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REVIEW ARTICLE/BRIEF REVIEW

Strategies for intraoperative glucose management: a scoping review

Stratégies de prise en charge peropératoire de la glycémie : une étude de portée

Nathaniel Morin, BSc · Sarah Taylor, BScH · Danae Krahn, MD · Leyla Baghirzada, MD · Michael Chong, MD · Tyrone G. Harrison, MD · Anne Cameron, MD, MSc · Shannon M. Ruzycki, MD, MPH

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Abstract

Purpose *Perioperative hyperglycemia is associated with adverse outcomes for patients with and without diabetes. Guidelines and published protocols for intraoperative glycemic management have substantial variation in their recommendations. We sought to characterize the current evidence-guiding intraoperative glycemic management in a scoping review.*

Sources *Our search strategy included MEDLINE (Ovid and EBSCO), PubMed, PubMed Central, EMBASE, CINAHL, Cochrane Library, SciVerse Scopus, and Web of Science and a gray literature search of Google, Google Scholar, hand searching of the reference lists of included articles, OAISter, institutional protocols, and ClinicalTrails.gov.*

Principal findings *We identified 41 articles that met our inclusion criteria, 24 of which were original research studies. Outcomes and exposures were defined heterogeneously across studies, which limited comparison and synthesis. Investigators often created arbitrary and differing categories of glucose values rather than analyzing glucose as a continuous variable, which limited our ability to combine results from different studies. In addition, the study populations and surgery types also varied considerably, with few studies performed during day surgeries and specific surgical disciplines. Study populations often included more than one type of surgery, indication, and urgency that were expected to have varying physiologic and inflammatory responses. Combining low- and high-risk patients in the same study population may obscure the harms or benefits of intraoperative glycemic management for high-risk procedures or patients.*

Conclusion *Future studies examining intraoperative glycemic management should carefully consider the study*

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N. Morin, BSc
Alberta Health Services, Calgary, AB, Canada

S. Taylor, BScH
Cumming School of Medicine, University of Calgary, Calgary, AB, Canada

D. Krahn, MD · L. Baghirzada, MD · M. Chong, MD
Department of Anesthesiology, Perioperative and Pain Medicine, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada

T. G. Harrison, MD · S. M. Ruzycki, MD, MPH (✉)
Department of Medicine, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada
e-mail: Shannon.Ruzycki@ucalgary.ca

Department of Community Health Sciences, Cumming School of Medicine, University of Calgary, Room 1422, 3330 Hospital Drive NW, Calgary, AB T2N 2T9, Canada

A. Cameron, MD, MSc
Department of Obstetrics and Gynecology, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada

population, surgical characteristics, and pre- and postoperative management of hyperglycemia.

Résumé

Objectif *L'hyperglycémie périopératoire est associée à des effets indésirables chez les patients diabétiques et non diabétiques. Les lignes directrices et les protocoles publiés pour la prise en charge glycémique peropératoire présentent des variations substantielles dans leurs recommandations. Nous avons cherché à caractériser les données probantes actuelles guidant la prise en charge glycémique peropératoire dans une étude de portée.*

Sources *Notre stratégie de recherche a inclus les bases de données MEDLINE (Ovid et EBSCO), PubMed, PubMed Central, EMBASE, CINAHL, Cochrane Library, SciVerse Scopus et Web of Science, ainsi qu'une recherche documentaire grise sur Google, Google Scholar, la recherche manuelle des listes de référence des articles inclus, OAISter, les protocoles institutionnels et ClinicalTrials.gov.*

Constatations principales *Nous avons identifié 41 articles qui répondaient à nos critères d'inclusion, dont 24 étaient des études de recherche originales. Les critères d'évaluation et les expositions étaient définis de manière hétérogène d'une étude à l'autre, ce qui a limité la comparaison et la synthèse. Les chercheurs ont souvent créé des catégories arbitraires et différentes de valeurs glycémiques plutôt que d'analyser la glycémie comme une variable continue, ce qui a limité notre capacité à combiner les résultats de différentes études. En outre, les populations étudiées et les types de chirurgie variaient également considérablement, avec peu d'études réalisées lors de chirurgies ambulatoires et dans certaines disciplines chirurgicales spécifiques. Les populations étudiées comprenaient souvent plus d'un type de chirurgie, d'indication et d'urgence, pour lesquelles des réponses physiologiques et inflammatoires variables étaient attendues. La combinaison de patients à faible et à haut risque dans la même population d'étude a pu masquer les inconvénients ou les avantages d'une prise en charge glycémique peropératoire pour les interventions ou les patients à haut risque.*

Conclusion *Les études futures portant sur la prise en charge glycémique peropératoire devraient examiner attentivement la population étudiée, les caractéristiques chirurgicales et la prise en charge pré- et postopératoire de l'hyperglycémie.*

Keywords hyperglycemia · intraoperative glucose · perioperative hyperglycemia

Perioperative hyperglycemia in patients with and without diabetes impacts as many as 35–50% of all patients undergoing noncardiac surgery[1–3] and is associated with adverse patient outcomes including increased risk of infection and greater 30-day mortality.[4–6] Observational data suggest that postoperative hyperglycemia may be more closely associated with adverse outcomes than preoperative hyperglycemia is,[4] but the independent contribution of intraoperative hyperglycemia to adverse outcomes is not as well described. Unsurprisingly, intraoperative hyperglycemia is associated with postoperative hyperglycemia,[7] but many major anesthesia[8,9] and diabetes society[10,11] guidelines do not make recommendations on appropriate monitoring or treatment of intraoperative hyperglycemia. Those who do make recommendations focus on patients with diabetes only,[12] though as many as 10% of patients without diabetes will have perioperative hyperglycemia.[3]

Previous quality improvement work has suggested significant intraoperative quality gaps in glycemic management, most notably in intraoperative monitoring. For example, two studies in different settings report that less than 30% of patients at risk of hyperglycemia had any glucose measurement during surgery.[13,14] Standardized intraoperative protocols have increased monitoring and reduced intraoperative hyperglycemia, though these protocols are typically based on expert opinion.[15–17] We undertook a scoping review of the extant literature to describe the evidence to guide intraoperative glycemic management. We aimed to identify evidence knowledge gaps, which may inform the direction of future research on intraoperative anesthetic management of patients at risk of hyperglycemia.

