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Systematic review with meta-analysis: Subcutaneous insulin glargine coadministration for diabetic ketoacidosis

Carlos Alberto Andrade-Castellanos[1] and Luis Enrique Colunga-Lozano[2]*

[1]Adult Emergency Department, Hospital Civil de Guadalajara Dr. Juan I. Menchaca; [2]Intensive Therapy Department, Hospital Civil de Guadalajara Fray Antonio Alcalde, Guadalajara, Jal., Mexico

Abstract

Background: *The standard treatment of diabetic ketoacidosis involves intravenous infusion of regular insulin until recovery of the episode: this is associated with high costs. Coadministration of insulin glargine from the onset of management may prove beneficial, potentially avoiding rebound hyperglycemia, and hopefully improving the time to resolution of the disease.* **Methods:** *We searched MEDLINE, EMBASE, and CENTRAL for randomized controlled trials comparing coadministration of insulin glargine versus standard treatment in patients with diabetic ketoacidosis. To be eligible, studies must assess the efficacy of insulin glargine and report clinically important outcomes. Two reviewers extracted data, assessed risk of bias and summarized strength of evidence using the GRADE approach.* **Results:** *Four studies (135 participants during hospital follow-up) were included in this review. Low-quality evidence from three trials suggested that subcutaneously administered insulin glargine, in addition to the standard treatment, significantly reduces the time to resolution of diabetic ketoacidosis (MD –4.19 hours; 95% CI: –7.81 to 0.57; p = 0.02). There was neutral difference between the two groups regarding length of hospital stay and hypoglycemic episodes.* **Conclusions:** *subcutaneously administered insulin glargine, in addition to standard treatment, significantly reduces the time to resolution of diabetic ketoacidosis, with neutral effects on hypoglycemic episodes.*
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Corresponding author: *Carlos Alberto Andrade-Castellanos, caandrade@hcg.gob.mx*

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Introduction

Diabetic ketoacidosis (DKA) is characterized by the hyperglycemia, ketosis and acidosis clinical triad, which results from insulin (quantitative or qualitative) decrease with a subsequent increase in the excretion of counter-regulating hormones (catecholamines, cortisol, glucagon and growth hormone). DKA is type 1 diabetes mellitus initial presentation in 21% of patients. In the case of type 2 diabetes mellitus, DKA is the initial presentation in approximately 10% of patients[1].

In countries such as the USA, the incidence of DKA is 4.6-8 episodes per 1,000 diabetic patients of all ages[2]. DKA-related estimated mortality is 0-19%[3], a figure that has varied very little over the years. In addition to DKA clinical impact, the economic impact of this condition is considerable: 2.4 billion dollars are spent yearly only in the USA[4]. These elevated costs are largely explained by the broad use of resources for

Correspondence:
*Carlos Alberto Andrade-Castellanos
Servicio de Urgencias Adultos
Hospital Civil de Guadalajara Dr. Juan I. Menchaca
Salvador Quevedo y Zubieta, 750
C.P. 44340, Guadalajara, Jal., México
E-mail: caandrade@hcg.gob.mx

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the management of these patients. Among these, the following stand out: care in Intensive Therapy Units[5,6], use of infusion pump for insulin IV administration, constant monitoring and prolonged hospital stay. With no doubt, one of the causative factors for a patient with DKA to stay at the hospital longer than scheduled is rebound hyperglycemia, which is observed in the transition from insulin pump to subcutaneous administration of this hormone once the DKA signs and symptoms have subsided[7]. The methods to determine the amount of subcutaneous insulin to be applied after this transition are based, in most occasions, on the IV insulin requirements administered on the previous day[8], which is a method that feels rather unpractical and prone to errors.

Based on their pharmacological properties, long-acting insulin analogs might prevent rebound hyperglycemia by helping to maintain plasma insulin more stable levels[9]. Insulin glargine, after subcutaneous administration, produces a concentration profile with no peaks throughout 24 h with an excellent safety profile with regard to hypoglycemia episodes. Based on this, Hsia et al.[10] conducted a randomized clinical trial where insulin glargine was subcutaneously administered within the first 12 h of insulin IV infusion initiation in diabetic patients with different conditions characterized by hyperglycemia, including DKA. Primary outcome measure was the percentage of patients who experienced rebound hyperglycemia. Data final analysis revealed that insulin glargine simultaneous administration significantly reduces such outcome[10]. However, the effects of this intervention on other even more relevant outcomes such as time to DKA resolution remain, to this moment, unknown. However, this is highly plausible in view of insulin glargine pharmacological properties, which might shorten IV insulin pump usage time.

