Management of diabetes and hyperglycaemia in the hospital

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Hyperglycaemia in people with and without diabetes admitted to the hospital is associated with a substantial increase in morbidity, mortality, and health-care costs. Professional societies have recommended insulin therapy as the cornerstone of inpatient pharmacological management. Intravenous insulin therapy is the treatment of choice in the critical care setting. In non-intensive care settings, several insulin protocols have been proposed to manage patients with hyperglycaemia; however, meta-analyses comparing different treatment regimens have not clearly endorsed the benefits of any particular strategy. Clinical guidelines recommend stopping oral antidiabetes drugs during hospitalisation; however, in some countries continuation of oral antidiabetes drugs is commonplace in some patients with type 2 diabetes admitted to hospital, and findings from clinical trials have suggested that non-insulin drugs, alone or in combination with basal insulin, can be used to achieve appropriate glycaemic control in selected populations. Advances in diabetes technology are revolutionising day-to-day diabetes care and work is ongoing to implement these technologies (ie, continuous glucose monitoring, automated insulin delivery) for inpatient care. Additionally, transformations in care have occurred during the COVID-19 pandemic, including the use of remote inpatient diabetes management—research is needed to assess the effects of such adaptations.

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See Online for appendix

Introduction

Diabetes and stress hyperglycaemia are common in the hospital setting and are associated with increases in hospital complications, length of stay, and mortality.[1–3] Furthermore, data from the COVID-19 pandemic have shown how vulnerable people with type 1 and type 2 diabetes are to developing complications in the hospital compared with people without diabetes.[4–8]

As with hyperglycaemia, inpatient hypoglycaemia is also associated with poor inpatient outcomes and health-care costs. This association might reflect the severity of illness and higher rates of comorbidities in patients who develop hypoglycaemia.[9] Experimental data have shown that insulin-induced hypoglycaemia can lead to an acquired long QT syndrome, which could precipitate fatal cardiac arrhythmias.[10] In view of such findings, it is generally accepted that hyperglycaemia and hypoglycaemia should be avoided in hospitalised patients.

For the past 15 years, insulin therapy has been considered the cornerstone of the management of patients with hyperglycaemia in the hospital;[2,3,11] however, practice varies widely internationally and findings from several randomised controlled trials have shown that non-insulin drugs can have a role in the management of inpatients with type 2 diabetes.[12] Diabetes technology is rapidly evolving, and preliminary data have shown the feasibility for inpatient use of continuous glucose monitoring devices and automated insulin delivery systems.[13–16] The COVID-19 pandemic is accelerating the use of technology in the hospital setting, including the use of remote continuous glucose monitoring.[17,18] In this Review, we summarise the evidence from observational studies and clinical trials focusing on inpatient care of people with diabetes and stress hyperglycaemia, including the use of insulin and non-insulin treatment strategies, treatment goals, and the application of new technologies in the hospital setting.

Recommendations and international variations in practice

Despite a paucity of good quality evidence on the inpatient management of diabetes, several international guidelines were developed to guide practice. The American Diabetes Association (ADA) produces an updated set of recommendations covering several aspects of inpatient diabetes care as part of their annual standards of medical care in diabetes.[19] In the UK, the Joint British Diabetes Societies (JBDS) for Inpatient Care has produced a suite of guidelines on various aspects of inpatient care for specific populations, including recent recommendations related to COVID-19 (appendix p 1).[20] The Endocrine Society in collaboration with other societies published guidelines for the management of diabetes and hyperglycaemia in non-intensive care settings in 2012.[3] Because the evidence has often been inadequate to determine how best to manage different aspects of inpatient care, these guidelines often have a large element of consensus-based medicine, with recommendations from medical societies that often reach different conclusions, with the most notable differences related to glucose targets and the use of non-insulin glucose-lowering drugs.[1,12] Recent reviews and consensus efforts have also suggested management strategies for patients with diabetes and COVID-19.[21,22]

Although the use of insulin therapy in the hospital is common in the USA and Canada,[23,24] this is not a universal practice. The use of non-insulin agents such as metformin and sulfonylureas is relatively common in other countries (UK, India, Israel).[25–28]

Diagnostic criteria and glycaemic targets

A random blood glucose concentration of more than 7·8 mmol/L (140 mg/dL) has been regarded as a threshold to consider the diagnosis of inpatient hyperglycaemia.[3,19] Several target ranges have been investigated in the intensive care unit (ICU) setting. Van den Berghe and colleagues[29] reported that attainment of euglycaemia (4·4–6·1 mmol/L [80–110 mg/dL]) in patients on a surgical

ICU was associated with lower mortality compared with aiming at blood glucose below the glycosuria threshold. However, these findings were not reproduced in randomised trials done in broader populations of patients,[2] with one possible reason being the difference in nutrition provided while on continuous insulin infusion. In 2009, the findings of a landmark trial (NICE-SUGAR) showed increased mortality risk with assignment to intensive insulin therapy in critically ill patients.[30] The high risk of iatrogenic hypoglycaemia seen in several randomised trials led medical societies to recommend against aggressive glycaemic control targeting euglycaemia.[2]

In 2009, an ADA and American Association of Clinical Endocrinologists (AACE) task force recommended targeting a glucose concentration of 7·8–10·0 mmol/L (140–180 mg/dL) for the majority of critically ill patients with hyperglycaemia and a lower glucose target range of 6·1–7·8 mmol/L (110–140 mg/dL) for selected ICU patients (eg, those at centres with extensive experience and appropriate nursing support, cardiac surgery patients).[2] The ADA–AACE consensus statement recommended against glucose targets greater than 10·0 mmol/L or less than 6·1 mmol/L.[2] Similarly, the Society of Critical Care Medicine recommends starting therapy for ICU patients with a blood glucose concentration of 8·3 mmol/L (150 mg/dL) or higher and maintaining glucose concentrations of less than 10·0 mmol/L with strategies that minimise the risk of hypoglycaemia.[31]

For **subcutaneous protocols adapted for COVID-19** see www.covidindiabetes.org

For non-critically ill patients with hyperglycaemia, the Endocrine Society guidelines[3] and the ADA–AACE consensus statement[2] recommended pre-meal glucose concentration targets of less than 7·8 mmol/L (140 mg/dL) and random blood glucose concentration targets of less than 10·0 mmol/L (180 mg/dL).[2,3] More recently, the ADA relaxed this recommendation, targeting glucose concentrations between 7·8 and 10·0 mmol/L for most general medicine and surgery patients.[19] Conversely, in terminally ill patients, those with severe comorbidities, or in inpatient care settings where frequent glucose monitoring or close nursing supervision is not feasible, higher glucose ranges (up to 11·1 mmol/L [200 mg/dL]) might be acceptable.[19]

Guidelines from the JBDS Inpatient Care group in the UK have recommend a blood glucose target range of 6·0–10·0 mmol/L (108–180 mg/dL) for inpatients with hyperglycaemia, with an acceptable range of 4·0–12·0 mmol/L (72–216 mg/dL).[20] However, the lower limit of the acceptable range (ie, 4·0 mmol/L) has been questioned because it might lead to an increased risk of hypoglycaemia.[32]

Pharmacological management of hyperglycaemia in the hospital

Insulin therapy

Critically ill patients and patients with hyperglycaemic crises

Continuous insulin infusion therapy is the preferred regimen for ICU patients with hyperglycaemia, including those without a diagnosis of diabetes, and for most patients with hyperglycaemic crises (figure 1).[2,20,33] Additionally, patients with severe hyperglycaemia induced by steroids or those undergoing solid transplant might also benefit from continuous insulin infusion. US and UK professional societies have produced algorithms for intravenous insulin management during diabetic ketoacidosis or hyperosmolar hyperglycaemic state.[33,34] Generally, patients with moderate-to-severe diabetic ketoacidosis should be treated with continuous insulin infusion; however, patients with mild-to-moderate diabetic ketoacidosis might be treated with frequent subcutaneous insulin injections.[35] During the COVID-19 pandemic, several centres modified their approach to treating patients with diabetic ketoacidosis with subcutaneous insulin, substantially reducing the number of point-of-care tests (adapted protocols have been made available online).[35]

