Conclusion: We showed that a higher glucocorticoid to androgen ratio and a flattened circadian steroid variation were associated with lower global and fluid cognition score. Steroid ratios reflecting steroidogenesis enzymatic activity demonstrated sex differences in relation to cognition. Additional studies should examine whether the steroid fingerprint associated with lower cognition is predictive of a future dementia onset.

Adrenal

ADRENAL – CLINICAL RESEARCH STUDIES

Urinary Steroid Metabolome Signature Is Associated With Pre-Frailty and Frailty Phenotype in Older Adults

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Background: Frailty is characterized by an increased vulnerability and a decline in physiological reserve. Frailty has been previously linked to cortisol concentrations and blunted diurnal cortisol secretion. Our objective was to determine the association of urine steroid metabolome and its diurnal variation with frailty and prefrailty in older adults. **Methods:** Cross-sectional study of community-dwelling adults ≥ 50 years. Participants with adrenal disorders, end-stage renal or liver disease, on exogenous steroids or drugs affecting steroid metabolism were excluded. All participants completed day and night separate urine collection. Frailty was assessed using a phenotype model (weight loss, exhaustion, grip strength, low physical activity, and slow walking pace). Participants were characterized as frail if they met at least three criteria, pre-frail if they fulfilled one or two criteria, and robust if no criteria were met. Urine samples were analyzed with the liquid-chromatography, high-resolution, accurate-mass mass spectrometry for 25 urine steroid metabolites. **Results:** Of 119 participants, 60 (50.4%) were women, without sex differences in age or education status. On frailty assessment, 5 (4.2%) participants were frail and 33 (27.7%) were prefrail, with equal sex distribution. Urine steroid metabolome analysis demonstrated 21/25 steroids were higher in men vs women. In an age adjusted model, presence of prefrailty or frailty was associated with a higher ratio of total cortisol metabolites/total androgen metabolites (TCM/TAM) in men (estimate 0.64, P-value= 0.0004), but not in women. In men, after adjusting for age, among cortisol metabolites, lower day to night ratio of 5α-Tetrahydrocortisol (estimate -0.36, P-value= 0.0419) and β-Cortol (estimate -0.35, P-value= 0.0238) were associated with frail or prefrail phenotype. After adjusting for age, higher ratio of TCM/TAM was associated lower gait speed in men (estimate -1.2, P-value= 0.046) and women (estimate -3.9, P-value= 0.012); and lower hand grip strength in men (estimate -0.04, P-value= 0.046) but not in women. **Conclusion:** We showed that a higher glucocorticoid to androgen ratio and a flattened circadian steroid variation were associated with presence of frail or prefrail phenotype in men. Further studies should examine the role of steroid metabolism and HPA axis impairment, and the associated sex differences, in the functional decline in aging population.

Adrenal

ADRENAL – CLINICAL RESEARCH STUDIES

Utility of Urinary Ratio of Cortisol to Aldosterone as Inflammatory and Metabolic Parameters

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Corticosteroids are important bioactive substances in the body that regulate inflammation, metabolism, immunity, and circulatory dynamics. Cortisol and aldosterone are two major naturally occurring steroids, which synthesized in the adrenal fasciculata and in the adrenal glomerulosa under the regulation of adrenocorticotropin (ACTH) and renin-angiotensin system (RAS), respectively. The conventional strategy for evaluating adrenocortical function has been to measure random serum cortisol or 24-hour stored levels of urine free cortisol (UFC). UFC is a more appropriate marker to avoid the effects of diurnal fluctuation of cortisol, serum cortisol-binding proteins, and cortisol clearance in the kidney. Thus, measurement of UFC has been a reliable test for diagnosis of Cushing's disease or adrenal insufficiency. However, since the normal range of UFC varies widely, it is often difficult to evaluate whether the UFC level is optimal or not for each patient. That is because UFC is greatly affected by the amount of fluid intake or urine volume, and an immunoassay for UFC, which is the usual method for measuring UFC, is susceptible to interference from other steroid metabolites and synthetic glucocorticoids. To explore an alternative indicator, we tried to standardize the levels of UFC by the levels of urinary aldosterone concentration (UAC) in the same urinary sample. Medical records of all 246 patients in whom daily excretions of UFC and UAC had been measured between 2015 and 2018 at our department were reviewed. 142 patients (including 93 females) were included after exclusion of 104 patients because of corticosteroid replacement therapy. UFC/UAC ratio showed significant positive and negative correlations with the levels of serum cortisol (R=0.287) and aldosterone (R=-0.762), respectively. UFC/UAC ratio increased with aging in female patients, while the ratio was not altered by the levels of BMI in either gender. Markers for metabolic and inflammatory status including hemoglobin A1c (R=0.327), albumin (R=-0.331), chorine esterase (R=-0.248), C-reactive protein (R=0.317), ferritin (R=0.473), and D-dimer (R=0.569) showed correlations to the ratio of UFC/UAC that were more significant than the correlations to the serum level of cortisol or UFC alone. Of note, the UFC/UAC ratio was shown as an indicator for risks of diabetes (AUC: 0.765), hypoalbuminemia (0.839), hyper-CRPemia (0.748), and thrombophilia (0.824), in which the cut-off levels of UFC/UAC ratios were found to be around 12. These results indicate that the UFC/UAC ratio is a suitable variable for the detection of metabolic and inflammatory complications related to adrenocortical dysfunction.