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Review

Management of in-hospital hyperglycemia in non-critical adult patients: therapeutic insulinization schemes and current use of oral hypoglycemic agents – A rapid systematic review

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Abstract

In-hospital hyperglycemia, defined as a serum glucose value ≥140 mg/dL, is a common condition that may occur in patients with a pre-existing diagnosis of diabetes mellitus or may develop secondary to stress phenomenon. There is extensive evidence in both critically ill and non-critically ill patients that demonstrates a strong association between hyperglycemia and various adverse clinical outcomes. Insulin therapy is the mainstay of treatment in almost all care settings today. However, new evidence has emerged that the use of certain oral hypoglycemic agents in non-critically ill hospitalized patients has been endorsed in terms of safety and efficacy. The objective of this article is to evaluate the therapeutic schemes currently recommended for the management of in-hospital hyperglycemia in non-critical patients. We conducted a systematic review of randomized clinical trials (RCTs) evaluating the treatment of hospitalized hyperglycemia in non-critically ill patients with insulin therapy and/or oral hypoglycemic agents. PubMed, Google Scholar and Clinical Key/Scopus were searched with the terms MESH, "hospitalized patient", "insulin", "hypoglycemic agents", and "efficacy" between the years 2014 to 2024. Based on the search criteria, 91 studies were identified, of which 27 were prioritized, and once the inclusion criteria were applied, 6 randomized clinical trials were chosen. The articles were selected according to the review's objectives and the clinical outcomes in efficacy and safety to be evaluated. Insulin therapy remains the best therapeutic option for glycemic control in hospitalized patients who develop hyperglycemia; however, recent evidence has emerged that, in terms of safety and efficacy, supports the use of oral hypoglycemic therapy in certain selected groups.

Keywords: in-hospital hyperglycemia, diabetes mellitus, insulin therapy, oral hypoglycemic agents, metabolic control

Introduction

Diabetes Mellitus (DM) is the most prevalent metabolic disorder worldwide; according to the International Diabetes Federation, by the year 2021, approximately 537 million adults will be living with diabetes, which means that about 1 in 10 people suffer from this condition and concerningly, 1 in 2 are unaware of their diagnosis [1]. Given the frequency of the disease and the complications derived from inadequate metabolic control, it is very common for these patients to be hospitalized.

A large amount of literature, including randomized clinical trials in patients with and without diabetes, in critical and non-critical conditions, has demonstrated a strong association between hyperglycemia and different adverse clinical outcomes, including increased risk of infections, prolonged hospital stay, moreover multiple complications such as transfusion requirement, renal replacement therapy, metabolic polyneuropathy, multi-organ failure and death [2, 3].

Hyperglycemia in hospitalized patients is defined as a serum glucose ≥140 mg/dl [2] and affects patients with a prior diagnosis of diabetes or those with stress-related hyperglycemia (i.e., without a prior diagnosis of diabetes). Most diabetes societies and guidelines currently recommend the use of insulin therapy as the mainstay treatment in almost all care settings; however, new evidence has recently emerged that in terms of safety and efficacy, the use of certain oral hypoglycemic agents could be used as a safe alternative in certain selected patients.

The recommendation about the use of oral hypoglycemic agents for the control of in-hospital hyperglycemia generally applies in the non-critical patient scenario, with mild to moderate hyperglycemia (less than 200 mg/dl) and with adequate food intake [4], the limitations of oral treatment are mostly related to the unpredictable response in terms of measurable effectiveness in glycemic control and safety, i.e. in the risk of hypoglycemia.

In this area, incretin agents, such as dipeptidyl peptidase 4 (DPPI-4) inhibitors and glucagon-like peptide-1 (a-GLP-1) receptor agonists [5–9] alone or in combination with basal or corrective insulin regimens, have been backed for their effectiveness and safety profile, while secretagogues such as sulfonylureas are not routinely recommended due to the risk of prolonged hypoglycemia; metformin could have indications for use in stable patients in the absence of risk factors for lactic acidosis, and who will presumably be discharged in the next 24 to 48 hours, however, at present they are not openly recommended by the different societies; sodium-glucose cotransporter type 2 (i-SGLT2) inhibitors have shown a great impact on hard outcomes such as mortality in patients with heart failure, however, their efficacy in hospital glycemic control is currently under active investigation.

Insulin therapy has been indicated for hospitalized patients in different scenarios; in the critical patient, commonly, the best therapeutic option is regular insulin at an infusion rate, and in the non-critical patient, it will depend on several factors, such as previous pharmacological management, the degree of metabolic control and the severity of documented hyperglycemia [5, 10]; however, the use of insulin is often complicated by the risk of hypoglycemia which is the most common side effect of insulin administration during hospitalization.

Hypoglycemia has been defined as a serum glucose level below 70mg/dL and is classified by levels according to severity: level 1 below 70 mg/dL, level 2 below 54 mg/dL and level 3 if the hypoglycemia is related to alterations in mental status and/or if the patient requires management assistance, this especially happens in patients with more than one risk factor such as previous records of hypoglycemia during the last three to six months, intensive insulin therapy, advanced renal disease or neurocognitive disorders [2].

Hyperglycemia and hypoglycemia should be avoided during hospitalization, considering that these events are associated with increased mortality, prolonged hospital stay and generally worse prognosis [11].

The principal objective of the present review is to evaluate the different therapeutic schemes currently recommended for managing in-hospital hyperglycemia in the non-critical patient.

Material and methods

General

PubMed, Google Scholar, and Clinicalkey/Scopus databases were searched for relevant RCTs in all languages, published from January 2014 to January 2024. We also searched ClinicalTrials.gov for ongoing trials on therapeutic schemes for the management of in-hospital hyperglycemia in non-critically patients and on the therapeutic approach to hyperglycemia in two special scenarios, glucocorticoid-induced and associated with nutritional support.

Studies of potential interest were identified by the Medical Subject Headings (MeSH) “hospitalized patient”, “insulin”, “hypoglycemic agents”, and “efficacy”. Six RCTs evaluating insulinization schedules and oral hypoglycemic agent options in monotherapy or in combination with insulin were included.

This rapid systematic review was reported according to the guidelines of the Cochrane Collaboration [12, 13], with preferred reporting elements for reviews (PRISMA). The study protocol was registered in PROSPERO CRD42024530944.

