Acromegaly is a disease that leads to not only significant morbidity but also premature mortality. It is estimated that untreated acromegaly results in at least a 10-yr shortening of life span (1, 2). For this reason, aggressive efforts have been made to cure or in most cases attempt to control the pathophysiological changes that occur in acromegaly. Because remission of signs and symptoms is not a highly reliable index of reversal of disease-related pathologies in acromegaly and because the abnormal tissue growth requires a long time to normalize and cannot be measured precisely over the long term, biochemical markers have been sought to determine whether patients who have been treated for acromegaly have entered into a remission. Furthermore, because surgery does not cure most patients with acromegaly, at some point in the treatment evaluation, a decision has to be made as to whether a second or third form of therapy will be added, and this decision has to be justified based on the persistent elevation of biochemical markers that correlate with long-term outcome. Most studies that have evaluated treatment results in acromegaly have compared improvement in symptoms with changes in GH secretion (3–6) after treatment, although some have analyzed other biochemical markers, such as urinary hydroxyproline or calcium excretion, serum glucose or serum phosphate (7–10). Although changes in these markers correlate with clinical improvement, only GH and IGF-I have been correlated with long-term mortality, specifically in attempting to determine whether a patient’s mortality risk has been lowered to that of the general population. Direct measurements of GH have been used with the rationale that GH is a tumor secretory product that will correlate most closely with the change in long-term outcome. The problem in using random GH measurements has been that the values fluctuate widely in normal subjects (thus rendering a definition of normal is impossible), and in patients with acromegaly it has been difficult to substantiate what constitutes normalization. Because glucose suppression of GH has been considered the gold standard for diagnosis, some mortality studies have used glucose suppressed GH as an index of cure (11–13). Other studies have used random or fasting GH measurements (14–17). Changes in GH assay methodologies have further complicated the usefulness of these measurements. These changes, although often improving the precision of the measurements, have resulted in lowering of the absolute values; thus, it has been difficult to make historical comparisons between GH assays. An additional problem with GH assays has been the differences among reference laboratories, which can vary as much as 4-fold across various laboratory measurements, thus making standardization for the purpose of long-term monitoring difficult (18, 19).

IGF-I is a peptide whose structure is similar to insulin and whose serum concentrations increase in response to GH (20). IGF-I has been shown to be increased in acromegaly (21). IGF-I has also been shown to be useful in predicting mortality in long-term follow-up studies of acromegalic patients (11, 12, 14). An advantage of IGF-I is that it can be used as a single measurement that can be obtained at any time of day because, unlike GH, it has a half-life of 16 h in serum and its values do not fluctuate acutely.

A recent study published by Ayuk et al. (13) has stated a strong case for utilizing glucose-suppressed GH or random GH measurements after a therapeutic intervention to determine long-term outcome. All subjects in this study had at least two GH measurements and a single IGF-I measurement. The investigators compared the results of GH testing to IGF-I measurements. They report that the results of multiple GH measurements correlate much better than the single IGF-I measurement with long-term outcome. The overall standardized mortality ratio (SMR) was increased, with borderline significance, i.e. 1.55 (range, 0.97–2.50) in patients with GH levels greater than 2 μg/liter. In contrast, abnormal IGF-I only predicted an increase to 1.2 (range, 0.71–2.03). The authors conclude that only suppression of GH to less than 2 μg/liter is useful as a predictor of long-term outcome in acromegaly and that the use of IGF-I as a marker of effective treatment is not justified.

There are several problems with this study. First, some patients died before IGF-I measurements came into use in this multicenter study; therefore, they were not included in the IGF-I group, but were included in the GH group. The IGF-I data were available in only 360 of 419 patients, whereas GH data were used in 414 of 419 patients. The authors showed unequivocally that cerebrovascular mortality was increased in patients who received radiation treatment. They do not state how many of the 54 patients who received only GH measurements had radiotherapy. Because radiotherapy was the best predictor of accelerated mortality, it is possible that if a disproportionate number of cases who received radiotherapy were in the GH measurement alone group, this could have biased the results. A second problem that has plagued several studies attempting to evaluate usefulness of IGF-I is inadequate numbers of normative subjects that are used to define normal ranges. IGF-I values decrease as a function of increasing age; therefore, normative data have to be age stratified to properly assess IGF-I values (22). This necessitates the use of a large number of normal subjects to precisely define the age-adjusted reference range. The final problem is the IGF-I assay method. A relatively older method (e.g. acid/ethanol extraction) for removing IGF-I binding

Abbreviations: IGFBP, IGF binding protein; SMR, standardized mortality ratio.

