Plasma insulin-like growth factor-I (IGF-I) in the diagnosis of acromegaly

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Abstract

Insulin-like growth factor-I (IGF-I) has been suggested to be a good alternative marker for the diagnosis of acromegaly. In this study, 42 samples collected from 25 treated acromegalic patients over 2 years were assayed for fasting growth hormone (GH), IGF-I and IGF-binding protein-3 (IGFBP-3). 23/42 (54.8%) samples were considered normal based on the normal cut-off value of 10 mIU/L for random GH secretion, but only 9 (21.4%) and 16 (38.1%) samples were within the age-matched reference values for IGF-I and IGFBP-3 respectively. Three patients had persistently elevated levels of GH, IGF-I and IGFBP-3, while 2 patients were diagnosed biochemically cured when these markers remained normal up to 8 months. IGF-I remained high in 2 other patients despite normalised GH and IGFBP-3, and disease activity subsequently returned when IGFBP-3 also became elevated. Similarly, 2 patients diagnosed normal following OGTT also had high IGF-I, and subsequently, showed increased secretions of GH and IGFBP-3. IGF-I has a curvilinear relationship with GH, plateauing at higher GH levels. Failure to recognise this relationship caused many investigators to doubt the usefulness of IGF-I. Nevertheless, this study has shown that IGF-I is indeed a reliable prognostic index for acromegaly, provided results are interpreted with reference to well establised, age-matched normal values.

Key Words: acromegaly; insulin-like growth factor-1; growth hormone

Introduction

Acromegaly is the result of growth hormone (GH) hypersecretion, usually of intrinsic pituitary neoplasm origin, although in some rare cases, could also be due to GHRH-secreting gangliocytoma (Sano *et al.*, 1988), GHRH-secreting carcinoids (Sonksen *et al.*, 1976; Shalet *et al.*, 1979) or GH-secreting islet cell tumours (Thorner *et al.*, 1982). Early diagnosis and monitoring of treatment are crucial to prevent mortality or reduce morbidity from respiratory, metabolic, cardiovascular or malignant complications that are normally associated with the disease (Rajasoorya *et al.*, 1994; Melmed 1990; Melmed *et al.*, 1995). Since GH secretion is pulsatile, high GH level from a single random sampling is not a reliable indicator of acromegaly (Wan Nazaimoon *et al.*, 1992; Roth *et al.*, 1963) and confirmatory diagnosis of the disease has been based on the failure to suppress GH to the level between 2-4 mIU/L following a 75g oral glucose load (Wan Nazaimoon *et al.*, 1992; Schuster *et al.*, 1981; Stewart *et al.*, 1989). However, as the test involves multiple sampling, is expensive and time-consuming, a GH level of <10 mIU/L on a single measurement has often been used as the criteria for normalcy, either during diagnosis or when reviewing therapy (Tucker *et al.*, 1980; Laws *et al.*, 1979). Nevertheless, there are now several studies to suggest that insulin-like growth factor-1 (IGF-I) (Ho *et al.*, 1990; Schaison *et al.*, 1983; Dobrashian *et al.*, 1993; Bates *et al.*, 1995) and IGF-binding protein-3 (IGFBP-3) (Grinspoon *et al.*, 1995), both being GH-dependent (Daughaday *et al.*, 1987; Blum *et al.*, 1990), are good alternatives and useful indicators of GH hypersecretion.

We report the results of our evaluation on the sensitivity and usefulness of a single determination of IGF-I in monitoring response to treatment of acromegaly and compared the results to that of GH and IGFBP-3.

Subjects and Methods

Twenty-five treated acromegalic patients (age range 18-72 years) from the Endocrine Clinic, Universiti Kebangsaan Malaysia, participated in the study. Patients gave informed consent prior to the study, and were clinically and biochemically assessed over a period of 2 years, for disease activity following therapy.

Fasting venous blood sample was obtained from the forearm vein and plasma aliquots for GH, IGF-I and IGFBP-3 were stored frozen at -40°C until assayed. Three patients were also subjected to the 75g oral glucose tolerance test (OGTT). GH was determined by an in-house enzyme immunoassay (Wan Nazaimoon *et al.*, 1993) and IGF-1 by RIA after acid-ethanol cryoprecipitation (Blum & Breier, 1994) using antiserum B-71 supplied by Dr BH Breier, Research Centre for Developmental Medicine and Biology, University of Auckland, New Zealand. IGFBP-3 was assayed by RIA using Nichols Diagnostic kit. Intra- and inter-assay coefficient variations were 5.8 and 9.1% respectively for IGF-I, 4.9 and 8.4% respectively for IGFBP-3, and

7.4 and 9.6% respectively for GH.

