women seen for a PCOS evaluation were selected sequentially and identified as PCOS or non-PCOS (controls) based on meeting NIH criteria at the time of evaluation. In addition to obtaining gonadotropin and metabolic profiles, classical androgens and 11OxyAs were measured using mass spectrometry. The relationship of these androgens to modified Ferriman-Gallwey (mFG) scores and ovarian morphology were also assessed.
Results: Out of 131 women selected, 83 met NIH PCOS criteria at the time of evaluation and 48 did not (controls). Age and BMI did not differ among the two groups. As expected, total T, A4 and LH were all significantly higher in NIH PCOS. A trend towards higher HOMA-IR levels was also seen in NIH PCOS, but this did not reach statistical significance (3±3.9 mg/dL vs. 1.9±1.7 mg/dL, $p = 0.12$). No difference was seen in all four 11OxyAs between NIH PCOS and controls. Unlike previous studies, we also did not find mean 11KT levels to exceed that of T in both controls (T 393±143 pg/mL vs. 11KT 389±206 pg/mL) and PCOS (T 530±245 pg/mL vs. 11KT 388±201 pg/mL). In addition, no relationship was seen between HOMA-IR and 11β-hydroxyandrostenedione (11OHA4) or 11-ketoandrostenedione (11KA4) levels. Within PCOS, DHEAS and A4 were noted to have a weak but inverse relationship to BMI (r^2 0.05 $p = 0.05$; r^2 0.08 $p = 0.007$), whereas no correlation was seen between any of the four 11OxyAs or T and BMI. Lastly, 11OxyAs, T, and A4 levels did not predict mFG scores or polycystic ovarian morphology.
Conclusions: 11OxyAs levels were not statistically higher among women with NIH PCOS compared to at risk women who did not meet NIH criteria. There was no significant relationship between these androgens and mFG scores or ovarian morphology. Further studies are necessary to show the utility of 11OxyAs levels as a marker for hyperandrogenism or metabolic risk.

Pediatric Endocrinology

PEDIATRIC SEXUAL DIFFERENTIATION, PUBERTY, AND BONE BIOLOGY

Low-Dose Infigratinib Treatment Does Not Lead to Changes in Phosphorous Preclinically in Mice

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SUN-098
Background: Infigratinib (BGJ398) is a potent and selective FGFR1-3 inhibitor under evaluation for the treatment of achondroplasia, the most common form of disproportionate short stature. Low doses of infigratinib were shown to be effective in improving skeletal abnormalities in a mouse model of achondroplasia [Demuynck et al. 2019; Komla-Ebri et al. 2016]. At higher doses in adult patients (e.g. 10-100-fold the dose shown to have efficacy in preclinical models of achondroplasia) infigratinib appears to be associated with elevation in phosphorus, an effect known to be associated with FGFR1 inhibition. Specifically, FGFR1 inhibition leads to decreases in FGF23, which, in turn, leads to decreased excretion of phosphate by the kidneys. We sought to understand the relationship between lower doses of infigratinib and changes in phosphorus in preclinical animal models. **Methods:** Changes in phosphorus were tested at multiple doses in three different species - mouse, rat, and dog - across five different studies. Infigratinib was given orally at doses ranging from 0.03 mg/kg to 30 mg/kg. Both PK and PD (i.e., phosphorus) data was available in all species. Measurement days ranged from day 10 to week 12, although PK/PD measurements occurred within 1 day of each other. All animals were treated in accordance with AVMA guidelines. **Results:** No significant dose-phosphorus relationship was observed in rats and mice treated with doses of infigratinib ranging from 0.03 mg/kg to 5 mg/kg. A dose-phosphorus and exposure ($AUC_{0\text{-}24}$)-phosphorus relationship was observed at doses of infigratinib ≥10 mg/kg across transgenic mouse, rat, and dog studies. At low doses, the exposure ($AUC_{0\text{-}24}$)-phosphorus relationship showed a shallow slope with linear regression analysis in rats and mice. **Conclusions:** These findings from five studies in three different species indicate that the exposure-phosphorus relationship is consistent. Importantly, no relationship was observed between dose and phosphorus levels in rats and mice treated with infigratinib at or below 5 mg/kg. Despite the fact that infigratinib is a FGFR1, 2 and 3 inhibitor, low doses of infigratinib shown previously to exert a significant effect in improving skeletal abnormalities in an achondroplasia mouse model, do not seem to result in meaningful changes in phosphorus. These experiments demonstrate that at doses of infigratinib much lower than used in oncology - like those being considered for use in clinical studies of achondroplasia - infigratinib is less likely to cause hyperphosphatemia. Infigratinib will be evaluated in global clinical studies in children with achondroplasia in 2020.

