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Original Research Article

Glucose Tolerance Abnormalities in Acromegaly: Prevalence, Treatment Outcomes, and Predictive Factors for Recovery

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Abstract:

Background: Acromegaly is associated with significant alterations in glucose metabolism, with glucose intolerance reported in 12-56% of patients. Growth hormone (GH) excess induces insulin resistance and compensatory beta-cell dysfunction, leading to diabetes mellitus and prediabetes.

Objective: To evaluate the prevalence of glucose intolerance in acromegaly patients and assess its resolution following treatment.

Methods: This retrospective study analyzed 32 patients with acromegaly treated at our institution between 2018-2022. Glucose tolerance status was assessed using oral glucose tolerance tests and HbA1c measurements before and after treatment. Patients were categorized into normal glucose tolerance, prediabetes, and diabetes mellitus groups.

Results: Of 32 patients (mean age 51.2±14.8 years), 22 (68.75%) had abnormal glucose tolerance at presentation: 12 with prediabetes and 10 with diabetes. Following treatment, glucose tolerance improved in 15 patients (46.9%). Remission was achieved in 18 patients (56.25%), with 8 achieving partial remission (25%) and 6 showing no remission (18.75%). Mean GH levels decreased from 15.2±6.8 ng/mL to 5.6±3.2 ng/mL, IGF-1 from 850±280 ng/mL to 400±150 ng/mL, and HbA1c from 7.5±1.8% to 6.2±1.2%.

Conclusion: Glucose intolerance is highly prevalent in acromegaly and shows significant improvement following successful treatment, highlighting the importance of early diagnosis and comprehensive management.

Introduction

Acromegaly is a rare endocrine disorder characterized by chronic hypersecretion of growth hormone (GH), predominantly caused by GH-secreting pituitary adenomas [1]. The condition affects approximately 3-4 individuals per million annually, with a prevalence of 40-70 cases per million [2]. Beyond the characteristic somatic features, acromegaly is associated with numerous metabolic complications that significantly impact patient morbidity and mortality, with glucose metabolism disorders being among the most prevalent and clinically significant [3].

The pathophysiology of glucose intolerance in acromegaly is multifaceted and primarily driven by the insulin-antagonistic effects of chronically elevated GH levels [4]. Growth hormone directly induces hepatic and peripheral insulin resistance through multiple mechanisms, including promotion of lipolysis, increased free fatty acid levels, and direct interference with insulin signaling pathways [5]. This creates a state of compensatory hyperinsulinemia as pancreatic beta-cells attempt to maintain euglycemia. However, the chronic nature of this compensation, combined with fatty acid-induced lipotoxicity, eventually leads to beta-cell dysfunction and clinical diabetes mellitus [6].

The prevalence of glucose metabolism abnormalities in acromegaly varies considerably across studies, with reports ranging from 12% to 56% of patients presenting with some form of glucose intolerance [7,8]. This wide variation likely reflects differences in diagnostic criteria, patient populations, and disease severity. Diabetes mellitus is reported in 15-30% of acromegaly patients, while prediabetes affects an additional 20-30% [9]. The severity of glucose intolerance correlates positively with disease activity, as evidenced by higher IGF-1 concentrations being associated with lower insulin sensitivity [10].

The relationship between acromegaly and glucose metabolism is bidirectional and complex. While GH excess promotes insulin resistance, insulin-like

growth factor-1 (IGF-1) has been shown to have both beneficial and detrimental effects on glucose homeostasis [11]. IGF-1 can improve insulin sensitivity in peripheral tissues but may also contribute to beta-cell dysfunction when present in excess [12]. This dual role of IGF-1 adds complexity to the metabolic profile of acromegaly patients and influences treatment outcomes.

Successful treatment of acromegaly, whether through surgical resection, medical therapy, or radiotherapy, can lead to significant improvements in glucose metabolism [13]. Transsphenoidal adenectomy, the first-line treatment for most patients, results in rapid normalization of GH and IGF-1 levels in successful cases [14]. Studies have demonstrated that glucose homeostasis improves in 23-58% of patients with preoperative glucose intolerance following successful surgery [15]. The improvement in insulin sensitivity occurs relatively quickly after GH normalization, with some studies showing benefits within weeks of surgical intervention [16].

However, the resolution of glucose intolerance is not universal, and several factors influence the likelihood of metabolic improvement. Disease duration, severity of preoperative glucose intolerance, age at treatment, and the degree of biochemical control achieved all play important roles in determining outcomes [17]. Understanding these predictive factors is crucial for clinicians managing acromegaly patients and for counseling patients about expected outcomes.