Hypokalaemia is common (about 50%) during treatment of hyperglycaemic crises, and severe hypokalaemia (<2·5 mEq/L) is associated with increased inpatient mortality.[30] Therefore, careful monitoring of potassium concentrations is recommended and a systematic assessment of modifications in practice is warranted.[36]

For patients with ischaemic events (myocardial infarction or ischaemic stroke), rapid control of glucose values might be warranted in view of the known potential harms associated with hyperglycaemia; however, attempts to lower glucose concentrations intensively have not shown additional benefit and might increase the risk of hypoglycaemia.[37–39] Targeting a lower glucose range (100–140 mg/dL), as opposed to a conventional range (140–180 mg/dL), may improve clinical outcomes in cardiac surgery patients when using a computerised algorithm that minimises the risk of iatrogenic hypoglycaemia.[40]

Once patients are stable and close to discharge from ICU, they can be transitioned to subcutaneous insulin regimens. Factors to consider when transitioning patients from continuous insulin infusion to subcutaneous insulin include stable glucose measurements for at least 4–6 h consecutively, normal anion gap and resolution of acidosis in diabetic ketoacidosis, haemodynamic stability (not on vasopressors), stable nutrition plan, and stable intravenous infusion rates.[41] To safely transition to subcutaneous insulin, an estimate of the combined basal and nutritional subcutaneous insulin requirements can be derived from the average amount of insulin infused during the 12 h before transition.[42] For a patient receiving an average of 1·5 units (U) per h, the estimated daily dose would correspond to 36 U/24 h. The proportion of basal insulin and prandial insulin depends on the type of insulin to be used (isophane [neutral protamine Hagedorn] insulin *vs* longer-acting insulins) and the nutritional status of the patient.[41]

Insulin regimens

Various regimens with human and analogue insulin formulations administered subcutaneously have been

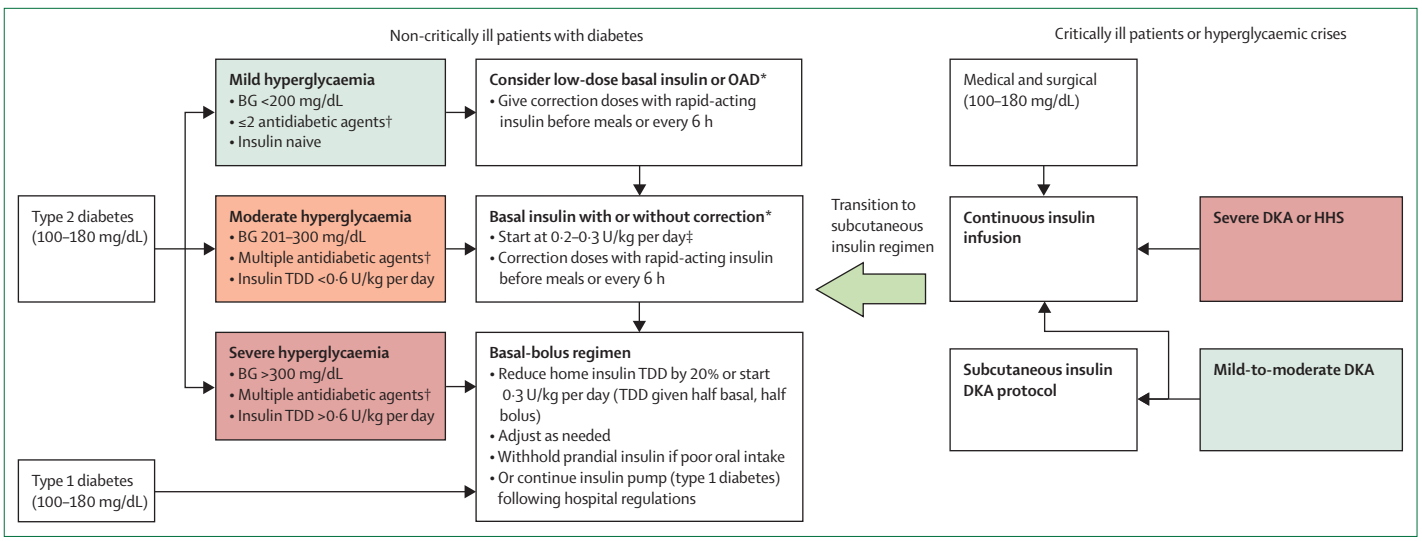

Figure 1: **Individualised antihyperglycaemic therapy in hospitalised patients with diabetes**
In critically ill patients, continuous insulin infusion is recommended followed by transition to subcutaneous insulin regimens once patients are stable and close to discharge from the intensive care unit.[2] Subcutaneous insulin DKA protocols might be considered in patients with mild-to-moderate DKA (subcutaneous insulin protocol examples adapted for COVID-19 are available online). We discourage the widespread use of premixed insulin regimens in the hospital setting. BG=blood glucose. DKA=diabetic ketoacidosis. HHS=hyperosmolar hyperglycaemic state. OAD=oral antidiabetes drug. TDD=total daily dose. U=units. *Consider OAD if no contraindications (only DPP-4 inhibitors have been studied in randomised controlled trials); metformin is commonly used in the hospital setting but might be associated with lactic acidosis in high-risk patients (eg, sepsis, shock, renal or liver failure). †Antidiabetic agents include OADs and GLP-1 receptor agonists. ‡In patients with hypoglycaemia risk (frail, elderly, acute kidney injury), reduce starting dose to 0·15 U/kg per day (basal alone) or TDD 0·3 U/kg per day (basal–bolus).

tested in non-critically ill patients with type 2 diabetes (table 1).[2,3,45,47]

Subcutaneous sliding scale insulin or correctional insulin, used to treat hyperglycaemia after it has already occurred, is widely used in some hospitals despite condemnation in clinical guidelines.[3,11,54] The use of sliding scale insulin is associated with clinically significant hyperglycaemia in many patients and its use has been discouraged.[3] In patients without diabetes who have mild stress hyperglycaemia, the use of sliding scale insulin might be appropriate. However, sliding scale insulin alone should not be used in patients with type 1 diabetes.

Findings from randomised trials have consistently shown better glycaemic control with a basal–bolus approach than with sliding scale insulin alone in patients with type 2 diabetes.[55,56] The basal-bolus approach was associated with a reduction in complications estimated with a composite outcome that included postoperative wound infection, pneumonia, bacteraemia, and acute renal and respiratory failure.[45] A basal–bolus regimen includes the administration of basal insulin given once or twice daily along with rapid-acting insulin given before meals, plus corrective doses of rapid-acting insulin. For insulin-naive patients or those treated with low doses of insulin, a total daily insulin dose between 0·3 and 0·5 U/kg is recommended,[3] with half of the total daily insulin dose allocated to basal insulin dosing (1–2 times daily) and the other half to rapid-acting insulin (divided three times daily before meals). Lower doses are reserved for patients with higher risk of hypoglycaemia (ie, older patients [>65 years], those with renal failure, and those with poor oral intake).[3,57] For patients treated with higher doses of insulin at home (≥0·6 U/kg per day), a 20% reduction in the total daily insulin dose is recommended while they are in hospital to prevent hypoglycaemia in patients with poor oral intake.[3] Although effective in correcting hyperglycaemia, the basal–bolus approach is associated with a risk of iatrogenic hypoglycaemia and might lead to over-treatment in patients with mild hyperglycaemia (blood glucose <11·1mmol/L [200 mg/dL]). In controlled settings, the incidence of mild iatrogenic hypoglycaemia when using a basal–bolus approach is about 12–30%.[3,45]

A basal-plus approach might be preferred for patients with mild hyperglycaemia, those with decreased oral intake, and for patients undergoing surgery.[3,47,57] This regimen consists of a single dose of basal insulin (about 0·1–0·25 U/kg per day) along with corrective doses of insulin for increased glucose concentrations before meals or every 6 h (if nil by mouth).

