BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (http://bmjopen.bmj.com).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

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

SCHOLARONE™
Manuscripts

1   # Management of hyperglycemia in persons with non-insulin-

2   # dependent Type 2 Diabetes mellitus that are started on systemic

3   # glucocorticoid therapy: a systematic review

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

5   **Milos Tatalovic[1,2], Roger Lehmann[3], Albina Nowak[3], Edouard Battegay[1,4,5], Silvana K.**

6   **Rampini[1]**

7   [1]Department of Internal Medicine, University Hospital Zurich, University of Zurich,

8   Rämistrasse 100, CH-8091 Zurich, Switzerland

9   [2]current affiliation: Stadt Zürich Stadtspital Waid, Tièchestrasse 99, 8037 Zurich, Switzerland

10   [3]Department of Endocrinology, Diabetes and Clinical Nutrition, University Hospital Zurich,

11   Raemistrasse 100, 8091 Zurich, Switzerland

12   [4]Center of Competence Multimorbidity, University of Zurich, Switzerland

13   [5]University Research Priority Program Dynamics of Healthy Aging, University of Zurich,

14   Switzerland

15   **Corresponding author:** Silvana K. Rampini, Email**:** silvana.rampini@usz.ch

16   **KEY WORDS**

17   Type 2 Diabetes, hyperglycemia, glucocorticoid therapy, hypoglycemic agent, insulin, NPH

18   insulin, long-acting insulin, BBI, SSI, multimorbidity, disease-disease medication interaction

1

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

19 **ABSTRACT**

20 **Objectives**

21 To define the evidence-based best management of glucocorticoid-induced hyperglycemia in

22 persons with Type 2 Diabetes mellitus (DM) who start glucocorticoid therapy.

23 **Data sources**

24 We searched Medline, Embase and Cochrane Library databases as well as Google for articles

25 from 2002 to July 2018 using all search terms related to DM, glucocorticoids and treatment.

26 **Study selection**

27 Two authors screened articles for the notion "adult persons with Type 2 DM who received

28 glucocorticoid therapy", and evaluated identified articles according to predefined eligibility

29 criteria. Randomized controlled trials and observational studies were included.

30 **Data collection and analysis**

31 One author extracted data from included articles and another checked extracted data. We

32 assessed the risk of bias and overall quality of evidence and performed a qualitative, descriptive

33 analysis.

34 **Results**

35 We ultimately included 8/2'365 screened articles, five open-label RCTs and three observational

36 studies. All articles but one focused on inpatient insulin treatment. The included studies suggest

37 standard basal-bolus insulin (BBI) treatment and compared it to various insulin strategies.

38 However, study heterogeneity did not allow to systematically and quantitatively analyze

39 specific insulin regimens. Thus, four studies examining intermediate-acting insulin as basal

40 insulin did not find convincing advantages despite theoretical pharmacodynamical advantages

2

41 vis-à-vis long-acting insulin glargine. In addition, glycemic control with sliding scale insulin

42 (SSI) was inferior in two studies compared to BBI or intermediate-acting insulin. Two studies

43 suggest that pharmacodynamical profiles of insulins should be reconciled with corresponding

44 profiles of glucocorticoids. However, there is insufficient evidence for supporting this

45 recommendation. It is unclear, whether anticipatory outdoes compensatory insulin treatment.

46 **Conclusion**

47 Studies on treatment of glucocorticoid-induced hyperglycemia in Type 2 DM are

48 heterogeneous, and optimal insulin management remains uncertain. Hence, no specific insulin

49 regimen proved superior to another. Notwithstanding, we discourage SSI for use in this setting

50 and encourage aligning pharmacodynamics profiles of used glucocorticoids and insulin

51 treatment.

52 **STRENGTHS AND LIMITATIONS OF THIS STUDY:**

53 • Systematic review approach with extensive literature search for a very common but

54 unresolved daily problem in managing Type 2 DM.

55 • The power to make firm conclusions is limited by the small number of available high quality

56 studies and the overall small number of study participants.

57 • Heterogeneity of included studies preclude a full quantitative analysis and to give formal

58 recommendations on a specific insulin regimen.

59

3

INTRODUCTION

60

61 The number of persons with DM has grown globally from 108 million in 1980 to 422 million

62 in 2014, *i.e.*, the global prevalence has almost doubled during this period from 4.7% to 8.5% [1].

63 DM occurs in about 25-30% of hospitalized persons [2], and DM management appears

64 inappropriate in many of them [3][4]. In a retrospective cohort study, poor glycemic control

65 correlated with higher hospitalization costs and associated with higher rates of DM-related

66 hospital utilization per 100 patient-years [5]. In addition, persons with Type 2 DM had longer

67 hospital stays and more hospitalizations directly related to complications of DM [6]. In an

68 observational study, newly discovered hyperglycemia correlated with higher in-hospital

69 mortality [7]. Hyperglycemia also related to more postoperative infections [8], complications after

70 transplantation [9] and increased mortality [10].

71 Glucocorticoid therapy improves outcomes in respiratory diseases such as acutely exacerbated

72 COPD, asthma, inflammatory or autoimmune disease, transplantat rejection and symptoms of

73 chemotherapy [11][12]. In most cases, glucocorticoid regimens last less than 5 days. However, in

74 22% of all cases, they remain prescribed for longer than 6 months [13][14]. In the UK, long-term

75 glucocorticoid prescriptions irrespective of the diagnosis have increased by 34% over 20 years

76 [13]. The prevalence of glucocorticoid use in hospitals is more than 10% of all admitted persons

77 [15]. Thus, glucocorticoid treatment in persons with Type 2 DM is common and will steadily

78 increase in parallel with increased prevalence of DM and better life expectancy of these persons.

79 At the same time, many other diseases or conditions multiply in the same persons that interact

80 with DM, i.e., multi-morbidity [16].

81 Glucocorticoids instantly increase basal endogenous glucose production and lower insulin

82 sensitivity [17-19], which leads to hyperglycemia. The rate of glucocorticoid-induced

83 hyperglycemia or DM was 32.3% and 18.6% respectively in persons without prior DM on

4

84 glucocorticoid therapy given for more than one month [20 21]. The type and doses of administered

85 glucocorticoids vary widely and are tapered or stopped within days. Mostly, prednisolone intake

86 is in the morning and results in a pronounced elevation of blood glucose 4-8 hours later, *i.e.*, in

87 the afternoon and evening [22 23]. Thus, treatment will aim at controlling the hyperglycemia at

88 these hours.

89 Recommendations promote the basal-bolus insulin (BBI) strategy for blood glucose control in

90 insulin dependent DM. BBI improves glycemic control and reduces morbidity and mortality [24-

91 26]. Furthermore, BBI results in superior glucose control as compared to sliding-scale insulin

92 (SSI) regimens [27]. Plasma concentration of intermediate-acting Neutral Protamin Hagedorn

93 (NPH) insulin peaks 4-8 h after injection [28]. NPH insulin may therefore better control afternoon

94 peaks of blood glucose concentration caused by glucocorticoids than other insulins [29].

95 In this study, we have conducted a systematic review to define the best treatment options for

96 glycemic control in persons with Type 2 DM on diet or OHA and on concomitant newly-

97 initiated glucocorticoid therapy. More specifically, we looked for the type of insulin

98 therapy/strategy that provides the best glycemic control. In addition, we have evaluated whether

99 insulin started at the same time with glucocorticoids (anticipatory) or with a delay, i.e., when

100 blood glucose level (BGL) rise above upper limits of normal (compensatory), confer better

101 results.

102

5

103   **METHODS**

104   **Protocol and registration**

105   Review methods and eligibility criteria were specified in advance, documented in a study

106   protocol and registered online with the "International Prospective Register of Systematic

107   Reviews" (PROSPERO), May 31st 2016 (Registration Number CRD42015024739) and

108   recorded with a PRISMA statement [30]. We updated the protocol once on October 21st 2016, to

109   broaden inclusion criteria.

110   **Eligibility Criteria**

111   For eligibility, we followed the PICOS criteria, i.e., **P**atients, **I**nterventions, **C**omparisons,

112   **O**utcomes and **S**ettings [30]. **Patients:** We included articles on non-critically ill (non-ICU) in- or

113   outpatients (> 16 years), who suffered from Type 2 DM treated with diet or OHA (*i.e.*,

114   biguanide, gliflozins, gliptins, sulfonylureas, glinides, incretins or glitazones) and were started

115   on a once or multiple daily oral or intravenous glucocorticoid therapy (*i.e.*, hydrocortisone,

116   prednisone, prednisolone, methylprednisolone, dexamethasone, betamethasone or

117   fludrocortisone) irrespective of the indication. **Interventions:** The articles and studies had to

118   address specific treatment interventions for glycemic control, *e.g.* stop routine DM medication,

119   starting insulin treatment, etc. **Comparisons:** We included all types of comparisons, *i.e.*,

120   comparison of the study population to populations i) without DM, ii) without glucocorticoid

121   treatment, iii) with adjusted OHA, or iv) with differing insulin treatments. **Outcomes:** We

122   accepted outcomes reflecting glycemic control, *i.e.,* time outside target glucose range, mean

123   BGL, hypo- or hyperglycemic episodes and daily insulin dose. **Settings:** We included

124   randomized controlled trials (RCTs) and observational studies, *i.e.*, cohort studies, case-control

125   studies or cross-sectional studies, without restriction to language, country of origin or

126   publication types. We excluded letters to the editor and conference abstracts. We also consulted

6

127 guidelines, reviews and expert opinions. We considered only papers published after 2002

128 because of the introduction of long-acting insulin; long-acting insulins are, nowadays, an

129 integral part of treatment in insulin dependent DM.

Search strategy

131 We identified articles based on search terms related to DM and glucocorticoids in the following

132 databases: Medline and Pre-Medline using OVID, EMBASE and Cochrane Library electronic

133 databases (Supplementary Table 1). Additionally, we performed a Google search to retrieve

134 grey literature with exclusive focus on pdf-files. The search was conducted on July 8th 2016

135 and updated on July 2nd 2018.

Study Selection

137 MT and SKR independently screened a pilot-set of 100 papers by studying the title and abstract

138 using the selection criteria 'adult persons with preexisting DM that received a glucocorticoid

139 therapy'. If no abstract was available but the title seemed relevant, MT and SKR reviewed the

140 full-text. One abstract was translated from Japanese. MT and SKR evaluated the first 100 papers

141 in consensus to determine consistent screening of all further papers. MT performed the

142 screening of all papers, and SKR independently double-screened a random sample of 10% of

143 all articles. All articles were assigned to one of the three eligibility groups, *i.e.,* "Yes", "No"

144 and "Maybe". The "Maybe" group was discussed by MT and SKR for eligibility after full-text

145 review in a consensus conference. Initial review of eligible articles exposed the necessity for

146 modification of the inclusion criterion '$\geq$ 20 mg/d prednisolone-equivalent for $\geq$ 5 days' to

147 'intermediate or high-dose glucocorticoid therapy' since a large number of articles did not

148 specify exact dosages of glucocorticoids. MT and SRK independently performed a full-text

149 review of all eligible papers for inclusion considering the PICOS criteria. Disagreements

7

150 between reviewers were resolved by consensus. Finally, the reference lists of all included

151 articles were screened for additional eligible papers, guidelines and review articles.

