy).

Ethics

Patients gave consent regarding the completion of questionnaires and data extraction from their medical records. Surgical and perioperative treatment follow usual practice without any changes; hence, according to Danish law, ethical approval was unnecessary.

Trial registration: Permission to collect, store and process data was approved by the Region of Southern Denmark (Journal No 22/39454), and the study is registered with ClinicalTrials.gov (NCT05613439).

Results

We included 426 patients (**Table 1**) with T2D treated with GLP1-RAs (**Figure 1**). Data on administration of GLP1-Ras before surgery were available for 396 (93%) patients, of whom 393 (92%) had continued their usual treatment regimen with the GLP1-RA up to the day of surgery. Only three (1%) patients had postponed long-acting GLP1-RAs as their weekly injection was planned on the same day as surgery. In all three cases, the injection was postponed to the day after surgery, meaning that they had their last GLP1-RA dose seven days before surgery. Furthermore, we had no data on GLP1-RA administration before surgery in 30 (7%) patients. In total, 14.8% of patients were treated with a GLP1-RA alone, 59% were treated with a GLP1-RA in combination with other non-insulin antihyperglycaemic medications, and 26.2% were treated with a GLP1-RA and insulin.

TABLE 1 Demographics in 426 patients with diabetes mellitus type 2 treated with glucagon-like peptide-1 receptor agonists undergoing fast-track hip or knee arthroplasty.

	Data	Patients, n (%)	
		with all data	with missing data
<i>Overall</i>			
Age, mean (\pm SD), yrs	69 (\pm 8)		0
BMI, mean (\pm SD), kg/m ²	34 (\pm 9)		2 (0.5)
Prescribed medications, n (%)	11 (5)		0
<i>Individually</i>			
Female		236 (55)	0
Walking aid		217 (52)	7 (2)
Fall > 2 \times in the past 3 mos.		35 (8)	4 (1)
Living alone		146 (34)	4 (1)
Living in institutions		9 (2)	8 (2)
Working		95 (23)	9 (2)
Smoking		39 (9)	6 (1)
Alcohol > 15 U ^a wk		31 (7)	7 (2)
Psychotropic drug treatment		58 (14)	3 (1)
Cardiac disease ^b		378 (89)	0
Anticoagulant treatment		195 (46)	0
Pulmonary disease ^c		80 (19)	1 (0.2)
Previous cerebral attack		51 (12)	4 (1)
Opioid use before surgery		93 (22)	0

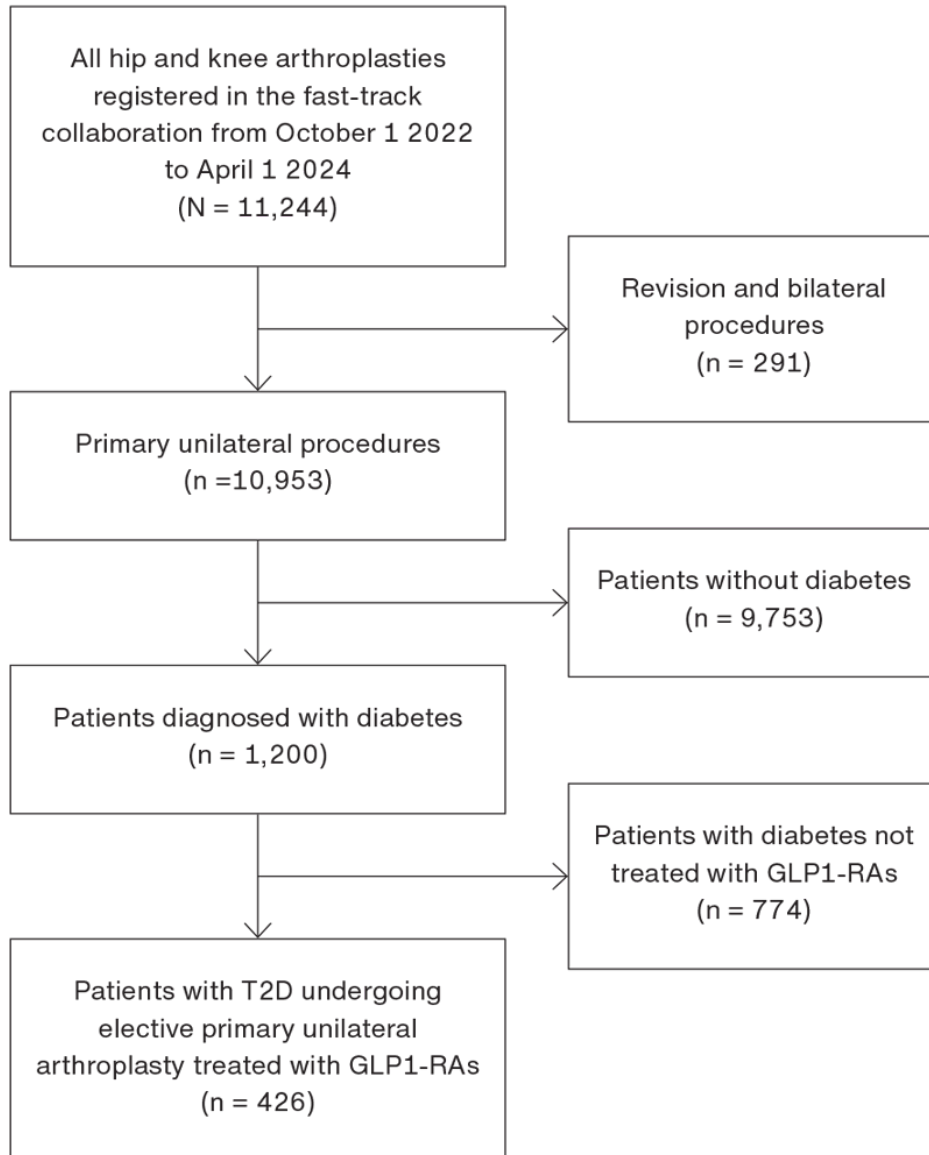
SD = standard deviation.

