leptin (metreleptin). Previous case series have reported dramatic weight loss and metabolic improvements with treatment, but metreleptin's only FDA-approved indication is acquired generalized lipodystrophy (AGL). Metreleptin has a black box warning for risk of T-cell lymphoma, which has been reported in AGL patients, both treated and untreated with metreleptin.

Clinical Case: Two sisters ages 18 yrs (sister A; BMI 45.2 kg/m^2) and 20 yrs (sister B; 45.0 kg/m^2) were referred for evaluation of obesity. They are of Pakistani origin with a family history of consanguinity. Birth weight was normal, but hyperphagia and excessive weight gain developed by age 3 months. They had been seen by endocrinologists, obesity specialists, and a geneticist during childhood but work-up for monogenic obesity was not pursued. They were treated with combination OCPs in adolescence due to primary amenorrhea and hypogonadotropic hypogonadism. Sister A was diagnosed with type 2 diabetes at age 15 years. Sister B had comorbidities of hydrocephalus s/p VP shunt, developmental delay, hyponatremia, autoimmune thyroid disease, growth hormone deficiency, and prediabetes. At the time of their present evaluation, serum leptin levels were obtained and were undetectable in both sisters. After discontinuing OCPs, testing confirmed hypogonadotropic hypogonadism. Both patients were homozygous for the pathogenic variant c398delG in exon 3 of the leptin gene (LEP), which causes a frameshift/premature stop codon. On MR elastography performed for hepatic steatosis, sister B had an incidental finding of axillary lymphadenopathy. Surgical biopsy and staging work-up confirmed diagnosis of nodular lymphocyte predominant Hodgkin lymphoma (a B cell lymphoma), Stage II disease. She was treated with R-ABVD with adjuvant radiation and achieved clinical remission, prior to treatment with metreleptin. The patients were enrolled in an observational treatment protocol, and responses to metreleptin therapy will be reported in future.

Conclusion: To our knowledge, these are the first cases of CLD diagnosed in the U. S. In previous reports, CLD and other monogenic obesity disorders were prevalent among children with severe obesity in a consanguineous Pakistani population. Leptin deficiency should be considered in all patients with early onset obesity and hypothalamic amenorrhea. Furthermore, to our knowledge, this is the first report of lymphoma in a patient with CLD, occurring prior to any treatment with metreleptin. The risk for lymphoma associated with metreleptin may relate to preexisting autoimmune disease or immunologic abnormalities related to leptin deficiency rather than medication adverse effect.

Bone and Mineral Metabolism

BONE DISEASE FROM BENCH TO BEDSIDE

Bone Marrow Adipose Tissue Is Associated with Fracture Prevalence in Anorexia Nervosa

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Anorexia nervosa, a psychiatric disorder predominantly affecting women, is characterized by self-induced starvation, low body weight, low subcutaneous and visceral fat depots, and low bone mass. More than 85% of women with anorexia nervosa have bone mineral density (BMD) values more than one standard deviation below the mean of women of comparable age. Although there is a significantly increased risk of fracture in women with anorexia nervosa, low BMD has not been shown to consistently predict the increased fracture rate in this population. Despite low subcutaneous and visceral adipose tissue stores, women with anorexia nervosa have increased bone marrow adiposity, which is inversely associated with BMD. We hypothesized that increased bone marrow adipose tissue would be associated with the increased fracture rate in women with anorexia nervosa. We studied sixty-two women: 34 with anorexia nervosa (mean age + SEM: 28.3 + 0.9 years) and 28 normal-weight controls of similar age (28.3 + 1.1 years; p=0.72). We examined associations between lifetime self-reported fracture history and 1) BMD of the lumbar spine (L1-L4), lateral spine (L2-L4), total hip, and femoral neck measured by dual energy X-ray absorptiometry and 2) bone marrow adipose tissue at the spine (L4 vertebra) and hip (femoral metaphysis, diaphysis and epiphysis) measured by ^{1}H-magnetic resonance spectroscopy. Women with anorexia nervosa had significantly lower BMD at the spine and hip (p<0.0001 at all sites) and significantly higher bone marrow adipose tissue at the L4 vertebra (p<0.0001) and femoral metaphysis (p=0.001) as compared to normal-weight controls. Forty-seven percent (n=16) of women with anorexia nervosa versus 39% (n=11) of normal-weight controls reported a lifetime history of fracture (p=0.54). In women with anorexia nervosa, there was no significant association between fracture history and BMD at the spine or hip (p=0.27-0.98). In the group as a whole, bone marrow adipose tissue was greater in the L4 vertebra in individuals with a history of fracture compared to those without a fracture history (p=0.02). In subjects with anorexia nervosa, those with a history of fracture had greater bone marrow adipose tissue at the L4 vertebra (p=0.01) and femoral diaphysis (p=0.01) compared to those without a history of fracture; these differences in bone marrow adipose tissue remained significant after controlling for BMI (p=0.01-0.03) and also after controlling for BMD (p<0.01 for both). Higher bone marrow adipose tissue is associated with increased fracture prevalence and may be a better predictor of fracture risk than BMD in women with anorexia nervosa. Future prospective studies will be necessary to better understand the association between bone marrow adiposity and fracture risk in this population.

Bone and Mineral Metabolism

BONE DISEASE FROM BENCH TO BEDSIDE

Real-World Clinical Profiles of Adults with Hypophosphatasia (HPP) from the Global HPP Registry

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