World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(REVIEW ARTICLE)

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Growth hormone therapy in Turner Syndrome (TS): A focused review on glucose metabolism outcomes

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World Journal of Advanced Research and Reviews, 2024, 22(03), 1738–1746

Publication history: Received on 16 May 2024; revised on 24 June 2024; accepted on 27 June 2024

Article DOI: https://doi.org/10.30574/wjarr.2024.22.3.1919

Abstract

Introduction: Turner Syndrome (TS) patients inherently possess a higher risk of developing glycemic abnormalities due to their unique genetic makeup, and the administration of growth hormone (GH) therapy, while beneficial for growth, might exacerbate this tendency towards disturbed glucose metabolism.

Objective of the Review: To evaluate the existing literature on the effects of GH therapy on glucose metabolism in TS patients, highlighting the balance between therapeutic benefits and potential metabolic risks.

Methods: This review scrutinizes studies published from 2000 to 2024, focusing on the outcomes related to glucose metabolism in TS individuals undergoing GH therapy, encompassing aspects like insulin sensitivity, glucose tolerance, and metabolic health.

Results: Insulin Sensitivity and Resistance: Initial findings suggest that GH therapy may exacerbate insulin resistance and elevate insulin levels, although these effects appear transient and potentially reversible after the cessation of therapy.

Long-term Metabolic Outcomes: Later studies indicate that long-term GH therapy may lead to an improvement in insulin sensitivity and a normalization of carbohydrate metabolism, particularly after the therapy is discontinued.

Variable Impacts on Glucose Tolerance: The reviewed literature shows mixed effects on glucose tolerance, with some studies reporting no significant changes, while others highlight a potential risk for worsening glucose metabolism.

Body Composition and Metabolic Profile: Positive changes in body composition and lipid profiles were noted, which could confer metabolic benefits, yet the therapy's role in increasing insulin levels warrants careful consideration.

Individual Variability and Monitoring Needs: The diverse responses to GH therapy underscore the necessity for individualized treatment plans and diligent metabolic monitoring to mitigate potential risks and optimize therapeutic outcomes.

Conclusion: The administration of GH therapy in TS requires a delicate balance, considering its potential to both benefit and pose risks to glucose metabolism. Tailored monitoring and a comprehensive understanding of the individual patient's metabolic response are essential for maximizing the therapy's efficacy while minimizing associated metabolic complications.

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Keywords: Turner Syndrome; Growth hormone therapy; Glucose metabolism; Insulin sensitivity; Metabolic risk; Individualized monitoring

1. Introduction

Turner Syndrome (TS) is a chromosomal disorder affecting approximately 1 in 2,500 to 1 in 3,000 live female births, characterized by the partial or complete absence of one X chromosome. This condition is associated with various clinical features, including short stature, gonadal dysgenesis, and a broad spectrum of congenital malformations. Beyond these hallmark characteristics, individuals with TS are also at an increased risk for a range of metabolic disturbances, notably in glucose metabolism. [1-3]

Glucose abnormalities in TS encompass a spectrum of disorders ranging from insulin resistance to an elevated risk of developing type 2 diabetes mellitus. These metabolic concerns are compounded by the standard use of growth hormone (GH) therapy to address short stature in TS patients. GH therapy, while effective in promoting height, carries potential metabolic effects, including alterations in glucose metabolism. The interaction between GH therapy and glucose homeostasis in TS patients presents a complex clinical challenge, necessitating careful management and monitoring. [4-7]

The literature from 2000 to 2024 presents a mixed view on the impact of GH therapy on glucose metabolism in individuals with TS. Some studies report a detrimental effect on insulin sensitivity, increased risk of glucose intolerance and diabetes mellitus, suggesting that GH therapy exacerbates underlying metabolic susceptibilities in TS. Conversely, other research indicates that GH treatment may have neutral or even beneficial effects on body composition and metabolic parameters, including insulin sensitivity and lipid profiles, particularly after the cessation of therapy. [4, 8-11]

