# Metabolic Aspects of Acromegaly and Its Treatment

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**Growth hormone (GH) affects virtually all facets of metabolism. This review concentrates on the effects of GH excess on carbohydrate, lipid, and bone metabolism, and on body composition. The effect of treatment with the somatostatin analog, octreotide, on the gastrointestinal-pancreatic axis is also discussed.**


## PHYSIOLOGY

GROWTH HORMONE (GH) affects virtually all facets of metabolism. Insulin-like growth factor-1 (IGF-1) is transported in the blood bound to carrier proteins, with IGF-1 binding protein-3 (IGFBP-3) possibly being the most important of these. The concentration of binding protein is in turn regulated by GH. Many effects of GH are mediated by IGF-1. The concentrations of both IGF-1 and IGFBP-3 are elevated in acromegalic patients. GH secretion is influenced by metabolic and nutritional factors. Lack of glucose or free fatty acids enhances, and their excess suppresses, GH secretion.[1] GH acts as an agonist of insulin to promote postprandial protein synthesis. During prolonged fasting it becomes an insulin antagonist, promoting lipolysis and ketogenesis.[2,3] The metabolic information is relayed in a feedback loop via the hypothalamus and possibly also directly to the pituitary.[1,4]

Binding of GH to its cell membrane receptor in the liver induces nuclear IGF-1 transcription.[5] Serum IGF-1 is modulated by metabolic influences. Thus, malnutrition and diabetes mellitus are accompanied by low serum IGF-1 concentrations.[6,7] In addition, many tissues—including the epiphyseal cartilage of the long bones—generate their own IGF-1, which acts locally as a paracrine/autocrine factor.[8] This tissue-specific IGF-1 generation is also influenced by circulating GH.

Recently, the discovery of IGF-1– and IGFBP-degrading enzymes has added a new aspect to the overall control of the GH/IGF-1/IGFBP axis.[9,10]

## PATHOPHYSIOLOGY

### *Intermediate Metabolism*

Chronic GH excess causes insulin resistance and impairment of glucose tolerance. Muscle glucose uptake and metabolism are diminished. This is overcome by a concomitant increase in insulin secretion, but the pancreatic β-cell reserves may become exhausted. In approximately one third of acromegalic patients, insulin resistance leads to impaired glucose tolerance or overt diabetes mellitus. Long-term treatment of dogs with high-dose GH produces permanent metahypophyseal diabetes mellitus ("Houssay dog"[3]) but in acromegalic patients successful treatment usually normalizes glucose tolerance.[11,12]

During octreotide treatment of acromegalic patients, the early (first 90 minutes) insulin response to oral glucose is diminished, followed by a later near normal increase.[13] Due to the concomitant suppression of GH, peripheral insulin resistance is reduced and glucose tolerance remains unimpaired in most, but not in all, patients. The insulinotropic intestinal hormone glucagon-like intestinal polypeptide (7-36)-amide (GLIP-1[14]) is affected in parallel with insulin. Unlike GH suppression, both also show a partial escape from the octreotide effect during chronic treatment.[15] The effect on GLIP-1 may thus play a role in the diminished insulin secretion during octreotide therapy.

The increased fat mobilization and ketone body production of GH excess[3] are also partially offset by the simultaneous insulin augmentation. Increased amino acid retention and stimulation of protein synthesis are direct effects of GH.[16,17] Together, these metabolic actions of GH lead to the relative decrease in body fat and increased lean body mass of acromegaly.[18] However, muscle strength is not necessarily greater.

### *Body Composition*

GH excess causes an increase in total body water and extracellular fluid volume, due to the antinatriuretic action of GH. These changes probably explain the mild arterial hypertension found in acromegaly. The role of the renin-angiotensin-aldosterone system in these alterations is at present controversial.[19,20] Skeletal muscle and total body potassium are also increased. Body composition reverts to normal after normalization of the GH concentration, despite persistence of an increased body cell mass.[21,22] It is of note that complete reversal occurs only at mean GH concentrations less than 2 to 3 μg/L, which is in accordance with the stricter criteria for cure of acromegaly that are now accepted.

### *Bone Metabolism*

The direct and indirect effects of GH excess on bone, cartilage, and soft tissue are the hallmarks of acromegaly. GH excess stimulates calcium absorption from the gastrointestinal tract, but also excretion of calcium and phosphate in the urine.[8] Bone turnover is increased. Both markers of bone formation (osteocalcin) and of bone resorption (colla-

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gen crosslinks) are increased. However, serum parathyroid hormone (PTH), vitamin $D_3$, and calcium levels are usually within normal limits in acromegaly.[23-25] The net effect on bone of the GH and IGF-1 excess in acromegaly is an increase of cortical bone. Whether trabecular bone is decreased or unchanged is still somewhat controversial, partly due to confounding effects of hypogonadism in many acromegalic patients.

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