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Eligibility criteria

This review included randomized clinical trials that examined adult patients, women and men over 18 years hospitalized with hyperglycemia, with or without a previous diagnosis of diabetes mellitus, treated with human insulins or insulin analogs, oral hypoglycemic agents, such as a-GLP1 injections. Patients in intensive care settings, outpatient services or admissions due to acute complications of diabetes such as diabetic ketoacidosis (DKA) or hyperosmolar hyperglycemic state (HSS) were excluded, as well as patients who were pregnant or in palliative care.

Selection process

The study selection process is described in the PRISMA diagram (see Supplementary Figure S1). A total of 91 studies were reviewed, of which 27 were prioritized. After applying the inclusion criteria, 6 randomized clinical trials were selected. Articles were selected according to the objectives of the review and the clinical outcomes to be assessed demonstrating their clinical safety and effectiveness (Supplementary Figure S1).

Study risk of bias assessment

The risk of bias in each study was assessed using the Cochrane Risk of Bias 2 (RoB 2) scoring system for assessing the risk of bias in randomized trials, which showed an overall low risk of bias for each of the studies included in the review (Table 1).

The domains evaluated were:

- Domain 1a: Randomization process;
- Domain 1b: Risk of bias derived from the time of identification or recruitment of participants;
- Domain 2: Deviations from the intended interventions;
- Domain 3: Missing Outcome Data;
- Domain 4: Outcome measurement;
- Domain 5: Selection of reported outcome;
- Domain 6: Overall bias.

Data collection process

The following data were extracted from a selected randomized controlled trial: general characteristics of the trial (name of the trial, first author, country of publication, study design and setting), highlighting the population sample, type of intervention (insulin, oral hypoglycemic agents), general objectives of the trial and outcomes, common and serious adverse events in each group.

Results

Study selection by patient characteristics

Six RCTs conducted between 2014 and 2024, reporting 1,109 patients, were included. Supplementary Figure S1 shows the selection of studies in a PRISMA flowchart. For standard insulin therapy, comparing human insulin with insulin analogues, two trials and 182 patients were included.

Four trials and 927 patients were included for patients treated with oral hypoglycemic agents, mainly i-DPP4 or i-SGLT2 or the injectable incretin agent a-GLP1. The results showed that the two most studied drugs were a-GLP1 and i-DPP4, with one study investigating i-SGLT2. The study populations were non-critically ill hospitalized patients. Table 2 shows the studies and the characteristics of the patients included.

Comparison of glycemic control results

It was shown that in the group treated with exenatide alone or in combination with basal insulin (Fayfman *et al.* study, USA), mean blood glucose concentration was similar between patients treated with exenatide plus basal and basal-bolus regimens (154±39 *vs.* 166± 40 mg/dL, p=0.31). Exenatide plus basal insulin resulted in a lower mean daily blood glucose concentration than exenatide alone (177±41 mg/dL, p=0. 02), and it also showed a higher proportion of mean blood glucose concentration levels in the target range between 70 and 180 mg/dL compared with exenatide and basal-bolus (78% *vs.* 62% *vs.* 63%, p=0.023) [8].

In the basal-bolus insulin analog *versus* human insulin treatment group (Bueno *et al.*, Paraguayan study), there was no difference in mean daily average blood glucose concentration (157±37 mg/dL *vs.* 158±44 mg/dL; p=0.90) and premeal blood glucose concentrations within target <140 mg/dL (76% *vs.* 74%) between the glargine/glulisine and NPH/regular regimens [14]. Similarly, the Dapagliflozin plus basal insulin treatment group *versus* basal insulin alone (Dapa Hospital Trial Study, India) had no difference in mean daily blood glucose concentrations (149 *vs.* 150 mg/dL), the mean percentage of readings within the target blood glucose range of 70–180 mg/dL (82.7% *vs.* 82.5%) [15].

Table 1: Risk of bias assessment for included articles.

Study	Study ID	Weight	D1a	D1b	D2	D3	D4	D5	Overall
A Randomized Controlled Trial on the Safety and Efficacy of Exenatide Therapy for the Inpatient Management of General Medicine and Surgery Patients with Type 2 Diabetes. Maya Fayfman *et al.*	NCT02455076	14	+	+	+	+	+	+	+
Basal-Bolus Regimen with Insulin Analogues *versus* Human Insulin in Medical Patients with Type 2 Diabetes: A Randomized Controlled Trial in Latin America. Elvio Bueno *et al.*	NA	12	+	+	+	+	+	+	+
Dapagliflozin for Inpatient Hyperglycemia in Cardiac Surgery Patients with Type 2 Diabetes: Randomized Controlled Trial (Dopa-Hospital Trial). Mohammad Shaf Kuchay *et al.*	NCT05457933	23	+	+	+	+	+	+	+
Efficacy of Sitagliptin for the Hospital Management of General Medicine and Surgery Patients with Type 2 Diabetes (Sita-Hospital): A Multicentre, Prospective, Open-Label, Non-Inferiority Randomised Trial. Francisco J Pasquel *et al.*	NCT01845831	25	+	+	+	+	+	+	+
Glycaemic Efficacy and Safety of Linagliptin Compared to a Basal-Bolus Insulin Regimen in Patients with Type 2 Diabetes Undergoing Non-Cardiac Surgery: A Multicentre Randomized Clinical Trial. Priyathama Vellanki *et al.*	NCT02004366	23	+	+	+	+	+	+	+
Treatment of prednisolone-induced hyperglycaemia in hospitalized patients: Insights from a randomized-controlled study. Anjana Radhakutty *et al.*	ACTRN12612000817842	4	+	+	+	+	+	+	+

Note: Domain 1a (D1a): Randomization process; Domain 1b (D1b): Risk of bias due to timing of participant identification or recruitment; Domain 2 (D2): Deviations from intended interventions; Domain 3 (D3): Missing outcome data; Domain 4 (D4): Outcome measurement; Domain 5 (D5): Selection of reported result; Domain 6: Overall bias.

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Table 2: Characterization of patients in the included studies.

