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Follicle-Stimulating Hormone Is Associated with Insulin Sensitivity Derived from Oral Glucose Tolerance Testing in Girls and Adolescents With Turner Syndrome

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Abstract

Purpose

Turner syndrome (TS) is associated with abnormalities in glucose metabolism, but the relationship between follicle-stimulating hormone (FSH) concentrations and insulin sensitivity remains unclear. We investigated the association between FSH and oral glucose tolerance test (OGTT)-derived insulin sensitivity in girls and adolescents with TS.

Methods

This single-centre prospective observational study included 31 girls and adolescents with TS. Fasting FSH and glucose and insulin concentrations during OGTT were analyzed cross-sectionally. Insulin sensitivity was assessed using the Matsuda insulin sensitivity index (ISI), and glucose exposure using glucose area under the curve (AUC_{0-120}). Multivariable models adjusted for age, body mass index standard deviation score, and hormone replacement therapy. Exploratory segmented regression with 10,000-resample bootstrap procedures assessed nonlinearity.

Results

Median FSH was 52.49 IU/L (IQR, 7.14–95.48) and median Matsuda ISI was 7.58 (IQR, 3.62–12.55). Each 10-IU/L increase in FSH was associated with a 7.0% lower adjusted Matsuda ISI (ratio of geometric means, 0.930; 95% CI, 0.868–0.996; p = 0.039). Exploratory segmented modelling suggested attenuation above 64.3 IU/L (bootstrap 95% CI, 2.9–87.2), but did not significantly outperform the linear model (p = 0.059). FSH was not associated with glucose AUC_{0-120} or early glucose or insulin responses.

Conclusions

Higher FSH concentrations were associated with lower OGTT-derived insulin sensitivity in TS. The suggested attenuation at higher FSH concentrations was exploratory and should not be interpreted as a clinical threshold.

INTRODUCTION

Turner syndrome (TS), caused by complete or partial loss of the second sex chromosome, is associated with increased cardiometabolic morbidity, including impaired glucose tolerance (IGT) and diabetes mellitus [1–3]. Dysglycaemia may emerge during childhood and adolescence and cannot be explained solely by adiposity or hypogonadism. Women with TS have shown higher post-load glucose concentrations and impaired glucose-stimulated insulin secretion compared with age- and BMI-matched women with primary ovarian insufficiency [3]. Subsequent studies have implicated X-chromosome gene

dosage and abnormalities in both insulin secretion and insulin sensitivity in TS-associated glucose dysregulation [4–6]. In youth with TS, reduced insulin sensitivity and β-cell responsivity may occur despite normal HbA1c, while fasting glucose and HbA1c may have limited sensitivity for detecting OGTT-defined abnormalities [5, 7].

Although follicle-stimulating hormone (FSH) is classically regarded as a regulator of gonadal function, experimental evidence suggests extragonadal metabolic actions. Inhibition of FSH signalling has been associated with reduced adiposity and increased thermogenic adipose tissue [8]. FSH receptor expression was demonstrated in human and mouse pancreatic β-cells, where FSH influenced glucose-stimulated insulin secretion in a concentration-dependent, nonlinear manner [9]. These findings do not establish causality in humans but provide a rationale for examining whether metabolic associations of FSH vary across its concentration range.

TS provides a distinctive clinical setting in which to examine this possibility because gonadal dysgenesis results in a broad spectrum of circulating FSH concentrations. FSH levels vary with age and karyotype [10, 11]. Glucose metabolism in TS is heterogeneous, and X-chromosome biology may contribute to this variability [12]. Higher prepubertal FSH has been associated with subsequent metabolic syndrome and nonlinear relationships with markers of insulin resistance in children [13]. However, the relationship of circulating FSH with OGTT-derived insulin sensitivity and total glucose exposure has not been well characterized in girls and adolescents with TS.

We therefore examined the association between baseline serum FSH and OGTT-derived insulin sensitivity, assessed using the Matsuda insulin sensitivity index, with total glucose AUC_{0-120} as a secondary outcome. Exploratory segmented analyses assessed whether the FSH–insulin sensitivity association varied across the observed FSH range and whether hormone replacement therapy modified this relationship. We hypothesized that higher FSH would be associated with lower insulin sensitivity and that this association might not remain constant across the FSH spectrum.