This divergence in findings underscores the complexity of GH therapy in TS and highlights several areas of controversy and uncertainty. For instance, the variability in GH dosing regimens, the timing of therapy initiation, the duration of treatment, and the onset of puberty induction are factors that might influence metabolic outcomes. Additionally, individual patient characteristics, including baseline metabolic status and genetic background, may modulate the response to GH therapy. [12-16]

Given the critical implications for clinical practice, there is a need for an update review of recent data spanning from 2000 to 2024. Such a review would synthesize current evidence on the effects of GH therapy on glucose metabolism in TS, clarifying the conditions under which GH therapy alters glucose homeostasis and identifying best practices for monitoring and managing metabolic risk in this population.

2. Methods

This review systematically examines the scientific literature spanning from 2000 to 2023, focusing on studies that assess the impact of growth hormone (GH) therapy on glucose metabolism outcomes in individuals with TS. The selection criteria aimed to include peer-reviewed articles that provided clear data on the effects of GH therapy related to various aspects of glucose metabolism, such as insulin sensitivity, glucose tolerance, and the incidence of diabetes mellitus in TS patients.

The method involved a comprehensive search of electronic databases including PubMed, Web of Science, and Scopus, using key terms like "Turner Syndrome," "growth hormone therapy," "glucose metabolism," "insulin sensitivity," and "metabolic outcomes." Studies were screened for relevance based on their titles and abstracts, followed by a full-text review to ensure they specifically addressed the research question.

Both observational studies and clinical trials were considered, with a preference for those providing longitudinal data or comparing pre- and post-treatment metabolic parameters. The selected articles were then synthesized to highlight the consensus, divergences, and the overall trend in the findings regarding the metabolic effects of GH therapy in TS, particularly focusing on its influence on glucose homeostasis.

The review also considered the variations in treatment duration, and the timing of therapy initiation in this unique population.

2.1. Inclusion Criteria

- **Study Period:** Research articles published between January 2000 and December 2023, providing a comprehensive overview of recent and relevant data.
- **Population:** Studies involving individuals diagnosed with TS, irrespective of age, to capture a broad spectrum of data on the impact of GH therapy across different life stages.
- **Intervention:** Research focusing on the administration of growth hormone therapy, considering its various dosages, durations, and administration protocols.
- **Outcomes:** Studies must specifically assess glucose metabolism outcomes, including insulin sensitivity, glucose tolerance, risk of diabetes mellitus, changes in body composition affecting glucose metabolism, and any other relevant metabolic parameters influenced by GH therapy.
- **Study Design:** Inclusion of randomized controlled trials, cohort studies, case-control studies, and longitudinal observational studies to ensure a robust analysis of the available evidence. Reviews, meta-analyses, and expert opinions were also considered for a comprehensive understanding of the topic.
- **Publication Type:** Peer-reviewed journal articles published in English to ensure the reliability of the data and the broadest accessibility for analysis.

2.2. Exclusion Criteria

- **Non-English Articles:** Studies not published in English were excluded to ensure the comprehensibility and accurate interpretation of the findings.
- **Unrelated Topics:** Studies not specifically addressing the relationship between GH therapy and glucose metabolism in TS patients were excluded.
- **Non-human Studies:** Research involving animal models, in vitro studies, or any non-human subjects were omitted to maintain clinical relevance to human TS patients.
- **Incomplete Data:** Articles with incomplete data, preliminary results, or abstracts without full-text availability were excluded to ensure a thorough and reliable synthesis of evidence.
- **Case Reports and Small Case Series:** Single case reports and small case series (less than 10 participants) were excluded due to their limited generalizability and higher risk of bias.
- **Duplicate Studies:** Multiple publications reporting on the same patient population or dataset were excluded to avoid redundancy and potential overestimation of treatment effects.

