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Thyroid function changes during growth hormone therapy in pediatric patients: a controlled study and review of recent data

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Abstract

Introduction: Growth hormone therapy is a cornerstone treatment for children with GHD and ISS. Its impact on the hypothalamic-pituitary-thyroid axis, however, has been a subject of ongoing research. This review compiles findings from several studies spanning three decades and contrasts them with recent data to enhance our understanding of thyroid function dynamics during GH therapy.

Review of Literature: Early Observations (1992-2005)

Pirazzoli et al. (1992) and Tang et al. (1997) were among the first to document changes in thyroid function due to GH therapy, noting enhanced peripheral conversion of T4 to T3 and a prevalence of subclinical hypothyroidism. Wyatt et al. (1998) reported significant decreases in T4 and increases in T3, indicating a notable shift in thyroid hormone levels early in GH therapy.

- Mid-Term Studies (2005-2015)

Seminara et al. (2005) and Kalina-Faska et al. (2004) reported changes in thyroid function, particularly a decrease in T4 levels and a transient increase in fT3 during the early stages of GH therapy.

- Recent Developments (2016-Present)

Wang Ying and Liang Furong (2016) emphasized the need for vigilant monitoring of thyroid hormone levels, aligning with Zheng et al. (2014) who noted improvements in lipid metabolism without significant thyroid function impacts. Glynn et al. (2017, 2018) and Kucharska et al. (2021) focused on the complexities of the biological effects of GH-induced changes in thyroid hormones.

Comparison with our Data Our recent study reveals subtle changes in thyroid function in GH-treated children with GHD and ISS. We observed a slight decrease in mean FT4 and an increase in mean TSH in the GH treatment group, stable TSH and decreased FT4 in the ISS treatment group, and significant decreases in both FT4 and TSH in the no-treatment group. These findings corroborate the trend seen in earlier studies, highlighting the multifaceted nature of thyroid function changes during GH therapy.

Conclusions: The review underscores that GH therapy can significantly influence thyroid function, necessitating regular monitoring of thyroid hormone levels. The variation in thyroid responses suggests a complex interaction between GH

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therapy and the hypothalamic-pituitary-thyroid axis, which may be influenced by factors like age, severity of GHD, and duration of GH treatment.

Keywords: Growth Hormone Therapy; Thyroid Function Dynamics; Hypothalamic-Pituitary-Thyroid Axis; Free T4; TSH.

1. Introduction

Growth hormone (GH) therapy is a cornerstone intervention for children with growth hormone deficiency (GHD) and idiopathic short stature (ISS), aiming to promote normal growth and development. However, the interrelationship between GH and thyroid function has garnered significant attention due to emerging evidence suggesting that GH therapy may influence thyroid hormones, particularly Free Thyroxine (FT4), Thyroid Stimulating Hormone (TSH), and Free Triiodothyronine (FT3) (1-3).

Literature spanning several decades has documented variations in these thyroid hormones in response to GH therapy. Studies have consistently reported a decrease in FT4 levels, while the impact on TSH and FT3 has been more variable. The mechanism underlying these changes is complex, rooted in the intricate crosstalk between GH and the hypothalamic-pituitary-thyroid (HPT) axis. GH has been shown to exert influence on the synthesis, secretion, and metabolism of thyroid hormones. It can modulate the sensitivity of the thyroid gland to TSH and alter the peripheral conversion of T4 to T3, predominantly in the liver and kidneys, where a significant number of thyroid hormones are metabolized (4,5).

Furthermore, GH can affect the deiodinases enzymes that are responsible for the conversion process. Specifically, GH may upregulate deiodinase type 2 (D2), which converts the prohormone T4 into the metabolically active T3, and downregulate deiodinase type 3 (D3), which inactivates T4. This modulation could potentially lead to increased levels of FT3, despite a decrease in FT4, which is commonly observed during GH treatment. Additionally, GH might influence the expression of thyroid hormone transporters and receptors, thereby affecting the bioavailability and action of thyroid hormones at the cellular level (6,7).