METHODS

Study design and participants

This single-centre prospective observational study included girls and adolescents with Turner syndrome (TS) followed at the Department of Pediatric Endocrinology, University of Health Sciences, Şişli Hamidiye Etfal Training and Research Hospital, between November 2023 and May 2026. The present cross-sectional analysis included 31 participants and used data from the first eligible oral glucose tolerance test (OGTT) of each participant. TS was defined by cytogenetic evidence of complete or partial monosomy of the X chromosome in a phenotypic female [14]. Eligibility required a documented TS karyotype, fasting FSH, and paired glucose and insulin measurements at 0, 30, 60, 90, and 120 minutes; 10- and 20-minute samples were used only for exploratory analyses. All eligible participants during the predefined study period were included; no formal a priori sample-size calculation was performed.

The study was approved by the Clinical Research Ethics Committee of the University of Health Sciences, Şişli Hamidiye Etfal Training and Research Hospital (approval no. 4159; November 7, 2023). Written parental/legal guardian consent and age-appropriate participant assent were obtained, and the study complied with the Declaration of Helsinki.

Clinical, treatment, and laboratory assessments

Height, weight, BMI, waist circumference, and blood pressure were obtained using standardized paediatric procedures; height, weight, and BMI SDS were calculated using Turkish reference data [15]. Demographic, clinical, treatment, and karyotype data were obtained from medical records. Karyotypes were classified as 45,X, mosaic without structural X abnormalities, or structural/marker X abnormalities with or without mosaicism. Because of small subgroup sizes, karyotype was analysed descriptively only. HRT use was defined as estrogen-containing replacement therapy at OGTT and was included a priori as a binary covariate; treatment was not interrupted before testing. Estradiol was excluded because HRT was continued and many values were below the assay lower limit of quantification.

Glucose and lipids were measured on a Roche Cobas chemistry platform, and insulin and FSH by electrochemiluminescence immunoassay on a Roche Cobas e601 analyser (Roche Diagnostics, Mannheim, Germany). Baseline FSH was defined as the fasting 0-minute concentration immediately before glucose administration.

OGTT and derived measures

After an overnight fast of 8–10 hours, participants received oral glucose at 1.75 g/kg (maximum 75 g), consumed within 5 minutes. Venous glucose, insulin, and FSH samples were collected at 0, 10, 20, 30, 60, 90, and 120 minutes; principal OGTT outcomes used the 0-, 30-, 60-, 90-, and 120-minute glucose and insulin values. Although measured serially, fasting 0-minute FSH was selected as the clinically interpretable exposure.

Total glucose AUC_{0-120} was calculated by the linear trapezoidal rule. Whole-body insulin sensitivity was estimated using the Matsuda insulin sensitivity index (ISI) [16], with higher values indicating greater insulin sensitivity. Glucose tolerance was classified from fasting and 120-minute glucose according to the 2026 American Diabetes Association criteria [17]. A 60-minute glucose concentration ≥ 155 mg/dL was additionally recorded as an exploratory marker of intermediate hyperglycaemia [18]. Definitions of dyslipidaemia and additional early-phase OGTT indices are provided in the Supplementary Methods.

Outcomes and statistical analysis

The principal analysis evaluated the association between fasting FSH and Matsuda ISI. The secondary analysis evaluated fasting FSH versus total glucose AUC_{0-120}. Segmented regression, HRT effect

modification, quadratic FSH–AUC modelling, early-phase OGTT measures, and FSH-tertile comparisons were exploratory.

Continuous variables were summarized as mean ± standard deviation or median (interquartile range), as appropriate, and categorical variables as n (%). Associations between baseline FSH and continuous OGTT outcomes were initially assessed using Spearman correlation. Matsuda ISI was compared between participants with IGT or biochemical diabetes criteria and those without either condition using the exact Mann–Whitney U test.

Because Matsuda ISI was right-skewed, the principal multivariable model used natural-log-transformed Matsuda ISI as the outcome. Baseline FSH was scaled per 10 IU/L, with age at OGTT, BMI SDS, and HRT status included a priori as covariates. HC3 heteroskedasticity-consistent covariance estimates with finite-sample t-based inference were used. Exponentiated coefficients were reported as ratios of geometric means. Model adequacy was assessed using residual, leverage/influence, and variance-inflation diagnostics.

