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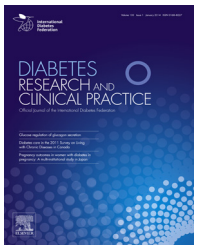

Physician's attitudes towards diagnosing and treating glucocorticoid induced hyperglycaemia: Sliding scale regimen is still widely used despite guidelines

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ABSTRACT

Aims: Treatment with glucocorticoids for neoplasms and inflammatory disorders is frequently complicated by glucocorticoid induced hyperglycaemia (GCIH). GCIH is associated with adverse outcomes and its treatment has short term and long term benefits. Currently, treatment targets and modalities depend on local protocols and habits of individual clinicians. We explored current practice of screening and treatment of GCIH in patients receiving glucocorticoid pulse therapy.

Methods: A factorial survey with written case vignettes. All vignette patients received glucocorticoid pulse therapy. Other characteristics (e.g., indication for glucocorticoid therapy, pre-existent diabetes) varied. The survey was held between November 2013 and May 2014 on 2 nationwide conferences and in hospitals across The Netherlands. Pulmonologists and internists expressed their level of agreement with statements on ordering capillary glucose testing and treatment initiation.

Results: Respondents ordered screening for GCIH in 85% of vignette patients and initiated treatment in 56%. When initiating treatment, respondents opt for sliding scale insulin in 62% of patients. Sliding scale insulin was more frequently prescribed in patients with pre-existent insulin dependent diabetes (OR 2.4, CI 1.3–4.2) and by residents (vs. specialists, OR 2.1, CI 1.2–3.5). Sixty-nine percent of clinicians experienced a lack of guidelines for GCIH.

Conclusions: Clinicians have a strong tendency to screen for GCIH but subsequent initiation of treatment was low. Sliding scale insulin is still widely used in episodic GCIH despite evidence against its effectiveness. This may be due to lacking evidence on feasible treatment options for GCIH.

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1. Introduction

Temporary high dose glucocorticoid therapy ('pulse therapy') is complicated by hyperglycaemia in 42–69% of patients [1,2]. Synthetic glucocorticoids have similar biologic activity as endogenous cortisol. Cortisol induces peripheral insulin resistance, diminishes insulin production and secretion and stimulates endogenous glucose production [3,4]. Glucocorticoids are frequently used in treatment of COPD exacerbation and autoimmune disorders and as a component of antineoplastic chemotherapy. The effect of pulse therapy on glucose metabolism is dose dependent and often transient [5,6].

Glucocorticoid induced hyperglycaemia (GCIH) is associated with adverse clinical outcomes in patients treated for COPD exacerbation, patients receiving chemotherapy and patients with other intercurrent illnesses requiring glucocorticoid therapy [7–9]. From preclinical studies, it can be hypothesized that hyperglycaemia leads to adverse outcomes by inducing a procoagulant state and impaired functioning of the immune system [10,11]. Treating in-hospital hyperglycaemia is likely to have short- and long-term beneficial effects [12,13]. However, in the absence of evidence for effective treatment regimens for GCIH episodes, current practice depends on local protocols and habits of individual clinicians.

Our aim is to explore the current practice of screening for GCIH, the intention to start treatment for hyperglycaemia and the treatment choice in patients receiving glucocorticoid pulse therapy.

2. Methods

We studied clinician's decision-making in a factorial survey [14]. We designed written case vignettes of fictive patients receiving glucocorticoid pulse therapy either as a part of chemotherapeutic regimen or as treatment for COPD exacerbation for 5–12 days.

Case vignettes varied on 8 characteristics (factors), namely age, gender, diabetes status, history of GCIH, admission status, duration of pulse therapy, glucose level before start and during pulse therapy. Combining all factors resulted in 256 case vignettes. We excluded unrealistic vignettes, ending up with 176 different vignettes. Strict control was defined as target glucose <10 mmol/l according to guidelines for non-critically ill patients [12,13].

