

Methods: We conducted a retrospective review of patients (n = 645) who had histopathologically confirmed diagnosis of CD from 2005-2019 (NCT NCT00060541). We selected patients that had ≥ 3 plasma ACTH values over a 7 day span prior to surgical or medical intervention. We grouped the ACTH measurements into morning (AM) and midnight (PM) values to account for diurnal variation in ACTH secretion. We then analyzed post-operative hormone measurements performed every 6 hours prior to administration of replacement corticosteroids. Remission was assigned to patients with nadir serum cortisol level ≤ 5 mcg/dL within ten days post-operatively^{3,4}.

Results: We found 54 patients with multiple PM (n = 27) and AM (n = 41) ACTH measurements within a 7 day span. We found that the median coefficient of variation (CV) of intra-patient variability was 19.7% (N=41) (95% CI:12.5-27.5) for the AM and was 24% (N=27) (95% CI: 9.6-31.8) for the PM. Age, the number of tests, or the length of test period were not correlated with CV or absolute levels of ACTH. The intraclass correlation coefficient (ICC) of the AM data set was 0.59 and the PM data set was 0.79 which demonstrates a good and excellent reliability respectively. We found that that, in general, 30-60% decrease from pre-operative ACTH levels predicted remission from CD. ACTH decrease $>50\%$ on POD2 and 3 had 100% specificity and sensitivity in predicting remission. The decrease in ACTH preceded cortisol nadir in 3/10 patients by 24 hours.

Conclusion: We found significant intra-patient variability in plasma levels of ACTH at individual diurnal timepoints in CD patients. We also found that the change in ACTH $>50\%$ on POD2 or 3 is an excellent predictor of remission from CD.

Reproductive Endocrinology

OVARIAN FUNCTION — FROM OLIGOMENORRHEA TO AMENORRHEA

Emergence of Ovarian Hyperandrogenism and Luteal Insufficiency Following ESR1 Knockdown in the Mediobasal Hypothalamus of Adult Female Rhesus Monkeys

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Diminished estradiol (E2) negative feedback action by neuronal ESR1 in the arcuate nucleus (ARC) of the mediobasal hypothalamus (MBH) is hypothesized to cause gonadotropin-releasing hormone (GnRH) hypersecretion, and thus LH excess, contributing to ovarian

hyperandrogenism in polycystic ovary syndrome (PCOS). In primates, including humans, however, the mediating estrogen receptor is unknown. Thus, to test the hypothesis that diminished E2 action on ARC ESR1 contributes to female primate ovarian hyperandrogenism, eleven, ovary intact, adult female rhesus macaques, pair housed with female peers, received five 12 μ l MRI-guided MBH infusions into the rostral-to-caudal extent of both right and left ARC. Each infusion comprised gadolinium contrast agent and $\sim 3\text{-}4 \times 10^{10}$ adeno-associated virus 8 (AAV8) particles containing either a shRNA specific for ESR1 (n=6, ERaKD) or scrambled shRNA (n=5, control). Mid-surgery MRI scans identified targeting accuracy. 2-2.5 years following AAV8 infusion, EIA-determined P4 values were obtained from twice weekly serum samples; samples obtained during the follicular phase of menstrual cycles or anovulatory periods were submitted to liquid chromatography, tandem mass spectrometry (LCMS) for additional steroid hormones. LCMS-determined values were also obtained 0 hours (h) and 24 h following an IM injection of 200IU hCG. Both ERaKD (28.5 ± 1.3 days, mean \pm SEM) and control (34.0 ± 3.3 days) female groups exhibited comparably regular menstrual cycles. ERaKD exhibited higher circulating levels of LH (2.8 ± 0.2 ng/ml, p=0.03), androstenedione (A4, 0.43 ± 0.03 ng/ml, p=0.03) and testosterone (T, 0.23 ± 0.03 ng/ml, p=0.09), and LH/FSH ratio (1.7 ± 0.2 , p=0.05) compared to controls (LH, 2.1 ± 0.4 ; A4, 0.30 ± 0.05 ; T, 0.18 ± 0.01 ng/ml; LH/FSH 1.3 ± 0.2). Following an ovarian androgen-stimulating hCG injection, ERaKD 24-h peak levels for T (0.28 ± 0.01 ng/ml) were higher (p=0.03) compared to controls (0.21 ± 0.01 ng/ml). In addition, luteal insufficiency emerged in ERaKD females, with mean (2.4 ± 0.3 ng/ml), peak (3.6 ± 0.4 ng/ml) and area-under-the-curve (AUC, 23.2 ± 4.2 ng/ml/days) P4 values diminished compared to controls (mean, 3.6 ± 0.1 , p=0.01; peak 5.7 ± 0.1 ng/ml, p=0.01; AUC, 43.7 ± 6.7 ng/ml/days, p=0.03). Taken together, these results suggest that knockdown of ARC ESR1 disrupts Gn stimulation of ovarian function, contributing to female monkey ovarian hyperandrogenism and menstrual cycle impairment emulating PCOS in women.

Bone and Mineral Metabolism

NEW INSIGHTS INTO PTH AND CALCIUM RECEPTOR SIGNALING

The Roles of GNAQ and GNA11 in Calcium-Sensing Receptor (CaSR) Signalling

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The G-protein subunits $G\alpha_{11}$ and $G\alpha_q$, which share $>90\%$ peptide sequence identity and are encoded by the *GNA11* and *GNAQ* genes, respectively, mediate signalling by the calcium-sensing receptor (CaSR), a class C G-protein coupled receptor (GPCR) that regulates extracellular