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The Challenge of the Biochemical Control of Acromegaly

Alessandro Ciresi* and Carla Giordano

Biomedical Department of Internal and Specialist Medicine (DIBIMIS), University of Palermo, Italy

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***Corresponding author:** Alessandro Ciresi, Section of Endocrinology, Diabetology and Metabolic Diseases, Biomedical Department of Internal and Specialist Medicine (DIBIMIS), University of Palermo, Piazza delleCliniche 2, 90127 Palermo, Italy, Tel: 916552709; Email: a.ciresi@virgilio.it

Opinion

Acromegaly is a rare andslowly progressive disease characterized by an excessive growth hormone (GH) secretion and increased circulating levels of insulin-like growth factor 1 (IGF-1), more frequently caused by a pituitary adenoma [1,2]. Unfortunately, its diagnosis is often delayed of about 5 years due to the insidious nature of the disease [3,4] and, consequently, acromegalic patients often show overt systemic complications and comorbidities at diagnosis, with a decreased life expectancy [5-7]. The most common complications of acromegaly, including cardiovascular, metabolic andrespiratoryalterations, have been demonstrated to be closely related to GH levels [8]. Therefore, the achievement of optimal biochemical control of acromegaly is crucial and it has been shown to be correlated with improvement of clinical signs and symptoms, comorbidities and mortality risk [9,10]. A "safe" GH or IGF-1 level should be the level of hormone below which the increased mortality associated with acromegaly is reduced to that seen in the general population.

During the years various guidelines and consensus statements provided algorithms to clarify the interpretation of GH and IGF-1 levels during the management of acromegaly, also differentiating them according to the treatment, and the criteria of cure have changed over time. From the first official criteria defined in 2000 [11], many advances have been made in the subsequent years. Random GH does not always provide a reliable measure of disease activity, because of overlaps between the upper range of normal GH levels of healthy subjects and levels of acromegalic patients [12]. To date, the current GH nadir limits after OGTT seem to be adequate to define remission of acromegaly [13]. If after pituitary surgery the GH nadir after OGTT of less than 1μg/l (0.4μg/l with ultrasensitive assays) with a concomitant normalization of IGF1, defines control of acromegaly, on the other hand the GH suppression during OGTT is of limited value in evaluating biochemical control in patients who are receiving pharmacological treatment. In these cases, IGF-1 and a random GH<1μg/l are sufficient for assessment of biochemical response, with the exception of patients treated with pegvisomant, in whom IGF-1 becomes the main and reliable biochemical marker of therapeutic efficacy [14,15]. However, despite the advances in acromegaly management and treatment, some aspect of the biochemical control remain a challenge, because of the availability of standardized assays, the difficult comparison of hormonal levels measured by traditional vs. modern GH assays or the discrepant hormonal results in a fair number of patients. In addition, the GH levels adopted as criteria for biochemical control of acromegaly must be considered not only assay, but also gender, age, and BMI specific, indicating the need of individual cutoff limits for each assay and in groups of subjects with homogeneous gender, age and BMI. Indeed, to date, these factors are not considered for the interpretation of the GH levels, although this point could represent a limit in the interpretation of many results [11,16]. In this light, IGF-1 represents a more reliable marker of disease activity because of the availability of gender-, age- and assay-normalized values [17].

Generally, in cases of discrepant values of GH and IGF-1 is mandatory to require biochemical confirmation with an expectant approach before starting additional treatment or increasing the dose of actual treatment after excluding all possible interfering causes and in these cases a closely follow-up is needed [18].

A challenge also remains the question on the optimal frequency of hormonal measurementsduring the follow-up. Due to the different half-lives of GH and IGF-1 and the rate of discordant hormonal levels, it is important to define the appropriate and optimal timing intervals to assess the biochemical evaluation for each treatment. To date, the biochemical evaluation after 12 weeks from surgery seems to be a reliable marker of remission [11,13], while the biochemical effectiveness of medical treatment should be assessed initially at 3-6 months intervals [19], although the optimal frequency of follow-up measurements remain to

be clarified. However, finding new biochemical markers could certainly help to guide treatment decision when discordant hormonal levels are obtained.

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