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Quality of life in patients with adrenal insufficiency correlates stronger with hydrocortisone dosage, than with long-term systemic cortisol levels

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ABSTRACT

In patients with adrenal insufficiency (AI) a higher hydrocortisone intake has been associated with more impairment in quality of life (QoL). Irrespective of age, sex and severity of AI the dosage of hydrocortisone is titrated around 20 mg/D in all patients with AI based on physical and mental signs and symptoms. However, until now it is unknown whether these QoL impairments are related to increased systemic cortisol exposure. Measurement of hair cortisol levels ($CORT_{hair}$) can be used to assess chronic systemic cortisol exposure. This study aimed to explore whether QoL in patients with AI is associated with $CORT_{hair}$ and daily hydrocortisone intake. We performed a cross-sectional study in 120 patients with AI on stable hydrocortisone replacement, in whom hair samples and QoL data were collected. $CORT_{hair}$ were measured with ELISA, and QoL was assessed with validated questionnaires (SF-36, EQ-5D, HADS, MFI-20). Patients reported impairments in 14 of 15 QoL subscales ($p < 0.001$). More impairments in physical aspects of QoL correlated with higher $CORT_{hair}$ and higher daily hydrocortisone intake ($p < 0.05$), an effect that was more pronounced in female patients. Regression analyses including both $CORT_{hair}$ and hydrocortisone intake revealed a significant negative contribution of higher hydrocortisone intake on physical aspects of QoL ($p \leq 0.046$), whereas no significant contribution was found for $CORT_{hair}$.

The present study showed that patients with AI report several impairments in QoL which are associated with hydrocortisone intake, and to a lesser extent reflected by chronic systemic cortisol exposure as measured by hair cortisol. This suggests that QoL impairments in patients with AI are not per se the effect of prolonged exposure to elevated systemic cortisol levels.

1. Introduction

Adrenal insufficiency (AI) is treated with glucocorticoid replacement therapy, usually 20–30 mg of hydrocortisone daily, divided in three dosages (10–15 mg in the morning, 5–10 mg in the afternoon, 4–5 mg in the evening), in order to mimic the natural circadian secretion of cortisol (Gardner and Shoback, 2011). However, even when patients with primary AI are in a stable medical condition, they report impaired quality of life (QoL) (Alonso et al., 2004; Bleicken et al., 2008; Hahner et al., 2007; Joustra et al., 2014; Tiemensma et al., 2014). In addition, in patients with secondary AI due to pituitary disease, hypopituitarism was found to be an important predictor of QoL impairments (Andela et al., 2015a; van Aken et al., 2005; Wagenmakers et al., 2012). It has been suggested that these QoL impairments are associated with intrinsic imperfections in glucocorticoid replacement therapy, and therefore, it is advised that hydrocortisone replacement should be individualized (Romijn et al., 2003). For instance, there is large individual variation in sensitivity to cortisol, which is partly explained by polymorphisms of the glucocorticoid receptor gene (van Rossum and Lamberts, 2004). However, determining an optimal hydrocortisone replacement dose is complicated by the lack of reliable chronic parameters, and as a result many patients may be chronically under- or overtreated with potential paramount consequences for well-being and health.

Until now, it is not well established whether QoL is affected by the degree of cortisol exposure (i.e., adequacy of

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hydrocortisone replacement) in patients with AI. In a single study, authors investigated plasma cortisol day curves and well-being in a small sample of seven patients with AI and demonstrated that subphysiological cortisol levels correlated with lower well-being (Groves et al., 1988). Other studies examined the relation between the dosage and intake scheme of glucocorticoid replacement therapy and QoL, and demonstrated that in patients with AI, QoL was inversely correlated with the hydrocortisone dose (Bleicken et al., 2010; Tiemensma et al., 2014).Importantly, associations between hydrocortisone intake and QoL do not provide any information about causality, since it might be that high cortisol levels cause QoL impairments, but it might also be that patients with worse QoL need more hydrocortisone.

Addressing this relationship is further complicated by the difficulty of adequately measuring cortisol levels throughout the day, since cortisol levels vary depending on different treatment regimens (i.e., varying hydrocortisone doses, as well as differences in timing, absorption, and metabolism of hydrocortisone), and currently available cortisol measurements (i.e., plasma, urinary, salivary) are limited to short-term assessments.

A promising method to assess cortisol for prolonged periods of time is the analysis of cortisol levels in scalp hair ($CORT_{hair}$) (Manenschijn et al., 2011; Wennig, 2000). We (and others) recently assessed the use of this measure in AI patients treated with exogenous hydrocortisone. Patients with AI have increased levels and hydrocortisone intake has been found to correlate with $CORT_{hair}$ (Gow et al., 2011; Staufenbiel et al., 2015). A significant gender effect has been reported in $CORT_{hair}$ in patients with AI treated with glucocorticoid replacement therapy, with male patients demonstrating higher $CORT_{hair}$ than females while using the same dose of hydrocortisone (Gow et al., 2011; Staufenbiel et al., 2015).