For exploratory nonlinearity, a continuous one-change-point segmented regression model was fitted to ln(Matsuda ISI) with the same covariates [19]. The change point was selected by profile least squares across the observed FSH range, requiring observations on both sides of each candidate point. Conditional slopes were estimated with HC3 inference. Model fit was compared descriptively using the Akaike information criterion. Change-point uncertainty was assessed using a participant-level nonparametric percentile bootstrap with 10,000 resamples, repeating the complete change-point search in each sample. A separate 10,000-replicate residual-bootstrap comparison tested whether improvement over the linear model exceeded that expected under the null linear model. HRT effect modification was assessed using a global two-degree-of-freedom Wald test for interactions with the pre- and post-change-point slopes.

For the secondary outcome, fasting FSH and total glucose AUC_{0-120} were first assessed using Spearman correlation. A quadratic FSH model was explored; because it provided no evidence of association, no AUC change-point modelling was undertaken. The adjusted AUC model included FSH per 10 IU/L, age, BMI SDS, and HRT status and was fitted by ordinary least squares.

Exploratory early-phase associations were assessed using Spearman correlation. FSH-tertile comparisons used Kruskal–Wallis tests, followed, when appropriate, by exact Mann–Whitney U tests with Holm adjustment. No missing values were imputed. The principal analysis used a two-sided α of 0.05; secondary and exploratory analyses were not globally adjusted for multiplicity and were considered hypothesis-generating.

Analyses were performed using IBM SPSS Statistics version 32 and jamovi version 2.7. Bootstrap analyses used 10,000 resamples.

RESULTS

Baseline Demographic, Anthropometric, and Clinical Characteristics

Thirty-one girls and adolescents with Turner syndrome were included. Mean age at diagnosis was 10.11 ± 3.09 years and mean age at OGTT was 11.90 ± 3.22 years. Hypertension was present in 5 patients (16.1%).

Monosomy X (45,X) was the most common karyotype, followed by mosaic and structural X chromosome abnormalities. At OGTT, 12 patients (38.7%) were receiving hormone replacement therapy; median treatment duration was 0.81 years (IQR 0.32–1.49) (Table 1).

Table 1
Baseline demographic, anthropometric, and clinical characteristics of the study cohort

Parameter	Value
C-peptide, ng/mL*	2.20 (1.14–2.83)
SHBG, nmol/L	42.4 (31.5–65.2)
HbA1c, %	5.37 ± 0.28
Total cholesterol, mg/dL	163.3 ± 34.8
HDL cholesterol, mg/dL	55.0 (49.0–60.5)
LDL cholesterol, mg/dL	90.0 (67.0–105.0)
Triglycerides, mg/dL	87.4 ± 27.4
Baseline FSH, IU/L	52.49 (7.14–95.48)
TSH, mIU/L	2.97 (2.08–4.43)
Free T4, ng/dL	1.15 ± 0.29
Free T3, pg/mL*	3.59 ± 1.27
Islet cell antibody positive, n (%)	2 (6.5)
Anti-insulin antibody positive, n (%)	0 (0.0)
Anti-GAD antibody positive, n (%)	0 (0.0)

Data are presented as mean ± standard deviation, median (IQR), or n (%), as appropriate. SHBG, sex hormone-binding globulin; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; FSH, follicle-stimulating hormone; TSH, thyroid-stimulating hormone; GAD, glutamic acid decarboxylase. *n = 30.

Baseline Hormonal, Metabolic, and Serological Parameters

Baseline laboratory parameters are summarized in Table 2. Median baseline FSH concentration was 52.49 IU/L (IQR, 7.14–95.48), and mean glycated hemoglobin (HbA1c) was 5.37 ± 0.28%. Islet cell antibodies were detected in 2 patients (6.5%), whereas anti-insulin and anti-GAD antibodies were negative in all patients.