The purpose of this systematic review with meta-analysis is to assess the effect of insulin glargine co-administration on the management of DKA (added to IV insulin infusion standard management). To this end, and in order to have a more complete perspective on the usefulness of this intervention, we decided to carry out a systematic review with meta-analysis of randomized clinical trials assessing the administration of this drug versus standard management of DKA episodes.

Material and methods

A systematized and exhaustive search was carried out in Embase, Medline via Ovid and CENTRAL until August 01, 2015, without language restrictions and using the following MeSH terms and descriptors: *diabetic ketoacidosis; diabetic coma; dka; hyperglycemic; insulin glargine; insulin; long-acting; lantus: blind; randomised controlled trial; random; controlled; placebo; clinical trial*, following the PRISMA recommendations[11]. In addition, searches were made in clinical trials registries (ClinicalTrials.gov), conference abstracts and other manual searches. Furthermore, all relevant authors were contacted via e-mail.

For the performance of the present systematic review, a protocol was a priori designed, which was registered in PROSPERO[12].

Study selection

Randomized clinical trials of patients with DKA regardless of age, severity (according to the American Diabetes Association Criteria)[13] or type of diabetes (1, 2 or gestational), in whom insulin glargine co-administration with standard management versus standard management with insulin IV infusion alone was studied, were included. To be included in the analysis, the clinical trials had to report important patient clinical outcomes and not only subrogated outcomes. In addition, the intervention had to have started in a period no longer than 12 h since IV insulin infusion pump initiation. The exclusion criteria were: a) subjects with persistent hypotension managed with vasoactive amines, b) patients with chronic renal failure and c) patients with known liver failure. The assessment of studies' inclusion or exclusion criteria was independently performed by two investigators. Disagreements were solved by consensus.

Data extraction and quality assessment of the studies

Data extraction and quality assessment of the studies were performed by two investigators. Clinical outcomes of interest were: time to DKA resolution (according to the American Diabetes Association definition)[13], rebound hyperglycemia (as defined by the authors), hospital length of stay and intervention-emergent adverse effects, especially hypoglycemia (≤ 70 mg/dl) and hypokalemia (< 3.5 mEq/l). The quality of the studies was assessed with the Cochrane Collaboration bias tool[14]. The GRADE system was used to evaluate the quality of evidence with regard to important outcomes[15]. The GRADE system assesses the quality of studies according to the following parameters: design, bias risks, inconsistency, indirect data, inaccuracy and other considerations (e.g., publication bias). This system

