Dr. Mishaela Rubin

The parent study for this ancillary proposal, the Targeting INflammation using SALsalate in Type 2 Diabetes (TINSAL) trial, found that a high dose salicylate, salsalate, improved glycemic control in patients with T2D. These results support the concept that inflammation is an important pathophysiologic element in Type 2
Diabetes Mellitus (T2D). Chronic inflammation has been shown to negatively influence bone remodeling by increasing bone resorption and reducing bone formation. These abnormalities are being described in the skeleton of subjects with T2D along with the new recognition that the skeleton is a target organ for complications of T2DM. T**he hypothesis of this proposal is that reducing inflammation in T2D will lead to a rebalancing of the bone remodeling process.**
To test this hypothesis, we will measure biochemical markers of bone turnover in stored samples from the TINSAL study. In the parent study, 108 T2D subjects were randomized to placebo or salsalate (3.0, 3.5 or 4.0 g/d tid) for 14 weeks. All 3 salsalate doses significantly improved glycemic control and other metabolic parameters of T2D. This ancillary proposal will investigate whether biochemical markers of bone remodeling similarly improve with salsalate treatment. We will also determine whether reductions in inflammatory markers and adiponectin levels, already measured in TINSAL, predict changes in bone remodeling, and whether changes in bone remodeling in turn predict the observed improvements in the glycemic parameters. The data to be obtained will address fundamental issues of abnormal skeletal dynamics in T2DM as they may relate directly to the inflammatory process. This study promises to provide insight into the etiology of skeletal abnormalities in T2D and may suggest therapeutic, or mechanistic, approaches to the skeletal complications of T2D. Until recently, the skeleton has not been traditionally recognized as a target organ for complications in T2D. Newly emerging lines of evidence, however, suggest that T2D and the skeleton may, in fact have important relationships to each other. One of the key cellular products of the osteoblast, the cell in bone that directs processes associated with bone formation, is osteocalcin. It has been shown recently that osteocalcin participates in glucose homeostasis by signaling pancreatic cells as well as adipocytes. This finding may be related to epidemiologic studies which associate T2D with increased fracture risk. The dynamic of reduced bone formation in T2D thus may relate to reduced osteocalcin activity. Reduced osteocalcin activity, in turn, may be related to abnormal glucose homeostasis. Inflammation, which is an important participant in the pathogenesis of T2D, may link these two systems together.