Table 2
Baseline hormonal, metabolic, and serological parameters

Parameter	Value
Fasting glucose, mg/dL	85.5 ± 8.8
30-min glucose, mg/dL	165.7 ± 23.3
60-min glucose, mg/dL	150.4 ± 38.4
90-min glucose, mg/dL	137.1 ± 36.1
120-min glucose, mg/dL	128.9 ± 30.0
Total glucose AUC_{0-120}, mg/dL·min	16,811.8 ± 2,877.8
Fasting insulin, μIU/mL	7.60 (2.90–12.89)
30-min insulin, μIU/mL	32.50 (22.85–70.77)
60-min insulin, μIU/mL	46.60 (28.20–68.46)
90-min insulin, μIU/mL	34.00 (21.00–50.25)
120-min insulin, μIU/mL	29.00 (10.60–45.50)
Matsuda insulin sensitivity index	7.58 (3.62–12.55)
Normal glucose tolerance, n (%)	18 (58.1)
Isolated impaired fasting glucose, n (%)	0 (0.0)
Isolated impaired glucose tolerance, n (%)	10 (32.3)
Combined IFG and IGT, n (%)	2 (6.5)
Biochemical criteria for diabetes mellitus, n (%)	1 (3.2)
60-min plasma glucose ≥ 155 mg/dL, n (%)	14 (45.2)
Dyslipidaemia, n (%)	8 (25.8)

Data are presented as mean ± standard deviation, median (IQR), or n (%), as appropriate. AUC, area under the curve; ISI, insulin sensitivity index; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

OGTT-Derived Glucose Metabolism and Insulin Sensitivity

Total glucose AUC_{0-120}, calculated by the trapezoidal method using the 0-, 30-, 60-, 90-, and 120-minute glucose concentrations, was 16,811.8 ± 2,877.8 mg/dL·min. Median Matsuda insulin sensitivity index (ISI) was 7.58 (IQR, 3.62–12.55).

Glucose tolerance categories were mutually exclusive: 18 patients (58.1%) had normal glucose tolerance, 10 (32.3%) had isolated impaired glucose tolerance (IGT), 2 (6.5%) had combined impaired fasting glucose (IFG) and IGT, and 1 (3.2%) met biochemical criteria for diabetes mellitus. No patient had isolated IFG. Fourteen patients (45.2%) had a 60-minute plasma glucose concentration ≥ 155 mg/dL. Patients with IGT or diabetes mellitus had lower Matsuda ISI values than those without either condition (median [IQR], 3.62 [2.63–9.67] vs 9.82 [6.71–15.46]; exact Mann–Whitney U test, p = 0.005) (Table 3).

Table 3
OGTT-derived glucose and insulin measures and glucose tolerance classification

Predictor / model feature	Estimate	95% CI	p value
Panel A. Primary model: natural-log-transformed Matsuda ISI (HC3-robust linear regression)			
Baseline FSH, per 10 IU/L	0.930	0.868–0.996	0.039
Age at OGTT, per year	1.112	0.909–1.360	0.290
BMI SDS, per 1-SDS increase	0.713	0.565–0.900	0.006
HRT use, yes vs no	0.607	0.246–1.500	0.267
Panel B. Exploratory segmented model for natural-log-transformed Matsuda ISI			
Model-derived change point, IU/L	64.3	2.9–87.2	—
FSH slope below change point, per 10 IU/L	0.799	0.698–0.915	0.002
FSH slope above change point, per 10 IU/L	1.012	0.899–1.138	0.843
Global FSH-slope × HRT interaction	—	—	0.804
Panel C. Secondary model: total glucose AUC_{0-120} (ordinary least-squares regression)			
Baseline FSH, per 10 IU/L	286.4	-2.1 to 574.9	0.052
Age at OGTT, per year	-413.9	-1086.1 to 258.4	0.217
BMI SDS, per 1-SDS increase	516.0	-211.4 to 1243.4	0.157
HRT use, yes vs no	-722.5	-3898.4 to 2453.4	0.644

Regression slope estimates in Panels A and B are presented as ratios of geometric means; ratios < 1 indicate lower Matsuda ISI. The model-derived change point in Panel B is reported in IU/L. Panel C estimates are β coefficients in mg/dL·min. All models were adjusted for age at OGTT, BMI SDS, and HRT status. Panel A used HC3-robust standard errors. Panel B reports conditional slope estimates around the profile-selected change point; the percentile bootstrap confidence interval for the change point was 2.9–87.2 IU/L, and the residual-bootstrap comparison with the linear model was p = 0.059. AUC, area under the curve; BMI, body mass index; CI, confidence interval; FSH, follicle-stimulating hormone; HRT, hormone replacement therapy; ISI, insulin sensitivity index; OGTT, oral glucose tolerance test; SDS, standard deviation score.

