Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Growth Hormone Therapy Improves Cardiometabolic Risk Markers in Girls With Turner Syndrome: Findings From the Korean OUTSPREAD Cohort

Aram Yang
Kangbuk Samsung Hospital
Jung Eun Moon
Kyungpook National University Hospital
Su Jin Kim
Inha University Hospital
Junghwan Suh
Severance Hospital
Chan Jong Kim
Chonnam National University Hospital
Moonbae Ahn
Catholic University of Korea
Minsun Kim
Jeonbuk National University
Chong Kun Cheon
Pusan National University Hospital
Hae Sang Lee
Ajou University Hospital
Yoonha Lee
CHA Bundang Medical Center
Il Tae Hwang
Kangdong Sacred Heart Hospital
Jin-Ho Choi
Asan Medical Center
Jaehyun Kim
Seoul National University Bundang Hospital
Shin-Hye Kim
Inje University Sanggye Paik Hospital
Young Lim Shin
Soonchunhyang University Hospital

Eungu Kang
Korea University Medical Center
Jin Kyung Kim
Daegu Catholic University Medical Center
Hae Soon Kim
Ewha Womans University Medical Center
Eun Young Kim
Chosun University Hospital
Won Kyoung Cho
St. Vincent's Hospital
Seung Yang
Hanyang University Seoul Hospital
Sejin Kim
Keimyung University Dongsan Medical Center
Sochung Chung
Konkuk University Medical Center
Kye Shik Shim
Kyung Hee University Hospital at Gangdong
Yun Jeong Lee
Seoul National University Children's Hospital
Young Ah Lee
Seoul National University Children's Hospital
Han Hyuk Lim
Chungnam National University Hospital
Minji Im
Samsung Medical Center
Juyoung Sung
Samsung Medical Center
Myeongjin Kim
Kangbuk Samsung Hospital
Jungmin Oh
Samsung Medical Center
Mideum Kim
Samsung Medical Center
Minwhae Choi
Samsung Medical Center
Sung Yoon Cho
sungyoon.cho@samsung.com

Samsung Medical Center

Article

Keywords: Turner Syndrome, Human Growth Hormone, Dyslipidemias, Liver Function Tests, Cardiovascular Diseases

Posted Date: September 3rd, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9975045/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License

Additional Declarations: No competing interests reported.

Abstract

Turner syndrome (TS) is associated with short stature and increased cardiometabolic risk, but the long-term metabolic impact of growth hormone therapy (GHT) remains debated. We evaluated cardiometabolic changes associated with GHT in girls with TS using the nationwide multicenter Korean OUTSPREAD cohort. Girls with TS who had longitudinal cardiometabolic measurements were analyzed. Changes in growth parameters, lipid profiles, liver enzymes, and glucose metabolism were assessed from baseline to the last follow-up visit. Within-subject changes were evaluated using paired nonparametric tests, and adjusted associations were assessed using multivariable linear regression and ANCOVA-type models. The final analytic cohort included 116 girls with TS, comprising 96 GHT-treated patients and 20 untreated controls. GHT improved height Z-score without increasing BMI Z-score. Total cholesterol remained stable in the GHT-treated group (179.0 to 174.0 mg/dL, $P = 0.058$) but increased in untreated controls (174.0 to 186.0 mg/dL, $P < 0.001$). GHT was independently associated with attenuation of total cholesterol worsening (β=-32.8 mg/dL, $P = 0.006$). In the GHT-treated group, HDL-C increased, whereas LDL-C and non-HDL-C decreased. ALT decreased significantly, HbA1c remained within the normal range, and glucose levels were stable. These findings support the cardiometabolic safety and potential lipid benefit of GHT in pediatric TS.

1. INTRODUCTION

Turner syndrome (TS), caused by partial or complete loss of one X chromosome, affects mortality. Beyond short stature and gonadal dysgenesis, girls and women with TS display an adverse cardiometabolic profile characterized by central obesity, dyslipidemia, hypertension, impaired glucose tolerance, and early atherosclerosis (1). Large cohort and imaging studies have shown that these abnormalities contribute to a markedly higher burden of ischemic heart disease, stroke, and premature cardiovascular death compared with the general population (2–6).

Recombinant human growth hormone (GH) therapy is the standard of care to improve linear growth in TS and is strongly recommended by recent international clinical practice guidelines. While its auxological efficacy is well established, the long-term impact of GH on cardiometabolic health in TS remains uncertain (7–9). Early trials from the 1990s and 2000s suggested neutral or modestly favorable effects of GH on lipids during short-term treatment (10–14). Subsequent longitudinal studies, including large-scale studies reporting neutral findings (15), have shown decreases in total and LDL cholesterol, improvements in body composition, and preservation of glucose homeostasis during several years of GH therapy (7, 16–18).

