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RESEARCH LETTER

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Adrenal insufficiency treated with conventional hydrocortisone leads to elevated levels of Interleukin-6: a pilot study

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Adrenal insufficiency is a rare disease with an estimated prevalence of 100–126 cases per million for primary adrenal insufficiency (PAI) and 450 cases per million for secondary/tertiary adrenal insufficiency (SAI/TAI) [1, 2]. Glucocorticoid replacement therapy (GRT) is the gold standard and only viable treatment for AI [3]. The present guideline on PAI recommends the use of hydrocortisone (HC) or prednisolone for GRT [3]. However, currently used GRT regimens inadequately mimic the physiological rhythm of endogenous cortisol secretion leading to temporary hypercortisolism and hypocortisolism [4]. The consequences of these conditions are not completely understood but may be associated with deleterious effects on body composition [5]. In fact, patients with AI on GRT have an increased cardiovascular and cerebrovascular mortality [6, 7].

Since inflammation is known to have a role in the pathogenesis of cardiovascular diseases, measurement of inflammatory markers has been suggested for risk assessment. Atherosclerosis is a chronic inflammatory disease with IL-6 as a main player in the vascular inflammatory cascade. Only few data are available about IL-6 in patients receiving GRT. Previous studies have shown an increased secretion of IL-6 and to a lesser extent of TNF-α and IL-1 in patients with hypocortisolism [8–10]. Higher serum levels of IL-6 may lead to increased cardiovascular risk (CVR) and overall mortality from cardiovascular disease [11, 12].

Aim of this pilot study was to evaluate inflammatory markers in AI patients treated with conventional HC replacement therapy. In particular, elevation of IL-6 and the time of increase were assessed in a clinical setting.

Material and methods

Ten patients with either PAI or SAI receiving HC replacement therapy were included in this study (PAI 7, SAI 3). Eight patients were female and two were male. Mean age was 53.4 years (range: 28–69), mean HC dose was 27 mg/d (range: 15–42.5).

Over the course of 2 days, cortisol and IL-6 profiles were analyzed in AI patients and compared to healthy controls. The control group was comparable with respect to age, weight, and sex.

Blood was drawn at 12:00, 15:00, 18:00, 21:00, 24:00 h on the first day and at 06:00 h (before HC intake), 08:45 h (after HC intake and before stress ECG), 09:15 h (after stress ECG), 10:00, 11:00, 12:00, and 15:00 h on the second day. Cortisol levels were analyzed using a chemiluminescence test (Centaur XP; Siemens Healthcare Diagnostics) and IL-6 was analyzed with flow cytometry (BD Facscanto II; BD). A cardiopulmonary stress test (GE eBike L GE Healthcare) was performed on the second day to induce stress. Study exclusion criteria were systemic inflammatory disorders, acute myocardial infarction and structural or valvular heart disease.

The study protocol was approved by the Ethics Committee of the University of Lübeck, Germany (AZ: A 171/07). Informed consent was obtained from all study participants.

Data are expressed as mean ± standard deviation. Results were compared using the unpaired t test. Statistical analysis was performed and figures created using GraphPad Prism 8. A p value of less than 0.05 was considered significant.

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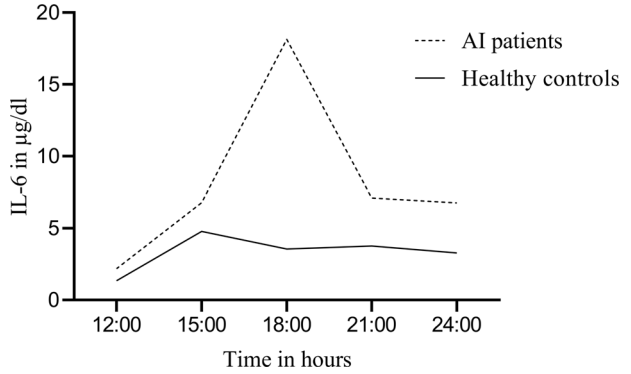

Fig. 1 Circadian increase of IL-6 in AI patients vs. healthy controls during the first day

