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Elucidating the relationship between blood glucose dynamics and growth hormone responses in glucagon stimulation tests among children with short stature

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Abstract

Introduction: The use of glucagon as a provocative agent for growth hormone (GH) assessment is a cornerstone in pediatric endocrinology. Glucagon's role as a GH secretagogue is integral to growth hormone stimulation tests (GHSTs), which diagnose suspected GH deficiency (GHD) in children. These tests are crucial for assessing the hypothalamic-pituitary-adrenal (HPA) axis's integrity. Despite its prevalent use, the exact mechanisms by which glucagon prompts GH release and the impact of ensuing blood glucose (BG) fluctuations are not fully understood.

Objectives: This study aims to explore the relationship between GH and BG levels in children with short stature following glucagon administration.

Patients and Methods: A retrospective cohort study involved 42 pediatric patients, aged 6 to 11, with short stature. We analyzed GH and BG levels before and after intramuscular glucagon Simulation test (GST). Blood samples were taken at baseline and multiple intervals post-injection.

Results: The results revealed that the mean glucose peaked at 60 minutes and declined to a nadir at 120 minutes, which corresponded with a significant rise in GH levels. GH concentrations peaked at 120 minutes post-injection, with 31% of children showing peak GH levels of less than 7 µg/L. Notably, the study found an inverse correlation between BG and GH at peak glucose times, suggesting a complex interplay between glucose dynamics and GH response.

Discussion: Our findings indicate a dynamic interrelation between BG and GH post-glucagon injection, challenging traditional interpretations of GST results. The study reinforces the notion that GHST results should be interpreted with consideration of patient-specific factors such as BMI to ensure accurate evaluation of GH reserve and subsequent clinical decision-making.

Conclusion: The study corroborates the dynamic nature of GH and glucose responses following glucagon administration and highlights the need for personalized approaches in interpreting GHSTs. Further investigation is warranted to elucidate the mechanisms influencing this complex relationship, which is crucial for accurate diagnosis and management of GHD in children.

Keywords: Growth hormone; Glucagon stimulation test; Blood glucose; Pediatric endocrinology; Growth hormone deficiency; Short stature

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1. Introduction

The role of glucagon as a provocative agent for growth hormone (GH) assessment is well-established in the pediatric endocrinology domain. As a GH secretagogue, glucagon's administration is central to the growth hormone stimulation tests (GHSTs) used for diagnosing suspected growth hormone deficiency (GHD) in children. This diagnostic approach involves serial measurements of GH following an intramuscular glucagon injection and is pivotal for evaluating the integrity of the hypothalamo-pituitary-adrenal (HPA) axis. [1] Despite its widespread use, the precise mechanisms by which glucagon influences GH release, and the impact of subsequent blood glucose (BG) fluctuations, are yet to be fully elucidated.

GHSTs, including the glucagon stimulation test (GST), are crucial in determining whether a child's growth pattern is within a healthy range or indicative of underlying endocrinopathies. However, there exists a variability in response, both in terms of GH secretion and changes in BG levels, which may not always follow the classical understanding of glucagon's role in stimulating hyperglycemia followed by hypoglycemia-which induce GH release. Vallet et al. (1971) noted that glucagon induces significant GH level increases at 90 to 120 minutes after injection. Interestingly, GH-deficient patients showed higher mean glucose levels than normal patients, indicating a possible altered glucose homeostasis in GH deficiency. [2] Giuffrida et al. (2009) did not observe hypoglycemia during glucagon stimulation tests in children and found no association between BG decrease and GH response. They concluded that BG decrease occurred at levels above those physiologically expected to stimulate GH release, suggesting BG reduction was not directly associated with GH response [3] This variability suggests a more complex interplay at the biochemical level that current literature has not entirely captured. This is corroborated by Yuen et al. (2013), who reported that factors such as age, BMI, and glucose tolerance might inversely influence peak GH levels in adults undergoing GST, thus advocating for a broader scope of consideration when interpreting GST results [3].