a) \approx 120 g.

b) On prescription cardiac medication.

c) On prescription medication for a pulmonary condition.

FIGURE 1 STROBE diagram of the study population.



GLP1-RA = glucagon-like peptide-1 receptor agonist; STROBE = Strengthening the Reporting of Observational Studies in Epidemiology; T2D = diabetes mellitus type 2.

Among the 426 included patients, 81 (19%) had spinal anaesthesia without propofol sedation, whereas 226 (53%) had spinal anaesthesia with propofol sedation, and 119 (28%) had general anaesthesia (TIVA). Median LOS was one day (IQR: 1-1 days). We found no cases of perioperative pulmonary aspiration (0%; 95% CI: 0-1%) or LOS > 2 days caused by potentially GLP1-RA-associated delayed gastric emptying (0%; 95% CI: 0-1%) (Table 2).

TABLE 2 Reasons for length of stay > 2 days after surgery for patients with diabetes mellitus type 2 treated with glucagon-like peptide-1 receptor agonists undergoing fast-track hip or knee arthroplasty (N = 28).

	Patients, n
Mobilisation	11
Pain	9
Anaemia	4
Other medical complications: DVT	1
Surgical complications	3

DVT = deep vein thrombosis.

Discussion

In this detailed study on perioperative use of GLP1-RAs in patients with T2D undergoing fast-track hip and knee arthroplasty, we found no cases of pulmonary aspiration or prolonged hospitalisation potentially related to GLP1-RA-associated delayed gastric emptying. Median LOS was one day, which is less than previously reported in patients with DM undergoing hip and knee arthroplasty in the same multicentre setup [1]. Most patients had taken GLP1-RAs before surgery in accordance with their usual administration plan, suggesting that most patients had their usual GLP1-RA exposure at the time anaesthesia was induced.

A scoping review summarising current evidence on GLP1-RAs in the perioperative setting argues that drug clearance (requiring 4-5 half-lives) could compromise glycaemic control. Nevertheless, pre-inventory conditions of gastric emptying return after 8-12 weeks of treatment with semaglutides due to tachyphylaxis [4]. However, poor glycaemic control may delay gastric emptying [12]. In contrast, a recent meta-analysis on gastric emptying delay in 658 non-surgical patients treated with GLP1-Ras, regardless of indication, only found a short gastric emptying delay (~ 36 minutes) relative to standard perioperative fasting periods. This was so regardless of treatment duration and with no significant differences in gastric emptying on modalities that reflected fluid emptying. Consequently, the authors recommended continued GLP1-RA treatment, a liquid diet one day before the procedure and standard preoperative fasting in these patients [16]. A newly published systematic review on the use of GLP1-RAs in surgery suggests that surgeons may leverage GLP1-RAs before surgery, highlighting improved glycaemic control and preoperative weight loss. It further emphasises potential complications, such as delayed gastric emptying, and calls for appropriate patient screening and further exploration of complication rates in this growing patient population [17].