The possibility of GH-induced modifications in thyroid hormone levels necessitates a careful assessment of thyroid function during GH therapy. Understanding these interactions is crucial for optimizing treatment regimens, ensuring effective therapy while mitigating potential adverse effects on the HPT axis. This introduction sets the stage for a detailed exploration of the effects of GH therapy on thyroid hormones and the potential mechanisms involved, as documented in the literature. (8)

2. Patients and Methods

2.1. Study Population

This retrospective study examines the effects of Growth Hormone (GH) therapy on thyroid function, specifically focusing on Free Thyroxine (FT4) and Thyroid Stimulating Hormone (TSH) levels, in children with Growth Hormone Deficiency (GHD) and Idiopathic Short Stature (ISS). The participants were divided into three distinct groups: those receiving GH treatment (n=90), ISS patients undergoing GH treatment (n=16), and a control group without treatment (n=25). The study measured FT4 and TSH levels at baseline (T0) and after one year (T1) of GH therapy.

2.2. Review Data Collection

We conducted a comprehensive literature search of databases, including PubMed, Scopus, and Web of Science, to identify studies that reported changes in thyroid function in response to GH therapy. Key search terms included "growth hormone therapy," "thyroid function," "pediatric endocrinology," "TSH," "FT4," and "GH deficiency." The studies reviewed range from 1992 to 2022, covering a broad spectrum of patient demographics and treatment protocols.

2.3. Inclusion Criteria

Studies were included if they:

- Were published in peer-reviewed journals.
- Reported original research on pediatric patients.
- Provided clear data on thyroid hormone levels before and after GH therapy.

- Had a clear description of GH therapy protocols.

2.3.1. Exclusion Criteria

Studies were excluded if they:

- Focused on adult populations.
- Lacked pre- and post-therapy thyroid function data.
- Were case reports, editorials, or review articles without original data.
- Data Extraction: From each study, we extracted:
- The number of participants.
- Age range and gender distribution.
- Baseline thyroid function tests (TSH and FT4).
- Post-treatment thyroid function tests after 1 year.
- GH dosing regimens.
- Duration of GH therapy.
- Any reported adverse effects on thyroid function.

Statistical Analysis: Correlation coefficients were calculated to assess the relationships between TSH and FT4 with growth parameters. We used Pearson's correlation for normally distributed variables and Spearman's rank correlation for non-parametric data. A correlation coefficient (r) value of >0.5 was considered to indicate a strong correlation, 0.3-0.5 moderate, 0.1-0.3 weak, and <0.1 as negligible.

Ethical Considerations: The review was conducted following the ethical guidelines of the Declaration of Helsinki. As this was a literature-based study, no direct patient contact or intervention was involved. Therefore, institutional review board approval was not required.

Comparative Analysis: Our data was compared with findings from the literature. We analyzed the patterns of thyroid hormone changes and discussed potential physiological mechanisms and clinical implications. Our analysis aimed to synthesize the collective understanding of thyroid function response to GH therapy in pediatric patients.

2.4. Ethical Consideration

The protocol of this retrospective study was approved by the local Ethics Review Committees (IRB) of HGH in accordance with national and international regulations.

3. Results

In our study, in GH-treated GHD group, the mean FT4 level showed a minor decrease from 15.94 to 15.53, while the mean TSH level increased from 2.66 to 3.23. Additionally, the standard deviation for TSH at T1 indicated a rise in variability (SD: 4.02). Initially, 4 out of 90 children had elevated TSH, and 2 had reduced FT4. Post one year of GH therapy, 4 additional children developed elevated TSH, and 2 more had reduced FT4. (table1, figures 1,2)

Table 1 Data on thyroid function during GH therapy in children with GHD and ISS

Group	N	FT4 Pre-Treatment (Mean ± SD)	TSH Pre-Treatment (Mean ± SD)	FT4 Post 1 Year (Mean ± SD)	TSH Post 1 Year (Mean ± SD)
GHD Treated	90	15.94 ± 2.36	2.66 ± 1.78	15.53 ± 2.85	3.23 ± 4.02
ISS treated	16	13.48 ± 1.39	2.32 ± 1.43	12.75 ± 2.07	2.33 ± 1.65
ISS No Treatment	25	14.96 ± 2.09	2.73 ± 1.17	13.51 ± 1.01	1.60 ± 0.68

For the ISS-treated group, the mean FT4 reduced from 13.48 to 12.75, with mean TSH showing stability (2.32 to 2.33). The non-treated group experienced a notable decrease in mean FT4 from 14.96 to 13.51, alongside a decrease in mean TSH from 2.73 to 1.60.

