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The impact of growth hormone (GH) therapy on glucose metabolism: A narrative review mainly focused on GH-deficient (GHD) children and adolescents

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Abstract

Introduction: Growth hormone (GH) deficiency (GHD) in children and adolescents is traditionally managed with GH therapy, which, while effective for promoting growth, poses potential metabolic repercussions, particularly concerning glucose metabolism. This review delineates the complex interplay between GH therapy, insulin sensitivity, and glucose homeostasis.

Objective: To synthesize existing literature on the effects of GH therapy on glucose metabolism, insulin secretion, and insulin sensitivity in GH-deficient pediatric populations, aiming to illuminate the nuanced metabolic consequences and to optimize therapeutic outcomes.

Results: The reviewed studies illuminate a complex influence of GH therapy on metabolic parameters. While GH promotes growth and improves body composition, it may concurrently impair insulin sensitivity, elevate fasting glucose levels, and, in some cases, induce glucose intolerance. However, the dysglycemic effect during GH therapy appears to be transient and reversible on discontinuation of therapy. The counterbalancing role of insulin-like growth factor 1 (IGF-1) and its contribution to maintaining glucose homeostasis is also highlighted, illustrating a complex metabolic interplay induced by GH therapy.

Discussion: The findings underscore the variability in individual metabolic responses to GH therapy. The balance between GH-induced insulin resistance and IGF-1-mediated insulin sensitivity is crucial. Monitoring and adjusting GH therapy based on glycemic response is imperative to prevent adverse metabolic outcomes.

Conclusion: GH therapy in GH-deficient children and adolescents requires careful consideration of its metabolic effects. Personalized treatment strategies and vigilant monitoring of glucose metabolism are essential to optimize therapeutic outcomes and minimize the risk of metabolic complications. Further research is warranted to establish comprehensive guidelines for managing the metabolic aspects of GH therapy in this vulnerable population.

Keywords: Growth hormone deficiency; GH therapy; Insulin sensitivity; Glucose homeostasis; Metabolic monitoring; Pediatric patients.

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1. Introduction

The interplay between growth hormone (GH) therapy and metabolic regulation, particularly concerning glucose metabolism, insulin secretion, and insulin sensitivity, presents a complex and critical area of endocrinological research. GH, along with Insulin-like Growth Factor 1 (IGF-1), plays pivotal roles in various metabolic processes, including those governing glucose homeostasis. While GH is recognized for its potential to impair insulin sensitivity, thus possibly elevating insulin and glucose levels, IGF-1 is often seen as a balancing factor with its insulin-enhancing effects. (1-3) Therefore, the interaction between these hormones suggests a nuanced impact of GH therapy on metabolic functions, warranting an in-depth review to elucidate its potential adverse effects and guide therapeutic strategies.

GH and IGF-1 are instrumental in metabolic regulation, impacting glucose homeostasis. GH may induce insulin resistance, elevating glucose, and insulin levels, whereas IGF-1 counterbalances these effects, enhancing insulin sensitivity. This complex interplay suggests that GH's potential diabetogenic effects are modulated by IGF-1, underlining the importance of understanding these mechanisms, especially in the context of GH therapy. (4)

Moreover, the intricate relationship between GH, IGF-1, and metabolic pathways extends to lipid and protein metabolism, with significant implications for insulin sensitivity and glucose homeostasis. GH is known to promote lipolysis, potentially affecting insulin sensitivity, while IGF-1's insulin-like properties might mitigate such metabolic disturbances. This duality underscores the critical nature of their roles in glucose regulation and the potential consequences of GH therapy, especially regarding insulin antagonism and glucose tolerance. (5)

The potential negative effects of GH therapy on metabolic health, particularly its role in inducing insulin resistance and glucose intolerance, remain contentious, highlighted by varying research findings. Some studies suggest that GH therapy can significantly disrupt metabolism, while others report minimal or reversible impacts. This discrepancy emphasizes the need for a thorough review, which would synthesize existing data, clarify the conditions under which GH therapy impacts glucose regulation, and offer insights for managing any adverse metabolic effects. (6,7)

Incorporating such knowledge, a review into the scientific literature is essential for dissecting the nuanced effects of GH on glucose metabolism and for formulating well-informed clinical therapeutic approaches. This endeavor would not only reconcile conflicting evidence but also enhance our understanding of GH's broader metabolic consequences, ensuring more informed clinical decisions regarding its therapeutic use.