Data extraction and quality assessment

153 We extracted the following data from included articles: study population; participants; age.

154 Then we assessed indication, dosage and duration of glucocorticoid therapy; target glucose;

155 insulin strategy; the management of OHA interruption, continuation or adjustment of dosages;

156 outcome measures, *e.g.,* time in target glucose range, mean BGL, hypo- and hyperglycemic

157 episodes, insulin requirement. Differing assessments were discussed between MT and SKR.

158 We used the Cochrane risk of bias tool [31] to evaluate the risk of bias in RCTs and observational

159 studies. The overall quality of evidence was assessed using the grading of recommendations

160 assessment, development and evaluation (GRADE) criteria [32].

Data synthesis

162 We performed a descriptive analysis of RCTs and observational studies because the missing

163 concordance in study designs of articles on this topic precluded performing a meta-analyses.

164 Included articles were evaluated and compared in detail and findings summarized.

165

8

166   **RESULTS**

167   **Study inclusion**

168   Our initial search provided 3'521 articles. 2'365 articles remained after eliminating duplicate

169   entries. Of these 37 qualified for full text review. Eight articles met full eligibility criteria,

170   namely, four RCTs [33-36] with open-label and parallel group design, one RCT with open-label

171   and cross-over design [37], and three observational studies [38-40] with retrospective cohort design

172   (Fig. 1 and Table 1).

173   The eight studies had included a total of 481 persons, 343/481 persons with DM and 138/481

174   persons with glucocorticoid-induced hyperglycemia. One study included persons with both

175   Type 1 and 2 DM but did not take this distinction into consideration for outcomes [33]. At least

176   85/481 persons had prior treatment with insulin; three studies did not provide this information

177   [33 34 39]. Seven studies included inpatients only [33-36 38-40], and one study both in- and outpatients

178   [37]. Capillary blood glucose was measured four times a day, by continuous glucose monitoring,

179   or by using all available capillary and serum blood glucose readings (Table 2). The upper limit

180   was a BGL of 10mmol/l in all studies. The lower BGL limit was 3.9-4.5mmol/l in all but two

181   studies, where it was 5.6mmol/l [33 40] (Table 2). Insulin dose adjustments were done if BGL was

182   outside target glucose range according to specific study protocols.

183   In six studies, authors treated control groups with a BBI regimen using insulin glargine as basal

184   insulin [33-36 38 39], in one study with a BBI regimen using twice-daily insulin detemir [40] and SSI

185   added to established DM medication in one other study [37]. Strikingly, treatment interventions

186   in experimental groups diverged substantially: One study compared glycemic control of BBI

187   regimen in persons with Type 2 DM without prednisolone to those with prednisolone treatment

188   [38]. Another study compared glycemic control of BBI regimen to SSI regimen [40]. One study

189   compared addition of SSI to routine DM medication with the addition of intermediate-acting

9

190　insulin [37]. Three studies compared BBI regimens with long-acting insulins to BBI regimens

191　with NPH insulin [35 36 39] but in one of these studies NPH was given in three equal prandial doses

192　[36]. One study compared BBI regimen with long-acting insulin to the same regimen adding NPH

193　insulin [34]. Finally, the latest study added the insulin type which matched the glycemic profile

194　of the glucocorticoid administered [33]. This divergence in study designs of RCTs precluded a

195　clean and coherent quantitative meta-analysis.

BBI strategy in persons under systemic glucocorticoid therapy

197　Two observational studies [38 40] support BBI to be superior in glucocorticoid-treated persons

198　with Type 2 DM [41 42]. Gosmanov *et al.* [40] found more hyperglycemic events in persons with

199　Type 2 DM under dexamethasone for 3 days for a hematologic malignancy when treated with

200　SSI therapy than in those with a BBI therapy (Table 2). In the SSI group, mean daily BGL was

201　significantly higher (p<0.001) and average insulin requirement was significantly lower

202　(p<0.001). No hypoglycemic events occurred in either groups but 3/28 (11%) persons treated

203　with SSI were referred to an intensive care unit (ICU) because of hyperglycemic events.

204　Burt *et al.* [38] studied the effectiveness of a BBI regimen in hospitalized persons with Type 2

205　DM treated with prednisolone in the morning for an acute medical condition compared to

206　persons without glucocorticoid treatment. Half of the calculated daily dose (0.3-0.4 IU/kg) was

207　given as long-acting insulin Glargine at 9 pm and half as bolus evenly split into three meal

208　dosages of rapid-acting insulin with additional correctional insulin if necessarily. Mean daily

209　BGL was significantly higher in the prednisolone group (p<0.001) (Table 2). More specifically,

210　BGL was significantly higher at 5 and 9 pm but not significantly higher at 7 and 12 am. In

211　addition, the daily insulin dose was significantly higher in the prednisolone-treated group than

212　in the control group, especially at 12 am and 5 pm. Thus, BBI treatment did not provide a

213　sufficient glucose control most notably in the afternoon and evening.

10

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

215 Two RCTs [36][35] and one observational study [39] compared NPH insulin with the long-acting

216 insulin Glargine in a BBI regimen for their efficacy to control BGL in hospitalized persons

217 treated with medium- to high-dose glucocorticoids [36][39]. The studies differed substantially in

218 their design (Table 1). Radhakutty *et al.* [35] included persons with or without Type 2 DM treated

219 with a single dose of glucocorticoids for respiratory disease or gout. Glargine in control and

220 NPH in experimental group was administered at 7 am. Ruiz de Adana *et al.* [36] studied persons

221 with Type 2 DM receiving multiple daily doses of glucocorticoids for respiratory disease. The

222 Glargine group received its basal insulin as one dose at 9 am, and the NPH group received it

223 before breakfast, lunch and dinner in three equal doses. Dhital *et al.* [39] retrospectively studied

224 adults treated with prednisone, who were on a BBI regimen with either insulin glargine or NPH.

225 Notably, the target glucose range, the time of application and number of doses of basal insulins

226 were not indicated here, and persons with hyperglycemia without underlying Type 2 DM were

227 also included.

228 All three studies show a similar overall glycemic control for NPH or Glargine as basal insulin

229 [35][36][39]. More specifically, the mean daily BGL and the number of mild hypoglycemic episodes

230 per day were similar (Table 2). Notably, severe hypoglycemia (BGL < 2.22 mmol/l) occurred

231 in two persons in the NPH group in the study by Ruiz de Adana *et al.* [36]. Only Dhital *et al.* [39]

232 found significantly lower daily insulin requirement in the NPH group.

233 **Addition of insulin to established DM medication**

234 Gerards *et al.* [37] compared addition of SSI insulin vs. intermediate-acting insulin (IMI) to

235 established DM medication for glycemic control. The types of insulin were not further defined.

236 Half of the persons had prior insulin treatment. Addition of IMI resulted in significantly longer

237 time in target glucose range ($p<0.001$) and lower mean daily BGL ($p<0.05$). This was achieved

11

238 with an increased insulin requirement in IMI group. Remarkably, mean daily BGL of both

239 groups (SSI 13.5 ± 2.8, IMI 12.4± 2.9) were higher than in all other studies (Table 2).

240 Two RCTs added insulin to an existing BBI regimen in persons with or without Type 2 DM [33]

241 [34] (Table 1). Grommesh *et al.* [34] studied the addition of NPH insulin along with a glucocorticoid

242 to a BBI regimen. The algorithm for NPH dosing based on glucocorticoid type, dose and prior

243 DM diagnosis. There was no advantage in doing so, neither for glycemic control, mean total

244 daily insulin dose nor hypo- and hyperglycemia (Table 2). Similarly, a RCT by Lakhani *et al.*

245 [33] studied the addition of a so-called 'correctional insulin' along with the glucocorticoid to a

246 BBI regimen. The type of 'correctional insulin' matched the glycemic profile of the type of

247 glucocorticoid administered, *e.g.* NPH insulin for prednisolone or insulin glargine for

248 dexamethasone treatment [33]. 'Correctional insulin' significantly improved "time in target pre-

249 meal glucose range" defined as 5.6-10mmol/l (p=0.002) and mean daily BGL (p=0.0001), but

250 not time in "bedtime target glucose range" (p=0.09). The hyperglycemic events were reduced

251 (p<0.001). No data on subgroups without DM or with Type 1 DM as well as data on daily

252 insulin doses were given.

Anticipatory or compensatory approach to glycemic control

254 We had wanted to study whether anticipatory or compensatory adjustments are superior for

255 glycemic control. No screened or included study did address this issue. While screening articles,

256 we found some recommendations concerning this issue in guidelines [41 43-45] and reviews [2 46-49],

257 which we comment in the discussion section.

Risk of bias and grading of evidence

259 Risk of bias was assessed in five RCTs for seven domains and four outcomes (mean BGL, time

260 in target glucose, daily insulin dose and hypoglycemia) (Supplementary table 2a). All RCTs

261 were un-blinded for participants and personal. Although placebo effects are very unlikely, un-

12

262   blinding may have affected the attention of staff. This might be the most relevant risk for bias

263   in these studies. The lack of or the lack of description of random sequence generation and

264   allocation concealment might be another common bias. The three observational studies were

265   divided in low [38], middle [39] and high [40] range of risk of bias (Supplementary table 2b). The most

266   common risk of bias was the failure to control confounding.

267   Applying the GRADE criteria on each individual study, we had to decrease the level of evidence

268   for the primary outcomes "mean BGL" and "time in target glucose range" mainly because of

269   risk of bias and publication bias but also for inconsistency and imprecision in the five RCTs

270   and one observational study (Supplementary Table 3). Hence, we classified the overall quality

271   of evidence for the individual interventions as moderate [33 36 37], low [35 38 39] or very low [34 40].

DISCUSSION

273   Glucocorticoid treatment inevitably causes hyperglycemia in persons with Type 2 DM. Here,

274   we have systematically reviewed the evidence on strategies for best glycemic control in this

275   predictable and detrimental disease-disTypeease medication interaction. We found that: i)

276   Optimal insulin management in glucocorticoid-induced hyperglycemia in Type 2 DM remains

277   uncertain. We lack high quality of evidence studies to make formal and final recommendations.

278   Evidence so far is very low to moderate. ii) The studies suggest to use BBI without preference

279   for long-or intermediate-acting insulin as basal insulin but SSI to be abandoned. iii) Two studies

280   suggest that pharmacodynamic profiles of insulins should be reconciled with corresponding

281   profiles of glucocorticoids. However, there is insufficient evidence to recommend this. iv) It is

282   unclear, whether one should initiate anticipatory or compensatory insulin treatment.