Methods

Study design

A scoping review protocol was developed in accordance with the Joanna Briggs Institute methodology (Electronic Supplementary Material [ESM] eAppendix 1).[18] A scoping review method was selected to answer the study question because of the anticipated heterogeneity in study design and outcomes in this topic area. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews guidelines informed composition of this manuscript.[19]

Research question

The population was defined as nonpregnant adults with or without diabetes undergoing noncardiac surgery of any

type, duration, urgency, and anesthetic management. We included articles that examined any intraoperative exposure or intervention (e.g., use of dexamethasone, insulin formulation, diabetes medication selection, blood glucose measurement protocol) with a postoperative glycemic outcome, or any clinical outcome.

Data sources and search strategy

The search strategy was developed by a medical librarian (M. V.) for MEDLINE and adapted for other databases (ESM eAppendix 2). The following electronic databases were searched from inception to 14 July 2021: MEDLINE (Ovid), PubMed, PubMed Central, EMBASE, CINAHL, Medline (EBSCO), Cochrane Library, SciVerse Scopus, and Web of Science. A gray literature search (14 July 2021) included Google and Google Scholar,[20] hand searching the reference lists of included articles,[21] OAISter, review of institutional protocols, and search on ClinicalTrails.gov.

Study selection

All study designs were eligible for inclusion. Studies that were not available in the English language were translated for review and data extraction. Articles that reported on cardiac or obstetrical surgeries were excluded because the interaction between blood glucose and outcomes after cardiac surgery likely differs from those after noncardiac surgeries[4] and glycemic targets for pregnant people differ from those of nonpregnant people.[22] Studies that included only people younger than 18 yr of age or did not report on an intraoperative strategy or glucose values were excluded. Studies that reported data in duplicate with another citation or published in a predatory journal were excluded.

All identified studies were uploaded into Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia), which automatically removed duplicates. Article titles and abstracts were screened by two independent reviewers for eligibility, and articles without an abstract were screened in full for inclusion criteria. A third reviewer resolved disagreements regarding whether an article met the inclusion criteria for this scoping review.

Data extraction

A data extraction form was created by members of the study team (ESM eAppendix 3) and pilot tested on four articles. The study characteristics; population; surgery characteristics; hospital admission; exposures/interventions in the pre-, intra-, and postoperative periods; comparisons; and clinical and glycemic outcomes were extracted. Data were extracted independently in parallel by two independent study team members and reconciled. Differences were resolved through discussion and consulting the primary article. Remaining disagreements were resolved by a third independent reviewer.

Analysis

Studies were grouped into original research or review methods and compared by study characteristics such as study design and country of origin. When available, we compared surgical characteristics (urgency, discipline, admission type), included population (patients with and/or without diabetes), outcomes and exposures, and pre- or postoperative glycemic management. Where possible, results from studies were converted to an absolute risk reduction (ARR) or absolute risk increase (ARI) or an odds ratio (OR) to allow comparison between studies.

Results

Study characteristics

The search strategy identified 134 studies (Fig. 1). After removing duplicates and title and abstract screening, 76 citations underwent full-text review, and 41 of these met the eligibility criteria. Of these, 24 were original research studies and 17 were reviews, including the Society for Ambulatory Anesthesia (SAMBA) guidelines for perioperative glycemic management (Table 1).[23] Most original research studies focused on patients admitted to hospital for elective surgery. There were no studies that compared intraoperative glucose monitoring protocols (Table 2). The most common surgical discipline was neurosurgery, though most studies combined surgical disciplines or did not report the disciplines included (Table 3).

Intraoperative glycemic targets

Eleven studies examined intraoperative glucose targets; one was a randomized trial,[24] two were systematic reviews,[25,26] and eight were observational studies[27–34] (Table 1). Most (but not all[29]) studies included patients with and without diabetes, though not all studies stratified their results for patients with and without diabetes separately. The surgical types also varied in urgency, duration, and specialty. These studies reported on a range of outcomes using differing lengths of time for ascertainment, including intensive care unit (ICU) admission,[24,28,29] postoperative infections,[25,27–29,31,33,34]