2. Materials and Methods

2.1. Study Design

This review was conducted following a structured methodology to assess the impact of GH therapy on glucose metabolism in GH-deficient children and adolescents. The approach was comprehensive, focusing on synthesizing existing literature to provide a clear understanding of the metabolic implications of GH therapy.

2.2. Data sources and search strategy:

A systematic search was performed across multiple electronic databases, including PubMed, Scopus, Web of Science, and Google Scholar. The search terms used were "growth hormone therapy", "GH deficiency in children", "glucose metabolism", "insulin sensitivity", and adolescents". Both *Medical Subject Headings* (MeSH terms and free-text terms were utilized to ensure the breadth of the search. The time frame for the literature search was not restricted to capture all relevant studies.

2.3. Inclusion and exclusion criteria

Studies were selected based on predefined criteria.

- Inclusion: Peer-reviewed articles reporting on GH-deficient (GHD) pediatric populations undergoing GH therapy, with outcomes measured in terms of glucose metabolism, insulin sensitivity, or insulin secretion.
- Exclusion: Non-English articles, reviews, commentaries, and studies focusing on adults or non-GH-deficient populations.

2.4. Data extraction and quality assessment

Two independent reviewers extracted data from the selected studies, including author details, year of publication, study design, sample size, duration of GH therapy, and key findings related to glucose metabolism. Discrepancies were resolved through discussion or consultation with a third reviewer. The quality of the included studies was assessed using standardized checklists appropriate for observational studies and clinical trials.

2.5. Synthesis of results

The data were synthesized narratively, focusing on the impact of GH therapy on various aspects of glucose metabolism, including insulin resistance, glucose tolerance, and changes in fasting glucose levels. The synthesis aimed to draw correlations between GH therapy and metabolic outcomes, considering variations in study design, duration of therapy, and baseline characteristics of the populations studied (Figure 1).

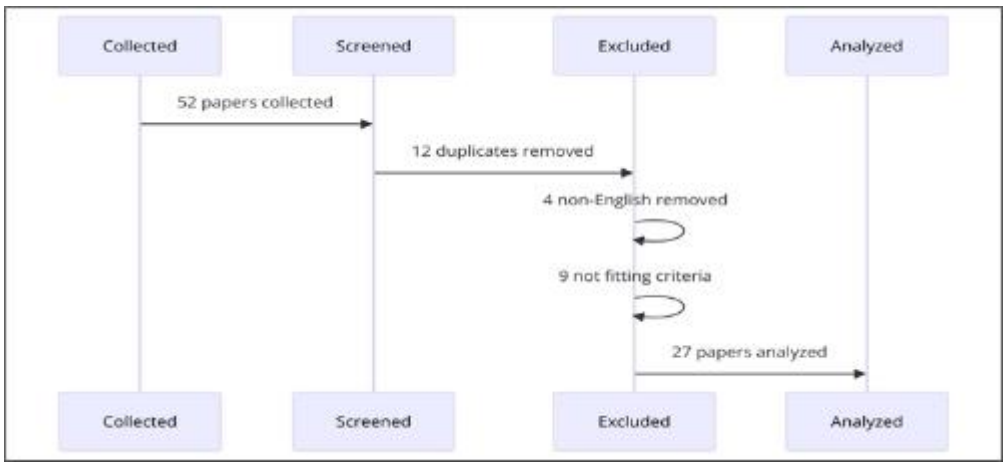

Figure 1 PRISMA flow chart

2.6. Ethical considerations

As this was a literature review, no primary data collection was involved, and therefore, ethical approval was not required. The review was conducted adhering to ethical standards of scientific reporting.

2.7. Statistical analysis

Due to the heterogeneity of the studies in terms of design, population, and outcomes, a meta-analysis was not feasible. Instead, a qualitative synthesis of the findings was provided, highlighting trends and significant outcomes reported across the studies.

2.8. Interpretation of findings

The results were interpreted in the context of the existing body of evidence, considering the biological plausibility of the observed associations and the potential clinical implications for managing GH-deficient children and adolescents undergoing GH therapy.

3. Results

We reviewed and analyzed 27 studies on the effect of GH therapy on glucose dynamics, insulin secretion and sensitivity, oral glucose tolerance, HbA1c, and fasting blood glucose mainly in children and adolescents with GHD (Table1).