We asked respondents to rate a random hard-copy sample of 8 different vignettes and we investigated respondents' attitudes on episodic GCIH. Response options were in multiple choice format or 1 till 6 Likert scale (Fig. 1). Applicability of the survey was evaluated by the think-aloud technique [15]. We actively recruited internists and pulmonologists on 2 nationwide conferences and in hospitals across the Netherlands.

We analysed the predictive value of vignette factors and clinician's characteristics on the respondent's decisions in an ordinal regression model. Therapy options were analysed as dummy outcome variables in a logistic regression model. Results of regression analysis are expressed as odds ratios and 95% confidence interval (OR, 95% CI). In the ordinal regression model, a higher odds ratio indicates that clinicians have a higher chance to agree with a specific decision as compared to when the predictor variable is not present. Confidence intervals were adjusted for the fact that respondents rated multiple vignettes by a generalized estimating equation. We performed all analyses in SPSS version 21 and vignettes were generated in MS Excel 2003.

3. Results

3.1. General characteristics of respondents

Between November 2013 and May 2014, we received response from 106 clinicians (70% internal medicine, 30% pulmonology, response rate 42%) from 31 different secondary and tertiary teaching hospitals. Respondents were employed in the

A 70-year old woman is hospitalized for a COPD exacerbation. As part of her treatment, she gets prednisone 60mg for 2 days and thereafter 30mg for another 8-10 days. At admission, her non-fasting glucose was 7.8 mmol/l. She is not diagnosed with diabetes. During an earlier episode of glucocorticoid pulse therapy, she had high blood glucose values.

	Strongly agree					Strongly disagree
Q1. I think that this patient will develop temporary glucocorticoid induced hyperglycaemia	1	2	3	4	5	6
Q2. I will order capillary glucose testing to diagnose temporary glucocorticoid induced hyperglycaemia	1	2	3	4	5	6

On the 2nd day of glucocorticoid treatment, the following glucose values are measured:

Fasting	Before lunch	2h after lunch
7.7	8.1	11.3

	Strongly agree					Strongly disagree
Q3. I will initiate treatment for temporary glucocorticoid induced hyperglycaemia in this patient.	1	2	3	4	5	6
Q4. Which treatment? SU / metformin / short acting insulin in fixed dose / sliding scale insulin / long acting insulin / other (specify: .....)						

Fig. 1 – Example of a written patient vignette.

Netherlands (98%) or Belgium (2%). The majority was medical specialist (65%) and others were resident (29%) or diabetes nurse (6%).

3.2. Screening

Clinicians were more likely to order capillary glucose testing for GCIH in patients with pre-existent type 2 diabetes (OR 3.5, CI 2.3–5.4), in patients with random hyperglycaemia before onset of glucocorticoid therapy (OR 2.9, CI 2.1–4.0) and in patients who were hospitalized (OR 1.7, CI 1.2–2.3) as compared to patients without these risk factors (Fig. 2). Unsurprisingly, clinicians who aimed at strict glycaemic control during glucocorticoid pulse therapy had a stronger tendency to order capillary glucose testing (OR 2.1, CI 1.5–2.9) as compared to clinicians who aimed at more lenient glucose levels. Age and sex of the patient and also former episodes GCIH did not contribute to the decision to screen for GCIH.

3.3. Augmentation of glucose lowering therapy

Fifty-five percent of respondents indicated to aim at more lenient glucose targets than advised in guidelines for glycaemic control in non-critically ill patients [12,13]. More specialists (68%) than residents (35%) indicated to aim at lenient glucose targets. Sixty-nine percent of respondents declared that there is a lack of evidence for treatment of GCIH.

