of insulin/glucagon was measured and used as an index of insulin-medicated suppression of plasma glucagon. FPG concentration increased from 97±4 to 140±4 mg/dl during the 72 hour glucose infusion. Following chronic glucose infusion, plasma insulin levels were significantly higher during the basal state and during each hyperglycemic clamp step (by 59% and 78%). There was no difference in plasma glucagon levels following chronic glucose infusion and the degree of suppression of glucagon during 2-step hyperglycemic (+125 and +300 mg/dl) were similar. However, the plasma insulin/glucagon ratio was significantly higher during the fasting state (by 76%) and during the first (by 128%) and second (by 178%) hyperglycemic clamp steps. Similarly during the three step euglycemic clamp (10, 20, 40 mU/m^2·min) studies following 48 hr glucose infusion, despite similar plasma glucose concentrations during each clamp step, plasma insulin and glucagon concentrations were higher following chronic glucose infusion. These results demonstrate that sustained physiologic hyperglycemia for 48 hrs or 72 hours (i.e. glucotoxicity) does not affect the glucose mediated suppression of glucagon, but impairs insulin-mediated suppression of glucagon, and could contribute to fasting and post-prandial hyperglycemia in T2DM patients.

Adrenal

ADRENAL - HYPERTENSION

Age-Dependent Progression of Renal Dysfunction After Adrenalectomy for Aldosterone-Producing Adenomas in Japan

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MON-208

Context: In patients with aldosterone-producing adenomas (APAs), adrenalectomy causes a rapid decrease in blood pressure and increase in blood potassium levels; however, the effects of these intensive metabolic changes on kidney function with age have not yet been examined in Japan.

Objective: To investigate factors related to the progression of kidney dysfunction after adrenalectomy in different age groups.

Participants: Fifty Japanese patients with APAs with 27,572 health check-up subjects as controls were examined.

Main Outcome Measures: We investigated changes in eGFR after adrenalectomy and characterized patients who progressed to chronic kidney disease (CKD).**Results:** Receiver Operating Characteristic and multivariate analyses revealed the postoperative cut-off age of CKD to be 50 years (sensitivity, 57%; specificity; 82%; AUC, 0.69) and identified age as a unique factor for the progression of CKD after adrenalectomy. Among preoperative patients with APAs, CKD was 6% for those younger than 50 years (<50) and 40% for those 50 years and older (≥50). As a control, in 27,572 health check-up subjects, the prevalence of CKD was 4.2% in men and 2.5% in women aged 41-50 years and 18.9% in men and 13.3% in women older than 61 years, clearly demonstrating the higher prevalence of CKD in patients with APAs than in healthy subjects, particularly those with APAs ≥50 years. In patients with APAs <50 years, median eGFR before and after adrenalectomy were 95 mL/min/1.73m^2 and 88 mL/min/1.73m^2, respectively, indicating that the percentage of the decrease in eGFR was -7%, which was not significant (paired *t*-test, p=0.13). In contrast, in patients with APAs ≥50 years, median eGFR after adrenalectomy decreased to 42 mL/min/1.73m^2 from 67 mL/min/1.73m^2 (adjusted by age, paired *t*-test, p=0.01) (percent decrease in eGFR, -24%) Patients with APAs ≥50 years who progressed to CKD showed higher preoperative aldosterone/renin ratios, lower potassium and chloride levels, lower BMI, and a higher incidence of a history of cardiovascular events and KCNJ5 mutation rates.**Conclusion:** Age is the most important predictor of the progression of kidney dysfunction after adrenalectomy in Japanese patients with APAs, particularly those with a history of cardiovascular events and positivity for KCNJ5 mutations.

Neuroendocrinology and Pituitary

NEUROENDOCRINE & PITUITARY PATHOLOGIES

Spectrum of Imaging in Immune Checkpoint Inhibitor Induced Hypophysitis

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SUN-298

Background: Hypophysitis (HP) is a known immune related adverse event of immune checkpoint inhibitors (CPIs), commonly associated with CTLA-4 inhibitors and rarely with PD-1/PD-L1 inhibitors. Prior studies of MRIs at HP diagnosis noted pituitary enlargement with resolution within a few weeks. In this study, we examine MRI changes in patients with CPI-induced HP.

Methods: Subjects with biochemical evidence of central hypothyroidism or central adrenal insufficiency and MRIs were reviewed by endocrinology and neuroradiology. MRIs were classified relative to HP diagnosis: baseline (at least 21 days prior), diagnosis (within 21 days), and follow up (over 21 days). Patient characteristics included age at CPI initiation, sex, race/ethnicity, personal and family history of autoimmunity, type of cancer and CPI.

