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Management of hyperglycemia in persons with non-insulin-dependent Type 2 Diabetes mellitus that are started on systemic glucocorticoid therapy: a systematic review

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Management of hyperglycemia in persons with non-insulin-dependent Type 2 Diabetes mellitus that are started on systemic glucocorticoid therapy: a systematic review

Running Title: Management of glucocorticoid-induced hyperglycemia in Type 2 DM

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KEY WORDS

Type 2 Diabetes, hyperglycemia, glucocorticoid therapy, hypoglycemic agent, insulin, NPH insulin, long-acting insulin, BBI, SSI, multimorbidity, disease-disease medication interaction

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ABSTRACT

Objectives

To define the evidence-based best management of glucocorticoid-induced hyperglycemia in persons with Type 2 Diabetes mellitus (DM) who start glucocorticoid therapy.

Data sources

We searched Medline, Embase and Cochrane Library databases as well as Google for articles from 2002 to July 2018 using all search terms related to DM, glucocorticoids and treatment.

Study selection

Two authors screened articles for the notion "adult persons with Type 2 DM who received glucocorticoid therapy", and evaluated identified articles according to predefined eligibility criteria. Randomized controlled trials and observational studies were included.

Data collection and analysis

One author extracted data from included articles and another checked extracted data. We assessed the risk of bias and overall quality of evidence and performed a qualitative, descriptive analysis.

Results

We ultimately included 8/2'365 screened articles, five open-label RCTs and three observational studies. All articles but one focused on inpatient insulin treatment. The included studies suggest standard basal-bolus insulin (BBI) treatment and compared it to various insulin strategies. However, study heterogeneity did not allow to systematically and quantitatively analyze specific insulin regimens. Thus, four studies examining intermediate-acting insulin as basal insulin did not find convincing advantages despite theoretical pharmacodynamical advantages

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vis-à-vis long-acting insulin glargine. In addition, glycemic control with sliding scale insulin (SSI) was inferior in two studies compared to BBI or intermediate-acting insulin. Two studies suggest that pharmacodynamical profiles of insulins should be reconciled with corresponding profiles of glucocorticoids. However, there is insufficient evidence for supporting this recommendation. It is unclear, whether anticipatory outdoes compensatory insulin treatment.

Conclusion

Studies on treatment of glucocorticoid-induced hyperglycemia in Type 2 DM are heterogeneous, and optimal insulin management remains uncertain. Hence, no specific insulin regimen proved superior to another. Notwithstanding, we discourage SSI for use in this setting and encourage aligning pharmacodynamics profiles of used glucocorticoids and insulin treatment.

STRENGTHS AND LIMITATIONS OF THIS STUDY:

- Systematic review approach with extensive literature search for a very common but unresolved daily problem in managing Type 2 DM.
- The power to make firm conclusions is limited by the small number of available high quality studies and the overall small number of study participants.
- Heterogeneity of included studies preclude a full quantitative analysis and to give formal recommendations on a specific insulin regimen.

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INTRODUCTION

The number of persons with DM has grown globally from 108 million in 1980 to 422 million in 2014, *i.e.*, the global prevalence has almost doubled during this period from 4.7% to 8.5% [1]. DM occurs in about 25-30% of hospitalized persons [2], and DM management appears inappropriate in many of them [3 4]. In a retrospective cohort study, poor glycemic control correlated with higher hospitalization costs and associated with higher rates of DM-related hospital utilization per 100 patient-years [5]. In addition, persons with Type 2 DM had longer hospital stays and more hospitalizations directly related to complications of DM [6]. In an observational study, newly discovered hyperglycemia correlated with higher in-hospital mortality [7]. Hyperglycemia also related to more postoperative infections [8], complications after transplantation [9] and increased mortality [10].

Glucocorticoid therapy improves outcomes in respiratory diseases such as acutely exacerbated COPD, asthma, inflammatory or autoimmune disease, transplantat rejection and symptoms of chemotherapy [11 12]. In most cases, glucocorticoid regimens last less than 5 days. However, in 22% of all cases, they remain prescribed for longer than 6 months [13 14]. In the UK, long-term glucocorticoid prescriptions irrespective of the diagnosis have increased by 34% over 20 years [13]. The prevalence of glucocorticoid use in hospitals is more than 10% of all admitted persons [15]. Thus, glucocorticoid treatment in persons with Type 2 DM is common and will steadily increase in parallel with increased prevalence of DM and better life expectancy of these persons. At the same time, many other diseases or conditions multiply in the same persons that interact with DM, i.e., multi-morbidity [16].

Glucocorticoids instantly increase basal endogenous glucose production and lower insulin sensitivity [17-19], which leads to hyperglycemia. The rate of glucocorticoid-induced hyperglycemia or DM was 32.3% and 18.6% respectively in persons without prior DM on

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glucocorticoid therapy given for more than one month [20 21]. The type and doses of administered glucocorticoids vary widely and are tapered or stopped within days. Mostly, prednisolone intake is in the morning and results in a pronounced elevation of blood glucose 4-8 hours later, *i.e.*, in the afternoon and evening [22 23]. Thus, treatment will aim at controlling the hyperglycemia at these hours.

Recommendations promote the basal-bolus insulin (BBI) strategy for blood glucose control in insulin dependent DM. BBI improves glycemic control and reduces morbidity and mortality [24-26]. Furthermore, BBI results in superior glucose control as compared to sliding-scale insulin (SSI) regimens [27]. Plasma concentration of intermediate-acting Neutral Protamin Hagedorn (NPH) insulin peaks 4-8 h after injection [28]. NPH insulin may therefore better control afternoon peaks of blood glucose concentration caused by glucocorticoids than other insulins [29].

In this study, we have conducted a systematic review to define the best treatment options for glycemic control in persons with Type 2 DM on diet or OHA and on concomitant newly-initiated glucocorticoid therapy. More specifically, we looked for the type of insulin therapy/strategy that provides the best glycemic control. In addition, we have evaluated whether insulin started at the same time with glucocorticoids (anticipatory) or with a delay, i.e., when blood glucose level (BGL) rise above upper limits of normal (compensatory), confer better results.

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METHODS

Protocol and registration

Review methods and eligibility criteria were specified in advance, documented in a study protocol and registered online with the "International Prospective Register of Systematic Reviews" (PROSPERO), May 31st 2016 (Registration Number CRD42015024739) and recorded with a PRISMA statement [30]. We updated the protocol once on October 21st 2016, to broaden inclusion criteria.

Eligibility Criteria

For eligibility, we followed the PICOS criteria, i.e., **P**atients, **I**nterventions, **C**omparisons, **O**utcomes and **S**ettings [30]. **Patients:** We included articles on non-critically ill (non-ICU) in- or outpatients (> 16 years), who suffered from Type 2 DM treated with diet or OHA (*i.e.*, biguanide, gliflozins, gliptins, sulfonylureas, glinides, incretins or glitazones) and were started on a once or multiple daily oral or intravenous glucocorticoid therapy (*i.e.*, hydrocortisone, prednisone, prednisolone, methylprednisolone, dexamethasone, betamethasone or fludrocortisone) irrespective of the indication. **Interventions:** The articles and studies had to address specific treatment interventions for glycemic control, *e.g.* stop routine DM medication, starting insulin treatment, etc. **Comparisons:** We included all types of comparisons, *i.e.*, comparison of the study population to populations i) without DM, ii) without glucocorticoid treatment, iii) with adjusted OHA, or iv) with differing insulin treatments. **Outcomes:** We accepted outcomes reflecting glycemic control, *i.e.,* time outside target glucose range, mean BGL, hypo- or hyperglycemic episodes and daily insulin dose. **Settings:** We included randomized controlled trials (RCTs) and observational studies, *i.e.*, cohort studies, case-control studies or cross-sectional studies, without restriction to language, country of origin or publication types. We excluded letters to the editor and conference abstracts. We also consulted

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guidelines, reviews and expert opinions. We considered only papers published after 2002 because of the introduction of long-acting insulin; long-acting insulins are, nowadays, an integral part of treatment in insulin dependent DM.

Search strategy

We identified articles based on search terms related to DM and glucocorticoids in the following databases: Medline and Pre-Medline using OVID, EMBASE and Cochrane Library electronic databases (Supplementary Table 1). Additionally, we performed a Google search to retrieve grey literature with exclusive focus on pdf-files. The search was conducted on July 8th 2016 and updated on July 2nd 2018.

Study Selection

MT and SKR independently screened a pilot-set of 100 papers by studying the title and abstract using the selection criteria 'adult persons with preexisting DM that received a glucocorticoid therapy'. If no abstract was available but the title seemed relevant, MT and SKR reviewed the full-text. One abstract was translated from Japanese. MT and SKR evaluated the first 100 papers in consensus to determine consistent screening of all further papers. MT performed the screening of all papers, and SKR independently double-screened a random sample of 10% of all articles. All articles were assigned to one of the three eligibility groups, *i.e.,* "Yes", "No" and "Maybe". The "Maybe" group was discussed by MT and SKR for eligibility after full-text review in a consensus conference. Initial review of eligible articles exposed the necessity for modification of the inclusion criterion '≥ 20 mg/d prednisolone-equivalent for ≥ 5 days' to 'intermediate or high-dose glucocorticoid therapy' since a large number of articles did not specify exact dosages of glucocorticoids. MT and SRK independently performed a full-text review of all eligible papers for inclusion considering the PICOS criteria. Disagreements

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between reviewers were resolved by consensus. Finally, the reference lists of all included articles were screened for additional eligible papers, guidelines and review articles.

Data extraction and quality assessment

We extracted the following data from included articles: study population; participants; age. Then we assessed indication, dosage and duration of glucocorticoid therapy; target glucose; insulin strategy; the management of OHA interruption, continuation or adjustment of dosages; outcome measures, *e.g.,* time in target glucose range, mean BGL, hypo- and hyperglycemic episodes, insulin requirement. Differing assessments were discussed between MT and SKR.

We used the Cochrane risk of bias tool [31] to evaluate the risk of bias in RCTs and observational studies. The overall quality of evidence was assessed using the grading of recommendations assessment, development and evaluation (GRADE) criteria [32].

Data synthesis

We performed a descriptive analysis of RCTs and observational studies because the missing concordance in study designs of articles on this topic precluded performing a meta-analyses. Included articles were evaluated and compared in detail and findings summarized.

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RESULTS

Study inclusion

Our initial search provided 3'521 articles. 2'365 articles remained after eliminating duplicate entries. Of these 37 qualified for full text review. Eight articles met full eligibility criteria, namely, four RCTs [33-36] with open-label and parallel group design, one RCT with open-label and cross-over design [37], and three observational studies [38-40] with retrospective cohort design (Fig. 1 and Table 1).

The eight studies had included a total of 481 persons, 343/481 persons with DM and 138/481 persons with glucocorticoid-induced hyperglycemia. One study included persons with both Type 1 and 2 DM but did not take this distinction into consideration for outcomes [33]. At least 85/481 persons had prior treatment with insulin; three studies did not provide this information [33 34 39]. Seven studies included inpatients only [33-36 38-40], and one study both in- and outpatients [37]. Capillary blood glucose was measured four times a day, by continuous glucose monitoring, or by using all available capillary and serum blood glucose readings (Table 2). The upper limit was a BGL of 10mmol/l in all studies. The lower BGL limit was 3.9-4.5mmol/l in all but two studies, where it was 5.6mmol/l [33 40] (Table 2). Insulin dose adjustments were done if BGL was outside target glucose range according to specific study protocols.

In six studies, authors treated control groups with a BBI regimen using insulin glargine as basal insulin [33-36 38 39], in one study with a BBI regimen using twice-daily insulin detemir [40] and SSI added to established DM medication in one other study [37]. Strikingly, treatment interventions in experimental groups diverged substantially: One study compared glycemic control of BBI regimen in persons with Type 2 DM without prednisolone to those with prednisolone treatment [38]. Another study compared glycemic control of BBI regimen to SSI regimen [40]. One study compared addition of SSI to routine DM medication with the addition of intermediate-acting

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insulin [37]. Three studies compared BBI regimens with long-acting insulins to BBI regimens with NPH insulin [35 36 39] but in one of these studies NPH was given in three equal prandial doses [36]. One study compared BBI regimen with long-acting insulin to the same regimen adding NPH insulin [34]. Finally, the latest study added the insulin type which matched the glycemic profile of the glucocorticoid administered [33]. This divergence in study designs of RCTs precluded a clean and coherent quantitative meta-analysis.

BBI strategy in persons under systemic glucocorticoid therapy

Two observational studies [38 40] support BBI to be superior in glucocorticoid-treated persons with Type 2 DM [41 42]. Gosmanov *et al*. [40] found more hyperglycemic events in persons with Type 2 DM under dexamethasone for 3 days for a hematologic malignancy when treated with SSI therapy than in those with a BBI therapy (Table 2). In the SSI group, mean daily BGL was significantly higher ($p<0.001$) and average insulin requirement was significantly lower ($p<0.001$). No hypoglycemic events occurred in either groups but 3/28 (11%) persons treated with SSI were referred to an intensive care unit (ICU) because of hyperglycemic events.

Burt *et al.* [38] studied the effectiveness of a BBI regimen in hospitalized persons with Type 2 DM treated with prednisolone in the morning for an acute medical condition compared to persons without glucocorticoid treatment. Half of the calculated daily dose (0.3-0.4 IU/kg) was given as long-acting insulin Glargine at 9 pm and half as bolus evenly split into three meal dosages of rapid-acting insulin with additional correctional insulin if necessarily. Mean daily BGL was significantly higher in the prednisolone group ($p<0.001$) (Table 2). More specifically, BGL was significantly higher at 5 and 9 pm but not significantly higher at 7 and 12 am. In addition, the daily insulin dose was significantly higher in the prednisolone-treated group than in the control group, especially at 12 am and 5 pm. Thus, BBI treatment did not provide a sufficient glucose control most notably in the afternoon and evening.

