Reviewer’s report

Title: Transient symptomatic hyperglycaemia secondary to inhaled fluticasone propionate in a young child: a case report

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Reviewer: Konstantinos Samitas

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In their article Lelii et al. present an interesting and unusual case of transient hyperglycaemia in a 2-year old child being treated with inhaled fluticasone propionate (FP) for asthma. The manuscript is very well-written and of interest mainly to paediatricians and general practitioners. After thoroughly reading the manuscript I have, however, some comments regarding this case report.

First of all, it is rather unusual that a blood glucose level of approximately 180 mg/dl would result in significant glycosuria (even in children), blood alkalosis and, especially, clinical symptomatology, which is ordinarily expected over the range of 240 mg/dl.

Second and more important, as the authors readily acknowledge in the discussion, this case of symptomatic hyperglycaemia development is quite difficult to explain solely in the context of inhaled corticosteroid (ICS) treatment. Oral corticosteroid (OCS) treatment is frequently associated with dysglycemia; however, inhaled corticosteroids in general, and FP in particular, in the doses mentioned by the authors, have essentially proven to have no clinically relevant side-effects in children. The comment the authors make in the discussion that previous studies on FP safety in children have only examined the development of hypoglycaemia (and not hyperglycaemia) is not accurate; routine blood chemistry assessment and hematologic testing (that include blood glucose levels) take place in most, if not all, such studies, both in the distant (i.e. Turpeinen M et al., JACI 1991, Goldstein DE et al., Pediatrics 1983) and more recent past (i.e. Wasserman et al., Ann Allergy Asthma Immunol. 2006;96:808-818). To my knowledge, and possibly with the exception of only one study (Suissa et al., Am J Med 2010), no such events of hyperglycaemia have ever been reported merely in the context of ICS treatment without a history of diabetes. Moreover, a recent pooled analysis assessing the risk of new onset diabetes mellitus retrospectively in asthma patients >4 years old (26 trials; budesonide: n=9067; placebo: n=5926) has also not shown any differences in blood glucose levels at baseline and at the end of treatment. All these aforementioned findings do not preclude the distant possibility of such an event, however the authors should include them in the discussion and be less assertive regarding their conclusion in the abstract and discussion.

Moreover, the authors should consider the differential diagnosis for this case (i.e. diabetes mellitus, MODY etc.) and present their reasoning of exclusion (i.e. based on the negative glucose
tolerance test etc.) in a more methodical way. The fact that the patient had already received oral corticosteroids during the past year (and possibly very close to the initiation of inhaled FP - or even during FP treatment that was not reported by the parents) and that no baseline blood glucose or HbA1c levels were measured before inhaled FP initiation is a concern. Glycated hemoglobin levels are reported as normal in the case report; however, no absolute value is given. It is possible that these levels would be on the higher normal range prior to the initiation of FP (i.e. due to recent OCS treatment) or at the end of inhaled FP treatment, as HbA1c has been found to be marginally higher in children with asthma receiving ICS as compared to the controls (Yücel O et al., Indian Pediatr 2009). The lack of a baseline value makes it impossible to draw any conclusions and this should be noted.

Finally, although the term "hyperglycaemia" has been used throughout the manuscript, the authors have used "hyperglicemia" in the article's title, which is probably an orthographical error and should be corrected.

Are the methods appropriate and well described?  
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?  
If not, please specify which controls are required in your comments to the authors.

Unable to assess

Are the conclusions drawn adequately supported by the data shown?  
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No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?  
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Not relevant to this manuscript

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