Results

A total of 42 estimations for fasting GH, IGF-I and IGFBP-3 levels were carried out during the 2 year study period. 23/42 (54.8%) samples were considered normal if based on the cut-off value of 10 mIU/L for normal, random GH secretion (Laws *et al.*, 1979; Tucker *et al.*, 1980). However, when compared to the age-matched reference values (Table 1), only 9 (21.4%) and 16 (38.1%) of these samples had normal levels of IGF-I and IGFBP-3 respectively. Of the 7 patients who were being assessed on more than one occasion, 3 patients continued to exhibit disease activity with persistently elevated levels of GH, IGF-I and IGFBP-3. Conversely, 2 patients were diagnosed biochemically "cured" based on the fact that their GH, IGF-I and IGFBP-3 levels had remained within the reference values even at 8 months follow-up visit. On the other hand, in another 2 patients, there was initial normalisation of GH and IGFBP-3 secretion following therapy, but their IGF-I levels were above the age-matched normal reference values (Table 1). On subsequent visits, although the GH secretion was still normal, there was abnormal increase in IGFBP-3 and persistently elevated IGF-I levels, suggesting the possibility of disease recurrence.

The GH, IGF-1 and IGFBP-3 results following OGTT are summarised in Table 2. GH secretion was suppressible in two patients, while in one patient, the 2-hour post-glucose GH level remained at 5.7 mIU/L

Table 1. Normal adult reference values for IGF-I and IGFBP-3 (95% confidence interval)

Age Group (y)	IGF-1 ((g/L)	IGFBP-3 (mg/L)
20 - 30	172 - 473	2.4 - 4.5
31 - 40	155 - 378	1.6 - 4.4
41 - 50	103 - 291	1.6 - 4.4
51 - 80	111 - 192	1.6 - 3.8

Table 2. Plasma levels of GH, IGF-I and IGFBP-3 of patients who were subjected to OGTT.

Patient (Age/Sex)	Visit 1					Visit 2		
	GH at OGTT (mIU/L)			IGF-1	IGFBP-3	GH	IGF-1	IGFBP-3
	0 hr	1 hr	2 hrs	(µg/L)	(mg/L)	(mIU/L)	(µg/L)	(mg/L)
1 (35/M)	1.7	1.5	1.3	532[a]	5.4	185[a]	683[a]	6.4[a]
2 (30/M)	6.9	0.6	0.6	352	3.6	1.8	236	3.7
3 (25/M)	7.1	6.0	5.7	547[a]	3.3	11.9	1018[a]	6.5[a]

