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Examining the association between salivary cortisol levels and subclinical measures of atherosclerosis: The Multi-Ethnic Study of Atherosclerosis

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Summary
Objective: To investigate the association between salivary cortisol and two markers of subclinical cardiovascular disease (CVD), coronary calcification (CAC), and ankle-brachial index (ABI).
Methods: Data from an ancillary study to the Multi-Ethnic Study of Atherosclerosis (MESA), the MESA Stress Study, were used to analyze associations of salivary cortisol data collected six times per day over three days with CAC and ABI. The authors used mixed models with repeat cortisol measures nested within persons to determine if specific features of the cortisol profile were associated with CAC and ABI.
Results: A total of 464 participants were included in the CAC analysis and 610 in the ABI analysis. The mean age of participants was 65.6 years. A 1-unit increase in log coronary calcium was associated with a 1.77% flatter early decline in cortisol (95% CI: 0.23, 3.34) among men and women combined. Among women low ABI was associated with a steeper early decline (−13.95% CI: −25.58, −3.39) and a marginally statistically significant flatter late decline (1.39% CI: −0.009, 2.81). The cortisol area under the curve and wake to bedtime slope were not associated with subclinical CVD.

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Conclusions: This study provides weak support for the link between cortisol and measures of subclinical atherosclerosis. We found an association between some features of the diurnal cortisol profile and coronary calcification and ABI but associations were not consistent across subclinical measures. There are methodological challenges in detecting associations of cortisol measures at a point in time with health outcomes that develop over a lifetime. Studies of short-term mechanisms linking stress to physiological processes related to the development of early atherosclerosis may be more informative.

1. Introduction

Exposure to chronic stress has been linked to cardiovascular disease (CVD) (Hemingway and Marmot, 1999; Rosengren et al., 2004). Stress may impact the risk of CVD through the alteration of the functioning of the hypothalamic—pituitary—adrenal (HPA) axis (Cohen et al., 1997). This alteration may result in differential exposure to the stress hormone cortisol. In addition to its metabolic, immunologic and homeostatic functions, cortisol has numerous physiologic effects relevant to the development of cardiovascular disease. For example, cortisol affects the development of insulin resistance (Phillips et al., 1998; Reynolds and Walker, 2003) and central adiposity (Björntorp and Rosmond, 2000), influences blood pressure regulation (Whitworth et al., 1995) and inflammatory processes (Petrovsky et al., 1998). In population studies levels of salivary cortisol within the first 30 min of awakening have been found to be positively associated with central obesity (Björntorp, 1997; Björntorp and Rosmond, 2000; Epel et al., 2000; Ranjit et al., 2005; Strike and Steptoe, 2004); flatter cortisol slopes throughout the day have been linked to inflammation (DeSantis et al., 2012; Nijm and Jonasson, 2009; Petrovsky et al., 1998), and to absence of nocturnal blood pressure dipping (Holt-Lunstad and Steffen, 2007); and higher total cortisol output and flatter early declines have been associated with diabetes (Champaneri et al., 2012; Chiodini et al., 2005; Oltmanns et al., 2006).

Existing evidence of the association between cortisol and CVD risk factors has raised questions about the link between cortisol and the development of atherosclerosis. The investigation of subclinical atherosclerotic disease is of special relevance because it allows for examination of whether cortisol levels are related to early asymptomatic disease. Although there is not sufficient evidence to draw conclusions about the links between chronic stress and measured levels of cortisol, it has been suggested that chronic stress results in alteration of the daily cortisol pattern (Miller et al., 2007). Thus finding an association between alterations in the diurnal cortisol pattern and subclinical atherosclerosis would be consistent with the theory that chronic stress contributes to the development of early CVD. In addition, the use of subclinical measures avoids reverse causation biases that may occur if, for example, clinical events are themselves the cause of the cortisol alteration.

Research to date has investigated the association between cortisol and several CVD related outcomes. Data from the Whitehall II study found flatter cortisol slopes across the day were associated with CVD mortality (Kumari et al., 2011). Another prospective study reported the association between higher levels of urinary cortisol and CVD mortality (Vogelzangs et al., 2010). Others have found that high levels of serum cortisol were independent predictors of cardiac events and mortality among patients with chronic heart failure (Guder et al., 2007; Yamaji et al., 2009). In terms of subclinical atherosclerosis, a few studies have found an association between cortisol and coronary calcification (CAC) (Hamer et al., 2010, 2012; Matthews et al., 2006), while others have found some evidence for an association of cortisol with intima media thickness (IMT), a measure of early atherosclerosis in the carotid artery (Eller et al., 2001). The number of lesions in either coronary or carotid arteries, and stenosis of these arteries have also been linked to cortisol (Alevizaki et al., 2007; Dekker et al., 2008; Koertge et al., 2002). In addition, studies have documented a link between cortisol and endothelial dysfunction (Broadley et al., 2005, 2006; Fantidis, 2010; Violanti et al., 2009). Although the literature in general suggests an association between subclinical atherosclerosis and cortisol, only two studies were based on population based samples (Dekker et al., 2008; Matthews et al., 2006), many had very small sample sizes (Alevizaki et al., 2007; Broadley et al., 2005; Eller et al., 2001, 2005; Peppa-Patrikiou et al., 1998; Troxler et al., 1977; Violanti et al., 2009) and several collected only one serum or urine cortisol sample thus making it impossible to assess diurnal cortisol profiles (Alevizaki et al., 2007; Koertge et al., 2002; Peppa-Patrikiou et al., 1998; Reynolds et al., 2009).

The Multi-Ethnic Study of Atherosclerosis (MESA) provides a unique opportunity to improve upon previous studies in the examination of the association between salivary cortisol and well-established measures of subclinical cardiovascular disease. Detailed cortisol data allows for characterization of cortisol profiles over several days, while the availability of measures of subclinical disease allows for an examination with measures of atherosclerosis in different vascular beds. The nature of the data also allows for an analytic approach that quantifies the association of various features of the daily cortisol curve with subclinical atherosclerosis. The goal of this study is to investigate the association between salivary cortisol and subclinical CVD in two vascular beds: CAC (a marker of atherosclerosis in coronaries) and ankle brachial index (ABI) (a marker of atherosclerosis in the lower extremities). Our a priori hypothesis was that there would be evidence of alterations of the daily cortisol profile (such as flatter slopes) among those with more advanced subclinical atherosclerosis.

2. Methods

The Multi-Ethnic Study of Atherosclerosis (MESA) is a longitudinal study, designed to investigate risk factors for subclinical cardiovascular diseases and its progression to clinical