Table 1 A comprehensive chronological summary of the research findings on the effects of GH therapy on glucose metabolism in GH-deficient pediatric populations.

Author(s)	Year	Number of patients	Main findings
Nørrelund et al. (1)	2000	18	Discontinuation of GH therapy improved insulin sensitivity and fat mass in GH-deficient adolescents, suggesting the importance of monitoring these parameters during the transition to adulthood.
Rosenfalck et al. (2)	2000	11	Long-term GH therapy induced significant changes in insulin and C-peptide kinetics, leading to impaired glucose tolerance and reduced insulin sensitivity, despite positive changes in body composition.
Svensson et al. (8)	2002	11	Long-term GH therapy in GH-deficient adults showed sustained body composition improvement without significant changes in insulin sensitivity, suggesting a potential preventive effect against age-related insulin sensitivity decline.
de Zegher et al. (9)	2002	13	High-dose GH therapy in short children born small-for-gestational age (SGA) was associated with improved height but led to increased insulin levels, reduced insulin sensitivity, and reversible glucose tolerance changes.
Schwarz et al. (10)	2002	5 HIV-infected adults with fat accumulation	GH treatment increased fasting plasma glucose and insulin levels, influenced by GH's lipolytic activity, suggesting a need for cautious use in patients at risk of diabetes.
Jeffcoate (11)	2002	Review	Review highlights the relationship between GH therapy and increased risks of insulin resistance, glucose intolerance, and diabetes, advocating for regular glucose monitoring during treatment.
Kishi et al. (12)	2003	36	GH therapy in GH-deficient children led to increased insulin resistance and secretion over time, indicating the need for careful glucose metabolism monitoring during treatment.
Segerlantz et al. (13)	2003	10 Adults (GHD)	Inhibition of lipolysis during GH therapy improved insulin sensitivity, suggesting that GH's diabetogenic effects can be mitigated with appropriate management.
Bramnert et al. (14)	2003	- Adults (GHD)	GH replacement therapy induced insulin resistance by enhancing lipolysis and increasing free fatty acid (FFA) levels, underscoring the complex relationship between GH and insulin resistance.
Radetti et al. (15)	2004	Not specified	Long-term GH therapy in GH-deficient children resulted in unchanged insulin sensitivity but variable effects on glucose metabolism, emphasizing the need for individualized monitoring.
Maison et al. (16)	2004	Meta-analysis	GH treatment in GH-deficient adults reduced LDL cholesterol and fat mass but decreased insulin sensitivity, highlighting the need for careful metabolic monitoring.
Liang et al. (17)	2006	44	Children undergoing rhGH therapy may be at increased risk of insulin resistance, especially during the first year, and therapy may induce transitory glucose metabolic disorders in a small proportion of patients.
Le Roith & Yakar (18)	2007	Review	Overview of GH and IGF-1's metabolic effects, illustrating GH's role in insulin resistance and its implications for glucose metabolism.
Trepp et al. (19)	2010	10 Adults (previously untreated GHD)	Acute GH administration increased insulin levels and reduced insulin sensitivity; co-treatment with acipimox (antilipolytic) improved insulin sensitivity, suggesting GH-induced effects are modifiable.