[a]$p<0.01$ compared to age-matched normal reference range

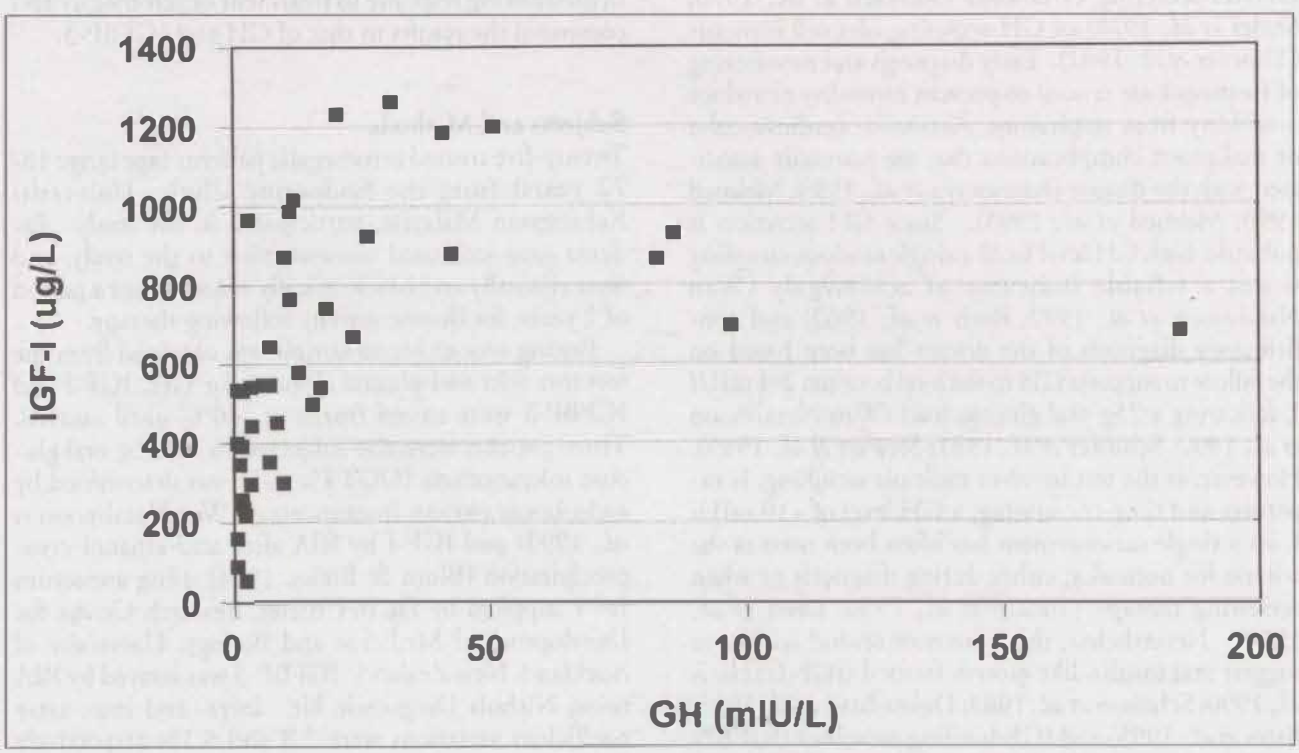

Fig. 1. Correlation between IGF-I and GH in 42 specimens of 25 treated acromegalic patients.

which was above the cut-off value of 4 mIU/L used by our laboratory to confirm diagnosis of acromegaly or presence of disease activity (Wan Nazaimoon *et al.*, 1992). Hence, if assessment was based on the suppressible GH response to OGTT, 2 patients would have been diagnosed cured. However, 2 of these patients actually had high basal IGF-I levels and on follow-up visits, both of these patients were found to have increased secretions of GH, IGF-I and IGFBP-3, indicating returning of disease activity .

Basal GH and IGF-1 levels has a curvilinear relationship (Fig. 1). Plasma IGF-1 levels, which plateaued at approximately 1200 µg/L, showed no further increase at GH concentrations above 20 mIU/L. Although a number of patients with GH concentrations higher than 50 mIU/L had lower levels of IGF-1, the values were still significantly higher than the age-matched normals. Similar curvilinear relation was also observed between GH and IGFBP-3; IGFBP-3 plateaued at about 10 mg/L and declined to lower levels at GH concenrrations above 50 mIU/L (Fig. 2). In contrast, the association between IGF-1 and IGFBP-3 was linear (r=0.625, p=0.0001, Fig. 3).

Discussion

Growth hormone, a useful biochemical marker for the diagnosis of acromegaly, is one of the most important regulators of IGF-I and IGFBP-3 synthesis (Baxter 1991; Blum *et al.*, 1993). Due to the pulsatile nature of GH secretion, and since IGF-1 and IGFBP-3 have longer half-lives, many studies have been carried out to determine whether single measurement of either of these peptides could replace the need of multiple measurements of GH when diagnosing acromegaly and/or assessing effectiveness of therapy. Indeed, compared to the random basal GH level, IGF-I has been found to be a more practical alternative and a reliable biochemical index of GH hypersecretion (Schaison *et al.*, 1983; Barkan *et al.*, 1988). IGF-I correlates with GH levels, and is a good indicator of GH status (Dobrashian *et al.*, 1993; Barken *et al.*, 1988). However, as observed in this study, and in accordance with several previous studies (Schaison *et al.*, 1983; Dobrashian *et al.*, 1993; Oppizzi *et al.*, 1986; Barreca *et al.*, 1989), the positive relationship between GH and IGF-I was linear only up to GH level of about 20 mIU/L, with IGF-1 plateauing at about 1200 µg/L. At higher GH concentrations, IGF-I had instead, showed a decline. As a result of failure to recognise this curvilinear association, and by relying merely on the computed results which showed poor overall linear regression correlation coefficients, several investigators have doubted the usefulness of IGF-I when assessing treatment of acromegaly (Schaison *et al.*, 1983; Dobrashian *et al.*, 1993; Barreca *et al.*, 1989; Nortier *et al.*, 1985). However, with the availability of method-based, age-matched, normal adult reference values, IGF-I was found to be a reliable prognostic marker of acromegaly. A number of the patienrs studied who later showed recurrence of the disease would have been diagnosed cured if based on their normalised basal GH or GH response to glucose. Technically, low fasting GH level suggests absence of disease recurrence and the patient need not be subjected to OGTT. In this study, the 3 patients who had to undergo the OGTT were