These findings indicate that GH therapy in children with GHD and ISS can significantly impact thyroid function, evidenced by the increased variability in TSH and a decrease in FT4 levels. Regular monitoring of thyroid function is essential during GH therapy, as these hormonal changes could have critical implications for the growth and development of affected children.

The comprehensive review of 25 studies dating from 1992 to 2022 reveals significant insights into the thyroid function alterations in children undergoing growth hormone (GH) therapy. Key findings from these studies are as follows: (table 2) (9-32).

3.1. Early Observations (1992-2000)

Pirazzoli et al. (1992) (9) noted enhanced peripheral conversion of T4 to T3 in children under GH therapy, highlighting the impact on growth-promoting activity1.

Tang et al. (1997) (10) observed a decrease in serum T4 and FT4 levels, with 45% of children with GHD developing subclinical hypothyroidism after 12 months of rhGH treatment.

Wyatt et al. (1998) and Portes et al. (2000) found significant decreases in T4 and increases in T3 during GH therapy, indicating a shift in thyroid hormone metabolism. (11,12)

A consistent finding across studies, including those by Giavoli et al. (2003), Kalina-Faska et al. (2004), and Smyczynska et al. (2010), was a significant reduction in FT4 levels during GH therapy, especially pronounced in the initial months and in patients with multiple pituitary hormone deficiencies (13-15)

3.2. Therapeutic Implications (2007-2011)

Martins et al. (2007) suggested that GH replacement might improve the biological effects of T4, advocating for targeting high-normal FT4 levels during GH therapy (16).

Behan et al. (2011) emphasized the need for close thyroid function monitoring due to alterations in thyroid function following GH replacement (19).

3.3. Recent Developments (2014-2022)

Zheng et al. (2014) and Wang Ying and Liang Furong (2016) reported improvements in lipid metabolism and stressed the importance of monitoring thyroid hormone levels (20,21). Glynn et al. (2018), Kucharska et al. (2021), and Yao et al. (2021) noted complex effects of GH therapy on thyroid hormone levels and metabolism, with a common observation being a decrease in fT4 levels (26). Salazar et al. (2022) found that 21% of children developed hypothyroidism during GH therapy, with significant decreases in FT4 and TSH levels (31)

3.4. Our Study (2022-2023)

In line with previous findings, our study observed a slight decrease in mean FT4 and an increase in mean TSH in the GH Treatment group. The ISS Treatment group showed stable TSH but decreased FT4, while the ISS No Treatment group exhibited a significant decrease in both FT4 and TSH. (figure 1 and 2)

These results collectively highlight the dynamic and complex nature of thyroid function changes in response to GH therapy in pediatric populations. The observations underscore the necessity for diligent monitoring and tailored management of thyroid function in children undergoing GH treatment.