In total, in 55.5% of GCIH-cases respondents intended to initiate or augment glucose lowering treatment (Fig. 3). The strongest predictor for the decision to adjust treatment for transient GCIH was the severity of hyperglycaemia in the capillary glucose curve. Twenty-two percent of all respondents started treatment for patients with a slightly elevated glucose curve, which increased to 92% for patients with the highest glucose curve. Other factors that made clinicians adjust glucose lowering treatment were being diagnosed with diabetes (OR 2.0, CI 1.4–2.9), longer duration of glucocorticoid pulse therapy (OR 1.6, CI 1.2–2.2) and being treated by a physician aiming at strict glucose levels during episodic GCIH (OR 2.0, CI 1.5–2.7). The decision whether or not to adjust treatment for episodic GCIH was not affected by admission status of the patient or the clinician's vigilance for hypoglycaemia during treatment of GCIH.

3.4. Treatment modality

If glucose lowering treatment was considered necessary, subcutaneous sliding scale insulin (SSI) with short acting insulin was chosen in 62% of the vignettes followed by oral glucose lowering agents (18%) and other insulin regimens (19%) (Fig. 4). Respondents frequently used the free text option to choose for non-pharmacologic strategies like a watch and wait policy or pulmonologists consulting an internist for treatment advice.

Within the subset of vignettes in which a treatment was prescribed, the strongest trigger to prescribe SSI instead of other treatments (i.e. other insulin regimens or oral agents) was pre-existent insulin treated type 2 diabetes (OR 2.4, CI 1.3–4.2). Hospitalization was another trigger to prescribe SSI (OR 1.9, CI 1.3–3.0). Furthermore, residents were twice more likely to prescribe SSI than specialists (OR 2.1, CI 1.2–3.5).

The clinician's concern for hypoglycaemia during treatment of episodic GCIH was not explanatory for the choice for SSI (OR 0.7, CI 0.4–1.0). We saw a trend that clinicians who said not to encounter problems with treatment of GCIH and not to experience a lack of guidelines for GCIH were more likely to prescribe SSI (OR 1.3, CI 0.9–2.0 and OR 1.6, CI 0.99–2.5).

In the group that was diabetes treatment-naïve, clinicians started oral glucose lowering agents in 31% of cases (27% metformin and 4% sulfonylurea) and that fraction of oral therapy increased when hyperglycaemia was present before onset of pulse therapy (OR 2.4, CI 1.3–4.2).