Recent studies, such as those by Akkar et al. (2022), have also shown that obesity is associated with both a blunted and delayed GH response to GST, indicating that glucagon's stimulatory effects on GH secretion are not solely reliant on BG levels. [4]. Additionally, Wilson et al.'s retrospective analysis indicated that while BG dynamics were not significantly correlated with GH response during GST in the total population, but they reported that alterations in BG profiles during GST in obese individuals might contribute to an impaired GH response [5].

Collectively, these findings show a picture of a complex physiological scenario where the relationship between BG and GH after glucagon injection is not simple. The absence of a consistent hypoglycemic event during the test and the variable physiological response of GH to decreasing BG levels present challenges to the conventional interpretation of the GST. Furthermore, the influence of factors such as obesity on BG profiles during GST necessitates a nuanced approach to the analysis and interpretation of GHST results. These insights emphasize the importance of individual patient factors, including BG levels, which must be carefully considered to ensure accurate GH release assessment and appropriate clinical decision-making.

Objectives

To investigate the changes in GH concentrations in relation to BG levels before and after glucagon injection in children with short stature.

2. Patients and Methods

We conducted a retrospective cohort study involving 42 pediatric patients aged between 2 to 11 years who were presented with short stature, defined as height standard deviation scores (HtSDS) less than -2. The participants were selected from those who underwent GST at our institution between September 2022 to December 2023. Patients were included if they had complete records of their GST results and if they had not received any GH therapy prior to the test. We excluded patients with known confounding factors for GH secretion, such as chronic systemic illness, uncontrolled diabetes mellitus, or those on medications known to affect glucose metabolism or GH secretion.

2.1. Glucagon Stimulation Test Procedure

All tests were carried out in a controlled clinical environment. Each participant underwent an 8-hour fast before the test, which was conducted in the morning to minimize diurnal variation. Blood samples for plasma glucose and GH levels were collected at baseline (0 minutes) before the intramuscular administration of glucagon. Glucagon was administered at a dose of 0.1 mg/kg, up to a maximum dose of 1 mg. Subsequent blood samples were taken at 60, 90-, 120-, 150-, and 180-minutes post-injection to assess the temporal response of BG and GH levels.

2.2. Laboratory Analysis

Plasma glucose was measured using a standardized enzymatic method, and GH concentrations were determined using an ImmunoChem luminescence assay. All assays were conducted in the same laboratory with strict quality control measures in place to ensure the reliability and reproducibility of results.

2.3. Data Collection

Data were extracted from electronic medical records, including demographic information (age, sex, height, weight, BMI), baseline BG and GH levels, and subsequent measurements at the specified time intervals post-glucagon administration. Additional data included any reported side effects during the test, such as nausea or symptoms suggestive of hypoglycemia.

2.4. Statistical Analysis

Descriptive statistics were used to summarize the patient characteristics and the main outcomes. The GH and BG levels were presented as means with standard errors. The Spearman's rank correlation coefficient was calculated to assess the relationship between the GH peaks and BG levels at the various time points. Multivariate regression analysis was performed to adjust for potential confounders such as age, sex, and BMI. A P-value of less than 0.05 was considered statistically significant.

2.5. Ethical Considerations

The study protocol was reviewed and approved by the institutional review board. As a retrospective analysis of existing clinical data, patient consent was waived, but the confidentiality of patient information was strictly maintained throughout the study.

3. Results

3.1. Glucose Levels: (table 1 , Figure 1)

The mean glucose level starts at 4.87 mmol/L before the glucagon injection. It peaks at 60 minutes post-injection with a mean of 6.5 mmol/L, which is likely a response to glucagon's hyperglycemic effect. Subsequently, there is a decline in the mean glucose level, reaching its lowest point at 120 minutes post-injection with a mean of 3.96 mmol/L. After 120 minutes, the glucose levels begin to rise slightly again but remain below the peak level at 180 minutes (4.45 mmol/L). The difference between peak and nadir glucose level after glucagon injection = 3.1 +/- 1.1 mmol/L.