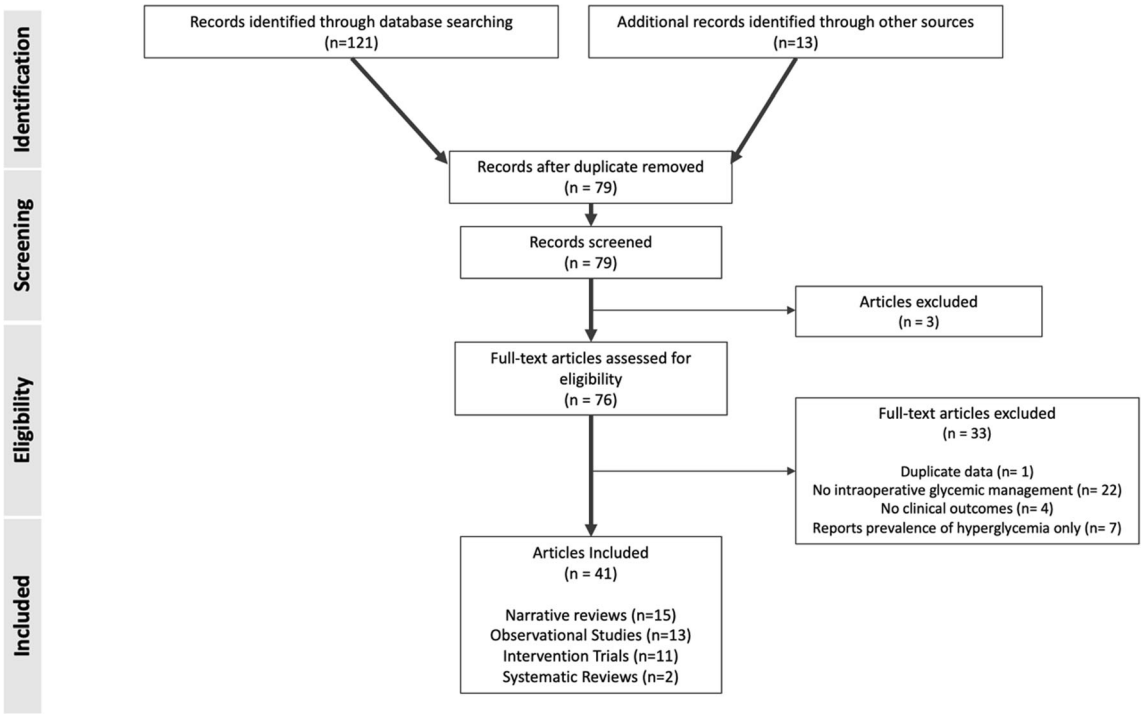

Figure 1 PRISMA flow diagram of included and excluded citations in this study

cardiovascular events,[25,28] surgical site infections,[30] anastomotic leaks,[32] complications,[28] and mortality (Table 4).[25,27,29,33] All studies defined the exposure (intraoperative glucose values) categorically rather than continuously and used a range of cut-offs to define hyperglycemia (Table 5).

Postoperative infections were variably associated with intraoperative hyperglycemia across observational studies (Table 1). Four studies found that intraoperative glucose measurements more than about 8.0 mmol·L^{-1} were associated with a greater risk of infection compared with patients with lower measurements. These studies examined liver transplant recipients,[27] patients with diabetes undergoing emergent orthopedic surgery,[28] patients undergoing elective knee replacement,[31] or patients undergoing general, vascular, or urologic procedures.[34] Effect estimates of postoperative infections ranged from an ARI of 18.0%[27] to an OR of 1.3 (95% confidence interval [CI], 1.0 to 1.7)[34] to 4.3 (95% CI, 1.9 to 9.6).[28] Only one study of liver transplant recipients focused on surgical site infections specifically and reported an association with intraoperative hyperglycemia ($\geq$ 11.1 mmol·L^{-1}).[30] In contrast, two observational studies found no association of intraoperative hyperglycemia (defined as greater than 8.8 mmol·L^{-1}) with infection in patients without diabetes undergoing elective major abdominal procedures[29] or patients undergoing any general, vascular, endocrine, or hepatobiliary surgeries.[33] None of these studies adjusted for pre- or postoperative glycemic values.

Intraoperative hyperglycemia was not associated with admission to the ICU in a single trial that randomized nearly 400 patients undergoing any major elective surgery to "strict" (4.4–6.1 mmol·L^{-1}) or "loose" (10.0–11.1 mmol·L^{-1}) intraoperative glycemic targets, though the authors did not stratify their results by diabetes status.[24] This result was supported by an observational study of patients with diabetes undergoing emergent orthopedic surgeries who had stress hyperglycemia ($\geq$ 7.0 mmol·L^{-1} fasting) that found no association between hyperglycemia and ICU admission.[28] In contrast, an observational study of patients without diabetes undergoing elective major abdominal surgeries found that patients with one or more intraoperative measurements greater than 8.8 mmol·L^{-1} had an ARI of 8.7% of requiring postoperative ICU admission compared with patients that had intraoperative glucose of 6.9–8.8 mmol·L^{-1} and an ARR of 9.7% compared with patients with normal measurements ($<$ 7.0 mmol·L^{-1}; P = 0.02).[29] Both studies were adjusted for multiple potential confounders, including surgical approach, anesthetic modality, and duration of the procedure.

A single study including patients undergoing a liver transplant with and without diabetes reported that intraoperative glucose greater than 8.3 mmol·L^{-1} was associated with an ARI of 13.1% ($P < 0.05$) in one-year

Table 1 Select characteristics of the original research articles included in this review, divided into intervention or exposure

