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Diurnal salivary cortisol, glycemia and insulin resistance: The multi-ethnic study of atherosclerosis

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ABSTRACT

Hypercortisolism is associated with insulin resistance (IR) and diabetes mellitus (DM); however, to our knowledge prior studies have not examined the association of diurnal cortisol curve features with measures of glycemia or IR in a population-based setting. Using log-transformed salivary cortisol data on 850 ethnically diverse men and women from the Multi-Ethnic Study of Atherosclerosis, we investigated the cross-sectional association of cortisol curve features with (1) glycemia in those with and without DM and (2) IR, in non-diabetic subjects. The log-transformed salivary cortisol curve features included wake-up cortisol, cortisol awakening response (CAR), early decline slope (30 min to 2 h post-awakening), late decline slope (2 h post-awakening to bedtime), overall decline slope (0 min to bedtime, excluding 30 min cortisol), bedtime cortisol and total area under the curve (AUC). Overall, following multivariable adjustment, among those with diabetes mellitus (DM), early decline slope, overall decline slope, bedtime cortisol, and AUC were significantly and positively associated with a 5.4% (95% CI: 1.3, 9.7), 54.7% (95% CI: 12.4, 112.9), 4.0% (95% CI: 1.6,6.4), and 6.8% (95% CI: 3.3,10.4) higher HbA1c per 1 unit increase in log cortisol feature, respectively. Cortisol curve features were not associated with HbA1c among non-diabetic participants; however, wake-up cortisol and AUC were associated with a 8.2% lower (95% CI: −13.3,−2.7) and 7.9% lower (95% CI: −14.6, −0.6) log HOMA-IR, respectively. This was attenuated by adjustment for waist circumference. Among participants with DM, cortisol curve parameters suggestive of higher hypothalamic-pituitary-adrenal (HPA) axis activity and dysfunction were associated with higher HbA1c. In non-diabetic participants, greater HPA activity was paradoxically associated with lower insulin resistance.

1. Introduction

The hypothalamic-pituitary-adrenal (HPA) axis is altered by various psychological (e.g. stress, post-traumatic stress disorder, depression) and physiological (e.g. sleep insufficiency/disturbance) stressors, leading to HPA axis dysfunction. The normal HPA axis diurnal rhythm consists of high morning and low afternoon-evening cortisol levels with normal feedback control to lower elevated cortisol levels following acute stress. Repeated acute stresses lead to hippocampal and pituitary glucocorticoid receptor downregulation, poor feedback inhibitory control with increased cortisol secretion and loss of diurnal cortisol rhythm (Rosmond, 2003). Prior studies have shown that depressive disorders activate and alter the function of the HPA axis and increase the risk for type 2 diabetes (DM) (Stetler and Miller, 2011). Hypercortisolism in the setting of repeated psychological and physiological stresses leads to increased visceral adiposity, further promoting insulin resistance and hyperglycemia (Kahn et al., 2006).

The impact of cortisol on glycemia and insulin resistance can be assessed using glycated hemoglobin (HbA1c) and the homeostasis model assessment of insulin resistance (HOMA-IR), respectively. HbA1c is a measure of the average blood glucose levels over the

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prior 90 days with higher levels indicating worse glucose control (normal <5.7%, prediabetes 5.7–6.4%, DM ≥6.5%)(American Diabetes Association, 2010). The HOMA-IR is a model using steady-state (fasting) insulin and glucose to estimate insulin resistance, with higher levels indicating greater insulin resistance (Matthews et al., 1985). In previous analysis, higher fasting and mean overnight serum cortisol levels have been associated with higher HOMA-IR and fasting glucose (Anagnostis et al., 2009). Individuals with the metabolic syndrome have also been shown to have higher circulating cortisol concentrations in both the basal setting and in response to dynamic hypothalamic-pituitary-adrenal (HPA) axis testing (Duclos et al., 2005; Ward et al., 2003). Subclinical hypercortisolism has been documented in individuals with DM, with higher 24-hour urine free cortisol (Chiodini, 2005), higher dexamethasone suppressed cortisol (Chiodini, 2005; Godoy-Matos et al., 2006), higher basal plasma cortisol, (Chiodini, 2005) and larger adrenal gland volume (Godoy-Matos et al., 2006) than individuals without diabetes. One study showed a positive association between dexamethasone-suppressed cortisol and HbA1c, suggesting that hypercortisolism may also be related to glycemic control (Bruehl et al., 2007). We previously showed in the Multi-Ethnic Study of Atherosclerosis (MESA) Stress I Ancillary study that women with diabetes had higher total cortisol area under the curve (AUC) compared to women without diabetes whereas men with diabetes had a lower total cortisol AUC compared to men without diabetes (Champaneri et al., 2012). An important limitation in our prior cross-sectional analysis is that we lacked data on glycemic control at the time hormonal measures were assessed and were unable to assess its contribution to our observed associations. The only glycemic marker was a HbA1c value from 2 to 4 years prior to collection of salivary cortisol data. In this study, the objective was to use data from the MESA Stress II Ancillary Study, a diverse population-based study of adults, to assess whether glycemia, assessed via HbA1c, was cross-sectionally associated with diurnal cortisol curve features (wake-up cortisol, cortisol awakening response (CAR), early decline slope, late decline slope, overall decline slope, bedtime and total cortisol AUC). In our second analysis, we examined the association of cortisol curve features with insulin resistance, assessed via HOMA-IR, in non-diabetic individuals. To our knowledge, there are no prior studies examining the association of glycemia and insulin resistance with the full diurnal cortisol curve profile in diabetic and non-diabetic participants.

