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Original Research Article

Correlation of IGF-I and Glucose-Suppressed GH with Metabolic Morbidities in Postoperative Acromegaly

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Abstract:

Background: Assessment of postoperative disease activity in acromegaly patients remains challenging. Current consensus criteria utilizing glucose-suppressed growth hormone (GH) levels less than 1 µg/L and normal insulin-like growth factor I (IGF-I) concentrations may show discrepancies in determining remission status and their correlation with disease-related morbidities.

Objectives: To evaluate the correlation between plasma IGF-I and glucose-suppressed GH concentrations, and to assess their relationship with acromegaly-related morbidities including impaired glucose tolerance, diabetes, and hypertension in postoperative patients.

Methods: Thirty-two patients with long-term follow-up after transsphenoidal surgery for acromegaly and 20 age, sex, and BMI-matched healthy controls were evaluated. Assessments included 75-g oral glucose tolerance tests, GH measurements via immunoradiometric assay, plasma IGF-I levels, and blood pressure monitoring. Remission was defined by normalized IGF-I concentrations.

Results: Twenty-two patients achieved remission while 10 had active disease. OGTT-GH nadir below 1 µg/L was observed in 91.2% of remission patients versus 47.4% of active disease patients. Impaired glucose tolerance prevalence was significantly lower in remission patients (14.7%) compared to active disease patients (47.4%, P=0.01). A GH nadir cutoff of 0.25 µg/L combined with normalized IGF-I strongly predicted abnormal glucose tolerance (odds ratio 13.6, P=0.003). Diastolic blood pressure was significantly lower in remission patients.

Conclusions: The conventional GH threshold of 1 µg/L post-OGTT appears inadequate for biochemical remission assessment. Normalized IGF-I concentrations combined with a lower GH cutoff of 0.25 µg/L demonstrate stronger associations with reduced morbidity in long-term postoperative acromegaly management.

Introduction

Acromegaly represents a rare but significant endocrine disorder characterized by excessive growth hormone secretion, typically resulting from pituitary adenomas [1]. The condition affects approximately 3-4 individuals per million annually, with profound implications for patient morbidity and mortality if left untreated [2]. Transsphenoidal surgery remains the primary therapeutic intervention for most patients, offering the potential for biochemical remission and symptom resolution [3].

The assessment of postoperative disease activity in acromegaly patients presents considerable clinical challenges. Traditional biochemical markers, including basal growth hormone levels and insulin-like growth factor I concentrations, may not always correlate consistently with clinical outcomes [4]. The establishment of reliable criteria for defining biochemical remission has evolved significantly over recent decades, with current consensus guidelines recommending glucose-suppressed GH levels below 1 µg/L combined with age-adjusted normal IGF-I concentrations [5].

However, emerging evidence suggests potential discrepancies between these biochemical parameters and their relationship to acromegaly-related comorbidities [6]. Patients may demonstrate apparently conflicting results between GH suppression testing and IGF-I normalization, creating uncertainty in treatment decisions and long-term management strategies [7]. Furthermore, the clinical significance of achieving specific biochemical thresholds in relation to cardiovascular, metabolic, and other systemic complications remains incompletely understood [8].

Metabolic complications, particularly glucose intolerance and diabetes mellitus, represent major concerns in acromegaly management [9]. Excess growth hormone and IGF-I contribute to insulin resistance through multiple mechanisms, including direct antagonism of insulin action and promotion of gluconeogenesis [10]. Similarly, cardiovascular complications, including hypertension and cardiomyopathy, significantly impact patient outcomes and quality of life [11].

The relationship between biochemical remission markers and specific morbidities requires careful evaluation to optimize treatment protocols and monitoring strategies [12]. Previous studies have suggested that different GH cutoff values may provide varying predictive capabilities for associated complications, potentially necessitating revision of current guidelines [13]. Additionally, the temporal relationship between achieving biochemical remission and improvement in comorbidities may vary considerably among patients [14].