3.2. Growth Hormone (GH) Levels: (table 1 , Figure 1)

The mean GH level initially decreases slightly from a baseline of 2.15 µg/L to 1.65 µg/L at 60 minutes. At 90 minutes, there's an increase in mean GH level to 3.08 µg/L. A sharp increase in GH is observed at 120 minutes, with the mean GH level peaking at 9.51 µg/L. Following the peak, GH levels decrease but remain elevated compared to the baseline at 150 minutes (6.68 µg/L) and 180 minutes (3.85 µg/L).

Peak GH concentrations of less than 7 micrograms/L were observed in 13 of the 42 children (31%) and < 10 micrograms /L in 20/42 children (47.6%).

No side effects were reported during the procedure. Asymptomatic hypoglycemia (< 50 mg/dl) occurred in 4 of the 42 children at least once between 90 and 120 minutes. Hyperglycemia (BG > 150 mg/dL) was noted in 6 children at 60 minutes post-injection.

The highest mean glucose concentration was recorded at 60 minutes, and the lowest at 120 minutes post-glucagon. At 180 minutes no hypoglycemia was noted in any child.

Table 1 The mean glucose and growth hormone (GH) levels at different time intervals after glucagon injection

Time (min)	Mean Glucose (mmol/L)	Glucose SE	Mean GH (µg/L)	GH SE
0	4.87	0.16	2.15	0.56
60	6.50	0.22	1.65	0.38
90	4.38	0.20	3.09	0.55
120	3.97	0.14	9.51	1.24
150	4.35	0.13	6.68	0.69
180	4.46	0.16	3.85	0.35

standard error (SE)

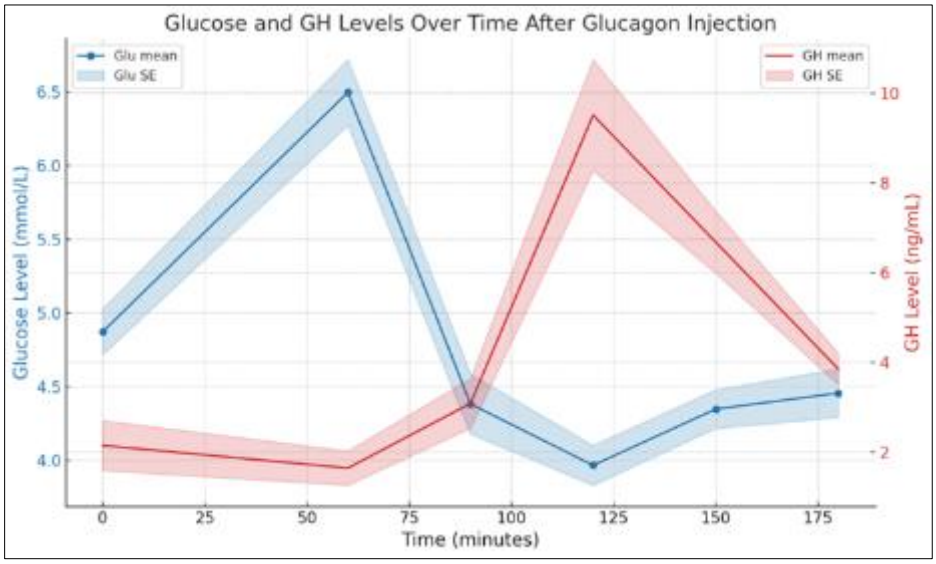

Figure 1 Glucose (Glu) and growth hormone (GH) levels over time after glucagon injection. The blue line and shaded area represent the mean and standard error (SE) of glucose levels, while the red line and shaded area represent the mean and SE of GH levels

At all times after glucagon injection glucose levels after glucagon stimulation did not differ between those with GHD and normal GH (GHN) (figure 2)

