software system for bone age assessment and validate its feasibility in clinical practice. Materials and Methods: Greulich-Pyle (GP) and Tanner-Whitehouse (TW3) hybrid method-based deep-learning technique was used to develop the automated software system for bone age assessment. Total 102 radiographs from children with the chronological age of 4.9-17.0 years (mean age 10.9±2.3, 51 cases for females and 51 cases for males) were selected and bone age was estimated with this software. For validation of the automated software system, three human experts have manually performed BAAs at expert's discretion based on GP method for accuracy estimation and one naïve radiologist performed BAAs with automated software system assist and BAAs reading time was recorded in each session for efficiency evaluation. The performance of automated software system was assessed by comparing mean absolute difference (MAD) between the system estimates and the experts manual BAAs.Results: The results of bone age assessment by human experts and automated software system showed no significant difference between the two groups. Each assessed average of bone age were 11.39 ± 2.74 and 11.35 ± 2.76, respectively. MAD was 0.39 years between automated software system BAAs and experts manual BAAs. The 95% confidence interval of the MAD was 0.33 years and 0.45 years. BAAs reading time was reduced from 56.81 sec (95% confidence interval 52.81 - 60.81 sec) in naïve manual BAAs to 31.72 sec (95% confidence interval 29.74 - 33.69 sec) in automated software system assisted BAAs and statistically significant ($p < 0.001$). MAD showed 0.42 years between naïve manual BAAs and the software-assisted BAAs (95% confidence interval 0.31-0.47 years).Conclusion: The newly developed GP and TW3 hybrid automated software system were reliable for bone age assessments with equivalent accuracy to human experts. Also, the automated system appeared to enhance efficiency by reducing reading times without compromising diagnostic accuracy.

Bone and Mineral Metabolism

BONE DISEASE FROM BENCH TO BEDSIDE

The Relationship Between Estrogen Exposure and Bone Health in Women With Cystic Fibrosis

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SUN-LB72

Patients with cystic fibrosis (CF) are at risk for cystic fibrosis-related bone disease (CFBD) characterized by low bone mineral density and fractures. Nutritional status, cystic fibrosis-related diabetes (CFRD), lung health, and sex hormone insufficiency affect CFBD. CF Foundation guidelines recommend exogenous estrogen treatment for women with CFBD and sex hormone deficiency. There is a lack of data regarding effects of exogenous estrogen supplementation on the bone health of CF women. This Emory IRB approved case-control study examined the association of estrogen on bone health in CF women. Data included demographics, sex hormone treatments, CFBD modifiers, and bone mineral density. 35 estrogen exposed subjects were matched 1:2 to 70 estrogen unexposed subjects for age, BMI, and transplant status. Statistical tests analyzed differences in bone health outcomes between the estrogen and non-estrogen exposed groups. At baseline, age, BMI, transplant status, and CFRD were not statistically different ($p>0.05$) between the two groups. The unexposed group had higher rates of pancreatic insufficiency ($p=0.02$). The exposed and unexposed subjects did not have statistically significant differences in areal bone mineral density at lumbar spine, femoral neck, or total hip ($p>0.05$). Our study demonstrates that there are no differences in bone mineral density at 3 different sites between estrogen exposed versus estrogen unexposed women. One limitation is that factors that may also influence bone density including vitamin D status, family history, and severity of CF mutation were not corrected for. Future longitudinal studies should determine if estrogen treatment can increase bone density over time in CF women.

Neuroendocrinology and Pituitary

ADVANCES IN NEUROENDOCRINOLOGY

Repeated Once-Daily Administration of the Non-Hormonal Neurokinin 1,3 Receptor Antagonist NT-814 Reduces LH, Estradiol and Progesterone in Healthy Women

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SUN-LB58

Introduction: Uterine fibroids (UF) affect up to 25% of women and endometriosis (EM) 10% of women worldwide. An ideal therapy would lower estradiol concentrations to reduce hormonal drive to the endometrium and myometrium, but not to the levels which cause the hot flashes and bone loss associated with current treatments. A target estradiol range of 110-180 pmol/L has been proposed[1]. GnRH secretion is modulated by neurokinin B (NKB) acting at the NK3 receptor via hypothalamic neurons expressing kisspeptin, NKB & dynorphin (KNDy neurons). In addition, Substance P acting at the NK1 receptor may also stimulate reproductive hormone release. We hypothesised that NT-814, a dual NK1,3 receptor antagonist, would reduce GnRH release and hence LH, estradiol and progesterone levels in women. This preliminary clinical study in healthy pre-menopausal women evaluated this hypothesis.

