Reviewer's report

Title: Depression, Smoking, Physical Inactivity and Season independently associated with Midnight Salivary Cortisol in Type 1 Diabetes

Version: 2

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Reviewer: NICHOLAS MEZITIS

Reviewer's report:

Depression, Smoking, Physical Inactivity, and Season Independently Associated with Midnight Salivary Cortisol in Type 1 Diabetes

Melin EO, Thunander M, Landin-Olsson M, Hillman M, Thulesius HO

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The HPA axis and cortisol secretion express a circadian rhythm entrained to the local environment through a variety of local cues (‘zeitgebers’), the most important of which is daylight. Artificial light of specific wavelengths, supratentorial perturbations, chemical stimulants and medications also influence cortisol secretion.

The present study addresses cortisol (MSC) levels of patients with diabetes mellitus in the context of specific behaviors. Additional conclusions are drawn based on the season during which samples were collected.

The following points should be clarified:

1. The total number of patients screened (196 + 85) should be stated, with an explanation for why such a large number ‘dropped out’ of the study after having presumably signed informed consent for participation

2. How many of the 85 ‘dropouts’ were on antidepressants or had a psychiatric diagnosis?

3. Patients receiving antidepressants (13) were grouped with those identified as depressed based on HADS-D questionnaire, who were not taking medication for this problem (7). It is important to distinguish MSC levels corresponding to these two groups separately, as antidepressant use.

4. MSC levels were collected once for each participant, but these collection dates varied over the course of the year. Were subjects with specific characteristics (e.g. smoking, physically active etc.) clustered in particular seasons for their sampling?

5. The hours of daylight in the Nordic countries vary widely according to season and in a study on cortisol this issue should be addressed in the discussion at least.
6. Reference studies on MSC collection allow for 5-6 hrs of fasting prior to sampling. The present study considered 30 minutes an adequate interval before sampling, yet subjects were advised not to brush their teeth 60 minutes before sampling. Does this imply that food remnants could have been in the oral cavity during sampling?

7. How was the diagnosis of Type 1 diabetes mellitus confirmed?

8. The frequency of hypoglycemia episodes was not addressed, yet this is a major factor generating both a stress response and depression in this population.

9. The stratification of groups is confusing with one group (34) featuring all risk factors, a reference cohort (137) without risk factors, and mention made of a third (?) group (45) with at least one risk factor.

10. Waist circumference was measured, but MSC results are not reported in relationship to abdominal obesity.

In summary, the subject is complex and although the topic and the information collected are important, the text of this submission must be revised with focus on clarity and brevity.