Premixed insulin therapy (human insulin 70/30) has been associated with an unacceptably high rate of iatrogenic hypoglycaemia and is not recommended in the hospital.[50] Premixed insulin has been recommended for patients receiving enteral nutrition but data remain scarce.[58]

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Insulin therapy and hypoglycaemia

In critically ill patients with hyperglycaemia, the targeting of euglycaemia (4·4–6·1 mmol/L [80–110 mg/dL]) has been associated with a substantial increase in the risk of iatrogenic hypoglycaemia and

	Treatment groups (intervention *vs* control)	Population	Primary outcome	Key findings
Umpierrez et al (2007)[43]	Basal–bolus (glargine–glulisine) *vs* SSI	130 medicine patients with type 2 diabetes; blood glucose 7·8–10·0 mmol/L (140–400 mg/dL); on OADs or low-dose insulin therapy (≤0·4 U/kg per day)	Mean difference in inpatient blood glucose	Mean blood glucose of 9·2 mmol/L (SD 1·8; 166 mg/dL [SD 32]) in basal–bolus *vs* 10·7 mmol/L (3·0; 193 mg/dL [54]) in SSI (p<0·001); two patients in each group with blood glucose <3·33 mmol/L (60 mg/dL); no patients with blood glucose <2·2 mmol/L (40 mg/dL) in either group
Umpierrez et al (2009)[44]	Human insulin (NPH and regular; two-thirds before breakfast and one-third before dinner) *vs* basal–bolus (detemir–aspart)	130 medicine patients with type 2 diabetes; blood glucose of 7·8–10·0 mmol/L (140–400 mg/dL); any therapy before admission	Mean difference in inpatient blood glucose	No difference in glycaemic control; about a quarter of patients had a blood glucose concentration of 2·2–3·3 mmol/L in both groups; blood glucose was <2·2 mmol/L in 3 (4·5%) of 67 with detemir–aspart and 1 (1·6%) of 63 with human insulin
Umpierrez et al (2011)[45]	Basal–bolus (glargine–glulisine) *vs* SSI	211 surgical patients with type 2 diabetes; blood glucose 7·8–10·0 mmol/L (140–400 mg/dL); on OADs or low-dose insulin therapy (≤0·4 U/kg per day)	Mean difference in inpatient blood glucose and a composite of complications	Better glycaemic control with basal–bolus and lower composite of complications ((9 [9%] of 104 *vs* 26 [24%] of 107; p=0·003), but with higher risk of hypoglycaemia (24 [23%] *vs* 5 [5%]; p=0·001); 4 (4%) of 104 with blood glucose <2·2 mmol/L (4% with basal-bolus vs 0% with SSI)
Schroeder et al (2012)[46]	NPH plus regular three times per day *vs* SSI	141 orthopaedic surgery patients with type 2 diabetes or recurrent hyperglycaemia (>180 mg/dL; >10 mmol/L)	Mean difference in inpatient blood glucose	Mean blood glucose was lower in the NPH–regular group *vs* SSI (8·9 mmol/L [SD 0·2; 161·2 mg/dL (SD 3·2)] *vs* 9·7 mmol/L [0·1; 175·8 mg/dL (2·3)]; p<0·0005); two episodes of severe hypoglycaemia in NPH–regular group
Umpierrez et al (2013)[47]	Basal-plus *vs* basal–bolus (both glargine–glulisine) *vs* SSI	375 patients with type 2 diabetes; blood glucose 7·8–10·0 mmol/L (140–400 mg/dL); on OADs or low-dose insulin therapy (≤0·4 U/kg per day)	Mean difference in inpatient blood glucose	Basal-plus resulted in similar glycaemic control compared with basal–bolus; more treatment failure with SSI (14 [19%] of 74) compared with basal–bolus (0 [0%] of 144) or basal-plus (3 [2%] of 133)
Mader et al (2014)[48]	Basal–bolus (glargine–aspart) *vs* standard management (OADs, insulin, or both)	74 patients with type 2 diabetes; blood glucose 7·8–22·2 mmol/L; any therapy before admission	Mean difference in inpatient blood glucose	Basal–bolus algorithm group had higher percentage of glucose concentrations in the target range (5·6–7·8 mmol/L; 33% *vs* 23%; p<0·001) and in the range 3·9–10·0 mmol/L (73% *vs* 53%; p<0·001)*
Bueno et al (2015)[49]	Basal–bolus (glargine–glulisine) *vs* NPH (twice daily) and regular (before meals)	134 non-surgical patients with type 2 diabetes	Mean difference in inpatient blood glucose	No difference in glycaemic control; 23 (35%) of 66 with basal–bolus and 26 (38%) of 68 with NPH and regular insulin had hypoglycaemia (<70 mg/dL [3·9 mmol/L]); 5 (8%) with basal–bolus and 17 (25%) with NPH and regular insulin had blood glucose <40 mg/dL (2·22 mmol/L)
Bellido et al (2015)[50]	Basal–bolus (glargine–glulisine) *vs* premixed 70/30 (NPH and regular; 60% before breakfast and 40% before dinner)	72 medicine and surgical patients with type 2 diabetes; on OADs, insulin, or both	Mean difference in inpatient blood glucose	Study stopped after interim analysis; no difference in glycaemic control, but with unacceptable rate of hypoglycaemia in premixed group (25 [64%] of 39 *vs* 8 [24%] of 33 in the basal–bolus group)
Vellanki et al (2015)[51]	Basal–bolus (glargine–aspart) without bedtime supplement *vs* basal–bolus (glargine–aspart) with bedtime supplement	206 medicine and surgical patients with type 2 diabetes; blood glucose 7·8–10·0 mmol/L (140–400 mg/dL); on insulin, OADs, or both	Mean difference in inpatient blood glucose	No differences in mean daily blood glucose or hypoglycaemia (32 [30%] of 106 with supplemental bedtime insulin *vs* 26 [26%] of 100 without p=0·5)
Gracia-Ramos et al (2016)[52]	Premixed analogue insulin (lispro 25/75; two-thirds with breakfast and one-third with dinner) *vs* basal-plus (glargine–lispro)	54 patients with type 2 diabetes; blood glucose 7·8–10·0 mmol/L (140–400 mg/dL); on OADs or low-dose insulin therapy (≤0·4 U/kg per day)	Mean difference in inpatient blood glucose	No difference in mean daily blood glucose; less postprandial excursion with premixed analogue insulin, lower fasting blood glucose with basal-plus; hypoglycaemia was similar in both groups (4 [16%] of 25 for premixed analogue insulin *vs* 4 [16%] of 25 for basal-plus)
Pasquel et al (2020)[53]	Basal–bolus (glargine U300–glulisine) *vs* basal–bolus (glargine U100–glulisine)	176 patients with type 2 diabetes; blood glucose 7·8–10·0 mmol/L (140–400 mg/dL); any therapy at home	Mean difference in inpatient blood glucose	No differences in mean daily blood glucose; glargine U300 resulted in significantly lower rate of clinically significant hypoglycaemia (<54 mg/dL [3 mmol/L]) compared with glargine U100 (0 [0%] of 92 *vs* 5 [6·0%] of 84; p=0·023); no difference was observed in a subgroup of patients using continuous glucose monitoring

ICU=intensive care unit. SSI=sliding-scale insulin. OADs=oral antidiabetes drugs. U=units. NPH=neutral protamine Hagedorn (isophane) insulin. *Absolute numbers not provided.