283   Five open label RCTs and three observational studies included in this systematic review address

284   the issue of this review. BBI is widely accepted as intensive insulin therapy in DM. The question

285   remains, however, whether BBI performs best in Type 2 DM under glucocorticoid treatment.

286   Gosmanov *et al.* [40] shows that BBI exceeds SSI in terms of glycemic control. This is in line

287   with data showing the superiority of BBI to SSI in controlling hyperglycemia in various clinical

288   settings [27][50]. Regarding SSI, Gerards *et al.* [37] corroborates inferiority of SSI to IMI as addition

289   to routine DM regimen. Thus, SSI treatment, although very popular among non-

290   endocrinologists, should not be prescribed anymore in this setting. Nevertheless, Burt *et al.* [38]

291   found insufficient glycemic control at 5pm and 9pm with BBI with long-acting insulin in

292   persons with Type 2 DM treated with prednisolone compared to Type 2 DM without

293   prednisolone. These findings are in line with previous descriptions of afternoon and evening

294   hyperglycemia under glucocorticoids in persons without DM [22][23][51] . Thus, BBI with long-

295   acting insulin is not the ultimate solution.

14

296 NPH insulin controls afternoon peaks of blood glucose caused by glucocorticoids well [29] and

297 might have advantages over long-acting insulin because of a similar timeline of its effects to

298 glucocorticoids on hyperglycemia. Three included articles [35] [36] [39] compared NPH insulin to

299 insulin Glargine as basal insulin in a BBI treatment in a randomized controlled [36] [35] resp.

300 retrospective [39] manner and found no significant differences in glycemic control. However,

301 NPH insulin caused more hypoglycemic events when NPH and bolus insulin were administered

302 in equally divided pre-prandial doses for controlling hyperglycemia in persons given multiple

303 daily doses of glucocorticoids [36]. Such a protocol may be poorly flexible and may not

304 sufficiently consider the night-time fasting period with risk of nocturnal hypoglycemia. Insulin

305 requirement, however, was higher in BBI with long-acting insulin compared to NPH as basal

306 insulin in two studies [36] [39] but similar in the other study [35]. Addition of NPH along with the

307 glucocorticoid to BBI treatment did not improve glycemic control either [34]. The most recent

308 study by Lakhani *et al.* [33] suggests a unique approach to fit the pharmacodynamical properties

309 of insulins and glucocorticoids. This elaborated approach resulted in significantly lower mean

310 daily BGL and pre-meal time in target glucose range. This appears promising but needs

311 corroboration in a larger study.

312 We found no primary data on anticipatory versus compensatory treatment adjustments for

313 glycemic control when starting glucocorticoids. This lack of data causes partially controversial

314 expert opinions in guidelines. The American Endocrine Society Clinical Practice Guidelines [41]

315 recommends an anticipatory approach with discontinuation of OHA at the time of hospital

316 admission and initiation of insulin with persistent hyperglycemia. Exceptionally, selected

317 persons who are stable, regularly eating and have no contraindication "may be candidates for

318 continuation of previously prescribed OHA". The Canadian Diabetes Association guideline [45]

319 recommends that "glycemic monitoring for 48 hours after initiation of steroids may be

320 considered". In contrast the Joint British Diabetes Societies for inpatient care guideline [43] and

15

321 the Imperial College Clinical Guidance [44] recommend to up-titrate OHA first. They recommend

322 to add [43] or switch [44] to insulin if BGL remains above 10mmol/l. Experience or evidence to

323 suggest the use of DDP-4 inhibitors, GLP-1 receptor agonists or SGLT-2 inhibitors is missing.

324 The strength of our systematic review is the extensive literature search for a common practical

325 but unresolved problem in managing DM. Our systematic analysis also precludes premature

326 conclusions on the preferred approach to insulin therapy, *e.g.,* based on theoretical

327 considerations of pharmacodynamics or due to publication bias. The thorough evaluation of

328 evidence level indicates moderate to very low evidence for single approaches.

329 The major limitation for answering the questions raised in this study is the heterogeneity of the

330 experimental designs and the lack of highly powered, high quality studies. Populations,

331 interventions, target glucose levels and glucose monitoring all differed from study to study.

332 This permits a descriptive review only, and precludes formal recommendations. We need more

333 well-designed studies with more homogeneous patient populations. Our study has specifically

334 focused on persons with known Type 2 DM without prior insulin treatment. Still our analysis

335 centers on mixed populations, namely persons with Type 2 DM with and without prior insulin

336 treatment or Type 1 DM. Data on these subgroups are not available. It is also unlikely that a

337 'one size fits all' approach solves all challenges in all DM phenotypes.

CONCLUSION

339 Hyperglycemia in persons with Type 2 DM initiated on glucocorticoids is highly predictable.

340 Nevertheless, therapeutic strategies infrequently address glycemic control in persons started on

341 glucocorticoids in daily practice. Unfortunately, RCTs and observational studies on this topic

342 show heterogeneous approaches in diverse populations. Therefore, we were not able to conduct

343 a meta-analysis. Nevertheless, we can favor the use of a BBI regimen based on several

344 corresponding studies as the most appropriate solution in controlling hyperglycemia in persons

16

1
2
3   345   with DM initiated on glucocorticoid therapy [34 36 38-40]. Furthermore, based on two studies [33 37]
4
5
6   346   we feel that matching pharmacodynamics profiles of insulins to glycemic profiles of the used
7
8   347   glucocorticoid might be beneficial for glycemic control. Based on our systematic review, we
9
10   348   strongly support the call to action on research in inpatient DM management of The PRIDE
11
12
13   349   group [52] and to expend this to outpatient care. A concerted effort of Diabetes Societies would
14
15   350   be needed to elaborate powerful study designs taking into account different DM phenotypes,
16
17   351   settings and treatment approaches. If so, we recommend to focus on an approach adjusted for
18
19   352   insulin-glucocorticoid pharmacodynamics.
20
21
22   353
23
24

17

354 **DECLARATIONS**

355 **Competing interests**

356 The authors have no competing interests to declare.

357 **Funding**

358 SKR was supported by a personal development grant from University Hospital Zurich.

359 **Authors contributions**

360 MT drafted the study, contributed to the development of the selection criteria and data

361 extraction criteria, developed the search strategy, elaborated the study selection, data extraction

362 and data synthesis, wrote the manuscript, provided feedback and approved the final manuscript.

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

364 manuscript.

365 AN read, provided feedback and approved the final manuscript.

366 EB drafted the study, contributed to the development of the selection criteria and data extraction

367 criteria, read the manuscript, provided feedback and approved the finals manuscript.

368 SKR is the guarantor, drafted the study, contributed to the development of the selection criteria

369 and data extraction criteria, did the study selection, data extraction and data synthesis, wrote

370 the manuscript, provided feedback and approved the final manuscript.

371 **Acknowledgements**

372 We thank Martina Gosteli (MG), University of Zurich, for assistance in constructing the

373 database.

18

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

374 **Data sharing statement**

375 All available data is included into the manuscript.

19

REFERENCES

1. WHO. Global Health Report on Diabetes. 2016:1-87.

2. Gosmanov AR. A practical and evidence-based approach to management of inpatient diabetes in non-critically ill patients and special clinical populations. *Journal of Clinical & Translational Endocrinology* 2016;5:1-6. doi: https://doi.org/10.1016/j.jcte.2016.05.002

3. Wallymahmed ME, Dawes S, Clarke G, et al. Hospital in-patients with diabetes: increasing prevalence and management problems. *Diabet Med* 2005;22(1):107-9. doi: 10.1111/j.1464-5491.2004.01355.x [published Online First: 2004/12/21]

4. Hirsch IB. Sliding scale insulin--time to stop sliding. *Jama* 2009;301(2):213-4. doi: 10.1001/jama.2008.943 [published Online First: 2009/01/15]

5. Menzin J, Korn JR, Cohen J, et al. Relationship between glycemic control and diabetes-related hospital costs in patients with type 1 or type 2 diabetes mellitus. *Journal of managed care pharmacy : JMCP* 2010;16(4):264-75. doi: 10.18553/jmcp.2010.16.4.264 [published Online First: 2010/05/04]

6. Khalid JM, Raluy-Callado M, Curtis BH, et al. Rates and risk of hospitalisation among patients with type 2 diabetes: retrospective cohort study using the UK General Practice Research Database linked to English Hospital Episode Statistics. *International Journal of Clinical Practice* 2014;68(1):40-48. doi: 10.1111/ijcp.12265

7. Umpierrez GE, Isaacs SD, Bazargan N, et al. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. *J Clin Endocrinol Metab* 2002;87(3):978-82. doi: 10.1210/jcem.87.3.8341 [published Online First: 2002/03/13]

8. Pomposelli JJ, Baxter JK, 3rd, Babineau TJ, et al. Early postoperative glucose control predicts nosocomial infection rate in diabetic patients. *JPEN Journal of parenteral and enteral nutrition* 1998;22(2):77-81. [published Online First: 1998/04/07]

9. Bloom RD, Crutchlow MF. Transplant-associated hyperglycemia. *Transplantation Reviews* 2008;22(1):39-51.

10. Inzucchi SE. Management of hyperglycemia in the hospital setting. *New England Journal of Medicine* 2006;355(18):1903-11.

11. Vu K, Busaidy N, Cabanillas ME, et al. A randomized controlled trial of an intensive insulin regimen in patients with hyperglycemic acute lymphoblastic leukemia. *Clinical Lymphoma, Myeloma and Leukemia* 2012;12(5):355-62.

12. Ghisdal L, Van Laecke S, Abramowicz MJ, et al. New-onset diabetes after renal transplantation: Risk assessment and management. *Diabetes Care* 2012;35(1):181-88.

13. Fardet L, Petersen I, Nazareth I. Prevalence of long-term oral glucocorticoid prescriptions in the UK over the past 20 years. *Rheumatology (Oxford)* 2011;50(11):1982-90. doi: 10.1093/rheumatology/ker017 [published Online First: 2011/03/12]

14. Wood-Baker RR, Gibson PG, Hannay M, et al. Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. *Cochrane database of systematic reviews (Online)* 2005(1):CD001288.

15. Narwani V, Swafe L, Stavraka C, et al. How frequently are bedside glucose levels measured in hospital inpatients on glucocorticoid treatment? *Clinical Medicine, Journal of the Royal College of Physicians of London* 2014;14(3):327-28.

16. Barnett K, Mercer SW, Norbury M, et al. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *The Lancet* 2012;380(9836):37-43. doi: https://doi.org/10.1016/S0140-6736(12)60240-2

17. Van Raalte DH, Nofrate V, Bunck MC, et al. Acute and 2-week exposure to prednisolone impair different aspects of (beta)-cell function in healthy men. *European Journal of Endocrinology* 2010;162(4):729-35.

20

18. Van Raalte DH, Brands M, Van Der Zijl NJ, et al. Low-dose glucocorticoid treatment affects multiple aspects of intermediary metabolism in healthy humans: A randomised controlled trial. *Diabetologia* 2011;54(8):2103-12.