Conversely, concerns have been raised that high-dose GH and associated increases in insulin resistance could transiently worsen cardiometabolic risk (7). Furthermore, patients with TS are inherently at an increased risk for metabolic dysfunction-associated steatotic liver disease (MASLD) and unexplained liver enzyme elevations due to chronic estrogen deficiency and altered lipid metabolism (19, 20). However, data on the real-world cardiometabolic impact of GH in pediatric TS, particularly from Asian

populations, remain limited. Recent reviews emphasize that TS is already a high-risk condition for metabolic syndrome and type 2 diabetes, and recommend careful monitoring of blood pressure, lipids, liver function, and glucose during GH therapy (2).

In addition, patients with TS frequently show unexplained elevations in liver enzymes and are at increased risk for metabolic dysfunction-associated steatotic liver disease (MASLD), possibly related to estrogen deficiency and altered lipid metabolism (19, 20). However, data on the real-world cardiometabolic impact of GH in pediatric TS, particularly from Asian populations, remain limited

Using the multicenter Korean OUTSPREAD cohort, we therefore aimed to evaluate the cardiometabolic effects of GH therapy in girls with TS, focusing on changes in atherogenic lipid fractions and liver enzymes as surrogate markers of future cardiovascular risk.

2. MATERIAL AND METHODS

Study Design and Population

This was a multicenter, prospective, and retrospective analysis using the OUTSPREAD (Multicenter Networks for Ideal Outcomes of Rare Pediatric Endocrine and Metabolic Diseases in Korea) cohort database. The OUTSPREAD TS cohort collected standardized clinical data across 30 Korean centers between 2022 and 2024 and included females with TS confirmed by peripheral blood karyotype analysis. Among the parent cohort, we initially screened 704 patients diagnosed with TS. Inclusion criteria for the present analysis were: (1) confirmed diagnosis of TS via karyotyping, (2) available information on recombinant human GH exposure, and (3) available longitudinal laboratory data including lipid profiles and liver enzymes at baseline and follow-up. Patients with pre-existing diabetes or those taking lipid-lowering medications were excluded. Finally, 116 patients (96 in the GH-treated group and 20 untreated controls) were included in the analysis. The study protocol was approved by the Institutional Review Board of each participating center (lead IRB: Seoul National University Hospital, IRB No. 2206-211-1336).

Measurements and Definitions

Auxological data, including height, weight, and body mass index (BMI), were measured at each visit. Height and BMI were converted to Z-scores (Standard Deviation Scores, SDS) based on the Korean National Growth Charts. Baseline was defined as the visit closest to GH initiation for the GHT-treated group and the first eligible metabolic assessment for untreated controls; follow-up was defined as the last available eligible assessment. When dates were unavailable because of de-identification, age-at-event variables recorded in the electronic case report forms were used to define the temporal sequence. Details of GH formulation, starting dose, titration schedule, and estrogen initiation timing were extracted when available; however, these variables were incompletely captured and were therefore handled descriptively rather than as primary covariates. For the GHT group, recombinant human GH (somatropin) was initiated and titrated according to standard clinical practice (e.g., 0.33 mg/kg/week). Estrogen

replacement therapy (ERT) was initiated at a median age of 14.0 years [IQR: 13.0–16.0] for the induction of puberty.

Laboratory assessments included total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), non-HDL cholesterol (calculated as total cholesterol minus HDL-C), aspartate aminotransferase (AST), alanine aminotransferase (ALT), fasting/random glucose, and HbA1c. Karyotypes were categorized into 45,X (Monosomy) and Mosaicism/Other structural abnormalities. All baseline laboratory parameters were measured within ± 3 months of GH initiation (or at the time of diagnosis for the untreated group), and follow-up data were collected at the last available clinic visit. Laboratory values obtained before GH initiation and at the last eligible follow-up visit were used for the main paired analyses; repeated measurements between these two time points were reserved for sensitivity analyses where available.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation or median [interquartile range, IQR], as appropriate, and categorical variables are presented as numbers and percentages. Between-group comparisons were performed using the Mann–Whitney U test or Wilcoxon rank-sum test for continuous variables and the chi-square test or Fisher's exact test for categorical variables, as appropriate. Within-subject changes from baseline to follow-up were assessed using the paired Wilcoxon signed-rank test. Follow-up duration was compared between the GHT-treated and untreated groups using the Wilcoxon rank-sum test.