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Comparison of BBI regimen with long-acting insulin to NPH as basal insulin

Two RCTs [36 35] and one observational study [39] compared NPH insulin with the long-acting insulin Glargine in a BBI regimen for their efficacy to control BGL in hospitalized persons treated with medium- to high-dose glucocorticoids [36 39]. The studies differed substantially in their design (Table 1). Radhakutty *et al.* [35] included persons with or without Type 2 DM treated with a single dose of glucocorticoids for respiratory disease or gout. Glargine in control and NPH in experimental group was administered at 7 am. Ruiz de Adana *et al.* [36] studied persons with Type 2 DM receiving multiple daily doses of glucocorticoids for respiratory disease. The Glargine group received its basal insulin as one dose at 9 am, and the NPH group received it before breakfast, lunch and dinner in three equal doses. Dhital *et al.* [39] retrospectively studied adults treated with prednisone, who were on a BBI regimen with either insulin glargine or NPH. Notably, the target glucose range, the time of application and number of doses of basal insulins were not indicated here, and persons with hyperglycemia without underlying Type 2 DM were also included.

All three studies show a similar overall glycemic control for NPH or Glargine as basal insulin [35 36 39]. More specifically, the mean daily BGL and the number of mild hypoglycemic episodes per day were similar (Table 2). Notably, severe hypoglycemia (BGL < 2.22 mmol/l) occurred in two persons in the NPH group in the study by Ruiz de Adana *et al.* [36]. Only Dhital *et al.* [39] found significantly lower daily insulin requirement in the NPH group.

Addition of insulin to established DM medication

Gerards *et al.* [37] compared addition of SSI insulin vs. intermediate-acting insulin (IMI) to established DM medication for glycemic control. The types of insulin were not further defined. Half of the persons had prior insulin treatment. Addition of IMI resulted in significantly longer time in target glucose range ($p<0.001$) and lower mean daily BGL ($p<0.05$). This was achieved

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with an increased insulin requirement in IMI group. Remarkably, mean daily BGL of both groups (SSI 13.5 ± 2.8, IMI 12.4± 2.9) were higher than in all other studies (Table 2).

Two RCTs added insulin to an existing BBI regimen in persons with or without Type 2 DM [33] [34] (Table 1). Grommesh *et al.* [34] studied the addition of NPH insulin along with a glucocorticoid to a BBI regimen. The algorithm for NPH dosing based on glucocorticoid type, dose and prior DM diagnosis. There was no advantage in doing so, neither for glycemic control, mean total daily insulin dose nor hypo- and hyperglycemia (Table 2). Similarly, a RCT by Lakhani *et al.* [33] studied the addition of a so-called 'correctional insulin' along with the glucocorticoid to a BBI regimen. The type of 'correctional insulin' matched the glycemic profile of the type of glucocorticoid administered, *e.g.* NPH insulin for prednisolone or insulin glargine for dexamethasone treatment [33]. 'Correctional insulin' significantly improved "time in target pre-meal glucose range" defined as 5.6-10mmol/l (p=0.002) and mean daily BGL (p=0.0001), but not time in "bedtime target glucose range" (p=0.09). The hyperglycemic events were reduced (p<0.001). No data on subgroups without DM or with Type 1 DM as well as data on daily insulin doses were given.

Anticipatory or compensatory approach to glycemic control

We had wanted to study whether anticipatory or compensatory adjustments are superior for glycemic control. No screened or included study did address this issue. While screening articles, we found some recommendations concerning this issue in guidelines [41] [43-45] and reviews [2] [46-49], which we comment in the discussion section.

Risk of bias and grading of evidence

Risk of bias was assessed in five RCTs for seven domains and four outcomes (mean BGL, time in target glucose, daily insulin dose and hypoglycemia) (Supplementary table 2a). All RCTs were un-blinded for participants and personal. Although placebo effects are very unlikely, un-

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blinding may have affected the attention of staff. This might be the most relevant risk for bias in these studies. The lack of or the lack of description of random sequence generation and allocation concealment might be another common bias. The three observational studies were divided in low [38], middle [39] and high [40] range of risk of bias (Supplementary table 2b). The most common risk of bias was the failure to control confounding.

Applying the GRADE criteria on each individual study, we had to decrease the level of evidence for the primary outcomes "mean BGL" and "time in target glucose range" mainly because of risk of bias and publication bias but also for inconsistency and imprecision in the five RCTs and one observational study (Supplementary Table 3). Hence, we classified the overall quality of evidence for the individual interventions as moderate [33 36 37], low [35 38 39] or very low [34 40].

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DISCUSSION

Glucocorticoid treatment inevitably causes hyperglycemia in persons with Type 2 DM. Here, we have systematically reviewed the evidence on strategies for best glycemic control in this predictable and detrimental disease-disTypeease medication interaction. We found that: i) Optimal insulin management in glucocorticoid-induced hyperglycemia in Type 2 DM remains uncertain. We lack high quality of evidence studies to make formal and final recommendations. Evidence so far is very low to moderate. ii) The studies suggest to use BBI without preference for long-or intermediate-acting insulin as basal insulin but SSI to be abandoned. iii) Two studies suggest that pharmacodynamic profiles of insulins should be reconciled with corresponding profiles of glucocorticoids. However, there is insufficient evidence to recommend this. iv) It is unclear, whether one should initiate anticipatory or compensatory insulin treatment.

Five open label RCTs and three observational studies included in this systematic review address the issue of this review. BBI is widely accepted as intensive insulin therapy in DM. The question remains, however, whether BBI performs best in Type 2 DM under glucocorticoid treatment. Gosmanov *et al.* [40] shows that BBI exceeds SSI in terms of glycemic control. This is in line with data showing the superiority of BBI to SSI in controlling hyperglycemia in various clinical settings [27 50]. Regarding SSI, Gerards *et al.* [37] corroborates inferiority of SSI to IMI as addition to routine DM regimen. Thus, SSI treatment, although very popular among non-endocrinologists, should not be prescribed anymore in this setting. Nevertheless, Burt *et al.* [38] found insufficient glycemic control at 5pm and 9pm with BBI with long-acting insulin in persons with Type 2 DM treated with prednisolone compared to Type 2 DM without prednisolone. These findings are in line with previous descriptions of afternoon and evening hyperglycemia under glucocorticoids in persons without DM [22 23 51] . Thus, BBI with long-acting insulin is not the ultimate solution.

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NPH insulin controls afternoon peaks of blood glucose caused by glucocorticoids well [29] and might have advantages over long-acting insulin because of a similar timeline of its effects to glucocorticoids on hyperglycemia. Three included articles [35 36 39] compared NPH insulin to insulin Glargine as basal insulin in a BBI treatment in a randomized controlled [36 35] resp. retrospective [39] manner and found no significant differences in glycemic control. However, NPH insulin caused more hypoglycemic events when NPH and bolus insulin were administered in equally divided pre-prandial doses for controlling hyperglycemia in persons given multiple daily doses of glucocorticoids [36]. Such a protocol may be poorly flexible and may not sufficiently consider the night-time fasting period with risk of nocturnal hypoglycemia. Insulin requirement, however, was higher in BBI with long-acting insulin compared to NPH as basal insulin in two studies [36 39] but similar in the other study [35]. Addition of NPH along with the glucocorticoid to BBI treatment did not improve glycemic control either [34]. The most recent study by Lakhani *et al.* [33] suggests a unique approach to fit the pharmacodynamical properties of insulins and glucocorticoids. This elaborated approach resulted in significantly lower mean daily BGL and pre-meal time in target glucose range. This appears promising but needs corroboration in a larger study.

We found no primary data on anticipatory versus compensatory treatment adjustments for glycemic control when starting glucocorticoids. This lack of data causes partially controversial expert opinions in guidelines. The American Endocrine Society Clinical Practice Guidelines [41] recommends an anticipatory approach with discontinuation of OHA at the time of hospital admission and initiation of insulin with persistent hyperglycemia. Exceptionally, selected persons who are stable, regularly eating and have no contraindication "may be candidates for continuation of previously prescribed OHA". The Canadian Diabetes Association guideline [45] recommends that "glycemic monitoring for 48 hours after initiation of steroids may be considered". In contrast the Joint British Diabetes Societies for inpatient care guideline [43] and

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the Imperial College Clinical Guidance [44] recommend to up-titrate OHA first. They recommend to add [43] or switch [44] to insulin if BGL remains above 10mmol/l. Experience or evidence to suggest the use of DDP-4 inhibitors, GLP-1 receptor agonists or SGLT-2 inhibitors is missing.

The strength of our systematic review is the extensive literature search for a common practical but unresolved problem in managing DM. Our systematic analysis also precludes premature conclusions on the preferred approach to insulin therapy, *e.g.,* based on theoretical considerations of pharmacodynamics or due to publication bias. The thorough evaluation of evidence level indicates moderate to very low evidence for single approaches.

The major limitation for answering the questions raised in this study is the heterogeneity of the experimental designs and the lack of highly powered, high quality studies. Populations, interventions, target glucose levels and glucose monitoring all differed from study to study. This permits a descriptive review only, and precludes formal recommendations. We need more well-designed studies with more homogeneous patient populations. Our study has specifically focused on persons with known Type 2 DM without prior insulin treatment. Still our analysis centers on mixed populations, namely persons with Type 2 DM with and without prior insulin treatment or Type 1 DM. Data on these subgroups are not available. It is also unlikely that a 'one size fits all' approach solves all challenges in all DM phenotypes.

CONCLUSION

Hyperglycemia in persons with Type 2 DM initiated on glucocorticoids is highly predictable. Nevertheless, therapeutic strategies infrequently address glycemic control in persons started on glucocorticoids in daily practice. Unfortunately, RCTs and observational studies on this topic show heterogeneous approaches in diverse populations. Therefore, we were not able to conduct a meta-analysis. Nevertheless, we can favor the use of a BBI regimen based on several corresponding studies as the most appropriate solution in controlling hyperglycemia in persons

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with DM initiated on glucocorticoid therapy [34 36 38-40]. Furthermore, based on two studies [33 37] we feel that matching pharmacodynamics profiles of insulins to glycemic profiles of the used glucocorticoid might be beneficial for glycemic control. Based on our systematic review, we strongly support the call to action on research in inpatient DM management of The PRIDE group [52] and to expend this to outpatient care. A concerted effort of Diabetes Societies would be needed to elaborate powerful study designs taking into account different DM phenotypes, settings and treatment approaches. If so, we recommend to focus on an approach adjusted for insulin-glucocorticoid pharmacodynamics.

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DECLARATIONS

Competing interests

The authors have no competing interests to declare.

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Authors contributions

MT drafted the study, contributed to the development of the selection criteria and data extraction criteria, developed the search strategy, elaborated the study selection, data extraction and data synthesis, wrote the manuscript, provided feedback and approved the final manuscript.

RL provided expertise on DM, read the manuscript, provided feedback and approved the final manuscript.

AN read, provided feedback and approved the final manuscript.

EB drafted the study, contributed to the development of the selection criteria and data extraction criteria, read the manuscript, provided feedback and approved the finals manuscript.

SKR is the guarantor, drafted the study, contributed to the development of the selection criteria and data extraction criteria, did the study selection, data extraction and data synthesis, wrote the manuscript, provided feedback and approved the final manuscript.

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Data sharing statement

All available data is included into the manuscript.

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Table 1: Overview of included studies characteristics (alphabetic order)