Primary Association Between Baseline FSH Concentrations and Insulin Sensitivity

Baseline FSH showed an inverse but non-significant unadjusted correlation with Matsuda ISI (Spearman's ρ=-0.32, p = 0.084). After adjustment for age at OGTT, BMI SDS, and HRT status, each 10-IU/L increase in FSH was associated with a 7.0% lower Matsuda ISI (ratio of geometric means, 0.930;

95% CI, 0.868–0.996; HC3-robust p = 0.039). Higher BMI SDS was also associated with lower Matsuda ISI, whereas age and HRT status were not associated with Matsuda ISI (Table 4, Panel A).

Exploratory Segmented Analysis of the FSH–Insulin Sensitivity Association

Exploratory segmented modelling identified a model-derived change point at 64.3 IU/L (bootstrap 95% CI, 2.9–87.2). Below this point, each 10-IU/L increase in FSH was associated with a 20.1% lower Matsuda ISI (ratio, 0.799; 95% CI, 0.698–0.915; p = 0.002), whereas the slope above it was close to zero (ratio, 1.012; 95% CI, 0.899–1.138; p = 0.843), suggesting limited additional decline at higher FSH concentrations (Fig. 1; Table 4, Panel B).

Table 4. Primary, exploratory segmented, and secondary multivariable models for Matsuda insulin sensitivity and total glucose AUC

Predictor / model feature	Estimate	95% CI	p value
Panel A. Primary model: natural-log-transformed Matsuda ISI (HC3-robust linear regression)			
Baseline FSH, per 10 IU/L	0.930	0.868–0.996	0.039
Age at OGTT, per year	1.112	0.909–1.360	0.290
BMI SDS, per 1-SDS increase	0.713	0.565–0.900	0.006
HRT use, yes vs no	0.607	0.246–1.500	0.267
Panel B. Exploratory segmented model for natural-log-transformed Matsuda ISI			
Model-derived change point, IU/L	64.3	2.9–87.2	—
FSH slope below change point, per 10 IU/L	0.799	0.698–0.915	0.002
FSH slope above change point, per 10 IU/L	1.012	0.899–1.138	0.843
Global FSH-slope × HRT interaction	—	—	0.804
Panel C. Secondary model: total glucose AUC_{0-120} (ordinary least-squares regression)			
Baseline FSH, per 10 IU/L	286.4	-2.1 to 574.9	0.052
Age at OGTT, per year	-413.9	-1086.1 to 258.4	0.217
BMI SDS, per 1-SDS increase	516.0	-211.4 to 1243.4	0.157
HRT use, yes vs no	-722.5	-3898.4 to 2453.4	0.644

Regression slope estimates in Panels A and B are presented as ratios of geometric means; ratios <1 indicate lower Matsuda ISI. The model-derived change point in Panel B is reported in IU/L. Panel C estimates are β coefficients in mg/dL·min. All models were adjusted for age at OGTT, BMI SDS, and HRT status. Panel A used HC3-robust standard errors. Panel B reports conditional slope estimates around the

profile-selected change point; the percentile bootstrap confidence interval for the change point was 2.9–87.2 IU/L, and the residual-bootstrap comparison with the linear model was p=0.059. AUC, area under the curve; BMI, body mass index; CI, confidence interval; FSH, follicle-stimulating hormone; HRT, hormone replacement therapy; ISI, insulin sensitivity index; OGTT, oral glucose tolerance test; SDS, standard deviation score.

The segmented model had a lower AIC than the linear model (68.9 vs 73.0), but the residual-bootstrap comparison did not reach statistical significance (p = 0.059). HRT did not modify the association (global interaction p = 0.804). The change point should therefore be interpreted as exploratory rather than as a biological, diagnostic, or treatment threshold.