To evaluate the association between GHT and cardiometabolic changes, multivariable linear regression models were fitted using the change from baseline to follow-up as the dependent variable. Models were adjusted for baseline age, follow-up duration, estrogen replacement therapy, and thyroid medication. For lipid fractions, additional ANCOVA models were fitted using follow-up values as dependent variables and the corresponding baseline values as covariates. These models were further adjusted for baseline age, follow-up duration, change in BMI Z-score, estrogen replacement therapy, and thyroid medication. Subgroup analyses according to karyotype and GHT duration were performed using the Mann–Whitney U test. A two-sided P value < 0.05 was considered statistically significant. All analyses were performed using R software (R version 4.2.2).

3. RESULTS

Baseline Characteristics

The baseline characteristics of the study population are summarized in Table 1. A total of 116 patients with TS were analyzed, comprising 96 patients in the GHT-treated group and 20 patients in the untreated control group. The mean age at TS diagnosis was 7.2 ± 4.5 years, and for the treated group, GHT was initiated at a mean age of 8.7 ± 4.2 years. The median follow-up duration was 9.95 years [IQR, 6.89–13.5] overall, 10.4 years [IQR, 7.48–13.6] in the GHT-treated group, and 6.22 years [IQR, 3.64–11.8] in untreated

controls (*P* = 0.005). Monosomy 45,X was present in 23.3% of the patients, while the remaining 76.7% had mosaicism or other structural X-chromosome abnormalities. At baseline, the median height Z-score was − 2.5. There were no significant baseline differences in karyotype distribution or BMI Z-scores between the GHT-treated and untreated groups.

Table 1
Baseline Characteristics of the Study Population

Characteristics	**Total (N = 116)**	**GHT-Treated (n = 96)**	**Untreated (n = 20)**	***P*-value**
Age at diagnosis, years	7.2 ± 4.5	7.4 ± 4.4	6.5 ± 4.8	0.412
Follow-up duration, years	10.0 [6.9; 13.5]	10.4 [7.5; 13.6]	6.2 [3.6; 11.8]	0.005
Karyotype, n (%)				0.725
45,X (Monosomy)	27 (23.3)	23 (24.0)	4 (20.0)	
Mosaicism & others	89 (76.7)	73 (76.0)	16 (80.0)	
Baseline Height Z-score	-2.5 [-3.1; -1.9]	-2.5 [-3.1; -1.9]	-2.4 [-2.9; -1.8]	0.610
Baseline BMI Z-score	0.6 [0.0; 1.7]	0.6 [0.0; 1.7]	0.5 [-0.2; 1.5]	0.550
Thyroid medication, n (%)	13 (11.2)	12 (12.5)	1 (5.0)	0.451
Estrogen replacement therapy, n (%)	61 (52.6)	50 (52.1)	11 (55.0)	0.812

Data are expressed as mean ± standard deviation, median [interquartile range], or number (percentage). *P*-values were calculated using the Mann-Whitney U test for continuous variables and the Chi-square or Fisher's exact test for categorical variables, comparing the GHT-treated and untreated groups at baseline.

Auxological and Metabolic Changes During Follow-up

Changes in clinical and metabolic parameters during the follow-up period are detailed in Table 2. In the GHT group, linear growth significantly improved, with the median height Z-score increasing from − 2.5 to -1.8 (*P* = 0.035), while the BMI Z-score remained stable (0.6 to 0.8, *P* = 0.655).Regarding lipid profiles (Fig. 1A-C), total cholesterol remained stable in the GHT-treated group (179.0 to 174.0 mg/dL, *P* = 0.058), whereas untreated controls showed a significant increase over follow-up (174.0 to 186.0 mg/dL, *P* < 0.001). Furthermore, the GHT group demonstrated significant improvements in other lipid parameters: HDL-C increased (56.0 to 60.0 mg/dL, *P* < 0.001), LDL-C decreased (103.0 to 96.0 mg/dL, *P* = 0.024), and non-HDL-C declined (121.0 to 114.0 mg/dL, *P* = 0.015).Liver enzyme responses also differed between groups (Fig. 1D, E). For liver enzymes, AST decreased in both the GHT-treated and untreated groups (both *P* < 0.001), whereas ALT showed a significant reduction only in the GHT-treated group (19.0 to 15.0 U/L,

P = 0.006; untreated controls, *P* = 0.440). Therefore, the AST finding was interpreted as a within-group change rather than a GHT-specific effect.