Study	Country	Design	Sample	Intervention	Objectives	Results
A Randomized Controlled Trial on the Safety and Efficacy of Exenatide Therapy for the Inpatient Management of General Medicine and Surgery Patients With Type 2 Diabetes. Maya Fayfman *et al.*	USA	Multicenter, open, randomized	N=150	Exenatide alone (5 mg twice daily) (n=47), exenatide plus basal insulin (n=51), or a basal-bolus insulin regimen (n=52)	To examine the safety and efficacy of exenatide alone or in combination with basal insulin in non-critically ill patients with T2D.	• Mean blood glucose (BG) concentration was similar between patients treated with exenatide plus basal and a basal-bolus regimen (154±39 *vs.* 166±40 mg/dL, P=0.31), and exenatide plus basal resulted in a lower daily BG than exenatide alone (177±41 mg/dL, P=0.02). • Exenatide plus basal-bolus resulted in a greater proportion of BG levels in the target range between 70 and 180 mg/dL compared to exenatide and basal-bolus (78% *vs.* 62% *vs.* 63%, respectively, P=0.023). • More patients in the exenatide and exenatide plus basal groups experienced nausea or vomiting than in the basal-bolus group (10% *vs.* 11% *vs.* 2%, P=0.17), with three patients (6%) discontinuing exenatide due to adverse events. • There were no differences in hypoglycemia <54 mg/dL (2% *vs.* 0% *vs.* 4%, P=0.77) or length of stay (5 *vs.* 4 *vs.* 4 days, P=0.23) between the basal plus exenatide, exenatide and basal-bolus groups.
Basal-Bolus Regimen with Insulin Analogues *versus* Human Insulin in Medical Patients with Type 2 Diabetes: A Randomized Controlled Trial in Latin America. Elvio Bueno *et al.*	Paraguay	Prospective, open, randomized	N=134	Basal-bolus regimen with glargine once daily and glulisine before meals (n=66) or regimen with Neutral Protamine Hagedorn (NPH) twice daily and regular insulin before meals (n=68)	To compare the safety and efficacy of a basal-bolus regimen with insulin analogues and human insulins in general medicine patients admitted to a university hospital in Asunción, Paraguay.	• There were no differences in average daily BG (157±37 mg/dL *versus* 158±44 mg/dL; P=0.90) or in the number of within-target BG readings <140 mg/dL before meals (76% *versus* 74%) between the glargine/glulisine and NPH/regular regimens. • The mean insulin dose in the glargine/glulisine group was 0.76±0.3 units/kg/day (glargine, 22±9 units/day; glulisine, 31±12 units/day) and was not different compared to the group NPH/regular [0.75±0.3 units/kg/day (NPH, 28±12 units/day; regular, 23±9 units/day)]. • The overall prevalence of hypoglycemia (<70 mg/dL) was similar between patients treated with NPH/regular and glargine/glulisine (38% *versus* 35%; P=0.68), but more patients treated with human insulin had severe hypoglycemia (<40 mg/dL) (7.6% *versus* 25%; P=0.08). • There were no differences in length of hospital stay or mortality between groups.

Table 2: Continued.

Study	Country	Design	Sample	Intervention	Objectives	Results
Dapagliflozin for Inpatient Hyperglycemia in Cardiac Surgery Patients with Type 2 Diabetes: Randomised Controlled Trial (Dapa-Hospital Trial). Mohammad Shaf Kuchay *et al.*	India	Prospective, randomized	N=250	Dapagliflozin plus basal insulin U300 -bolus Lispro (DAPA group) (n=125) or only basal insulin U300 -bolus Lispro (INSULIN group) (n=125) in the early postoperative period	To examine the efficacy and safety of dapagliflozin in the treatment of hyperglycemia in patients undergoing cardiac surgery with type 2 diabetes (T2D).	• There were no differences between the DAPA and INSULIN groups in terms of mean daily blood glucose (BG) concentrations (149 *vs.* 150 mg/dL), the average percentage of BG readings within the target range of 70–180 mg/dL (82.7% *vs.* 82.5%), total daily insulin dose (mean, 39 *vs.* 40 units/day), number of daily insulin injections (median, 3.9 *vs.* 4), length of hospital stay (median, 10 *vs.* 10 days), or incidence of in-hospital complications (21.6% *vs.* 24.8%). • Mean plasma ketone levels were significantly higher in the DAPA group compared to the INSULIN group on days 3 (0.71 *vs.* 0.30 mmol/L) and 5 (0.42 *vs.* 0.19 mmol/L) after randomization. Six patients in the DAPA group developed severe ketonemia; however, no cases of diabetic ketoacidosis (DKA) were reported. There were also no differences in the proportion of patients with BG <70 mg/dL (9.6% *vs.* 7.2%) between the two groups.
Efficacy of Sitagliptin for the Hospital Management of General Medicine and Surgery Patients with Type 2 Diabetes (Sita-Hospital): A Multicentre, Prospective, Open-Label, Non-Inferiority Randomised Trial. Francisco J Pasquel *et al.*	USA	Multicenter, prospective, open-label, non-inferior randomized clinical trial	N=277	Sitagliptin plus basal insulin glargine once daily (sitagliptin-basal group) (n=138) or basal-bolus regimen with glargine once daily and insulin lispro or aspart before meals (basal-bolus group) (n=139) during the hospital stay	To compare the safety and efficacy of a dipeptidyl peptidase-4 inhibitor (sitagliptin) plus basal insulin with a basal-bolus regimen for the management of patients with type 2 diabetes in general medicine and surgery in hospitals.	• There were no differences in the length of hospital stay between the groups. • The mean daily blood glucose concentration in the sitagliptin-basal group was not lower than that in the basal-bolus group, with a mean blood glucose difference of 0.1 mmol/L (95% CI: -0.6 to 0.7). • There were no deaths in the study. • Treatment failure occurred in 16% of patients in the sitagliptin-basal group and in 19% in the basal-bolus group. • Hypoglycemia occurred in 9% of patients in the sitagliptin-basal group and in 12% in the basal-bolus group. • No differences were observed in hospital complications between the groups.

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Table 2: Continued.

