All 11-oxy-androgens correlated with each other (r_s range: 0.6-0.8, $P < .05$) in both groups. There was no difference in the proportionate contribution of 11-oxy-androgens to the total circulating androgenic pool in patients vs. controls. **Conclusion:** Elevated 11-oxy-androgens in patients with severe insulin resistance suggests that both adrenal and ovarian androgens are upregulated by hyperinsulinemia. Lower 11KT/T in patients compared to controls despite higher 11-oxy-androgens than in controls is consistent with predominant ovarian T excess in patients with severe IR. Correlation between insulin and fold elevation of T relative to controls supports hyperinsulinemia as the cause of high T in states of hyperinsulinism. **Acknowledgement:** This research was supported by the Intramural Program of NIH Clinical Center and NIDDK.

Cardiovascular Endocrinology

ENDOCRINE HYPERTENSION AND ALDOSTERONE EXCESS II

RAAS Triple-A Analysis for the Screening of Primary Aldosteronism

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SUN-LB98

Primary aldosteronism (PA) is recognized as the most frequent cause of secondary hypertension, and its screening is expected to become a routine evaluation in most patients with hypertension. The interference of antihypertensive therapies with the aldosterone-to-renin ratio (ARR) during screening process is a major confounder. Renin-Angiotensin-Aldosterone System Triple-A (RAAS Triple-A) testing is a novel mass-spectrometry based assay for quantification of Angiotensin I (Ang I), Angiotenisn II (Ang II) and Aldosterone in a single sample of serum by RAAS equilibrium analysis. Obtained hormone levels are used to calculate markers for plasma-renin-activity (PRA-S, Ang I + Ang II), plasma angiotensin-converting-enzyme activity (ACE-S, Ang II-to-Ang I ratio) and adrenal function (AA2-Ratio, Aldosterone-to-Ang II ratio), with the latter being useful to screen for PA in hypertension. We performed a comparative evaluation of the diagnostic performance of the AA2-Ratio and 5 renin-based diagnostic ratios, differing in methods to determine aldosterone levels and renin activity in a cohort of 110 patients with hypertension (33 patients with confirmed primary aldosteronism and 77 with essential hypertension). All ratios showed comparable areas under the curves ranging between 0.924 and 0.970 without significant differences between each other. The evaluation of the ACE-S revealed persistent drug intake in some patients as cause for suppressed renin-based diagnostic ratios, while the AA2-Ratio remained unaffected. The Youden index optimal cutoff value for the AA2-Ratio was 6.6 ([pmol/L]/[pmol/L]) with a sensitivity of 90% and a specificity of 93%, proving non-inferiority compared with the ARR while pointing to the potential for an interference-free application in patients under ACE inhibitor therapy. This study shows for the first time the accuracy and reliability of RAAS Triple-A analysis for the screening of primary aldosteronism that can be applied in clinical routine.

Adipose Tissue, Appetite, and Obesity

ADIPOSE TISSUE BIOLOGY AND OBESITY

Insulin Sensing by Astrocytes Is Critical for Normal Thermogenesis and Body Temperature Regulation

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SAT-LB107

The important role of astrocytes in the central control of energy balance and glucose homeostasis has only recently been recognized. Changes in thermoregulation can lead to metabolic dysregulation, but the role of astrocytes in this process is not yet clear. Therefore, we generated mice congenitally lacking insulin receptors (IR) in astrocytes ($IRKO^{GFAP}$ mice) to investigate the involvement of astrocyte insulin signaling. $IRKO^{GFAP}$ mice displayed a significant decrease in energy expenditure and a striking decrease in basal and fasting body temperature. When exposed to cold, however, they were able to mount a thermogenic response. Brown adipose tissue in $IRKO^{GFAP}$ mice exhibited increased adipocyte size, more apoptosis, loss of innervation, and decreased βAR3 expression levels. These findings identify a novel role for astrocyte insulin signaling in the development of normal body temperature control and sympathetic activation of BAT. Targeting insulin signaling in astrocytes has the potential to serve as a novel target for increasing energy expenditure.

Neuroendocrinology and Pituitary

HYPOTHALAMIC-PITUITARY DEVELOPMENT AND FUNCTION

The Spectrum of Genomic and Transcriptomic Alterations in ACTH-Producing and ACTH-Silent Corticotroph Adenomas

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SAT-LB57

Corticotroph adenomas (CA) are rare pituitary tumors that impose several challenges in clinical management - CA are difficult to diagnose, often recur, and are associated with high morbidity and mortality. CA are characteristically Tpit-positive and PIT1-negative and comprise ACTH-producing (Cushing's disease (CD)) and ACTH-silent (AS)