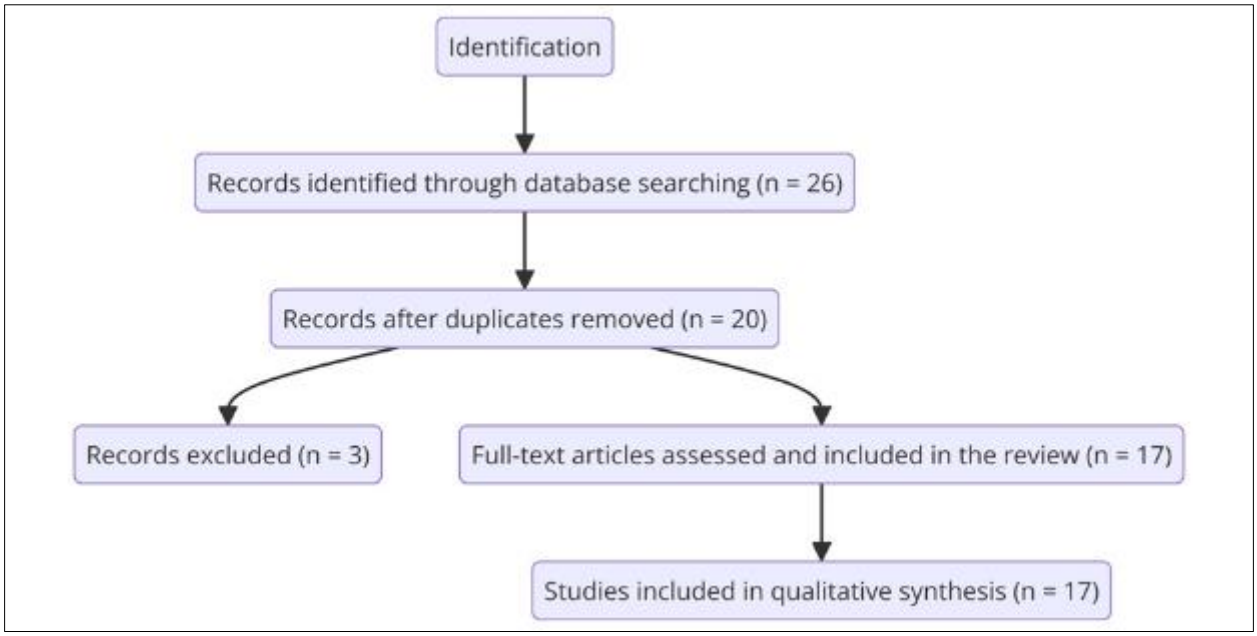

Figure 1 PRISMA diagram for the review

3. Results

The results of the reviewed research studies (n =27) are summarized in table 1.

Table 1 Chronological Overview of Growth Hormone Therapy Effects on Glucose Metabolism in TS.