First author (year)	Study population	Prednisolone equiv. Dose (range or SD) mg; duration	Participants n (control/exp.)); Age average (range or SD)	Intervention in control group	Intervention in experimental group
Randomized control trials (all open-label and parallel-groups, except Gerards [37] cross-over design)					
Gerards (2016) [37]	In- or outpatients with or without Type 2 DM and hyperglycemia under cyclic glucocorticoid-containing chemotherapy	50.4 (36.6-55.3) 3-4 days per cycle.	26 (13/13) • 24 Type 2 DM (13 prior insulin) • 22/26 outpatients 67 years (58-71)	Additional SSI regimen to routine DM medication during prednisone containing cycles • 4 times daily short-acting insulin according to BGL	Additional IMI regimen during cycles to routine DM medication • IMI single morning dose 0.01 IU/mg per kg prednisolone equivalent, max. 0.5 IU per kg; reduced to 40% in > 70 years or GFR < 60mL/min; daily increases 10% according to BGL
Grommesh (2016) [34]	Inpatients with or without Type 2 DM and hyperglycemia within 24h of glucocorticoids for any indication	57.2 (±31.5) ≤5 days	61 (31/30) • 30 Type 2 DM (prior insulin n/a) 64.8 years (±16.1)	BBI regimen 1:1 basal and bolus • Basal: insulin glargine • Bolus: prandial insulin lispro • additional correctional insulin aspart • Algorithm for initial dosing based on DM diagnosis, HbA1c and previous treatment (see ref.)	Additional NPH insulin to BBI regimen • NPH along with glucocorticoid (three times if multiple dosing) • Algorithm for NPH doses based on glucocorticoid dose and DM diagnosis
Lakhani (2018) [33]	Inpatients with or without DM (Type 1 or 2) under glucocorticoids for any indication with postprandial hyperglycemia	20.75 (±12.7) Duration n/a	67 (34/33) • DM (Type and prior insulin n/a) in 14 control / 21 experimental 54.2 years (±11.9)	BBI regimen 1:1 basal and bolus, 0.3-0.5 U/kg/d according to HbA1c • Basal: insulin glargine at bedtime • Bolus: prandial insulin lispro • additional correctional insulin lispro	Additional correctional insulin which matches glycemic profile of the glucocorticoid administered according protocol (see ref) given along with glucocorticoid: • regular insulin with hydrocortisone • NPH with prednisolone or methylprednisolone • Insulin glargine with dexamethasone
Radhakutty (2017) [35]	Inpatients with or without Type 2 DM and hyperglycemia under glucocorticoids for COPD, pneumonia, interstitial lung disease or gout.	33 (±9.6) >1 day	48 (23/25) • 34 Type 2 DM (10 prior insulin) 72.1 years (±11.5)	BBI regimen 1:1 basal and bolus, 0.5 U/kg/d • Basal: insulin glargine • Bolus: prandial insulin aspart in three equal doses • additional correctional insulin if needed	BBI regimen 1:1 basal and bolus • Basal: NPH insulin, morning dose • Bolus: prandial insulin aspart, 20% before breakfast, 40% before lunch and 40% before dinner • additional correctional insulin if needed
Ruiz de Adana (2016) [36]	Inpatients with Type 2 DM on pneumology under glucocorticoids treatment for respiratory disease.	appx. 100mg day 1 appx. 33mg day 6	53 (27/26) • 23 prior insulin 68.6 years (±7.3) years	BBI regimen 1:1 basal and bolus, 0.3-0.5 U/kg/d or regular insulin dose multiplied by 1.5 • Basal: insulin glargine at 9:00 am • Bolus: prandial insulin glulisine in three equal doses • additional correctional insulin if needed	BBI regimen 1:1 basal and bolus, 0.3-0.5 U/kg/d or regular insulin dose multiplied by 1.5 • Basal: NPH insulin in three equal prandial doses • Bolus: prandial insulin glulisine in three equal doses • additional correctional insulin if needed
Observational studies (all retrospective cohort studies)					
Burt (2015) [38]	Inpatients with Type 2 DM with or without prednisolone for inflammatory disease	33.2±9.0 day1 21.1±7.2 day 5	66 (42/24) • 24 prior insulin 75.7 years (±12.9)	BBI regimen 1:1 basal and bolus, 0.3-0.4 U/kg/d • Basal: insulin glargine • Bolus: insulin aspart or lispro or glulisin devided into three meal time bolus • additional correctional insulin if needed	BBI regimen as control and additional prednisolone single morning dose >3 days
Dhital (2012) [39]	Inpatients with or without Type 2 DM treated with prednisolone at day before discharge; comparison of NPH insulin vs. insulin glargine in BBI regimen.	31±24.4	120 (60/60) • 61 Type 2 DM (prior insulin n/a) 58 years (±14)	BBI regimen 1:1 basal and bolus • Basal: insulin glargine • Bolus: insulin aspart • additional correctional insulin if needed	BBI regimen 1:1 basal and bolus insulin • Basal: NPH insulin • Bolus: regular insulin • additional correctional insulin if needed

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Gosmanov (2013) [40]	Inpatients with Type 2 DM treated with dexamethasone for hematologic malignancies	57.2±9.9	40 (12/28) • 15 prior insulin 56.1 years (±7.8)	BBI regimen 1:1 basal and bolus, 0.33 U/kg • Basal: insulin detemir twice daily • Bolus: insulin aspart • additional correctional insulin if needed • daily insulin dose correction if out of target 20-30%	SSI regimen with regular insulin (for protocol see ref.)

BBI: basal-bolus insulin; BGL: blood glucose level; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; IMI: intermediate-acting insulin; NPH: Neutral Protamine Hagedorn, isophane insulin; SSI: sliding-scale insulin

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Table 2: Outcomes of included original articles (alphabetic order)

First author [ref]	Target glucose (mmol/l)	Glycemic control						Mean total daily insulin dose (IU/kg/day or U/d)			Hypoglycemia <3.9mmol/l	Hyperglycemia >16.7mmol/l	Other
		Time in target glucose range (%)			Mean daily BGL (mmol/l)								
		Control	Exper.	p value	Control	Exper.	p value	Control	Exper.	p value			
Randomized control trials													
Gerards [37]	3.9-10	20.9 [1]	34.3 [1]	< 0.001	13.5 ± 2.8 [1]	12.4± 2.9 [1]	<0.05	26.0 (13.5-63.0)	40.3 (28.7-61.0)	0.01	mild p=0.21 no severe	n/a	Persons prefer SSI/IMI 29/71%
Grommesh [34]	3.9-10	54.6 [2]	62.0 [2]	0.24	9.9 ± 1.7 [2]	9.4±2.0 [2]	0.17	34.8	35.8	0.13	0.1% both groups	2.9%, p=0.89	MAGE p=0.0001
Lakhani [33]	5.6-10	15.0 [3] 16.7 [4]	33.3 [3] 29.3 [4]	0.002 0.09	12.3 ± 2.8 [2]	9.5±1.9 [2]	0.0001	n/a	n/a	n/a	mild p=0.3 no severe	20.7 events, p<0.001	MAGE p=0.0001
Radhakutty [35]	4-10	50 [2, 5]	58 [2, 5]	0.28	11.8 [2, 5]	10.5 [2, 5]	0.57	0.67±0.08	0.61±0.04	0.57	mild p=0.92 no severe	n/a	MAGE p=0.2
Ruiz de Adana [36]	4.5-10	42 [1]	38 [1]	0.61	10.88 ± 2.99 [1] 11.43 ± 3.44 [6]	11.10 ± 3.55 [1] 11.88 ±2.94 [6]	0.62 0.97	56.9±40.6	55.4±27.5	0.43	mild p=0.35 severe p=0.13	no events	MAGE p=0.377
Observational studies													
Burt [38]	4-10	n/a	n/a	n/a	10 ± 0.1 [2]	12.2 ± 0.3 [2]	<0.001	0.60-0.65	0.67-0.70	0.001	all p=0.28 no severe	n/a	BGL at 6 and 12 am similar, at 5 and 9 pm higher
Dhital [39]	n/a	n/a	n/a	n/a	9.2±2.9 [7]	9.3±2.6 [7]	0.79	0.34 ±0.2 basal 0.36 ±0.2 bolus	0.27 ±0.2 0.26 ±0.2	0.04 0.03	all p=0.77 no severe	n/a	
Gosmanov [40]	5.6-10	n/a	n/a	n/a	12.2±2.8 [7]	16.7±3.2 [7]	<0.001	122±39 0.63±0.25	49±29 0.46±0.16	<0.001	no events	3 events exper. group	

BGL: blood glucose level; IMI: intermediate insulin; MAGE: mean amplitude of gylcemic excursions; n/a: not applicable; SSI: sliding scale insulin

[1] CGM: continuous glucose monitoring

[2] capillary blood glucose monitoring four times a day (three times before meals and at bedtime)

[3] pre-meal blood glucose in target range; pre-meal target range defined as BGL 5.6-7.8 mmol/l;

[4] bedtime blood glucose in target range; bedtime target range defined as BGL 7.8-9.99 mmol/l;

[5] approximation, because article indicates 'time outside target glucose range'

[6] capillary blood glucose monitoring pre-meal and 2h post-meal

[7] all available BGL

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FIGURE LEGEND

Fig. 1: Flow diagram of study selection

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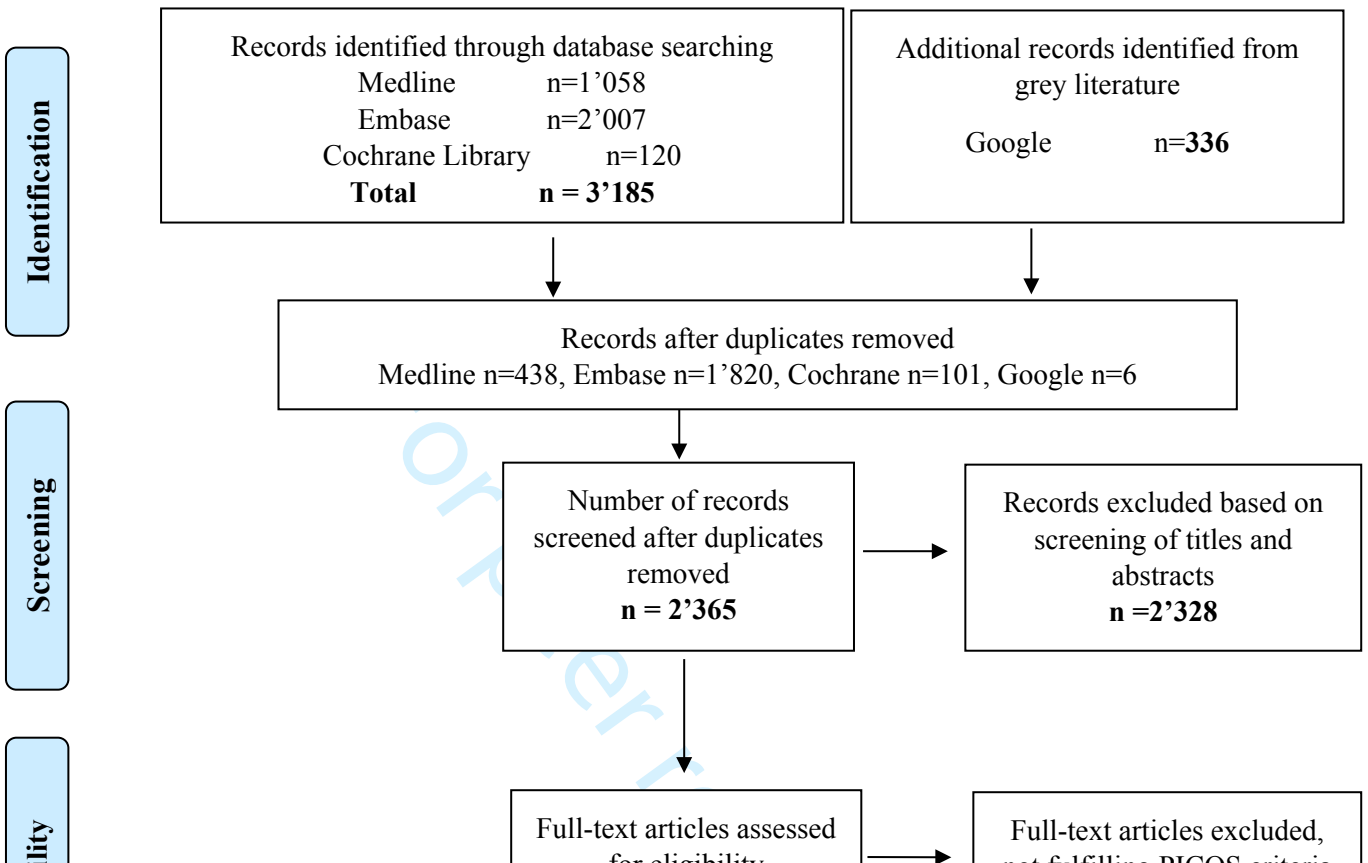
Figure 1:


Identification
Screening
Eligibility
Included
Records identified through database searching
Medline n=1'058
Embase n=2'007
Cochrane Library n=120
Total n = 3'185
Additional records identified from grey literature
Google n=336
Records after duplicates removed
Medline n=438, Embase n=1'820, Cochrane n=101, Google n=6
Number of records screened after duplicates removed
n = 2'365
Records excluded based on screening of titles and abstracts
n =2'328
Full-text articles assessed for eligibility
n = 37
Full-text articles excluded, not fulfilling PICOS criteria
n = 29
Randomized controlled trials included with data colleted
n = 5
Observational studies included with data colleted
n = 3

Supplementary Table 1: Search strategies

a) OVID search strategy

1	exp Diabetes Mellitus/
2	diabet*.tw.
3	1 or 2
4	hyperglyc*.ab,ti.
5	((serum* or level* or blood*) adj5 (glucose* or sugar* or level*)).ab,ti.
6	exp Hyperglycemia/
7	exp Blood Glucose/
8	4 or 5 or 6 or 7
9	3 and 8
10	exp Adrenal Cortex Hormones/ad, ae, dt, to [Administration & Dosage, Adverse Effects, Drug Therapy, Toxicity]
11	exp Steroids/ad, ae, dt, th, to [Administration & Dosage, Adverse Effects, Drug Therapy, Therapy, Toxicity]
12	((corti* or predni* or glucocorticoid* or steroid* or 'adrenal cortex hormone' or beclomethasone or betamethasone or budesonide or clobetasol or desoximetasone or dexamethasone or diflucortolone or flumethasone or 'fluocinolone acetonide' or fluocinonide or flucortolone or fluorometholone or fluprednisolone or flurandrenolone or 'melengestrol acetate' or methylprednisolone or paramethasone or prednisolone or prednisone or triamcinolone or aldosterone or corticosterone or '18 hydroxycorticosterone' or cortisone or cortodoxone or hydrocortisone or tetrahydrocortisol or tetrahydrocortisone or '18 hydroxydesoxycorticosterone' or 'desoxycorticosterone acetate' or '17 alphahydroxypregnenolone' or hydroxysteroid* or finasteride) adj10 (effect* or influenc* or impact* or therap* or medic* or induc* or administ* or dosage or treatm*)).ab,ti.