2. Methods

2.1. Study population

We used data from MESA, a multi-center, longitudinal cohort study of the prevalence and correlates of subclinical cardiovascular disease and the factors that influence its progression (Bild, 2002). Between July 2000 and August 2002, 6814 men and women without clinical cardiovascular disease who identified themselves as White, Black, Hispanic or Chinese, and were 45–84 years of age were recruited from six U.S. communities: Baltimore City and Baltimore County, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; and St. Paul, Minnesota. Details on the sampling frames and the cohort examination procedures have been published previously (Bild, 2002). The MESA Stress II Study collected detailed measures of stress hormones, including salivary cortisol measures, on a subsample of 1,082 participants at the New York, Los Angeles and Baltimore MESA study sites between 2010 and 2012 during MESA Exam 5. These populations represent an ethnically and socioeconomically diverse group of participants. Written informed consent was obtained from each participant, and the study was approved by the Institutional Review Boards of each MESA institution.

2.2. Hormonal measures

Salivary cortisol measures were collected over 2 days with 8 time points measured per day. The first sample was taken immediately after awakening (and before getting out of bed), the second sample 30 min later, and 6 additional timed samples throughout the day including a sample right before bedtime. Participants were instructed not to eat or drink or brush their teeth 15 min before collecting the salivary samples. They were also instructed to leave the cotton swab in their mouths for less than 2 min until soaked, moving it around inside their mouth. Participants were instructed to record the exact time of sample collection on a special card, which was facilitated by a provided alarm clock. Saliva samples were stored at −20 °C until analysis. Before biochemical analysis, samples were thawed and centrifuged at 3000 rpm for 3 min to obtain clear saliva with low viscosity. Cortisol levels were determined using a commercially available chemiluminescence assay with a high sensitivity of 0.16 ng/mL (IBL, Hamburg, Germany). Intra- and inter-assay coefficients of variation were less than 8%.

In MESA Stress II, 98% of participants collected valid samples (i.e. valid cortisol sample and valid time of sample collection) on both days and 96% of participants collected at least 5 valid samples per day for both days. Collection rates were similar to MESA Stress I, where 97% of participants collected samples on all 3 days and 85% of participants collected at least 5 samples per day for all days on which they collected samples (Golden et al., 2014; Hajat et al., 2010). Participants recorded collection time on special cards. Based on prior work in our population, the median difference between the actual collection time and recorded times was between 2 and 4 min depending on the sample. The 25th and 75th percentiles were between 1 and 2 and 5 and 13 min, respectively, with the longest times corresponding to the last sample of the day. Overall, the first sample was taken within 5 min of wake-up for 78% of days across participants and the median difference between the first and second sample was 34 min. While lower compliance with the collection protocol was associated with a less pronounced CAR, compliance was not associated with any other cortisol features and adjustment for compliance did not affect the associations of cortisol features with sociodemographic characteristics (Golden et al., 2014).

2.3. Cortisol features

Normal diurnal cortisol regulation follows a circadian pattern, in which levels are typically high upon waking, increase by 50–75% during the 30–40 min post-awakening (CAR); and decline across the remainder of the day, reaching a nadir in the late evening some 18+ hours after awakening (Golden et al., 2014). We investigated seven features of the daily cortisol curve: Wake-up cortisol levels, CAR, standardized total cortisol AUC, early decline slope, late decline slope, overall decline slope and bedtime cortisol (Fig. 1). Due to its positively skewed distribution, cortisol was log-transformed before the cortisol features were calculated (Adam et al., 2006; Champaneri et al., 2013, 2012; Hajat et al., 2010; Wang et al., 2014). Wake-up cortisol was defined as the salivary cortisol obtained at time 0. CAR was the cortisol rise from time 0 to 30 min post-awakening. Early decline in cortisol was defined as the decline in cortisol from 30 min post-awakening to 2 h post-awakening. Late decline in cortisol was the decline in cortisol from 2 h post-awakening to bedtime. The overall decline slope was calculated as the rate of decline using all samples except the 2nd sample (30 min post-awakening). To calculate the AUC, we used linear splines to connect the values from each of the sample times and then cal-