Study	Country	Design	Sample	Intervention	Objectives	Results
Glycaemic Efficacy and Safety of Linagliptin Compared to a Basal-Bolus Insulin Regimen in Patients with Type 2 Diabetes Undergoing Non-Cardiac Surgery: A Multicentre Randomized Clinical Trial. Priyathama Vellanki *et al.*	USA	Prospective, open-label, multicenter, randomized clinical trial	N=250	Daily linagliptin (n=128) or basal-bolus regimen with glargine once daily and rapid-acting insulin before meals (n=122)	To determine the glycemic efficacy and safety of linagliptin compared to a basal-bolus insulin regimen in hospitalized surgical patients with T2D.	• Mean daily glucose was higher in the linagliptin group compared to the basal-bolus group (9.5±2.6 *vs.* 8.8±2.3 mmol/L, P=0.03) with a mean daily glucose difference of 0.6 mmol/L (range 95% confidence interval 0.04, 1.2). • In patients with random glucose <11.1 mmol/L (63% of group), mean daily glucose was similar in the linagliptin and basal-bolus groups (8.9±2.3 *vs.* 8.7±2.3 mmol/L, P=0.43); however, patients with glucose ≥11.1 mmol/L treated with linagliptin had higher glucose compared to the basal-bolus group (10.9±2.6 *vs.* 9.2±2.2 mmol/L, P<0.001). • Linagliptin resulted in fewer hypoglycemic events (1.6% *vs.* 11%, P=0.001; 86% relative risk reduction), with similar insulin supplementation and fewer daily insulin injections (2.0±3.3 *vs.* 3.1±3.3, P<0.001) compared to the basal-bolus group.
Treatment of prednisolone-induced hyperglycemia in hospitalized patients: Insights from a randomized-controlled study. Anjana Radhakutty *et al.*	Australia	Randomized clinical trial	N=48	Isophane insulin is taken before breakfast and as parts before meals. Isophane Aspart (n=25); Glargine Aspart (n=23)	To evaluate whether an insulin isophane regimen is safer and more effective than an insulin glargine regimen in hospitalized patients.	• On day 1, there were no significant differences in percentage time outside a target glucose range of 4–10 mmol/L (41.3±5.5 *vs.* 50.0±5.7%, p=0.28), mean daily glucose (10.2±0.7 *vs.* 10.8±0.8 mmol/L, p=0.57) or glucose <4 mmol/L (2.2±1.1 *vs.* 2.0±1.3%, p=0.92) in patients randomized to isophane and glargine. In patients treated for 3 days, the prednisolone dose was reduced (p=0.02), and the insulin dose increased over time (p=0.02), but the percentage time out of the glucose range of 4–10 mmol/L was not did not differ over time (p=0.45) or between groups (p=0.24).

In the sitagliptin plus basal insulin *versus* basal-bolus treatment group (Sita Hospital Study, USA), mean daily blood glucose concentrations were not lower in the sitagliptin-basal group than in the basal-bolus group, with mean blood glucose differences of 0.1 mmol/L (9.5 mmol/L + 2. 7 and 9.4 mmol/L + 2.7), with no difference in efficacy (achieving blood glucose concentrations between 3.9 and 10.0 mmol/L) in patients with baseline blood glucose concentrations greater than 10.0 mmol/L (odds ratio [OR] 1.9, 95% CI 0.17–21.69) or equal to or less than 10 mmol/L (OR 0.85, 95% CI 0.33–2.20) [6, 16].

The results of the linagliptin *versus* basal-bolus insulin study (Vellanki *et al.*, USA) showed higher mean daily glucose values in the linagliptin group compared to the basal-bolus group (9.5±2.6 *vs.* 8.8± 2.3 mmol/L, p=0.03), with patients with random glucose <11.1 mmol/L (63% of the group), the mean daily glucose was similar in the linagliptin and basal-bolus groups (8.9±2.3 *vs.* 8.7± 2.3 mmol/L, p=0.43). However, in patients with glucose ≥11.1 mmol/L treated with linagliptin, glucose presented higher values compared to the basal-bolus group (10.9±2.6 *vs.* 9.2±2.2 mmol/L, p<0.001) [7, 17].

In the case of the Isofana plus aspart *versus* glargine plus aspart treatment group (Radhakutty *et al.*, Australia study), there were no significant differences in the percentage of time outside a target glucose range of 4–10 mmol/L, mean daily glucose, or glucose <4 mmol/L between patients randomized to Isofana and glargine. A unique situation in this group is the corticosteroid treatment the patients were receiving, in which the prednisolone dose was reduced after 3 days of treatment, and the insulin dose was increased over time, but the percentage of time outside the glucose range of 4–10 mmol/L did not differ over time or between groups [18, 19].

Adverse event comparison

Exenatide alone or combined with the basal insulin treatment group (Study by Fayfman *et al.*, USA) had more patients in the exenatide and exenatide plus basal groups who experienced nausea or vomiting than in the basal-bolus group, with three patients (6%) discontinuing exenatide due to adverse events [8].

For the basal-bolus regimen treatment group with insulin analogs *versus* human insulins (Study by Bueno *et al.*, Paraguay), differences in the overall prevalence of hypoglycemia were observed between the groups, with an overall prevalence of hypoglycemia (<70 mg/dL) similar between NPH/regular and glargine/glulisine-treated patients (38% *versus* 35%; p=0.68), but more human insulin-treated patients had severe hypoglycemia (<40 mg/dL) (7.6% *versus* 25%; p=0.08) [14].

For the Dapagliflozin plus basal insulin treatment group *versus* basal insulin by itself (Dapa Hospital Trial Study, India), six patients (5%) in the DAPA developed severe ketonemia compared with zero in the basal insulin alone group (p=0.013), but no patients developed diabetic ketoacidosis (DKA). Mean plasma ketone levels were higher in the DAPA group than in the basal Insulin group on days 3 (0.71 *vs.* 0.30 mmol/L) and 5 (0.42 *vs.* 0.19 mmol/L) [15].

When examining the treatment group with Sitagliptin plus basal insulin *versus* basal-bolus regimen (Sita Hospital Study, USA), no differences in hypoglycemia were observed between these groups [6]. On the other hand, in the group under Linagliptin treatment *versus* basal-bolus insulin regimen (Vellanki *et al.* Study, USA), it was highlighted that the group treated with Linagliptin resulted in fewer hypoglycemia events (1.6% *vs.* 11%, p=0.001) [7].

Discussion

Clinical practice guidelines, including the American Diabetes Association (ADA) guidelines in their latest version of 2024 [2], recommend insulin therapy as the mainstay of treatment for hospitalized patients who develop in-hospital hyperglycemia. Insulin has been considered an effective treatment in both critical and non-critical patients since it is possible to measure a predictable clinical response; however, its use is associated with a higher risk of hypoglycemia, which poses a great challenge to achieving therapeutic goals without increasing the risk of adverse effects.