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13	10 or 11 or 12
14	exp Hypoglycemic Agents/
15	(intensive insulin or glucose or basal bolus or basal-bolus or multiple-dose insulin or basal insulin or prandial insulin or continuous subcutaneous insulin infusion or acetohexamide or biphasic insulins or buformin or butoxamine or carbutamide or chlorpropamide or gliclazide or glipizide or glyburide or insul* or insulin aspart or insulin lispro or isophane insulin or lente insulin or long-acting insulin or regular pork insulin or short-acting insulin or ultralente insulin or metformin or phenformin or tolazamide or tolbutamide).ab,ti.
16	14 or 15
17	exp Guideline/
18	((glyc* or hyperglyc* or diab* or gluco* or clinic*) adj10 (guide* or manage* or contro* or treatm* or therap* or protoc* or 'expert opinion' or target* or adjust* or admin* or chang* or regim* or requir* or monitor*)).ab,ti.
19	((treat* or diseas* or therap* or proced* or proto* or clinic*) adj10 (guid* or sugg* or advice* or recommend* or manage* or rule* or outline* or princip* or 'evidence based' or contro* or 'expert opinion' or regim*)).ab,ti.
20	17 or 18 or 19
21	9 and 13 and 16 and 20
22	limit 21 to animals
23	limit 22 to humans
24	22 not 23
25	21 not 24
26	limit 25 to yr="2001 -Current"

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b) EMBASE and Cochrane library search strategy

1	'diabetes mellitus'/exp
2	diabet*
3	#1 OR #2
4	hyperglyc*:ab,ti
5	((serum* OR blood* OR level*) NEAR/5 (glucose* OR sugar* OR level*)):ab,ti
6	'hyperglycemia'/exp
7	'blood glucose level'/exp
8	#4 OR #5 OR #6 OR #7
9	#3 AND #8
10	'corticosteroid'/exp/dd_do,dd_dt,dd_ae,dd_to,dd_ad,dd_it
11	((corti* OR predni* OR glucocorticoid* OR steroid* OR 'adrenal cortex hormone' OR beclomethasone OR betamethasone OR budesonide OR clobetasol OR desoximetasone OR dexamethasone OR diflucortolone OR flumethasone OR 'fluocinolone acetonide' OR fluocinonide OR fluocortolone OR fluorometholone OR fluprednisolone OR flurandrenolone OR 'melengestrol acetate' OR methylprednisolone OR parametasone OR prednisolone OR prednisone OR triamcinolone OR aldosterone OR corticosterone OR '18 hydroxycorticosterone' OR cortisone OR cortodoxone OR hydrocortisone OR tetrahydrocortisol OR tetrahydrocortisone OR '18 hydroxydesoxycorticosterone' OR 'desoxycorticosterone acetate' OR '17 alphahydroxypregnenolone' OR hydroxysteroid* OR finasteride) NEAR/10 (effect* OR influenc* OR impact* OR therap* OR medic* OR induc* OR administ* OR dosage OR treatm*)):ab,ti
12	#10 OR #11

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13	'antidiabetic agent'/exp
14	'intensive insulin':ab,ti OR glucose:ab,ti OR 'basal bolus':ab,ti OR 'basal-bolus':ab,ti OR 'multiple-dose insulin':ab,ti OR 'basal insulin':ab,ti OR 'prandial insulin':ab,ti OR 'continuous subcutaneous insulin infusion':ab,ti OR acetohexamide:ab,ti OR 'biphasic insulins':ab,ti OR buformin:ab,ti OR butoxamine:ab,ti OR carbutamide:ab,ti OR chlorpropamide:ab,ti OR gliclazide:ab,ti OR glipizide:ab,ti OR glyburide:ab,ti OR insul*:ab,ti OR 'insulin aspart':ab,ti OR 'insulin lispro':ab,ti OR 'isophane insulin':ab,ti OR 'lente insulin':ab,ti OR 'long-acting insulin':ab,ti OR 'regular pork insulin':ab,ti OR 'short-acting insulin':ab,ti OR 'ultralente insulin':ab,ti OR metformin:ab,ti OR phenformin:ab,ti OR tolazamide:ab,ti OR tolbutamide:ab,ti
15	#13 OR #14
16	'practice guideline'/exp
17	'diabetic control'/exp
18	((treat* OR diseas* OR therap* OR proced* OR proto* OR clinic*) NEAR/10 (guid* OR sugg* OR advice* OR recommend* OR manage* OR rule* OR outline* OR princip* OR 'evidence based' OR contro* OR 'expert opinion' OR regim*)):ab,ti
19	((glyc* OR hyperglyc* OR diab* OR gluco* OR clinic*) NEAR/10 (guide* OR manage* OR contro* OR treatm* OR therap* OR protoc* OR 'expert opinion' OR target* OR adjust* OR admin* OR chang* OR regim* OR requir* OR monitor*)):ab,ti
20	#16 OR #17 OR #18 OR #19
21	#9 AND #12 AND #15 AND #20
22	#9 AND #12 AND #15 AND #20 AND [animals]/lim
23	#9 AND #12 AND #15 AND #20 AND [humans]/lim AND [animals]/lim
24	#22 NOT #23
25	#21 NOT #24
26	#25 NOT [conference abstract]/lim

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27	#26 AND (2001:py OR 2002:py OR 2003:py OR 2004:py OR 2005:py OR 2006:py OR 2007:py OR 2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py)

c) Google advanced search

"management" or "steroid therapy" or "guideline" and diabet* or hypergly* or corti* or predni* or glucocorticoid* or steroid*or glycemic control

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Supplementary Table 2: Risk of bias

a) Risk of bias in five RCTs for seven domains and four different outcomes: mean BGL, time in target glucose range, insulin dose, hypoglycemia

Randomized control trials (all open-label and parallel-group {except Gerards [9] cross over design})							
First author (year)	**Risk of bias**						
	Sequence generation	**Allocation concealment**	**Selective reporting**	**Other sources of bias**	**Blinding (participants and personnel)**	**Blinding (outcome assessment)**	**Incomplete outcome data**
Gerards (2016) [37]	-Mean BGL: **low** -Time in target range: **low** -Insulin dose: **low** -Hypoglycemia: **low** -Overall: **low**	-Mean BGL: **low** -Time in target range: **low** -Insulin dose: **low** -Hypoglycemia: **low** -Overall: **low**	-Mean BGL: **low** -Time in target range: **low** -Insulin dose: **low** -Hypoglycemia: **low** -Overall: **low**	-Mean BGL: **low** -Time in target range: **low** -Insulin dose: **low** -Hypoglycemia: **low** -Overall: **low**	-Mean BGL: **high** -Time in target range: **high** -Insulin dose: **high**- Hypoglycemia: **high** -Overall: **high**	-Mean BGL: **low** -Time in target range: **low** -Insulin dose: **high** -Hypoglycemia: **high** -Overall:**n/a**	-Mean BGL: **low** -Time in target range: **low** -Insulin dose: **low** -Hypoglycemia: **low** -Overall: **low**
Grommesh (2016) [34]	-Mean BGL: **nk** -Time in target range: **nk** -Insulin dose: **nk** -Hypoglycemia: **nk** -Overall: **nk**	-Mean BGL: **nk** -Time in target range: **nk** -Insulin dose: **nk** -Hypoglycemia: **nk** -Overall: **nk**	-Mean BGL: **low** -Time in target range: **low** -Insulin dose: **low** -Hypoglycemia: **low** -Overall: **low**	-Mean BGL: **high** -Time in target range: **high** -Insulin dose: **high** -Hypoglycemia: **high** -Overall: **high**	-Mean BGL: **high** -Time in target range: **high** -Insulin dose: **high** -Hypoglycemia: **high** -Overall: **high**	-Mean BGL: **high**-Time in target range: **high** -Insulin dose: **high** -Hypoglycemia: **high**- Overall: **high**	-Mean BGL: **low** -Time in target range: **low** -Insulin dose: **low** -Hypoglycemia: **low** -Overall: **low**
Lakhani (2018) [33]	-Mean BGL: **low** -Time in target range: **low** -Insulin dose: **low** -Hypoglycemia: **low** -Overall: **low**	-Mean BGL: **nk** -Time in target range: **nk** -Insulin dose: **nk** -Hypoglycemia: **nk** -Overall: **nk**	-Mean BGL: **low** -Time in target range: **low** -Insulin dose: **high** -Hypoglycemia: **low** -Overall: **low**	-Mean BGL: **low** -Time in target range: **low** -Insulin dose: **low** -Hypoglycemia: **low** -Overall: **low**	-Mean BGL: **high** -Time in target range: **high** -Insulin dose: **high** -Hypoglycemia: **high** -Overall: **high**	-Mean BGL: **high** -Time in target range: **high** -Insulin dose: **high** -Hypoglycemia: **high**- Overall: **high**	-Mean BGL: **low** -Time in target range: **low** -Insulin dose: **high** -Hypoglycemia: **low** -Overall: **low**
Radhakutty (2017) [35]	-Mean BGL: **low** -Time in target range: **low** -Insulin dose: **low** -Hypoglycemia: **low** -Overall: **low**	-Mean BGL: **low** -Time in target range: **low** -Insulin dose: **low** -Hypoglycemia: **low** -Overall: **low**	-Mean BGL: **low** -Time in target range: **low** -Insulin dose: **low** -Hypoglycemia: **low** -Overall: **low**	-Mean BGL: **low** -Time in target range: **low** -Insulin dose: **low** -Hypoglycemia: **low** -Overall: **low**	-Mean BGL: **high** -Time in target range: **high** -Insulin dose: **high**- Hypoglycemia: **high** -Overall: **high**	-Mean BGL: **high** -Time in target range: **high** - Insulin dose: **high** -Hypoglycemia: **high**- - Overall: **high**	-Mean BGL: **low** -Time in target range: **low** -Insulin dose: **low** -Hypoglycemia: **low** -Overall: **low**
Ruiz de Adana (2016) [36]	-Mean BGL: **high** -Time in target range: **high** -Insulin dose: **high** -Hypoglycemia: **high** -Overall: **high**	-Mean BGL: **nk** -Time in target range: **nk** -Insulin dose: **nk** -Hypoglycemia: **nk** -Overall: **nk**	-Mean BGL: **low** -Time in target range: **low** -Insulin dose: **low** -Hypoglycemia: **low** -Overall: **low**	-Mean BGL: **low** -Time in target range: **low** -Insulin dose: **low** -Hypoglycemia: **low** -Overall: **low**	-Mean BGL: **high** -Time in target range: **high** -Insulin dose: **high** -Hypoglycemia: **high** -Overall: **high**	-Mean BGL: **high**-Time in target range: **high** -Insulin dose: **high** -Hypoglycemia: **high** -Overall: **high**	-Mean BGL: **low** -Time in target range: **low** -Insulin dose: **low** -Hypoglycemia: **low** -Overall: **low**

nk: not known as either unclear or not reported; n/a: not applicable

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b) Risk of bias in three included observational studies

Observational studies (all retrospective cohort studies)				
First author (year)	**Risk of bias**			
	Failure to develop and apply appropriate eligibility criteria	**Flawed measurement of both exposure and outcome**	**Failure to adequately control confounding**	**Incomplete follow-up**
Burt (2015) [38]	**low**	**low**	**low**	**low**
Dhital (2012) [39]	**low**	**low**	**high**	**low**
Gosmanov (2013) [40]	**high**	**low**	**high**	**low**

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Supplementary Table 3: Quality of evidence for mean BGL and time in target glucose range (high, moderate, low or very low)

First author	Limitations/ Risk of bias (serious/not serious)	Inconsistency (Yes/No/not relevant)	Indirectness (Yes/No/not relevant)	Imprecision (Yes/No/not relevant)	Publication bias (likely/unlikely)	Quality of evidence after up-/downgrading
Randomized control trial						
Gerards (2016) [37]	**Not serious**	Mean BGL: **No** Time in target glucose: **No**	Mean BGL: **No** Time in target glucose: **No**	Mean BGL: **Yes** Time in target glucose: **Yes**	Mean BGL: **unlikely** Time in target glucose: **unlikely**	**High downgrade to moderate** [a]
Grommesh (2016) [34]	**Serious**	Mean BGL: **Yes** Time in target glucose: **Yes**	Mean BGL: **No** Time in target glucose: **No**	Mean BGL: **No** Time in target glucose: **No**	Mean BGL: **likely** Time in target glucose: **likely**	**High downgrade to very low** [b]
Lakhani (2016) [33]	**Serious**	Mean BGL: **No** Time in target glucose: **No**	Mean BGL: **No** Time in target glucose: **No**	Mean BGL: **No** Time in target glucose: **No**	Mean BGL: **unlikely** Time in target glucose: **unlikely**	**High downgrade to moderate** [c]
Radhakutty (2016) [35]	**Serious**	Mean BGL: **No** Time in target glucose: **No**	Mean BGL: **No** Time in target glucose: **No**	Mean BGL: **No** Time in target glucose: **No**	Mean BGL: **likely** Time in target glucose: **likely**	**High downgrade to low** [d]
Ruiz de Adana (2016) [36]	**Serious**	Mean BGL: **No** Time in target glucose: **No**	Mean BGL: **No** Time in target glucose: **No**	Mean BGL: **No** Time in target glucose: **No**	Mean BGL: **unlikely** Time in target glucose: **unlikely**	**High downgrade to moderate** [e]
Observational studies						
Burt (2015) [38]	**Not serious**	Mean BGL: **No**	Mean BGL: **No**	Mean BGL: **No**	Mean BGL: **unlikely**	**Low**
Dhital (2012) [39]	**Not serious**	Mean BGL: **No**	Mean BGL: **No**	Mean BGL: **No**	Mean BGL: **unlikely**	**Low**
Gosmanov (2013) [40]	**Serious**	Mean BGL: **No**	Mean BGL: No	Mean BGL: **No**	Mean BGL: **unlikely**	**Low downgrade to very low** [f]

[a] downgrading because of serious imprecision with lack of CI; [b] downgrading because of serious limitations/risk of bias; lack of blinding and attending physicians were not obliged to follow the study protocol while titrating insulin doses, and inconsistency with small sample groups and publications bias with lack of significant results; [c] downgrading because of serious limitations/risk of bias; lack of blinding; [d] downgrading because of serious limitations/risk of bias; lack of blinding, and industry funding; [e] downgrading because of serious limitations/risk of bias, not randomised sequence generation, lack of allocation concealment; [f] downgrading because of serious limitation in eligibility criteria as "self-reported diagnosis of diabetes".