Table 1: **Randomised clinical trials assessing insulin regimens in non-ICU patients in hospital**

such targets are discouraged.[2,19] The estimated risk of hypoglycaemia with basal–bolus insulin is about 4–6 times higher than with sliding scale insulin therapy (for blood glucose ≤3·9 mmol/L [70 mg/dL], risk ratio 5·75 [95% CI 2·79–11·83]; for blood glucose ≤3·3 mmol/L [60 mg/dL], 4·21 [1·61–11·02]).[55] Although the incidence of severe hypoglycaemia is low in controlled settings (table 1), in real-world practice severe hypoglycaemia might occur more frequently and can be life-threatening.[54]

To avoid hypoglycaemia, we recommend a basal-plus approach for patients with diabetes that are fasting or are expected to undergo procedures. In patients without diabetes or for those with good metabolic control treated with an oral antidiabetes drug at home, we recommend a sliding scale insulin alone approach. However, basal

insulin may be required if patients are unable to keep glucose levels below 10.0 mmol/L (180 mg/dL).[59,60]

Non-insulin drugs

Outdated practice guidelines for the management of inpatient hyperglycaemia and diabetes recommend against the use of non-insulin medications in the hospital because of safety and efficacy concerns.[2,3,11] Despite such recommendations, the use of oral antidiabetes drugs in patients with type 2 diabetes is not uncommon in inpatient clinical practice.[12,61] Data from recent randomised controlled trials and observational studies suggest that the use of non-insulin drugs, either in the hospital[62–69] or after hospital discharge,[70] can be effective in improving glycaemic control in general medicine and surgery patients with type 2 diabetes who have mild or moderate hyperglycaemia, and are associated with a low risk of hypoglycaemia (figure 1).[64–66,68,69]

Metformin

Despite inadequate evidence from clinical trials, metformin and other oral antidiabetes drugs are used frequently in the hospital setting in patients with type 2 diabetes.[25–27,71] In patients at risk for lactic acidosis, such as those with anaerobic metabolism (ie, sepsis, hypoxia), impaired metformin clearance (significant renal impairment), or impaired lactic acid clearance (liver failure), metformin should be avoided.[72] Dose reduction is recommended if the estimated glomerular filtration rate (eGFR) is 30–45 mL/min per 1·73 m²; metformin should be discontinued if the eGFR is less than 30 mL/min per 1·73 m².[72] In a recent study from China, including more than 1200 patients with type 2 diabetes and COVID-19, inpatient use of metformin was associated with increased incidence of lactic acidosis (adjusted hazard ratio 4·46, 95% CI 1·11–18·0). Lactic acidosis among patients treated with metformin was associated with higher doses, worse kidney function, and a higher severity of COVID-19.[73] Lactate concentrations should be measured in fragile patients and metformin should be withdrawn if increased lactate concentrations are apparent.[74] Metformin should also be discontinued in patients at risk for lactic acidosis (ie, acute kidney injury, hypoxia, shock) or before an iodinated contrast imaging procedure in patients with reduced eGFR (<60 mL/min per 1·73 m²), a history of liver disease, alcoholism, acute heart failure, or in those receiving intra-arterial contrast. Kidney function should be reassessed before treatment is restarted.[75]

Sulfonylureas

Retrospective reports suggest sulfonylureas are commonly used in the hospital setting among patients with type 2 diabetes.[25,71,76] Up to one in five patients treated with sulfonylureas might develop at least one episode of hypoglycaemia in the hospital; risk of such episodes is associated with older age, concurrent treatment with insulin, and renal impairment.[26,77] Professional societies recommend against the use of sulfonylureas in the hospital because of the potential risk of sustained hypoglycaemia.[78,79] An exception are UK recommendations that suggest sulfonylureas might be useful in managing glucocorticoid-induced hyperglycaemia.[28]

Thiazolidinediones

The use of thiazolidinediones in patients with type 2 diabetes has decreased substantially in the past decade and they are not often used in the inpatient setting.[80,81] The potential increase in fluid retention and risk of heart failure, as well as delayed onset of action, make thiazolidinediones less appealing than other drug classes for hospital use.[3,80]

SGLT2 inhibitors

SGLT2 inhibitors are currently the glucose-lowering drugs of choice for patients with type 2 diabetes and heart failure or diabetic kidney disease.[82] Concerns regarding inpatient use include the risk of euglycaemic diabetic ketoacidosis (particularly among patients with poor food intake)[83] and the risk of genitourinary infections (particularly mycotic infections). In a recent pilot randomised trial, empagliflozin did not improve dyspnoea, N-terminal pro B-type natriuretic peptide concentrations, diuretic response, or length of stay compared with placebo. However, empagliflozin use was associated with a reduction in a combined endpoint of worsening heart failure, rehospitalisation for heart failure, or death at 60 days.[84] Two larger clinical trials are testing the use of SGLT2 inhibitors in the hospital and at hospital discharge in patients with heart failure (NCT04157751 and NCT04249778). We do not recommend the routine use of SGLT2 inhibitors in the hospital.

DPP-4 inhibitors

Findings from several randomised controlled trials and observational studies in the hospital setting have shown that DPP-4 inhibitors are well tolerated and effective for glycaemic control, with a low risk of hypoglycaemia in patients with mild-to-moderate hyperglycaemia (table 2).[65–67,69,75]

The results of the first pilot trial suggested the use of a DPP-4 inhibitor was effective alone or in combination with basal insulin in patients with type 2 diabetes with mild hyperglycaemia (<10 mmol/L [180 mg/dL]).[64] These findings were later confirmed in a larger trial (figure 1, figure 2) that enrolled patients with insulin doses up to 0·6 U/kg per day. Participants with type 2 diabetes were randomly assigned to either sitagliptin plus basal insulin or basal–bolus insulin therapy.[69] Both groups had similar improvement in glycaemic control, with reduced insulin use and fewer injections in the sitagliptin group. Treatment failure was similar in both groups and was independently associated with higher HbA_{1c} values.[92] The odds of failing therapy in either group increased per one

unit change in HbA_{1c} (odds ratio 1·3, 95% CI 1·2–1·5).[69] Similar findings were reported in a study of non-cardiac surgical patients with type 2 diabetes, in which linagliptin was as effective as basal–bolus insulin therapy among participants with a blood glucose of less than 11·1 mmol/L (200 mg/dL), but less effective in patients with higher glucose concentrations at randomisation.[65] Linagliptin resulted in substantial reduction in the incidence of hypoglycaemia compared with basal–bolus therapy (2 [2%] of 128 *vs* 14 [11%] of 122; p=0·001; 86% relative risk reduction).[65] Similar results were reported in a study of saxagliptin versus basal–bolus therapy in patients with type 2 diabetes with very mild hyperglycaemia (admission blood glucose of about 150 mg/dL and mean HbA_{1c} <7% [53 mmol/mol]).[66] Very preliminary observational data, with obvious limitations, suggest that sitagliptin