Table 2
Changes in Clinical and Biochemical Parameters

Parameter	GHT-Treated (n = 96)			Untreated (n = 20)		
	Baseline	Follow-up	*P*-value	Baseline	Follow-up	*P*-value
Height Z-score	-2.5 [-3.1; -1.9]	-1.8 [-2.5; -1.0]	0.035	-2.4 [-2.9; -1.8]	-2.3 [-2.8; -1.6]	0.510
BMI Z-score	0.6 [-0.0; 1.7]	0.8 [0.1; 1.9]	0.655	0.5 [-0.2; 1.5]	0.6 [0.0; 1.6]	0.712
AST (GOT) (U/L)	28.0 [25.0; 36.0]	21.0 [18.0; 27.0]	< 0.001	27.0 [24.0; 34.0]	22.0 [18.0; 29.0]	< 0.001
ALT (GPT) (U/L)	19.0 [14.0; 29.0]	15.0 [12.0; 24.0]	0.006	17.0 [14.0; 24.2]	15.5 [12.0; 26.0]	0.440
Total Cholesterol (mg/dL)	179.0 [161.0; 203.0]	174.0 [157.0; 196.0]	0.058	174.0 [152.5; 188.0]	186.0 [165.0; 212.0]	< 0.001
LDL-Cholesterol (mg/dL)	103.0 [86.0; 119.0]	96.0 [79.0; 117.0]	0.024	104.0 [90.5; 130.0]	115.0 [103.5; 127.5]	0.268
HDL-Cholesterol (mg/dL)	56.0 [44.0; 63.0]	60.0 [52.0; 68.0]	< 0.001	57.0 [54.0; 63.0]	59.0 [53.0; 68.0]	0.095
Non-HDL-C (mg/dL)	121.0 [103.0; 145.0]	114.0 [95.0; 136.0]	0.015	127.0 [108.8; 150.5]	129.0 [116.5; 153.8]	0.189
Fasting Glucose (mg/dL)	90.0 [85.0; 96.0]	91.0 [86.0; 96.0]	0.450	92.0 [86.0; 102.0]	90.0 [86.0; 99.0]	0.444
HbA1c (%)	5.2 [5.0; 5.5]	5.4 [5.2; 5.5]	< 0.001	5.4 [5.0; 5.7]	5.5 [5.3; 6.1]	0.102

Data are expressed as median [interquartile range]. *P*-values represent the statistical significance of within-group changes from baseline to follow-up, calculated using the Wilcoxon signed-rank test.

Abbreviations: GHT, growth hormone therapy; BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HbA1c, glycated hemoglobin.

Table 3
Multivariable Linear Regression Analysis for Changes in Cardiometabolic Parameters

Dependent Variable	Predictor	*β* Coefficient	95% CI	*P*-value
Δ Total Cholesterol	GHT (vs. Untreated)	-32.85	-55.94 to -9.76	0.006
	Δ BMI Z-score	4.41	-1.73 to 10.55	0.157
Δ AST (GOT)	GHT (vs. Untreated)	-9.36	-20.79 to 2.08	0.108
	Δ BMI Z-score	4.76	1.80 to 7.72	0.002
Δ ALT (GPT)	GHT (vs. Untreated)	-13.65	-30.39 to 3.09	0.109
	Δ BMI Z-score	6.77	2.44 to 11.11	0.003
Δ HbA1c	GHT (vs. Untreated)	-0.95	-2.54 to 0.64	0.234
Δ Fasting Glucose	GHT (vs. Untreated)	-13.44	-39.31 to 12.43	0.305

The multivariable linear regression models were adjusted for baseline age, follow-up duration, estrogen replacement therapy (ERT), and thyroid medication. *Δ* represents the change in the respective parameter from baseline to the end of follow-up.

Abbreviations: CI, confidence interval; GHT, growth hormone therapy; BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HbA1c, glycated hemoglobin.

Regarding glucose metabolism, HbA1c showed a numerical increase in the GHT group (from 5.2% to 5.4%, $P < 0.001$), and a similar trend was observed in the untreated group (from 5.4% to 5.5%, $P = 0.102$). Fasting glucose levels remained stable in both groups (GHT: 90.0 to 91.0 mg/dL, $P = 0.450$; Untreated: 92.0 to 90.0 mg/dL, $P = 0.444$). Throughout the follow-up, absolute HbA1c and fasting glucose values remained within the normal reference ranges for all patients.

Multivariable Analysis for Cardiometabolic Outcomes

In multivariable linear regression models adjusted for baseline age, follow-up duration, change in BMI Z-score, estrogen replacement therapy, and thyroid medication, GHT was associated with a smaller increase in TC from baseline to follow-up (β = -13.62 mg/dL; 95% CI, -24.22 to -3.02; $P = 0.012$). This association remained significant in an ANCOVA model additionally accounting for baseline TC (β = -9.16 mg/dL; 95% CI, -18.21 to -0.11; $P = 0.047$).

In multivariable models for other lipid fractions, adjusted associations between GHT and changes in LDL-C, HDL-C, and non-HDL-C were evaluated using delta and ANCOVA models. These analyses did not show statistically significant adjusted associations for LDL-C or HDL-C, while non-HDL-C showed a borderline association in the ANCOVA model. Detailed results are presented in Supplementary Table 3.

