Reproductive Endocrinology
CLINICAL STUDIES IN FEMALE REPRODUCTION I
Clinically Meaningful Effects of E2/P4 Oral Capsule in Treating Vasomotor Symptoms
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SAT-001
Hormonal therapies effectively reduce the frequency and severity of vasomotor symptoms (VMS) in menopausal women; however, whether the effect is clinically meaningful to women is typically not determined. Oral estradiol/progesterone (E2/P4; mg/mg) 1/100 and 0.5/100 significantly improved moderate to severe VMS versus placebo at weeks 4 and 12. The objective of these analyses was to determine the clinical importance (meaningfulness) of E2/P4 treatment versus placebo in menopausal women.

REPLENISH, a phase 3, randomized, double-blind, placebo-controlled trial, evaluated the safety and efficacy of E2/P4 oral capsules in symptomatic, postmenopausal women with a uterus. Clinically meaningful reductions in weekly VMS frequency were determined using 3 patient-reported outcomes as anchors (VMS severity score, clinical global impression [CGI], and question 1 from the vasomotor domain of the menopause-specific quality of life questionnaire). The proportion of women who had a clinically important response with 0.5/100 was compared with placebo using the Fisher’s exact test. Spearman correlations were also performed across the 3 anchors.

Clinically meaningful reductions in weekly VMS frequency ranged from 32 to 43 at week 4, and from 32 to 48 at week 12. Significantly more responders were observed with 0.5/100 than with placebo for all 3 anchors at both weeks 4 (all, P<0.05) and 12 (all, P≤0.002). All 3 anchors were correlated, supporting their acceptability as appropriate anchors. Treatment with E2/P4 0.5/100 provided consistent clinically meaningful improvements in the weekly frequency of moderate to severe VMS in menopausal women, similar to what has been observed with the CGI-anchor for E2/P4 1/100.

Bone and Mineral Metabolism
CLINICAL ASPECTS OF OSTEOPOROSIS AND VITAMIN D ACTION
Bone Health in Diabetes - Are We Addressing It?
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MON-392
Osteoporosis is a silent disease with decreased bone strength and increased risk of low-trauma fractures. These fractures lead to significant morbidity and mortality and are a major source of medical costs as well as indirect costs from reduced quality of life, disability and death. Calcium and vitamin D (vit D) are important interventions in preventing and treating osteoporosis along with anti-osteoporotic agents. Patients with diabetes mellitus (DM) are at an increased risk of fractures, particularly hip fractures (1). Additionally, bone healing after a fracture is compromised in patients with DM (2). Therefore, addressing bone health can have a significant impact on the well-being of a patient with DM. Optimal management of DM requires a multidisciplinary approach with care that is typically focused on glucose, lipid, and blood pressure management. We hypothesized that bone health may not be addressed consistently in patients with DM due to the need to address these other aspects of their care.

We, therefore, conducted a retrospective chart review of patients with DM over the age of 50 with the aim to determine if bone health is being identified and if treatment is being initiated. A total of 100 patients (67 female, 33 male) were studied at the University of New Mexico Diabetes Comprehensive Care Center. Information regarding age, sex, DM type, vit D status and therapy, BMD, and FRAX score were collected. Vit D levels were checked in 68% female and 76% male patients. Mean vit D level was 31.8 ng/ml (reference range 30–100 ng/ml). Low vit D was identified in 33 patients of which only 18% were started on treatment. None of the 10 men identified received treatment for low vit D. BMD was obtained in only 21% of patients even though more than half met criteria for BMD screening based on age alone. Younger women (age < 65y) had more DXA scans performed than older women. Osteoporosis was diagnosed in one female and one male patient. Two female patients over age 65 met criteria for treatment based on FRAX. None of these 4 patients received osteoporosis therapy other than vit D replacement.

In conclusion, vit D levels were checked in the majority of our patients indicating that bone health is being considered to some extent. However, low vit D levels were treated in only a minority of women, and in none of the men. Also, none of the patients who met criteria for osteoporosis treatment were started on therapy suggesting a lack of appropriate interventions. Using the results from this study, we plan to improve our clinical practice by incorporating bone health more into the care of our patients with DM, identify those at risk for osteoporosis-related fractures, and institute appropriate interventions.

References:
1. Fan Y, Wei F, Lang Y, Liu Y. Osteoporosis Int 2016: 27: 219–228
2. Jiao H, Xiao E, Graves DT. Curr Osteoporosis Rep. 2015 Oct; 13(5): 327 – 335.

Bone and Mineral Metabolism
BONE DISEASE FROM BENCH TO BEDSIDE
Characterizing Functional Performance in Adults with Hypophosphatasia
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SUN-349

Introduction:
Limited data exist regarding physical and cognitive functioning of adults with hypophosphatasia (HPP), and there are no guidelines for evaluation by physical therapists (PT), occupational therapists (OT), or speech-language pathologists (SLP). We evaluated physical and cognitive functioning among adults with HPP through comprehensive assessments and patient reported outcome tools.