	Treatment groups (intervention *vs* control)	Population	Primary outcome	Key findings
Umpierrez et al (2013)[64]	Sitagliptin plus SSI or sitagliptin plus glargine *vs* basal–bolus (glargine–lispro)	90 medical or surgical patients with type 2 diabetes; blood glucose 7·8–10·0 mmol/L (140–400 mg/dL); on OADs or low-dose insulin therapy (≤0·4 U/kg per day)	Mean difference in inpatient blood glucose	No difference in glycaemic control between groups; lower TDD and fewer injections in the sitagliptin groups; sitagliptin alone was less effective if blood glucose at baseline was >10 mmol/L (>180 mg/dL)
Pasquel et al (2017)[69]	Sitagliptin plus basal insulin (glargine) *vs* basal–bolus (glargine plus lispro or aspart)	278 medical or surgical patients with type 2 diabetes; blood glucose 7·8–10·0 mmol/L (140–400 mg/dL); on OADs or low-dose insulin therapy (≤0·6 U/kg per day)	Mean difference in inpatient blood glucose	No difference in glycaemic control between groups; lower TDD and fewer injections in the sitagliptin plus basal insulin group
Garg et al (2017)[66]	Saxagliptin *vs* basal–bolus (glargine–aspart)	66 medical or surgical patients with type 2 diabetes; HbA_{1c} ≤7·5% on ≤1 non-insulin antihyperglycaemic agent or HbA_{1c} ≤7·0% on ≤2 non-insulin antihyperglycaemic agents	Mean difference in inpatient blood glucose	No difference in glycaemic control between groups; lower glycaemic variability with saxagliptin
Vellanki et al (2019)[65]	Linagliptin plus SSI *vs* basal–bolus (glargine plus lispro or aspart)	250 surgical patients with type 2 diabetes; blood glucose 7·8–10·0 mmol/L (140–400 mg/dL); on OADs or low-dose insulin therapy (≤0·5 U/kg per day)	Mean difference in inpatient blood glucose	No difference in glycaemic control in patients with mild-to-moderate hyperglycaemia (blood glucose <11·1 mmol/L [200 mg/dL]); linagliptin alone was not effective in patients with blood glucose >11·1 mmol/L at randomisation; hypoglycaemia risk significantly reduced in the linagliptin group
Abuannadi et al (2013)[85]	Exenatide infusion *vs* intensive target (90–119 mg/dL) or moderate target (100–140 mg/dL; both historical controls)	40 coronary ICU patients without diabetes and non-insulin-dependent type 2 diabetes; blood glucose 7·8–10·0 mmol/L (140–400 mg/dL); admission for primary cardiac diagnosis	Median glucose values during steady state	Non-randomised study with historical controls (main limitation); good glycaemic control with exenatide (median 7·3 mmol/L [IQR 6·1–8·7]; similar to the moderate target control, higher than the intensive target control)
Kohl et al (2014)[86]	Native GLP-1 *vs* placebo	77 patients with or without diabetes; elective cardiac surgery	Mean glucose concentration 30 min after bypass	Mean blood glucose lower in GLP-1 group than in placebo group (6·3 mmol/L [SD 1·2; 113 mg/dL (SD 21)] *vs* 7·1 mmol/L [1·2; 128 mg/dL (21)]; p=0·001)
Besch et al (2017)[87]	Exenatide infusion *vs* insulin infusion	104 perioperative patients with CABG either without diabetes or with non-insulin-dependent type 2 diabetes	Proportion of patients with ≥50% of time within glucose target range of 5·6–7·8 mmol/L (100–139 mg/dL)	Primary outcome observed in 38 (72%) of 53 patients in the exenatide group and 41 (80%) of 51 in the insulin group (p=0·3); study stopped prematurely after futility analysis; exenatide use delayed the start of insulin infusion but was considered insufficiently efficient for blood glucose control after CABG
Polderman et al (2018)[88]	0·6 mg subcutaneous liraglutide on the evening before surgery and 1·2 mg after induction of anaesthesia *vs* glucose, insulin, and potassium infusion 30 min before surgery until 4 h after surgery bolus insulin	150 perioperative non-cardiac surgery patients with type 2 diabetes; on diet, OADs, or insulin <1 U/kg	Differences in median blood glucose 1 h after surgery	Median blood glucose 1 h after surgery was lower with liraglutide (6·6 mmol/L [IQR 5·6–7·7]) than with insulin infusion (7·5 mmol/L [6·4–8·3]) or bolus insulin (7·6 mmol/L [6·4–8·9]; p=0·006); more nausea was reported with liraglutide (p=0·007)
Lipš et al (2017)[89]	Continuous exenatide infusion add-on to standard insulin therapy *vs* 0·9% saline plus standard insulin therapy	40 patients with and without diabetes with heart failure undergoing CABG surgery	Improvement in left ventricular ejection fraction	No significant effect on cardiac function with the exception of a reduced need for temporary postoperative pacing; improved glycaemic control with exenatide (absolute difference −0·83 mmol/L (95% CI −1·25 to −0·40)
Fayfman et al (2019)[68]	Exenatide 5 mg twice daily *vs* exenatide 5 mg twice daily plus basal insulin (glargine or levemir) *vs* basal–bolus (glargine or levemir plus aspart or lispro)	150 medical or surgical patients with type 2 diabetes; blood glucose 7·8–10·0 mmol/L (140–400 mg/dL); on diet, OADs, or low-dose insulin (≤0·5 U/kg per day)	Differences in hospital mean daily blood glucose after day 1	Exenatide plus basal insulin resulted in lower mean blood glucose than exenatide alone (8·6 mmol/L [SD 2·2; 154 mg/dL (SD 39)] *vs* 9·8 mmol/L [2·3; 177 mg/dL (41)]; p=0·02) and similar to basal bolus (9·2 mmol/L [2·2; 166 mg/dL (40)]; p=0·31); exenatide plus basal insulin resulted in higher percentage of blood glucose within target range compared with exenatide alone and basal-bolus insulin (78% *vs* 62% *vs* 63%; p=0·023)

(Table 2 continues on next page)

	Treatment groups (intervention *vs* control)	Population	Primary outcome	Key findings
(Continued from previous page)				
Kaneko et al (2018)[90]	Perioperative liraglutide *vs* insulin therapy	92 patients with type 2 diabetes undergoing elective surgery	Perioperative glycaemic control	Better glycaemic control with liraglutide; lower proportion of patients requiring correction doses of insulin in the liraglutide group and lower overall insulin requirements
Hulst et al (2020)[91]	0·6 mg subcutaneous liraglutide on the evening before surgery and 1·2 mg after induction of anaesthesia *vs* placebo	278 cardiac surgery patients (84% without diabetes and 16% with type 2 diabetes)	Difference between groups for any insulin given to control blood glucose <8·0 mmol/L between entrance and exit from the operating room	18% absolute reduction in patients requiring insulin with liraglutide (p=0·003); dose and number of insulin injections were lower in liraglutide group than in placebo group; no difference in hypoglycaemia

ICU=intensive care unit. CABG=coronary arterial bypass graft. OADs=oral antidiabetes drugs. SSI=sliding-scale insulin. TDD=total daily dose. U=units.

Table 2: **Randomised clinical trials assessing incretin-based therapies in non-ICU patients in hospital**

might provide a survival benefit for patients with COVID-19; however, well designed clinical trials would be needed to confirm this potential benefit.[93]

GLP-1 receptor agonists

GLP-1 receptor agonists are potent and safe drugs for the management of type 2 diabetes in patients with and without cardiovascular risk. Recent guidelines have recommended the use of GLP-1 receptor agonists as first-line drugs in patients with type 2 diabetes and established atherosclerotic cardiovascular disease.[82] Both GLP-1 receptor agonists and native GLP-1 have been tested in the inpatient setting.[94–96] Findings from randomised controlled trials suggest preoperative treatment with liraglutide can improve glycaemic control in the perioperative period in patients with and without diabetes (table 2).[88,91,97] In a study of non-ICU patients with type 2 diabetes, treatment with exenatide plus basal insulin resulted in a higher proportion of glucose readings within the target range of 3·9–10·0 mmol/L (78%) compared with exenatide alone (62%) or basal–bolus insulin (63%).[68] As expected, trials with GLP-1 receptor agonists have shown increased frequencies of gastrointestinal side-effects.[68,88,91,97] More research is needed with these drugs to determine if the potential for improved glycaemic control with a reduction of hypoglycaemic events counterbalances the increase in gastrointestinal side-effects in the hospital setting.