Another recent study included 43,356 T2D patients undergoing upper gastrointestinal endoscopy and found no significant difference in pulmonary aspiration rates between patients treated with GLP1-RAs and those treated with sodium-glucose cotransporter-2 inhibitors (SGLT-2i). However, procedure cancellations occurred twice as often in the GLP1-RA group as in the SGLT-2i group. A potential but speculative reason for this could be the

presence of food contents in the stomach. However, as highlighted in the discussion, the authors noted that their findings are limited to endoscopic procedures, emphasising the need for additional data in other procedures requiring general anaesthesia [18].

Additionally, a surgical study found no increased risk of pulmonary complications in GLP1-RA-treated patients with T2D (n = 3,502) compared to patients with T2D who were treated with other antihyperglycaemic medications (n = 23,679) [19], further questioning the need for prolonged perioperative GLP1-RA pausation [10]. However, this was a retrospective claims-based study with patients undergoing 13 different types of surgeries and without data on pre- and peri-operative GLP1-RA use and fasting times. In contrast, our procedure-specific study provides reassuring data on minimal aspiration risk even during propofol sedation with spontaneous respiration in elective major joint arthroplasty.

Our study does carry some limitations. Firstly, we lack precise data on the last day of administration for the long-acting GLP1-RAs and information on the duration of GLP1-RA use before surgery. Thus, we were unable to provide insights on tachyphylaxis. Nor did we register the exact fasting time, which may have exceeded the minimum recommendation of six hours for solids. Furthermore, GLP-1 RAs differ, and we lack information on the specific types and doses of GLP1-RAs. However, > 99% of all GLP1-RA prescription sales in Denmark from 2012 to 2023 were long-acting GLP1-RAs, with the most common types being semaglutide (85.9% of sales) and liraglutide (12.7% of sales). These drugs have half-lives ($T_{1/2}$) of 165 hours and 12-13 hours, respectively. The effect on gastric emptying is primarily observed with the short-acting GLP1-RAs with a $T_{1/2}$ of 2.4-3.0 hours since substantial tachyphylaxis develops in treatment with the long-acting GLP1-RAs [2], potentially influencing our results. We also only included patients with DM2 treated with GLP1-Ras. Therefore we cannot say anything about aspiration risk in patients treated with GLP1-RA for weight loss only.

Secondly, the non-randomised nature of our study can provide information only on the lack of association and not direct lack of causation with GLP1-RA treatment. However, due to the rarity of aspirations, a randomised clinical trial on this subject may not be feasible. In this context, a retrospective analysis estimated the incidence of perioperative pulmonary aspiration to be one in 7,103 [20]. Thus, the rarity of perioperative pulmonary aspiration is an important limitation in our cohort of 426 patients, of whom 81 received no sedation, leaving only 345 in actual risk of perioperative pulmonary aspiration. Furthermore, we do not know if some patients were cancelled on the day of surgery due to the potential risk of aspiration, which is a potential selection bias in the study population. Finally, as our registration of aspiration was based on the notes from the electronic health records, any lack of recording of aspiration would result in missing outcomes. However, the entire health record was reviewed, including the intraoperative notes from the anaesthesia records, minimising the risk of overlooking aspiration events. As pulmonary aspiration is a critical event with potential treatment-related consequences and a high priority and focus on prevention among anaesthesia providers, we believe that the risk of non-recorded events is minimal. The strengths of our study include being the first detailed, procedure-specific, fast-track study with prospective recording on perioperative GLP1-RA management and 100% follow-up through medical records rather than diagnostic codes.

Conclusion

The arguments for prolonged withholding of GLP1-RAs due to the risk of perioperative aspiration should be reconsidered and weighted against compromising glucose control. Our results indicate no increased risk of pulmonary aspiration during GLP-RA treatment. They also suggest that it may be safe to continue GLP1-RA treatment until the day of surgery in patients with T2D undergoing hip and knee arthroplasty with and without sedation in a fast-track setup.

Correspondence *Luma Mahmoud Issa*. E-mail: luma.mahmoud.issa@regionh.dk

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