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proteins (IGFBPs) was used, and this method does not always remove all of the binding proteins from the samples. These proteins can interfere with the IGF-I measurement. Furthermore, the assay sensitivity was relatively low, e.g. 2 nm, suggesting that the antibody used was of relatively low affinity. This makes it likely that the IGF-I assay will be more prone to interference from residual IGFBPs. These problems make extrapolation of these data to the other studies of the usefulness of IGF-I in predicting mortality difficult.

Two recent studies that were also published in *JCEM* and compared the usefulness of GH and IGF-I measurements in predicting increased mortality in acromegaly have provided additional insight. A study by Holdaway *et al.* (14) evaluated prognostic markers in 208 acromegalic patients followed for 13 yr. The SMR was 2.6 for those with a GH after glucose of greater than 5 μg/liter. It was 1.6 for those with a suppressed GH between 2.5 and 5 μg/liter, and it was 1.1 for those with a GH less than 1 μg/liter. IGF-I values in Holdaway’s study were converted to sp scores. The SMR was 3.5 (95% confidence interval, 2.8–4.2) for those with an sp score greater than 2, 1.6 (not significant) for those with an sp score between 0 and 2, and 1.0 for those with an sp score less than 0. Survival was related to the last GH measurement and independently to the last IGF-I measurement. The authors concluded that both factors relate independently to mortality and that reduction of either measurement into the normal range reduced mortality risk to that of the general population. This study confirmed the previous results of Swearingen *et al.* (23) who had also noted a SMR of 1.7 (significantly increased) in acromegals with IGF-I values greater than 2 sp above the mean. It should be noted that in the study by Holdaway *et al.* (14), an attempt was made to adjust GH values for the changes in standards and assays that occurred over the study interval. Likewise, an attempt was made to adjust the IGF-I values. All patients received both GH and IGF-I measurements at the same intervals, and for the data analysis the results of the single GH measurement were compared with a single IGF-I measurement. A recent study (12) has confirmed these results. This study compared the results of four serial IGF-I measurements taken over 10 yr to serial GH measurements taken at the same time intervals. The study included 164 patients (12). The SMR for subjects having serial IGF-I values that were more than 2 sp above the mean for the 10-yr interval was 4.78:1. Using a GH value for normal of less than 2 μg/liter, the SMR was 1.6:1 (range, 0.8–3.94), which was not significantly increased. Glucose-suppressed GH had a lower SMR of 1.3:1, and this was not increased.

All studies that have attempted to predict mortality risk in acromegaly clearly suffer from the necessity to conduct a very long-term study with a relatively small number of deaths because this is a rare condition. Therefore, several errors related to ascertainment bias may confound interpretation of the results. However, all three of these studies discussed herein were remarkably consistent in that a GH value greater than 2 μg/liter predicted an increased SMR of approximately 1.7:1 (range, 1.6–1.8). Although this was not statistically significant in the study of Biermasz *et al.* (12), the number of patients deaths was relatively low, presumably because the initial surgery was very effective in normalizing IGF-I. In contrast, two of the studies (12, 14) showed significantly increased SMRs when elevated IGF-I was used. Significant differences exist among the three studies in the use of age-adjusted normative data, the types of IGF-I assays that were performed, and the number of IGF-I measurements that were used in making the prediction. The greatest difference exists among the number of measurements that were performed; that is, the two studies that found a high predictive value for IGF-I used either a single IGF-I measurement compared with a single GH measurement or multiple IGF-I and GH measurements obtained at the same intervals. In contrast, the study that found no correlation used multiple GH measurements compared with a single IGF-I measurement. In clinical practice, it is routine to use acromegals at relatively frequent intervals (i.e. at least twice per year) and to obtain IGF-I measurements at these intervals. Therefore, for the practicing clinician multiple IGF-I measurements should be available to guide therapeutic decisions. Based on the four large published trials that have used IGF-I measurements, the study of Bates *et al.* (16) notwithstanding, a clinician should be able to make a reliable judgment as to whether the patient is in the lowest mortality risk group, based on whether the IGF-I is within the age-adjusted normal range. If doubt exists, it would certainly be prudent and appropriate to measure GH both fasting and after oral glucose administration and to use this as an adjunct measurement to guide therapeutic decisions. However, the published data do not justify eliminating IGF-I measurements as a useful prognostic indicator. Furthermore, the recent development of a GH receptor antagonist that can normalize IGF-I in 97% of subjects with acromegaly (24) and with which GH measurements will not be useful because the receptor has been blocked further emphasizes the importance of being able to reliably conclude that the measurement of IGF-I in treated acromegaly accurately predicts long-term prognosis in this disease.

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