Insulin regimens and types of insulin in the non-critically ill patient

In the non-critical patient scenario, the RABBIT 2 trial and RABBIT 2 surgery [14, 15] are two prospective, multicenter, randomized studies that compared the efficacy and safety of a basal-bolus insulin regimen with that of regular insulin on a sliding scale. The studies showed that the basal-bolus regimen achieved better glycemic control, so insulin on a sliding scale is not currently recommended in any scenario.

When comparing the safety and efficacy of the basal-bolus regimen with insulin analogues *versus* human insulin, several studies have shown a trend in

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favor of insulin analogues due to the lower risk of attributable hypoglycemia, One of these studies was developed in Latin America [16], where 134 nonsurgical patients with glycemia between 140 and 400 mg/dL were randomized to a basal bolus regimen of glargine once daily and glulisine before meals (n=66) or neutral protamine Hagedorn (NPH) twice daily and regular insulin before meals (n=68), and found that there was no difference in mean daily blood glucose (157±37 mg/dL *vs*. 158± 44 mg/dL; p=0.90) nor in the overall prevalence of hypoglycemia, however, more patients treated with human insulin had severe hypoglycemia (<40 mg/dL), without being statistically significant but showing a trend, based on this study it is proposed that in patients with risk factors for developing hypoglycemia, it should preferably be treated with insulin analogues.

Insulin therapy in the non-critical patient will depend on several factors, such as the severity of hyperglycemia, the number of oral antidiabetic drugs received on an outpatient basis, whether the patient is insulin naïve (i.*e*. no history of previous insulin administration), and the degree of metabolic control based on glycosylated hemoglobin (HbA1C) levels. In the patient with mild hyperglycemia, using less than two oral antidiabetic agents, naive to insulin and with acceptable metabolic control, oral hypoglycemic agents are recommended upfront based on the currently available evidence, mainly i-DPP4 [6, 7] a-GLP1 [8] alone or in combination with rapid-acting corrective insulin.

In patients with moderate hyperglycemia (200 mg/dl and above), multiple oral antidiabetic medications and suboptimal metabolic control, it is recommended that a basal insulin regimen be discontinued at the outset, which may be accompanied by oral hypoglycemic agents, the latter only if there is adequate food intake, with or without correction insulin, and in the case of documented severe hyperglycemia (>300 mg/dl), to switch to a basal-bolus insulin regimen with or without correction insulin (Figure 1) [2, 5, 10].

Oral hypoglycemic agents by itself or in combination with insulins

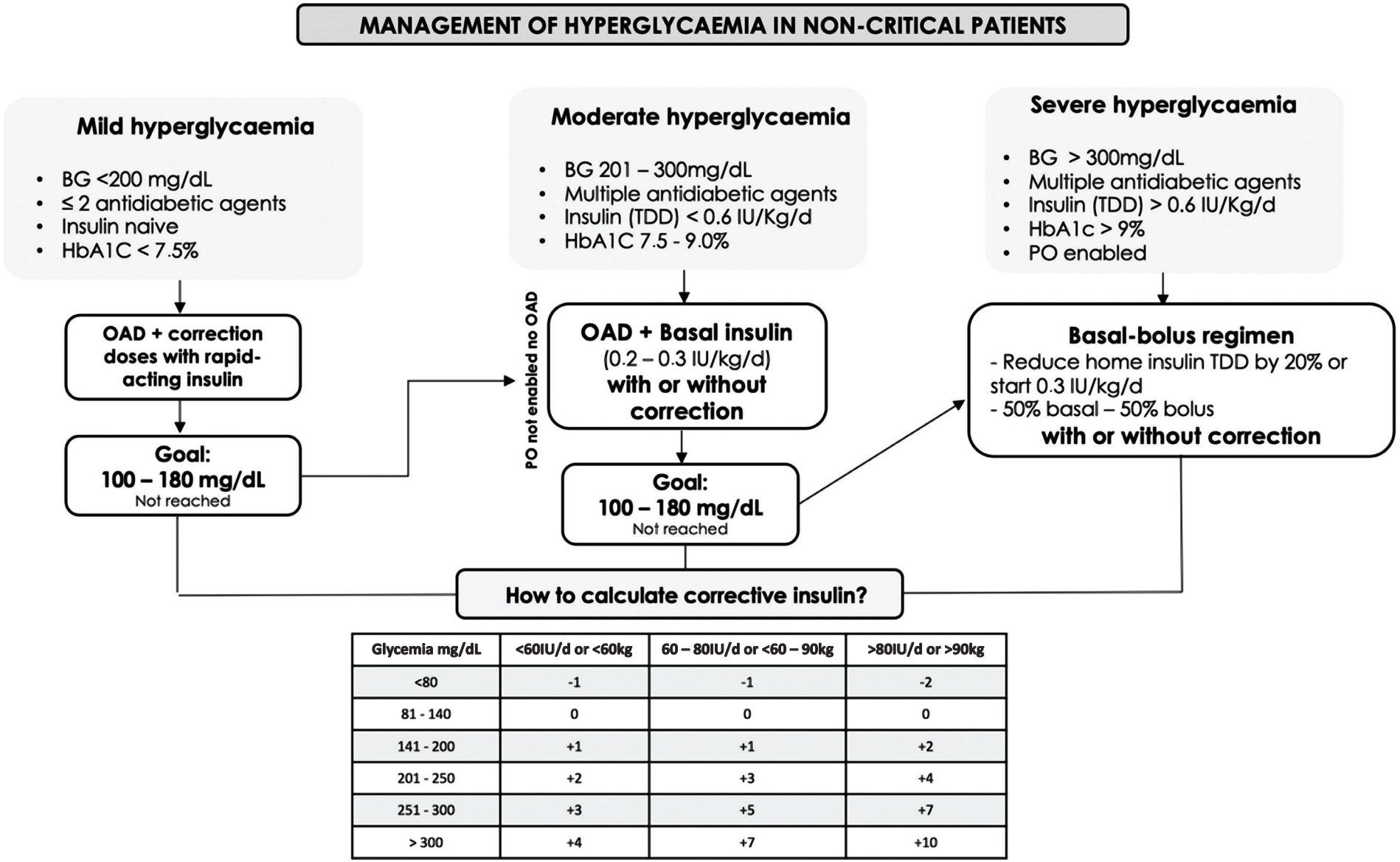
Compared to treatment with insulin alone, non-insulin therapies in non-critical care settings in patients with mild to moderate hyperglycemia resulted in a significantly lower rate of hypoglycemia and were equally effective in glycemic control, both Sitagliptin [6] and Linagliptin [7] showed a good safety and efficacy profile as therapy alone or in combination with basal insulin or corrective insulin.