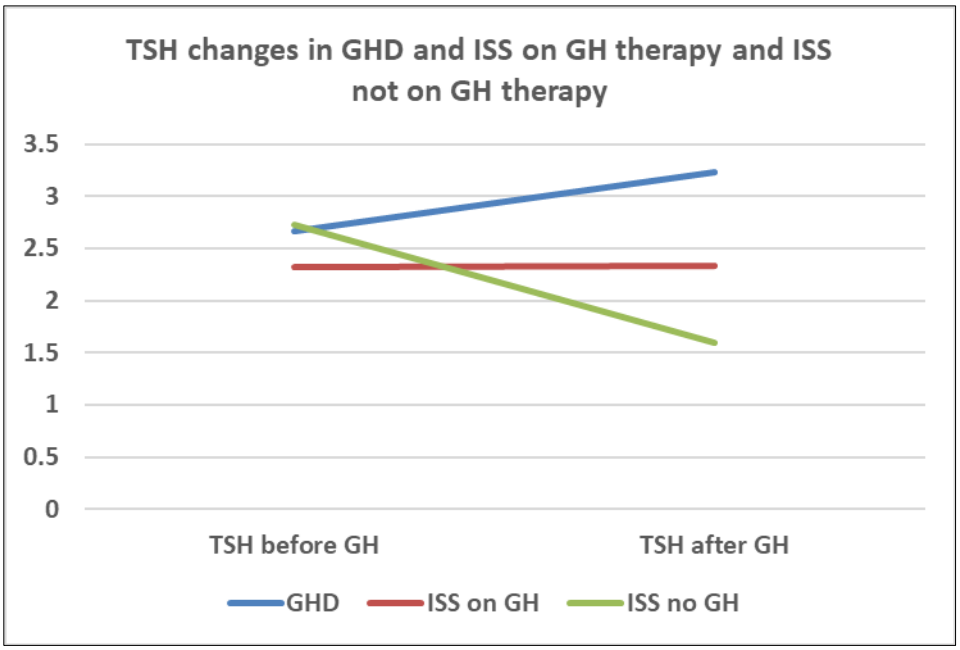

Figure 1 TSH changes during GH therapy

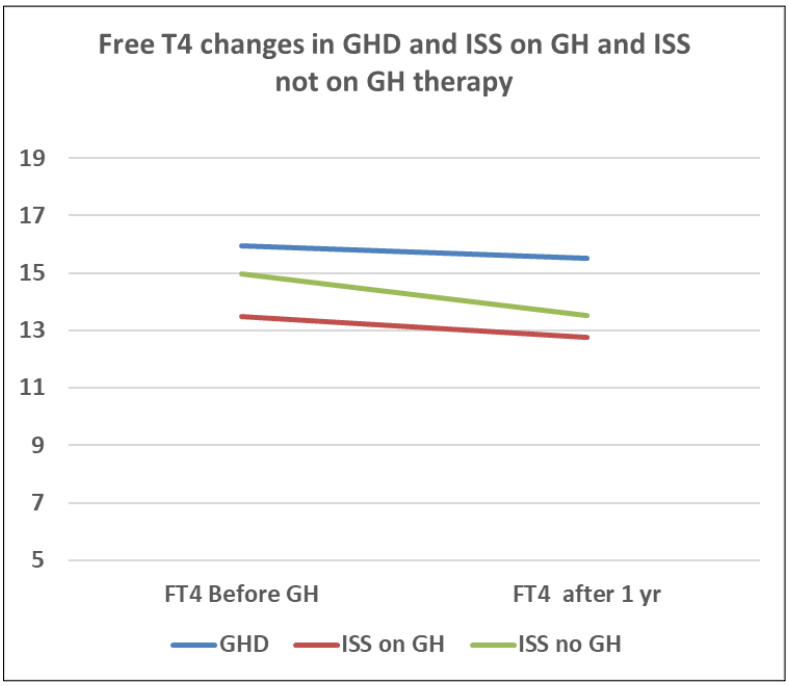

Figure 2 Free T4 changes during GH theraoy

Table 2 Chronological Overview of Research on Thyroid Function in Children Undergoing growth Hormone Therapy.