Secondary Association Between Baseline FSH Concentrations and Total Glucose AUC

Baseline FSH concentrations were not correlated with total glucose AUC_{0-120} (Spearman's ρ = 0.10, p = 0.591). A quadratic model including linear and squared FSH terms was not statistically significant (R^2=0.046; overall p = 0.514); therefore, no further change-point modelling of total glucose AUC was undertaken.

In the exploratory multivariable model adjusted for age at OGTT, BMI SDS, and HRT status, each 10-IU/L increase in baseline FSH was associated with a 286.4-mg/dL·min higher total glucose AUC_{0-120}, but the 95% confidence interval included the null (-2.1 to 574.9; p = 0.052). The overall model was not statistically significant (R^2=0.232; adjusted R^2=0.114; overall p = 0.130) (Table 4, Panel C).

Additional Secondary and Sensitivity Analyses

Secondary and exploratory analyses were not adjusted for multiplicity and should be interpreted as hypothesis-generating; Holm adjustment was applied only to pairwise tertile comparisons. Early-phase glucose and insulin dynamics were evaluated using the 0-, 10-, 20-, and 30-minute measurements. Mean glucose excursions were 38.5 ± 22.2 mg/dL for $\Delta glucose_{0-10}$, 63.4 ± 20.1 mg/dL for $\Delta glucose_{0-20}$, and 80.2 ± 23.2 mg/dL for $\Delta glucose_{0-30}$. Mean early glucose AUC_{0-30} was 3,985.7 ± 530.1 mg/dL·min. No early-phase glucose or insulin response measure was significantly correlated with baseline FSH; the largest correlation was observed for 60-minute glucose (ρ = 0.34, p = 0.064) (Supplementary Table S1).

In a descriptive sensitivity analysis, total glucose AUC_{0-120} did not differ across baseline FSH tertiles (Kruskal–Wallis p = 0.838). Matsuda ISI differed overall across tertiles (p = 0.035), but the pattern was non-monotonic, and no pairwise comparison remained statistically significant after Holm correction (Supplementary Table S2).

DISCUSSION

In this study of girls and adolescents with Turner syndrome, higher baseline FSH concentrations were associated with lower OGTT-derived insulin sensitivity after adjustment for age, BMI SDS, and HRT status. Each 10-IU/L increase in FSH was associated with approximately 7% lower Matsuda ISI, whereas no clear association was observed between FSH and total glucose AUC_{0-120} or early-phase glucose and insulin responses. Participants with IGT or biochemical diabetes criteria also had substantially lower Matsuda ISI than those without either condition. These findings suggest that variation in FSH may be more closely related to insulin sensitivity than to contemporaneous glucose exposure in young individuals with TS and raise the possibility that FSH may identify metabolically distinct endocrine phenotypes. However, the cross-sectional nature of the analysis precludes inference regarding directionality or causality.

The metabolic phenotype of TS is heterogeneous, and previous studies have differed regarding the relative contributions of impaired insulin secretion and insulin resistance [20–22]. Bakalov et al. reported impaired glucose-stimulated insulin secretion in women with TS despite preserved insulin sensitivity, supporting an intrinsic β-cell component potentially related to X-chromosome biology [3]. Subsequent work similarly demonstrated higher glycaemic responses and lower insulin responses during OGTT, with diabetes risk varying according to X-chromosome gene dosage [4]. More recent paediatric data indicate that abnormalities in insulin action and secretion may coexist. Sheanon et al. demonstrated reductions in insulin sensitivity, β-cell responsivity, and disposition index in youth with TS even after adjustment for BMI z-score [5], while recent adult data have also linked dysglycaemia with greater adiposity and insulin resistance [6]. Our findings are therefore compatible with a model in which reduced insulin sensitivity contributes to TS-associated dysglycaemia alongside previously recognized abnormalities in β-cell function.