Results: Twenty-six subjects met the inclusion criteria. The mean age was 59 years; 62% were male and 86% were non-Hispanic white. Nineteen percent had a personal history and 31% a family history of autoimmunity. Fifty percent had melanoma. At HP diagnosis, 46% were on PD-1/

PD-L1 inhibitors, 42% were on combination PD-1/CTLA-4 inhibitors and 12% were on CTLA-4 inhibitors.
Median time from CPI initiation to HP diagnosis was 95 days. Time to HP was shorter on a CTLA-4 inhibitor combination or monotherapy (median 82 days) compared to a PD-1/PD-L1 inhibitor monotherapy (median 220 days; Wilcoxon rank sum, p <0.01). Central adrenal insufficiency was present in all patients not yet on steroids. Central hypothyroidism was common (10/19) in those without primary thyroid disease and was not associated with type of CPI (Fisher's exact, p=0.18).
Thirteen subjects had baseline MRIs, 18 had MRIs at HP diagnosis and 13 had MRIs in the follow up period. Baseline MRIs were normal in 12/13; one subject had an enlarged pituitary. At diagnosis, 10 had an enlarged pituitary, 7 a normal pituitary and 1 a partially empty sella. CTLA-4 inhibitor exposure was associated with pituitary enlargement at diagnosis: 9/11 compared to 1/7 on PD-1/PD-L1 inhibitor (Fisher's exact, p <0.04). Of the subjects who had follow-up MRIs, 3 had an enlarged pituitary, 7 a normal pituitary and 3 a partially empty sella. Follow up imaging did not differ between treatment types (Fisher's exact, p >0.05). Timing of MRI was significantly associated with pituitary appearance (Fisher's exact, p <0.01).
Conclusion: The MRI appearance of HP presents as a spectrum, from a partially empty sella, normal pituitary to an enlarged pituitary. HP diagnosed in the setting of CTLA-4 inhibitor treatment occurs earlier and is more likely to induce an enlarged pituitary gland compared to PD-1/PD-L1 monotherapy, which occurs later and is associated with a normal appearing MRI at diagnosis. This suggests that the pathogenesis of HP following CPI exposure may vary depending on the type of CPI.

Tumor Biology

TUMOR BIOLOGY: DIAGNOSTICS, THERAPIES, ENDOCRINE NEOPLASIAS, AND HORMONE DEPENDENT TUMORS

TMEPAI Inhibits SMAD 2/3 Mediated Muscle Wasting

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SUN-140

Inhibition of myostatin and activin activity using ligand traps, such as soluble receptors, follistatin and propeptides, can markedly increase skeletal muscle mass in healthy mice and ameliorate wasting in models of cancer cachexia and muscular dystrophy. Though effective, clinical translation of these approaches has been hindered by off-target effects. Toward the goal of developing tissue-specific myostatin/activin interventions, we explored the ability of transmembrane prostate androgen-induced (TMEPAI) to promote growth of skeletal muscle. TMEPAI, a transcriptional target of activin in muscle, is a known inhibitor of TGF-β1-mediated SMAD 2/3 signalling. In this study we show that TMEPAI also blocks activin A, activin B, myostatin and GDF-11 *in vitro* activity. Adeno-associated viral (AAV) gene delivery of TMEPAI into healthy mice increased local muscle mass by as much as 30%. Increased muscle mass was attributed to hypertrophy of fibres in TMEPAI-expressing muscles, and was coincident with an upregulation in markers of protein synthesis (*pAkt, pMTOR, p70S6K*). The ability of TMEPAI to block activation of the canonical activin/myostatin-SMAD 2/3 axis, was demonstrated by co-injecting AAV6:activin A and AAV6:TMEPAI into healthy mice. In this setting, TMEPAI blocked activin-induced phosphorylation of SMAD3 and associated skeletal muscle wasting. Finally, delivery of AAV6:TMEPAI into tibialis anterior muscles of mice bearing C26 tumours prevented muscle atrophy normally associated with this model. The results support that viral gene delivery of TMEPAI can effectively increase muscle mass via inactivation of the activin/myostatin-SMAD 2/3 pathway.

Adrenal

ADRENAL CASE REPORTS I

POEMS: A Medical Odyssey

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SAT-205

Introduction: POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes) syndrome is a rare disorder with poorly understood pathogenesis. The incidence of endocrinopathy associated with POEMS syndrome has been recognized more frequently in the last two decades, ranging between 67-84%. The cause of endocrine dysfunction associated with the syndrome is not known, but has been described to include hypogonadism, hypothyroidism, abnormalities of glucose metabolism, hyperprolactinemia, gynecomastia in men, hyperestrogenemia, calcium abnormalities and adrenal insufficiency (AI).
Case: A 38 y/o Hispanic male was initially referred to nephrology with complaint of leg swelling. Subsequently, the patient was referred to endocrinology for abnormal thyroid function studies and ongoing fatigue. Patient had prior medical history of recently diagnosed hypothyroidism treated with levothyroxine 100 mcg daily. The most bothersome complaint was pitting edema in the lower extremities with associated pain. He also endorsed right shoulder pain exacerbated by use of the right arm. He reported unintentional weight loss of about 30 pounds in the past 2-3 years, denying night sweats. He did endorse feeling fatigued, skin darkening, and erectile dysfunction. On exam patient was afebrile, BP 120/71 mm/Hg, HR 87 bpm, no goiter, no gynecomastia, skin hyperpigmentation, darkening creases of the palms, pitting edema in lower extremities. Work up showed abnormal lambda monoclonal bands in plasma and monoclonal lambda free light chain in urine. Bone survey showed lytic lesion in right scapula. [prolactin 15.6 ng/ml (normal (NL)= 0-25), free testosterone 23.1 pg/ml (NL= 35.0-155.0), total testosterone 205 ng/dl (NL=