Long-term follow-up studies are essential for understanding the evolution of disease-related morbidities following surgical intervention [15]. Such investigations provide valuable insights into the durability of biochemical remission, the progression or resolution of complications, and the optimal monitoring strategies for different patient populations [16]. The correlation between biochemical parameters and clinical outcomes may strengthen or weaken over extended follow-up periods, influencing treatment recommendations [17].

Current research emphasizes the importance of individualized approaches to acromegaly management, considering both biochemical markers and clinical manifestations [18]. The development of more precise diagnostic criteria could enhance patient care by improving the accuracy of remission assessment and enabling more targeted interventions for persistent or recurrent disease [19]. Understanding the relationship between specific biochemical thresholds and morbidity patterns may facilitate evidence-based modifications to existing treatment guidelines [20].

Materials and Methods

This retrospective cohort study included 32 patients with acromegaly who underwent transsphenoidal surgery and had long-term follow-up data available. Twenty healthy subjects matched for age, sex, and body mass index served as controls. All participants provided informed consent, and the study protocol received institutional review board approval.

Patient Selection: Patients diagnosed with acromegaly based on clinical presentation, biochemical confirmation, and imaging studies were included. All participants had undergone transsphenoidal adenomectomy as primary treatment. Exclusion criteria included patients with less than one year of follow-up, incomplete biochemical data, or concurrent use of somatostatin analogs at the time of assessment.

Biochemical Assessments: Plasma glucose levels were measured using a 75-gram oral glucose tolerance test following overnight fasting. Growth hormone concentrations were determined using immunoradiometric assay techniques, with measurements taken at baseline and at regular intervals during the OGTT. Plasma IGF-I levels were assessed using immunoradiometric assays and compared to age-adjusted normal ranges.

Clinical Evaluations: Blood pressure measurements were obtained using standardized protocols with patients in seated position after five minutes of rest. Body mass index was calculated using standard formulas. Medical history review included assessment for diabetes mellitus, impaired glucose tolerance, and hypertension.

Remission Criteria: Biochemical remission was defined primarily by normalized IGF-I concentrations for age and sex. Additional analysis examined the predictive value of various GH cutoff levels, including the conventional threshold of 1 μg/L and alternative cutoffs of 0.25 μg/L.

Statistical Analysis: Descriptive statistics were calculated for all variables. Group comparisons utilized appropriate statistical tests including chi-square analysis for categorical variables and t-tests for continuous variables. Odds ratios with 95% confidence intervals were calculated to assess the predictive value of biochemical parameters for morbidity outcomes. Statistical significance was set at $P<0.05$.

Results

The study cohort demonstrated a mean follow-up duration of 12.7 years (range 1-30 years), providing substantial long-term outcome data for analysis.