Emerging experimental evidence provides a biological rationale for examining FSH in this context. Inhibition of FSH signalling has been associated with reduced adiposity and increased thermogenic adipose tissue in experimental models, suggesting extragonadal metabolic actions of the FSH–FSHR axis [8]. Cheng et al. subsequently demonstrated FSH receptor expression in human and mouse pancreatic β-cells and reported a concentration-dependent, nonlinear effect of FSH on glucose-stimulated insulin secretion [9]. Clinical observations also suggest that FSH–metabolic relationships may not be uniformly linear; higher prepubertal FSH was associated with subsequent metabolic syndrome and nonlinear relationships with markers of insulin resistance in children [13]. Nevertheless, these findings should not be directly extrapolated to the present cohort. Experimental pancreatic FSH signalling primarily concerns insulin secretion, whereas our principal outcome was insulin sensitivity, and FSH was not significantly associated with early insulin responses or insulinogenic indices. Accordingly, our findings do not establish a direct metabolic action of FSH but provide clinical support for further investigation of concentration-dependent FSH–metabolic relationships in TS.

The exploratory segmented analysis suggested that the association between FSH and insulin sensitivity may vary across the observed FSH range. Below the model-derived change point of approximately 64 IU/L, increasing FSH was associated with a pronounced reduction in Matsuda ISI, whereas the estimated

slope above this point was close to zero. This pattern is more appropriately interpreted as attenuation of the association at higher FSH concentrations rather than as a physiological plateau. Importantly, uncertainty around the change point was substantial, as reflected by the wide bootstrap confidence interval. Although the segmented model had a lower AIC than the linear model, the residual-bootstrap comparison accounting for data-driven change-point selection did not reach statistical significance ($p = 0.059$). Moreover, the tertile analysis showed a non-monotonic pattern, with no pairwise comparison remaining significant after Holm correction. The estimated change point should therefore be regarded strictly as hypothesis-generating and not as a physiological threshold, diagnostic cut-off, or treatment target.

The absence of a convincing association between FSH and total glucose AUC_{0-120} provides additional insight into the metabolic phenotype observed. FSH was essentially uncorrelated with glucose AUC in the unadjusted analysis, the quadratic model was not statistically significant, and the confidence interval for the adjusted FSH coefficient included the null. Insulin sensitivity and total glucose exposure represent related but distinct components of glucose homeostasis. OGTT glucose concentrations reflect the integrated effects of insulin action, β-cell secretion, hepatic glucose handling, and glucose absorption; therefore, an association with insulin sensitivity need not be accompanied by a parallel change in total glucose exposure. The absence of significant associations with early glucose excursions or insulinogenic indices is consistent with the interpretation that FSH may be associated with a specific component of metabolic regulation rather than with generalized deterioration across all OGTT-derived measures.

HRT was an important potential confounder because estrogen replacement may both suppress circulating FSH and influence glucose metabolism. HRT status was therefore included a priori in the principal model and formally evaluated as an effect modifier in the segmented analysis. No significant modification of the FSH–Matsuda relationship by HRT was identified. Previous studies have reported heterogeneous metabolic effects of HRT in TS; for example, Segerer et al. found attenuation of GH-associated hyperinsulinaemia with HRT, without a significant relationship with longitudinal changes in HOMA-IR [23]. Our findings likewise provide no evidence that HRT materially modifies the observed FSH–insulin sensitivity association. However, the limited number of HRT-treated participants, continuation of estrogen therapy during OGTT, and absence of a washout period preclude conclusions regarding metabolic equivalence between treated and untreated individuals.

From a clinical perspective, the present findings do not support the immediate use of FSH as a stand-alone marker of dysglycaemia or as a clinical treatment threshold. FSH concentrations in TS are influenced by ovarian reserve, age, karyotype, and exogenous estrogen exposure and may therefore integrate several biological processes rather than represent a direct metabolic driver. Nevertheless, the association with Matsuda ISI raises the possibility that FSH may help identify endocrine phenotypes associated with differences in insulin sensitivity. This is relevant because OGTT-defined abnormalities may occur despite relatively unremarkable fasting glucose or HbA1c in TS [7]. Although the present study was not designed to establish clinically applicable screening thresholds or diagnostic cut-offs, the

observed association between FSH and insulin sensitivity supports further investigation of FSH as a potential marker of metabolic heterogeneity in Turner syndrome. Larger studies specifically designed for prediction and validation will be required before FSH can be considered for risk stratification or screening purposes.