19. Geer EB, Islam J, Buettner C. Mechanisms of glucocorticoid-induced insulin resistance: Focus on adipose tissue function and lipid metabolism. *Endocrinology and Metabolism Clinics of North America* 2014;43(1):75-102.

20. Liu XX, Zhu XM, Miao Q, et al. Hyperglycemia induced by glucocorticoids in nondiabetic patients: a meta-analysis. *Annals of nutrition & metabolism* 2014;65(4):324-32. doi: 10.1159/000365892 [published Online First: 2014/11/18]

21. Vidler J, Rogers C, Yallop D, et al. Outpatient management of steroid-induced hyperglycaemia and steroid-induced diabetes in people with lymphoproliferative disorders treated with intermittent high dose steroids. *J Clin Transl Endocrinol* 2017;9:18-20. doi: 10.1016/j.jcte.2017.06.003 [published Online First: 2017/10/27]

22. Yuen KCJ, McDaniel PA, Riddle MC. Twenty-four-hour profiles of plasma glucose, insulin, C-peptide and free fatty acid in subjects with varying degrees of glucose tolerance following short-term, medium-dose prednisone (20 mg/day) treatment: Evidence for differing effects on insulin secretion and action. *Clinical Endocrinology* 2012;77(2):224-32.

23. Burt MG, Roberts GW, Aguilar-Loza NR, et al. Continuous monitoring of circadian glycemic patterns in patients receiving prednisolone for COPD. *J Clin Endocrinol Metab* 2011;96(6):1789-96. doi: 10.1210/jc.2010-2729 [published Online First: 2011/03/18]

24. Umpierrez GE, Smiley D, Zisman A, et al. Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes (RABBIT 2 Trial). *Diabetes Care* 2007;30(9):2181-86.

25. Association AD. Standards of medical care in diabetes. 2015

26. Umpierrez GE, Hellman R, Korytkowski MT, et al. Management of hyperglycemia in hospitalized patients in non-critical care setting: An endocrine society clinical practice guideline. *Journal of Clinical Endocrinology and Metabolism* 2012;97(1):16-38.

27. Roberts GW, Aguilar-Loza N, Esterman A, et al. Basal-bolus insulin versus sliding-scale insulin for inpatient glycaemic control: a clinical practice comparison. *The Medical journal of Australia* 2012;196(4):266-9. [published Online First: 2012/03/14]

28. Lepore M, Pampanelli S, Fanelli C, et al. Pharmacokinetics and pharmacodynamics of subcutaneous injection of long-acting human insulin analog glargine, NPH insulin, and ultralente human insulin and continuous subcutaneous infusion of insulin lispro. *Diabetes* 2000;49(12):2142-8. [published Online First: 2000/12/16]

29. Seggelke SA, Gibbs J, Draznin B. Pilot study of using neutral protamine Hagedorn insulin to counteract the effect of methylprednisolone in hospitalized patients with diabetes. *Journal of hospital medicine* 2011;6(3):175-6. doi: 10.1002/jhm.874 [published Online First: 2011/03/10]

30. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ (Clinical research ed)* 2015;349:g7647. doi: 10.1136/bmj.g7647 [published Online First: 2015/01/04]

31. Higgins JP, Altman D. Assessing the risk of bias in included studies. . *Higgins JPT, Green S (editors) Cochrane Handbook for Systematic Reviews of Interventions Version 510 [updated March 2011] The Cochrane Collaboration, 2011* 2011;, :33-49.

32. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology* 2011;64(4):383-94. doi: https://doi.org/10.1016/j.jclinepi.2010.04.026

33. Lakhani OJ, Kumar S, Tripathi S, et al. Comparison of Two Protocols in the Management of Glucocorticoid-induced Hyperglycemia among Hospitalized Patients. *Indian J Endocrinol Metab* 2017;21(6):836-44. doi: 10.4103/ijem.IJEM_226_17 [published Online First: 2017/12/30]

21

34. Grommesh B, Lausch MJ, Vannelli AJ, et al. HOSPITAL INSULIN PROTOCOL AIMS FOR GLUCOSE CONTROL IN GLUCOCORTICOID-INDUCED HYPERGLYCEMIA. *Endocrine Practice* 2015;22(2):180-89. doi: 10.4158/EP15818.OR

35. Radhakutty A, Stranks JL, Mangelsdorf BL, et al. Treatment of prednisolone-induced hyperglycaemia in hospitalized patients: Insights from a randomized, controlled study. *Diabetes Obes Metab* 2017;19(4):571-78. doi: 10.1111/dom.12859 [published Online First: 2016/12/21]

36. Ruiz de Adana MS, Colomo N, Maldonado-Araque C, et al. Randomized clinical trial of the efficacy and safety of insulin glargine vs. NPH insulin as basal insulin for the treatment of glucocorticoid induced hyperglycemia using continuous glucose monitoring in hospitalized patients with type 2 diabetes and respiratory disease. *Diabetes Research and Clinical Practice* 2015;110(2):158-65.

37. Gerards MC, de Maar JS, Steenbruggen TG, et al. Add-on treatment with intermediate-acting insulin versus sliding-scale insulin for patients with type 2 diabetes or insulin resistance during cyclic glucocorticoid-containing antineoplastic chemotherapy: a randomized crossover study. *Diabetes Obes Metab* 2016;18(10):1041-4. doi: 10.1111/dom.12694 [published Online First: 2016/05/19]

38. Burt MG, Drake SM, Aguilar-Loza NR, et al. Efficacy of a basal bolus insulin protocol to treat prednisolone-induced hyperglycaemia in hospitalised patients. *Internal Medicine Journal* 2015;45(3):261-66.

39. Dhital SM, Shenker Y, Meredith M, et al. A retrospective study comparing neutral protamine hagedorn insulin with glargine as basal therapy in prednisone-associated diabetes mellitus in hospitalized patients. *Endocrine Practice* 2012;18(5):712-19.

40. Gosmanov AR, Goorha S, Stelts S, et al. Management of hyperglycemia in diabetic patients with hematologic malignancies during dexamethasone therapy. *Endocrine Practice* 2013;19(2):231-35.

41. Umpierrez GE, Hellman R, Korytkowski MT, et al. Management of hyperglycemia in hospitalized patients in non-critical care setting: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2012;97(1):16-38. doi: 10.1210/jc.2011-2098 [published Online First: 2012/01/10]

42. AmericanDiabetesAssociation. Standards of Medical Care in Diabetes. *Diabetes Care* 2016;39(Suppl 1):1-119.

43. JBDS-IP JBDSfIC. Management of Hyperglycaemia and Steroid (Glucocorticoid) Therapy. *wwwdiabetologists-abcdorguk/JBDS/JBDShtm* 2014

44. Jairam Carol NO. Steroid Therapy and Management of Hyperglycaemia. 2010

45. Malcolm J, Halperin I, Miller DB, et al. In-Hospital Management of Diabetes. *Canadian Journal of Diabetes* 2018;42:S115-S23. doi: https://doi.org/10.1016/j.jcjd.2017.10.014

46. Clore JN, Thurby-Hay L. Glucocorticoid-induced hyperglycemia. *Endocr Pract* 2009;15(5):469-74. doi: 10.4158/ep08331.rar [published Online First: 2009/05/21]

47. Baldwin D, Apel J. Management of hyperglycemia in hospitalized patients with renal insufficiency or steroid-induced diabetes. *Current Diabetes Reports* 2013;13(1):114-20.

48. Suh S, Park MK. Glucocorticoid-Induced Diabetes Mellitus: An Important but Overlooked Problem. *Endocrinology and metabolism (Seoul, Korea)* 2017 [published Online First: 2017/05/31]

49. Khazai NB, Hamdy O. Inpatient Diabetes Management in the Twenty-First Century. *Endocrinology and Metabolism Clinics of North America* 2016;45(4):875-94. doi: https://doi.org/10.1016/j.ecl.2016.06.013

50. Browning LA, Dumo P. Sliding-scale insulin: an antiquated approach to glycemic control in hospitalized patients. *Am J Health Syst Pharm* 2004;61(15):1611-4. [published Online First: 2004/09/18]

51. Brady VJ, Grimes D, Armstrong T, et al. Management of steroid-induced hyperglycemia in hospitalized patients with cancer: a review. *Oncology nursing forum* 2014;41(6):E355-65.

22

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

525   52. Draznin B, Gilden J, Golden SH, et al. Pathways to quality inpatient management of hyperglycemia
526   and diabetes: a call to action. *Diabetes Care* 2013;36(7):1807-14. doi: 10.2337/dc12-2508
527   [published Online First: 2013/06/27]

23

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 glulisine, 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

24

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/d • 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

25

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'

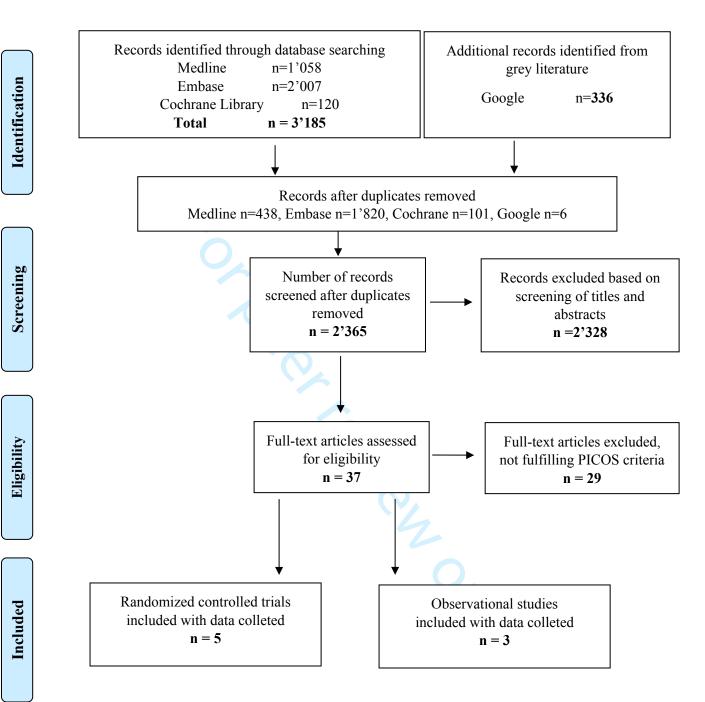[6] capillary blood glucose monitoring pre-meal and 2h post-meal

[7] all available BGL

26

FIGURE LEGEND

Fig. 1: Flow diagram of study selection

27

Figure 1:

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 fluocortolone 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.

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"

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 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) 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

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

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

Restriction to PDF Files.

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

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

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".

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.