Vijayakumar et al. (20)	2010	Review	GH-induced insulin resistance is primarily due to increased lipolysis; however, long-term metabolic consequences of GH therapy need further investigation.
Roemmler et al. (21)	2010	52 Various	Long-term GH substitution showed a trend towards beneficial effects on fasting glucose and glucose tolerance without significant impact on insulin sensitivity or lipid metabolism.
Cavlan et al. (22)	2013	Type 1 diabetic patient	Acute hyperglycemia and ketonuria observed with GH replacement, highlighting the necessity for careful diabetes management during GH initiation.
Prodam et al. (23)	2014	23	GH withdrawal in adolescents with non-confirmed GH deficiency led to improvements in insulin sensitivity and fasting glucose levels, underscoring the metabolic impact of GH therapy cessation.
Wang et al. (24)	2015	3 cases	Reports of GH therapy inducing transitory glucose metabolic disorders, which were reversible after discontinuing GH, suggesting a need for monitoring glucose metabolism.
Baronio et al. (25)	2016	99	Longitudinal study in GH-deficient children showed GH treatment did not significantly affect insulin sensitivity or β-cell secretory capacity, suggesting a neutral effect on glucose metabolism.
Münzer et al. (26)	2009	131 (older adults: 65-88 years)	GH and sex steroid therapy in older individuals showed increased insulin resistance with minor beneficial effects on lipids; necessitates monitoring of metabolic parameters.
Pellegrin et al. (27)	2019	101	In GH-deficient children, rhGH therapy increased HbA1c and insulin resistance, highlighting the importance of close monitoring for glucose abnormalities during treatment.
Lutski et al. (28)	2019	23 Various	No increase in diabetes prevalence in isolated GHD and SGA group compared to the general population. Increased prevalence in those treated for multiple deficiencies, suggesting close glucose monitoring during GH therapy.
Zhou et al. (29)	2021	Systematic review Adults	GH replacement in adults showed a sustained effect on fasting plasma glucose but not on insulin sensitivity or HbA1c in long-term treatment.
Takahashi et al. (30)	2023	Large cohort Adults	Weekly somapacitan (a long-acting GH) showed no adverse effects on glucose metabolism in adults with GHD, maintaining stable glucose and insulin levels over 86 weeks.
Sharma et al. (31)	2020	Review	GH affects insulin signaling by increasing lipolysis and free fatty acid flux, leading to potential insulin resistance; emphasizes the need for monitoring during GH therapy.
Huang et al. (32)	2020	Review	Discussion on the balance between insulin and GH, emphasizing the diabetogenic potential of GH and the importance of monitoring metabolic outcomes during therapy.

4. Summary of the results

4.1. Variability in insulin sensitivity

Multiple studies, such as those by Nørrelund et al. (1) and Radetti et al. (15), indicate that GH therapy can lead to changes in insulin sensitivity, with some showing improvement post-therapy and others indicating no significant change.

4.2. Risk of impaired glucose tolerance

Rosenfalck et al. (2) and de Zegher et al. (4) observed that long-term GH therapy could induce significant metabolic alterations, leading to impaired glucose tolerance, though some effects were reversible or variable.

4.3. Induction of insulin resistance

Several reports, including those from Kishi et al. (12) and Bramnert et al. (9), highlight that GH treatment may induce insulin resistance, primarily by enhancing lipolysis and increasing free fatty acid (FFA) levels.

4.4. Transient glucose metabolic disorders

Instances of GH therapy inducing transitory glucose metabolic disorders were noted by Wang et al. (24) and Liang et al. (17), emphasizing the need for close monitoring of glucose metabolism during treatment.

4.5. GH therapy and diabetes risk

Studies like Lutski et al. (28) and Schwarz et al. (10) suggest a need for cautious use of GH therapy in patients at risk of diabetes, with some groups showing an increased prevalence of diabetes when treated for multiple deficiencies.

4.6. Neutral effects on glucose metabolism

Baronio et al. (25) reported that GH therapy did not significantly affect insulin sensitivity or β-cell secretory capacity in a longitudinal study, indicating a possible neutral effect on glucose metabolism in some populations.

4.7. Importance of monitoring glucose levels

The need for regular glucose monitoring during GH treatment is advocated by Jeffcoate (11) and Maison et al. (16), considering the relationship between GH therapy and increased risks of insulin resistance and glucose intolerance.

4.8. Beneficial effects without significant metabolic impact

Roemmler et al. (21) showed a trend towards beneficial effects on fasting glucose and glucose tolerance, without a significant impact on insulin sensitivity or lipid metabolism, in a long-term GH substitution study.

4.9. Reversible effects post GH therapy discontinuation

Findings from Nørrelund et al. (1) and Prodam et al. (23) suggest improvements in insulin sensitivity and fasting glucose levels upon GH therapy withdrawal, highlighting the reversible nature of some of GH's metabolic effects.

4.10. Long-acting GH and stable glucose levels

Takahashi et al. (30) demonstrated that weekly administration of a long-acting GH formulation maintained stable glucose and insulin levels over an extended period, showing no adverse effects on glucose metabolism.