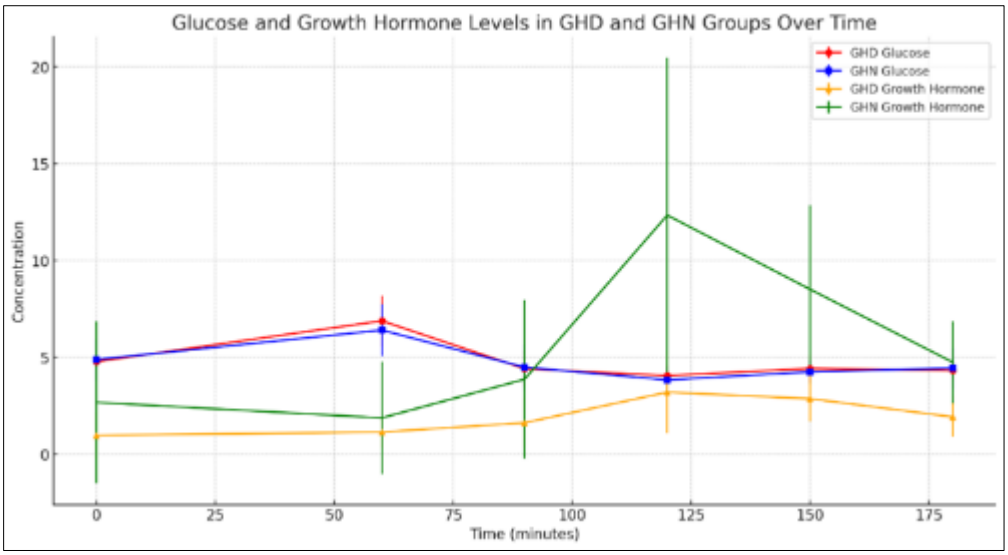

Figure 2 The glucose and growth hormone (GH) levels over time for individuals with Growth Hormone Deficiency (GHD) and those with Normal Growth Hormone (GHN). The error bars represent the standard deviation (SD) for each mean value, providing a visual representation of the variation within each group

Correlations:

A significant positive correlation was found between glucose at 90 min and GH concentrations at 180 min (Spearman's Rs=−0.26 ; P<0.04) (fig 3).

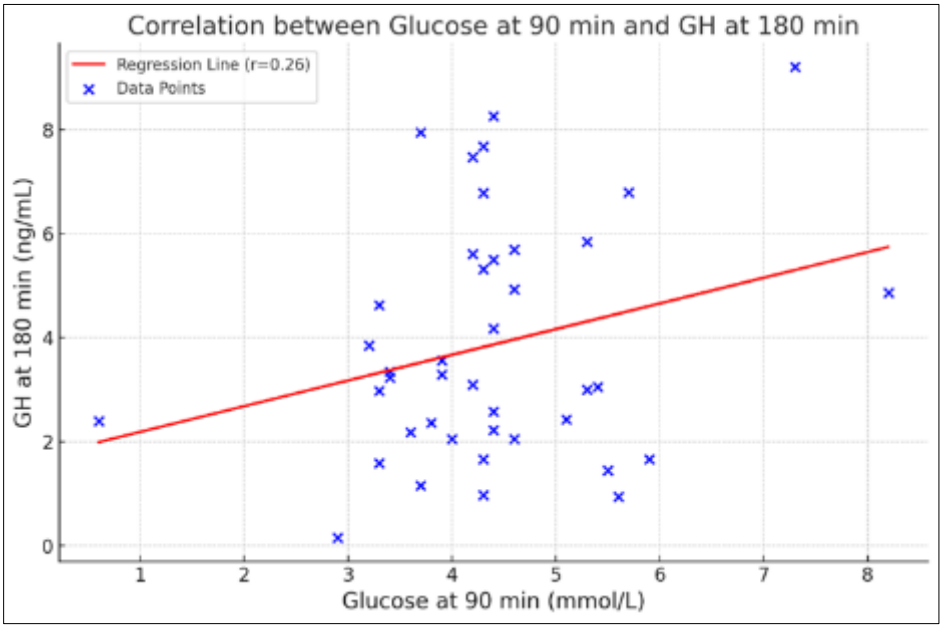

Figure 3 The correlation between glucose levels at 90 minutes and growth hormone (GH) levels at 180 minutes. The blue points represent the individual data points from the dataset, and the red line is the linear regression line that indicates the trend between the two variables