Special situations

Medical nutrition therapy

Hyperglycaemia is common during parenteral nutrition and enteral nutrition.[98,99] For patients with diabetes receiving enteral nutrition, the use of a formula with lower glycaemic index is recommended. Data from a study of patients receiving parenteral nutrition suggest benefits of admixing short-acting insulin into the parenteral bag as opposed to subcutaneous insulin administration only.[99] For patients with diabetes or for those without diabetes with sustained hyperglycaemia on enteral nutrition, basal insulin (isophane insulin every 8 h, detemir every 12 h, or glargine every 24 h) along with short-acting insulin every 4–6 h is recommended.[99] Starting intravenous 10% dextrose infusion at 50 mL/h is recommended if tube feeding is interrupted. UK guidelines suggest giving 70/30 mixed insulin, with half at the start of the feed and the rest half way through the feed.[58] A recent randomised trial showed promising preliminary results for the use of closed-loop insulin administration among patients receiving medical nutrition therapy.[15] The potential advantages and disadvantages of several insulin regimens used for patients with diabetes and COVID-19 receiving continuous tube feeding was recently summarised by Hamdy and Gabbay.[100] The authors recommend counterbalancing contact frequency, glycaemic control, glycaemic variability, and risk of hypoglycaemia between intensive versus less intensive regimens and their potential mitigation strategies (eg, relaxed glucose target with less frequent testing [every 2–4 h] during intravenous insulin infusion). We recommend a systematic evaluation of such changes in practice.[100]

Glucocorticoid use

Glucocorticoid use is common in hospitalised patients.[11] When higher and repeated doses of steroids are used, afternoon and evening hyperglycaemia are common.[102] In an observational study, multiple-dose insulin therapy initiated at 1–1·2 U/kg per day, distributed as 25% basal and 75% prandial, seemed to be effective to treat hyperglycaemia in patients who were receiving high-dose dexamethasone as part of a chemotherapy regime and who had two blood glucose readings greater than 13·9 mmol/L (250 mg/dL).[103] Among patients without diabetes, a single dose of isophane insulin in the morning might be appropriate.[28] Achieving optimal glycaemic control during glucocorticoid use is much more challenging in patients with diabetes who already use insulin therapy at home. In a randomised trial,[104] the addition of isophane insulin (0·1–0·3 U/kg per day), with doses determined according to steroid dose and oral intake, to the usual insulin regimen of patients with diabetes significantly improved glycaemic

control. Diabetes UK recently published additional guidance on dexamethasone-induced hyperglycaemia management during the COVID-19 pandemic.[105] To correct initial dexamethason-related hyperglycaemia, a more resistant sliding scale might be required in some patients. To maintain glucose levels recommendations include the use of insulin isophane insulin twice a day (for more flexibility in dose adjustment) with a total dose 0·3 units/kg per day [give 2/3 of the total daily dose in the morning and the remaining dose in the early evening]). Insulin requirements can decline rapidly after dexamethasone is stopped and insulin doses should be adjusted accordingly. The use of sulfonylureas is not recommended in this clinical scenario.

Perioperative management

High perioperative glucose concentrations are associated with increased risk of infective and non-infective complications in patients with and without diabetes.[106] High HbA_{1c} values are less strongly associated with poor outcomes. However, HbA_{1c} is often the target for preoperative intervention.[107] The UK National Confidential Enquiry into Patient Outcome and Death recently published recommendations on how the perioperative care for people with diabetes could be improved, including guidance to implement policies for multidisciplinary management, referral processes for glycaemic optimisation, glucose monitoring recommendations, or appropriate handover of patients from the recovery room (appendix p 2).[108]

Findings from clinical trials enrolling non-critically ill patients with type 2 diabetes undergoing surgery have shown adequate glycaemic control with a basal–bolus approach.[45,47] Results from other trials also suggest the potential benefits of GLP-1 receptor agonists on glycaemic control during the immediate perioperative period (table 2).[88,91] Studies with DPP-4 inhibitors have not been able to meaningfully reduce the incidence of hyperglycaemia in the perioperative period and are not recommended for this purpose.[109–11] The US Food and Drug Administration (FDA) recently recommended to withhold SGLT2 inhibitors 3–4 days before surgery because of the potential risk of euglycaemic diabetic ketoacidosis.[112]

Diabetes technology in the hospital

Rapid evolution of diabetes technology over the past decades has revolutionised patient care. The use of continuous glucose monitoring and continuous subcutaneous insulin infusion (insulin pump therapy) continues to grow in the ambulatory setting. More recently, automated insulin delivery, integrating both technologies, has become available.[14] Recent studies and ongoing efforts are determining the feasibility of translating these technologies to the inpatient setting. During the COVID-19 pandemic, remote inpatient diabetes management is rapidly evolving, and several research efforts have shown the feasibility of remote consults and remote glucose monitoring.

Point-of-care testing and continuous glucose monitoring

Point-of-care testing has been for many years the standard of care in the hospital setting. A substantial advancement in documentation has been the use of networked glucose meters to incorporate results in the electronic health record.[113]

Work has been done to incorporate continuous glucose monitoring in the hospital setting. The FDA has approved two continuous glucose monitoring systems (GlucoScout and OptiScanner 5000) that extract venous blood frequently and intermittently from a central or peripheral vein catheter for use in the hospital setting. However, data for patient-centred outcomes are scarce.[14,114]

Experience with wearable continuous glucose monitoring devices in the hospital is scarce.[115] The Abbott Freestyle Libre flash glucose monitoring system takes glucose readings when it is intermittently scanned (with a more recent version providing real-time alarms), whereas Dexcom and Medtronic devices provide real-time continuous glucose monitoring. Senseonics Eversense is an implanted device (real-time continuous glucose monitoring for 5–6 months). In addition to providing continuous readings, these devices provide trends and tracking patterns to help detect episodes of hypoglycaemia and hyperglycaemia.[14] Concerns for inpatient use include the accuracy of continuous glucose monitoring data when acute physiological disturbances are present (ie, hypoxaemia, vasoconstriction, severe dehydration, and rapidly changing glucose concentrations in diabetic ketoacidosis) or chemical interference with glucose readings (eg, high doses of paracetamol [>4 g per day], salicylic acid, ascorbic acid).[18,116] Glucose monitoring devices should also be removed for certain procedures—with each company having their own list—such as MRI and diathermy.[117] Results from small clinical trials in patients with type 2 diabetes have suggested that real-time continuous glucose monitoring can be used successfully to improve glycaemic control in the hospital setting.[118,119] Reports during the COVID-19 pandemic have described the potential promise of using real-time continuous glucose monitoring in real-world hospital settings for remote inpatient diabetes management in non-ICU[120–122] and ICU patients.[123,124]

Continuous subcutaneous insulin infusion

Standalone insulin pumps

Data from observational studies suggest that the use of continuous subcutaneous insulin infusion is associated with reductions in severe hyperglycaemic events (blood glucose >16·7 mmol/L [300 mg/dL]) and hypoglycaemic events (<2·8 mmol/L [50 mg/dL]) in hospitalised patients with diabetes.[125] Professional societies advocate for continuation of continuous subcutaneous insulin infusion therapy in appropriate hospitalised patients, with

the support of hospital policies, inpatient diabetes management teams, and a signed agreement from the patient.[14,126,127]

In the absence of key elements that would allow a patient to remain on an insulin pump (eg, hospital policies and resources), the alternative is to switch to basal–bolus insulin therapy. The dose of the long-acting insulin is often derived from the 24-h total basal dose from the insulin pump settings. Contraindications to the use of insulin pumps in the hospital include impaired level of consciousness (except during short-term anaesthesia), patient's inability to correctly use appropriate pump settings, inability to self-manage diabetes, hyperglycaemic crises, lack of pump supplies, lack of trained health-care providers, and health-care decision.[14,126–128] Pumps must also be removed for certain radiological procedures such as MRI.[128] Potential safety issues (eg, software problems, alarm errors, human factors, site infection, broken components, cybersecurity issues) related to insulin pump and continuous glucose monitoring devices used in the hospital setting have been recently summarised.[127] Hospital policies should ideally incorporate guidance on transitioning a patient from continuous insulin infusion back to their pump if applicable, and on transferring a patient on insulin pump across areas within the hospital.[128–130]