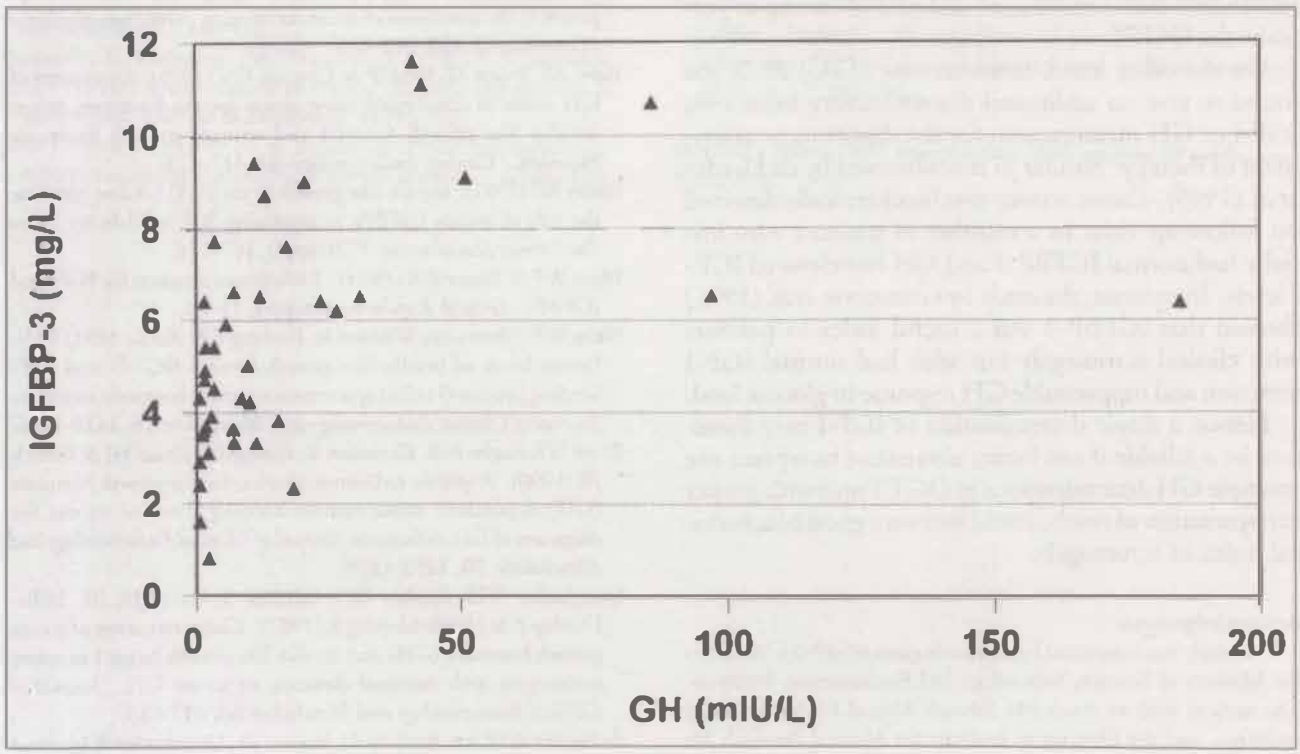

Fig. 2. Correlation between IGFBP3 and GH in 42 specimens of 25 treated acromegalic patients.