First author	Study design	Population/surgeries	Treatment arm	*N*	Comparison arm	*N*	Select outcome(s)	Effect estimate
Intraoperative glucose values								
Abdelmalak[24]	Randomized trial	Patients with and without diabetes, older than 40 years, ASA < IV scheduled for major, elective noncardiac surgeries	Intraoperative target: 4.4–6.1 mmol·L^{-1}	166	Intraoperative target: 10.0–11.1 mmol·L^{-1}	160	ICU admission	2% ARR (ns)
Ammori[27]	Retrospective observational study	Adult liver transplant recipients	Strict intraoperative glucose management (< 8.3 mmol·L^{-1})	69	Loose intraoperative glucose management (> 8.3 mmol·L^{-1})	124	Postoperative infections (ARR)	18.0% ($P < 0.02$)
							1-year survival (ARR)	+13.1% ($P < 0.05$)
Di Luzio[28]	Prospective observational study	Patients over the age of 18 admitted with injuries requiring orthopedic surgery and hyperglycemia (fasting BG > 7 mmol·L^{-1} or > 8 mmol·L^{-1} random) at the time of admission	Patients with diabetes and stress hyperglycemia	52	Patients with diabetes without stress hyperglycemia	144	Postoperative infections (OR, 95% CI)	4.32 (1.94 to 9.6)
							Cardiovascular events (OR, 95% CI)	5.5 (1.83 to 18.8)
							ICU admission (OR, 95% CI)	1.95 (0.44 to 8.7)
							Any adverse event (OR, 95% CI)	4.03 (1.95 to 8.3)
Gianotti[29]	Prospective observational study	Adult (> 18 yr), patients without diabetes undergoing elective major abdominal surgery	No intraoperative or postoperative hyperglycemia (POCT ≥ 7.0 mmol·L^{-1})	137	One or more episodes of intraoperative or postoperative mild hyperglycemia (POCT 7.0–8.8 mmol·L^{-1})	211	Infection (ARR)	2.0% (normal to mild); 3.7% (normal to severe) $P = 0.68$
					One or more episodes of intraoperative or postoperative hyperglycemia (POCT > 8.8 mmol·L^{-1})	104	ICU admission (ARR)	1.0% (normal to mild); 9.8% (normal to severe) $P = 0.02$
							30-day mortality	0% (normal to mild); 3.1% (normal to severe) $P = 0.06$
Park[30]	Case-control study	Adults who underwent liver transplantation	Developed an SSI	76	Did not develop an SSI	604	Risk of SSI in patients with postoperative hyperglycemia (≥ 11.1 mmol·L^{-1}) (aOR, 95% CI)	2.25 (1.26 to 4.03)

Table 1 continued

First author	Study design	Population/surgeries	Treatment arm	*N*	Comparison arm	*N*	Select outcome(s)	Effect estimate
Retáegui[31]	Retrospective observational study	Adult patients with and without diabetes who underwent a total knee replacement	Had postoperative hyperglycemia (>7.0 mmol·L^{-1})	67	Did not have postoperative hyperglycemia (< 7.0mmol·L^{-1})	766	Infections (OR)	1.76 ($P < 0.0006$)
Reudink[32]	Prospective observational study	Adults undergoing colorectal surgery with formation of primary anastomosis for benign or malignant disease	Had intraoperative hyperglycemia (>7.0 mmol·L^{-1}) [stratified by diagnosis of diabetes]	737	Did not have intraoperative hyperglycemia (<7.0 mmol·L^{-1}) [stratified by diagnosis of diabetes]	737	Anastomotic leak (OR)	4.81 ($P = 0.02$)
Shah[33]	Retrospective observational study	Patients with and without diabetes undergoing surgery	Intraoperative glucose greater than 10 mmol·L^{-1}	1,414	Intraoperative glucose less than 10 mmol·L^{-1}	3,600	Infection (aOR, 95% CI)	0.9 (0.7 to 1.2)
							30-day mortality (aOR, 95% CI)	1.1 (0.9 to 1.3)
Shanks[34]	Retrospective observational study	Adults with and without diabetes undergoing surgery who had an intraoperative glucose. Excluded ASA V and VI, pregnancy, and preoperative infections	Normoglycemia (< 8.3 mmol·L^{-1})	1,619	Had moderate intraoperative hyperglycemia (11.1–16.6 mmol·L^{-1})	442	Infections (OR, 95% CI)	1.30 (1.01 to 1.68; mild to none); 1.67 (1.09 to 2.28; moderate to none); 1.06 (0.80 to 1.40; severe to none)
			Had mild intraoperative hyperglycemia (8.3–11.0 mmol·L^{-1})	1,042	Had severe intraoperative hyperglycemia (≥ 16.7 mmol·L^{-1})	47		
Buchleitner[25]	Systematic review and meta-analysis	Patients with diabetes undergoing surgery	RCT of prespecified intraoperative glucose targets - "intensive"	694	RCT of prespecified intraoperative glucose targets - "conventional"	709	Infection (RR, 95% CI)	0.46 (0.18 to 1.18)
							CV events (RR, 95% CI)	1.03 (0.21 to 5.1)
							Mortality (RR, 95% CI)	1.19 (0.89 to 1.59)
Kao[26]	Systematic review without meta-analysis	Adult patients (18+ yrs) undergoing a surgical procedure, regardless of diabetes status	A strict glycemic control regimen was used (BG 4.4–6.7 mmol·L^{-1}) using intravenous insulin	40	A conventional glycemic control regimen was used (BG 4.4–12.2 mmol·L^{-1}) using intravenous insulin	38	Due to heterogeneity, results could not be combined in a meta-analysis for any outcomes.	
Anesthetic selection								

Table 1 continued

First author	Study design	Population/surgeries	Treatment arm	*N*	Comparison arm	*N*	Select outcome(s)	Effect estimate
Haldar[42]	Randomized trial	Adults patients without diabetes, ASA I–II, with small (<5cm) supratentorial gliomas, intact neurologic status (GCS 15) and no midline shift or mass effect	Received sevoflurane	30	Received propofol Received desflurane	30 30	Mean change in blood glucose from preoperative to 4 hours intraoperative	+0.3 mmol·L^{-1} (sevoflurane); +1.0.mol/L (desflurane); +0.1 mmol·L^{-1} (propofol) (*P* = 0.003)
Kim[41]	Retrospective cohort study	Adult patients with type 2 diabetes undergoing general anesthesia	Received sevoflurane	87	Received propofol	89	Mean difference in immediate postoperative blood glucose	0.7 mmol·L^{-1} (*P* = 0.02)
							SSI (ARR)	2.2% (*P* = 0.24)
							MI (ARR)	1.1% (*P* = 0.49)
							Length of stay [median difference]	1 day (*P* = 0.16)
							30-day mortality (ARR)	2.2% (*P* = 0.24)
Insulin formulation								
Arun[43]	Randomized trial	Patients with DM2, aged 18–70 years undergoing noncardiac surgery greater than one hour	Bolus insulin for intraoperative glycemic management	60	Infusion insulin intraoperative glycemic management	60	Difference in proportion of surgical time target (5.5–10.0 mmol·L^{-1})	14.4% (*P* < 0.05)