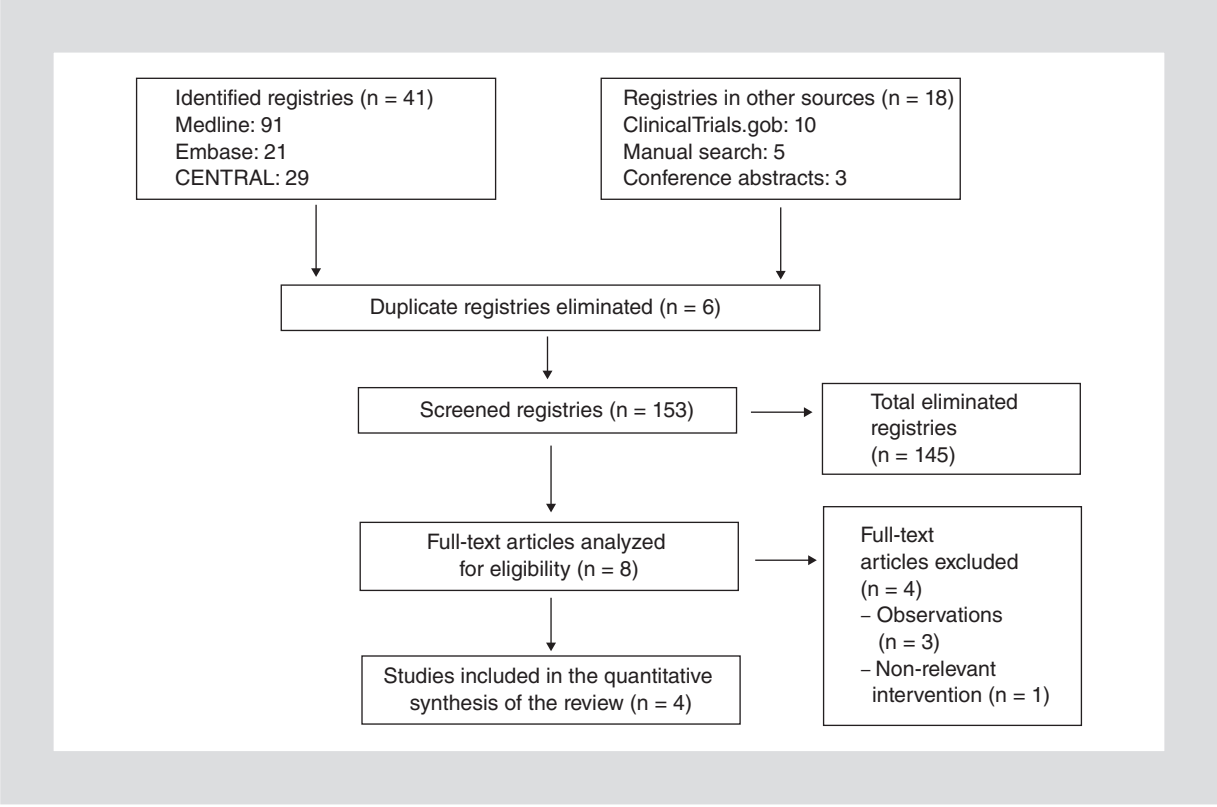

Figure 1. *PRISMA flow chart of the systematic review.*

grades the quality of evidence as high, moderate, low or very low.

Data synthesis and analysis

The statistical analysis was carried out aided by the Review Manager program, version 5.3 (Nordic Cochrane Center, Copenhagen, Denmark). The results were expressed as the mean difference (MD) for continuous outcomes and relative risk (RR) for dichotomous outcomes with the corresponding 95% confidence interval (CI). The DerSimonian-Laird random effects model was chosen for effect estimation in view of the expected variability between trials[16]. Heterogeneity was assessed with the I^2 statistic, which was considered to be mild if lower than 25%, moderate if equal to 50% and substantial if it was 75%[17]. Funnel plot-publication bias analysis was not possible because less than 10 clinical trials were assessed[18].

Results

Based on the electronic search strategy and other relevant sources, 159 titles and abstracts were identified. After eliminating duplicate registries, 145 were excluded, since they were review articles or randomized clinical trials in patients without DKA. Eight studies were reviewed in detail, out of which 4 were excluded according to the inclusion and exclusion criteria (Fig. 1). There is one study registered at ClinicalTrials.gov (NCT00179127) that could be relevant; however, and in spite of our efforts to contact the main author and the university that hosted the study, at the moment this manuscript was submitted, no answer from them had been received.

In total, only four clinical trials were included in the analysis[10,19-21]. The pooled population of these studies was 135 individuals who were randomly assigned to receive subcutaneous insulin glargine plus insulin IV infusion (n = 67) or standard management with insulin IV infusion (n = 68). Insulin glargine subcutaneous dose ranged from 0.25 to 0.4 U/kg, which was administered between the first 2[20], 3[21], 6[19] and 12 h[10] of having initiated the insulin IV infusion, to subsequently continue with a subcutaneous dose every 24 h until DKA resolution. The IV insulin dose was the same in all studies and for both treatment groups, following the American Diabetes Association recommendations[13]. Treatment duration and follow-up offered to participants was only during hospital stay. Trials' characteristics are shown in table 1.