BMI was correlated with IGF1 level (r = 0.38, p <0.01) but not with the peak GH level. (Fig 4). IGF1 level was not correlated with peak GH. IGF1 was correlated significantly with the GH level at 180 min after glucagon injection (r =0.33, p = 0.02) (fig 5)

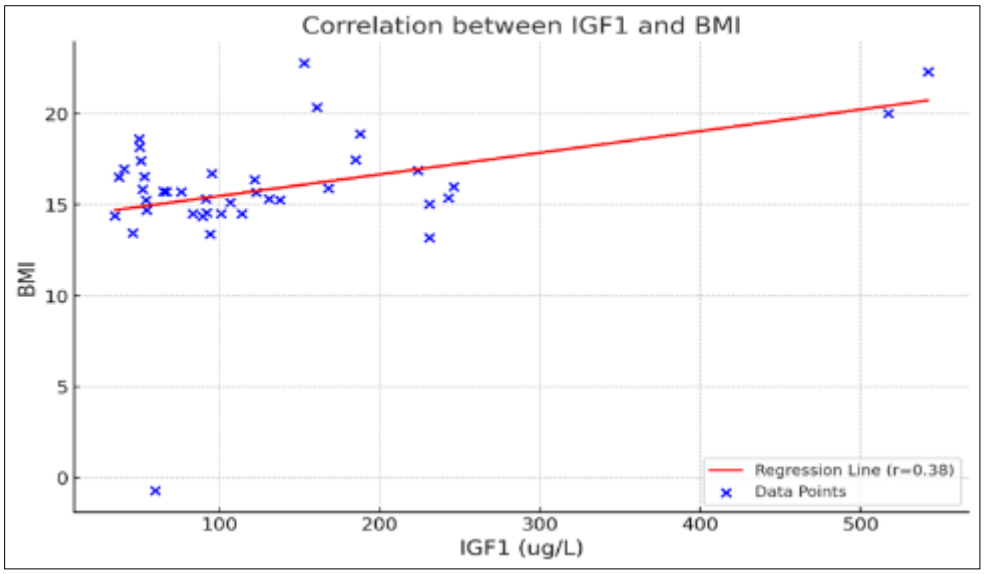

Figure 4 The correlation between IGF1 levels (in ug/L) and BMI. The blue points represent the individual data points from your dataset, and the red line is the linear regression line, indicating the trend between the two variables. The correlation coefficient (r) is 0.38, suggesting a moderate positive correlation between IGF1 levels and BMI.