Table 1 continued

First author	Study design	Population/surgeries	Treatment arm	*N*	Comparison arm	*N*	Select outcome(s)	Effect estimate
Di Luzio[44]	Randomized trial	Adult patients with or without diabetes who had injuries requiring emergent or elective surgery who had hyperglycemia	Received basal bolus insulin therapy perioperatively and *iv* insulin intraoperatively	80	Received home diabetes medications and sliding scale insulin only for hyperglycemia	122	Mean difference in blood glucose on postoperative day 1	-1.1 mmol·L^{-1} ($P <$ 0.001)
							Systemic infections (ARR)	27.4% ($P < 0.001$)
							ICU Admission (ARR)	0.7% ($P = 0.81$)
							Cardiovascular events (ARR)	10.2% ($P = 0.02$)
							Any complication (ARR)	28.8% ($P < 0.001$)
Dexamethasone								
Abdelmalak[37]	Randomized trial	Patients with and without diabetes, older than 40 years, ASA<IV scheduled for major, elective noncardiac surgeries	Received 8 mg *iv* dexamethasone at induction of anesthesia	90	Received matched placebo at induction of anesthesia	95	Maximal change in glucose, patients with diabetes (SD)	+0 (1.9) mmol·L^{-1}
							Maximal change in glucose patients without diabetes (SD)	+1.6 (2.5) mmol·L^{-1}
Sethi[38]	Randomized trial	Patients without diabetes who are ASA I or II aged 18–64 years	Received 8 mg *iv* dexamethasone at induction of anesthesia	20	Received placebo	20	Change from preoperative to peak intraoperative POCT (mean difference)	"Significantly higher"
Tien[39]	Randomized trial	Adults with and without diabetes undergoing elective surgeries under general anesthesia for more than 1 hour and were admitted for at least 24 hours	Received 8 mg *iv* dexamethasone	40	Received 4 mg IV ondansetron	45	Mean change in blood glucose pre- and postoperative (patients with diabetes)	+2.1 mmol·L^{-1} ($P < 0.01$)
							Mean change in blood glucose pre- and postoperative (patients without diabetes)	+0.9 mmol·L^{-1} ($P = 0.10$)

Table 1 continued

First author	Study design	Population/surgeries	Treatment arm	*N*	Comparison arm	*N*	Select outcome(s)	Effect estimate
Ali[35]	Prospective cohort		Patients undergoing elective/urgent intracranial tumor resection who received 10 mg dexamethasone after induction	35	Patients undergoing surgery for emergent subarachnoid hemorrhage who did not receive intraoperative steroids	35	Mean change in blood glucose from preoperative to intraoperative peak (difference)	+1.0 mmol·L^{-1} ($P < 0.05$)
Nurok[40]	Retrospective cohort study	Adult patients with and without diabetes who underwent THA/TKA	Received dexamethasone (4–8 mg *iv*)	474	Did not receive dexamethasone	146	Risk of postoperative hyperglycemia (POCT>11.1 mmol·L^{-1}) (aOR, 95% CI)	0.76 (0.28 to 2.07)
Wasfie[36]	Retrospective cohort study	Patients with diabetes undergoing elective surgery and staying in hospital for 24–48 hours	Received 8 mg *iv* intraoperative dexamethasone	119	Did not receive intraoperative dexamethasone	235	Median change in blood glucose from preoperative to intraoperative	+2.6 mmol·L^{-1} ($P < 0.001$)
							Median change in blood glucose from intraoperative to postoperative	+2.3 mmol·L^{-1} ($P = 0.02$)
Perioperative management pathways or guidelines								
Colibaseanu[46]	Pre/post-intervention	All patients over the age of 18 who were scheduled to undergo elective surgery in the inpatient or outpatient setting with known diabetes, or with a diabetes diagnostic A1C or BG above 8.3 mmol·L^{-1}	Post-implementation of a perioperative glycemic management pathway	96	Pre-implementation of a perioperative glycemic management pathway	103	Length of stay [median difference]	0.1 days ($P = 0.56$)
							30-day readmissions (ARR)	4.5% ($P = 0.33$)
							30-day mortality (ARR)	1.9% ($P = 0.30$)
Dinardo[15]	Pre/post-intervention	Adults patients undergoing same-day surgery with a known diagnosis of diabetes	Standardized perioperative management protocol	60	"Usual care" (not defined)	55	Change from preoperative to postoperative POCT (mean difference)	+1.0 mmol·L^{-1} ($P < 0.001$)