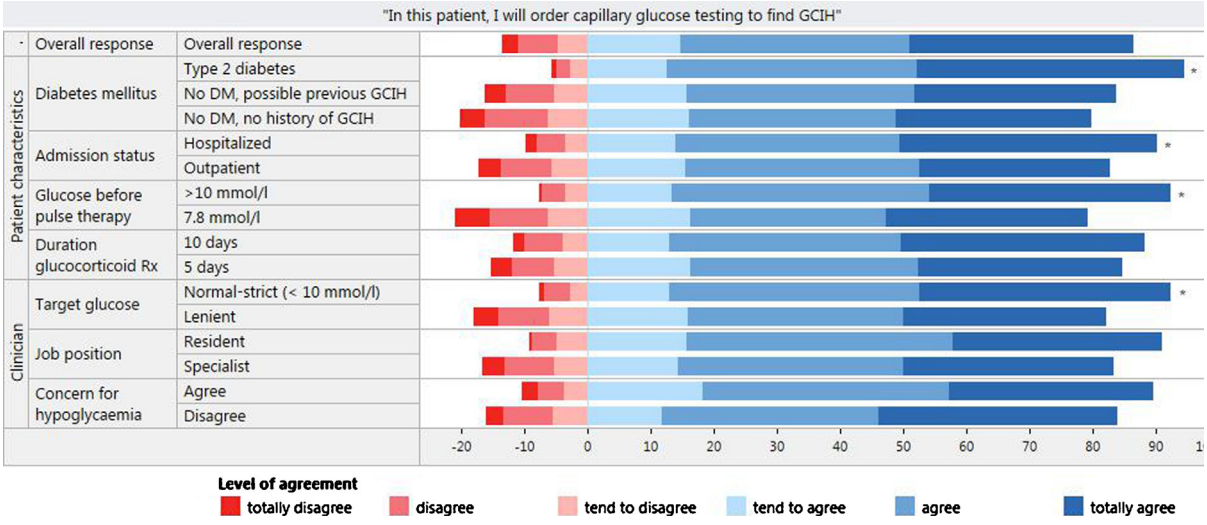

Fig. 2 – Decision to screen for GCIH. The Bars indicate the level of agreement of the clinicians with the statement to order capillary glucose testing to diagnose GCIH. The level of agreement is split up for the patient and respondent factors in the left column. A * indicates the factors that significantly influence the decision process in the multivariate ordinal regression model ($p < 0.05$).

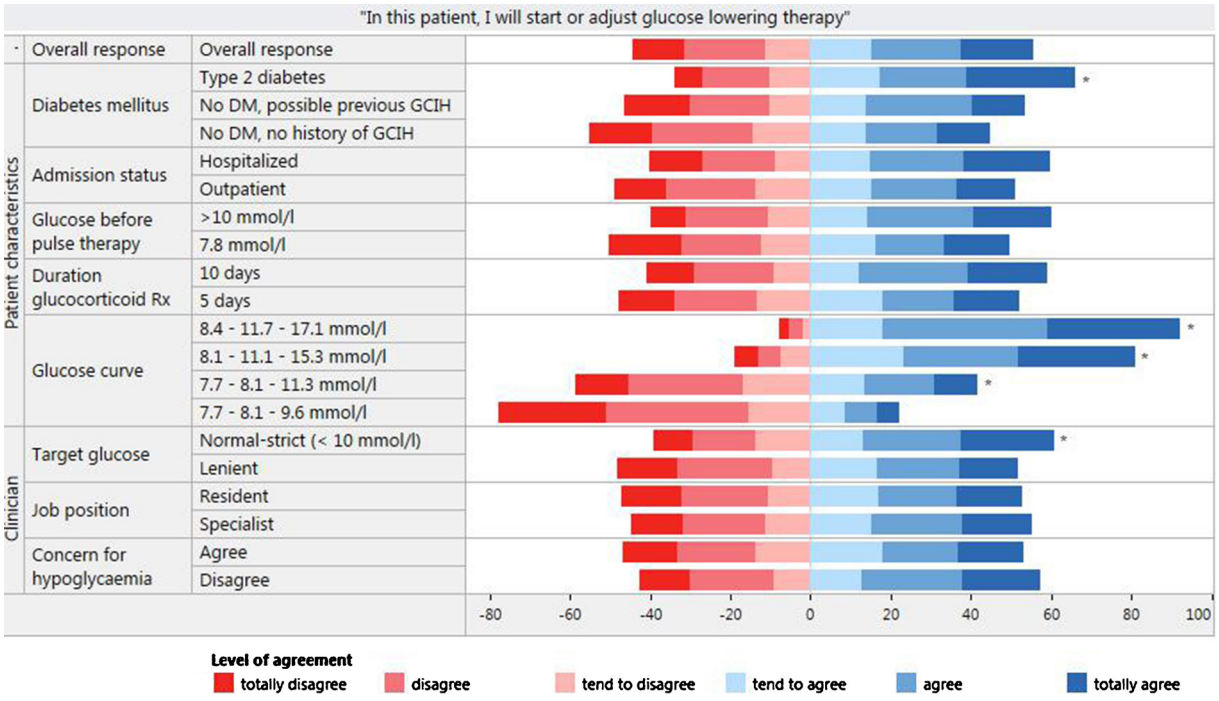

Fig. 3 – Decision to initiate treatment for GCIH. The bars indicate the level of agreement of the clinicians with the statement to start treatment for GCIH. The level of agreement is split up for the patient and respondent factors in the left column. A * indicates the factors that significantly influence the decision process in the multivariate ordinal regression model ($p < 0.05$).