5. Discussion

Growth hormone (GH) therapy exerts multifaceted effects, primarily enhancing tissue growth and regeneration through its anabolic properties. This therapeutic increase in GH levels can paradoxically reduce insulin sensitivity, which may result in insulin resistance. At the same time, GH prompts the liver to produce insulin-like growth factor 1 (IGF-1) that possesses insulin-mimetic and anabolic capabilities. IGF-1 significantly influences insulin secretion and action, playing a pivotal role in glucose homeostasis by working alongside insulin to augment glucose uptake across tissues. It achieves this by boosting the activity of glucose transporters on the cell membrane, facilitating glucose entry into cells. Moreover, IGF-1's enhances beta-cell function and consequently insulin output, aligning with increased metabolic demands. Besides its insulin-like roles, IGF-1 promotes protein synthesis and curtails proteolysis, indirectly modulating insulin's metabolic functions. (33-35) The interplay between the induced insulin resistance by GH and the counteractive IGF-1 presents a complex regulatory mechanism of metabolic functions. Collectively, these hormone-driven processes exert a significant impact on the regulation of insulin efficacy, overall glucose management, and metabolic health, underscoring the comprehensive influence of GH therapy in metabolic regulation. (35-37) In particular, several studies have reported the following:

5.1. Increased risk of glucose dysregulation in children with GH-deficiency (GHD):

Children with GHD might inherently have a predisposition to glucose abnormalities and diabetes, even without GH therapy.

Rosenfalck et al. (2), Nørrelund et al.(1) and Prodam et al. (23), provide insights into how GHD impacts insulin kinetics and metabolic parameters, indicating a complex interplay between GH levels and glucose metabolism. This underscores

the importance of close monitoring of glucose levels in GHD individuals irrespective of therapy status. In addition, children with growth hormone GHD have increased body fat, particularly abdominal fat, which can significantly impact insulin secretion and glucose dynamics, potentially leading to metabolic syndrome. (38)

5.2. Impact of GH therapy on glucose metabolism:

The impact of GH therapy on glucose metabolism in GHD children is debated, with studies showing both negative effects and no significant impact.

While Rosenfalck et al. (2) and Kishi et al. (12) reported that GH therapy could exacerbate glucose intolerance and insulin resistance, Baronio et al. (25) found no significant changes in insulin sensitivity, highlighting a spectrum of responses depending on individual patient characteristics. However, Ciresi et al. have suggested that different methods used to study glucose metabolism, and different doses and duration of GH therapy may explain the inconsistency in the results. (39) Based on these observations, studies by de Zegher et al. (4) and Pellegrin et al. (27) have emphasized the need for individualized therapy to mitigate potential risks. Nevertheless, the relationship between the dose/duration of GH therapy and the development of metabolic abnormalities remains a critical area of study. While some evidence suggests that higher doses or longer duration might exacerbate metabolic disturbances, definitive conclusions are challenging to draw.

5.3. Effects of GH therapy on body composition and glucose metabolism

GH therapy has been found to modify body composition by decreasing body fat and, specifically, abdominal visceral fat, which is closely linked to insulin resistance and metabolic syndrome. This reduction in fat mass can lead to improvements in insulin sensitivity and reductions in the risk factors associated with metabolic syndrome. (38) Moreover, studies by Bramnert et al. (9) and Trepp et al. (19) reveal that GH can induce insulin resistance by modifying lipolysis and FFA levels, which in turn impacts insulin secretion and sensitivity, pointing towards the need for tailored therapeutic strategies taking in consideration that GH therapy may deteriorate glucose metabolism in muscles (9), and could impair insulin-stimulated glucose turnover into glycolytic flux and glycogen synthesis/glucose storage. (8,40)

5.4. Reversibility of glucose abnormalities

The literature suggests that the glucose metabolic disorders induced by GH therapy are often reversible upon its discontinuation. This is supported by studies reported by Prodam et al. (23) and Wang et al. (24), where cessation of GH led to improvements in insulin sensitivity and resolution of glucose metabolic disorders, highlighting the transient nature of GH-induced metabolic changes.

5.5. Strong points in the review

This review enriches the existing literature by offering a focused, comprehensive synthesis of the effects of GH therapy on glucose metabolism in large number of GHD children and adolescents. It analyzes the balance between GH's growth-promoting benefits and its potential metabolic risks, especially concerning insulin sensitivity and glucose homeostasis. By integrating the latest research, the review presents updated insights, highlights the complex interplay between GH and IGF-1, and provides informed guidance for clinical management. It also identifies gaps in current knowledge, setting a direction for future research to optimize therapeutic outcomes and ensure the metabolic well-being of this vulnerable population.

5.6. Limitations

The review acknowledges potential limitations, including publication bias, variability in study quality, and the inherent challenges in synthesizing data from heterogeneous studies. The potential impact of these limitations on the review's conclusions is discussed.