Author	Year	Results: Glycemic Effect of GH Therapy	No. of Patients
T. Sas et al. [17]	2000	GH treatment increased insulin levels without significant change in glucose levels, indicating relative insulin resistance; insulin levels decreased to near pre-treatment values after discontinuation.	68
C. Gravholt et al. [18]	2002	Short-term GH treatment induced insulin resistance, with increments in fasting glucose and insulin levels; GH-treated girls demonstrated lower adiposity compared with untreated girls.	Not specified
G. Radetti et al. [19]	2004	GH treatment in TS girls does not significantly increase the prevalence of impaired glucose tolerance or type 2 diabetes mellitus, while it does decrease insulin sensitivity.	47
B. Spiliotis [12]	2008	Recombinant hGH therapy in TS has improved the height potential with varied effects on glucose metabolism; studies show no adverse effects on cardiac function, glucose metabolism or association with tumors.	Not specified
Nicole Wooten et al. [20]	2008	Lower abdominal adiposity and improved glucose tolerance in GH-treated girls with TS.	102
Ellen Bannink et al. [21]	2009	GH therapy has additional beneficial effects on serum lipids; GH-induced decrease in insulin sensitivity remained unchanged.	39
E. Bannink et al. [21]	2009	Several years after GH discontinuation, insulin sensitivity remained lower, while β-cell function and fasting insulin levels remained higher than before treatment.	39
L. Mazzanti et al. [22]	2006	Insulin sensitivity improved after cessation of GH treatment, indicating a return to pre-therapy values; progressive improvement in carbohydrate tolerance and insulin function in patients with TS.	Not specified
Z. Zhang Qion [23]	2011	After 6 months of GH intervention, lipid metabolism improved, and glucose metabolism could be aggravated; monitoring of patient's glucose and lipid metabolism further is necessary.	28
F. Baronio et al. [24]	2016	No negative influence of GH treatment on insulin sensitivity and β-cell secretory capacity in girls with TS.	104
Federico Baronio et al. [25]	2017	No negative influence of GH treatment on insulin sensitivity and β-cell secretory capacity in girls with TS.	104
Sabine Elisabeth Segerer et al. [26]	2020	Increased insulin concentrations during GH treatment in girls with TS were ameliorated by HRT.	31
Adriana Claudia Lopes Carvalho-Furtado et al. [27]	2019	No significant liver health modification after 6 months of GH replacement; importance of CAP in liver steatosis identification highlighted.	22
Nicole Sheanon et al [28].	2021	β-Cell dysfunction is present in youth with TS compared to controls; reduced insulin secretion and SI suggest a unique TS-related glycemic phenotype.	120
Maria Gnacińska et al. [29]	2023	GH therapy leads to beneficial change in body composition; connected with a trend toward increased insulin sensitivity.	53
Ewa Błaszczyk et al. [30]	2023	Development of insulin resistance and carbohydrate metabolism impairment observed during GH therapy in girls with TS.	89

Sunetra Mondal et al. [31]	2023	High risk for prediabetes in Indian girls with TS, irrespective of underlying karyotype; close monitoring for dysglycemia recommended.	99

The impact of growth hormone (GH) therapy on glucose metabolism in TS patients has been widely studied, with varying outcomes reported across different studies. These outcomes range from beneficial effects on body composition to potential concerns regarding insulin sensitivity and glucose tolerance.

Several studies, including those by T. Sas et al. (2000) [17], C. Gravholt et al. (2002) [18], and G. Radetti et al. (2004) [19], have explored the immediate effects of GH therapy. Sas and colleagues [17], noted an increase in insulin levels without a significant change in glucose levels, suggesting a state of relative insulin resistance that appeared to revert to near pre-treatment values post-therapy discontinuation. Gravholt et al. [18], found that short-term GH treatment induced insulin resistance, accompanied by increased fasting glucose and insulin levels, albeit with reduced adiposity. Similarly, Radetti et al. [19] reported a decrease in insulin sensitivity but no significant uptick in glucose intolerance or diabetes mellitus incidence, suggesting a nuanced impact of GH on glucose homeostasis.

The long-term consequences of GH therapy have been the focus of other researchers. For instance, L. Mazzanti et al. [22,24,25] and E. Bannink et al. (2009) [21] observed that insulin sensitivity improved and returned to pre-treatment values after the cessation of GH therapy, indicating a reversible effect. These findings suggest a temporal relationship between GH therapy and insulin sensitivity, with potential long-term benefits in carbohydrate tolerance and insulin function.

A few studies have reported neutral or beneficial outcomes. Nicole Wooten et al. (2008) [20] observed lower abdominal adiposity and improved glucose tolerance in GH-treated girls, suggesting potential metabolic benefits. F. Baronio et al. (2016, 2017) [24,25] found no negative influence of GH treatment on insulin sensitivity and β-cell secretory capacity, reinforcing the notion that GH therapy can be metabolically safe for some individuals. Moreover, Maria Gnacińska et al. (2023) [29] linked GH therapy to beneficial changes in body composition and a trend toward increased insulin sensitivity.

