parameters in 38 subjects with LD (18 GLD, 20 PLD) who were treated with metreleptin in open-label clinical studies at the National Institutes of Health. 27 had repeat echo after 1y of metreleptin (mean 1.0 ± 0.2y), and 23 after 3 to 5y (mean 3.7±0.6y). In GLD, metreleptin significantly improved metabolic disease, including reduced TG (median(IQR) 740(403–1239), 138(88–196), 211(136–558) mg/dL at baseline, 1y, & 3-5y, P<0.0001), hemoglobin A1c (9.5±3.0, 6.5±1.6, 6.5±1.9% at baseline, 1y, & 3-5y, P<0.001), and insulin resistance by HOMA-IR (34.1 (15.2–43.5), 8.7 (2.4–16.0), 8.9 (2.1–16.4), P<0.001). Only HOMA-IR improved in PLD (P<0.01). Systolic BP and HR decreased after metreleptin in GLD (BP 120±11, 117±10, 109±16 mmHg, P=0.046; HR 89±9, 82±12, 80±16 bpm, P=0.018; at baseline, 1y, 3-5y, respectively) but not PLD. Metreleptin improved cardiac parameters in patients with GLD, including reduced posterior wall thickness (9.8±1.7, 9.1±1.3, 8.3±1.7 at baseline, 1y, & 3-5y, P<0.01), LV mass (140.7±45.9, 128.7±37.9, 110.9±29.1 at baseline, 1y, & 3-5y, P<0.01), and LV mass index (88.6±22.0, 81.6±16.9, 81.6±16.9 at baseline, 1y, & 3-5y, P<0.01). Metreleptin also improved septal e' velocity, a measure of early diastolic cardiac function, in GLD (8.6±1.7, 10.0±2.1, 10.7±2.4 at baseline, 1y, & 3-5y, P<0.01). All changes remained significant after adjustment for BP. In GLD, multivariate variable selection models suggested that changes in posterior wall thickness and LV mass index related to metreleptin-induced reductions in TG, and changes in septal e' velocity related to metreleptin-induced reductions in hemoglobin A1c. No changes in echo parameters were seen in PLD. These findings suggest that metreleptin improves cardiac hypertrophy and diastolic function in patients with GLD, and these improvements may be mediated by reduced lipotoxicity and glucose toxicity. The applicability of these findings to a broader, leptin-sufficient population with LV hypertrophy and/or diabetic cardiomyopathy remains to be determined.

Cardiovascular Endocrinology
LIPIDS AND STEROIDS IN CARDIOVASCULAR DISEASE

The Impact of ACTH on Peripheral Steroids Differs between Unilateral and Bilateral Primary Aldosteronism

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Background: ACTH is thought to contribute to aldosterone excess in primary aldosteronism (PA), possibly via aberrant melanocortin type 2 receptor (MC2R) expression in aldosterone producing adenomas (APAs). Dynamic manipulation of the hypothalamic-pituitary-adrenal (HPA) axis has been proposed as a non-invasive tool for distinguishing unilateral PA (UPA) from bilateral PA (BPA), but existing data are minimal. **Objective:** To characterize the steroid responses to intrinsic ACTH variations and extrinsic HPA manipulation in UPA and BPA. **Methods:** We conducted comprehensive dynamic testing in PA patients, who were subtyped based on adrenal vein sampling. Peripheral plasma samples were collected from each patient at 6 time-points: morning; midnight; after 1 mg dexamethasone suppression (DST); and after cosyntropin stimulation (at 15', 30', and 60'). We quantified 15 steroids by mass spectrometry in each sample. Next generation sequencing was used to detect aldosterone-driver somatic mutations in APAs from 39 cases with available tissue. The Mann-Whitney test, Wilcoxon signed rank test, and repeated measures two-way ANOVA were employed, as appropriate. Penalized logistic regression was used to select steroids that best distinguished UPA from BPA. Receiver operating characteristic (ROC) curves were then plotted using the predicted score from the logistic regression model with the selected steroids, and area under the curves (AUC) were computed. **Results:** We included 80 PA patients, median age 51 (range, 26–76), 50% men, 40 with each subtype, both groups with similar age and sex distribution. Morning and midnight concentrations of 18-hydroxycortisol (18OHF), 18-oxocortisol (18oxoF), aldosterone, and 18-hydroxycorticosterone (18OHB) were higher in patients with UPA vs. BPA (*p*<0.001 for all). In response to cosyntropin stimulation, the UPA group had larger increments of aldosterone, 18oxoF, 11-deoxycorticosterone, corticosterone, and 11-deoxycortisol than the BPA group (*p*<0.05 for all). Following DST, aldosterone,18OHF, and 18oxoF were higher in UPA than in BPA patients (*p*<0.01 for all). Overall, cortisol and cortisone serum concentrations were similar between the two subtypes. Of the UPA cases, 27 (69%) had *KCNJ5* mutations. Relative to UPA patients with other mutations, the *KCNJ5* group had higher 18oxoF and 18OHF at baseline; higher 18oxoF and corticosterone after both dynamic tests; and lower aldosterone after DST. The highest AUC for PA subtyping was achieved using cosyntropin stimulated steroids (0.957), while baseline data reached an AUC of 0.909. **Conclusions:** Steroid responses to dynamic HPA testing differs between UPA and BPA: 18oxoF and 18OHF are less suppressible, while several steroids are disproportionally amplified by ACTH in patients with UPA vs. BPA. Such non-invasive tests could circumvent the need for adrenal vein sampling in a subset of PA patients.

Diabetes Mellitus and Glucose Metabolism
BENCH TO BEDSIDE: NOVEL MECHANISMS IN DIABETES AND METABOLISM

Analysis of Novel Histone Methylase MLL Function for Glucose Metabolism in Mouse Pancreas