Year	Study/Your Results	Population	Key Findings on Thyroid Function	Reference
1992	Pirazzoli et al.	Children under GH therapy	Observed enhanced peripheral conversion of T4 to T3, impacting growth-promoting activity.	9
1997	Tang et al.	Children with GHD	Found significant decreases in average serum levels of T4 and FT4, and 45% of patients developed subclinical hypothyroidism after 12 months of rhGH treatment.	10
1998	Wyatt et al.	Euthyroid children with GHD	Observed significant decreases in T4, free T4 index, and rT3, and increases in T3 and the T3/T4 ratio within the first month of GH therapy.	11
2000	Portes et al.	GH-deficient children	Found that GH replacement therapy significantly decreases serum FT4 and rT3 levels and increases serum T3 levels.	12
2003	Giavoli et al.	Children with GHD	Reported a significant reduction in FT4 levels during rhGH therapy, especially in patients with multiple pituitary hormone deficiencies.	13
2004	Kalina-Faska et al.	GH-deficient children	Noted a transient decrease in T4 concentrations in the 3rd month with unchanged T3 and an increase in fT3 concentrations during rGH therapy.	14
2005	Seminara et al.	Children with idiopathic GHD	Reported changes in thyroid function due to long-term GH therapy.	15
2007	Martins et al.	GH-deficient patients	Showed that GH replacement improves the biological effects of T4, suggesting serum FT4 should be targeted at the high-normal range during GH replacement.	16
2008	Lania et al.	Patients with CH	Discussed GH deficiency masking subclinical forms of central hypothyroidism that become evident after GH replacement therapy.	17
2010	Smyczynska et al.	Children with GHD	Observed a significant decrease of FT4 serum concentration during the initial 3-6 months of rhGH administration.	18
2011	Behan et al.	Hypopituitary patients	Reported alterations in thyroid function following GH replacement, necessitating close monitoring for the development of central hypothyroidism.	19
2014	Zheng et al.	Children with ISS	Reported improvement in lipid metabolism without significant impacts on thyroid function during r-hGH therapy.	20
2016	Wang Ying and Liang Furong	Children with short stature	Emphasized the need for monitoring thyroid hormone levels before and after GH therapy.	21
2017	Cerbone et al.	Patients with GHD	Discussed progression from isolated GHD to combined pituitary hormone deficiency, highlighting the need for lifelong monitoring.	22
2017	Glynn et al.	Patients with hypopituitarism	Examined the relationship between changes in serum thyroid hormones and deiodinase activity in subcutaneous adipose tissue before and after GH replacement.	23

2018	Wang et al.	ISS children with low-normal FT4	Evaluated the effects of thyroid hormone supplementation on growth rate during GH therapy, finding a positive effect of supplementation in low-normal FT4 children.	24
2018	Witkowska-Sędek et al.	Children under GH therapy	Noted a decrease in fT4 levels during GH replacement therapy, with TSH levels remaining unaffected, especially in prepubertal children.	25
2018	Glynn et al.	Hypopituitary men	Reported alterations in thyroid hormone levels following GH replacement and their complex biological effects on different tissues.	23
2020	Binder et al.	Patients with isolated GHD	Reviewed evolving pituitary hormone deficits in primarily isolated GHD, including the risk of progression to combined pituitary hormone deficiency.	26
2020	Ebuchi et al.	GHD and non-GHD children	Showed serum FT4 concentration transiently decreased in GHD but not in non-GHD children during GH therapy.	27
2021	Kucharska et al.	GH-deficient patients	Described a decrease of thyroxine level as the most frequent observation in patients treated with rhGH.	28
2021	Profka et al.	Adult patients with GHD	Explored the complex interplay between the GH/IGF-I system and other hypothalamic-pituitary axes, emphasizing the need for accurate diagnosis and management.	29
2021	Witkowska-Sędek et al.	Children with GHD	Reported a long-term decrease in fT4 levels during rhGH therapy in initially euthyroid GHD children.	30
2021	Yao et al.	Pediatric patients with GHD	Found that GH replacement therapy may affect thyroid hormone metabolism, underscoring the need for regular monitoring of thyroid function.	31
2022	Salazar et al.	Children with isolated idiopathic GHD	Found that 21% of children developed hypothyroidism during GH therapy, with FT4 and TSH levels decreasing significantly.	32
2022	Our Study	GH Treatment, ISS Treatment, and No Treatment groups	- GH Treatment group showed a slight decrease in mean FT4 and an increase in mean TSH. ISS Treatment group had stable TSH and decreased FT4.No Treatment group showed a significant decrease in FT4 and TSH.	

4. Discussion

In GHD group, the minor decrease in mean FT4 levels from 15.94 to 15.53, coupled with an increase in mean TSH levels from 2.66 to 3.23, suggests a subtle but notable impact of GH therapy on thyroid function. The increased standard deviation in TSH at one-year post-therapy (SD: 4.02) indicates a greater variability in TSH responses among individuals, which may imply differential sensitivity to GH therapy among children.

In the ISS-treated group the stability of mean TSH levels (2.32 to 2.33) despite the reduction in mean FT4 (13.48 to 12.75) in the ISS-treated group is intriguing. This could suggest a compensatory mechanism at play or a differential impact of GH on thyroid function in ISS compared to GHD.