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

For more information, visit: **www.prisma-statement.org**

PRISMA 2009 Checklist

Page 2 of 2

BMJ Open

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

SCHOLARONE™
Manuscripts

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

Milos Tatalovic[1,2], Roger Lehmann[3], Marcus Cheetham[1,4,5], Albina Nowak[3], Edouard Battegay[1,4,5], Silvana K. Rampini[1]

[1]Department of Internal Medicine, University Hospital Zurich, University of Zurich, Rämistrasse 100, 8091 Zurich, Switzerland

[2]current affiliation: Stadt Zürich Stadtspital Waid, Tièchestrasse 99, 8037 Zurich, Switzerland

[3]Department of Endocrinology, Diabetes and Clinical Nutrition, University Hospital Zurich, Raemistrasse 100, 8091 Zurich, Switzerland

[4]Center of Competence Multimorbidity, University of Zurich, Zurich, Switzerland

[5]University Research Priority Program Dynamics of Healthy Aging, University of Zurich, Zurich, Switzerland

Corresponding author: Silvana K. Rampini, Email**:** silvana.rampini@usz.ch

KEY WORDS

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

1

19 **ABSTRACT**

20 **Objectives** What is the most effective pharmacological intervention for glycemic control in

21 known Type 2 Diabetes mellitus (DM) without prior insulin treatment and newly started on

22 systemic glucocorticoid therapy?

23 **Design** We conducted a systematic literature review.

24 **Data Sources** We searched Medline, Embase, Cochrane Library databases and Google for

25 articles from 2002 to July 2018.

26 **Eligibility Criteria** We combined search terms relating to DM (patients, > 16 years of age),

27 systemic glucocorticoids, glycemic control, randomized controlled trials (RCTs) and

28 observational studies.

29 **Data extraction and synthesis** We screened and evaluated articles, extracted data, and assessed

30 risk of bias and quality of evidence, according to Grading of Recommendations assessment,

31 Development, and Evaluation (GRADE) guidelines.

32 **Results** Eight of 2'365 articles met full eligibility criteria. Basal-bolus insulin (BBI) strategy

33 for patients under systemic glucocorticoid therapy was comparatively effective but provided

34 insufficient glucose control depending on time of day. BBI strategy with long-acting insulin

35 and Neutral Protamin Hagedorn as basal insulin provide similar overall glycemic control.

36 Addition of various insulin strategies to standard BBI delivered mixed results. Intermediate-

37 acting insulin as additional insulin conferred no clear benefits and glycemic control with sliding

38 scale insulin was inferior to BBI or intermediate-acting insulin. No studies addressed whether

39 anticipatory or compensatory insulin adjustments are better for glycemic control.

40 **Conclusion** The lack of suitably designed RCTs and observational studies, heterogeneity of

41 interventions, target glucose levels, and glucose monitoring, poor control of DM subgroups,

42 and low-to-moderate quality of evidence render identification of optimal pharmacological

2

43 interventions for glycemic control and insulin management difficult. Even findings on widely

44 recommended BBI regimen as intensive insulin therapy for DM patients on glucocorticoids are

45 inconclusive. High quality evidence in studies with well-defined DM phenotypes, settings and

46 treatment approaches is needed to determine optimal pharmacological intervention for

47 glycemic control.

48 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

49 • Systematic review with extensive literature search to provide comprehensive data on a very

50   common but unresolved daily problem in managing Type 2 DM.

51 • Lack of comparability between studied populations and interventions and low to moderate

52   quality of evidence does not permit full quantitative analysis and provision of formal

53   recommendations on specific insulin regimens.

54 • Firm conclusions on optimal pharmacological interventions for glycemic control awaits

55   studies of sufficient power, quality and testing of well-defined DM phenotypes, settings and

56   treatments.

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

4

80   delayed start of insulin, when blood glucose level (BGL) exceeds normal upper limits

81   (compensatory treatment adjustment), is more effective.

5

82 **METHODS**

83 **Protocol and registration**

84 The review methods and eligibility criteria were specified in advance, documented in a study

85 protocol, registered online with the International Prospective Register of Systematic Reviews

86 (PROSPERO), May 31st 2016 (Registration Number CRD42015024739), and recorded with a

87 PRISMA statement [28]. We updated the protocol once on October 21st 2016 to broaden inclusion

88 criteria.

89 **Eligibility Criteria**

90 For eligibility, we followed the Patients, Interventions, Comparisons, Outcomes and Settings

91 (PICOS) criteria [28]. **Patients:** We included articles on non-critically ill (non-ICU) in- or

92 outpatients (> 16 years of age) who suffered from Type 2 DM treated with diet or OHA (*i.e.*,

93 biguanide, gliflozins, gliptins, sulfonylureas, glinides, incretins or glitazones) and were started

94 on a once or multiple daily oral or intravenous glucocorticoid therapy (*i.e.*, hydrocortisone,

95 prednisone, prednisolone, methylprednisolone, dexamethasone, betamethasone or

96 fludrocortisone) irrespective of the indication. **Interventions:** The articles and studies had to

97 address specific treatment interventions for glycemic control, including, for example, stop

98 routine DM medication and starting insulin treatment. **Comparisons:** We included all types of

99 comparisons of the study population with those i) without DM, ii) without glucocorticoid

100 treatment, iii) with adjusted OHA, or iv) with differing insulin treatments. **Outcomes:** We

101 accepted outcomes reflecting glycemic control, that is, time outside target glucose range, mean

102 BGL, hypo- or hyperglycemic episodes, and daily insulin dose. **Settings:** We included

103 randomized controlled trials (RCTs) and observational studies, that is, cohort studies, case-

104 control studies or cross-sectional studies, without imposing any restriction on language, country

105 of origin, or publication type. We excluded letters to the editor and conference abstracts. We

6

106 consulted also guidelines, reviews, and expert opinions. We considered only papers published

107 after 2002 because of the subsequent introduction of long-acting insulin; long-acting insulins

108 are, nowadays, an integral part of treatment in insulin dependent DM.

Search strategy

110 We identified articles based on search terms related to DM and glucocorticoids in the following

111 databases: Medline and Pre-Medline using OVID, EMBASE and Cochrane Library electronic

112 databases (Supplementary Table 1). The combined use of the databases (PubMed, Medline,

113 Embase and Cochrane) allows coverage of up to 97% of available publications [29]. To enhance

114 coverage further, we conducted also a Google search to retrieve grey literature with exclusive

115 focus on pdf-files. The search was conducted on July 8th 2016 and updated on July 2nd 2018.

Study Selection

117 MT and SKR independently screened a sample of 100 papers by studying the title and abstract

118 according to the selection criteria 'adult persons with preexisting DM that received a

119 glucocorticoid therapy'. If no abstract was available but the title appeared relevant, MT and

120 SKR reviewed the full-text. One abstract was translated from Japanese.

121 MT and SKR then evaluated the first 100 papers in consensus to establish the basis for

122 consistent screening of all further papers. MT performed the screening of all papers and SKR

123 independently double-screened a random sample of 10% of all articles. All articles were

124 assigned to one of the three eligibility groups, "Yes", "No" and "Maybe". The "Maybe" group

125 was discussed by MT and SKR for eligibility after full-text review in a consensus conference.

126 Initial review of eligible articles revealed the necessity for modification of the inclusion

127 criterion '≥ 20 mg/d prednisolone-equivalent for ≥ 5 days' to 'intermediate or high-dose

128 glucocorticoid therapy' because a large number of articles did not specify exact dosages of

129 glucocorticoids.

7

130   MT and SRK independently performed a full-text review of all eligible papers for inclusion,

131   considering the PICOS criteria. Disagreements between reviewers were resolved by consensus.

132   Finally, the reference lists of all included articles were screened for additional eligible papers,

133   guidelines, and review articles.

134   **Data extraction and quality assessment**

135   We extracted the following data from the included articles: study population, participants, and

136   age. Then, we assessed indication, dosage and duration of glucocorticoid therapy, target

137   glucose, insulin strategy, the management of OHA interruption, continuation or adjustment of

138   dosages, and outcome measures, such as, time in target glucose range, mean BGL, hypo- and

139   hyperglycemic episodes, insulin requirement. Differing assessments were discussed and

140   resolved between MT and SKR.

141   We used the Cochrane risk of bias tool [30] to evaluate the risk of bias in RCTs and applied the

142   key criteria of the Grading of Recommendations Assessment, Development and Evaluation

143   (GRADE) guidelines for observational studies to assess the methodological quality of

144   nonrandomized studies [31]. The overall quality of evidence was assessed using the GRADE

145   criteria [32].

146   **Data synthesis**

147   We performed a descriptive analysis of RCTs and observational studies. This was because the

148   lack of concordance in the study designs in the included articles precluded the performance of

149   meta-analyses. Included articles were evaluated and compared in detail and findings

150   summarized.

1
2
3   151   **Patient or public involvement**
4
5
6   152   Neither patients nor public were directly involved in the development of the research question,
7
8   153   selection of the outcome measures, design and implementation of the study, or interpretation of
9
10   154   the results.
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

9

155 **R**ESULTS

156 **Study inclusion**

157 Our initial search generated 3'521 articles. 2'365 articles remained after eliminating duplicate

158 entries. Of these, 37 qualified for full text review. Eight articles met full eligibility criteria,

159 namely, four RCTs [33-36] with open-label and parallel group design, one RCT with open-label

160 and cross-over design [37], and three observational studies [38-40] with retrospective cohort design

161 (Fig. 1 and Table 1).

162 The eight articles reported studies that included a total of 481 persons, 343/481 persons with

163 DM and 138/481 persons with glucocorticoid-induced hyperglycemia. One study included

164 persons with both Type 1 and 2 DM but did not take this distinction into consideration for

165 outcomes [33]. At least 85/481 persons had prior treatment with insulin; three studies did not

166 provide this information [33 34 39]. Seven studies included inpatients only [33-36 38-40], and one study

167 included both in- and outpatients [37]. Capillary blood glucose was measured four times a day,

168 by continuous glucose monitoring or by using all available capillary and serum blood glucose

169 readings (Table 2). The upper limit was a BGL of 10mmol/l in all studies. The lower BGL limit

170 was 3.9-4.5mmol/l in all but two studies in which it was 5.6mmol/l [33 40] (Table 2). Insulin dose

171 adjustments were applied if BGL was outside target glucose range, according to specific study

172 protocols.

173 In six studies, authors treated control groups with a basal-bolus insulin (BBI) regimen using

174 insulin glargine as basal insulin [33-36 38 39], in one study with a BBI regimen using twice-daily

175 insulin detemir [40], and one study using sliding-scale insulin (SSI) in addition to established DM

176 medication [37]. Strikingly, treatment interventions in the experimental groups diverged

177 substantially: One study compared glycemic control of BBI regimen in Type 2 DM patients

178 without prednisolone with those with prednisolone treatment [38]. Another study compared

10

179 glycemic control of BBI regimen with SSI regimen [40]. One study compared addition of SSI to

180 routine DM medication with the addition of intermediate-acting insulin [37]. Three studies

181 compared BBI regimens with long-acting insulins to BBI regimens with intermediate-acting

182 Neutral Protamin Hagedorn (NPH) insulin [35 36 39], but in one of these studies NPH was given in

183 three equal prandial doses [36]. One study compared BBI regimen with long-acting insulin to the

184 same regimen with the addition of NPH insulin [34]. Finally, the most recent study added the

185 insulin type that matched the glycemic profile of the administered glucocorticoid [33]. This

186 divergence in study designs of RCTs precluded a clean and coherent quantitative meta-analysis.