Table 1. Characteristics of the clinical trials included in the meta-analysis

	Assaad-Khalil et al (2011)[19]	**Hsia et al. (2012)[10]**	**Doshi et al. (2015)[20]**	**Houshyar et al (2015)[21]**
Population characteristics	Patients with DKA (moderate and severe) between 15 and 60 years of age Country: Egypt	Diabetic patients with hyperglycemia (61 in total, 25 with DKA) Country: USA	Adult patients (> 18 years of age) with DKA Country: USA	Patients older than 12 years of age with DKA Country: Iran
Treatment				
Intervention	Glargine 0.3 U/kg SC + IVII	Glargine 0.25 U/kg SC + IVII	Glargine 0.3 U/kg SC + IVII	Glargine 0.4 U/kg SC + IVII
Control	IVII (standard management)	IVII (standard management)	IVII (standard management)	IVII (standard management)
Number of patients (males %)	30 (53)	25 (56)	40 (60)	40 (45)
Age in years with mean ± SD	20.7 ± 4.9 vs. 21.2 ± 4.4	ND*	38.5 ± 7.0 vs. 41.5 ± 10.7	29.6 ± 13.6 vs. 29.2 ± 15.6
DKA severity (cases)				
Mild	0	ND*	ND*	ND*
Moderate	5 vs. 4	ND*	ND*	ND*
Severe	10 vs. 11	ND*	ND*	ND*
Baseline variables with mean ± SD				
Glucose	634.4 ± 106 vs. 626.2 ± 212	ND*	640.5 ± 112 vs. 542.0 ± 125	540 ± 190 vs. 497.3 ± 102
Bicarbonate (mg/dl)	6.3 ± 3.3 vs. 7.1 ± 3.3	ND*	12.5 ± 3.2 vs. 13.0 ± 2.7	6.51 ± 3.3 vs. 6.37 ± 3.4
pH	7.12 ± 0.10 vs. 7.13 ± 0.11	ND*	7.2 ± 0.10 vs. 7.1 ± 0.10	7.09 ± 0.15 vs. 7.09 ± 0.14
Anion gap	41.1 ± 5.7 vs. 40.9 ± 9.1	ND*	18.5 ± 4.2 vs. 19.5 ± 2.0	ND*
Potassium (mEq/l)	ND*	ND*	ND*	4.65 ± 0.74 vs. 4.59 ± 0.59
HbA1c (%)	ND*	11.0 ± 2.2 vs. 12.1 ± 1.9	ND*	12.3 ± 2.4 vs. 12.7 ± 2.4
Type of diabetes (%)				
Type 1	ND*	25 (41)	16 (40)	33 (82.5)
Type 2	ND*	0	24 (60)	7 (17.5)
Triggering factor (%)				
DM new onset	ND*	ND*	3 (7.5)	16 (40)
Transgression	ND*	ND*	30 (75)	17 (42.5)
Infection	ND*	ND*	7 (17.5)	7 (17.5)
Main studied outcome	Time to DKA resolution	Rebound hyperglycemia	Time to DKA resolution	Time to DKA resolution

*ND: no data.
HbA1c: glycated hemoglobin; IVII: IV insulin infusion; SD: standard deviation; SC: subcutaneous.

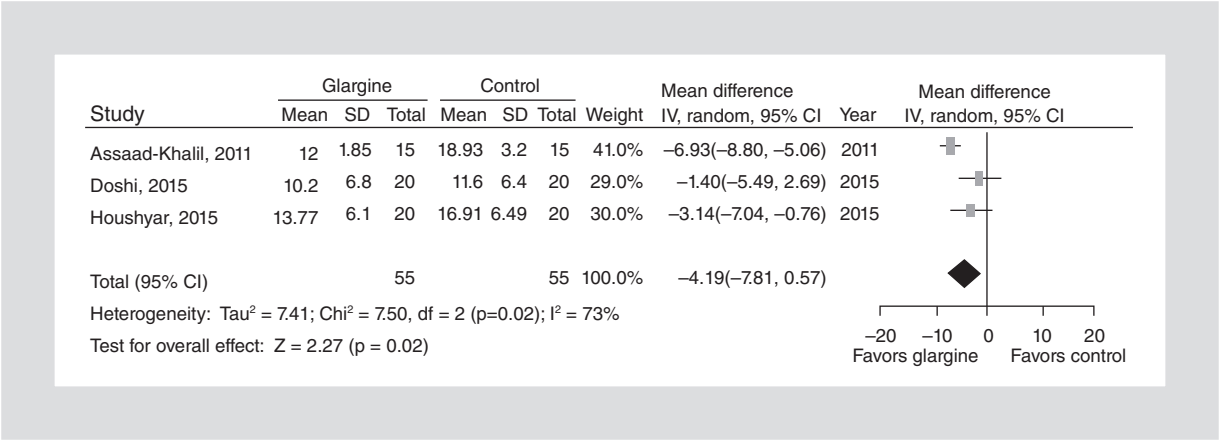

Figure 2. *Forest plot of the comparison of glargine versus standard management (control). Outcome: time to DKA resolution.*