Methods: We undertook a randomized, single-blind, placebo-controlled study. 32 healthy women attended for 2 consecutive menstrual cycles. In each cycle blood samples were taken on days 3/4, 9/10, 15/16 and 21/22 to measure serum sex hormone concentrations. No treatment was given in cycle 1 (baseline). During cycle 2, participants received

placebo or one of three doses of NT-814 once per day; 40mg, 80mg or 120mg (n=8 per group) for up to 21 days.
Results: Compared to placebo, NT-814 reduced LH, estradiol and progesterone concentrations in a dose-related manner. The median changes in average LH (IU/L) during cycle 2 compared to cycle 1 were: placebo, 0.16; 40mg, -0.13; 80mg, -0.46; 120mg, -0.58. Median change in average estradiol (pmol/L) in cycle 2 was: placebo, -16.5; 40mg, -9.3; 80mg, -92.1; 120mg, -141.4. The median changes in progesterone (nmol/L) on day 21/22 in cycle 2 compared to cycle 1 were: placebo, 3.2; 40mg, 8.0; 80mg, -5.7; 120mg, -19.4. The reductions in estradiol and progesterone with 120 mg NT-814 were significant (p=0.038 & p=0.046, respectively). There were no clear changes in FSH concentrations. Of note, in women treated with 120mg NT-814, the average estradiol level reduced from 310.8 pmol/L in cycle 1 to 179.8 pmol/L in cycle 2. Cycle length was extended by at least 6 days in 5 of 8 women receiving the 120 mg dose. NT-814 was well tolerated; no participant experienced hot flashes during treatment.
Conclusions: Once-daily administration of the non-hormonal NK1,3 receptor antagonist NT-814 reduced serum LH, estradiol and progesterone in healthy women in a dose-related manner without causing vasomotor symptoms. The 120 mg dose of NT-814 lowered estradiol levels to potentially ideal levels for UF and EM treatment. These preliminary data support further studies with NT-814 to establish its efficacy and safety in treating patients with these hormone driven disorders.
References: [1]Barbieri RL Am J Obstet Gynaecol 1992 166 740-5.

Cardiovascular Endocrinology
ENDOCRINE HYPERTENSION AND ALDOSTERONE EXCESS II

The Arg16/Gln27 Polymorphism of the Beta2-Adrenergic Receptor Impacts Blood Pressure Levels in a Transgenic Mouse Model via Sex-Specific Mechanisms.

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SUN-LB91
Background: The β2-adrenergic receptor (β2-AR) has been implicated in blood pressure (BP) homeostasis via its effects on the sympathetic nervous system, cardiac function, peripheral vascular resistance, and renin release. We also have documented that a β2-AR diplotype (Arg16/Gln27), carried by 15% of hypertensives, have salt sensitive hypertension (SSBP) and increased aldosterone (ALDO).
Gap in knowledge: it has been reported that hypertensive men and women respond differently to beta blockers. However, information regarding sex differences in carriers of the β2-AR risk diplotype is limited.
Hypothesis: In mice, the phenotype in female carriers of the mutant β2-AR risk diplotype will differ from male carriers.
***Methods*:** The CRISPR/Cas9 approach was used to generate transgenic mice carrying 0, 1 or 2 Arg16/Gln27 variant alleles (i.e. wild-type (WT), heterozygous (Het) or mutant (Mut)). The experimental design included twelve weeks old mice divided into 6 genotype/gender groups (male and female; WT, Het and Mut) maintained on low (0.03% Na+, LS) and high sodium diets (1.6% Na+, HS) for a week each.
Results: 1) Both male and female mice displayed significantly increased BP on LS and HS with increasing number of mutated alleles.
2) Only Mut females displayed SSBP ($P<0.05$).
3) As compared to WT, urine and plasma ALDO levels were lower in male (but not female) carriers of the mutated allele ($P<0.05$).
4) As anticipated, urine K^+ excretion was significantly lower in the Mut male (but not female) mice ($P<0.05$).
5) Doppler ultrasound measurements of renovascular function shows that the resistive index was significantly lower in Mut vs WT males ($P<0.05$), consistent with an appropriate increase in renal blood flow (RBF) in the face of an elevated BP. However, in the Mut females the RBF was inappropriately decreased compared to the WT ($P<0.05$).
6) β2-AR expression was significantly lower in female vs. male WT mice; however, this difference was lost in the carriers of the mutated allele, as B2-AR expression levels were significantly higher in female carriers of the mutated allele, as compared to WT ($P<0.05$). Interestingly, the B2-AR genotype had no effect on the receptor expression levels in males.
Conclusion: Both male and female Mut animals have increased BP compared to WT mice, but the mechanisms underlying their increased BP differ by sex. Female Mut mice have SSBP, inappropriately non-suppressed ALDO and decreased RBF. Male Mut mice do not have SSBP and have appropriate ALDO and RBF response to the salt load.

Cardiovascular Endocrinology
VASCULAR DISEASE AND PATHOPHYSIOLOGY

Inflammation May Mediate Coronary Artery Disease in Women With Hypothalamic Hypoestrogenemia: Findings From the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE)

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SAT-LB99
Inflammation may Mediate Coronary Artery Disease in Women with Hypothalamic Hypoestrogenemia: Findings