However, some research highlights potential risks. Ewa Błaszczyk et al. (2023) [10,30] and Z. Zhang Qion (2011) [23] reported the development of insulin resistance and potential aggravation of glucose metabolism, underscoring the necessity for vigilant monitoring of metabolic parameters during GH therapy. Similarly, Sabine Elisabeth Segerer et al. [11,26] noted increased insulin concentrations during treatment, which were ameliorated by hormone replacement therapy, hinting at complex interplays between GH therapy, insulin levels, and hormonal balances

4. Discussion

Turner Syndrome (TS) is characterized by the partial or complete absence of one X chromosome, affecting various clinical features, including short stature, which is commonly treated with growth hormone (GH) therapy.

There is a known relationship between TS and obesity. Turner syndrome, a chromosomal disorder affecting females where one of the X chromosomes is missing or partially missing, can lead to various medical and developmental issues, including an increased risk of obesity. Factors contributing to this increased risk include hormonal imbalances such as growth hormone deficiency and hypothyroidism, which affect metabolism; the short stature characteristic of TS, which can lead to a higher body mass index (BMI); and insulin resistance, a common issue in TS that is a risk factor for type 2 diabetes and contributes to obesity. Additionally, physical inactivity and psychosocial factors, such as low self-esteem or social isolation, may also play roles in weight gain. Therefore, regular monitoring and management of weight and metabolic health, including lifestyle modifications like a balanced diet and regular physical activity, are crucial for individuals with TS. [32-34] Therefore, GH therapies can have a potentially negative impact on glucose metabolism in TS patients which represents a complex picture, with varying findings across studies. (figure 2)

Incorporating the main findings from the review table provides a broader understanding of the nuanced effects of growth hormone (GH) therapy on glucose metabolism in TS patients. The table chronologically summarizes research findings on the glycemic effects of GH therapy, showcasing varied outcomes across different studies:

Insulin Sensitivity and Resistance: The review table highlights studies where GH therapy was associated with an initial increase in insulin levels and a potential induction of insulin resistance, as noted in the early years of the studies. For

example, Sas et al. (2000) [17], and Gravholt et al. (2002) [18], reported increased insulin levels and insulin resistance, respectively, with GH treatment, although glucose levels remained stable in some cases.

Long-term Metabolic Outcomes: Interestingly, studies such as those by Mazzanti et al. (2006) [22] and Bannink et (2009) [21] suggest that insulin sensitivity might improve after the cessation of GH therapy, indicating that some of the metabolic effects could be reversible or may adjust back to baseline levels post-treatment.

Variability in Glucose Tolerance: The table documents varying impacts of GH therapy on glucose tolerance, ranging from no significant change to the development of impaired glucose tolerance. For instance, Radetti et al. (2004) [19] and Baronio et al. (2016) [21] found no significant increase in the prevalence of impaired glucose tolerance or type 2 diabetes mellitus, while others observed changes in glucose and insulin parameters during treatment.

Body Composition and Metabolic Profile: Several studies in the table report beneficial effects on body composition, such as reduced adiposity and improvements in lipid profiles, which are important considering the increased risk of metabolic syndrome in TS. However, there's also evidence of increased insulin concentrations during treatment, which needs to be balanced against the potential benefits.

Individual Responses and Monitoring: The review underscores the importance of individualized monitoring, as the response to GH therapy can vary widely among TS patients. The diverse findings reflect the complexity of GH's effects on metabolism and the necessity for personalized treatment plans that consider the metabolic risks and benefits for each patient.

In conclusion, while GH therapy holds promise for improving height outcomes in TS patients, its impact on glucose metabolism is multifaceted and variable. The evidence suggests both potential risks, like induced insulin resistance, and benefits, such as improved body composition. The variability in these findings underscores the importance of individualized monitoring and the careful consideration of metabolic risks and benefits when managing TS patients with GH therapy.

