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This project builds on our novel, uniquely NIH-funded prospective study of 330 patients with acromegaly, a disease originating in a GH secreting pituitary tumor that is characterized by excess circulating GH and IGF-1 and the multi-system morbidity and increased mortality they produce. Acromegaly provides a model through which we can improve our knowledge of GH and IGF-1 effects on adipose tissue (AT), body composition and liver and muscle lipid accumulation, in this and other clinical settings. The leading cause of acromegaly death, CV disease, likely relates to the prevalent metabolic abnormalities, in particular insulin resistance. Our work suggests, however, that the paradigm linking metabolic and body composition abnormalities to CV disease in the general population does not apply in acromegaly. This project proposes, alternatively, that a novel acromegaly-specific lipodystrophy underlies the metabolic abnormalities and may impact long-term outcome. Based on our preliminary data, we hypothesize that the lipodystrophy produces a unique pattern of AT redistribution, reduced visceral adipose tissue mass and hepatic lipid despite insulin resistance and increased inter-muscular adipose tissue mass that cause insulin resistance. Understanding this process is important because acromegaly medical therapies may not uniformly reverse this lipodystrophy. Utilizing state of the art body composition methods Aim 1 tests new hypotheses emerging from our data, including that GH is a negative regulator of liver fat and somatostatin analogs (SSA) increase muscle lipid. These will be tested by comparisons to specially matched controls and to patients with GH deficiency and HIV lipodystrophy (HIVLD), two disorders with reduced GH secretion and increased VAT and CV risk. GHD and HIVLD patients will be examined before and after GH or GHRH analogue therapy, respectively, for a pattern of body composition change opposite to that with GH lowering. We will assess epicardial adipose tissue, a depot with important links to CV disease, but is understudied in acromegaly and HIVLD. Aim 2 investigates mechanisms for therapy-specific body composition changes, specifically the roles of ghrelin, gut and pancreatic hormone changes during SSA therapy on ectopic lipid accumulation and future risk of DM. Integral to the acromegaly lipodystrophy and its link with insulin resistance are GH's effects in AT. Aim 3 investigates biopsied AT, testing the hypothesis that acromegaly produces a novel dissociation of inflammatory and immune cell phenotypes that reverses with acromegaly treatment and that may relate to insulin resistance and altered lipid and energy metabolism in AT. The inflammatory profile of circulating monocytes, which may relate to CV risk, will also be tested in acromegaly, GHD and HIVLD. Aim 4 analyzes mortality and morbidity outcomes related to the lipodystrophy in our well-characterized, longitudinal cohort using modern GH and IGF-1 measures. This project provides important guidelines for acromegaly therapy. Understanding this lipodystrophy, its consequences and reversal, is crucial to optimally treating patients, correcting their metabolic abnormalities and excess CV risk.