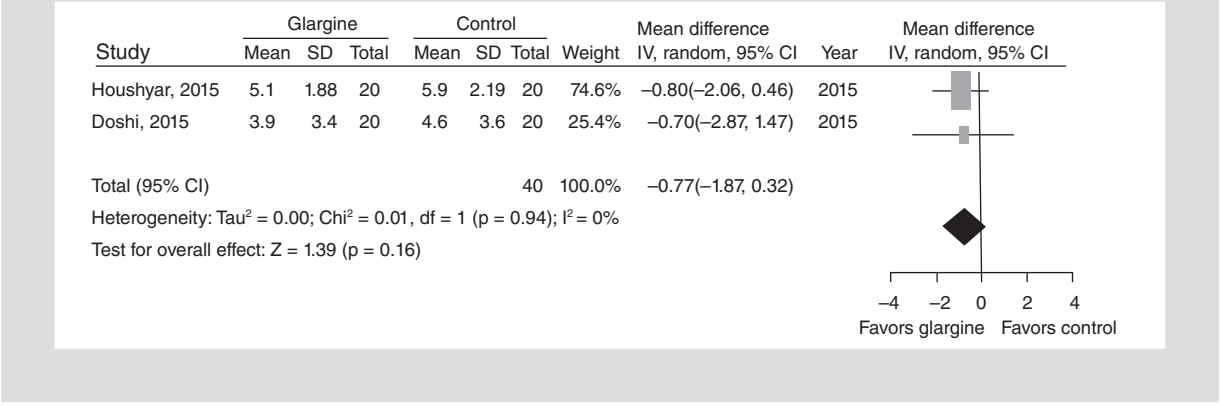

Figure 3. *Forest plot of the comparison of glargine versus standard management (control). Outcome: hospital length of stay.*

All studies assessed patients with DKA between 12 and 60 years of age, except for the study by Hsia et al.[10], where only half the participants had this condition (n = 25). In three of the studies, the types of diabetes were reported[10,20,21], with type 1 diabetes being the predominant type with 70% of analyzed cases. No cases of gestational diabetes complicated with DKA were analyzed. The acute symptoms triggering factor was reported only in one study[20]. According to the author's data, 75% of DKA cases occurred as a consequence of medical-dietary transgression. Similarly, only Assaad-Khalil et al.[19] reported DKA severity. The comparison of the above and the remaining relevant biochemical parameters between the intervention group and the control group is exposed, in turn, in table 1.

Clinical outcomes

The meta-analysis with the random effects model revealed that insulin glargine subcutaneous administration few hours after IV insulin infusion initiation is associated with a significant reduction in time to DKA resolution when compared with standard management only with IV insulin infusion (MD: -4.19 h [95% CI: -7.81-0.57]; p = 0.02; 110 participants; 3 trials). However, these data were significantly heterogeneous (I^2 = 73%) (Fig. 2).

Only two of the studies analyzed insulin glargine co-administration effect on rebound hyperglycemia[10,21]. In the study by Hsia et al.[10], rebound hyperglycemia, defined as blood sugar > 180 mg/dl within the first 12 h after insulin IV infusion withdrawal, occurred in 33.3% of participants assigned to the glargine group in comparison with 93.5% of participants assigned to the control group (p < 0.001). Through communication via e-mail with one of the authors, we were informed that none of the patients with DKA assigned to glargine experienced rebound hyperglycemia (data not published). Houshyar et al.[12] defined rebound hyperglycemia as blood sugar elevation > 149 mg/dl within the first 24 h after insulin IV infusion withdrawal. There was