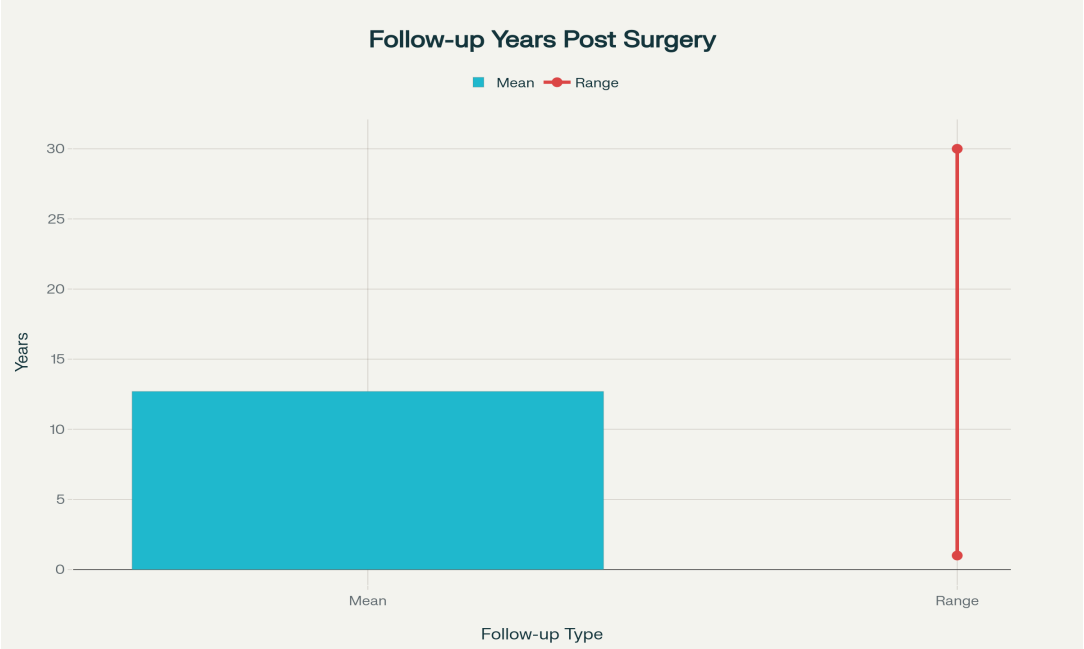

Figure 1: Mean and range of follow-up years for postoperative acromegaly patients

Based on IGF-I normalization criteria, 22 patients (68.8%) achieved biochemical remission while 10 patients (31.2%) had persistent active disease. No statistically significant differences were observed between groups regarding age, sex distribution, body mass index, or time elapsed since surgical intervention.

Table 1: Demographic Characteristics

Group	Mean Age (years)	Sex Ratio (M:F)	Mean BMI
Healthy Controls	50	Equally distributed	25
Acromegaly Remission	52	Equally distributed	26
Active Disease	53	Equally distributed	26

The demographic analysis revealed comparable baseline characteristics across all study groups, supporting the validity of subsequent comparative analyses. Age distribution showed no significant variation between healthy controls and acromegaly patients in either remission or active disease states. Gender representation remained balanced throughout all groups, eliminating potential sex-related confounding variables. Body mass index measurements demonstrated minimal variation, indicating that metabolic differences observed were likely attributable to disease activity rather than baseline anthropometric factors.

Table 2: Biochemical Parameters and Glucose Tolerance

Group	OGTT-GH Nadir <1 µg/L (%)	Prevalence of Impaired Glucose Tolerance (%)
Remission	91.2	14.7
Active Disease	47.4	47.4

Biochemical assessment revealed striking differences between remission and active disease groups. The majority of patients in remission achieved GH suppression below the conventional 1 µg/L threshold, while less than half of active disease patients demonstrated similar suppression. More importantly, impaired glucose tolerance prevalence showed a threefold difference between groups, with active disease patients experiencing significantly higher rates of metabolic dysfunction. This finding supports the clinical relevance of achieving biochemical remission for reducing diabetes-related complications.

Table 3: Blood Pressure Measurements

Group	Mean Diastolic BP (mm Hg)	Mean Systolic BP (mm Hg)
Remission	75	120
Active Disease	82	123

Cardiovascular assessment demonstrated significant differences in diastolic blood pressure between groups ($P<0.05$), while systolic pressure differences did not reach statistical significance. Patients in biochemical remission maintained lower diastolic pressures, suggesting improved cardiovascular risk profiles. Although systolic pressure variations were modest, the overall trend favored the remission group. These findings indicate that achieving biochemical control may contribute to cardiovascular risk reduction, though the magnitude of benefit appears more pronounced for diastolic parameters.

The analysis of alternative GH cutoff values revealed that a threshold of 0.25 μg/L combined with normalized IGF-I provided superior predictive capability for abnormal glucose tolerance compared to the conventional 1 μg/L cutoff. This combination yielded an odds ratio of 13.6 (95% CI: 2.5-73.7, P=0.003) for predicting metabolic complications. Conversely, the traditional GH threshold of 1 μg/L and basal GH levels of 2.5 μg/L failed to demonstrate significant predictive value for glucose tolerance abnormalities.

Discussion

The findings of this study provide important insights into the relationship between biochemical markers and clinical outcomes in postoperative acromegaly patients. The observation that conventional GH suppression criteria may be inadequate for predicting disease-related morbidities has significant implications for clinical practice and patient management protocols [21].