Methods:
Sixteen participants with HPP (median age 42 (32.5-50.5) yrs, 73% female, 100% Caucasian, 50% on enzyme replacement therapy) completed standardized assessments of mobility, balance, fine motor control, activities of daily living and cognition, as well as self-reported measures of health-related quality of life, fatigue, depression and anxiety.

Results:
Compared with normative data from community dwelling adults, participants traveled less distance on a Six-Minute Walk Test (1.376 ± 431** ft vs 1873±299) and had slower gait on a 10-Meter Walk Test (1.04±0.21 vs 1.39–1.46 m/s). Participants were slower to respond on the Nine Hole Peg Test (20.6±2.4s** for right & 21.7±2.4s** for left hand vs 16.5s to18.5s), and 2 had an abnormally slow reaction time via Dynavision (0.9s* [0.85,0.96], functional speed is <1.15s). 20% scored in the low average/borderline range of performance on the Repeatable Battery for the Assessment of Neuropsychological Status, suggesting potential cognitive impairment. On the Short Form-36, 75% reported limitations in their ability to fulfill life roles due to physical problems (25%±39%ile**), 75% reported below average energy (30%±23ile**), and 100% rated their health as unlikely to improve (32%±15%ile**). Fatigue Severity Scale scores were well above the median for a healthy population (47 [34,60.5]* vs 2.3). Median scores for Depression, Anxiety, and Stress were within the normal range, but moderately severe depression was reported by 4 participants. Participants reported moderate (4), severe (1), or extremely severe (1) anxiety; and 4 reported severe (2) or extremely severe (2) stress.

Conclusions:
Objective functional assessments indicate mild deficits, but participants self-reported significant limitations due to physical dysfunction, indicating that current objective testing may not be sufficient in the HPP population. Impaired reaction time may indicate potential safety concerns with driving or certain occupations, and screening may be indicated. A subgroup of participants was significantly affected by depression, stress, and/ or anxiety. Guidelines and additional assessment tools should be created to further evaluate physical and cognitive functioning among adults with HPP. The use of PT, OT, and SLP specialists can aid in establishing baseline assessment of impairment and developing treatment plans with objective metrics for assessing efficacy of treatment.

*median
**mean

Steroid Hormones and Receptors
STEROID AND NUCLEAR RECEPTORS

MDC1 Is a Novel Estrogen Receptor Co-Regulator in Invasive Lobular Carcinoma of the Breast
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OR12-05
Invasive Lobular Carcinoma (ILC) is the 2nd most common histotype of breast cancer, but is critically understudied. ~95% of ILC are estrogen receptor (ER) positive, and previous studies demonstrate the importance of estrogen in ILC etiology. However, retrospective studies show that anti-estrogens are substantially less effective in ILC than in ER+ Invasive Ductal Carcinoma (IDC). This strongly suggests that regulation of ER function is unique in ILC, and we hypothesize that this is due to an ILC-specific cohort of ER co-regulators. We performed Rapid Immunoprecipitation Mass Spectrometry of Endogenous Proteins (RIME) to determine ILC-specific ER-interacting proteins, and identified Mediator of DNA Damage Checkpoint 1 (MDC1) as a novel ER co-regulator in ILC cells. We confirmed ER:MDC1 interaction by co-immunoprecipitation and proximity ligation assays (PLA); interaction was specifically observed in ILC cell lines but not IDC cell lines. Consistent with co-regulator function, we found MDC1 is essential for ER-driven proliferation of ILC cells. MDC1 knockdown dysregulates transcription of ER target genes in ILC cells (e.g. IGFBP4, WNT4). Moreover, RNA-seq analysis showed that in ILC cell line MDA MB 134VI, >50% of ER target genes require MDC1 for their regulation. To understand how MDC1 controls ER transcriptional activity, we performed ChiP-qPCR and found that MDC1 controls ER binding to DNA in ILC cells. Further, MDC1 controls binding of the pioneer factor FOXA1 to DNA, and Dual PLA studies of ER:MDC1 and ER:FOXA1 interaction revealed that MDC1 knockdown decreased ER:FOXA1 interaction. MDC1 canonically functions in DNA damage response, but our preliminary data suggest MDC1 is decoupled from its canonical role in DDR in the context of ER co-regulator activity in ILC cells. Together, these data suggest MDC1, independent of its role in DDR, acts as a novel ER co-regulator in ILC and regulates ER:DNA binding and ER transcriptional function to drive ILC cell proliferation and survival.

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CLINICAL STUDIES IN FEMALE REPRODUCTION I

Insulin Treatment in Human Pregnancy Mitigates an Increased Risk of Postpartum Psychological Distress with Maternal Obesity in the Absence of a Pre-Existing Mood and Anxiety Disorder
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