In the present study, we aimed to explore whether $CORT_{hair}$ is correlated with QoL. We first compared QoL in patients with stable treatment for AI with QoL in healthy controls. Second, we examined potential correlations between QoL, $CORT_{hair}$, and daily hydrocortisone intake as another parameter to assess cortisol exposure.

2. Patients and methods

2.1. Patients

Scalp hair samples were collected of 132 patients with primary or secondary AI on hydrocortisone replacement from the Endocrinology out-patient clinic of the Leiden University Medical Center (cohort previously described in (Staufenbiel et al., 2015)). Of this group, nine patients did not fill out QoL questionnaires and three patients filled out less than 75% of the questionnaires and were therefore excluded from the analysis. Thus, 120 patients with longstanding AI on a stable dose were included in the present study. Primary AI had been diagnosed by very low early morning cortisol concentrations (<120 nmol/l) or insufficient stimulation following ACTH test (below 550 nmol/l) usually in the presence of positive adrenal auto-antibodies or an alternative explanation. Secondary adrenal insufficiency was preferably diagnosed using an insulin tolerance test, or if contra-indicated, a CRH test using the same cut-off as for ACTH stimulation. Pituitary hormone replacement was prescribed dependent on the results of the annual evaluation of pituitary functions. In case of AI, hydrocortisone was prescribed (usually 20 mg per day divided into three dosages, adjusted at the discretion of the treating physicians) together with the advice to increase the hydrocortisone dose in case of exposure to severe somatic and psychological stressors.

Comparison QoL data of 437 healthy controls were derived from a previous study from our department (van der Klaauw et al., 2008).

The local ethics committee approved this study. All patients gave written informed consent.

2.2. QoL assessment

QoL was assessed with the following four validated questionnaires:

The *Short-Form 36* (*SF-36*) assesses functional status and general well-being and consists of 36 items covering nine health concepts: 1) physical functioning, 2) social functioning, 3) role limitation (physical), 4) role limitation (emotional), 5) mental health, 6) vitality, 7) pain, 8) general health perception, and 9) general perception of change in health. Scores are expressed on a 0–100 scale, and higher scores indicate better QoL (Ware and Sherbourne, 1992).

The *EuroQoL-5D (EQ-5D)* assesses the current health status reflected in five health dimensions; 1) mobility, 2) self-care, 3) usual activities, 4) pain/discomfort, and 5) anxiety/depression. Scores are expressed on a 1–3 scale per dimension, with higher scores indicating worse QoL. Also a visual analogue scale is included ranging from 0 to 100 for recording an individual's rating for their current health-related well-being, with higher scores indicating a better health status (EuroQoL group, 1990).

The *Hospital Anxiety and Depression Scale (HADS)* assesses both anxiety and depressive symptoms and consists of 14 items on a 4-point scale. Higher scores indicate more severe anxiety and depressive symptoms (Snaith and Zigmond, 1986; Spinhoven et al., 1997).

The *Multidimensional Fatigue Inventory (MFI-20)* consists of 20 statements assessing fatigue on a five-point scale covering five dimensions; 1) general fatigue, 2) physical fatigue, 3) reduced activity, 4) reduced motivation, and 5) mental fatigue. Scores vary from 0 to 20; with higher scores indicating greater fatigue (Smets et al., 1995).

2.3. QoL of healthy controls

QoL data of healthy controls were previously collected at our department (van der Klaauw et al., 2008). The EuroQoL-5D and two subscales of the Short-Form 36 (i.e., mental health, vitality) were not assessed in this group of healthy controls. QoL data of 437 healthy controls (136 males) with a mean age of 50.9 ± 13.6 years were available and the total group was used for comparison.

2.4. Hair collection, preparation, and analysis

A lock of approximately 150 hairs from the posterior vertex was cut as close to the scalp as possible. The hair samples were taped to paper and stored in the dark at room temperature until further analysis. One cm represents the average cortisol concentrations of one month (Wennig, 2000), since it is assumed that hair grows one cm per month, with a range of 0.6–1.4 cm/month (Pragst and Balikova, 2006).

Hair samples are specifically taken from the vertex region of the scalp because its most uniform growth pattern and phase (Bost, 1993; Harkey, 1993), and importantly, has been specifically been validated for cortisol with the lowest mean coefficient of intra-individual variation (Sauve et al., 2007). For analyses, the most proximal 3 cm of hair was used, corresponding to the most recent 3 months. A minimum of 10 mg of hair was weighed and cut into small pieces. For extraction, 1 mL of methanol was added and the samples were incubated for 16 h at 52 °C. After extraction, the methanol was transferred to another vial and evaporated under a constant stream of nitrogen. The samples were dissolved in 250 μL of phosphate buffered saline (PBS, pH 8.0). A commercially available ELISA Kit for salivary cortisol (DRG GmbH, Marburg, Germany) was used to measure cortisol levels. The procedure has been described