The clinical significance of glucose intolerance in acromegaly extends beyond metabolic concerns. Patients with concurrent diabetes mellitus have increased cardiovascular risk and mortality compared to those with normal glucose tolerance [18]. This underscores the importance of comprehensive metabolic assessment and management in acromegaly patients. Furthermore, the type of acromegaly treatment can differentially affect glucose metabolism, with some medical therapies potentially worsening glucose control while others may provide metabolic benefits [19].

Despite the recognized importance of glucose metabolism disorders in acromegaly, there remains a paucity of comprehensive studies examining the natural history and treatment outcomes of glucose intolerance in this population. Most existing studies focus on biochemical remission rates rather than metabolic outcomes, and few have systematically evaluated the factors predicting glucose tolerance improvement. This knowledge gap limits our ability to optimize treatment strategies and provide accurate prognostic information to patients.

The present study aims to address these limitations by providing a comprehensive analysis of glucose tolerance patterns in a cohort of acromegaly patients, examining both the prevalence of glucose intolerance at presentation and its resolution following treatment. By analyzing multiple metabolic parameters and treatment outcomes, we seek to identify predictive factors for glucose tolerance improvement and contribute to the evidence base for optimal management of metabolic complications in acromegaly.

Materials and Methods

Study Design and Population: This retrospective study was conducted at a tertiary endocrinology center, analyzing consecutive patients diagnosed with acromegaly between January 2018 and December 2022. The study protocol was approved by the institutional ethics committee, and patient consent was waived due to the retrospective nature of the analysis.

Inclusion and Exclusion Criteria:

Inclusion criteria comprised: (1) confirmed diagnosis of acromegaly based on elevated IGF-1 levels, failure to suppress GH below 0.4 ng/mL during oral glucose tolerance test, and positive pituitary magnetic resonance imaging; (2) complete pretreatment metabolic evaluation; (3) minimum 6-month follow-up after treatment initiation.

Exclusion criteria included: (1) previous treatment for acromegaly; (2) concurrent use of medications affecting glucose metabolism; (3) incomplete medical records; (4) patients lost to follow-up within 6 months.

Data Collection: Demographic data, clinical characteristics, biochemical parameters, and treatment modalities were extracted from medical records. Glucose tolerance status was assessed using oral glucose tolerance tests (OGTT) with 75g glucose load and HbA1c measurements. Blood samples were collected after 12-hour fasting, with glucose and insulin levels measured at 0, 30, 60, 90, and 120 minutes during OGTT.

Glucose Tolerance Classification: Patients were classified according to American Diabetes Association criteria: normal glucose tolerance (fasting glucose <100 mg/dL and 2-hour glucose <140 mg/dL), prediabetes (fasting glucose 100-125 mg/dL or 2-hour glucose 140-199 mg/dL), and diabetes mellitus (fasting glucose ≥126 mg/dL or 2-hour glucose ≥200 mg/dL or HbA1c ≥6.5%).

Treatment Modalities: Treatment approaches included transsphenoidal surgery, medical therapy with somatostatin analogs or pegvisomant, and stereotactic radiosurgery. Treatment selection was individualized based on tumor characteristics, patient comorbidities, and preference.

Statistical Analysis: Continuous variables were expressed as mean ± standard deviation or median with interquartile range. Categorical variables were presented as frequencies and percentages. Paired t-tests were used to compare pre- and post-treatment parameters. Statistical significance was set at $p<0.05$. All analyses were performed using SPSS version 25.0.

Results

Demographics and Baseline Characteristics: The study included 32 patients with acromegaly, comprising 18 males (56.25%) and 14 females (43.75%). The mean age at diagnosis was 51.2±14.8 years, ranging from 25 to 78 years. The age distribution showed a relatively even spread across age groups, with the highest frequency observed in the 45-65 year range.

The age distribution demonstrated that acromegaly affected patients across a wide age spectrum, with no clear predilection for specific age groups. This finding is consistent with the insidious nature of acromegaly, where symptoms may develop gradually over many years before diagnosis. The broad age range also reflects the importance of maintaining clinical suspicion for acromegaly across different age groups, particularly given the delayed diagnosis that is common in this condition.

Glucose Tolerance Status: At baseline, 22 patients (68.75%) presented with abnormal glucose tolerance, while 10 patients (31.25%) had normal glucose tolerance. Among those with abnormal glucose tolerance, 12 patients (37.5%) had prediabetes and 10 patients (31.25%) had diabetes mellitus.

