Dr. Pam Freda

Acromegaly is a rare disease characterized by excess GH and IGF-I and their multi-system adverse effects. Epidemiological data associate acromegaly with increased morbidity and mortality primarily from cardiovascular causes, which are often attributed to acromegaly's associated metabolic abnormalities including insulin resistance. However, these abnormalities' etiology and contribution to increased CV risk cannot necessarily be equated with those of similar metabolic syndrome components in other populations. Rather, as our novel preliminary data suggest, we hypothesize that a GH-IGF-I excess specific dysregulation of adipose tissue (AT) and lipodystrophy occur. This lipodystrophy, we propose, includes reduced central AT depots yet increased AT in muscle and contributes to insulin resistance, adipokine and appetite hormone dysregulation, endothelial cell dysfunction and ultimately increased CV risk in active acromegaly. Biochemical control of acromegaly should reverse these abnormalities. However, we have identified some patients whose remission is accompanied by significant weight gain and a rise in crp. In them, we hypothesize that as GH/IGF-I normalize, reversal of the lipodystrophy markedly increases central AT, macrophage infiltration and inflammation in AT and systemic inflammation. Whether inflammation persists and these patients' ultimate body composition as well as the role of post-therapy increases in ghrelin levels in stimulating weight gain need to be determined. We will test these hypotheses by studying patients with active acromegaly before and during therapies utilizing techniques novel to the study of acromegaly and the GH/IGF-I axis including examinations of muscle lipid by MRI and 1HMRS, hepatic lipid by 1HMRS, adipose tissue for macrophage infiltration and inflammation and function of biopsied endothelial cells. We will also relate these clinical endpoints to our modern biochemical markers of acromegaly and thereby establish clinically validated biochemical guidelines for acromegaly therapy. Understanding the consequences of this lipodystrophy and its reversal are crucial because new potent medical therapies for acromegaly now allow us to titrate therapy to particular biochemical goals and even a target for IGF-I within the spectrum of the normal range which may have long term clinical significance with regard to cardiovascular outcomes. This proposal is strengthened by its continuation of our unique, ongoing prospective acromegaly cohort study. This study, the only one on acromegaly funded by the NIH, has provided novel important data on a number of aspects of acromegaly in particular its biochemical markers. The endpoints and outcomes studied in the current application can only be achieved with long term follow up of a uniquely large, consecutive, well-characterized cohort, which we have well underway. Acromegaly provides a model through which we
can improve our knowledge about the effects of GH and IGF-I excess on adipose tissue, systemic inflammation, endothelial dysfunction and CV risk which is also applicable to our understanding of the effects of GH use and over-use in other clinical settings.