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5-6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Suppl Tbl 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7-8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	n.a.
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	n.a.

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8.
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n.a.
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9-10; Fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9-10; Tbl 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	12-13; Suppl Tbl 2 and 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10-12; Table 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9-12.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	n.a.
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n.a.
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14-15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16-17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Management of hyperglycemia in persons with non-insulin-dependent Type 2 Diabetes mellitus that are started on systemic glucocorticoid therapy: a systematic review

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Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Evidence based practice, General practice / Family practice, Pharmacology and therapeutics
Keywords:	Type 2 Diabetes, hyperglycemia, glucocorticoid therapy, hypoglycemic agent, NPH insulin, BBI

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Management of hyperglycemia in persons with non-insulin-dependent Type 2 Diabetes mellitus that are started on systemic glucocorticoid therapy: a systematic review

Running Title: Management of glucocorticoid-induced hyperglycemia in Type 2 DM

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KEY WORDS

Type 2 Diabetes, hyperglycemia, glucocorticoid therapy, hypoglycemic agent, insulin, NPH insulin, long-acting insulin, BBI, SSI, multimorbidity, disease-disease medication interaction

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ABSTRACT

Objectives What is the most effective pharmacological intervention for glycemic control in known Type 2 Diabetes mellitus (DM) without prior insulin treatment and newly started on systemic glucocorticoid therapy?

Design We conducted a systematic literature review.

Data Sources We searched Medline, Embase, Cochrane Library databases and Google for articles from 2002 to July 2018.

Eligibility Criteria We combined search terms relating to DM (patients, > 16 years of age), systemic glucocorticoids, glycemic control, randomized controlled trials (RCTs) and observational studies.

Data extraction and synthesis We screened and evaluated articles, extracted data, and assessed risk of bias and quality of evidence, according to Grading of Recommendations assessment, Development, and Evaluation (GRADE) guidelines.

Results Eight of 2'365 articles met full eligibility criteria. Basal-bolus insulin (BBI) strategy for patients under systemic glucocorticoid therapy was comparatively effective but provided insufficient glucose control depending on time of day. BBI strategy with long-acting insulin and Neutral Protamin Hagedorn as basal insulin provide similar overall glycemic control. Addition of various insulin strategies to standard BBI delivered mixed results. Intermediate-acting insulin as additional insulin conferred no clear benefits and glycemic control with sliding scale insulin was inferior to BBI or intermediate-acting insulin. No studies addressed whether anticipatory or compensatory insulin adjustments are better for glycemic control.

Conclusion The lack of suitably designed RCTs and observational studies, heterogeneity of interventions, target glucose levels, and glucose monitoring, poor control of DM subgroups, and low-to-moderate quality of evidence render identification of optimal pharmacological

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interventions for glycemic control and insulin management difficult. Even findings on widely recommended BBI regimen as intensive insulin therapy for DM patients on glucocorticoids are inconclusive. High quality evidence in studies with well-defined DM phenotypes, settings and treatment approaches is needed to determine optimal pharmacological intervention for glycemic control.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Systematic review with extensive literature search to provide comprehensive data on a very common but unresolved daily problem in managing Type 2 DM.
- Lack of comparability between studied populations and interventions and low to moderate quality of evidence does not permit full quantitative analysis and provision of formal recommendations on specific insulin regimens.
- Firm conclusions on optimal pharmacological interventions for glycemic control awaits studies of sufficient power, quality and testing of well-defined DM phenotypes, settings and treatments.

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INTRODUCTION

The worldwide prevalence of Type 2 Diabetes mellitus (DM) in adults has doubled since 1980 to 8.5% in 2014 [1]. While comparatively stable in recent years, the prevalence of hospitalized patients with DM is 25-40% [2 3]. Steroid treatment in patients with DM is common [4 5]. However, steroids are the main cause of drug-induced hyperglycemia [6] due to their effect of increasing basal endogenous glucose production and lowering insulin sensitivity [7-9]. Over half of patients receiving high-dose steroids develop hyperglycemia [10]. Significantly, steroids exacerbate hyperglycemia in patients with pre-existing DM [11 12] and enhance the likelihood of complications, length of stay and mortality in these patients [3 13-18].

The importance of detecting and actively managing hyperglycemia in DM patients receiving glucocorticoid therapy is acknowledged [13 19 20]. However, current management strategies are suboptimal [13 21] and the limited evidence available does not adequately inform the physician [6]. This is all the more important as the type and doses of administered glucocorticoids and the potencies (and duration of action) of different systemic glucocorticoids vary widely [22-24]. Shorter courses of steroids may lead to brief periods of hyperglycemia that do not require further intervention, though hyperglycemia and other side effects can occur at a wide range of doses [25]. However, longer courses of steroids at higher doses can lead to symptomatic hyperglycemia [26 27]. Optimal treatment strategies for glycemic control are therefore vital.

The aim of this study was to conduct a systematic review of treatment strategies for glycemic control in persons with Type 2 DM on diet or oral hypoglycemic agents (OHA) and newly-initiated glucocorticoid therapy. Specifically, we sought to identify the most effective pharmacological intervention for glycemic control. We evaluated also, whether the simultaneous start of insulin with glucocorticoids (anticipatory treatment adjustment) or

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delayed start of insulin, when blood glucose level (BGL) exceeds normal upper limits (compensatory treatment adjustment), is more effective.

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METHODS

Protocol and registration

The review methods and eligibility criteria were specified in advance, documented in a study protocol, registered online with the International Prospective Register of Systematic Reviews (PROSPERO), May 31st 2016 (Registration Number CRD42015024739), and recorded with a PRISMA statement [28]. We updated the protocol once on October 21st 2016 to broaden inclusion criteria.

Eligibility Criteria

For eligibility, we followed the Patients, Interventions, Comparisons, Outcomes and Settings (PICOS) criteria [28]. **Patients:** We included articles on non-critically ill (non-ICU) in- or outpatients (> 16 years of age) who suffered from Type 2 DM treated with diet or OHA (*i.e.*, biguanide, gliflozins, gliptins, sulfonylureas, glinides, incretins or glitazones) and were started on a once or multiple daily oral or intravenous glucocorticoid therapy (*i.e.*, hydrocortisone, prednisone, prednisolone, methylprednisolone, dexamethasone, betamethasone or fludrocortisone) irrespective of the indication. **Interventions:** The articles and studies had to address specific treatment interventions for glycemic control, including, for example, stop routine DM medication and starting insulin treatment. **Comparisons:** We included all types of comparisons of the study population with those i) without DM, ii) without glucocorticoid treatment, iii) with adjusted OHA, or iv) with differing insulin treatments. **Outcomes:** We accepted outcomes reflecting glycemic control, that is, time outside target glucose range, mean BGL, hypo- or hyperglycemic episodes, and daily insulin dose. **Settings:** We included randomized controlled trials (RCTs) and observational studies, that is, cohort studies, case-control studies or cross-sectional studies, without imposing any restriction on language, country of origin, or publication type. We excluded letters to the editor and conference abstracts. We

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consulted also guidelines, reviews, and expert opinions. We considered only papers published after 2002 because of the subsequent introduction of long-acting insulin; long-acting insulins are, nowadays, an integral part of treatment in insulin dependent DM.

Search strategy

We identified articles based on search terms related to DM and glucocorticoids in the following databases: Medline and Pre-Medline using OVID, EMBASE and Cochrane Library electronic databases (Supplementary Table 1). The combined use of the databases (PubMed, Medline, Embase and Cochrane) allows coverage of up to 97% of available publications [29]. To enhance coverage further, we conducted also a Google search to retrieve grey literature with exclusive focus on pdf-files. The search was conducted on July 8th 2016 and updated on July 2nd 2018.

Study Selection

MT and SKR independently screened a sample of 100 papers by studying the title and abstract according to the selection criteria 'adult persons with preexisting DM that received a glucocorticoid therapy'. If no abstract was available but the title appeared relevant, MT and SKR reviewed the full-text. One abstract was translated from Japanese.

MT and SKR then evaluated the first 100 papers in consensus to establish the basis for consistent screening of all further papers. MT performed the screening of all papers and SKR independently double-screened a random sample of 10% of all articles. All articles were assigned to one of the three eligibility groups, "Yes", "No" and "Maybe". The "Maybe" group was discussed by MT and SKR for eligibility after full-text review in a consensus conference. Initial review of eligible articles revealed the necessity for modification of the inclusion criterion '≥ 20 mg/d prednisolone-equivalent for ≥ 5 days' to 'intermediate or high-dose glucocorticoid therapy' because a large number of articles did not specify exact dosages of glucocorticoids.

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MT and SRK independently performed a full-text review of all eligible papers for inclusion, considering the PICOS criteria. Disagreements between reviewers were resolved by consensus. Finally, the reference lists of all included articles were screened for additional eligible papers, guidelines, and review articles.

Data extraction and quality assessment

We extracted the following data from the included articles: study population, participants, and age. Then, we assessed indication, dosage and duration of glucocorticoid therapy, target glucose, insulin strategy, the management of OHA interruption, continuation or adjustment of dosages, and outcome measures, such as, time in target glucose range, mean BGL, hypo- and hyperglycemic episodes, insulin requirement. Differing assessments were discussed and resolved between MT and SKR.

We used the Cochrane risk of bias tool [30] to evaluate the risk of bias in RCTs and applied the key criteria of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines for observational studies to assess the methodological quality of nonrandomized studies [31]. The overall quality of evidence was assessed using the GRADE criteria [32].

Data synthesis

We performed a descriptive analysis of RCTs and observational studies. This was because the lack of concordance in the study designs in the included articles precluded the performance of meta-analyses. Included articles were evaluated and compared in detail and findings summarized.

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Patient or public involvement

Neither patients nor public were directly involved in the development of the research question, selection of the outcome measures, design and implementation of the study, or interpretation of the results.

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RESULTS

Study inclusion

Our initial search generated 3'521 articles. 2'365 articles remained after eliminating duplicate entries. Of these, 37 qualified for full text review. Eight articles met full eligibility criteria, namely, four RCTs [33-36] with open-label and parallel group design, one RCT with open-label and cross-over design [37], and three observational studies [38-40] with retrospective cohort design (Fig. 1 and Table 1).

The eight articles reported studies that included a total of 481 persons, 343/481 persons with DM and 138/481 persons with glucocorticoid-induced hyperglycemia. One study included persons with both Type 1 and 2 DM but did not take this distinction into consideration for outcomes [33]. At least 85/481 persons had prior treatment with insulin; three studies did not provide this information [33 34 39]. Seven studies included inpatients only [33-36 38-40], and one study included both in- and outpatients [37]. Capillary blood glucose was measured four times a day, by continuous glucose monitoring or by using all available capillary and serum blood glucose readings (Table 2). The upper limit was a BGL of 10mmol/l in all studies. The lower BGL limit was 3.9-4.5mmol/l in all but two studies in which it was 5.6mmol/l [33 40] (Table 2). Insulin dose adjustments were applied if BGL was outside target glucose range, according to specific study protocols.

In six studies, authors treated control groups with a basal-bolus insulin (BBI) regimen using insulin glargine as basal insulin [33-36 38 39], in one study with a BBI regimen using twice-daily insulin detemir [40], and one study using sliding-scale insulin (SSI) in addition to established DM medication [37]. Strikingly, treatment interventions in the experimental groups diverged substantially: One study compared glycemic control of BBI regimen in Type 2 DM patients without prednisolone with those with prednisolone treatment [38]. Another study compared

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glycemic control of BBI regimen with SSI regimen [40]. One study compared addition of SSI to routine DM medication with the addition of intermediate-acting insulin [37]. Three studies compared BBI regimens with long-acting insulins to BBI regimens with intermediate-acting Neutral Protamin Hagedorn (NPH) insulin [35 36 39], but in one of these studies NPH was given in three equal prandial doses [36]. One study compared BBI regimen with long-acting insulin to the same regimen with the addition of NPH insulin [34]. Finally, the most recent study added the insulin type that matched the glycemic profile of the administered glucocorticoid [33]. This divergence in study designs of RCTs precluded a clean and coherent quantitative meta-analysis.

BBI strategy in persons under systemic glucocorticoid therapy

Two observational studies [38 40] report BBI as superior in glucocorticoid-treated Type 2 DM patients [41 42]. Gosmanov *et al*. [40] found more hyperglycemic events in Type 2 DM patients under dexamethasone for 3 days (for a hematologic malignancy) when treated with SSI therapy compared with a BBI therapy (Table 2). In the SSI group, mean daily BGL was significantly higher ($p<0.001$) and average insulin requirement was significantly lower ($p<0.001$). No hypoglycemic events occurred in either groups but 3/28 (11%) persons treated with SSI were referred to an intensive care unit because of hyperglycemic events.

