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COMMENTARY

Steroid-induced hyperglycaemia in hospitalised patients: does it matter?

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Abstract Steroid-induced hyperglycaemia is a common problem faced by endocrinologists in hospital wards. In this issue of *Diabetologia*, Popovic and colleagues (DOI 10.1007/s00125-016-4091-4) have conducted a subanalysis within a randomised controlled trial of prednisone therapy for community-acquired pneumonia. The authors found that the presence of diabetes or hyperglycaemia related to steroid therapy did not attenuate the clinical benefits of steroid therapy. The relevance and possible implications of these findings are discussed.

Keywords Blood glucose · Diabetes · Glucocorticoid · Hospitalised patient · Hyperglycaemia · Pneumonia · Prednisone · Steroid · Steroid-induced hyperglycaemia

Abbreviations

CAP	Community-acquired pneumonia
RCT	Randomised controlled trial
SIH	Steroid-induced hyperglycaemia
TTCS	Time to clinical stability

High dose glucocorticoid therapy was first shown to exacerbate hyperglycaemia in people with diabetes, or induce diabetes in some non-diabetic individualsin the 1940s. This was demonstrated shortly after the synthesis of cortisone acetate and its application in the treatment of chronic inflammatory conditions, such as rheumatoid arthritis [1]. Subsequently, the term 'steroid diabetes' was introduced, but the condition at that time was considered to be rare [2]. In the present day, however, with the widespread use of high dose steroid therapy, this has become a very common problem, particularly in hospitalised populations. In studies where glucose levels were tested systematically amongst patients treated with high dose prednisone or prednisolone in hospital, 53–70% of non-diabetic individuals developed hyperglycaemia [3, 4].

The concern regarding steroid-induced hyperglycaemia (SIH) arises from the large number of studies in a variety of clinical situations that have shown that hyperglycaemia is associated with adverse hospital outcomes. Hyperglycaemia is associated with an increased risk of infection and poor wound healing, and is proinflammatory, proapoptotic and prothrombotic [5]. A logical implication of this is that SIH may negate some of the benefits of steroid therapy on the condition for which the steroids have been administered, or predispose patients to other complications. Thus, hospitalists who are responsible for diabetes management frequently and vigorously target SIH, with the aim of minimising the immediate risks of hyperglycaemia to the patient.

A randomised controlled trial (RCT) involving patients with community-acquired pneumonia (CAP) and admitted to hospital was previously conducted [6], with the preplanned subanalysis by Popovic et al being reported in this issue of *Diabetologia* [7]. Together, this research provides some insight into the efficacy and safety of high dose steroid therapy, even when it causes or exacerbates hyperglycaemia. In this RCT, 785 individuals were randomised to treatment with 50 mg prednisone or placebo for 7 days. Prednisone-treated participants had a shorter median time to clinical stability (TTCS) vs placebo treated individuals (4.4 vs 3.0 days, hazard ratio 1.33, 95% CI 1.15–1.50, $p < 0.0001$), providing strong

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evidence for adjunctive prednisone therapy in the treatment of CAP [6].

The investigators had the foresight to include some detailed glycaemic elements in the protocol, enabling a subanalysis of the effect of prednisone therapy on and by glycaemic status [7]. The study protocol called for 4 times daily fingerstick glucose testing for all participants on days 1, 3, 5 and 7 of the trial; and on more occasions if hyperglycaemia was detected. If there was hyperglycaemia, intensification of anti-hyperglycaemia therapy was recommended, though no specific protocol was given.

As expected, patients in the prednisone group had higher mean glucose levels and higher blood glucose variability vs patients in the placebo group; this applied to the subgroup with known diabetes (10.6 ± 2.5 mmol/l vs 8.8 ± 2.1 mmol/l, $p < 0.001$) as well as non-diabetic individuals (7.6 ± 1.6 mmol/l vs 6.4 ± 1.0 mmol/l, $p < 0.001$). Hyperglycaemia (defined as the presence of at least one glucose reading >7 mmol/l preprandially or >11.0 mmol/l postprandially) was observed in 88% of diabetic and 52% of non-diabetic patients treated with prednisone. Despite experiencing hyperglycaemia, the beneficial effect of prednisone on the primary outcome of TTCS was no less for the individuals with diabetes (who accounted for 20% of the total cohort) than for the non-diabetic participants. Similarly, prednisone was as effective for individuals with admission hyperglycaemia (defined as an initial glucose level >11 mmol/l, irrespective of diabetes status) as it was for patients who were normoglycaemic on admission [7]. On regression analysis, higher glucose levels amongst prednisone-treated individuals did not negatively influence the TTCS. These are important findings, indicating that the presence of diabetes or SIH does not attenuate the benefit of prednisone therapy in this clinical situation.

Somewhat surprisingly, the amount of insulin used amongst the diabetic patients receiving prednisone was no greater than for the diabetic patients on placebo, even though they had higher mean glucose levels. Amongst the non-diabetic individuals, those treated with prednisone did receive more insulin than those on the placebo, though the actual dosage of insulin was modest (3.2 ± 18.8 units over 7 days) [7]. These insulin data, together with the fact that glucose levels were higher in the prednisone-treated participants, indicate that hyperglycaemia amongst the prednisone-treated patients was not fully addressed. Yet the benefit of steroid therapy on TTCS was maintained. This raises the question: how necessary is it to treat transient SIH?

Endocrinologists fret over elevated glucose levels and struggle valiantly to control SIH in hospital. Glucose targets of <7.8 mmol/l preprandially and <10 mmol/l at other times (as recommended by the American Association of Clinical Endocrinologist and American Diabetes Association Guidelines [8]) are often not achieved given the patient's changing clinical status and steroid dosage, and the limited opportunities for insulin dose titration within the typically short period of time that patients are in hospital. It should be noted that the evidence for these blood glucose targets is weak, with studies of tight glucose control in non-critically ill hospital patients demonstrating conflicting results [9] and an absence of RCTs of tight glycaemic control in general medical ward patients. Indirect RCT-derived support for tighter control in general wards primarily comes from the Randomized Study of Basal-Bolus Insulin Therapy in the Inpatient Management of Patients With Type 2 Diabetes Undergoing General Surgery (RABBIT 2 Surgery) which found that basal bolus insulin regimen (and thus better glucose control) resulted in a lower wound infection rate and fewer complications than sliding scale insulin, in a surgical cohort with diabetes [10].

But can the results of the RABBIT 2 Surgery study be extrapolated to medical patients with SIH? The results of the current study of prednisone therapy for CAP [7] suggests perhaps not. Its results should lead us to reconsider how aggressively we need to treat transient SIH and whether this depends on the patient's underlying condition. Our long held concerns regarding SIH may well be unfounded. Well designed RCTs targeting SIH are very much needed to answer these questions.

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