classes. The molecular programs contributing to disease pathogenesis in CA are still poorly characterized, largely restricted to the identification of somatic mutations in *USP8* in 40-60% of CD adenomas. To more fully characterize the mutational and transcriptional landscape driving both classes of CA, we performed whole-exome sequencing and RNA-seq in 19 CD and 16 AS adenomas. We identified *USP8* mutations in 53% of CD (10/19) and 6% of AS (1/16) samples. Strikingly, in 19% of AS tumors (3/16), all exhibiting an unusually aggressive disease course, including two cases with brain metastases, we identified recurrent somatic pathogenic mutations in *TP53* and novel loss-of-function mutations in telomere maintenance genes *DAXX* and *ATRX*. Furthermore, while all tumors with *USP8* mutations (regardless of CD/AS status) exhibited no chromosomal abnormalities as measured by copy-number variation (CNV) and loss of heterozygosity (LOH) analysis, 33% of CD (4/12, including 1 tumor with a *DAXX* mutation) and 36% of AS (4/11, including all *DAXX/ATRX*-mutated cases) samples exhibited profound chromosomal instability, characterized by hyperdiploidy, widespread whole-chromosome LOH events, and arm-level breakpoints. Using transcriptome analysis (n=22), we identified three classes of tumors (C1-C3), reflecting these distinct somatic alteration profiles. C1 tumors (n=6) are characterized by chromosomal stability, includes exclusively *USP8*-mutated CD, and exhibits upregulation of genes involved in metabolic processes and protein acetylation. C2 tumors (n=10) are comprised exclusively of AS (including all *TP53*- and/or *DAXX/ATRX*-mutated cases), are characterized by chromosomal instability, and exhibits concordant upregulation of cell cycle programs. Finally, C3 (n=6) contains a mixture of AS and CD cases (including CD without mutations in *USP8*) and features an expression profile that partly overlap with C1 tumors, but also exhibit higher expression of inflammatory genes. Taken together, our data suggest that CD and AS are distinct molecular subtypes of CA, highlighting the dominant role of *USP8* mutations in driving a unique transcriptional program and illustrate for the first time that unlike most cases of CD, AS cases are characterized by profound genomic instability and cell cycle activation, features associated with a more aggressive disease course.

Diabetes Mellitus and Glucose Metabolism

DIABETES DIAGNOSIS, TREATMENT AND COMPLICATIONS

A Continuous Remote Care Intervention Utilizing Carbohydrate Restriction Including Nutritional Ketosis Improves Markers of Metabolic Risk and Reduces Diabetes Medication Use in Patients With Type 2 Diabetes Over 3.5 Years

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SUN-LB113

Novel lifestyle, pharmaceutical, and/or surgical therapies for type 2 diabetes (T2D) are under study to assess lasting impact on metabolic risk. Among them, carbohydrate restriction including nutritional ketosis (CR) has emerged as a safe and effective nutrition therapy for reducing hyperglycemia in patients with T2D[1], yet longer term effects are unknown. At the conclusion of a 2-year study assessing a continuous remote care intervention utilizing CR (CCI) among patients who selected this therapy, intervention participants were offered the opportunity to consent to participate in a 3-year extension assessing outcomes at 3.5- and 5-y following initial enrollment. 143 of 169 extension-consented participants provided data at 3.5-y follow up. Among 3.5-y completers, linear mixed effects models were used to assess change over time in diabetes-related outcomes and McNemar's tests were used to assess for a difference in the proportion of participants meeting certain criteria at baseline compared to follow-up. At enrollment, 3.5-y completers were (mean±SE) 55±1 y of age, 40.8±0.7 kg/m^2, and 8±1 y since diagnosis. Following treatment with the CCI for 3.5 y, significant improvements compared to baseline were observed in HbA1c (-0.6±0.1 from 7.4±0.1%; $P = 1.9\text{x}10^{-5}$), weight (-10.9±1.1 from 117.4 kg; $P = 6.9\text{x}10^{-17}$), nonHDL-C (-10±4 from 139±3 mg/dL; $P = 0.005$), triglycerides (-41±11 from 189±10 mg/dl; $P = 2.1\text{x}10^{-4}$), and HDL-C (+9±1 from 43±1 mg/dl; $P = 3.0\text{x}10^{-11}$); total cholesterol and LDL-C were statistically unchanged. The percentage of participants prescribed diabetes medication decreased from 84.6 to 67.1% ($P = 5.0\text{x}10^{-6}$), while 50.2% of diabetes medications and 71.4% of diabetes medications other than metformin were discontinued. The percentage of participants treated with no pharmaceuticals or monotherapy increased from 52.5 to 81.9% ($P = 1.3\text{x}10^{-8}$). 45.5% (65/143) of participants achieved HbA1c <6.5% with either no medication (34/65, 52%) or only metformin (31/65, 48%) at 3.5 y; 37.8% of participants maintained this status from 1 through 3.5 y of treatment. 22% of participants achieved diabetes remission at 3.5 y, and 17.5% of participants maintained remission status from 2 through 3.5 y of treatment. This demonstrates that clinically meaningful improvements across multiple markers of metabolic risk can be sustained in patients with T2D who selected treatment with this CCI for 3.5 y. Improvements in metabolic risk markers reduced the need for diabetes medication, allowing some patients to achieve and sustain diabetes remission. This ongoing trial will assess 5-y effects.

1. American Diabetes Association. Standards of Medical Care in Diabetes. Diabetes Care. 2020; 43(Supplement 1): S48-S65. 2. Athinarayanan SJ, et al. Front Endocrinol. 2019; 10:348.

Genetics and Development (including Gene Regulation)

GENETICS AND DEVELOPMENT AND NON-STEROID HORMONE SIGNALING I

Association of Receptor for Advanced Glycation End Product (RAGE) Gene Polymorphisms & Serum Levels of Soluble RAGE (sRAGE) With Metabolic Syndrome (MS) in Mexican Population

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