The SITA hospital study compared the safety and efficacy of Sitagliptin plus basal insulin with a bolus basal insulin regimen [6], a multicenter, prospective, open-label, randomized clinical trial, where the primary endpoint was non-inferiority, i.*e*. a difference <1 mmol/L between the two groups, the mean daily blood glucose concentration in the basal Sitagliptin group (9.5 mmol/L [SD 2.7]) was not lower than that of the basal-bolus group (9.4 mmol/L [2.7]) with a mean blood glucose difference of 0.1 mmol/L (95% CI -0.6 to 0. 7), making treatment with Sitagliptin plus basal insulin as effective as basal-bolus insulin, and a very reasonable therapeutic alternative in patients with mild to moderate hyperglycemia (glucose below 180–200 mg/dl), as well as in frail or elderly patients, given its safety profile.

The efficacy of i-DPP4 for the management of in-hospital hyperglycemia has also been studied independently, i.*e*., not associated with co-administration of insulins; in this setting, Linagliptin was compared with a bolus basal insulin regimen in a prospective, open-label, multicenter trial [7], in which patients with type 2 diabetes mellitus undergoing non-cardiac surgery were randomized to receive Linagliptin (n=128) daily or basal-bolus insulin (n=122), the primary endpoint was the difference in mean daily blood glucose between the groups, finding that in patients with blood glucose <200 mg/dl (63% of the cohort), mean daily blood glucose was similar in the Linagliptin and basal-bolus groups; however, those patients with glycemia ≥200mg/dl who were treated with Linagliptin had higher glycemia compared to the basal-bolus group, with statistically significant differences, which points to the need for insulin therapy in this group to achieve control goals.

Similarly, Linagliptin resulted in fewer hypoglycemia events (1.6% *vs*. 11%, P=0.001; 86% relative risk reduction), thus concluding that daily Linagliptin is a reasonable alternative to in-hospital hyperglycemia treatment in both safety and efficacy in selected patients.

The a-GLP1s have also been evaluated in a particular multicenter, open-label, randomized trial that examined the safety and efficacy of exenatide [8] alone or in combination with basal insulin *versus* bolus basal insulinization scheme, a total of 150 patients were included where the main objective to be evaluated was the difference in mean daily serum glucose concentration, resulting very similar between patients treated with exenatide plus basal and a bolus basal regimen (154±39 *vs*. 166±40 mg/dL, P=0.31) and exenatide plus



Glycemia mg/dL	<60IU/d or <60kg	60 – 80IU/d or <60 – 90kg	>80IU/d or >90kg
<80	-1	-1	-2
81 - 140	0	0	0
141 - 200	+1	+1	+2
201 - 250	+2	+3	+4
251 - 300	+3	+5	+7
> 300	+4	+7	+10

Figure 1: Management of hyperglycemia in non-critical patients. BG – blood glucose; OAD – oral antidiabetes drug; TDD – total daily dose; IU – International Units; PO – orally; HbA1C – Glycated hemoglobin.

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basal insulin resulted in lower mean daily glucose than exenatide alone (177±41 mg/dL, P=0.02), however gastrointestinal symptoms such as nausea, vomiting were more common in the groups receiving Exenatide, in terms of safety profile there was no difference in hypoglycemia <54 mg/dL (2% *vs*. 0% *vs*. 4%, p=0.77).

Requiring a lower total insulin dose while achieving similar metabolic control and lower rates of hypoglycemia makes incretin agents a reasonable therapeutic option for hospitalized patients with mild to moderate hyperglycemia.

In recent years, a number of beneficial effects associated with i-SGLT2 delivery beyond glycemic control have been documented in different studies that impact hard outcomes such as mortality in patients with heart failure, improved renal function in those with diabetic kidney disease, decreased albuminuria and risk of progression to end-stage renal disease, however, in the setting of the patient with in-hospital hyperglycemia to optimize metabolic control, they are still under study.

Dapagliflozin, in particular, was shown to be safe in patients hospitalized for chronic obstructive pulmonary disease (COPD) who develop glucocorticoid-induced hyperglycemia (GICH), but it did not improve glycemic control or clinical outcomes.

Special situations

Glucocorticoid-induced hyperglycemia (SIHG)

Another important scenario is patients who develop glucocorticoid-induced hyperglycemia (SIHG), which may be new onset or due to worsening glycemia in those with pre-existing diabetes; there are no standardized and unified recommendations for management. In this group, what is currently suggested is to continuously monitor those who receive doses of prednisolone greater than or equal to 20 mg per day or equivalent doses of other steroids [18].

The treatment of hyperglycemia induced by glucocorticoids will depend on the type of medication, the duration of action of the drug, the dose and the schedule of administration [18, 19]; for example, fast-acting glucocorticoids such as hydrocortisone produce a peak of hyperglycemia of rapid onset and short duration. Therefore, the administration of regular insulin or short-acting analog insulin is preferred and must be administered concomitantly. On the other hand, intermediate-acting glucocorticoids that are the most used in the hospital setting, such as prednisolone and methylprednisolone, induce hyperglycemia that develops slowly but continuously, reaching maximum plasma levels in 4 to 6 hours. Given these characteristics, the insulin that best adapts to this pattern is NPH insulin, so it is recommended to administer it together with intermediate-acting steroids [20].

Since prednisolone causes hyperglycemia predominantly between noon and midnight, one study [21] evaluated whether an insulin regimen based on isophane human insulin (NPH) is safer and more effective than a regimen based on glargine in hospitalized patients, including 50 patients were randomly assigned to receive insulin Isophane or glargine before breakfast and insulin Aspart before meals and the average daily glucose was evaluated (10.2±0.7 *vs*. 10.8±0.8 mmol/L, P=0.57), in this study specifically there were no statistically significant differences in terms of efficacy or safety, however, due to the duration of action, chemical, pharmacokinetic and pharmacodynamic properties, the administration of NPH insulin is recommended.