Table 1 continued

First author	Study design	Population/surgeries	Treatment arm	*N*	Comparison arm	*N*	Select outcome(s)	Effect estimate
Shaw[16]	Pre/post-intervention	Adult patients undergoing vascular surgery	Post-implementation of a perioperative glycemic management pathway	3,013	Pre-implementation of a perioperative glycemic management pathway	1,278	Proportion with any perioperative hyperglycemia (ARR)	7.1% ($P < 0.01$)
							SSI	3.6% ($P < 0.05$)
Udovcic[47]	Pre/post-intervention	Adult patients undergoing elective surgery	Post-implementation of a perioperative glycemic management guideline	1,387	Pre-implementation of a perioperative glycemic management guideline	254	Mean difference in postoperative glucose	-0.7 mmol·L^{-1} ($P < 0.01$)
Miscellaneous comparisons								
Torphy[45]	Retrospective cohort study	Adult patients undergoing cytoreduction and HIPEC	Received chemotherapy carrier solution with dextrose	68	Received chemotherapy carrier solution with lactated ringers	68	Any severe hyperglycemia (POCT>11.1 mmol·L^{-1}) (ARR)	67.7% ($P < 0.001$)
							Infections (ARR)	20.6% ($P = 0.01$)
							Clavien–Dindo grade 3–5 complications (ARR)	17.6% ($P = 0.03$)

aOR = adjusted odds ratio; ARR = absolute risk ratio; ASA = American Society of Anesthesia Physical Status score; BG = blood glucose; CI = confidence interval; CV = cardiovascular; GCS = Glasgow coma scale; HIPEC = hyperthermic intraperitoneal chemotherapy; ICU = intensive care unit; *iv* = intravenous; MI = myocardial infarction; ns = nonsignificant; OR = odds ratio; POCT = point-of-care capillary blood glucose testing; RCT = randomized controlled trial; SD = standard deviation; SSI = surgical site infection; THA = total hip arthroplasty; TKA = total knee arthroplasty

Table 2 The number of studies included in this review by intervention or exposure and included population

Intraoperative exposure studied	Population studied			Total
	Patients with diabetes only	Patients without diabetes only	Both patients with and without diabetes	
Monitoring	0	0	0	0
Targets	0	1	8	9
Insulin formulation	1	0	1	2
Other medical management	2	2	5	9

Table 3 The surgical and patient characteristics of the population studied in the original research studies included in this review

	Number of studies
Surgery characteristics	
Admission type	
Day case	2
Admission > 24 hr	14
All surgeries	1
Not specified	9
Surgical discipline	
Liver transplant	2
Thoracic	1
Gynecology/gynecologic oncology	0
Orthopedic	2
Vascular surgery	1
Abdominal (including GU)	1
Gastrointestinal/colorectal	2
General surgery	0
Neurosurgery	4
"Major"	3
Multiple disciplines	5
Not specified	7
Surgical urgency*	
Elective	8
Emergency	2
Mixed	4
Not specified	6
Patient characteristics	
With diabetes	7
Without diabetes	3
With and without diabetes	16

*As defined by the included study

GU = genitourinary

postoperative mortality.[27] In contrast, two studies reported no increase in 30-day mortality for patients undergoing abdominal surgery who had intraoperative glucose greater than 7.0 mmol·L^{-1}[29] or those undergoing unspecified surgery types who had intraoperative glucose greater than 10.0 mmol·L^{-1} after adjustment for covariates.[33]

Dexamethasone

Five of six studies,[35,36] including three placebo-controlled randomized trials,[37–39] reported that patients receiving dexamethasone had higher intraoperative or postoperative glucose measurements than patients who did not. Most of these studies used 8 mg of intravenous dexamethasone for postoperative nausea and vomiting[36–39] though one used 10 mg for patients undergoing intracranial surgery.[35] This increase in glucose measurements ranged from 2.1[39] to 3.5 mmol·L^{-1}[37] in patients with diabetes and from 0.9[39] to 1.6 mmol·L^{-1}[37] in patients without. There was no increased risk of hyperglycemia reported in a single observational study that did not stratify outcomes by diabetes status and used a dose range of 4–8 mg of intravenous dexamethasone.[40]

Anesthetic selection

One cohort study[41] and one randomized trial[42] compared intraoperative glucose measurements in patients receiving sevoflurane, desflurane, and propofol; however, the trial excluded patients with diabetes and the cohort study was restricted to patients with type 2 diabetes. Despite these differences, sevoflurane and desflurane were associated with a slightly greater rise in intraoperative glucose measurements compared with propofol (0.3–1.0 mmol·L^{-1}) in both studies, though it is not clear whether this increase was clinically meaningful. There were no studies that compared anesthesia modalities and glycemic outcomes.

Insulin formulation and/or dosing

Two randomized trials examined the formulation and dosing regimen of intraoperative insulin delivery. In people with type 2 diabetes undergoing general anesthesia for an elective or emergent operation longer than one hour, those that received intravenous boluses of insulin once per hour

Table 4 The number of studies included in this review that examined an intraoperative glucose measurement with a clinical outcome. Studies may have reported on multiple different glucose categories and clinical outcomes

		Clinical outcomes														
Exposure (mmol·L^{-1})	Glucose value (mmol·L^{-1})	Total	Any adverse event	Postoperative infection	Surgical site infection	Thrombosis	Myocardial infarction	Cardiovascular events	Renal failure	Anastomotic leak	Postoperative fatigue	Length of stay	ICU admission	Quality of life	30-day mortality	1-year mortality
	4.4–6.1	**5**				1	1		1		1		1			
	4.4–6.7	**3**		1	1										1	
	7.0–8.8	**3**		1									1		1	
	> 7.0	**9**	1	3				1		1			2		1	
	> 8.3	**3**		2												1
	> 8.8	**3**		1									1		1	
	> 10.0	**2**		1											1	
	10.0–11.1	**1**											1			
	> 11.1	**2**		1	1											
	> 16.7	**1**		1												
	Not stated	**6**		1				1	1			1		1	1	
	Total	**38**	**1**	**12**	**2**	**1**	**1**	**2**	**2**	**1**	**1**	**1**	**6**	**1**	**6**	**1**