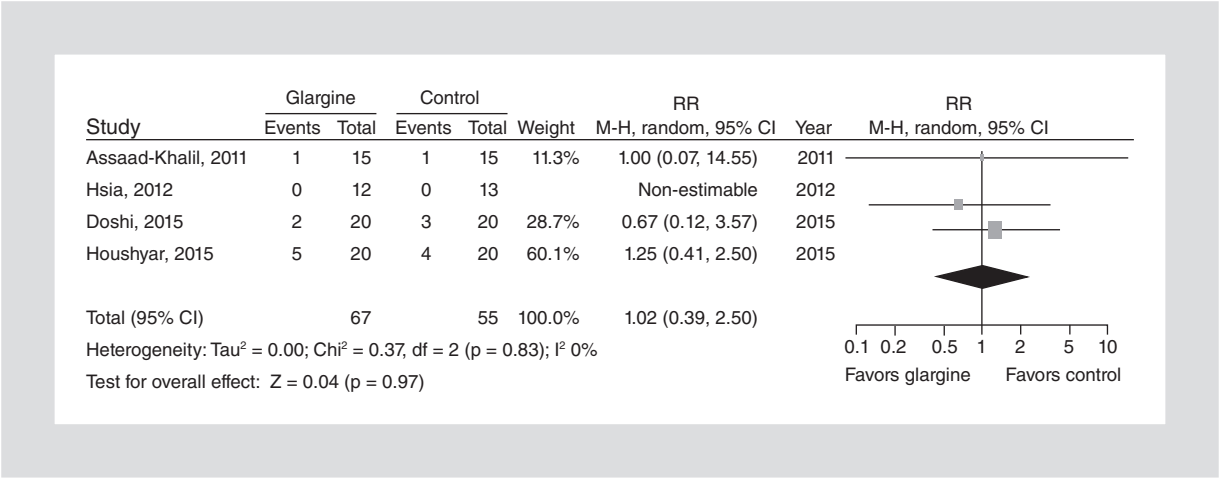

Figure 4. *Forest plot of the comparison of glargine versus standard management (control). Outcome: hypoglycemia.*

a statistically significant difference in the percentage of patients with these values in the glargine group (35%) in comparison with the control group (51%) (p = 0.046). Making a statistical synthesis of this outcome was not considered to be prudent.

With regard to hospital length of stay, there was no significant difference between comparisons (MD: -0.77 days [95% CI: –1.87-0.32]; p = 0.16; 80 participants; 2 trials), although some trend was observed favoring glargine in the reduction of global nosocomial length of stay (Fig. 3). Assaad-Khalil et al.[19] analyzed Intensive Therapy Unit length of stay, which was significantly shorter in the glargine group (14.00 ± 1.85 h) in comparison with the control group (20.93 ± 3.20 h) (p < 0.001).

Hypoglycemia is the most relevant adverse effect associated with insulin administration. There was no significant difference between comparisons with regard to hypoglycemia episodes (RR: 1.02 [95% CI: 0.41.2.50]; p = 0.97; 135 participants; 4 trials). Data related with the above were homogeneous (I^2 = 0%) (Fig. 4). Only one study explored the effect of the intervention on the change in potassium serum concentration. Houshyar et al.[21] reported 3 hypokalemia episodes in the glargine group versus 4 episodes in the control group, although this difference was not statistically significant (p = 0.68).

Discussion

Current evidence, in the form of randomized clinical trials, suggests a potential benefit of insulin glargine subcutaneous co-administration in patients with DKA. This treatment, added to standard management with IV insulin infusion pump, shortens the time to resolution of this important and common acute complication of diabetes mellitus. However, this evidence is insufficient to determine the efficacy of this intervention in view of the small numbers of analyzed patients.

The clinical benefit observed after insulin glargine subcutaneous administration can be partially explained by its pharmacological properties. By offering a constant dose free of peaks, reducing total IV insulin requirement to be administered is possible, which might explain the shorter time in hours to reach complete symptom resolution. In addition, by offering basal insulin coverage, the transition between insulin infusion and subsequent subcutaneous administration might be associated with a reduction in the incidence of rebound hyperglycemia[10]. Although in our analysis it was not possible to demonstrate a significant difference in hospital length of stay, the reduction in time to DKA resolution and the decreased incidence of rebound hyperglycemia might act together to reduce global hospital[20] or Intensive Therapy Unit length of stay[19], which with no doubt will translate into a considerable decrease of the economic impact on health systems.