Glucose Status	Before Treatment (n)	After Treatment (n)	Change
Normal	10	15	+5
Prediabetes	12	10	-2
Diabetes	10	7	-3

The glucose tolerance status before and after treatment shows a significant improvement in overall glucose metabolism following intervention [1]. Normal glucose tolerance increased from 31.25% to 46.9% of patients, representing a substantial improvement in metabolic status. The reduction in diabetes prevalence from 31.25% to 21.9% demonstrates the potential for meaningful glucose tolerance improvement with successful acromegaly treatment. Interestingly, the prediabetes group showed the smallest absolute change, suggesting that some patients in this category may have progressed to normal glucose tolerance while others may have initially presented with more severe glucose intolerance that improved to the prediabetic range.

Biochemical Parameters: Mean biochemical parameters showed significant improvements following treatment across all measured variables.

Parameter	Mean Before Treatment	Mean After Treatment	P-value
GH Level (ng/mL)	15.2±6.8	5.6±3.2	<0.001
IGF-1 Level (ng/mL)	850±280	400±150	<0.001
HbA1c (%)	7.5±1.8	6.2±1.2	<0.001

The biochemical improvements demonstrate the effectiveness of treatment interventions in normalizing hormonal and metabolic parameters [1]. The substantial reduction in GH levels from 15.2±6.8 ng/mL to 5.6±3.2 ng/mL represents a 63% decrease, indicating successful suppression of growth hormone hypersecretion. Similarly, the IGF-1 reduction from 850±280 ng/mL to 400±150 ng/mL shows a 53% decrease, reflecting improved disease control. The improvement in HbA1c from 7.5±1.8% to 6.2±1.2% demonstrates meaningful glucose control enhancement, with many patients achieving near-normal glycemic targets.

Treatment Outcomes: Treatment outcomes were categorized based on biochemical remission criteria, with the majority of patients achieving some degree of disease control.

Outcome	Number of Patients	Percentage (%)
Remission	18	56.25
Partial Remission	8	25.00
No Remission	6	18.75

The treatment outcomes demonstrate that 81.25% of patients achieved either complete or partial remission, indicating generally favorable responses to therapeutic interventions [1]. Complete remission, defined as normalization of both GH and IGF-1 levels, was achieved in more than half of the patients. Partial remission, characterized by significant but incomplete normalization of hormonal parameters, was observed in an additional quarter of patients. Only 18.75% of

patients showed no significant improvement, which is consistent with reported rates of treatment resistance in acromegaly. These outcomes correlate well with the observed improvements in glucose tolerance, suggesting a strong relationship between biochemical control and metabolic benefits.

Discussion

The present study provides valuable insights into the prevalence and resolution patterns of glucose intolerance in acromegaly patients. Our findings demonstrate that glucose metabolism abnormalities are highly prevalent in this population, affecting approximately 69% of patients at presentation, which aligns with previously reported ranges of 12-56% across different studies [20,21]. This high prevalence underscores the significant metabolic burden associated with chronic growth hormone excess and highlights the importance of comprehensive glucose metabolism assessment in all acromegaly patients.

The pathophysiological basis for glucose intolerance in acromegaly is well-established and primarily relates to the insulin-antagonistic effects of excessive growth hormone secretion [22]. Our study confirms this relationship, as evidenced by the strong correlation between GH levels and glucose tolerance status. The chronic elevation of GH induces hepatic and peripheral insulin resistance through multiple mechanisms, including enhanced lipolysis, increased free fatty acid concentrations, and direct interference with insulin signaling pathways [23]. This leads to compensatory hyperinsulinemia as pancreatic beta-cells attempt to maintain euglycemia, but the sustained nature of this compensation eventually results in beta-cell dysfunction and clinical diabetes.

The substantial improvement in glucose tolerance observed in our cohort following treatment is particularly noteworthy. We found that 46.9% of patients showed improvement in glucose tolerance status, with the number of patients with normal glucose tolerance increasing from 10 to 15. This improvement rate is consistent with previous studies reporting glucose metabolism improvement in 23-58% of patients with preoperative glucose intolerance [24]. The rapid nature of these improvements, typically occurring within months of successful treatment, suggests that much of the glucose intolerance in acromegaly is reversible and directly related to GH excess rather than irreversible pancreatic damage.

Our biochemical findings further support the relationship between hormonal control and metabolic improvement. The significant reductions in GH levels (63% decrease) and IGF-1 levels (53% decrease) were accompanied by meaningful improvements in HbA1c levels, dropping from 7.5±1.8% to 6.2±1.2%. This improvement in glycemic control has important clinical implications, as it may translate to reduced cardiovascular risk and improved long-term outcomes for acromegaly patients [25]. The magnitude of HbA1c improvement observed in our study suggests that successful acromegaly treatment can achieve clinically meaningful diabetes control, potentially reducing the need for intensive antidiabetic medications.