For their part, long-acting glucocorticoids such as dexamethasone induce hyperglycemia lasting more than 24 hours; in this context, long- or ultra-long-acting insulins are recommended for its control (Figure 2). The amount of insulin will depend on the dose of the glucocorticoid, generally doses of prandial insulin (if the patient has food intake) and correction insulin are needed.

A retrospective study found that increasing the ratio of insulin and glucocorticoids was associated with better glycemic control (70 to 180 mg/dL); however, there was an increase in hypoglycemia [22]. It is recommended to guide management according to blood glucose monitoring to reduce the risk of hypoglycemia and achieve optimal metabolic control.

Hyperglycemia associated with enteral/parenteral nutritional support

The insulin supply must cover basal, prandial, and correctional needs for patients who develop hyperglycemia associated with enteral or parenteral nutritional support and require insulin therapy [4]. Suppose the patient had previously been receiving insulin on a basal regimen. In that case, it must continue, and an adequate insulin dose must be calculated to provide coverage for the nutritional component supplied.

Therapeutic recommendations will depend on the administration method. If the patient receives continuous enteral nutrition, a basal insulinization scheme is suggested, accompanied by intermediate-acting insulin or regular insulin with a schedule and corrections as needed, with dose adjustment according to geometric

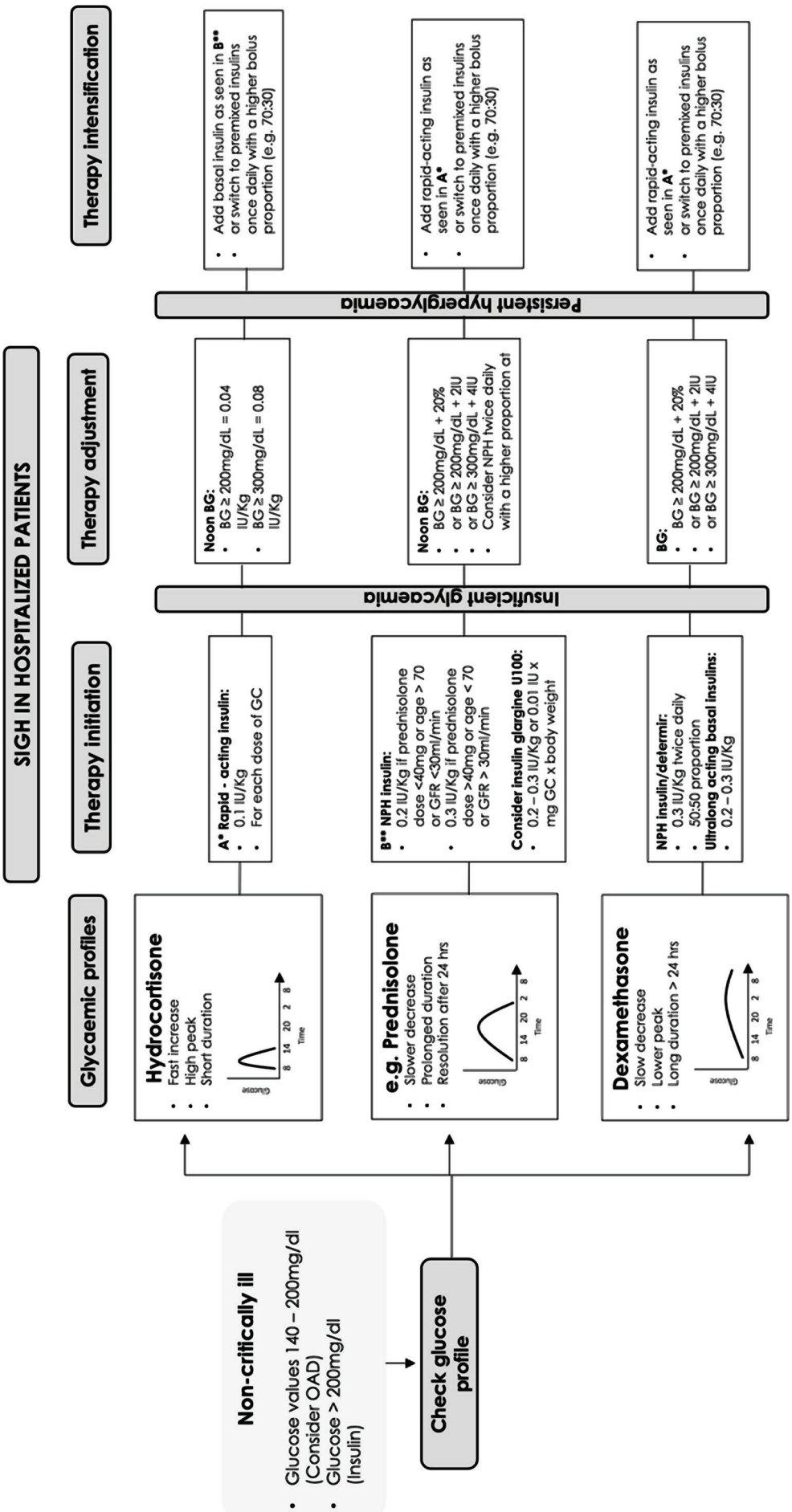

Figure 2: SIGH in hospitalized patients. Adapted from Aberer, F *et al.* (2021) [18]. SIHG – Steroid induced hyperglycaemia; OAD – oral antidiabetes drug; BG – blood glucose; GC – Glucocorticoid; IU – International Units; NPH – Neutral Protamine Hagedorn. A* – indicates recommendations for initiation of rapid-acting insulin; B** – indicates recommendations to initiate basal insulin.