Insulin pumps with continuous glucose monitoring integration

Initial advances in pump technology included suspending insulin delivery (sensor-augmented pumps) according to specific thresholds (threshold suspend) or according to a predicted low glucose concentration (predictive-low suspend). One consensus statement on inpatient use of diabetes technology recommended that the automatic threshold suspend features of sensor-augmented pumps be turned off in the hospital.[131] More recently, the insulin pump and continuous glucose monitoring technologies have been integrated with algorithms for automated insulin delivery (so-called closed-loop or artificial pancreas systems). Three hybrid closed-loop systems are currently commercially available (Medtronic 670G, Diabeloop, and Tandem Control-IQ) for use by people with type 1 diabetes. Several other companies are also developing commercial single-hormone closed-loop systems, including Insulet, Bigfoot Biomedical, Beta Bionics, and Roche.[132] With a different algorithm, researchers have shown benefits with respect to glycaemic control with a hybrid closed-loop system in the inpatient setting. The results of an initial pilot study were reproduced in a larger clinical trial that enrolled patients with type 2 diabetes.[16] In this trial, patients in the closed-loop group (n=70) attained a greater percentage of glucose readings in the target range of 5·6–10 mmol/L (100–180 mg/dL) compared with the control group (n=66; 65·8% *vs* 41·5%; p<0·001).[16] In a subgroup of 17 patients with end-stage renal disease receiving closed-loop insulin delivery, a significant increase in time in range was reported.[133] Furthermore, in another trial that enrolled patients receiving enteral or parenteral nutrition (or both) who required subcutaneous insulin therapy,[15] the proportion of time in range was remarkably higher with closed loop (68·4% [SD 15·5]) compared with the control group (36·4% [15·5]). However, the results obtained with a single automated insulin delivery system algorithm, by the same research team, need to be reproduced and expanded before routine clinical use in the hospital can be recommended.

Remote inpatient diabetes management during the COVID-19 pandemic

With the evolution of electronic health records, remote access has allowed providers to monitor the results of point-of-care tests remotely to adjust therapy. This technology has also allowed risk stratification for inpatient diabetes management, electronic consults (e-consults), and the development of insulin dosing software and calculators used as computerised decision support systems.[134] Recent reports suggest the feasibility of transitioning to a virtual model of care during the COVID-19 pandemic, using a population health management approach (with a dashboard identifying patients with blood glucose concentrations outside the target range) along with e-consults to maintain appropriate glycaemic control at a population level.[135] During the COVID-19 pandemic, interest in the use of continuous glucose monitoring has centred on the ability to avoid bedside capillary testing and reduce the burden of diabetes care for health-care workers while decreasing the risk of virus exposure. As of April, 2020, the FDA did not object to the use of continuous glucose monitoring in the hospital setting during the COVID-19 pandemic.[18]

Recently, the technology has advanced to allow remote monitoring with multiple followers, as well as the transfer of data to dashboards for population-level management. The incorporation of remote monitoring from the nurses station with a tablet computer to alert staff about potential low glucose values was associated with a reduction in hypoglycaemia in high-risk patients in one trial;[118] in another trial,[119] the incorporation of a tablet computer along with alarms for high glucose concentrations was associated with a modest reduction in hyperglycaemia in non-ICU patients with blood glucose concentrations of more than 200 mg/dL. Detailed steps for the implementation of continuous glucose monitoring were recently suggested in the hospital setting during the COVID-19 pandemic.[18] Current factory-calibrated devices include the Dexcom G6 and the Abbott Freestyle Libre. The technology allows remote monitoring (continuous data can be obtained if a receiver or smartphone is within about 6 m for the Dexcom sensors) or via intermittent flashing (Freestyle Libre). For remote monitoring, the sensor needs to be paired with a device specific app (Dexcom G6 app or Freestyle Librelink, both available for

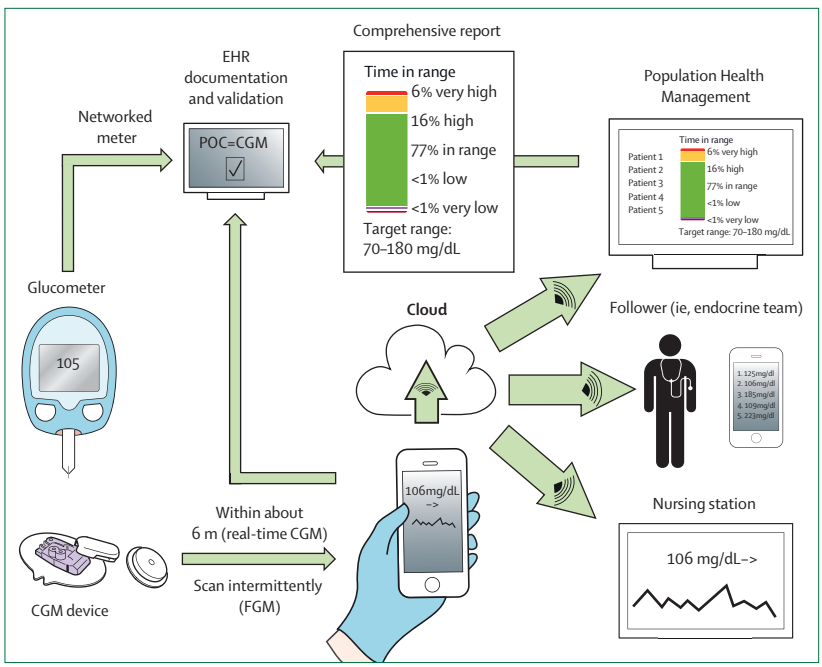

Figure 2: **Remote glucose management during the COVID-19 pandemic**
Real-time CGM or flash glucose monitoring data are transmitted via Bluetooth from the sensor to a receiver or smartphone. From a smartphone, sensor glucose data can be transferred to the cloud (via cellular signal or WiFi) and from there to real-time followers (health-care providers and telemetry) as well as to dashboard software (eg, LibreView or Dexcom CLARITY) for comprehensive assessment of multiple patients. Comprehensive glucose reports can be scanned and uploaded to the chart. Until more data on the reliability of inpatient CGM are available, a hybrid approach is recommended. Data can be documented and validated in the EHR (eg, sensor values are within 20% of POC glucose values for blood glucose concentrations >100 mg/dL). Steps for CGM implementation during COVID-19 were recently described by Galindo and colleagues.[18] Steps for direct integration of CGM data into the EHR were recently described by Espinoza and colleagues.[136] Additional information, scientific literature, and links are available online. CGM=continuous glucose monitoring. EHR=electronic health record. FGM=flash glucose monitoring. POC=point-of-care.

For more on **remote glucose management during the COVID-19 pandemic** see www.covidindiabetes.org

For **examples of COVID-19-adapted protocol** see https://www.covidindiabetes.org

For **resources on diabetes and COVID-19 from Diabetes UK** see https://www.diabetes.org.uk/professionals/resources/coronavirus-clinical-guidance

For **resources on diabetes and COVID-19 from the ADA** see https://professional.diabetes.org/content-page/COVID-19

For **resources on diabetes and COVID-19 from MyWay Digital Health** see https://mywaydigitalhealth.co.uk/COVID19/

Android or iOS), then invitations can be sent to followers (via a follower app [Dexcom Follow or LibreLinkUp]) such as remote diabetes consult teams or a nursing station (telemetry). Additionally, comprehensive reports can be accessed via dashboards (LibreView, Dexcom CLARITY) where data can be available to monitor multiple patients (figure 2).

There is thus far only anecdotal experience with automated insulin delivery and remote monitoring during the COVID-19 pandemic,[103] and more information is needed to understand efficacy, safety, barriers to implementation, and costs before recommending this technology in the hospital.

Efforts to integrate continuous glucose monitoring data into electronic health records are ongoing. Espinoza and colleagues[136] reported recently on the feasibility of electronic health record integration of continuous glucose monitoring for ambulatory care. An adapted model of care that includes electronic health record integration of relevant data specific to the inpatient setting (continuous glucose monitoring documentation with validation of glucose values as well as summary reports) is needed as experience grows with this technology in the hospital.

