

## Reproductive Endocrinology

### CLINICAL STUDIES IN FEMALE REPRODUCTION I

#### *Do Psychological Factors Influence Exercise Related Amenorrhea?*

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**Purpose:** The etiology of functional hypothalamic amenorrhea (FHA) can involve both metabolic and psychogenic stressors. The role of metabolic stress has been described in exercising women who develop FHA secondary to chronic energy deficiency attributable to inadequate dietary intake in the face of exercise training. The potential for psychological factors to contribute to exercise-related FHA is unknown. **Methods:** In our cross-sectional comparison of exercising women ((n=61), exercise  $\geq 2$  hours/week, age 18-35 years, BMI 16-25 kg/m<sup>2</sup>, we tested whether psychological factors discriminated participants who were deemed eumenorrheic or had FHA as confirmed by physical examination, health history, metabolic and endocrine screening, menstrual calendars and daily urinary collection for reproductive hormone metabolites. Body composition, energy balance, and metabolic and endocrine parameters were assessed in addition to psychological factors (Dysfunctional Attitudes Scale, Brief-Resilient Coping, Daily Stress Inventory, Perceived Stress Scale (PSS), Profile of Mood States (POMS), Beck Depression Inventory) and eating behaviors (Eating Disorder Inventory-2, Three-Factor Eating Questionnaire). **Results:** Exercising women with FHA had a significantly lower BMI (20.2 vs 21.5 m/kg<sup>2</sup>,  $p < 0.05$ ), less body fat (22.8 vs 25.8%,  $p < 0.05$ ), and a lower fat mass (56.2 vs 58.3 kg,  $p < 0.05$ ), compared to eumenorrheic women. Fasting total triiodothyronine (75.4 vs 89.8 ng/dL,  $p < 0.001$ ), leptin (5.2 vs 9.0 ng/dL,  $p < 0.01$ ), and the ratio of actual to predicted resting metabolic rate (0.84 vs 0.92,  $p < 0.01$ ) were significantly lower in FHA women. FHA women demonstrated a greater drive for thinness (2.9 vs 2.1,  $p < 0.05$ ), greater dietary cognitive restraint (11.3 vs 7.4,  $p < 0.001$ ), and displayed more dysfunctional attitudes, i.e., need for social approval (39.1 vs 33.7,  $p < 0.05$ ) compared to eumenorrheic women but there were no differences in perceived stress, depression, mood states, brief resilient coping, or daily stress ( $p > 0.05$ ). Notably, FHA women displayed a significant positive correlation between need for social approval and indicators of stress (PSS:  $r = 0.50$ ), depression (Beck:  $r = 0.59$ ), and mood (POMS-depression/dejection:  $r = 0.55$ ), which was not apparent in eumenorrheic women. Additionally, EDI-drive for thinness was significantly positively correlated with many of the variables associated with stress (PSS:  $r = 0.47$ ), depression (Beck:  $r = 0.51$ ), dysfunctional attitudes ( $r = 0.55$ ), and mood disorders (POMS-depression-dejection:  $r = 0.37$ ; tension/anxiety:  $r = 0.44$ ) (all  $p < 0.05$ ). **Conclusion:** In exercising women, psychological factors do not overtly discriminate reproductive status; however, in women with FHA, there appears to be a higher need for social approval and restrictive eating behaviors may be related to underlying indicators of psychological stress and depression. US DoD PR054531

## Bone and Mineral Metabolism

### BONE AND MINERAL CASE REPORTS II

#### *Treatment-Resistant Vitamin D Deficiency: Is It a Vitamin D Binding Protein Issue?*

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##### Introduction

Vitamin D is present in free and bound forms; the bound form is complexed mainly to vitamin D binding protein (DBP). Vitamin D levels are affected by age, pregnancy, liver disease, obesity, and DBP mutations. We report a patient with treatment-resistant vitamin D deficiency suggestive of a DBP with abnormal vitamin D binding.

##### Clinical Case

A 58-year-old Pakistani male with a history of hypertension, sleep apnea and hypogonadism presented to endocrine clinic with symptoms including fatigue, generalized muscle cramps, and joint pain. Evaluation of common causes of fatigue, such as anemia, thyroid dysfunction and adrenal insufficiency were ruled out with CBC, thyroid hormone levels and ACTH stimulation test results all within normal ranges. A 25-OH vitamin D level was profoundly low (4.2 ng/ml; normal 30-100), and a 1,25-OH vitamin D level was undetectable ( $< 8$  pg/ml; normal 18-72), leading to a presumptive diagnosis of severe vitamin D deficiency. However, his calcium, phosphorus, alkaline phosphatase and kidney function were in the normal range. Furthermore, the absence of osteoporosis, fracture history, or kidney stones suggested adequate vitamin D action at target tissues; PTH levels were high-normal to minimally elevated, ranging 70-94 pg/ml (12-88pg/mL). Aggressive supplementation with vitamin D3 at 50,000 IU 3 times a week and 5,000 IU daily failed to normalize 25-OH vitamin D (ranged 4.6-10ng/ml; normal 30-100) and 1,25-OH vitamin D levels remained undetectable. Addition of calcitriol resulted in mild hypercalcemia and was discontinued. Malabsorption did not appear to be a contributing factor, as a negative tTG antibody (with normal IgA) excluded celiac disease. Vitamin D metabolites levels measured with mass spectrometry showed undetectable 25-OH vitamin D levels (D2  $< 4$  ng/ml, D3  $< 2$  ng/ml; total  $< 6$ ng/ml; normal 20-50) and 1,25-OH vitamin D levels ( $< 8$  pg/ml). Urine N-telopeptide, 24-hour urine calcium (177mg; 100-240) and bone-specific alkaline phosphatase were all normal. Repeat testing over more than five years showed similar results. DBP levels of 269 ug/ml [104-477] excluded DBP deficiency.

##### Clinical Lesson

Vitamin D deficiency is increasingly part of routine testing in internal medicine and endocrinology clinics, as is repletion with high-dose vitamin D. However, in rare cases such as this, relying on 25-OH vitamin D levels can be misleading, and supplementation unnecessary or potentially harmful. Thus, treatment decisions should consider the full clinical context and further evaluation performed when warranted. This patient's labs are suggestive of an abnormality in the DBP, supporting future examination using molecular testing.