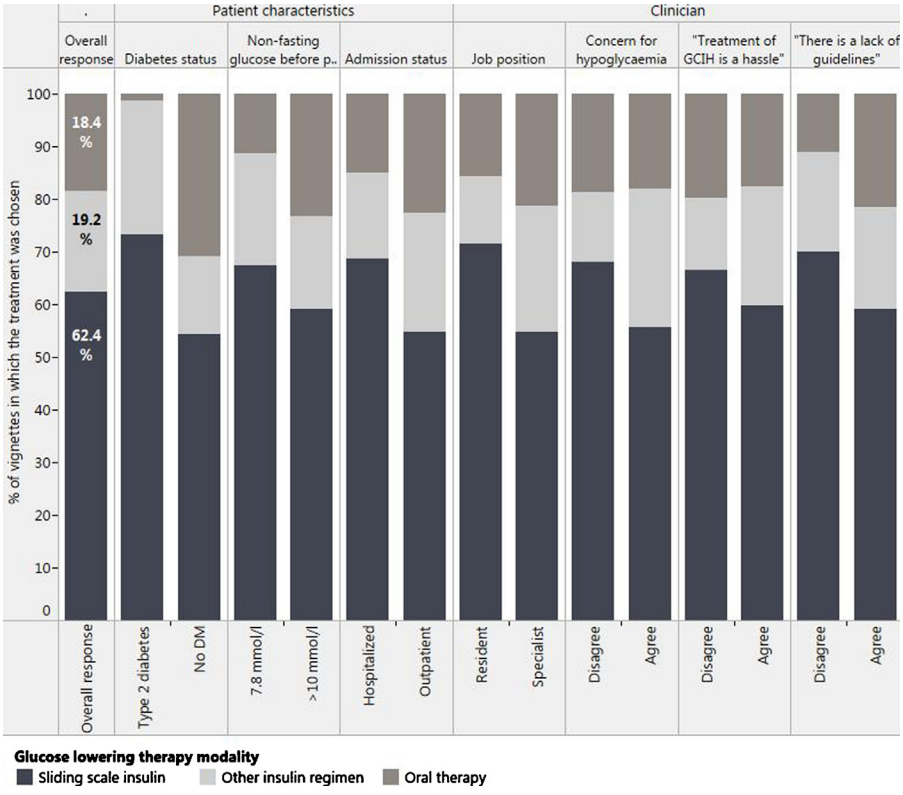

Fig. 4 – Choice of treatment type. A bar represents all respondents who choose to initiate treatment and the colors represent the fractions choosing a specific treatment modality. The different columns indicate how the choices differ for different patient and respondent characteristics.

4. Discussion

Our survey shows that SSI still is widely used in GCIH, especially in hospitalized patients treated by less experienced clinicians. We conclude that GCIH is recognized as a clinically significant condition as indicated by the high rate of screening for GCIH, but tendency to respond to transient hyperglycaemia by initiating or augmenting glucose lowering treatment was considerably lower. A factor contributing to this discrepancy may be that the majority of clinicians indicated to experience a lack of evidence for management of GCIH.

A strength of our study is the factorial survey method. Decisions in written case vignettes were shown to be representative for 'real-world' clinical practice [16]. A limitation is the response rate of 42%. Responding clinicians probably have a greater interest in the topic of GCIH as compared to non-responding clinicians. This may have resulted to a higher tendency to screen and treat GCIH than realworld practice.

A pre-existent diagnosis of diabetes mellitus was overall a strong incentive for decisions regarding screening as well as treatment of GCIH. We hypothesize that higher glucose excursions are expected in patients with diabetes that are treated with glucocorticoids. However, severe hyperglycaemia may very well occur in patients without a known diagnosis of diabetes and is more strongly associated with adverse outcomes in this group [17,18]. If clinicians initiated treatment in patients not previously diagnosed with diabetes, they had a preference for oral glucose lowering agents. This practice may reflect the chance of triggering type 2 diabetes by glucocorticoid therapy but it does not counter possible acute adverse effects of stress-hyperglycaemia [19].