In the untreated ISS group, the significant decrease in both mean FT4 (14.96 to 13.51) and mean TSH (2.73 to 1.60) in the non-treated group is noteworthy. This could be indicative of natural variations in thyroid function in this population or other external factors influencing thyroid hormone levels.

The observation that additional children developed elevated TSH and reduced FT4 post-therapy indicates a potential risk of developing subclinical or overt hypothyroidism during GH treatment.

In reviewing the chronological evolution of research on thyroid function in pediatric patients undergoing growth hormone (GH) therapy, a pattern emerges that indicates a complex relationship between GH therapy and thyroid hormone dynamics. Studies spanning from Pirazzoli et al. (1992) to Salazar et al. (2022) demonstrate both transient and sustained modifications in thyroid hormone levels, particularly in free thyroxine (FT4) and thyroid-stimulating hormone (TSH) (9-32).

The early research by Pirazzoli et al. (1992) (9) and Tang et al. (1997) identified changes in the conversion of T4 to T3 and the onset of subclinical hypothyroidism in a significant subset of patients. This was confirmed in subsequent studies, such as Wyatt et al. (1998), (10) which noted decreased T4 and corresponding T3 increases. The trend of declining FT4 levels during GH therapy was consistently observed in later studies, including Giavoli et al. (2003) and Kalina-Faska et al. (2004), emphasizing the need for close monitoring of thyroid function during GH therapy (13,14).

Our recent data align with these findings, showing a slight decrease in FT4 and an increase in TSH in the GH treatment group, which is indicative of the thyroid axis's responsiveness to GH therapy. The ISS treatment group's stable TSH and decreased FT4 levels, as well as the significant decrease in both FT4 and TSH in the no-treatment group, offer further evidence of the nuanced interplay between GH therapy and thyroid function.

Furthermore, studies by Martins et al. (2007) (16) and Glynn et al. (2018) (23) suggest that GH therapy may improve the biological effects of T4, and that a high-normal FT4 may be beneficial in GH-deficient patients, particularly when GH therapy is initiated. This suggests a need for an individualized approach to thyroid hormone monitoring and management during GH therapy.

The progression of thyroid function changes in response to GH therapy reported in the literature and observed in our study may be attributable to the direct and indirect effects of GH on the hypothalamic-pituitary-thyroid axis. Growth hormone (GH) therapy can influence thyroid function, and this interaction can be attributed to several physiological mechanisms (6,33-38)

Growth hormone (GH) therapy has multifaceted effects on thyroid function. It can enhance the production of thyroxine (T4) and triiodothyronine (T3), either by increasing the thyroid gland's sensitivity to thyroid-stimulating hormone (TSH) or directly via GH receptors on thyroid cells. GH also boosts the activity of type 2 deiodinase (DIO2), escalating the peripheral conversion of T4 to the more active T3, which may lead to lower circulating levels of free T4 (FT4). Additionally, GH influences the metabolism of thyroid hormones by affecting their clearance in the liver and kidneys, thus altering their overall serum concentrations. It can modify the binding affinity of thyroid hormones to their carrier proteins, impacting the levels of free T4 and T3 in the bloodstream. (33-38)

GH's impact extends to the hypothalamic-pituitary-thyroid (HPT) axis as well, potentially altering the secretion of thyrotropin-releasing hormone (TRH) and TSH, thereby influencing overall thyroid function. Changes in TSH receptor sensitivity due to GH therapy can affect thyroid hormone production. Furthermore, insulin-like growth factor 1 (IGF-1), whose production is stimulated by GH, may regulate TSH synthesis and secretion. GH also has the ability to modify the sensitivity of various tissues to the actions of thyroid hormones, which could change their metabolic effects without significantly altering serum hormone levels. These mechanisms illustrate the complex interactions between GH therapy and thyroid hormone dynamics, underscoring the importance of monitoring thyroid function in patients undergoing GH treatment. (33-38)

Recommendations: (Figure 3)

Regularly monitor thyroid hormone levels in pediatric patients undergoing growth hormone therapy to detect and manage potential thyroid dysfunctions early.

Adopt an individualized approach to thyroid hormone management, tailoring treatment to maintain hormone levels within a target range to enhance growth hormone therapy effectiveness.