Subgroup Analysis

Analysis by karyotype showed both monosomy 45,X and mosaicism groups had improvements in height Z-score and metabolic parameters (Supplementary Table 1). While the 45,X group had a larger median increase in HDL-C compared to mosaicism (+ 9.0 vs. +2.0 mg/dL), the difference between groups was not significant ($P = 0.724$). Analysis by treatment duration revealed that height gain was more pronounced in patients treated for ≥ 2 years ($P < 0.001$) (Supplementary Table 2). However, reductions in LDL-C and increases in HDL-C were observed in the < 2 years treatment group, with no significant difference in the magnitude of lipid improvement compared to the ≥ 2 years group ($P = 0.342$ and $P = 0.612$, respectively).

4. DISCUSSION

In this multicenter study, we demonstrated that GH therapy in girls with TS provides potentially beneficial cardiometabolic effects beyond its primary role in promoting linear growth. Most notably, GHT emerged as an independent protective factor against total cholesterol worsening. As the first longitudinal study utilizing a large-scale Asian TS cohort, our findings offer added value by demonstrating that GHT is not merely metabolically 'neutral', but actively induces concurrent improvements—specifically, an increase in HDL-C, a reduction in non-HDL-C, and a stabilization of ALT levels.

Our results extend previous interventional studies that examined the metabolic consequences of GH in TS. Early trials comparing different GH dosing regimens reported neutral effects on serum cholesterol and triglycerides during the first year of therapy (21). Furthermore, other early studies confirmed that short-term GHT did not induce significant changes in either cardiac structural parameters or overall metabolic indices, supporting the initial metabolic neutrality of the treatment (11, 12). Later, longer-term studies demonstrated that several years of GH treatment consistently decrease total and LDL cholesterol levels while inducing favorable body composition changes, such as increased fat-free mass and decreased body fat percentage (22). Notably, recent evidence supports that these metabolic improvements are closely linked to enhanced endothelial function and long-term cardiovascular stability (2, 23, 24). The consistent decreases in LDL-C and non-HDL-C observed in our cohort support the notion that GH can exert beneficial effects on atherogenic lipoprotein burden when initiated in childhood and continued under careful surveillance.

Our findings contrast with some previous studies suggesting that GH therapy may adversely affect metabolic parameters. For example, Błaszczyk et al. (2023) (7) reported increased insulin levels and insulin resistance during long-term GH therapy, while lipid parameters remained largely unchanged. In contrast, our study demonstrated a consistent improvement in the lipid profile. This discrepancy may be due to ethnic differences, variations in GH dosage, or the relatively early initiation of GH in our cohort, which might optimize metabolic health before the onset of adult-onset complications.

The reduction in ALT is particularly noteworthy. TS patients are prone to MASLD owing to chronic estrogen deficiency and multiple endocrine perturbations, including relative GH deficiency and atherogenic dyslipidemia. In this context, the observed fall in ALT in our GH-treated cohort suggests that

restoring GH activity may help prevent or attenuate hepatic steatosis, potentially through its lipolytic effects, improvement of visceral adiposity, and downstream amelioration of systemic and intrahepatic lipid burden (25, 26).

Regarding glucose metabolism, short-term randomized trials have raised concern that GH might adversely affect insulin sensitivity. For instance, a double-blind, placebo-controlled crossover study by Gravholt et al. (14) showed that a few months of GH treatment reduced total and trunk fat mass but simultaneously worsened insulin sensitivity indices. Although HbA1c increased modestly during treatment, values remained within the normal range and GHT was not independently associated with deterioration in glycemic parameters after adjustment.This favorable safety profile aligns with extensive registry data of over 15,000 GH-treated adults, which confirmed no increased cardiovascular or metabolic risks (15).

Nevertheless, GH may still represent an additional cardiometabolic stressor in TS, as long-term data from other cohorts have shown progressive rises in insulin and HOMA-IR (7). Taken together, these findings suggest that while the initial impact of GH on insulin sensitivity can be balanced by favorable changes in body composition over time, there remains a critical need for lifelong, comprehensive monitoring of carbohydrate and lipid metabolism in this high-risk population.

The primary strength of this study lies in its use of the OUTSPREAD cohort, a large-scale, multicenter registry involving prominent university hospitals in Korea. This robust multicenter design provides high credibility and ensures that our findings are highly representative of real-world clinical practice. Furthermore, the inclusion of comprehensive cardiometabolic markers and the rigorous use of multivariable adjustments allowed us to effectively isolate the independent metabolic benefits of GHT from confounding factors such as BMI changes and estrogen therapy.