ICU = intensive care unit

based on intraoperative blood sugars spent nearly 15% more operative time in target (5.5–10.0 mmol·L^{-1}) compared with patients who were placed on a continuous intravenous insulin infusion with dextrose 5% that was adjusted every hour based on intraoperative blood sugars.[43] In comparison, patients with and without diabetes who discontinued their home medications and were started on a basal bolus insulin regimen and received intravenous insulin during surgery had a lower mean glucose on the first postoperative day compared with patients who continued their home medications and received correction-only subcutaneous insulin.[44]

Other medications

A retrospective cohort study reported that patients who received heated intraperitoneal chemotherapy using dextrose-containing carrier solutions rather than lactated Ringers had greater prevalence of severe hyperglycemia (> 11.1 mmol·L^{-1}), postoperative infections (ARI, +20.6%; $P < 0.01$) and increased moderate and severe complications (ARI, +17.6%; $P = 0.03$).[45]

Perioperative glycemic management pathways

There were four studies that evaluated the influence of standardized protocols for perioperative glycemic management that contained advice on intraoperative management.[15,16,46,47] All protocols reduced hyperglycemia (variably defined), though implementation was not consistently associated with improved clinical outcomes; although the largest of these studies did show a reduction in surgical site infections after implementation (ARR, 3.6%; $P < 0.05$),[16] there was no difference in mortality, readmissions, or length of stay in another.[46] All identified protocols recommended monitoring blood glucose intraoperatively every one to two hours but were heterogeneous with respect to whether they were only used for patients with diabetes or for all patients, their target glucose measurements (ranging from less than 7.8[46,47] to 10.0[15,16] mmol·L^{-1}) and recommended insulin formulation (intravenous or subcutaneous). In addition, protocols generally had preoperative and postoperative pathways in addition to intraoperative recommendations and variably defined the perioperative period, and so any clinical benefit cannot be directly attributed to intraoperative glycemic management.

Narrative reviews

There were 15 narrative reviews, including consensus statements, which addressed some aspect of intraoperative glycemic management.[13,17,23,48–59] Most, including the SAMBA guidelines, recommended measuring a blood glucose at least every two hours during surgeries longer than one to two hours,[13,17,49,56–58] though some recommended twice hourly.[55,59] Similarly, nearly all reviews recommended a glucose target less than 10.0 mmol·L^{-1}. There was variation in recommendations on insulin regimens and formulations. Often these recommendations asked practitioners to consider the type and duration of surgery as well as patient-specific factors

Table 5 Treatment of intraoperative glucose as a continuous or categorical variable by studies included in this review, stratified by whether glucose was an exposure or the outcome

Study first author	Glucose as an exposure		
	Continuous	Categorical	Cut-offs (mmol·L^{-1})
Abdelmalak[24]		X	4.5–6.1
			10.0–11.1
Ammori[27]		X	< 8.4
			≥ 8.4
Di Luzio[28]		X	< 8.0
			≥ 8.0
Gianotti[29]		X	< 7.0
			7.0–8.9
			≥ 9.0
Park[30]		X	≥ 8.4
			≥ 10.0
			≥ 11.1
Reåtegui[31]		X	≤ 7.0
			≥ 7.0
Reudink[32]		X	4.4–5.5
			5.6–7.0
			7.1–11.0
			≥ 11.1
Shah[33]		X	< 10.0
			≥ 10.0
Shanks[34]		X	< 8.3
			8.3–11.0
			11.1–16.6
			≥ 16.7
Total (%)	0	9 (100)	
	Glucose as an outcome		
	Continuous	Categorical	Cut-offs (mmol·L^{-1})
Haldar[42]	X		
Kim[41]	X		
Arun[43]		X	< 6.0
			≥ 6.0
Di Luzio[44]	X		
Abdelmalak[72]	X		
Sethi[38]	X		
Tien[39]	X		
Ali[35]	X		
Nurok[40]		X	< 11.1
			≥ 11.1
Wasfie[36]	X		
Torphy[45]		X	< 11.1
			≥ 11.1
Total (%)	10 (76.9)	3 (23.1)	

when selecting subcutaneous or intravenous insulin. Only one review recommended avoiding dexamethasone and volatile anesthetics[17] in patients at risk of hyperglycemia.

Discussion

In this scoping review, we aimed to synthesize the literature examining intraoperative glycemic management to identify gaps requiring additional research, and make suggestions on how researchers can standardize their reporting and methods to best answer the remaining uncertainties in intraoperative glycemic management. The number and characteristics of included narrative reviews reflects the observed heterogeneity in original research studies; we identified nearly as many nonsystematic reviews and expert opinion articles as original research studies. Journals and granting agencies may act as gatekeepers to ensure that future studies analyze and report data in a consistent, usable fashion.

Consistent definitions of exposures and outcomes are needed to better understand the relationship between intraoperative glucose values and adverse clinical outcomes. For example, observational studies examining associations between intraoperative glucose measurements and postoperative outcomes should treat glucose values as continuous data rather than creating categories of "high" and "normal" glucose to facilitate comparison across studies. Current evidence suggests that postoperative hyperglycemia is more associated with adverse outcomes than preoperative hyperglycemia is[4] and that identification of patients with hyperglycemia reduces these outcomes;[60,61] however, the contribution of intraoperative hyperglycemia to adverse outcomes relative to the influence of pre- or postoperative hyperglycemia is not yet known.[62] The literature examining the relationship between diabetes and adverse surgical outcomes is similarly limited by inconsistent definitions of outcomes and exposure.[62] Investigators should consider how to adjust or control for pre- and postoperative hyperglycemia to better isolate the association of intraoperative hyperglycemia with adverse outcomes.