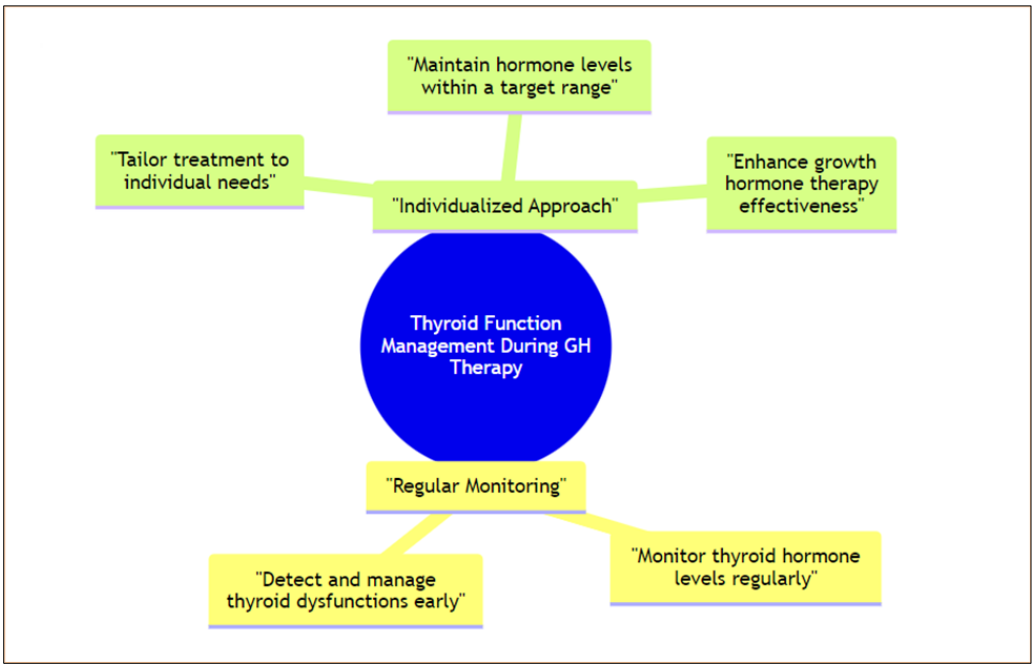

Figure 3 Recommendations regarding monitoring thyroid function during GH therapy.

5. Conclusion

In conclusion, the collective evidence from the literature and our findings underscores the importance of regular monitoring and potential adjustment of thyroid hormone therapy in pediatric patients undergoing GH treatment. The observed thyroid hormone changes necessitate a deeper understanding of the underlying mechanisms and the development of tailored treatment strategies to ensure optimal patient outcomes.

What this study adds

This study provides an insight into the specific thyroid function changes in children with Growth Hormone Deficiency (GHD) and Idiopathic Short Stature (ISS) undergoing GH therapy, emphasizing the importance of individualized monitoring and management of thyroid function during treatment.

The findings highlight the increased variability in Thyroid Stimulating Hormone (TSH) response and subtle fluctuations in Free Thyroxine (FT4) levels post-GH therapy, adding valuable data to the evolving understanding of the complex interplay between GH therapy and thyroid hormone dynamics in pediatric patients.

Limitations of the study

One limitation of this study is its observational design, which, while providing valuable insights, does not establish causality between growth hormone therapy and thyroid function changes, and may be influenced by confounding variables not accounted for in the analysis.

Another limitation is the lack of long-term follow-up data, restricting the ability to assess the sustained impact of growth hormone therapy on thyroid function over extended periods, which is crucial for understanding the full scope of GH therapy effects in pediatric patients.

Compliance with ethical standards

Disclosure of conflict of interest

There is no conflict between the authors regarding the study. All authors have participated, reviewed, and approved the publication of the study.

Author Contributions

AS was responsible for the conceptualization of the review study, setting the stage for the research with a clear outline of the scope and objectives. All authors actively participated in the data collection, screening, and analysis process, ensuring a comprehensive and meticulous evaluation of the research findings. All authors have given their final approval of the version to be published, collectively ensuring the manuscript's accuracy and integrity, and have agreed to the published version, thus upholding rigorous scholarly standards, and ensuring the work's credibility and reliability.

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