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Insulin-Like Growth Factor 1 as a Pillar in Acromegaly: From Diagnosis to Long-Term Management

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Acromegaly is a rare disease characterized by hypersecretion of growth hormone (GH) and its peripheral target, hormone insulin-like growth factor 1 (IGF-1), with most cases of acromegaly caused by GH-secreting pituitary tumors [1]. Worldwide, acromegaly has an annual incidence of 0.38 (95% confidence interval [CI], 0.32 to 0.44) per 100,000 person-years and a pooled prevalence of 5.9 (95% CI, 4.4 to 7.9) per 100,000 persons [2]. In Korea, the annual incidence in 2018 was estimated to be 3.4 per million persons, with a prevalence of 27.0 per million persons [3].

Elevated concentrations of GH and IGF-1 affect various organs, with most patients with acromegaly having multiple comorbidities, including sleep apnea, diabetes mellitus, and malignancy, further impairing patient quality of life (QoL). In addition, patients with acromegaly have a higher overall mortality of rate than the general population [3]. The primary goal of treatment is normalization of IGF-1 and GH concentrations, with additional goals including minimization of tumor growth, symptom relief, management of complications and improved patient QoL. These goals may be achieved by multimodal approaches, which include surgery, radiotherapy, and medical treatment with somatostatin receptor ligands, dopamine agonists, and GH receptor antagonists [1].

Early detection and treatment of acromegaly are hindered by the slow, insidious development of clinical features over decades, with the resultant physical changes unnoticed by patients, family members and physicians, thus delaying diagnosis [4]. The recent 14th Acromegaly Consensus Conference met to consider biochemical criteria for the diagnosis of acromegaly, to evaluate the therapeutic efficacy of current treatments, and to develop consensus recommendations suggesting new understandings of disordered GH and IGF-1 in patients with acromegaly [5]. Unlike previous guidelines, in which diagnosis was based on elevated IGF-1 for age and confirmed by a GH concentration >1 μg/L after a 75-g oral glucose tolerance test (OGTT), these consensus guidelines recommended that, in patients with typical features of acromegaly, an IGF-1 concentration >1.3 times the upper limit of normal for age is confirmatory of a diagnosis of acromegaly. These guidelines also recommend that patients with equivocal results undergo repeat testing of IGF-1 concentrations using the same validated assay. OGTT might also be useful, whereas GH suppression after OGTT was not required for a diagnosis of acromegaly [5].

Although GH concentrations diagnostic of acromegaly are dependent on the assays performed, reduced GH after OGTT has been considered the gold standard, both for diagnosis and the determination of biochemical remission [1]. This assay, however, has several limitations. First, there is no cut-off for glucose-suppressed GH that definitively excludes a diagnosis of acromegaly. In addition, several factors, including sex, body mass index, and use of estrogen-containing oral contraceptives, affect GH nadirs in healthy adults. Furthermore, up to one-third of patients with acromegaly may show a paradoxical increase in GH following OGTT [5]. Therefore, consensus guidelines rec-

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ommend that this test be performed in patients with equivocal baseline hormone concentrations.

Hormone levels are affected by various factors. For example, IGF-1 levels vary by race, age, and sex and GH levels vary by assay [6]. Although technical advances have improved assay sensitivity, absolute biochemical thresholds for cure have not been defined. Recent consensus guidelines adopted the term "remission," indicating an inability to detect active disease even if present. Follow-up assessments should include biochemical evaluations of treatment effectiveness, imaging modalities evaluating residual recurrent adenoma mass, and clinical determination of the signs and symptoms of acromegaly, as well as its complications and comorbidities [5].

Biochemical remission is the primary indicator of treatment outcome, but biochemical findings should be interpreted relative to the clinical signs and symptoms of acromegaly. In contrast to previous consensus guidelines, in which IGF-1 normalization and reduced GH after OGTT were considered indicative of therapeutic efficacy, current consensus guidelines recommend determining efficacy by measuring IGF-1. Although IGF-1 is an indirect indicator of endocrine activity and stabilization of IGF-1 levels after treatment is delayed, IGF-1 is a stable marker and may be a reliable alternative to OGTT after surgery for acromegaly. The area under the receiver operating characteristics curve (AUC) was found to be >0.8 at all postoperative time points, except for 1 week postoperatively, with the highest AUC (0.928) observed 6 months after surgery [7]. Moreover, 92.6% patients showed consistent normalization of IGF-1 levels [7].