Due to potential differences in the inflammatory response and baseline risk of complications between different types of surgeries, investigators should carefully consider restricting the selected surgical population, indication, and urgency to avoid missing important results when combining heterogeneous populations. For example, we identified only two studies that examined day surgery patients, and half of studies combined elective and emergent surgeries or did not specify the urgency. Similarly, 15 of 28 studies combined multiple disciplines or did not report the specific surgical disciplines that were included despite literature suggesting that adverse events differ greatly by procedure type.[63] A signal for harm associated with intraoperative hyperglycemia may be missed in studies that combine high- and low-risk procedures.

Similarly, decisions about the study population should be carefully considered. At minimum, investigators should report results separately for patients with and without diabetes and should differentiate patients with type 1 and type 2 diabetes. Perioperative management of patient's home medication regimens varies between centres[64] but may confound studies that examine intraoperative glycemic response to different management strategies, in particular dexamethasone or inhalational anesthetics.

In the interim, the evidence does suggest that intraoperative hyperglycemia is likely a modifiable risk factor for postoperative infection in patients with and without diabetes. Due to study heterogeneity, it is not possible to recommend a specific glucose cut-off for all surgeries and all patients. This heterogeneity is reflected in major society guidelines, which differ in their recommended intraoperative blood glucose targets from less than 10.0[23] $mmol \cdot L^{-1}$ to less than 12.0[12] $mmol \cdot L^{-1}$. Many societies, including Diabetes Canada and the American Diabetes Association, do not comment on intraoperative targets.[10,11] Future studies should examine the safety, feasibility, and impact on infections between different intraoperative glucose targets in populations at high risk of postoperative infection. In light of the available literature, anesthesiologists may consider measuring glucose and treating intraoperative hyperglycemia, while carefully monitoring patients for hypoglycemia throughout the perioperative period, including in the postoperative recovery room.

Because patients with and without diabetes who receive dexamethasone have increases in their blood glucose,[37,39] anesthesiologists may consider monitoring for and treating hyperglycemia in patients at greatest risk of hyperglycemia or adverse outcomes from hyperglycemia who receive dexamethasone. Although intraoperative glucose may increase with dexamethasone administration, a randomized placebo-controlled trial found that patients with and without diabetes who received dexamethasone did not have a greater incidence of surgical site infection compared with those who received placebo.[65] Alternatives to dexamethasone could be considered, when possible, for patients at greatest risk of hyperglycemia or postoperative infections regardless of diabetes status; although prediction models are not well established, this risk could be estimated based on patient characteristics (e.g., hemoglobin A1c,[66] use of immunosuppression medications[67]), surgical factors (e.g., surgical approach[68]), and the severity of the consequences of

infection (e.g., procedures involving implanted prosthetic materials). Similarly, the inhaled anesthetics sevoflurane and desflurane may raise intraoperative glucose values, and anesthesiologists could consider blood glucose monitoring in patients at greatest risk of hyperglycemia who receive these agents. It is not known whether intraoperative treatment of hyperglycemia reduces any potential adverse effects of using these medications, and the association of other anesthetic modalities with hyperglycemia has not been studied. There is an ongoing, randomized study comparing intraoperative glucose measurements and clinical outcomes for patients receiving total inhalational anesthesia and those receiving total intravenous anesthesia, which may address these questions.[69]

The optimal intraoperative management of patients with identified hyperglycemia is not clear based on the available evidence. No studies compared outcomes between patients who underwent different intraoperative monitoring regimens though most studies measured and most reviews recommended measuring a blood glucose value every one to two hours in surgeries greater than one hour, in keeping with guideline recommendations from the UK.[12] Although between 5 and 10% of patients without diabetes experience intraoperative and postoperative hyperglycemia,[1,3] it is not clear whether all patients without diabetes should undergo intraoperative glucose monitoring and at what interval. This likely would depend on surgery duration, although this was inconsistently reported across studies. Rigorous studies that compare the safety and efficacy of the route of intraoperative insulin dosing (e.g., subcutaneous *vs* intravenous) and the regimen (e.g., bolus *vs* continuous infusion) are needed to guide practice. At present, the SAMBA recommendations suggest using bolus-dosed subcutaneous rapid-acting insulin for surgeries less than four hours long with anticipated hemodynamic stability.[49] Although there is a risk of publication bias, formalized protocols to direct intraoperative glycemic management probably reduce intraoperative hyperglycemia and may improve clinical outcomes compared with a lack of standard guidelines. To reduce variation between anesthesiologists, organizations should consider standard perioperative glycemic protocols that define intraoperative glycemic targets, suggest insulin dosing protocols, and clarify communication about results and treatment between healthcare providers.[70]

An important limitation of this review may be that the search strategy was too specific in focusing only on studies that included at least one intraoperative exposure or intervention, thus restricting the available evidence. Because of this inclusion criteria, our strategy excluded the NICE-SUGAR study, which examined "conventional" (less than 10.0 $mmol{\cdot}L^{-1}$) *vs* "intensive" (4.5–6.0 $mmol{\cdot}L^{-1}$) glucose targets in critically ill patients without examining intraoperative values.[71] We focused on studies that included intraoperative glycemic management with the aim of informing the care delivered specifically by the anesthesia team during the surgical procedure rather than using pre- or postoperative management to direct intraoperative care. In addition, the low number of included citations examining each exposure and/or outcome makes drawing conclusions from the available literature difficult.

Conclusion

Altogether, there are multiple important research gaps in intraoperative glycemic management, most notably a lack of clear glycemic targets and optimal management strategy for intraoperative hyperglycemia. Heterogeneity within and between studies has limited our ability to compare or interpret their results, and investigators should carefully define their outcomes, surgical covariates, patient factors, and pre- and postoperative glycemic management to improve the generalizability of study data. Our synthesis of the available literature should guide future research rather than act as a definitive set of recommendations.

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