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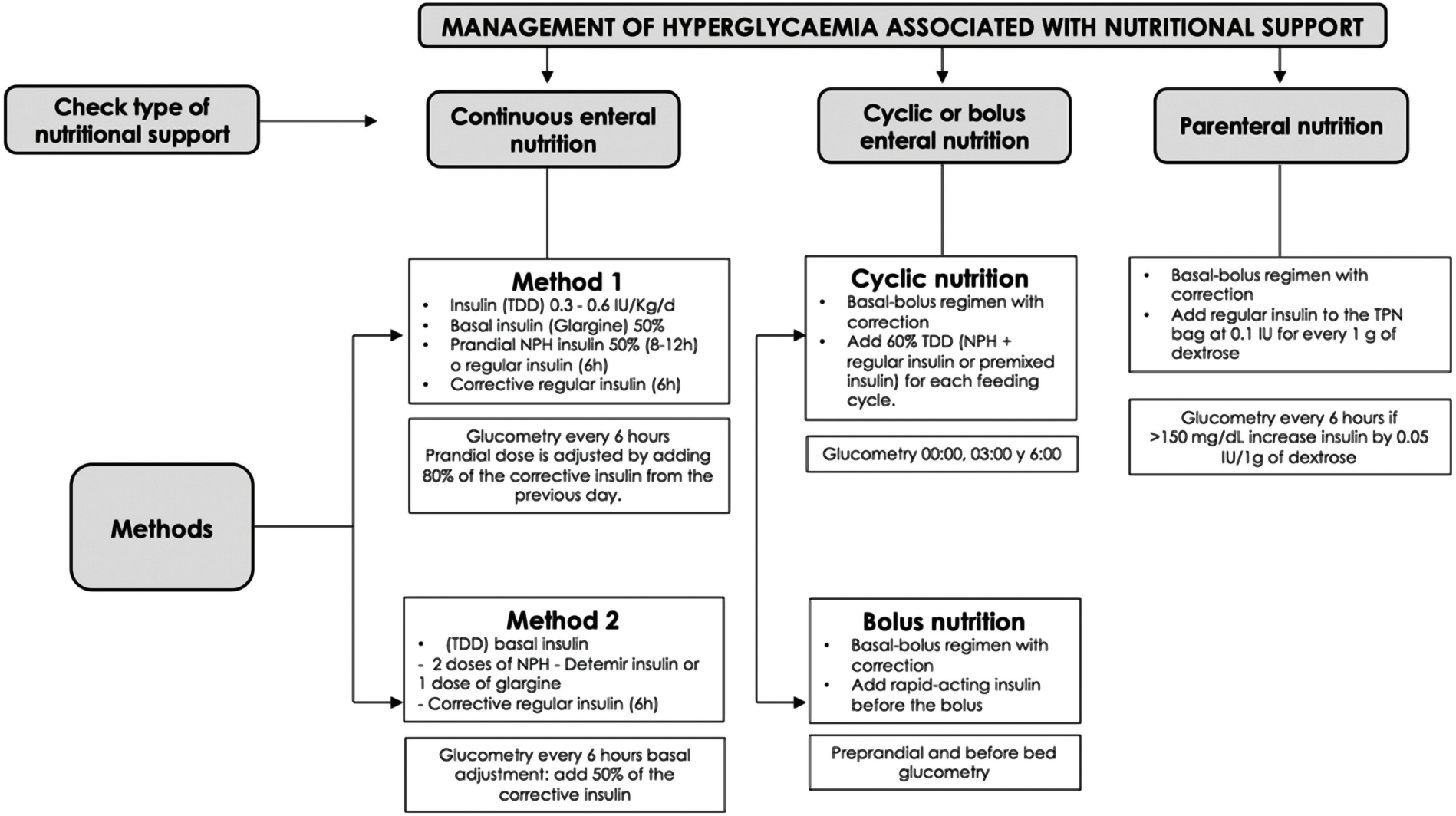

Figure 3: Management of hyperglycemia associated with nutritional support. TDD – total daily dose; IU –International Units; NPH – Neutral Protamine Hagedorn; TPN – Total parenteral nutrition.

control. which should be performed every 6 hours; for those who receive enteral bolus feeding, it is suggested to administer a basal-bolus regimen with correction or reasonably, it is recommended to administer subcutaneously approximately 1 IU of regular human insulin or rapid-acting insulin for every 10 to 15 g of carbohydrates, before each feeding and additionally a corrective scheme as needed [4].

In patients receiving cyclical enteral feeding, NPH insulin administered in conjunction with the initiation of feeding is the recommended option and for those receiving continuous peripheral or central parenteral nutrition, it is recommended to add regular insulin at 0.1 IU per 1 gram of dextrose to nutrition (Figure 3) [23].

It is not clear which is the best insulin regimen to treat hyperglycemia in hospitalized patients with nutritional support, in a systematic review of the literature with meta-analysis [24] different cohort studies and randomized clinical trials were included with the objective of evaluating the effectiveness of different insulin regimens in terms of mean serum glucose (MBG), risk of hypoglycemia, length of hospital stays and mortality.

In the enteral nutrition group, a total of 8 studies were included, 1203 patients receiving rapid insulin, glargine, NPH or premixed, obtaining a MBG of 108–225 mg/dl, in the indirect meta-analyses, NPH insulin occupied the best place. for glucose control (MD: 95% CI: -2.50 mg/dl [2.65 to -2.35]), however, the improved results using insulin regimens with NPH do not appear to be clinically relevant.

For its part, in the group of patients with parenteral nutrition, 4 studies were included: 228 patients receiving regular insulin and glargine or NPH, obtaining an MBG 137–202 mg/dl. In meta-analyses comparing regular insulin added to the parenteral nutrition bag with glargine, MBG (MD 95% CI -3.78 mg/dL [-11.93 to 4.37]; I2=0%) or frequency of hypoglycemia (RR 95% CI 1.37 [0.43–4.32]; I2=70.7%) no statistically significant differences were obtained.

It has not been possible to establish the best insulin regimen to treat hyperglycemia in hospitalized patients with nutritional support, but it is clear that close monitoring must be carried out to continually reevaluate the management offered and achieve metabolic control goals with the aim of minimizing risks of adverse outcomes.

Considerations

This review of the literature makes it difficult to compare results obtained in different clinical settings. Most guidelines focus on glycemic control recommendations for two main populations, critically ill and non-critically ill patients. The management approach for critically ill patients is different and has been evaluated in several clinical trials, which is why these patients were not included in our registry.

Conclusions

The management of in-hospital hyperglycemia has evolved over time according to the currently available evidence; achieving adequate metabolic control without increasing the risk of hypoglycemia is the main therapeutic goal; the use of oral hypoglycemic agents, mainly incretin agents, with or without co-administration of insulin in appropriately selected patients has been shown to be safe and effective.

Insulin, in combination with non-insulin agents, appears to be the preferred treatment option for many patients in non-critical care settings, a practice that should be encouraged. The important message of this review is that it should be individualized according to the treatment needs of each patient, making it reasonable to change the paradigm of insulin as the sole treatment option in the patient who develops hospital-acquired hyperglycemia.

Conflict of interest

The authors declare no conflict of interest.

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