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Cortisol and testosterone in hair as biological markers of systolic heart failure

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Summary
Background: Congestive heart failure (CHF) is associated with increased stress and alterations in metabolism, favoring catabolism over anabolism. Hormonal profiles of patients with heart failure have been assessed using serum and saliva as matrices, which are only point measurements and do not provide long-term information. Scalp hair is a novel matrix that allows for measurement of hormones over a period of several months.
Patients and methods: We aimed to evaluate whether levels of cortisol and testosterone and their ratio (C/T) in hair correlate with severity of heart failure. We conducted a prospective study in ambulatory male patients with a left ventricular ejection fraction (LVEF) $\leq$ 40%. Hormone levels were measured using immunoassays in the proximal 2 cm of hair (representing approximately two months of systemic hormone exposure). Primary endpoints included the correlation of hair cortisol, testosterone, and C/T levels with the New York Heart Association (NYHA) class, LVEF, exercise capacity and NT-proBNP.
Results: The 44 CHF patients had a median hair level (range) of cortisol of 207 (117.7—1277.3) ng/g. Hair cortisol levels correlated positively with NYHA class ($r = 0.48$, $p = 0.001$) and negatively with treadmill stress test performance, ($r = -0.37$, $p < 0.05$). The hair testosterone was 5.17 (2.39—24.64) ng/g and the C/T ratio was 39.89 (12.98—173.73). No associations were found between hair testosterone and C/T ratio and heart failure severity; however, the C/T ratio was higher in patients who required a CHF-related hospitalization than in patients who did not require this in the year following the inclusion in the study.

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Conclusions: Hair cortisol levels correlate with heart failure severity as assessed by the NYHA class and exercise capacity, while hair testosterone and C/T levels do not correlate with heart failure severity.

1. Introduction

Progression of chronic congestive heart failure (CHF) is associated with activation of neuro-endocrine stress response systems including the hypothalamic–pituitary–adrenal axis that modulates the production and secretion of glucocorticoids including cortisol from the adrenal cortex (Güder et al., 2007; Brotman et al., 2007). The prognostic value of serum cortisol levels has been evaluated in a single large study of patients with chronic heart failure who were admitted to hospital due to various causes (Güder et al., 2007). This study demonstrated that higher serum levels of cortisol were independent predictors of increased mortality risk. However, it is possible that the single serum cortisol measurement may have been influenced by the physical stress due to the acute illness and/or the emotional stress associated with the admission itself.

Furthermore, deficiency of anabolic sex steroids is common among patients with CHF, affecting up to two thirds of patients (Moriyama et al., 2000; Jankowska et al., 2006). Several studies have demonstrated that in patients with CHF, a low serum testosterone is an independent predictor of mortality (Jankowska et al., 2006; Güder et al., 2010; Wehr et al., 2011). Furthermore, low serum testosterone has been correlated with other poor prognostic factors of heart failure including lower left ventricular ejection fraction (LVEF) (Jankowska et al., 2006), poor exercise capacity (Jankowska et al., 2009; Pastor-Pérez et al., 2011), high New York Heart Association (NYHA) class (Jankowska et al., 2006; Güder et al., 2010) and increased levels of NT-proBNP (Jankowska et al., 2006, 2009).

Additionally, the ratio of catabolic to anabolic steroid hormones, as measured by serum cortisol over dehydroepiandrosterone (DHEA) ratio, was higher in patients with CHF compared to control patients (Anker et al., 1997). Further, the Caerphilly study found a positive linear association between the serum C/T ratio and future incident ischemic heart disease (Smith et al., 2005). While these studies were well designed, they all share the same limitation – the assessment of hormone levels was based on a single measurement. Given the level of intra-individual variability in hormone levels, one serum sample may not be sufficient to characterize an individual's hormone levels (Smith et al., 2005; Brambilla et al., 2007, 2009).

Cortisol and testosterone are typically measured in blood, urine, or saliva; however, these matrices only provide systemic hormone exposure over a period of 24 h or less, are subject to diurnal variation (blood and saliva), can be invasive, and may require repeated measurements. The measurement of these hormones in scalp hair is a novel method allowing retrospective assessment of average cortisol and testosterone exposure over a period of several months using only a single sample collection. Hair grows approximately 1 cm per month and therefore hair analysis reflects long-term endogenous production of cortisol and testosterone. For example, cortisol measurement from the most proximal 3 cm of hair represents the most recent 3 months of exposure (similar to the assessment of glucose levels using hemoglobin A1C). For the first time, this provides a reliable mode for measuring the accumulation of cortisol over time (Sauvé et al., 2007; Thomson et al., 2010). Several reports have demonstrated an association between high hair cortisol levels and various clinical conditions in both animal models and in humans (Yamada et al., 2007; Van Uum et al., 2008; Davenport et al., 2008; Stalder et al., 2010; Gow et al., 2011; Pereg et al., 2011; Manenschijn et al., 2012). A recent study assessed the relation between hair cortisol and presence of metabolic syndrome in 1258 employees of a large company undergoing a voluntary health assessment (Stalder et al., 2013). Participants whose hair cortisol levels fell into the third and fourth quartile had an odds ratio for having metabolic syndrome of 1.71 and 2.42, respectively, as compared to the first quartile. Another recent study in community dwelling elderly patients demonstrated that higher hair cortisol levels were associated with a history of cardiovascular disease (Manenschijn et al., 2013). This study found that participants in the highest hair cortisol quartile had a 2.7 times increased risk of CVD compared to the lowest quartile. Importantly, this risk was similar to the effect of traditional cardiovascular risk factors such as hypertension, obesity, and dyslipidemia, suggesting that long-term elevated cortisol may also be an important risk factor. However, this study cannot determine if increased hair cortisol also predicts future cardiovascular events. Furthermore, we have shown that testosterone levels in hair are lower in individuals with hypogonadism and normal in hypogonadal subjects on testosterone treatment (Thomson et al., 2009). The longitudinal assessment of cortisol and testosterone levels over time using the hair technique may be more reliable than a single random serum sample for the assessment of chronic heart failure status and prognosis.

Our objective was to evaluate whether levels of hair cortisol and testosterone and the ratio of catabolic to anabolic steroid hormones, as measured by hair cortisol over testosterone (C/T) ratio, correlate with heart failure severity and prognosis in ambulatory patients with stable chronic systolic heart failure.

2. Patients and methods

The study was approved by the research ethics committee at the Meir Medical Center and written informed consent was obtained from each participant. The study was registered in the ClinicalTrials system (ID: NCT01139697).

We included male patients above the age of 18 years with at least moderately reduced left ventricular systolic function defined as left ventricular ejection fraction (LVEF) $\leq$ 40%. All participants were routinely followed-up in either the