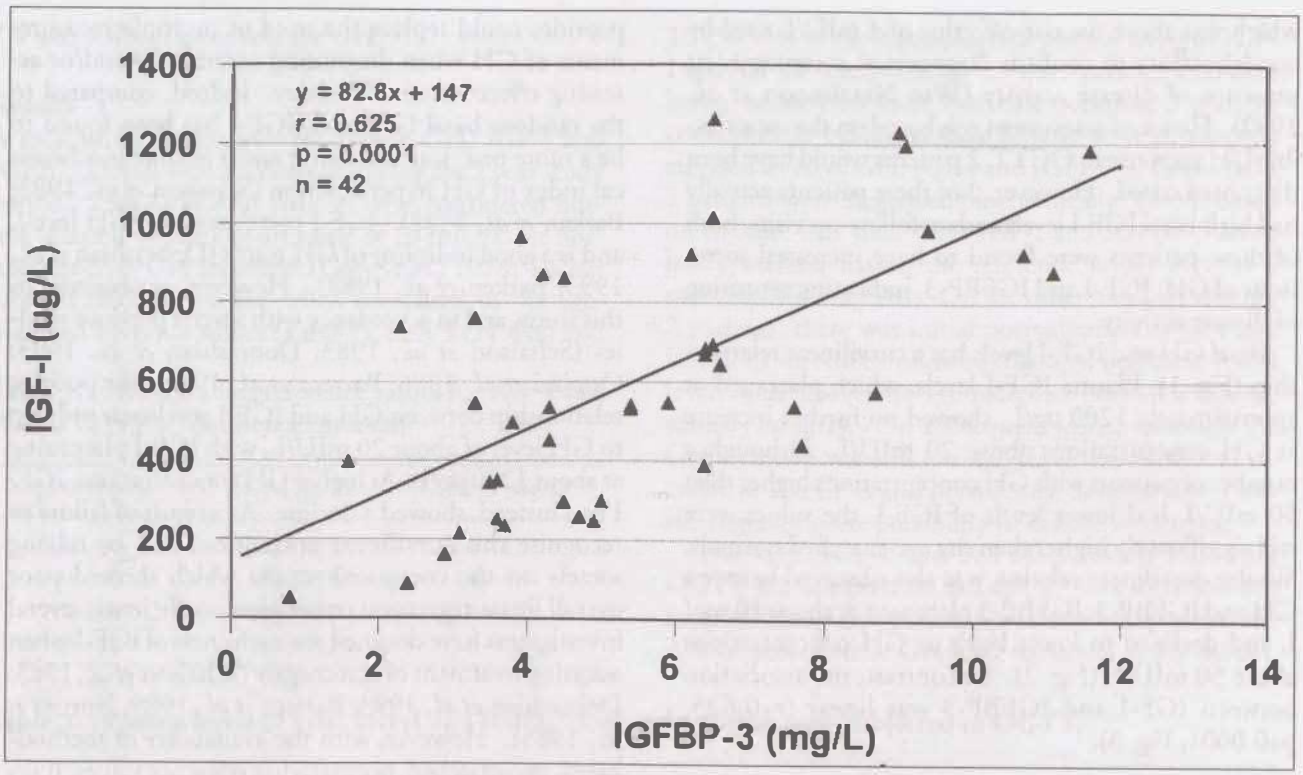

Fig. 3. Correlation between IGF-I and IGFBP-3 in 42 specimens of 25 treated acromegalic patients.

either because their GH levels were borderline (patients 2 and 3) and/or clinically, showed recurrence of disease activity (patients 1 and 3). In fact, as the IGF-I levels of 2 of these patients were above the normal reference values, implying that the growth factor is more reflective and consistent with disease activity and its single determination would reduce time and cost of having to perform the OGTT.

On the other hand, measurement of IGFBP-3 was found to give no additional discriminatory value over IGF-I or GH measurement for the diagnosis or assessment of therapy. Similar to that observed by de Herder *et al.* (1995), disease activity was biochemically detected on follow-up visits in a number of patients who initially had normal IGFBP-3 and GH but elevated IGF-I levels. In contrast, the study by Grinspoon *et al.* (1995) showed that IGFBP-3 was a useful index in patients with clinical acromegaly but who had normal IGF-I secretion and suppressable GH response to glucose load.

Hence, a single determination of IGF-I may therefore be a reliable if not better alternative to replace the multiple GH determinations in OGTT and with proper interpretation of result, could be a very good biochemical index of acromegaly.

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