6. Conclusion

While GH therapy is pivotal for promoting growth in deficient individuals, it necessitates a nuanced approach to manage its potential metabolic side effects. Personalized treatment plans, informed by ongoing research and clinical monitoring, are essential to optimize the therapeutic outcomes and safeguard against the risk of glucose abnormalities and diabetes. This review underscores the critical need for tailored GH regimens, continuous monitoring of metabolic parameters, and a readiness to adjust therapy based on individual metabolic responses (Figure2).

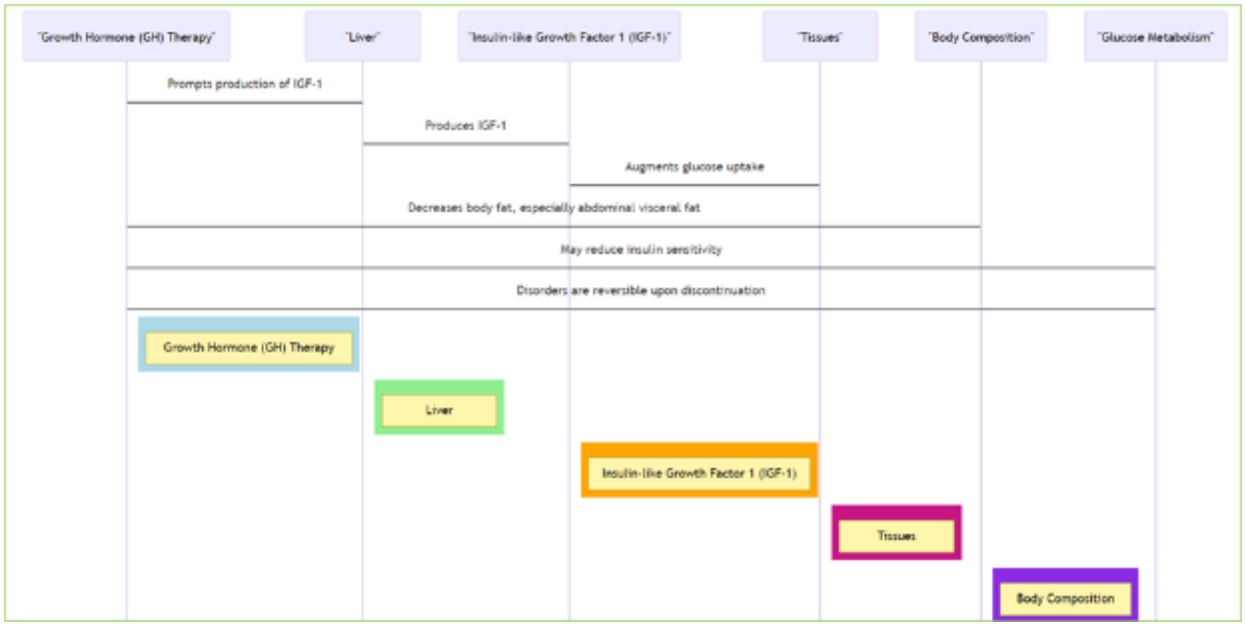

Figure 2 Summary of GH therapy on glucose metabolism and legend: GH therapy initiates a chain of events, starting with prompting the liver to produce IGF-1; IGF-1, in turn, augments glucose uptake across tissues, mimicking insulin's effects; GH therapy also impacts body composition by reducing body fat, particularly abdominal visceral fat; the diagram also highlights how GH therapy can reduce insulin sensitivity, affecting glucose metabolism; any disorder in glucose metabolism induced by GH therapy are reversible upon its discontinuation.

Recommendations

- Tailor GH therapy to individual patient needs, emphasizing personalized dosing and careful monitoring of glucose metabolism to mitigate potential metabolic disturbances.
- Implement routine and comprehensive metabolic assessments for GH-treated individuals to promptly identify and address any glucose abnormalities or insulin resistance.
- Educate patients and healthcare providers about the potential metabolic effects of GH therapy, ensuring a well-informed approach to treatment and monitoring.
- Encourage ongoing research to elucidate the long-term metabolic impacts of GH therapy, informing future guidelines and optimizing patient care strategies.

Compliance with ethical standards

Disclosure of conflict of interest

Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Author contributions

ATS: Data collection, screening, data analysis and original draft preparation; FA, NA, NH, SA and AB: participated to draft preparation and revisions and editing the content. VDS: provided expert editing and review; All authors: approved the final manuscript.

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