187 **BBI strategy in persons under systemic glucocorticoid therapy**

188 Two observational studies [38 40] report BBI as superior in glucocorticoid-treated Type 2 DM

189 patients [41 42]. Gosmanov *et al*. [40] found more hyperglycemic events in Type 2 DM patients under

190 dexamethasone for 3 days (for a hematologic malignancy) when treated with SSI therapy

191 compared with a BBI therapy (Table 2). In the SSI group, mean daily BGL was significantly

192 higher (p<0.001) and average insulin requirement was significantly lower (p<0.001). No

193 hypoglycemic events occurred in either groups but 3/28 (11%) persons treated with SSI were

194 referred to an intensive care unit because of hyperglycemic events.

195 Burt *et al.* [38] studied the effectiveness of a BBI regimen in hospitalized Type 2 DM patients

196 treated with prednisolone in the morning for an acute medical condition compared with those

197 without glucocorticoid treatment. Half of the calculated daily dose was given as long-acting

198 insulin Glargine at 9 pm and half as bolus evenly split into three meal dosages of rapid-acting

199 insulin with additional correctional insulin when necessary. Mean daily BGL was significantly

200 higher in the prednisolone group (p<0.001) (Table 2). More specifically, BGL was significantly

201 higher at 5 and 9 p.m. but not significantly higher at 7 and 12 a.m.. In addition, the daily insulin

202 dose was significantly higher in the prednisolone-treated group than in the control group,

11

203 especially at 12 a.m. and 5 p.m.. Thus, BBI treatment provided insufficient glucose control,

204 most notably in the afternoon and evening.

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

206 Two RCTs [36] [35] and one observational study [39] compared NPH insulin with the long-acting

207 insulin Glargine in a BBI regimen for their efficacy in controlling BGL in hospitalized persons

208 treated with medium- to high-dose glucocorticoids [36] [39]. The studies differed substantially in

209 their design (Table 1). Radhakutty *et al.* [35] included persons with or without Type 2 DM who

210 were treated with a single dose of glucocorticoids for respiratory disease or gout. Glargine was

211 administered in the control and NPH in the experimental group at 7 a.m.. Ruiz de Adana *et al.*

212 [36] studied Type 2 DM patients receiving multiple daily doses of glucocorticoids for respiratory

213 disease. The Glargine group received its basal insulin as one dose at 9 a.m. and the NPH group

214 received it before breakfast, lunch and dinner in three equal doses. Dhital *et al.* [39] retrospectively

215 studied adults treated with prednisone who were on a BBI regimen with either insulin glargine

216 or NPH. Notably, the target glucose range, the time of application and number of doses of basal

217 insulins were not indicated here, and persons with hyperglycemia without underlying Type 2

218 DM were also included.

219 All three studies show a similar overall glycemic control for NPH or Glargine as basal insulin

220 [35] [36] [39]. More specifically, the mean daily BGL and the number of mild hypoglycemic episodes

221 per day were similar (Table 2). Notably, severe hypoglycemia (BGL < 2.22 mmol/l) occurred

222 in two persons in the NPH group in the study by Ruiz de Adana *et al.* [36]. Only Dhital *et al.* [39]

223 found significantly lower daily insulin requirement in the NPH group.

Addition of insulin to established DM medication

225 Gerards *et al.* [37] compared the addition of SSI insulin compared with intermediate-acting insulin

226 (IMI) to established DM medication for glycemic control. The types of insulin were not further

12

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

227 defined. Half of the persons had prior insulin treatment. Addition of IMI resulted in significantly

228 longer time in target glucose range (p<0.001) and lower mean daily BGL (p<0.05). This was

229 achieved with an increased insulin requirement in IMI group. Remarkably, mean daily BGL of

230 both groups (SSI 13.5 ± 2.8, IMI 12.4± 2.9) were higher than in all other studies (Table 2).

231 Two RCTs added insulin to an existing BBI regimen in persons with or without Type 2 DM [33]

232 [34] (Table 1). Grommesh *et al.* [34] studied the addition of NPH insulin together with a

233 glucocorticoid to a BBI regimen. The algorithm for NPH dosing was based on glucocorticoid

234 type, dose, and pre-existing DM diagnosis. The study should that there was no advantage in this

235 for glycemic control, mean total daily insulin dose, or hypo- and hyperglycemia (Table 2).

236 Similarly, a RCT by Lakhani *et al.* [33] studied the addition of a so-called 'correctional insulin'

237 together with the glucocorticoid to a BBI regimen. The type of 'correctional insulin' matched

238 the glycemic profile of the type of administered glucocorticoid, *for example* NPH insulin for

239 prednisolone or insulin glargine for dexamethasone treatment [33]. 'Correctional insulin'

240 significantly improved "time in target pre-meal glucose range" (defined as 5.6-10mmol/l

241 [p=0.002]) and mean daily BGL (p=0.0001) but not time in "bedtime target glucose range"

242 (p=0.09). The hyperglycemic events were reduced (p<0.001). No data were provided on

243 subgroups without DM or with Type 1 DM and on daily insulin doses.

Anticipatory or compensatory approach to glycemic control

245 We aimed to determine whether anticipatory or compensatory adjustments are better for

246 glycemic control. No screened or included study addressed this issue. While screening articles,

247 we found some recommendations about this in guidelines [41] [43-45] and reviews [46-50] and we

248 address this in the discussion section.

Risk of bias and grading of evidence

250 Risk of bias was assessed in five RCTs for seven domains and four outcomes (mean BGL, time

251 in target glucose, daily insulin dose and hypoglycemia) (Supplementary Table 2a). All RCTs

252 were unblinded for participants and personal. Although placebo effects are very unlikely,

253 unblinding may have affected the attention of staff. This might be the most relevant risk for

254 bias in these studies. The lack of random sequence generation and allocation concealment might

255 be another common bias. The three observational studies were classified as having a low [38],

256 middle [39] and high [40] range of risk of bias (Supplementary Table 2b). The most common risk of

257 bias was the failure to control confounding. Notably, an overall risk of bias of an outcome for

258 all five RCTs is not so informative because the treatment interventions were not comparable.

259 Applying the GRADE criteria on each individual study, we had to decrease the level of evidence

260 for the primary outcomes "mean BGL" and "time in target glucose range." This was mainly

261 because of risk of bias and publication bias and because of inconsistency and imprecision in the

262 five RCTs and one observational study (for the overall rating of quality of evidence in RCTs

263 and observational studies, see Supplementary Table 3). Hence, we classified the overall quality

264 of evidence for the individual interventions as moderate [33,36,37], low [35,38,39] or very low [34,40].

14

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

265 **DISCUSSION**

266 Glucocorticoid treatment inevitably leads to hyperglycemia in persons with Type 2 DM. We

267 systematically reviewed the available evidence on pharmacological interventions for effective

268 glycemic control. We found, firstly, that there is some uncertainty as to the optimal management

269 of glucocorticoid-induced hyperglycemia in DM. The lack of studies reporting high quality

270 evidence makes it difficult to provide formal and final recommendations. This review shows

271 that the available evidence is of low to moderate quality. Second, the reviewed studies speak in

272 favour of the use of BBI without a specific preference for long- or intermediate-acting insulin

273 as basal insulin, but these studies do indicate that SSI should be abandoned. Third, two studies

274 suggested that pharmacodynamic profiles of insulins should be reconciled with corresponding

275 profiles of glucocorticoids. However, there is insufficient evidence to recommend this. Finally,

276 the reviewed studies do not clarify whether one should initiate anticipatory or compensatory

277 insulin treatment.

278 BBI is widely accepted and recommended as intensive insulin therapy in DM [42 51 52]. However,

279 the question remains whether BBI performs best in Type 2 DM under glucocorticoid treatment.

280 Five open label RCTs and three observational studies included in this systematic review address

281 this issue. Gosmanov et al. [40] shows that BBI is better than SSI in terms of glycemic control.

282 This is in line with data from various clinical settings that supports improved hyperglycemic

283 control using BBI compared with SSI[53 54]. Gerards et al. [37] corroborates that SSI delivers poorer

284 control compared with intermediate-acting insulin when used as an addition to the routine DM

285 regimen. Although very popular among non-endocrinologists, these findings suggest that SSI

286 treatment should not be prescribed in this setting anymore. On the other hand, Burt et al. [38] did

287 find that glycemic control was insufficient at 5 p.m. and 9 p.m. when using BBI with long-

288 acting insulin in Type 2 DM persons treated with prednisolone compared with those without

289 prednisolone treatment. These findings are in line with previous reports of afternoon and

15

290 evening hyperglycemia under glucocorticoids in persons without DM [24][27][55]. Thus, BBI with

291 long-acting insulin does not offer a final solution.

292 The intermediate-acting NPH insulin provides good control of afternoon peaks of blood glucose

293 caused by glucocorticoids. This approach might have an advantage over long-acting insulin

294 because its effects show a similar timeline to that of glucocorticoid-induced afternoon peaks of

295 hyperglycemia [56][57]. Three of the reviewed articles [35][36][39] compared NPH insulin with insulin

296 Glargine as basal insulin in a BBI treatment in randomized controlled [36][35] and retrospective [39]

297 studies, finding no significant differences in glycemic control. However, NPH insulin caused

298 more hypoglycemic events when NPH and bolus insulin were administered in equal pre-

299 prandial doses for the purpose of controlling hyperglycemia in persons receiving multiple daily

300 doses of glucocorticoids [36]. Such a protocol may not be flexible enough in that it does not give

301 sufficient consideration to the night-time fasting period and the associated risk of nocturnal

302 hypoglycemia. Insulin requirement, however, was higher in BBI with long-acting insulin

303 compared with NPH as basal insulin in two of the studies [36][39] but it was similar in the other [35].

304 The addition of NPH together with the glucocorticoid in the BBI treatment also failed to

305 improve glycemic control [34]. The most recent study by Lakhani *et al.* [33] suggests a unique

306 approach to better match the pharmacodynamical properties of insulins and glucocorticoids.

307 This resulted in significantly lower mean daily BGL and pre-meal time in target glucose range.

308 While the approach of Lakhani *et al.* [33] appears to be promising, it does need to be corroborated

309 in a larger study.

310 We found no primary data comparing anticipatory with compensatory treatment adjustments

311 for glycemic control when starting glucocorticoids. This lack of data is a source of some

312 controversial expert opinions in guidelines. The American Endocrine Society Clinical Practice

313 Guidelines [41] recommends an anticipatory approach with discontinuation of OHA at the time

314 of hospital admission and initiation of insulin with persistent hyperglycemia. In exceptional

16

315   cases, selected persons who are stable, eating regularly and have no contraindication "may be

316   candidates for continuation of previously prescribed OHA". The Canadian Diabetes

317   Association guideline [45] recommends that "glycemic monitoring for 48 hours after initiation of

318   steroids may be considered". In contrast, the Joint British Diabetes Societies for inpatient care

319   guideline [19] and the Imperial College Clinical Guidance [58] recommend the up-titration of OHA

320   first. They recommend adding [19] or switching [58] to insulin if BGL remains above 10mmol/l.