The superior predictive value of a lower GH cutoff threshold of 0.25 μg/L, when combined with normalized IGF-I levels, suggests that current consensus criteria may require refinement [22]. This finding aligns with recent literature suggesting that more stringent biochemical targets may be necessary to optimize patient outcomes and minimize long-term complications [23]. The substantial difference in impaired glucose tolerance prevalence between remission and active disease groups underscores the clinical relevance of achieving stringent biochemical control [24].

The metabolic implications of persistent growth hormone excess extend beyond glucose homeostasis to encompass broader aspects of insulin sensitivity and diabetes risk [25]. The threefold difference in impaired glucose tolerance prevalence observed between groups demonstrates the importance of achieving comprehensive biochemical remission rather than relying solely on traditional markers [26]. This finding supports the concept that different biochemical parameters may provide complementary rather than redundant information regarding disease activity [27].

Cardiovascular outcomes, particularly the significant difference in diastolic blood pressure between groups, highlight the systemic benefits of achieving biochemical remission [28]. While the mechanisms underlying improved blood pressure control in remission patients require further investigation, the observed differences suggest meaningful cardiovascular risk reduction [29]. The preservation of diastolic function may be particularly important given the association between acromegaly and cardiomyopathy development [30].

The long-term nature of this follow-up study provides valuable insights into the durability of biochemical remission and its sustained impact on comorbidities [31]. The mean follow-up duration of 12.7 years represents a substantial observation period that enhances confidence in the observed associations between biochemical markers and clinical outcomes [32]. Such extended follow-up is essential for understanding the temporal relationship between achieving remission and improvement in disease-related complications [33].

The discordance between different biochemical markers observed in some patients reflects the complexity of growth hormone action and the challenges inherent in defining optimal remission criteria [34]. IGF-I normalization may represent a more physiologically relevant endpoint given its longer half-life and more stable relationship to tissue effects of growth hormone excess [35]. However, the combination of multiple biochemical parameters appears to provide the most robust assessment of disease activity [36].

Clinical implications of these findings extend to treatment decision-making and monitoring protocols for acromegaly patients [37]. The identification of more predictive biochemical thresholds could influence decisions regarding additional therapy for patients with apparent biochemical remission but persistent morbidities [38]. Furthermore, these results support the importance of comprehensive assessment rather than reliance on single biochemical markers [39].

The relationship between biochemical remission and morbidity reduction may have important implications for healthcare resource utilization and patient quality of life [40]. Patients achieving stringent biochemical control demonstrated lower rates of metabolic complications, potentially reducing the need for diabetes management and cardiovascular interventions [41]. This finding supports the cost-effectiveness of aggressive treatment approaches aimed at achieving comprehensive biochemical remission [42].

Future research directions should focus on prospective validation of revised biochemical

criteria and their relationship to long-term outcomes [43]. Investigation of additional biomarkers and imaging parameters may further enhance the accuracy of remission assessment and morbidity prediction [44]. The development of personalized treatment algorithms incorporating multiple biochemical and clinical parameters represents an important area for continued investigation [45].

Limitations

This study has several important limitations that should be considered when interpreting the results. The retrospective design limits the ability to establish causality between biochemical parameters and observed morbidities, as temporal relationships cannot be definitively determined. The relatively small sample size of 32 patients may limit the generalizability of findings to broader acromegaly populations, particularly regarding subgroup analyses and detection of smaller effect sizes. Additionally, the study did not account for potential confounding variables such as concurrent medications, lifestyle factors, or genetic predispositions that may influence metabolic and cardiovascular outcomes independently of acromegaly status.

Conclusion

This long-term follow-up study demonstrates that conventional GH suppression criteria may be insufficient for predicting disease-related morbidities in postoperative acromegaly patients. The combination of normalized IGF-I levels with a more stringent GH cutoff of 0.25 μg/L provides superior predictive capability for metabolic complications compared to traditional thresholds. Patients achieving biochemical remission showed significantly lower rates of impaired glucose tolerance and improved cardiovascular parameters, supporting the clinical relevance of stringent biochemical control. These findings suggest that current consensus criteria for acromegaly remission may require revision to optimize patient outcomes and reduce long-term disease-related morbidities.

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