Although IGF-1 is thought to play a greater role than GH in the diagnosis and management of acromegaly, this consensus recommendation has not yet been adopted directly in Korea, especially in patients receiving medical treatment in Korea. A 2019 position statement of the Korean Endocrine Society recommended use of a GH cut-off level of 2.5 μg/L for changes in drugs and their doses. This position statement did not include IGF-1 concentration as a criterion for changes in drugs and their doses because IGF-1 secretion can be affected by factors other than acromegaly, and data on the normal range of IGF-1 concentrations in the Korean population are lacking [8]. Further studies of IGF-1 in the Korean population are needed prior to the adoption of the recent Acromegaly Consensus Conference statement.

Fig. 1 provides an overview of the diagnosis and management of acromegaly. Acromegaly is a chronic, slowly progressive disease. If suspected, it can be detected early and managed properly. Greater understanding of the roles of IGF-1 levels may improve disease management and QoL in patients with acromegaly.

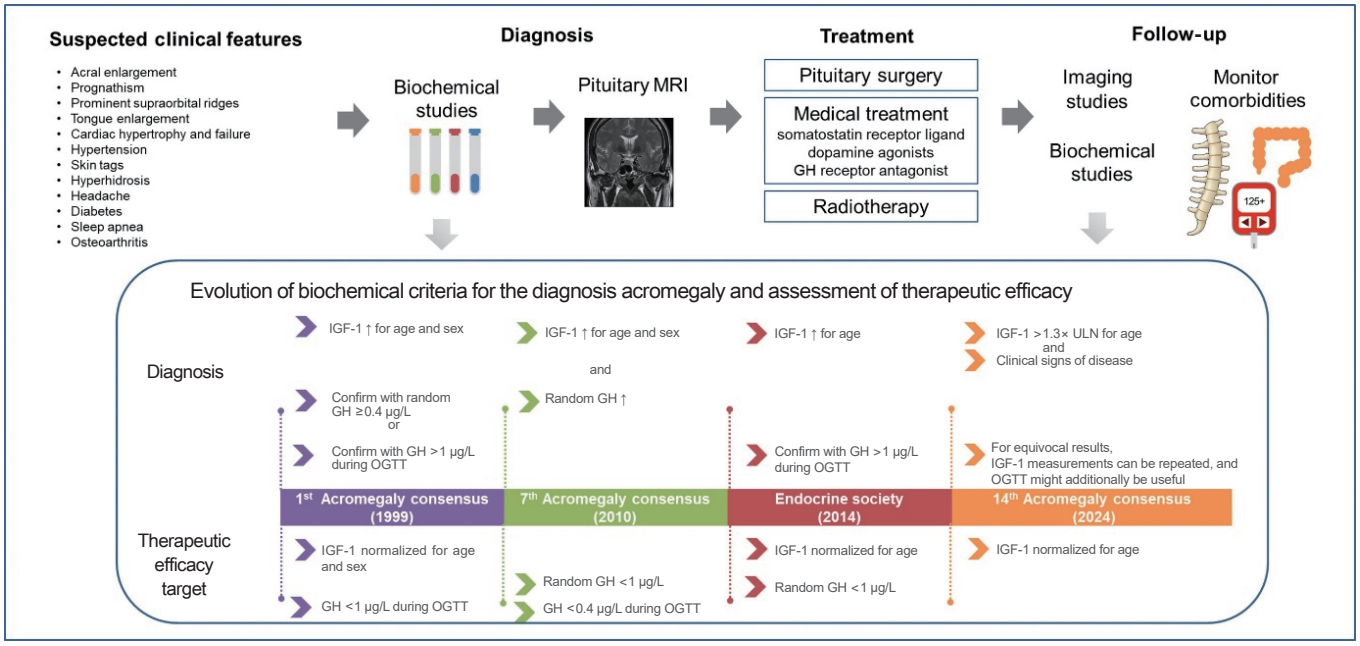

Fig. 1. Overview of the diagnosis and management of patients with acromegaly and evolution of biochemical criteria for the diagnosis of acromegaly and assessment of treatment efficacy. MRI, magnetic resonance imaging; GH, growth hormone; IGF-1, insulin-like growth factor 1; ULN, upper limit of normal; OGTT, 75-g oral glucose tolerance test.

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CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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