Tumor Biology

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

Preoperative Hematological Parameters Associated with Recurrence or Regrowth of Meningiomas

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SUN-130
Preoperative Hematological Parameters Associated with Recurrence or Regrowth of Meningiomas
Abstract: Meningiomas represent the most frequently diagnosed intracranial tumors. Inflammation and immune processes may play an important role in therapeutic response as well as in anti- and pro-tumor modulating function. In tumors, inflammatory markers have been able to provide useful prognostic information for treatment or clinical evaluation of patients. The aim of this study was to investigate preoperative hematological markers concerning

recurrence or regrowth and clinical variables in meningioma. Eighty nine patients with no corticosteroid therapy were included. Blood tests and tumor characteristics were collected from medical records. Recurrence-free survival was evaluated using Cox regression and Kaplan-Meier curves. Of the 89 cases, 73 (82%) were grade I and 16 (18%) grade II. The mean age was 53±13.9 years, with higher frequency in women, 2:1 proportion. The most frequent subtypes were meningothelial (40.4%), transitional (23.5%) and atypical (17.9%), 64% with peripheral location and 64% had a size greater than 3 cm. Regarding tumor resection, 49 (55.1%) underwent complete surgery (40 remained with tumor (81.6%) and 9 relapse (18.3%)) and 40 (44.9%) submitted to partial resection surgery (29 remained with persistent lesion (72.5%) and 11 regrowth (25%)). In total, 20 (22.4%) cases of recurrence or regrowth were observed. The median recurrence-regrowth free survival (RFS) was 62 months, 96.1% at 1 year, 67.4% at 3 years and 51.2% at 5 years. In univariate analysis, anemia (p=0.04), neutrophilia (p=0.02) and neutrophilis/lymphocyts ratio (NLR) (p=0.03) were associated with an increased risk of recurrence or regrowth and poor RFS. In multivariate, the interaction between anemia and NLR >4 represented a higher risk of recurrence or regrowth (p=0.003). The preoperative presence of anemia, neutrophilia, and NLR was associated with an increased risk of recurrence or regrowth in meningiomas, emphasizing the importance of preoperative evaluation of these parameters.

Diabetes Mellitus and Glucose Metabolism

CLINICAL AND TRANSLATIONAL GLUCOSE METABOLISM AND DIABETES

The Expression of TBC1 Domain Family, Member 4 (TBC1D4) in Skeletal Muscles of Insulin-Resistant Mice in Response to Sulforaphane.

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MON-613

The Expression of TBC1 Domain Family, member 4 (TBC1D4) in Skeletal Muscles of Insulin-Resistant Mice in Response to Sulforaphane.

Background: Obesity is commonly accompanied by impaired glucose homeostasis. Decreased glucose transport to the peripheral tissues, mainly skeletal muscle, leads to reduced total glucose disposal and hyperglycemia. TBC1D4 gene is involved in the trafficking of GLUT4 to the outer cell membrane in skeletal muscle. Sulforaphane (SFN) has been suggested as a new potential anti-diabetic compound acting by reducing blood glucose levels through mechanisms not fully understood (1). The aim of this study is to investigate the effects SFN on TBC1D4 and GLUT4 gene expression in skeletal muscles of DIO mice, in order to elucidate the mechanism(s) through which SFN improves glucose homeostasis.

Methodology: C57BL/6 mice (n=20) were fed with a high fat diet (60%) for 16 weeks to generate diet induced obese (DIO) mice with body weights between 45–50 gm. Thereafter, DIO mice received either SFN (5mg/kg BW) (n=10) or vehicle (n=10) as controls daily by intraperitoneal injections for four weeks. Glucose tolerance test (1g/kg BW, IP) and insulin sensitivity test (ITT) were conducted (1 IU insulin/ g BW, IP route) at the beginning and end of the third week of the injection.

At the end of 4 weeks of the injection, samples of blood and skeletal muscles of both hindlimbs were collected. The expression levels of GLUT4 and TBC1D4 genes were analyzed by qRT-PCR. Blood was also used for glucose, adiponectin and insulin measurements.

Results: SFN-treated DIO mice had significantly lower non-fasting blood glucose levels than vehicle-treated mice (194.16 ± 14.12 vs. 147.44 ± 20.31 mg/dL, vehicle vs. SFN, p value=0.0003). Furthermore, GTT results indicate that the blood glucose levels at 120 minutes after glucose infusion in was (199.83±34.53 mg/dl vs. 138.55±221.78 mg/dl) for vehicle vs. SFN with p=0.0011 respectively. ITT showed that SFN treatment did not enhance insulin sensitivity in DIO mice. Additionally, SFN treatment did not significantly change the expression of TBC1D4, and GLUT4 genes in skeletal muscles compared to vehicle treatment (p values >0.05).

Furthermore, SFN treatment did not significantly affect the systemic insulin (1.84±0.74 vs 1.54±0.55 ng/ml, p=0.436), or adiponectin (11.96 ±2.29 vs 14.4±3.33 ug/ml, p=0.551) levels in SFN vs. vehicle-treated DIO mice, respectively.

Conclusion: SFN treatment improves glucose disposal in DIO mice, which is not linked to the gene expression of GLUT4 and TBC1D4 and its mechanism of glucose disposal in skeletal muscles. Furthermore, SFN treatment did not improve insulin level, and the insulin sensitizer hormone adiponectin as potential players for enhancing insulin sensitivity.

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Axelsson AS, Tubbs E, Mecham B, Chacko S, Nenonen HA, Tang Y, et al. Sci Transl Med. 2017;9(394).

Thyroid

THYROID DISORDERS CASE REPORTS II

A Rare Case of Lithium-Induced Thyroiditis

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SAT-517

Background: Lithium is known to cause both hypo- and rarely hyper- thyroidism. It inhibits release of thyroid hormone and reduces the intrathyroidal iodothyronine/iodothyrosine ratio. Due to direct toxic or immunostimulatory effect, lithium can also cause thyroiditis. Lithium-induced thyroiditis is a rare entity with an incidence rate of about 1.3 cases per 1000 person-years. Given its generally painless and transient nature, symptoms of thyrotoxicosis may erroneously be attributed to an exacerbation of mania.

Clinical Case: We report the case of a 29 y/o man with bipolar disorder on lithium therapy who presented with a 2