Results

A total of ten AI patients and five healthy controls were included in this study. Overall, patients with PAI and SAI showed significantly higher levels of IL-6 over the course of 2 days (mean IL-6 AI group: 8.4 µg/dl (SD: ± 3.7) vs. healthy controls 5.46 µg/dl (SD ± 2.1); $p = 0.0189$). During the first day, IL-6 levels increased toward the evening and night in AI patients while a decrease of IL-6 was noted in healthy controls (Fig. 1). At midnight of the first day AI patients had higher levels of IL-6 than healthy controls (mean IL-6 AI: 6.77 µg/dl (SD ± 4.06) vs. healthy controls: 3.28 µg/dl (SD ± 2.19); $p = 0.09$). Mean cortisol was higher in patients with PAI/SAI compared to healthy controls (mean cortisol AI group: 9.34 µg/dl (SD ± 9.28) vs. healthy controls: 7.62 µg/dl (SD ± 4.21); $p = 0.5367$).

In the early morning of the second day (before HC intake) patients with both PAI and SAI had significantly lower levels of cortisol compared to the healthy controls (mean cortisol at 645 h: 1.42 µg/dl (SD ± 1.83) vs. 12.28 µg/dl (SD ± 2.80); $p \leq 0.0001$). Subsequently, serum cortisol levels rapidly rose to much higher levels in AI patients after the intake of HC while measured against healthy individuals (mean cortisol at 8:45 h: 29.70 µg/dl vs. 12.58 µg/dl; $p = 0.0067$).

Of interest, AI Patients showed a more rapid decrease in cortisol levels after the induction of physical stress using a cardiopulmonary exercise test than healthy controls. At the end of the second day of testing (1500 h) AI patients showed higher levels of IL-6 after the induction of physical stress at 8:45 h compared to the healthy controls (mean IL-6 AI: 9.69 µg/dl (SD ± 6.35) vs. healthy controls: 5.96 µg/dl (SD ± 4.04); $p = 0.26$).

Discussion

Our data suggest that there is an association between hypocortisolism and elevated IL-6 levels in AI patients treated with conventional HC substitution compared to healthy controls. For the past decades AI has been treated with GRT, in most cases with HC taken twice or thrice daily [13]. In recent years, newly developed dual-release HC formulas have been introduced to avoid rapid rises in cortisol levels in AI patients and to prevent temporary hypocortisolism with respect to circadian rhythm [14]. In a study by Isidori et al. [15] (DREAM study) switching to a dual-release HC lead to improved immune cell profiles, higher quality of a life and reduced susceptibility to infections.

Regarding IL-6 levels, more than two decades ago, Papanicolou et al. showed an inverse proportionality between preoperative and postoperative cortisol and IL-6 levels in patients with Cushing's disease [9]. Our data demonstrate a significant difference in IL-6 levels over the course of 2 days between AI patients and healthy controls in a clinical setting. Decreases in cortisol and a subsequent increase of IL-6 especially regarding circadian rhythm in AI patients may deliver a hint as to why AI patients suffer from higher cardiovascular risk and overall mortality.

Ridker et al. [16] conducted a case-control study among 28,263 healthy postmenopausal women showing a significant association between IL-6 and cardiovascular events. In fact, IL-6 blockade may reduce cardiovascular risk [17].

The induction of stress using a cardiopulmonary exercise test lead to a delayed increase in IL-6 after an initial rapid decrease of cortisol in AI patients. This is in accordance to Brydon et al. [18] who showed a delayed increase and variable peak levels of IL-6 after stress induction in 38 healthy males depending on socioeconomic status. Similar results were described by von Kaenel et al. with a peak IL-6 increase 105 min after stress induction in 21 healthy men using the trier social stress test [19]. Our results indicate that during stressful events additional doses of GC may be taken shortly *after* physical or mental stress is induced.

Our study may be limited by the low number of participants and heterogeneity of the AI group, but results were consistent and comparable. Follow-up studies on this subject could include a comparison between IL-6 levels using, e.g., dual-release HC and conventional HC in AI patients. Furthermore, IL-6 levels could be assessed in AI patients taking an HC stress dose immediately after stress induction.

In conclusion, our data show that inflammatory markers such as IL-6 may contribute to the observed increased CVR in AI. New therapeutic options should consider this mechanism when targeting to improve GRT.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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