321   Reports of experience or evidence to suggest the use of DDP-4 inhibitors, GLP-1 receptor

322   agonists or SGLT-2 inhibitors is lacking.

323   The strength of our systematic review is that it makes an important contribution to DM

324   management. It does this by highlighting the unresolved challenge of good glycemic control in

325   DM patients who are on systemic glucocorticoid therapy and by reporting an extensive

326   literature search on hyperglycemic control in these patients. However, we cannot draw

327   conclusions from our systematic analysis on the most effective management approach. This is

328   largely due to the low-to-moderate quality of available evidence and the lack of comparability

329   between the reviewed studies. In fact, this review draws attention to the heterogeneity of the

330   experimental designs and the lack of well powered, high quality studies. Given that the

331   populations, interventions, target glucose levels, and glucose monitoring differed from study to

332   study, the main limitation is that we can only provide a descriptive review of the studies but not

333   formal recommendations. Well-designed studies with more homogeneous patient populations

334   are needed in order to answer the questions raised in this review. The present review focused

335   on the population of persons with pre-existing Type 2 DM without prior insulin treatment.

336   However, we included articles with mixed populations, namely persons with Type 2 DM with

337   or without prior insulin treatment and Type 1 DM, because there is an insufficient number of

338   articles with the specific sub-group of interest. We acknowledge that this is not standard

339   practice in systematic reviews.

17

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.

353 **DECLARATIONS**

354 **Competing interests**

355 The authors have no competing interests to declare.

356 **Funding**

357 No funding to declare.

358 **Authors contributions**

359 MT drafted the study, contributed to the development of the selection criteria and data

360 extraction criteria, developed the search strategy, elaborated the study selection, data extraction

361 and data synthesis, wrote the manuscript, provided feedback and approved the final manuscript.

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

363 manuscript.

364 MC contributed to the writing of the manuscript.

365 AN read, provided feedback and approved the final manuscript.

366 EB drafted the study, contributed to the development of the selection criteria and data extraction

367 criteria, read the manuscript, provided feedback and approved the finals manuscript.

368 SKR is the guarantor, drafted the study, contributed to the development of the selection criteria

369 and data extraction criteria, did the study selection, data extraction and data synthesis, wrote

370 the manuscript, provided feedback and approved the final manuscript.

371 **Acknowledgements**

372 We thank Martina Gosteli (MG), University of Zurich, for assistance in constructing the

373 database.

19

374 **Data sharing statement**

375 All available data is included into the manuscript.

20

REFERENCES

1. WHO. Global Health Report on Diabetes. 2016:1-87.

2. NHS Digital. National Diabetes Inpatient Audit (NaDIA) - 2016. 2017 doi: http://www.content.digital.nhs.uk/catalogue/PUB23539.

3. Umpierrez GE, Isaacs SD, Bazargan N, et al. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. *The Journal of clinical endocrinology and metabolism* 2002;87(3):978-82. doi: 10.1210/jcem.87.3.8341 [published Online First: 2002/03/13]

4. Hans P, Vanthuyne A, Dewandre PY, et al. Blood glucose concentration profile after 10 mg dexamethasone in non-diabetic and type 2 diabetic patients undergoing abdominal surgery. *British journal of anaesthesia* 2006;97(2):164-70. doi: 10.1093/bja/ael111 [published Online First: 2006/05/16]

5. Fardet L, Petersen I, Nazareth I. Prevalence of long-term oral glucocorticoid prescriptions in the UK over the past 20 years. *Rheumatology (Oxford, England)* 2011;50(11):1982-90. doi: 10.1093/rheumatology/ker017 [published Online First: 2011/03/12]

6. Tamez-Perez HE, Quintanilla-Flores DL, Rodriguez-Gutierrez R, et al. Steroid hyperglycemia: Prevalence, early detection and therapeutic recommendations: A narrative review. *World journal of diabetes* 2015;6(8):1073-81. doi: 10.4239/wjd.v6.i8.1073 [published Online First: 2015/08/05]

7. Van Raalte DH, Nofrate V, Bunck MC, et al. Acute and 2-week exposure to prednisolone impair different aspects of (beta)-cell function in healthy men. *European Journal of Endocrinology* 2010;162(4):729-35.

8. Van Raalte DH, Brands M, Van Der Zijl NJ, et al. Low-dose glucocorticoid treatment affects multiple aspects of intermediary metabolism in healthy humans: A randomised controlled trial. *Diabetologia* 2011;54(8):2103-12.

9. Geer EB, Islam J, Buettner C. Mechanisms of glucocorticoid-induced insulin resistance: Focus on adipose tissue function and lipid metabolism. *Endocrinology and Metabolism Clinics of North America* 2014;43(1):75-102.

10. Fong AC, Cheung NW. The high incidence of steroid-induced hyperglycaemia in hospital. *Diabetes Res Clin Pract* 2013;99(3):277-80. doi: 10.1016/j.diabres.2012.12.023 [published Online First: 2013/01/10]

11. van Raalte DH, Ouwens DM, Diamant M. Novel insights into glucocorticoid-mediated diabetogenic effects: towards expansion of therapeutic options? *European journal of clinical investigation* 2009;39(2):81-93. doi: 10.1111/j.1365-2362.2008.02067.x [published Online First: 2009/02/10]

12. Perez A, Jansen-Chaparro S, Saigi I, et al. Glucocorticoid-induced hyperglycemia. *Journal of diabetes* 2014;6(1):9-20. doi: 10.1111/1753-0407.12090 [published Online First: 2013/10/10]

13. Wallymahmed ME, Dawes S, Clarke G, et al. Hospital in-patients with diabetes: increasing prevalence and management problems. *Diabetic medicine : a journal of the British Diabetic Association* 2005;22(1):107-9. doi: 10.1111/j.1464-5491.2004.01355.x [published Online First: 2004/12/21]

14. Khalid JM, Raluy-Callado M, Curtis BH, et al. Rates and risk of hospitalisation among patients with type 2 diabetes: retrospective cohort study using the UK General Practice Research Database linked to English Hospital Episode Statistics. *International Journal of Clinical Practice* 2014;68(1):40-48. doi: 10.1111/ijcp.12265

15. Pomposelli JJ, Baxter JK, 3rd, Babineau TJ, et al. Early postoperative glucose control predicts nosocomial infection rate in diabetic patients. *JPEN Journal of parenteral and enteral nutrition* 1998;22(2):77-81. [published Online First: 1998/04/07]

16. Menzin J, Korn JR, Cohen J, et al. Relationship between glycemic control and diabetes-related hospital costs in patients with type 1 or type 2 diabetes mellitus. *Journal of managed care*

21

pharmacy : JMCP 2010;16(4):264-75. doi: 10.18553/jmcp.2010.16.4.264 [published Online First: 2010/05/04]

17. Bloom RD, Crutchlow MF. Transplant-associated hyperglycemia. *Transplantation Reviews* 2008;22(1):39-51.

18. Inzucchi SE. Management of hyperglycemia in the hospital setting. *New England Journal of Medicine* 2006;355(18):1903-11.

19. Roberts A, James J, Dhatariya K. Management of hyperglycaemia and steroid (glucocorticoid) therapy: a guideline from the Joint British Diabetes Societies (JBDS) for Inpatient Care group. *Diabetic medicine : a journal of the British Diabetic Association* 2018;35(8):1011-17. doi: 10.1111/dme.13675 [published Online First: 2018/08/29]

20. Jannot-Lamotte MF, Raccah D. [Management of diabetes during corticosteroid therapy]. *Presse medicale (Paris, France : 1983)* 2000;29(5):263-6. [published Online First: 2000/03/04]

21. Hirsch IB. Sliding scale insulin--time to stop sliding. *Jama* 2009;301(2):213-4. doi: 10.1001/jama.2008.943 [published Online First: 2009/01/15]

22. Ericson-Neilsen W, Kaye AD. Steroids: pharmacology, complications, and practice delivery issues. *The Ochsner journal* 2014;14(2):203-7. [published Online First: 2014/06/19]

23. National Institute for Health and Clinical Excellence (NICE) Clinical Knowledge Summaries: Corticosteroids - Oral. *NICE* 2012 doi: http://www.cks.nhs.uk/corticosteroids_oral

24. Yuen KCJ, McDaniel PA, Riddle MC. Twenty-four-hour profiles of plasma glucose, insulin, C-peptide and free fatty acid in subjects with varying degrees of glucose tolerance following short-term, medium-dose prednisone (20 mg/day) treatment: Evidence for differing effects on insulin secretion and action. *Clinical Endocrinology* 2012;77(2):224-32.

25. Kendall EC. Nobel lecture: The development of cortisone as a therapeutic agent. *Nobelprizeorg* 1950 doi: http://www.content.digital.nhs.uk/catalogue/PUB23539.

26. Donihi AC, Raval D, Saul M, et al. Prevalence and predictors of corticosteroid-related hyperglycemia in hospitalized patients. *Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists* 2006;12(4):358-62. doi: 10.4158/ep.12.4.358 [published Online First: 2006/08/12]

27. Burt MG, Roberts GW, Aguilar-Loza NR, et al. Continuous monitoring of circadian glycemic patterns in patients receiving prednisolone for COPD. *The Journal of clinical endocrinology and metabolism* 2011;96(6):1789-96. doi: 10.1210/jc.2010-2729 [published Online First: 2011/03/18]

28. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ (Clinical research ed)* 2015;349:g7647. doi: 10.1136/bmj.g7647 [published Online First: 2015/01/04]

29. Harris JD, Quatman CE, Manring MM, et al. How to write a systematic review. *The American journal of sports medicine* 2014;42(11):2761-8. doi: 10.1177/0363546513497567 [published Online First: 2013/08/09]

30. Higgins JP, Altman D. Assessing the risk of bias in included studies. . *Higgins JPT, Green S (editors) Cochrane Handbook for Systematic Reviews of Interventions Version 510 [updated March 2011] The Cochrane Collaboration, 2011* 2011;, :33-49.