However, several limitations must be acknowledged. First, due to the inherent nature of real-world retrospective data, there were unavoidable missing values and challenges in data curation, which restricted the available sample size for specific parameters like insulin. Second, while we included an untreated control group to successfully demonstrate the natural trajectory of metabolic deterioration, its relatively small sample size limits the statistical power of some comparisons. Finally, as an observational study, the possibility of unmeasured residual confounding cannot be entirely excluded.

Conclusion

GH therapy in girls with TS was associated with favorable changes in lipid profiles and liver enzymes, suggesting potentially beneficial cardiometabolic effects in this high-risk population. These findings, together with substantial height gain, support GH therapy as an important component of comprehensive TS care, while highlighting the need for regular metabolic monitoring.

Declarations

Declaration of competing interests

All authors declare no conflicts of interests.

Funding

This research was supported and funded by SNUH Lee Kun-hee Child Cancer & Rare Disease Project, Republic of Korea (grant number: 26C-047-0000).

Acknowledgements

Not applicable.

Ethics approval

The study protocol was approved by the Institutional Review Board of each participating center (lead IRB: Seoul National University Hospital, IRB No. 2206-211-1336). All methods were performed in accordance with the relevant guidelines and regulations.

Patient consent statement

The requirement for informed consent was waived by the Institutional Review Board of Seoul National University Hospital (and the IRBs of all participating centers) owing to the use of anonymized data.

Authorship contributions

Conceptualization: A.Y., J.E.M., and S.Y.C.; methodology: A.Y., J.E.M., and S.Y.C.; formal analysis: A.Y. and J.E.M.; investigation and data acquisition: A.Y., J.E.M., S.J.K., J.S., C.J.K., M.A., M.K., C.K.C., H.S.L., Y.L., I.T.H., J.H.C., J.K., S.H.K., Y.L.S., E.K., J.K.K., H.S.K., E.Y.K., W.K.C., S.Y., S.K., S.C., K.S.S., Y.J.L., Y.A.L., H.H.L., M.I., J.S., M.K., J.O., M.K., M.C., and S.Y.C.; data curation and verification: A.Y., M.I., J.S., M.K., J.O., M.K., M.C., and S.Y.C.; funding acquisition: Y.A.L.; supervision: S.Y.C.; writing—original draft: A.Y. and J.E.M.; writing—review and editing: A.Y., J.E.M., S.J.K., J.S., C.J.K., M.A., M.K., C.K.C., H.S.L., Y.L., I.T.H., J.H.C., J.K., S.H.K., Y.L.S., E.K., J.K.K., H.S.K., E.Y.K., W.K.C., S.Y., S.K., S.C., K.S.S., Y.J.L., Y.A.L., H.H.L., M.I., J.S., M.K., J.O., M.K., M.C., and S.Y.C. All authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Data Availability

The datasets generated and/or analyzed during the current study are not publicly available due to privacy, ethical, and institutional restrictions related to patient-level clinical data. De-identified data may be available from the corresponding author upon reasonable request, subject to approval by the OUTSPREAD study group and the relevant institutional review boards.

