Dr. Adi Cohen

PROJECT SUMMARY
Idiopathic osteoporosis (IOP) affects otherwise healthy young men and women with intact gonadal function and no secondary cause of bone loss. In men, IOP is associated with osteoblast dysfunction and low bone formation that is related to deficient insulin-like growth factor 1 (IGF-1), a hormone produced in response to growth hormone (GH) that is anabolic to the bone-forming osteoblast. In our recently completed NIH-funded bone biopsy study of 64 premenopausal women with IOP, a subset had very low bone formation rates and significantly higher IGF-1 levels, in contrast to men with IOP. Moreover, women with IOP, low bone formation and high serum IGF-1 levels did not respond to teriparatide (TPTD), an osteo-anabolic medication that increases bone mineral density (BMD) by stimulating bone formation via IGF-1-dependant mechanisms. These findings lead us to hypothesize that women with IOP, low bone formation and high IGF-1 have IGF-1 resistance that renders them less responsive to IGF-1 and also TPTD, at the skeletal (osteoblast) level. We also hypothesize that such women may have evidence of IGF-1 resistance in non-skeletal tissues. IGF-1 resistance, whether related to abnormalities with the hormone itself, its binding proteins or its receptors, would be expected to have clinical features similar to those of adult growth hormone deficiency of pituitary origin: decreased BMD and lean body mass, increased visceral adiposity, insulin resistance, and elevated serum low-density-lipoprotein (LDL) cholesterol and cardiovascular risk markers such as C-reactive protein (CRP), interleukin-6 (IL-6) and homocysteine. The goals of this pilot study are to determine whether premenopausal women with IOP and low bone formation have evidence of IGF-1 resistance in skeletal and non-skeletal tissues, and whether skeletal and non-skeletal markers of IGF-1 resistance predict their response to TPTD. I will accomplish these goals in the context of a new randomized double-blind placebo-controlled phase 2 trial of TPTD for the treatment of premenopausal IOP funded by the FDA Orphan Diseases Program (FD003902). The primary outcome variables of this trial are limited to BMD, microarchitecture and remodeling. This R03 grant will capitalize upon and leverage the recruitment of 40 premenopausal women with IOP to investigate a set of research questions distinct from the parent grant and focused upon the contribution of IGF-1 resistance to the pathogenesis of premenopausal IOP and the response to TPTD assessed by 12 month increase in spine BMD. This work is innovative because it is the first study to investigate the influence of the GH/IGF-1 axis and visceral adiposity on the mechanism of action of the osteo-anabolic agent, TPTD, in humans. Moreover, a substantial proportion of postmenopausal women with osteoporosis do not respond to TPTD, for reasons that are not clear. This R03 will provide pilot data for a future R01 application focused on the interplay between the GH/IGF-1 axis, adipose distribution and response to TPTD in postmenopausal osteoporosis, a disease of high clinical impact that is far more common than IOP.