Burt *et al.* [38] studied the effectiveness of a BBI regimen in hospitalized Type 2 DM patients treated with prednisolone in the morning for an acute medical condition compared with those without glucocorticoid treatment. Half of the calculated daily dose was given as long-acting insulin Glargine at 9 pm and half as bolus evenly split into three meal dosages of rapid-acting insulin with additional correctional insulin when necessary. Mean daily BGL was significantly higher in the prednisolone group ($p<0.001$) (Table 2). More specifically, BGL was significantly higher at 5 and 9 p.m. but not significantly higher at 7 and 12 a.m.. In addition, the daily insulin dose was significantly higher in the prednisolone-treated group than in the control group,

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especially at 12 a.m. and 5 p.m.. Thus, BBI treatment provided insufficient glucose control, most notably in the afternoon and evening.

Comparison of BBI regimen with long-acting insulin to NPH as basal insulin

Two RCTs [36 35] and one observational study [39] compared NPH insulin with the long-acting insulin Glargine in a BBI regimen for their efficacy in controlling BGL in hospitalized persons treated with medium- to high-dose glucocorticoids [36 39]. The studies differed substantially in their design (Table 1). Radhakutty *et al.* [35] included persons with or without Type 2 DM who were treated with a single dose of glucocorticoids for respiratory disease or gout. Glargine was administered in the control and NPH in the experimental group at 7 a.m.. Ruiz de Adana *et al.* [36] studied Type 2 DM patients receiving multiple daily doses of glucocorticoids for respiratory disease. The Glargine group received its basal insulin as one dose at 9 a.m. and the NPH group received it before breakfast, lunch and dinner in three equal doses. Dhital *et al.* [39] retrospectively studied adults treated with prednisone who were on a BBI regimen with either insulin glargine or NPH. Notably, the target glucose range, the time of application and number of doses of basal insulins were not indicated here, and persons with hyperglycemia without underlying Type 2 DM were also included.

All three studies show a similar overall glycemic control for NPH or Glargine as basal insulin [35 36 39]. More specifically, the mean daily BGL and the number of mild hypoglycemic episodes per day were similar (Table 2). Notably, severe hypoglycemia (BGL < 2.22 mmol/l) occurred in two persons in the NPH group in the study by Ruiz de Adana *et al.* [36]. Only Dhital *et al.* [39] found significantly lower daily insulin requirement in the NPH group.

Addition of insulin to established DM medication

Gerards *et al.* [37] compared the addition of SSI insulin compared with intermediate-acting insulin (IMI) to established DM medication for glycemic control. The types of insulin were not further

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defined. Half of the persons had prior insulin treatment. Addition of IMI resulted in significantly longer time in target glucose range ($p<0.001$) and lower mean daily BGL ($p<0.05$). This was achieved with an increased insulin requirement in IMI group. Remarkably, mean daily BGL of both groups (SSI 13.5 ± 2.8, IMI 12.4± 2.9) were higher than in all other studies (Table 2).

Two RCTs added insulin to an existing BBI regimen in persons with or without Type 2 DM [33] [34] (Table 1). Grommesh *et al.* [34] studied the addition of NPH insulin together with a glucocorticoid to a BBI regimen. The algorithm for NPH dosing was based on glucocorticoid type, dose, and pre-existing DM diagnosis. The study should that there was no advantage in this for glycemic control, mean total daily insulin dose, or hypo- and hyperglycemia (Table 2). Similarly, a RCT by Lakhani *et al.* [33] studied the addition of a so-called 'correctional insulin' together with the glucocorticoid to a BBI regimen. The type of 'correctional insulin' matched the glycemic profile of the type of administered glucocorticoid, *for example* NPH insulin for prednisolone or insulin glargine for dexamethasone treatment [33]. 'Correctional insulin' significantly improved "time in target pre-meal glucose range" (defined as 5.6-10mmol/l [p=0.002]) and mean daily BGL (p=0.0001) but not time in "bedtime target glucose range" (p=0.09). The hyperglycemic events were reduced ($p<0.001$). No data were provided on subgroups without DM or with Type 1 DM and on daily insulin doses.

Anticipatory or compensatory approach to glycemic control

We aimed to determine whether anticipatory or compensatory adjustments are better for glycemic control. No screened or included study addressed this issue. While screening articles, we found some recommendations about this in guidelines [41] [43-45] and reviews [46-50] and we address this in the discussion section.

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Risk of bias and grading of evidence

Risk of bias was assessed in five RCTs for seven domains and four outcomes (mean BGL, time in target glucose, daily insulin dose and hypoglycemia) (Supplementary Table 2a). All RCTs were unblinded for participants and personal. Although placebo effects are very unlikely, unblinding may have affected the attention of staff. This might be the most relevant risk for bias in these studies. The lack of random sequence generation and allocation concealment might be another common bias. The three observational studies were classified as having a low [38], middle [39] and high [40] range of risk of bias (Supplementary Table 2b). The most common risk of bias was the failure to control confounding. Notably, an overall risk of bias of an outcome for all five RCTs is not so informative because the treatment interventions were not comparable.

Applying the GRADE criteria on each individual study, we had to decrease the level of evidence for the primary outcomes "mean BGL" and "time in target glucose range." This was mainly because of risk of bias and publication bias and because of inconsistency and imprecision in the five RCTs and one observational study (for the overall rating of quality of evidence in RCTs and observational studies, see Supplementary Table 3). Hence, we classified the overall quality of evidence for the individual interventions as moderate [33 36 37], low [35 38 39] or very low [34 40].

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DISCUSSION

Glucocorticoid treatment inevitably leads to hyperglycemia in persons with Type 2 DM. We systematically reviewed the available evidence on pharmacological interventions for effective glycemic control. We found, firstly, that there is some uncertainty as to the optimal management of glucocorticoid-induced hyperglycemia in DM. The lack of studies reporting high quality evidence makes it difficult to provide formal and final recommendations. This review shows that the available evidence is of low to moderate quality. Second, the reviewed studies speak in favour of the use of BBI without a specific preference for long- or intermediate-acting insulin as basal insulin, but these studies do indicate that SSI should be abandoned. Third, two studies suggested that pharmacodynamic profiles of insulins should be reconciled with corresponding profiles of glucocorticoids. However, there is insufficient evidence to recommend this. Finally, the reviewed studies do not clarify whether one should initiate anticipatory or compensatory insulin treatment.

BBI is widely accepted and recommended as intensive insulin therapy in DM [42 51 52]. However, the question remains whether BBI performs best in Type 2 DM under glucocorticoid treatment. Five open label RCTs and three observational studies included in this systematic review address this issue. Gosmanov *et al.* [40] shows that BBI is better than SSI in terms of glycemic control. This is in line with data from various clinical settings that supports improved hyperglycemic control using BBI compared with SSI[53 54]. Gerards *et al.* [37] corroborates that SSI delivers poorer control compared with intermediate-acting insulin when used as an addition to the routine DM regimen. Although very popular among non-endocrinologists, these findings suggest that SSI treatment should not be prescribed in this setting anymore. On the other hand, Burt *et al.* [38] did find that glycemic control was insufficient at 5 p.m. and 9 p.m. when using BBI with long-acting insulin in Type 2 DM persons treated with prednisolone compared with those without prednisolone treatment. These findings are in line with previous reports of afternoon and

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evening hyperglycemia under glucocorticoids in persons without DM [24 27 55] . Thus, BBI with long-acting insulin does not offer a final solution.

The intermediate-acting NPH insulin provides good control of afternoon peaks of blood glucose caused by glucocorticoids. This approach might have an advantage over long-acting insulin because its effects show a similar timeline to that of glucocorticoid-induced afternoon peaks of hyperglycemia [56 57]. Three of the reviewed articles [35 36 39] compared NPH insulin with insulin Glargine as basal insulin in a BBI treatment in randomized controlled [36 35] and retrospective [39] studies, finding no significant differences in glycemic control. However, NPH insulin caused more hypoglycemic events when NPH and bolus insulin were administered in equal pre-prandial doses for the purpose of controlling hyperglycemia in persons receiving multiple daily doses of glucocorticoids [36]. Such a protocol may not be flexible enough in that it does not give sufficient consideration to the night-time fasting period and the associated risk of nocturnal hypoglycemia. Insulin requirement, however, was higher in BBI with long-acting insulin compared with NPH as basal insulin in two of the studies [36 39] but it was similar in the other [35]. The addition of NPH together with the glucocorticoid in the BBI treatment also failed to improve glycemic control [34]. The most recent study by Lakhani *et al.* [33] suggests a unique approach to better match the pharmacodynamical properties of insulins and glucocorticoids. This resulted in significantly lower mean daily BGL and pre-meal time in target glucose range. While the approach of Lakhani *et al.* [33] appears to be promising, it does need to be corroborated in a larger study.

We found no primary data comparing anticipatory with compensatory treatment adjustments for glycemic control when starting glucocorticoids. This lack of data is a source of some controversial expert opinions in guidelines. The American Endocrine Society Clinical Practice Guidelines [41] recommends an anticipatory approach with discontinuation of OHA at the time of hospital admission and initiation of insulin with persistent hyperglycemia. In exceptional

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cases, selected persons who are stable, eating regularly and have no contraindication "may be candidates for continuation of previously prescribed OHA". The Canadian Diabetes Association guideline [45] recommends that "glycemic monitoring for 48 hours after initiation of steroids may be considered". In contrast, the Joint British Diabetes Societies for inpatient care guideline [19] and the Imperial College Clinical Guidance [58] recommend the up-titration of OHA first. They recommend adding [19] or switching [58] to insulin if BGL remains above 10mmol/l. Reports of experience or evidence to suggest the use of DDP-4 inhibitors, GLP-1 receptor agonists or SGLT-2 inhibitors is lacking.

The strength of our systematic review is that it makes an important contribution to DM management. It does this by highlighting the unresolved challenge of good glycemic control in DM patients who are on systemic glucocorticoid therapy and by reporting an extensive literature search on hyperglycemic control in these patients. However, we cannot draw conclusions from our systematic analysis on the most effective management approach. This is largely due to the low-to-moderate quality of available evidence and the lack of comparability between the reviewed studies. In fact, this review draws attention to the heterogeneity of the experimental designs and the lack of well powered, high quality studies. Given that the populations, interventions, target glucose levels, and glucose monitoring differed from study to study, the main limitation is that we can only provide a descriptive review of the studies but not formal recommendations. Well-designed studies with more homogeneous patient populations are needed in order to answer the questions raised in this review. The present review focused on the population of persons with pre-existing Type 2 DM without prior insulin treatment. However, we included articles with mixed populations, namely persons with Type 2 DM with or without prior insulin treatment and Type 1 DM, because there is an insufficient number of articles with the specific sub-group of interest. We acknowledge that this is not standard practice in systematic reviews.

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CONCLUSION

Glucocorticoid therapy exacerbates hyperglycemia in patients with pre-existing DM. Current management strategies give insufficient guidance for glycemic control in persons started on glucocorticoids. The lack of relevant RCTs and observational studies, heterogeneity of populations, interventions, target glucose levels, and glucose monitoring in available studies, and low to moderate quality of available evidence make it difficult to identify pharmacological interventions for effective glycemic control. Even for the widely recommended use of a BBI regimen as intensive insulin therapy in DM, the data on this regimen in DM patients on glucocorticoids is inconclusive. Indeed, the findings of our systematic review clearly speak in favour of the call to action on research in inpatient DM management of The PRIDE group [59] and in outpatient care. A concerted effort of Diabetes Societies would be needed to develop powerful study designs that take into account different DM phenotypes, settings and treatment approaches.

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DECLARATIONS

Competing interests

The authors have no competing interests to declare.

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Authors contributions

MT drafted the study, contributed to the development of the selection criteria and data extraction criteria, developed the search strategy, elaborated the study selection, data extraction and data synthesis, wrote the manuscript, provided feedback and approved the final manuscript.

RL provided expertise on DM, read the manuscript, provided feedback and approved the final manuscript.

MC contributed to the writing of the manuscript.

AN read, provided feedback and approved the final manuscript.

EB drafted the study, contributed to the development of the selection criteria and data extraction criteria, read the manuscript, provided feedback and approved the finals manuscript.

SKR is the guarantor, drafted the study, contributed to the development of the selection criteria and data extraction criteria, did the study selection, data extraction and data synthesis, wrote the manuscript, provided feedback and approved the final manuscript.

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Data sharing statement

All available data is included into the manuscript.