References

1. Khan, N., Farooqui, A. & Ishrat, R. Turner Syndrome where are we? *Orphanet J. Rare Dis.* **19** (1), 314 (2024).
2. Davis, S. M. & Geffner, M. E. Cardiometabolic health in Turner syndrome. *Am. J. Med. Genet. C Semin Med. Genet.* **181** (1), 52–58 (2019).
3. Mondal, S. et al. Abnormal Body Composition Increases the Cardiometabolic Risk in Adolescents and Young Adults With Turner Syndrome. *Endocr. Pract.* **30** (3), 259–269 (2024).
4. Sharma, L. D. S. Turner Syndrome.2026 Updated 2026 Feb 15.
5. Sandahl, K. J. et al. A Prospective Study of Lipids in Adult Women With Turner Syndrome. *J. Endocr. Soc.* ;**7**(11). (2023).
6. Schoemaker, M. J., Swerdlow, A. J., Higgins, C. D., Wright, A. F. & Jacobs, P. A. Mortality in women with turner syndrome in Great Britain: a national cohort study. *J. Clin. Endocrinol. Metab.* **93** (12), 4735–4742 (2008).
7. Błaszczyk, E., Shulhai, A-M., Gieburowska, J., Barański, K. & Gawlik, A. M. Components of the metabolic syndrome in girls with Turner syndrome treated with growth hormone in a long term prospective study. *Front. Endocrinol.* ;Volume 14–2023. (2023).
8. Dyrka, K., Rozkiewicz, N., Obara-Moszynska, M. & Niedziela, M. The influence of growth hormone therapy on the cardiovascular system in Turner syndrome. *J. Pediatr. Endocrinol. Metab.* **33** (11), 1363–1372 (2020).
9. Sas, T. C. et al. The effects of long-term growth hormone treatment on cardiac left ventricular dimensions and blood pressure in girls with Turner's syndrome. Dutch Working Group on Growth Hormone. *J. Pediatr.* **135** (4), 470–476 (1999).
10. Colao, A., Marzullo, P., Di Somma, C. & Lombardi, G. Growth hormone and the heart. *Clin. Endocrinol. (Oxf)*. **54** (2), 137–154 (2001).
11. Isgaard, J. et al. A placebo-controlled study of growth hormone in patients with congestive heart failure. *Eur. Heart J.* **19** (11), 1704–1711 (1998).
12. Webster, J. M. et al. The effect of growth hormone replacement therapy for up to 12 months on lipoprotein composition and lipoprotein(a) in growth hormone-deficient adults. *Atherosclerosis* **133** (1), 115–121 (1997).
13. Elgzyri, T. et al. The effects of GH replacement therapy on cardiac morphology and function, exercise capacity and serum lipids in elderly patients with GH deficiency. *Clin. Endocrinol. (Oxf)*. **61** (1), 113–122 (2004).
14. Gravholt, C. H. et al. Short-term growth hormone treatment in girls with Turner syndrome decreases fat mass and insulin sensitivity: a randomized, double-blind, placebo-controlled, crossover study. *Pediatrics* **110** (5), 889–896 (2002).
15. Johannsson, G. et al. Long-term Safety of Growth Hormone in Adults With Growth Hormone Deficiency: Overview of 15 809 GH-Treated Patients. *J. Clin. Endocrinol. Metab.* **107** (7), 1906–1919 (2022).

16. Gravholt, C. H. et al. Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome Meeting. European Journal of Endocrinology. ;177(3):G1-G70. (2017).
17. Bannink, E. M., van der Palen, R. L., Mulder, P. G. & de Muinck Keizer-Schrama, S. M. Long-term follow-up of GH-treated girls with Turner syndrome: metabolic consequences. *Horm. Res.* **71** (6), 343–349 (2009).
18. Irzyniec, T., Jeż, W., Lepska, K., Maciejewska-Paszek, I. & Frelich, J. Childhood growth hormone treatment in women with Turner syndrome - benefits and adverse effects. *Sci. Rep.* **9** (1), 15951 (2019).
19. Singh, I. et al. Hepatic abnormalities in youth with Turner syndrome. *Liver Int.* **42** (10), 2237–2246 (2022).
20. Viuff, M. H. et al. Increased occurrence of liver and gastrointestinal diseases and anaemia in women with Turner syndrome–a nationwide cohort study. *Aliment. Pharmacol. Ther.* **53** (7), 821–829 (2021).
21. De Schepper, J. et al. Growth hormone therapy in Turner's syndrome: one versus two daily injections. *J. Clin. Endocrinol. Metab.* **79** (2), 489–494 (1994).
22. Scarano, E. et al. Impact of Long-Term Growth Hormone Replacement Therapy on Metabolic and Cardiovascular Parameters in Adult Growth Hormone Deficiency: Comparison Between Adult and Elderly Patients. *Front. Endocrinol. (Lausanne)*. **12**, 635983 (2021).
23. O'Gorman, C. S., Syme, C., Bradley, T., Hamilton, J. & Mahmud, F. H. Impaired endothelial function in pediatric patients with turner syndrome and healthy controls: a case-control study. *Int. J. Pediatr. Endocrinol.* **2012** (1), 5 (2012).
24. Stefil, M., Kotalczyk, A., Blair, J. C. & Lip, G. Y. H. Cardiovascular considerations in management of patients with Turner syndrome. *Trends Cardiovasc. Med.* **33** (3), 150–158 (2023).
25. Xue, J., Liang, S., Ma, J. & Xiao, Y. Effect of growth hormone therapy on liver enzyme and other cardiometabolic risk factors in boys with obesity and nonalcoholic fatty liver disease. *BMC Endocr. Disord*. **22** (1), 49 (2022).
26. Hutchison, A. L., Tavaglione, F., Romeo, S. & Charlton, M. Endocrine aspects of metabolic dysfunction-associated steatotic liver disease (MASLD): Beyond insulin resistance. *J. Hepatol.* **79** (6), 1524–1541 (2023).