Resources for diabetes care during the COVID-19 pandemic

Many hospitals have adapted protocols to care for patients with diabetes and COVID-19. Common examples include changes in protocols to care for patients with diabetic ketoacidosis, remote consult teams, the use of non-insulin agents, and the use of continuous glucose monitoring in ICU and non-ICU settings (figure 2).[17,35,137,138] Examples of protocols for adapted inpatient diabetes care in the context of the COVID-19 pandemic can be accessed online. A systematic evaluation of these process changes is urgently needed. Guidance for diabetes care and other resources are also available from various sources, including Diabetes UK, the ADA, and elsewhere.

Considerations at hospital discharge

Transitions of care, clinical inertia, and risk of hypoglycaemia are relevant issues for patients with diabetes at the time of hospital discharge. Since insulin is commonly used to manage hyperglycaemia in the hospital, it is not uncommon that insulin use is included in the discharge regimen.[139]

Diabetes education is an essential component of care, necessary to achieve blood glucose targets and avoid long-term complications. Diabetes self-management education and support is essential in hospitalised patients.[140] Survival skill self-management education should include the following:[140] an understanding of diabetes diagnosis, goals, and meal planning; ability to monitor glucose concentrations at home to recognise, prevent, and treat hypoglycaemia and hyperglycaemia; how and when to take prescribed diabetes medications; and sick day rules (eg, continuing to take diabetes medications, appropriate hydration, monitoring glucose every 4 h, and checking temperature) and instructions for emergencies.

Pharmacotherapy adjustment at the time of discharge should take into account home regimen before admission, cardiorenal risk, inpatient response to therapy, and recent HbA_{1c} measurements. Two published discharge management algorithms suggest that patients with type 2 diabetes can significantly improve their glycaemic control with intensification of therapy upon hospital discharge, with intensification determined by HbA_{1c} values at admission.[70,141] For patients with an HbA_{1c} below 7% (53 mmol/mol) at admission, resuming the pre-admission regimen is appropriate.[70,141] For patients with HbA_{1c} at admission between 7% and 9% (53–75 mmol/mol), the addition of a small dose of basal insulin or intensification of the pre-admission regimen could be appropriate. For patients with uncontrolled diabetes, the combination of oral antidiabetes drugs with basal insulin or a basal–bolus insulin regimen at 80% of inpatient dose might be effective in most patients.[70,141]

In some countries and settings, cost can be an important barrier to successful discharge. The cost of insulin has increased substantially in recent years and the costs of non-insulin drugs might also be prohibitive in many

countries. In certain countries, including the USA, the costs of the proposed treatment regimen after discharge need to be discussed with the patient to determine whether it is affordable or covered by their health plan.

Priorities for future research

Further research is needed focusing on individualising therapy and determining specific glycaemic goals for patients with diabetes or hyperglycaemia in the hospital setting.[142] The field of diabetes medications and technology advances is rapidly changing the way clinicians manage type 1 and type 2 diabetes. Further efforts to simplify management and decrease the risk of iatrogenic hypoglycaemia in the hospital setting are needed. Pragmatic trials investigating the use of oral antidiabetes drugs in the hospital setting and clinical studies to identify patients at risk of stress hyperglycaemia and investigating how it can be prevented are necessary.

With further use of continuous glucose monitoring and automated insulin delivery, research with artificial intelligence that identifies different phenotypes of inpatient glycaemia might help to individualise therapy in this setting. Cost-effectiveness analyses of these newer technologies and guidance on the translation of such technologies into the hospital setting will be necessary. The use of remote glucose monitoring with alarms to alert staff about hypoglycaemia or severe hyperglycaemia is promising, but more research is needed.

Research is urgently needed to identify the best glycaemic control strategies in specific contexts (ICU, diabetic ketoacidosis, steroid-induced diabetes) during the COVID-19 pandemic, including the use of technology. Health services research focused on design and implementation strategies that facilitate electronic health record integration and interoperability of diabetes technologies could help to accelerate transformations in inpatient care, both in the context of the COVID-19 pandemic and beyond.

In view of the important findings of beneficial effects of SGLT2 inhibitors in patients with heart failure irrespective of diabetes status,[143,144] further research is needed on the acute non-glycaemic effects and risk profile of these drugs. Studies are ongoing to test the inpatient use of SGLT-2 inhibitors in hospitalised patients with heart failure (NCT04157751) or at hospital discharge (NCT04249778).

Conclusions

Hyperglycaemia in the hospital is common and associated with poor hospital outcomes. Continuous insulin infusion remains the therapy of choice during hyperglycaemic crises and critical illness. For non-critically ill patients, insulin also remains the agent of choice for patients with severe hyperglycaemia, high doses of insulin at home, type 1 diabetes, or those with steroid-induced hyperglycaemia. In patients with mild-to-moderate hyperglycaemia, the use of a basal-plus approach with or without non-insulin agents might simplify treatment regimens (less insulin, fewer injections, and less hypoglycaemia in those with lower blood glucose concentrations) compared with complex insulin regimens commonly associated with iatrogenic hypoglycaemia. For patients with mild hyperglycaemia (<11·1 mmol/L [<200 mg/dL]) who are either insulin naive, treated with very low doses of insulin at home, or have low HbA_{1c} on admission, simplified regimens are appropriate. The use of a DPP-4 inhibitor with or without a low basal insulin dose (ie, 0·1 U/kg per day) can achieve similar control to that achieved with a more complex insulin regimen in such patients. For those with moderate hyperglycaemia, a regimen with basal insulin (ie, 0·2 U/kg per day) with or without an oral antidiabetes drug (in the absence of contraindications) might be a reasonable option; however, for patients with severe hyperglycaemia (ie, >300 mg/dL [16·6 mmol/L]) or for those using high doses of insulin at home (>0·6 U/kg per day), a more complex regimen (ie, basal–bolus) is indicated. The use of GLP-1 receptor agonists seems to be safe and might decrease the need for insulin without increasing the risk of hypoglycaemia, but further research is needed.

The use of diabetes technology in the hospital is rapidly evolving but is not ready yet for widespread use. The experience gained with the use of such technologies in the hospital setting during the COVID-19 pandemic will be invaluable. Research and policy changes that facilitate electronic health record integration of diabetes technologies are urgently needed. Health-care systems should continue to adapt and transform inpatient care of diabetes and hyperglycaemia to provide cost-effective and patient-centred quality care.

Search strategy and selection criteria

We searched PubMed, MEDLINE, Google Scholar, and clinical trial registries for articles or protocols published in English up to Jan 7, 2021, 2021. Search terms included "diabetes", "inpatient", "hospitalized", "hyperglycaemia", "hyperglycemia", "hypoglycaemia", "hypoglycemia", "incretin therapy", "metformin", "sulfonylurea", "thiazolidinedione", "SGLT-2", "GLP-1", "DPP-4 inhibitor", "insulin", "basal bolus", "enteral nutrition", "parenteral nutrition", "corticosteroids", "glucocorticoid", "steroid induced hyperglycemia", "insulin pump", "CGM", "closed-loop", "clinical trial", "randomized", "outcomes", "COVID-19", and "complications". The reference lists of original articles, narrative reviews, clinical guidelines, positions statements, systematic reviews, and meta-analyses were screened for relevant publications. The final reference list was selected on the basis of relevance to the topic of this Review, with preference given to the most recent relevant publications.

Contributors

FJP wrote several sections of the Review and prepared the figures. KD and FJP prepared the tables. MCL and KD wrote several sections and reviewed successive drafts of the Review. GEU reviewed successive drafts of the Review and provided relevant references. All authors approved the final submitted version.

Declaration of interests

FJP has received research support from Merck and Dexcom and consulting fees from Merck, Boehringer Ingelheim, Sanofi, Lilly,

and AstraZeneca. KD is the chair of the Joint British Diabetes Societies for Inpatient Care and has received consulting fees and advisory board participation **fees** from Sanofi Diabetes and Novo Nordisk. GEU has received unrestricted research support for inpatient studies (to Emory University) from Dexcom, Novo Nordisk, and AstraZeneca. MCL declares no competing interests.

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