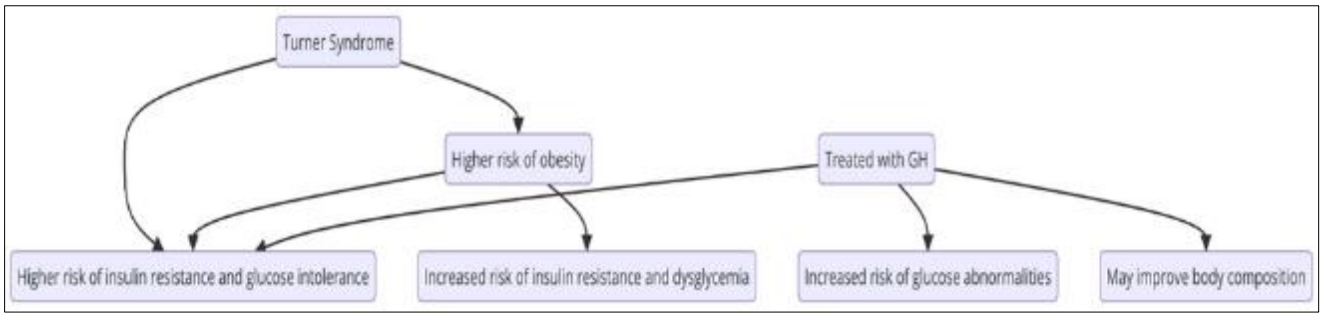

Figure 2 Turner syndrome and risk of dysglycemia

Recommendations based on this review: (figure 3)

- Tailor GH therapy treatment plans for each TS patient with regular monitoring of glucose metabolism to manage adverse metabolic effects promptly.
- Implement long-term follow-up strategies for TS patients to assess immediate and lasting metabolic outcomes of GH therapy, ensuring sustained improvements and early detection of complications.
- Educate patients and their families about the risks and benefits of GH therapy and the importance of lifestyle modifications to enhance health outcomes and mitigate adverse metabolic effects.

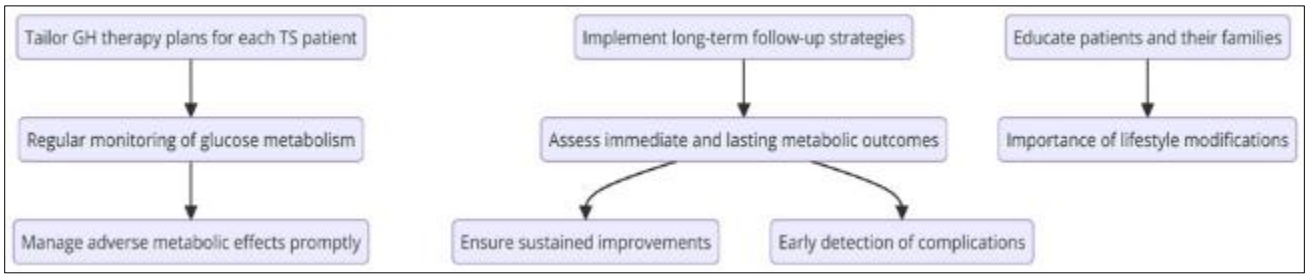

Figure 3 Recommendations based on the review data

4.1. Strengths

The manuscript provides a comprehensive review of the literature on the effects of growth hormone (GH) therapy on glucose metabolism in TS patients, covering studies published over a significant period (2000 to 2024). This extensive timeframe allows for a thorough examination of both short-term and long-term metabolic outcomes. The inclusion of a wide range of studies, including observational studies and clinical trials, enhances the robustness and credibility of the findings. Furthermore, the review highlights individual variability in responses to GH therapy, underscoring the importance of personalized treatment plans and diligent metabolic monitoring.

4.2. Weaknesses

One notable weakness of the manuscript is the variability in study methodologies, GH dosing regimens, and patient characteristics across the included studies, which complicates the synthesis of consistent conclusions. The review acknowledges these discrepancies but could benefit from a more detailed analysis of how these factors might influence the reported outcomes. Additionally, while the review covers a broad period, it does not provide a clear framework for how recent advances in GH therapy and monitoring practices might alter the observed metabolic effects.

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. The original draft preparation was undertaken by AS, who integrated the collected data and articulated the study's key insights. FA and AK significantly contributed to refining the manuscript, providing expert review and editing to enhance the intellectual content and clarity.

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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