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Table 1: Overview of included studies characteristics (alphabetic order)

First author (year)	Study population	Prednisolone equiv. Dose (range or SD) mg; duration	Participants n (control/exp.)); Age average (range or SD)	Intervention in control group	Intervention in experimental group
Randomized control trials (all open-label and parallel-groups, except Gerards [37] cross-over design)					
Gerards (2016) [37]	In- or outpatients with or without Type 2 DM and hyperglycemia under cyclic glucocorticoid-containing chemotherapy	50.4 (36.6-55.3) 3-4 days per cycle.	26 (13/13) • 24 Type 2 DM (13 prior insulin) • 22/26 outpatients 67 years (58-71)	Additional SSI regimen to routine DM medication during prednisone containing cycles • 4 times daily short-acting insulin according to BGL	Additional IMI regimen during cycles to routine DM medication • IMI single morning dose 0.01 IU/mg per kg prednisolone equivalent, max. 0.5 IU per kg; reduced to 40% in > 70 years or GFR < 60mL/min; daily increases 10% according to BGL
Grommesh (2016) [34]	Inpatients with or without Type 2 DM and hyperglycemia within 24h of glucocorticoids for any indication	57.2 (±31.5) ≤5 days	61 (31/30) • 30 Type 2 DM (prior insulin n/a) 64.8 years (±16.1)	BBI regimen 1:1 basal and bolus • Basal: insulin glargine • Bolus: prandial insulin lispro • additional correctional insulin aspart • Algorithm for initial dosing based on DM diagnosis, HbA1c and previous treatment (see ref.)	Additional NPH insulin to BBI regimen • NPH along with glucocorticoid (three times if multiple dosing) • Algorithm for NPH doses based on glucocorticoid dose and DM diagnosis
Lakhani (2018) [33]	Inpatients with or without DM (Type 1 or 2) under glucocorticoids for any indication with postprandial hyperglycemia	20.75 (±12.7) Duration n/a	67 (34/33) • DM (Type and prior insulin n/a) in 14 control / 21 experimental 54.2 years (±11.9)	BBI regimen 1:1 basal and bolus, 0.3-0.5 U/kg/d according to HbA1c • Basal: insulin glargine at bedtime • Bolus: prandial insulin lispro • additional correctional insulin lispro	Additional correctional insulin which matches glycemic profile of the glucocorticoid administered according protocol (see ref) given along with glucocorticoid: • regular insulin with hydrocortisone • NPH with prednisolone or methylprednisolone • Insulin glargine with dexamethasone
Radhakutty (2017) [35]	Inpatients with or without Type 2 DM and hyperglycemia under glucocorticoids for COPD, pneumonia, interstitial lung disease or gout.	33 (±9.6) >1 day	48 (23/25) • 34 Type 2 DM (10 prior insulin) 72.1 years (±11.5)	BBI regimen 1:1 basal and bolus, 0.5 U/kg/d • Basal: insulin glargine • Bolus: prandial insulin aspart in three equal doses • additional correctional insulin if needed	BBI regimen 1:1 basal and bolus • Basal: NPH insulin, morning dose • Bolus: prandial insulin aspart, 20% before breakfast, 40% before lunch and 40% before dinner • additional correctional insulin if needed
Ruiz de Adana (2016) [36]	Inpatients with Type 2 DM on pneumology under glucocorticoids treatment for respiratory disease.	appx. 100mg day 1 appx. 33mg day 6	53 (27/26) • 23 prior insulin 68.6 years (±7.3) years	BBI regimen 1:1 basal and bolus, 0.3-0.5 U/kg/d or regular insulin dose multiplied by 1.5 • Basal: insulin glargine at 9:00 am • Bolus: prandial insulin glulisine in three equal doses • additional correctional insulin if needed	BBI regimen 1:1 basal and bolus, 0.3-0.5 U/kg/d or regular insulin dose multiplied by 1.5 • Basal: NPH insulin in three equal prandial doses • Bolus: prandial insulin glulisine in three equal doses • additional correctional insulin if needed
Observational studies (all retrospective cohort studies)					
Burt (2015) [38]	Inpatients with Type 2 DM with or without prednisolone for inflammatory disease	33.2±9.0 day1 21.1±7.2 day 5	66 (42/24) • 24 prior insulin 75.7 years (±12.9)	BBI regimen 1:1 basal and bolus, 0.3-0.4 U/kg/d • Basal: insulin glargine • Bolus: insulin aspart or lispro or glulisin devided into three meal time bolus • additional correctional insulin if needed	BBI regimen as control and additional prednisolone single morning dose >3 days
Dhital (2012) [39]	Inpatients with or without Type 2 DM treated with prednisolone at day before discharge; comparison of NPH insulin vs. insulin glargine in BBI regimen.	31±24.4	120 (60/60) • 61 Type 2 DM (prior insulin n/a) 58 years (±14)	BBI regimen 1:1 basal and bolus • Basal: insulin glargine • Bolus: insulin aspart • additional correctional insulin if needed	BBI regimen 1:1 basal and bolus insulin • Basal: NPH insulin • Bolus: regular insulin • additional correctional insulin if needed

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Gosmanov (2013) [40]	Inpatients with Type 2 DM treated with dexamethasone for hematologic malignancies	57.2±9.9	40 (12/28) • 15 prior insulin 56.1 years (±7.8)	BBI regimen 1:1 basal and bolus, 0.33 U/kg • Basal: insulin detemir twice daily • Bolus: insulin aspart • additional correctional insulin if needed • daily insulin dose correction if out of target 20-30%	SSI regimen with regular insulin (for protocol see ref.)

BBI: basal-bolus insulin; BGL: blood glucose level; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; IMI: intermediate-acting insulin; NPH: Neutral Protamine Hagedorn, isophane insulin; SSI: sliding-scale insulin

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Table 2: Outcomes of included original articles (alphabetic order)

First author [ref]	Target glucose (mmol/l)	Glycemic control						Mean total daily insulin dose (IU/kg/day or U/d)			Hypoglycemia <3.9mmol/l	Hyperglycemia >16.7mmol/l	Other
		Time in target glucose range (%)			Mean daily BGL (mmol/l)								
		Control	Exper.	p value	Control	Exper.	p value	Control	Exper.	p value			
Randomized control trials													
Gerards [37]	3.9-10	20.9 [1]	34.3 [1]	< 0.001	13.5 ± 2.8 [1]	12.4± 2.9 [1]	<0.05	26.0 (13.5-63.0)	40.3 (28.7-61.0)	0.01	mild p=0.21 no severe	n/a	Persons prefer SSI/IMI 29/71%
Grommesh [34]	3.9-10	54.6 [2]	62.0 [2]	0.24	9.9 ± 1.7 [2]	9.4±2.0 [2]	0.17	34.8	35.8	0.13	0.1% both groups	2.9%, p=0.89	MAGE p=0.0001
Lakhani [33]	5.6-10	15.0 [3] 16.7 [4]	33.3 [3] 29.3 [4]	0.002 0.09	12.3 ± 2.8 [2]	9.5±1.9 [2]	0.0001	n/a	n/a	n/a	mild p=0.3 no severe	20.7 events, p<0.001	MAGE p=0.0001
Radhakutty [35]	4-10	50 [2, 5]	58 [2, 5]	0.28	11.8 [2, 5]	10.5 [2, 5]	0.57	0.67±0.08	0.61±0.04	0.57	mild p=0.92 no severe	n/a	MAGE p=0.2
Ruiz de Adana [36]	4.5-10	42 [1]	38 [1]	0.61	10.88 ± 2.99 [1] 11.43 ± 3.44 [6]	11.10 ± 3.55 [1] 11.88 ±2.94 [6]	0.62 0.97	56.9±40.6	55.4±27.5	0.43	mild p=0.35 severe p=0.13	no events	MAGE p=0.377
Observational studies													
Burt [38]	4-10	n/a	n/a	n/a	10 ± 0.1 [2]	12.2 ± 0.3 [2]	<0.001	0.60-0.65	0.67-0.70	0.001	all p=0.28 no severe	n/a	BGL at 6 and 12 am similar, at 5 and 9 pm higher
Dhital [39]	n/a	n/a	n/a	n/a	9.2±2.9 [7]	9.3±2.6 [7]	0.79	0.34 ±0.2 basal 0.36 ±0.2 bolus	0.27 ±0.2 0.26 ±0.2	0.04 0.03	all p=0.77 no severe	n/a	
Gosmanov [40]	5.6-10	n/a	n/a	n/a	12.2±2.8 [7]	16.7±3.2 [7]	<0.001	122±39 0.63±0.25	49±29 0.46±0.16	<0.001	no events	3 events exper. group	

BGL: blood glucose level; IMI: intermediate insulin; MAGE: mean amplitude of gylcemic excursions; n/a: not applicable; SSI: sliding scale insulin

[1] CGM: continuous glucose monitoring

[2] capillary blood glucose monitoring four times a day (three times before meals and at bedtime)

[3] pre-meal blood glucose in target range; pre-meal target range defined as BGL 5.6-7.8 mmol/l;

[4] bedtime blood glucose in target range; bedtime target range defined as BGL 7.8-9.99 mmol/l;

[5] approximation, because article indicates 'time outside target glucose range'

[6] capillary blood glucose monitoring pre-meal and 2h post-meal

[7] all available BGL

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FIGURE LEGEND

Fig. 1: Flow diagram of study selection

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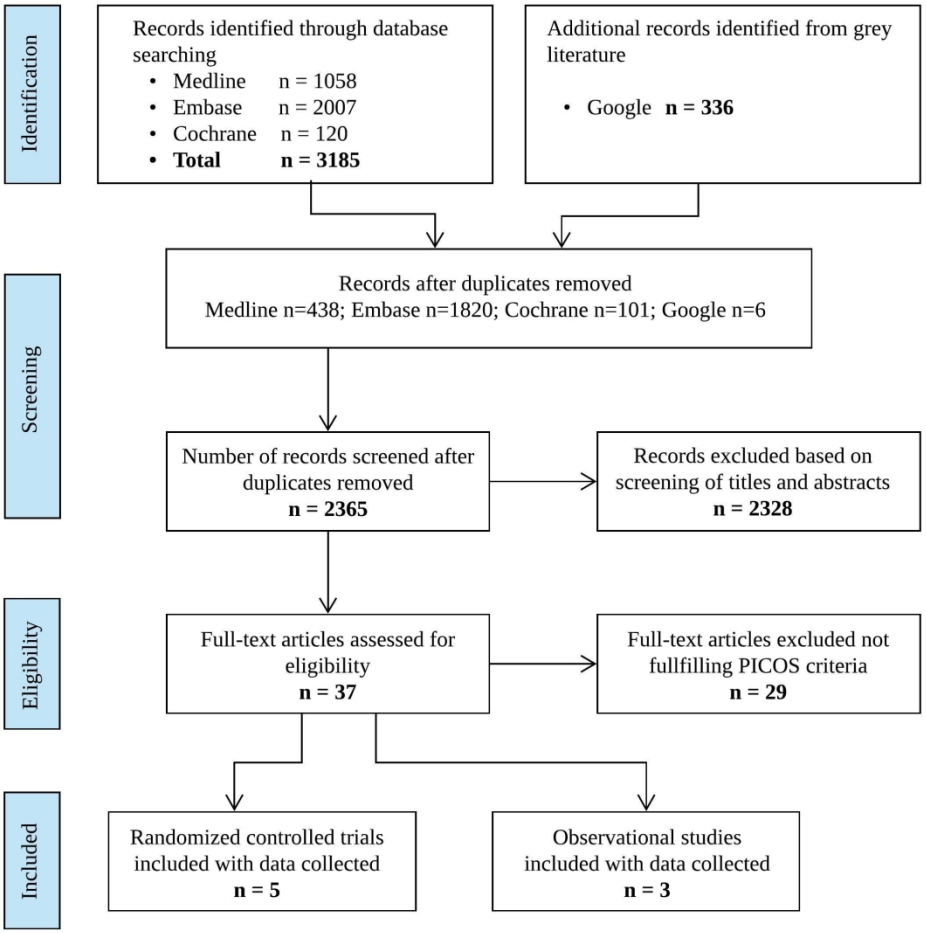

Fig. 1: Flow diagram of study selection

193x198mm (300 x 300 DPI)

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Supplementary Table 1: Search strategies

a) OVID search strategy

1	exp Diabetes Mellitus/
2	diabet*.tw.
3	1 or 2
4	hyperglyc*.ab,ti.
5	((serum* or level* or blood*) adj5 (glucose* or sugar* or level*)).ab,ti.
6	exp Hyperglycemia/
7	exp Blood Glucose/
8	4 or 5 or 6 or 7
9	3 and 8
10	exp Adrenal Cortex Hormones/ad, ae, dt, to [Administration & Dosage, Adverse Effects, Drug Therapy, Toxicity]
11	exp Steroids/ad, ae, dt, th, to [Administration & Dosage, Adverse Effects, Drug Therapy, Therapy, Toxicity]
12	((corti* or predni* or glucocorticoid* or steroid* or 'adrenal cortex hormone' or beclomethasone or betamethasone or budesonide or clobetasol or desoximetasone or dexamethasone or diflucortolone or flumethasone or 'fluocinolone acetonide' or fluocinonide or flucortolone or fluorometholone or fluprednisolone or flurandrenolone or 'melengestrol acetate' or methylprednisolone or paramethasone or prednisolone or prednisone or triamcinolone or aldosterone or corticosterone or '18 hydroxycorticosterone' or cortisone or cortodoxone or hydrocortisone or tetrahydrocortisol or tetrahydrocortisone or '18 hydroxydesoxycorticosterone' or 'desoxycorticosterone acetate' or '17 alphahydroxypregnenolone' or hydroxysteroid* or finasteride) adj10 (effect* or influenc* or impact* or therap* or medic* or induc* or administ* or dosage or treatm*)).ab,ti.

