PROJECT SUMMARY
The overall goal of this project is to support my continued professional development as an independent patient oriented investigator and successful mentor. A focus of my research has been to establish and validate optimal biochemical endpoints for acromegaly therapy based on highly sensitive GH and IGF-I measurements utilizing a uniquely large cohort of patients that I have established. We are now also assessing clinical endpoints of acromegaly therapy. This recent work has identified novel changes in body composition in patients with acromegaly. These findings have led us to hypothesize that a GH-IGF-I excess specific dysregulation of adipose tissue (AT) and lipodystrophy occur which is characterized by reduced central AT depots yet increased AT in muscle and may contribute to insulin resistance and increased cardiovascular risk. Acromegaly therapy may reverse this lipodystrophy, but in some patients this may increase central AT stores and thereby increase inflammation in AT as well as in circulation. This application?s first 4 scientific aims, funded by my R01 DK064720, test how the lipodystrophy and its recovery affect AT inflammation, adipokines, appetite hormones, endothelial function, cv risk markers and long-term outcome in acromegaly. We will utilize techniques novel to acromegaly studies including examinations of muscle lipid by MR spectroscopy, adipose tissue for macrophage infiltration and inflammation and endothelial cells for markers of endothelial dysfunction. Understanding the consequences of this lipodystrophy and its reversal are crucial because they may be of long-term clinical significance. This study, the only one on acromegaly funded by the NIH, will provide novel important data which is also applicable to our understanding of the effects of GH use and over-use in other clinical settings. This application includes a new investigation (Aim 5) into the affect of GH/IGF-I excess and its treatment on the skeleton. Fractures are increased in acromegaly, but bone mineral density (BMD) is not reduced. Utilizing the novel assessment of bone architecture by HRpQCT along will BMD, fracture prevalence and bone metabolism marker measurements we will determine, among other endpoints, if bone architecture (by HRpQCT) is impaired in patients with a seemingly normal BMD due to an artifact of increased bone size. My productive, ongoing, NIH funded clinical research program, my successful mentoring track record and my 16 years of experience in patient-oriented research make me well suited for renewal of the K24 award. The additional funds provided by the K24 will allow me to maintain my high level of effort on NIH funded patient oriented research and mentoring. The institutional environment at Columbia, with a strong and diverse Endocrine Division, CTSA, CRC, Diabetes and Obesity Research Centers, is ideal for attracting fellows and conducting our research. Renewal of this award is an ideal mechanism to ensure the continued support I need to maintain my success as a mentor and clinical researcher.