31. Guyatt GH, Oxman AD, Vist G, et al. GRADE guidelines: 4. Rating the quality of evidence--study limitations (risk of bias). *J Clin Epidemiol* 2011;64(4):407-15. doi: 10.1016/j.jclinepi.2010.07.017 [published Online First: 2011/01/21]

32. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology* 2011;64(4):383-94. doi: https://doi.org/10.1016/j.jclinepi.2010.04.026

33. Lakhani OJ, Kumar S, Tripathi S, et al. Comparison of Two Protocols in the Management of Glucocorticoid-induced Hyperglycemia among Hospitalized Patients. *Indian journal of endocrinology and metabolism* 2017;21(6):836-44. doi: 10.4103/ijem.IJEM_226_17 [published Online First: 2017/12/30]

22

34. Grommesh B, Lausch MJ, Vannelli AJ, et al. HOSPITAL INSULIN PROTOCOL AIMS FOR GLUCOSE CONTROL IN GLUCOCORTICOID-INDUCED HYPERGLYCEMIA. *Endocrine Practice* 2015;22(2):180-89. doi: 10.4158/EP15818.OR

35. Radhakutty A, Stranks JL, Mangelsdorf BL, et al. Treatment of prednisolone-induced hyperglycaemia in hospitalized patients: Insights from a randomized, controlled study. *Diabetes, obesity & metabolism* 2017;19(4):571-78. doi: 10.1111/dom.12859 [published Online First: 2016/12/21]

36. Ruiz de Adana MS, Colomo N, Maldonado-Araque C, et al. Randomized clinical trial of the efficacy and safety of insulin glargine vs. NPH insulin as basal insulin for the treatment of glucocorticoid induced hyperglycemia using continuous glucose monitoring in hospitalized patients with type 2 diabetes and respiratory disease. *Diabetes Research and Clinical Practice* 2015;110(2):158-65.

37. Gerards MC, de Maar JS, Steenbruggen TG, et al. Add-on treatment with intermediate-acting insulin versus sliding-scale insulin for patients with type 2 diabetes or insulin resistance during cyclic glucocorticoid-containing antineoplastic chemotherapy: a randomized crossover study. *Diabetes, obesity & metabolism* 2016;18(10):1041-4. doi: 10.1111/dom.12694 [published Online First: 2016/05/19]

38. Burt MG, Drake SM, Aguilar-Loza NR, et al. Efficacy of a basal bolus insulin protocol to treat prednisolone-induced hyperglycaemia in hospitalised patients. *Internal Medicine Journal* 2015;45(3):261-66.

39. Dhital SM, Shenker Y, Meredith M, et al. A retrospective study comparing neutral protamine hagedorn insulin with glargine as basal therapy in prednisone-associated diabetes mellitus in hospitalized patients. *Endocrine Practice* 2012;18(5):712-19.

40. Gosmanov AR, Goorha S, Stelts S, et al. Management of hyperglycemia in diabetic patients with hematologic malignancies during dexamethasone therapy. *Endocrine Practice* 2013;19(2):231-35.

41. Umpierrez GE, Hellman R, Korytkowski MT, et al. Management of hyperglycemia in hospitalized patients in non-critical care setting: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2012;97(1):16-38. doi: 10.1210/jc.2011-2098 [published Online First: 2012/01/10]

42. AmericanDiabetesAssociation. Standards of Medical Care in Diabetes. *Diabetes Care* 2016;39(Suppl 1):1-119.

43. Management of Hyperglycaemia and Steroid (Glucocorticoid) Therapy. *Joint British Diabetes Societies for inpatient care* 2014

44. Carol Jairam NO. Steroid Therapy and Management of Hyperglycaemia. 2010

45. Malcolm J, Halperin I, Miller DB, et al. In-Hospital Management of Diabetes. *Canadian Journal of Diabetes* 2018;42:S115-S23. doi: https://doi.org/10.1016/j.jcjd.2017.10.014

46. Clore JN, Thurby-Hay L. Glucocorticoid-induced hyperglycemia. *Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists* 2009;15(5):469-74. doi: 10.4158/ep08331.rar [published Online First: 2009/05/21]

47. Baldwin D, Apel J. Management of hyperglycemia in hospitalized patients with renal insufficiency or steroid-induced diabetes. *Current Diabetes Reports* 2013;13(1):114-20.

48. Suh S, Park MK. Glucocorticoid-Induced Diabetes Mellitus: An Important but Overlooked Problem. *Endocrinology and metabolism (Seoul, Korea)* 2017 [published Online First: 2017/05/31]

49. Khazai NB, Hamdy O. Inpatient Diabetes Management in the Twenty-First Century. *Endocrinology and Metabolism Clinics of North America* 2016;45(4):875-94. doi: https://doi.org/10.1016/j.ecl.2016.06.013

50. Gosmanov AR. A practical and evidence-based approach to management of inpatient diabetes in non-critically ill patients and special clinical populations. *Journal of Clinical & Translational Endocrinology* 2016;5:1-6. doi: https://doi.org/10.1016/j.jcte.2016.05.002

23

528 51. Umpierrez GE, Smiley D, Zisman A, et al. Randomized study of basal-bolus insulin therapy in the
529   inpatient management of patients with type 2 diabetes (RABBIT 2 Trial). *Diabetes Care*
530   2007;30(9):2181-86.
531 52. Umpierrez GE, Hellman R, Korytkowski MT, et al. Management of hyperglycemia in hospitalized
532   patients in non-critical care setting: An endocrine society clinical practice guideline. *Journal of*
533   *Clinical Endocrinology and Metabolism* 2012;97(1):16-38.
534 53. Browning LA, Dumo P. Sliding-scale insulin: an antiquated approach to glycemic control in
535   hospitalized patients. *American journal of health-system pharmacy : AJHP : official journal of*
536   *the American Society of Health-System Pharmacists* 2004;61(15):1611-4. [published Online
537   First: 2004/09/18]
538 54. Roberts GW, Aguilar-Loza N, Esterman A, et al. Basal-bolus insulin versus sliding-scale insulin for
539   inpatient glycaemic control: a clinical practice comparison. *The Medical journal of Australia*
540   2012;196(4):266-9. [published Online First: 2012/03/14]
541 55. Brady VJ, Grimes D, Armstrong T, et al. Management of steroid-induced hyperglycemia in
542   hospitalized patients with cancer: a review. *Oncology nursing forum* 2014;41(6):E355-65.
543 56. Lepore M, Pampanelli S, Fanelli C, et al. Pharmacokinetics and pharmacodynamics of subcutaneous
544   injection of long-acting human insulin analog glargine, NPH insulin, and ultralente human
545   insulin and continuous subcutaneous infusion of insulin lispro. *Diabetes* 2000;49(12):2142-8.
546   [published Online First: 2000/12/16]
547 57. Seggelke SA, Gibbs J, Draznin B. Pilot study of using neutral protamine Hagedorn insulin to
548   counteract the effect of methylprednisolone in hospitalized patients with diabetes. *Journal of*
549   *hospital medicine* 2011;6(3):175-6. doi: 10.1002/jhm.874 [published Online First: 2011/03/10]
550 58. Jairam C, Oliver N. Steroid Therapy and Management of Hyperglycaemia. *Imperial College Clinical*
551   *Guidance NHS Trust* 2010 doi: http://www.imperialendo.co.uk/Steroids
552 59. Draznin B, Gilden J, Golden SH, et al. Pathways to quality inpatient management of hyperglycemia
553   and diabetes: a call to action. *Diabetes Care* 2013;36(7):1807-14. doi: 10.2337/dc12-2508
554   [published Online First: 2013/06/27]

24

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 glulisine, 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

25

| 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/d
• 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

26

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

FIGURE LEGEND

Fig. 1: Flow diagram of study selection

28

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Identification

Records identified through database searching
- Medline   n = 1058
- Embase   n = 2007
- Cochrane   n = 120
- **Total**   **n = 3185**

Additional records identified from grey literature

- Google **n = 336**

Screening

Records after duplicates removed
Medline n=438; Embase n=1820; Cochrane n=101; Google n=6

Number of records screened after duplicates removed
n = 2365

Records excluded based on screening of titles and abstracts
n = 2328

Eligibility

Full-text articles assessed for eligibility
n = 37

Full-text articles excluded not fullfilling PICOS criteria
n = 29

Included

Randomized controlled trials included with data collected
n = 5

Observational studies included with data collected
n = 3

Fig. 1: Flow diagram of study selection

193x198mm (300 x 300 DPI)

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 fluocortolone 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.

1

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"

2

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 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) 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

3

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

4

| 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

Restriction to PDF Files.

5

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

6

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

7

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".

8

References

1. Gerards MC, de Maar JS, Steenbruggen TG, et al. Add-on treatment with intermediate-acting insulin versus sliding-scale insulin for patients with type 2 diabetes or insulin resistance during cyclic glucocorticoid-containing antineoplastic chemotherapy: a randomized crossover study. *Diabetes, obesity & metabolism* 2016;18(10):1041-4. doi: 10.1111/dom.12694 [published Online First: 2016/05/19]

2. Grommesh B, Lausch MJ, Vannelli AJ, et al. HOSPITAL INSULIN PROTOCOL AIMS FOR GLUCOSE CONTROL IN GLUCOCORTICOID-INDUCED HYPERGLYCEMIA. *Endocrine Practice* 2015;22(2):180-89. doi: 10.4158/EP15818.OR

3. Lakhani OJ, Kumar S, Tripathi S, et al. Comparison of Two Protocols in the Management of Glucocorticoid-induced Hyperglycemia among Hospitalized Patients. *Indian journal of endocrinology and metabolism* 2017;21(6):836-44. doi: 10.4103/ijem.IJEM_226_17 [published Online First: 2017/12/30]

4. Radhakutty A, Stranks JL, Mangelsdorf BL, et al. Treatment of prednisolone-induced hyperglycaemia in hospitalized patients: Insights from a randomized, controlled study. *Diabetes, obesity & metabolism* 2017;19(4):571-78. doi: 10.1111/dom.12859 [published Online First: 2016/12/21]

5. Ruiz de Adana MS, Colomo N, Maldonado-Araque C, et al. Randomized clinical trial of the efficacy and safety of insulin glargine vs. NPH insulin as basal insulin for the treatment of glucocorticoid induced hyperglycemia using continuous glucose monitoring in hospitalized patients with type 2 diabetes and respiratory disease. *Diabetes Research and Clinical Practice* 2015;110(2):158-65.

6. Guyatt GH, Oxman AD, Vist G, et al. GRADE guidelines: 4. Rating the quality of evidence--study limitations (risk of bias). *J Clin Epidemiol* 2011;64(4):407-15. doi: 10.1016/j.jclinepi.2010.07.017 [published Online First: 2011/01/21

7. Burt MG, Drake SM, Aguilar-Loza NR, et al. Efficacy of a basal bolus insulin protocol to treat prednisolone-induced hyperglycaemia in hospitalised patients. *Internal Medicine Journal* 2015;45(3):261-66.

8. Dhital SM, Shenker Y, Meredith M, et al. A retrospective study comparing neutral protamine hagedorn insulin with glargine as basal therapy in prednisone-associated diabetes mellitus in hospitalized patients. *Endocrine Practice* 2012;18(5):712-19.

9. Gosmanov AR, Goorha S, Stelts S, et al. Management of hyperglycemia in diabetic patients with hematologic malignancies during dexamethasone therapy. *Endocrine Practice* 2013;19(2):231-35.

9

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.

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

For more information, visit: **www.prisma-statement.org**.