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13	10 or 11 or 12
14	exp Hypoglycemic Agents/
15	(intensive insulin or glucose or basal bolus or basal-bolus or multiple-dose insulin or basal insulin or prandial insulin or continuous subcutaneous insulin infusion or acetohexamide or biphasic insulins or buformin or butoxamine or carbutamide or chlorpropamide or gliclazide or glipizide or glyburide or insul* or insulin aspart or insulin lispro or isophane insulin or lente insulin or long-acting insulin or regular pork insulin or short-acting insulin or ultralente insulin or metformin or phenformin or tolazamide or tolbutamide).ab,ti.
16	14 or 15
17	exp Guideline/
18	((glyc* or hyperglyc* or diab* or gluco* or clinic*) adj10 (guide* or manage* or contro* or treatm* or therap* or protoc* or 'expert opinion' or target* or adjust* or admin* or chang* or regim* or requir* or monitor*)).ab,ti.
19	((treat* or diseas* or therap* or proced* or proto* or clinic*) adj10 (guid* or sugg* or advice* or recommend* or manage* or rule* or outline* or princip* or 'evidence based' or contro* or 'expert opinion' or regim*)).ab,ti.
20	17 or 18 or 19
21	9 and 13 and 16 and 20
22	limit 21 to animals
23	limit 22 to humans
24	22 not 23
25	21 not 24
26	limit 25 to yr="2001 -Current"

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b) EMBASE and Cochrane library search strategy

1	'diabetes mellitus'/exp
2	diabet*
3	#1 OR #2
4	hyperglyc*:ab,ti
5	((serum* OR blood* OR level*) NEAR/5 (glucose* OR sugar* OR level*)):ab,ti
6	'hyperglycemia'/exp
7	'blood glucose level'/exp
8	#4 OR #5 OR #6 OR #7
9	#3 AND #8
10	'corticosteroid'/exp/dd_do,dd_dt,dd_ae,dd_to,dd_ad,dd_it
11	((corti* OR predni* OR glucocorticoid* OR steroid* OR 'adrenal cortex hormone' OR beclomethasone OR betamethasone OR budesonide OR clobetasol OR desoximetasone OR dexamethasone OR diflucortolone OR flumethasone OR 'fluocinolone acetonide' OR fluocinonide OR fluocortolone OR fluorometholone OR fluprednisolone OR flurandrenolone OR 'melengestrol acetate' OR methylprednisolone OR parametasone OR prednisolone OR prednisone OR triamcinolone OR aldosterone OR corticosterone OR '18 hydroxycorticosterone' OR cortisone OR cortodoxone OR hydrocortisone OR tetrahydrocortisol OR tetrahydrocortisone OR '18 hydroxydesoxycorticosterone' OR 'desoxycorticosterone acetate' OR '17 alphahydroxypregnenolone' OR hydroxysteroid* OR finasteride) NEAR/10 (effect* OR influenc* OR impact* OR therap* OR medic* OR induc* OR administ* OR dosage OR treatm*)):ab,ti
12	#10 OR #11

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13	'antidiabetic agent'/exp
14	'intensive insulin':ab,ti OR glucose:ab,ti OR 'basal bolus':ab,ti OR 'basal-bolus':ab,ti OR 'multiple-dose insulin':ab,ti OR 'basal insulin':ab,ti OR 'prandial insulin':ab,ti OR 'continuous subcutaneous insulin infusion':ab,ti OR acetohexamide:ab,ti OR 'biphasic insulins':ab,ti OR buformin:ab,ti OR butoxamine:ab,ti OR carbutamide:ab,ti OR chlorpropamide:ab,ti OR gliclazide:ab,ti OR glipizide:ab,ti OR glyburide:ab,ti OR insul*:ab,ti OR 'insulin aspart':ab,ti OR 'insulin lispro':ab,ti OR 'isophane insulin':ab,ti OR 'lente insulin':ab,ti OR 'long-acting insulin':ab,ti OR 'regular pork insulin':ab,ti OR 'short-acting insulin':ab,ti OR 'ultralente insulin':ab,ti OR metformin:ab,ti OR phenformin:ab,ti OR tolazamide:ab,ti OR tolbutamide:ab,ti
15	#13 OR #14
16	'practice guideline'/exp
17	'diabetic control'/exp
18	((treat* OR diseas* OR therap* OR proced* OR proto* OR clinic*) NEAR/10 (guid* OR sugg* OR advice* OR recommend* OR manage* OR rule* OR outline* OR princip* OR 'evidence based' OR contro* OR 'expert opinion' OR regim*)):ab,ti
19	((glyc* OR hyperglyc* OR diab* OR gluco* OR clinic*) NEAR/10 (guide* OR manage* OR contro* OR treatm* OR therap* OR protoc* OR 'expert opinion' OR target* OR adjust* OR admin* OR chang* OR regim* OR requir* OR monitor*)):ab,ti
20	#16 OR #17 OR #18 OR #19
21	#9 AND #12 AND #15 AND #20
22	#9 AND #12 AND #15 AND #20 AND [animals]/lim
23	#9 AND #12 AND #15 AND #20 AND [humans]/lim AND [animals]/lim
24	#22 NOT #23
25	#21 NOT #24
26	#25 NOT [conference abstract]/lim

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27	#26 AND (2001:py OR 2002:py OR 2003:py OR 2004:py OR 2005:py OR 2006:py OR 2007:py OR 2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py)

c) Google advanced search

"management" or "steroid therapy" or "guideline" and diabet* or hypergly* or corti* or predni* or glucocorticoid* or steroid*or glycemic control

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Supplementary Table 2: Risk of bias

a) Risk of bias in five RCTs for seven domains and four different outcomes: mean BGL, time in target glucose range, insulin dose, hypoglycemia

Randomized control trials (all open-label and parallel-group {except Gerards 1 cross over design})							
First author (year)	**Risk of bias**						
	Sequence generation	**Allocation concealment**	**Selective reporting**	**Other sources of bias**	**Blinding (participants and personnel)**	**Blinding (outcome assessment)**	**Incomplete outcome data**
Gerards (2016) [1]	-Mean BGL: **low** -Time in target range: **low** -Insulin dose: **low** -Hypoglycemia: **low** -Overall: **low**	-Mean BGL: **low** -Time in target range: **low** -Insulin dose: **low** -Hypoglycemia: **low** -Overall: **low**	-Mean BGL: **low** -Time in target range: **low** -Insulin dose: **low** -Hypoglycemia: **low** -Overall: **low**	-Mean BGL: **low** -Time in target range: **low** -Insulin dose: **low** -Hypoglycemia: **low** -Overall: **low**	-Mean BGL: **high** -Time in target range: **high** -Insulin dose: **high**- Hypoglycemia: **high** -Overall: **high**	-Mean BGL: **low** -Time in target range: **low** -Insulin dose: **high** -Hypoglycemia: **high** -Overall:**n/a**	-Mean BGL: **low** -Time in target range: **low** -Insulin dose: **low** -Hypoglycemia: **low** -Overall: **low**
Grommesh (2016) [2]	-Mean BGL: **nk** -Time in target range: **nk** -Insulin dose: **nk** -Hypoglycemia: **nk** -Overall: **nk**	-Mean BGL: **nk** -Time in target range: **nk** -Insulin dose: **nk** -Hypoglycemia: **nk** -Overall: **nk**	-Mean BGL: **low** -Time in target range: **low** -Insulin dose: **low** -Hypoglycemia: **low** -Overall: **low**	-Mean BGL: **high** -Time in target range: **high** -Insulin dose: **high** -Hypoglycemia: **high** -Overall: **high**	-Mean BGL: **high** -Time in target range: **high** -Insulin dose: **high** -Hypoglycemia: **high** -Overall: **high**	-Mean BGL: **high**-Time in target range: **high** -Insulin dose: **high** -Hypoglycemia: **high**- Overall: **high**	-Mean BGL: **low** -Time in target range: **low** -Insulin dose: **low** -Hypoglycemia: **low** -Overall: **low**
Lakhani (2018) [3]	-Mean BGL: **low** -Time in target range: **low** -Insulin dose: **low** -Hypoglycemia: **low** -Overall: **low**	-Mean BGL: **nk** -Time in target range: **nk** -Insulin dose: **nk** -Hypoglycemia: **nk** -Overall: **nk**	-Mean BGL: **low** -Time in target range: **low** -Insulin dose: **high** -Hypoglycemia: **low** -Overall: **low**	-Mean BGL: **low** -Time in target range: **low** -Insulin dose: **low** -Hypoglycemia: **low** -Overall: **low**	-Mean BGL: **high** -Time in target range: **high** -Insulin dose: **high** -Hypoglycemia: **high** -Overall: **high**	-Mean BGL: **high** -Time in target range: **high** -Insulin dose: **high** -Hypoglycemia: **high**- Overall: **high**	-Mean BGL: **low** -Time in target range: **low** -Insulin dose: **high** -Hypoglycemia: **low** -Overall: **low**
Radhakutty (2017) [4]	-Mean BGL: **low** -Time in target range: **low** -Insulin dose: **low** -Hypoglycemia: **low** -Overall: **low**	-Mean BGL: **low** -Time in target range: **low** -Insulin dose: **low** -Hypoglycemia: **low** -Overall: **low**	-Mean BGL: **low** -Time in target range: **low** -Insulin dose: **low** -Hypoglycemia: **low** -Overall: **low**	-Mean BGL: **low** -Time in target range: **low** -Insulin dose: **low** -Hypoglycemia: **low** -Overall: **low**	-Mean BGL: **high** -Time in target range: **high** -Insulin dose: **high**- Hypoglycemia: **high** -Overall: **high**	-Mean BGL: **high** -Time in target range: **high** - Insulin dose: **high** -Hypoglycemia: **high**- - Overall: **high**	-Mean BGL: **low** -Time in target range: **low** -Insulin dose: **low** -Hypoglycemia: **low** -Overall: **low**
Ruiz de Adana (2016) [5]	-Mean BGL: **high** -Time in target range: **high** -Insulin dose: **high** -Hypoglycemia: **high** -Overall: **high**	-Mean BGL: **nk** -Time in target range: **nk** -Insulin dose: **nk** -Hypoglycemia: **nk** -Overall: **nk**	-Mean BGL: **low** -Time in target range: **low** -Insulin dose: **low** -Hypoglycemia: **low** -Overall: **low**	-Mean BGL: **low** -Time in target range: **low** -Insulin dose: **low** -Hypoglycemia: **low** -Overall: **low**	-Mean BGL: **high** -Time in target range: **high** -Insulin dose: **high** -Hypoglycemia: **high** -Overall: **high**	-Mean BGL: **high**-Time in target range: **high** -Insulin dose: **high** -Hypoglycemia: **high** -Overall: **high**	-Mean BGL: **low** -Time in target range: **low** -Insulin dose: **low** -Hypoglycemia: **low** -Overall: **low**

nk: not known as either unclear or not reported; n/a: not applicable

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b) Risk of bias in three included observational studies. The criteria for risk of bias correspond to the key criteria to assess the methodological quality of nonrandomized studies summarized in Table 2 of the main article in the GRADE guidelines by Guyatt et al. [6]

Observational studies (all retrospective cohort studies)				
First author (year)	**Risk of bias**			
	Failure to develop and apply appropriate eligibility criteria	**Flawed measurement of both exposure and outcome**	**Failure to adequately control confounding**	**Incomplete follow-up**
Burt (2015) [7]	**low**	**low**	**low**	**low**
Dhital (2012) [8]	**low**	**low**	**high**	**low**
Gosmanov (2013) [9]	**high**	**low**	**high**	**low**

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Supplementary Table 3: Quality of evidence for mean BGL and time in target glucose range (high, moderate, low or very low)

First author	Limitations/ Risk of bias (serious/not serious)	Inconsistency (Yes/No/not relevant)	Indirectness (Yes/No/not relevant)	Imprecision (Yes/No/not relevant)	Publication bias (likely/unlikely)	Quality of evidence after up-/downgrading
Randomized control trial						
Gerards (2016) [1]	**Not serious**	Mean BGL: **No** Time in target glucose: **No**	Mean BGL: **No** Time in target glucose: **No**	Mean BGL: **Yes** Time in target glucose: **Yes**	Mean BGL: **unlikely** Time in target glucose: **unlikely**	**High downgrade to moderate** [a]
Grommesh (2016) [2]	**Serious**	Mean BGL: **Yes** Time in target glucose: **Yes**	Mean BGL: **No** Time in target glucose: **No**	Mean BGL: **No** Time in target glucose: **No**	Mean BGL: **likely** Time in target glucose: **likely**	**High downgrade to very low** [b]
Lakhani (2016) [3]	**Serious**	Mean BGL: **No** Time in target glucose: **No**	Mean BGL: **No** Time in target glucose: **No**	Mean BGL: **No** Time in target glucose: **No**	Mean BGL: **unlikely** Time in target glucose: **unlikely**	**High downgrade to moderate** [c]
Radhakutty (2016) [4]	**Serious**	Mean BGL: **No** Time in target glucose: **No**	Mean BGL: **No** Time in target glucose: **No**	Mean BGL: **No** Time in target glucose: **No**	Mean BGL: **likely** Time in target glucose: **likely**	**High downgrade to low** [d]
Ruiz de Adana (2016) [5]	**Serious**	Mean BGL: **No** Time in target glucose: **No**	Mean BGL: **No** Time in target glucose: **No**	Mean BGL: **No** Time in target glucose: **No**	Mean BGL: **unlikely** Time in target glucose: **unlikely**	**High downgrade to moderate** [e]
Observational studies						
Burt (2015) [7]	**Not serious**	Mean BGL: **No**	Mean BGL: **No**	Mean BGL: **No**	Mean BGL: **unlikely**	**Low**
Dhital (2012) [8]	**Not serious**	Mean BGL: **No**	Mean BGL: **No**	Mean BGL: **No**	Mean BGL: **unlikely**	**Low**
Gosmanov (2013) [9]	**Serious**	Mean BGL: **No**	Mean BGL: No	Mean BGL: **No**	Mean BGL: **unlikely**	**Low downgrade to very low** [f]

[a] downgrading because of serious imprecision with lack of CI; [b] downgrading because of serious limitations/risk of bias; lack of blinding and attending physicians were not obliged to follow the study protocol while titrating insulin doses, and inconsistency with small sample groups and publications bias with lack of significant results; [c] downgrading because of serious limitations/risk of bias; lack of blinding; [d] downgrading because of serious limitations/risk of bias; lack of blinding, and industry funding; [e] downgrading because of serious limitations/risk of bias, not randomised sequence generation, lack of allocation concealment; [f] downgrading because of serious limitation in eligibility criteria as "self-reported diagnosis of diabetes".

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5-6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Suppl Tbl 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7-8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	n.a.
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	n.a.

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8.
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n.a.
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9-10; Fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9-10; Tbl 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	12-13; Suppl Tbl 2 and 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10-12; Table 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n.a.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9-12
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n.a.
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14-15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16-17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

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