Figures

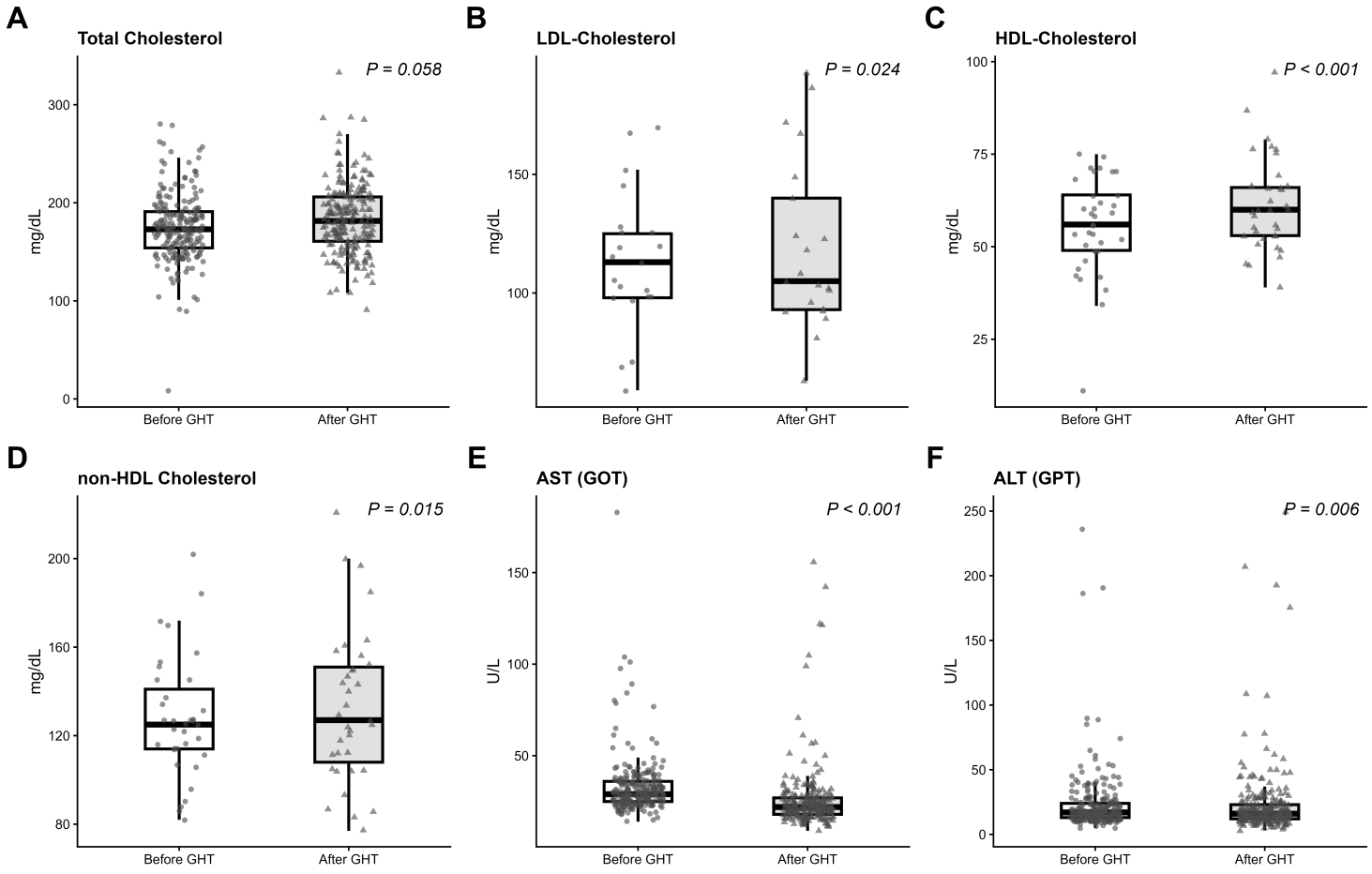


Figure 1

Changes in cardiometabolic and hepatic parameters from baseline to follow-up in the GHT-treated group.

Box-and-whisker plots illustrate longitudinal changes in metabolic markers from baseline to the end of follow-up among patients treated with growth hormone therapy (GHT). The horizontal line within each box represents the median, and the box boundaries indicate the interquartile range (IQR).

(A–D) Lipid profiles: Changes in (A) total cholesterol, (B) LDL-cholesterol, (C) HDL-cholesterol, and (D) non-HDL-cholesterol levels are shown. HDL-cholesterol increased, whereas LDL-cholesterol and non-HDL-cholesterol decreased during follow-up; total cholesterol showed a decreasing trend. (E–F) Liver enzymes: Changes in (E) AST and (F) ALT levels are shown. Both AST and ALT decreased during follow-up in the GHT-treated group.

P-values indicate the statistical significance of within-group changes from baseline to follow-up, calculated using the Wilcoxon signed-rank test. Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; GHT, growth hormone therapy; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- TSsupplementarytables20260531.docx