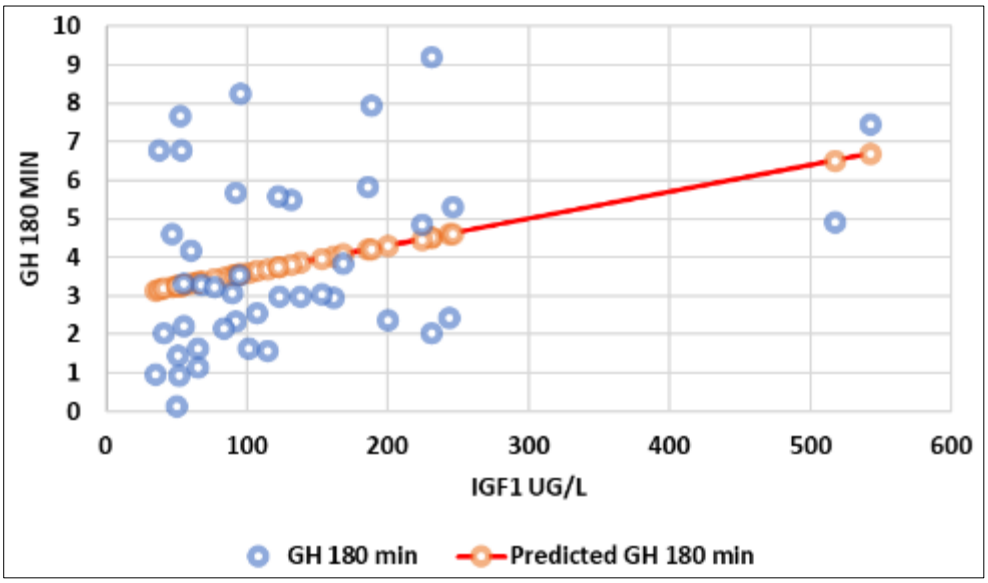

Figure 5 Correlation between IGF1 and GH at 180 min after glucagon injection (r = 0.33, p = 0.02)

There were no significant correlations between delta glucose change (peak – nadir) and peak GH or change in GH level. (table 2)

Table 2 Correlation between glucose and GH changes

	Glucose drops	**peak GH**	**Delta GH**
Glucose drops	1.00		
peak GH	-0.03	1.00	
Delta GH	0.14	0.00	1.00

4. Discussion

Our data show a dynamic response in both glucose and GH levels post-glucagon injection. The peak in glucose occurred at 60 minutes and was followed by a decline. This could be due to the glucagon's initial hyperglycemic effect and subsequent glucose utilization or clearance. The rise in GH levels starting at 90 minutes and peaking at 120 minutes could be reflective of a physiological response to glucagon, which is known to stimulate GH release, potentially in response to hypoglycemia or other metabolic signals【5,6】.

4.1. Timing of GH Peak

Our results indicate a sharp GH increase at 120 minutes, peaking at 9.51 μg/L, with elevated levels persisting up to 180 minutes. However, we did not detect a peak level of GH at 180 minutes. Secco et al.【6】found a median GH peak response to glucagon of 13.5 μg/L, significantly higher than after insulin tolerance test (ITT) and arginine, but the timing of the peak is not specified. 【7】Georeli et al. reported atypical timing of the peak in response to GST in 18 patients (19.57%) of their short children, where those with atypical timing had a significantly lower index of responsiveness.【8】Strich et al. also emphasized the importance of peak timing in GH tests and reported that 75% of atypical deficient GST results were followed by atypical timing in a clonidine test. 【9】Yuen et al. found that GH response may be influenced by factors such as BMI and glucose tolerance.

In agreement with previous studies, the peak GH concentration following glucagon administration (glucagon stimulation test for GH reserve) generally occurs between 90 and 120 minutes【10-12].

4.2. Percentage of Diagnosing GH Deficiency

In our study, 31% of children showed peak GH concentrations of less than 7 μg/L, and 47.6% less than 10 μg/L.【6】Secco et al. reported GH peak after glucagon was less than 10 μg/L in 41.7% of subjects. 【13】Yackobovitch-Gavan et al. found a subnormal GH response in 39.8% of children in their initial test using GST. Dichtel et al.【14】discussed how obesity impacts GH levels, indicating a need for lower peak GH cutoff values in overweight/obese individuals, but did not provide specific percentages relating to GH deficiency diagnosis.

Our data confirmed a decrease in mean BG concentration from its peak at 60 minutes to a nadir at 120 minutes. While a lower GH level was associated with relatively higher BG at 60 minutes, higher GH levels at 120 minutes were associated with a drop of BG between 60 and 90 minutes. From a clinical perspective, the rise in GH after the decrease in glucose could indicate an adequate GH reserve and response to glucagon. However, individual responses may vary, as suggested by the variability (SE) at the peak levels of both glucose and GH. The significant inverse correlation between BG and GH at the peak glucose time point, and the direct correlation as glucose levels decreased, provide insights into the glucose-GH dynamics during glucagon stimulation tests in short-stature children.