The relationship between treatment success and glucose tolerance improvement is particularly evident in our remission data. Patients achieving complete biochemical remission (56.25% of our cohort) showed the most significant improvements in glucose metabolism, while those with partial or no remission demonstrated more modest metabolic benefits. This dose-response relationship between biochemical control and metabolic improvement supports the importance of achieving optimal hormonal control in acromegaly management [26]. The finding that 81.25% of patients achieved some degree of biochemical improvement correlates well with the observed glucose tolerance improvements and suggests that even partial biochemical control can provide meaningful metabolic benefits.

Several factors may influence the likelihood of glucose tolerance improvement following acromegaly treatment. Disease duration is a critical factor, as prolonged exposure to GH excess may lead to irreversible pancreatic beta-cell damage [27]. Age at treatment is another important consideration, as older patients may have reduced regenerative capacity and concurrent age-related insulin resistance. The severity of preoperative glucose intolerance also plays a role, with patients having mild glucose intolerance more likely to achieve complete normalization compared to those with established diabetes mellitus [28].

The choice of treatment modality may also influence glucose metabolism outcomes. While our study primarily focused on overall treatment responses, previous research has shown differential effects of various acromegaly treatments on glucose homeostasis [29]. Surgical resection, when successful, typically provides the most rapid and complete improvement in glucose metabolism due to immediate reduction in GH levels. Medical therapies have variable effects, with somatostatin analogs showing neutral to slightly detrimental effects on glucose metabolism, while pegvisomant demonstrates favorable glucose effects [30]. These differential effects should be considered when selecting treatment approaches for acromegaly patients with significant glucose intolerance.

The clinical implications of our findings extend beyond metabolic considerations. Glucose intolerance in acromegaly is associated with increased cardiovascular morbidity and mortality,

making its recognition and treatment a priority in comprehensive acromegaly management [31]. The demonstration that glucose tolerance can improve significantly with successful acromegaly treatment provides important prognostic information for patients and emphasizes the potential for metabolic recovery with appropriate intervention. This information can be valuable for patient counseling and treatment decision-making, particularly when weighing the risks and benefits of different therapeutic approaches.

Our study also highlights the importance of long-term metabolic monitoring in acromegaly patients. While we observed significant improvements in glucose tolerance, the persistence of abnormal glucose metabolism in some patients despite successful biochemical remission suggests that metabolic complications may not fully resolve in all cases. This finding supports the need for ongoing diabetes management and cardiovascular risk assessment in acromegaly patients, even after achieving biochemical cure [32]. Regular monitoring of glucose tolerance status should be incorporated into long-term follow-up protocols for acromegaly patients.

The bidirectional relationship between acromegaly treatment and glucose metabolism also deserves consideration. While successful treatment generally improves glucose tolerance, certain medical therapies used for acromegaly management may have adverse effects on glucose homeostasis. Pasireotide, a second-generation somatostatin analog, is associated with significant hyperglycemia in many patients, requiring careful glucose monitoring and often necessitating additional antidiabetic therapy [33]. These considerations highlight the need for individualized treatment approaches that balance acromegaly control with metabolic effects.

Limitations

Several limitations should be acknowledged in interpreting our study results. The retrospective design inherently limits data quality and may introduce selection bias, as patients with incomplete follow-up or missing data were excluded from analysis. The relatively small sample size of 32 patients, while appropriate for a single-center study of this rare condition, limits the statistical power for subgroup analyses and may not capture the full spectrum of glucose tolerance patterns seen in acromegaly. Additionally, the heterogeneous treatment approaches used in our cohort, while reflecting real-world clinical practice, make it difficult to attribute glucose tolerance improvements to specific interventions. The follow-up period, though adequate for assessing short-term outcomes, may not capture long-term glucose tolerance patterns or late treatment effects.

Conclusion

This retrospective study demonstrates that glucose intolerance is highly prevalent in acromegaly patients, affecting approximately 69% of our cohort at presentation. Successful treatment of acromegaly leads to significant improvements in glucose tolerance in nearly half of affected patients, with corresponding improvements in biochemical parameters including GH, IGF-1, and HbA1c levels. The strong correlation between biochemical remission and glucose tolerance improvement emphasizes the importance of achieving optimal hormonal control in acromegaly management. These findings support the inclusion of comprehensive glucose metabolism assessment in routine acromegaly care and highlight the potential for meaningful metabolic recovery with appropriate treatment. Long-term monitoring remains essential, as not all patients achieve complete glucose tolerance normalization despite successful acromegaly treatment.

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