The outcome that SSI is still widely used is consistent with previous findings that it is difficult to ban SSI from clinical practice [20,21]. The first study indicating that SSI insulin is not effective for improving glycaemic control originates in the 1970s and was confirmed in more recent studies [22,23]. Even SSI as add-on treatment to routine glucose lowering agents has no clear benefit above routine medication only [24]. Our finding that clinicians who declare not to experience problems with treatment of GCIH had a stronger preference for SSI supports the notion that SSI is used more to 'fix the number' instead of intending to improve patient outcomes. It indicates a certain clinical inertia for glucose management in non-critically ill patients.

A possible reason for the persistence of SSI in daily practice is the lack of evidence for alternative effective and feasible treatment options. Review articles advocate screening for GCIH in patients with and without diabetes, pursuing glucose targets <10 mmol/l, treatment with insulin but discourage SSI without basal insulin [13,20]. One study found that the insulin requirement in subjects on prednisone 60 mg per day increased by 0.35 IU/kg body weight (69% increase compared to before prednisone therapy) and these requirements are not met with most subcutaneous SSI regimens [25,26].

Most guidelines recommend to discontinue all noninsulin glucose lowering agents in GCIH and stress hyperglycaemia for safety reasons. This is unfortunate since metformin with its capacity to counter insulin resistance might especially be effective in GCIH [27]. The safety concern originates from the perceived relationship between metformin and lactic-acidosis and this perception is fed by incidental case-reports [28]. However, the incidence of lactic-acidosis during metformin is equal to other glucose-lowering treatment modalities and a causal relationship is not established [29,30]. Discontinuing metformin is not recommended in Dutch guidelines – except when there are contraindications e.g., severe kidney disease or shock – and indeed none of our respondents chose to discontinue metformin in patients diagnosed with diabetes on glucocorticoid therapy [31].

We recommend to continue routine glucose lowering agents during GCIH as long as there are no contraindications and to augment routine therapy in case of insufficient glycaemic control. Acute and chronic kidney disease should be taken into account. Metformin and sulfonylureas themselves are not nephrotoxic but accumulation of these agents may occur if the glomerular filtration rate is less than 45 mL/min. In case of severe kidney disease, oral glucose lowering agents should be discontinued or administered in a reduced dose. If glycaemic control is suboptimal under the routine agents, insulin therapy should be initiated or augmented. Depending on the level of pre-existing and increased insulin resistance during glucocorticoid pulse therapy, the extra insulin requirement varies between 0.2 and 0.5 IU/kg [26]. Following the circadian pattern of GCIH, extra insulin should be targeted at afternoon and evening hours during which hyperglycaemia is more pronounced [32]. This can be achieved by administering intermediate-long acting insulin in the morning as add-on to existing glucose lowering treatment [33–35]. Another way to cover afternoon and evening is to augment or initiate prandial insulin by 0.2–0.5 IU/kg. The distribution of extra prandial insulin over the day should be approximately 1:4:5 for breakfast, lunch and dinner. Evidence on treatment of GCIH with incretin-based therapies and SGLT-2 inhibitors is emerging and these agents may become part of the therapeutic arsenal in future [36–38].

To conclude, clinicians have a strong tendency to screen and to initiate treatment for glucocorticoid induced hyperglycaemia. However, many clinicians still opt for ineffective SSI regimens to treat glucocorticoid induced hyperglycaemia. Future studies should focus on the outcome of glucose lowering treatment and on the development of safe, efficacious and easy-to-implement treatment options, to be used when glucose lowering treatment is indicated.

Conflict of interest

The authors declare that they have no conflict of interest.

Contribution

Maaike Gerards contributed to study design, data collection, data analysis and manuscript.

E.C. Cohen Tervaert contributed to study design, data collection and data analysis.

J.B.L. Hoekstra, T.M. Vriesendorp and V.E.A. Gerdes revised and edited the manuscript.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.diabres.2015.05.040.

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