However, Giuffrida et al.【1】did not observe hypoglycemia but reported a GH response independent of BG decreases. In two other studies on GH secretion after IV versus IM glucagon injection, it was found that both routes lead to a rise followed by a decrease in glucose level. However, IV glucagon induced no significant GH rise, while IM glucagon administration induced a clear-cut GH increase【15,16]. They suggested that the mechanisms underlying the GH responses to IM glucagon unlikely include glucose variations or stress.

Studies by Dichtel et al.【14】 and Corneli et al.【17】 recommend the need for personalized GH cut-off values considering factors like obesity, age, and BMI. In a review and meta-analysis of 58 studies, the impact of BMI SDS on peak GH values in response to provocation in children was investigated. It showed a significant negative relationship【18,19]. Authors suggested that because of the ever-rising prevalence of pediatric obesity, there is a necessity for finding BMI (SDS)-specific cutoff values for GH stimulation tests in children.

Yan et al.【20】, suggested that in children, beyond the intrinsic issues of testing (test length, GH assay, peak GH response cut-off and associated MRI findings), results of GH stimulation testing can be influenced by patient characteristics including age, gender, puberty, nutritional status, and body weight. Diri et al.【21】, reported that patient age, IGF-I, BMI, and the number of additional pituitary hormone deficiencies are efficient factors associated with the diagnosis of GHD.

Advantages of the glucagon stimulation test (GST) include its reproducibility, safety, and lack of influence by gender【22】. Disadvantages include the lengthy test duration (3h) and the requirement for an intramuscular injection. In adults, side effects include nausea, vomiting, and headaches, especially more pronounced in elderly subjects【23】.

Our data confirm the safety of GST with none of the children having symptomatic hypoglycemia. Asymptomatic hypoglycemia occurred in 4/42 (9.5%) at 60 minutes and was self-corrected【6,16】. Chanoine et al.【24】 study noted asymptomatic hypoglycemia in 11% of the infants at least once between 120-180 min. Lim et al.【12】 reported that 27/80 (33.7%) children had hypoglycemia during the GST. Eight of their children had both a falling BG trend and hypoglycemia at the end of the test. Whereas none of our children had hypoglycemia at the end of the test.

5. Conclusion

In summary, our study aligns with existing literature in demonstrating a dynamic response of glucose and GH levels after glucagon injection. However, the direct association between BG decrease and GH increase is a particular highlight of our findings, which some studies have not observed. The variability in individual responses advocates a careful and personalized approach when interpreting GST results.

Recommendations

Personalized Interpretation of GH Stimulation Tests: GH stimulation test results should be interpreted based on individual factors like BMI, age, and metabolic status to improve diagnostic accuracy.

Further Investigation into Glucose-GH Dynamics: More research is needed to explore the complex relationship between glucose levels and GH secretion for better management of growth hormone deficiencies.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that there are no conflicts of interest regarding the publication of this study. All authors have contributed to the research and manuscript preparation without any financial or personal relationships that could influence the outcomes or interpretations of the study.

Statement of ethical approval

This study was conducted as a retrospective analysis, and the requirement for informed consent was waived by the Hamad Medical Corporation (HMC) Research Center. Ethical approval for accessing and analyzing the patients' data was granted under this waiver, ensuring that patient confidentiality and data protection were strictly maintained throughout the study.

Authors contribution

The main author, Dr. Ashraf Soliman, served as the lead researcher and corresponding author, overseeing the study's design, data collection, analysis, and manuscript preparation. Co-authors Fawzia Alyafei, Nada Alaaraj, Noor Hamed, Shayma Ahmed,Ahmed Elawwa, Hendeh Zirak, and Mohamed Qusad, all from the Pediatric Division of Endocrinology at Hamad General Hospital, were responsible for clinical data collection, conducting the glucagon stimulation tests, writing the manuscript and patient management. Dr. Vincenzo De Sanctis from the Quisisana Hospital in Italy contributed to the study's methodology and analysis, bringing his expertise in pediatric endocrinology to enhance the interpretation of the data. Together, the team collaborated on the study's clinical execution and the writing of the final manuscript.

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