Currently, and thanks to evidence in the form of randomized clinical trials, the theory of an erratic and unpredictable absorption of insulin by the subcutaneous route in patients with DKA has been put aside. To date, more than five clinical trials have demonstrated safety and efficacy with the subcutaneous use of rapid-acting insulin analogs in the management of DKA[22-26]. Our group is currently carrying out a systematic review for the Cochrane Collaboration on the subject[27]. Therefore, subcutaneous insulin bioavailability in the management of DKA should no longer be a reason for

Table 2. Bias risk and quality of evidence assessment

Study	Sequence generation	Allocation concealing	Blinding	Data with incomplete results	Selective result reporting	Other sources of bias
Assaad-Khalil (2011)[19]	High risk	Unclear risk	High risk	Low risk	Low risk	Low risk
Hsia (2013)[10]	High risk	Unclear risk	High risk	Low risk	Low risk	Low risk
Doshi (2015)[20]	Unclear risk	Unclear risk	High risk	Low risk	Low risk	Low risk
Houshyar (2015)[21]	High risk	Unclear risk	High risk	Low risk	Low risk	Low risk
Patients with DKA (12-60 years)			Intervention: subcutaneous insulin glargine + standard management versus standard management			
Outcomes			Relative effect (95% CI)	Number of participants	Quality of evidence (GRADE)	
Time to DKA resolution			MD: –4.19 h (–7.81-0.57)	110	Low*,† ⊕⊕⊖⊖	
Hospital length of stay			MD: –0.77 d (–1.87-0.32)	80	Moderate* ⊕⊕⊕⊖	
Hypoglycemia			RR: 1.02 (0.41-2.50)	135	*,‡ ⊕⊕⊖⊖	

*The generation of the sequence of randomization to each group was carried out with high risk for bias in three studies; sequence concealing was uncertain in all trials, not to mention participants' and personnel lack of blinding; the quality of evidence drops to moderate owing to the risk for bias.
†Significant heterogeneity was observed in the main outcome: the quality of evidence drops to low owing to inconsistency.
‡Lack of blinding is not considered important in the measurement of the hypoglycemia outcome; however, the evidence drops to low owing to the CIs wide range: it drops due to lack of precision.

concern, except maybe in those patients in shock with vasoactive amine support.

This systematic review with meta-analysis has several limitations to be considered. The most important is related to the quality of the analyzed evidence: the randomization sequence generation method was applied with high risk of bias in three of the trials. In addition, all studies were open-label for the patients and the personnel at their care, which confers a high risk for bias, following the criteria of Cochrane Collaboration's tool (Table 2)[14]. According to the GRADE methodology[15], this evidence is qualified as being of low quality for important outcomes: time to DKA resolution and hypoglycemia (Table 2). In the main studied outcome, significant heterogeneity was observed, which suggests inconsistency between studies. In this regard, some characteristics that might introduce clinical heterogeneity were a priori introduced: age, DKA-precipitating factors and symptom severity. However, performing an analysis by subgroups was not possible in view that the patients were not separated by age groups; not to mention incomplete reporting about the remaining characteristics of interest. A post-hoc analysis revealed that heterogeneity disappears when the trial by Assaad-Khalil et al.[19] is excluded. This is maybe related to the fact that this was the study that included more patients with severe DKA symptoms (Table 1).

This systematic review with meta-analysis should be interpreted in the context of the limitations inherent to the included clinical trials and its methodology (of a retrospective nature, and without discarding the possibility of publication bias). However, it offers evidence on the potential benefit of insulin glargine co-administration in the management of DKA. Nevertheless, further studies, in the form of multicenter, double-blinded (using subcutaneous saline as placebo), randomized clinical trials with larger numbers of patients are required to clarify the uncertainty related to the cost-benefit of this intervention. Finally, it would be interesting to find out whether this approach is valid for all patients with DKA at different stages of severity and, if possible, it would be desirable to formally explore the economic effect this strategy may have on the national health system, by shortening hospital length of stay and reducing the use of resources.

Conflicts of interests

The authors declare not having conflicts of interests of any kind.

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