Strengths of this study include standardized OGTT sampling with contemporaneous serial FSH, glucose, and insulin measurements; use of the dynamic Matsuda ISI rather than fasting indices alone; independent quantification of total glucose exposure; and a predefined multivariable model incorporating clinically relevant covariates. The analytical strategy also included HC3 robust inference and 10,000-resample bootstrap procedures to quantify uncertainty surrounding the exploratory segmented model. Additional 10- and 20-minute sampling enabled detailed assessment of early-phase glucose and insulin responses.

Several limitations should be acknowledged. The sample size was small, reflecting the rarity of TS, and the single-centre tertiary-care design may limit generalisability. The cohort size restricted adjustment for additional potentially relevant factors, including detailed karyotype subgroups, pubertal stage, growth hormone exposure, body composition, and other treatment characteristics. The absence of a non-TS control group also prevents determination of whether the observed FSH–insulin sensitivity association is specific to TS. The cross-sectional analysis cannot establish temporal directionality, and residual confounding by pubertal development, endogenous ovarian function, estrogen exposure, and X-chromosome biology remains possible. Although FSH was measured serially during OGTT, fasting FSH was selected as the clinically interpretable principal exposure; the potential metabolic information contained in dynamic or longitudinal FSH variation was not evaluated. Matsuda ISI is a validated OGTT-derived estimate of whole-body insulin sensitivity but is not equivalent to direct assessment by hyperinsulinaemic-euglycaemic clamp. Finally, the segmented analysis was exploratory and data-driven, with substantial uncertainty around the estimated change point, and secondary and exploratory analyses were not globally adjusted for multiplicity. These findings therefore require confirmation in larger independent cohorts.

In conclusion, higher baseline FSH concentrations were associated with lower OGTT-derived insulin sensitivity in girls and adolescents with Turner syndrome after adjustment for age, BMI SDS, and HRT status, whereas no clear association was demonstrated with total glucose AUC or early-phase OGTT responses. Exploratory modelling suggested that the inverse association may attenuate at higher FSH concentrations, but the estimated change point was imprecise and should not be interpreted as a clinical threshold. These findings support FSH as a candidate marker of metabolic heterogeneity rather than an established predictor of dysglycaemia. Larger longitudinal and validation studies incorporating repeated hormonal assessment, detailed pubertal and treatment characterization, karyotype, body composition, and direct measures of insulin action and β-cell function are needed to determine whether FSH has predictive or biological relevance for altered glucose metabolism in Turner syndrome.

Declarations

Funding

No funding was received for conducting this study.

Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Ethics Approval

This study was reviewed and approved by the Clinical Research Ethics Committee of the University of Health Sciences, Şişli Hamidiye Etfal Training and Research Hospital, Istanbul, Türkiye (approval no. 4159; November 7, 2023). The study was conducted in accordance with the principles of the Declaration of Helsinki and its subsequent amendments.

Consent to Participate

Written informed consent to participate was obtained from the parents or legal guardians of all participants before enrolment, and age-appropriate written assent was obtained from the participants in accordance with institutional ethical requirements.

Data Availability

The datasets generated and/or analysed during the current study are not publicly available because they contain potentially identifiable clinical information from paediatric participants and are subject to institutional ethical and privacy restrictions. De-identified data may be made available from the corresponding author upon reasonable request and subject to approval by the relevant institutional ethics committee.

Author Contributions

L.G.B.Ö. conceived and designed the study, developed the methodology, coordinated the study, contributed to patient recruitment and clinical evaluation, supervised and curated the data, performed the statistical analyses, interpreted the results, prepared the figures and tables, conducted the literature review, and drafted the manuscript. S.A. contributed to patient recruitment, clinical evaluation, follow-up, and collection of clinical and laboratory data, and critically reviewed the manuscript. Ö.P.A. and B.A.B. contributed to patient evaluation, clinical data collection, interpretation of the findings, and critical revision of the manuscript. A.B. contributed to the study methodology, interpretation of the clinical and metabolic data, literature review, and critical revision of the manuscript. A.D.Ç. and A.U. contributed to the study design and methodology, interpretation of the results, supervision of the study, and critical revision of the manuscript for important intellectual content.

All authors reviewed and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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Figures

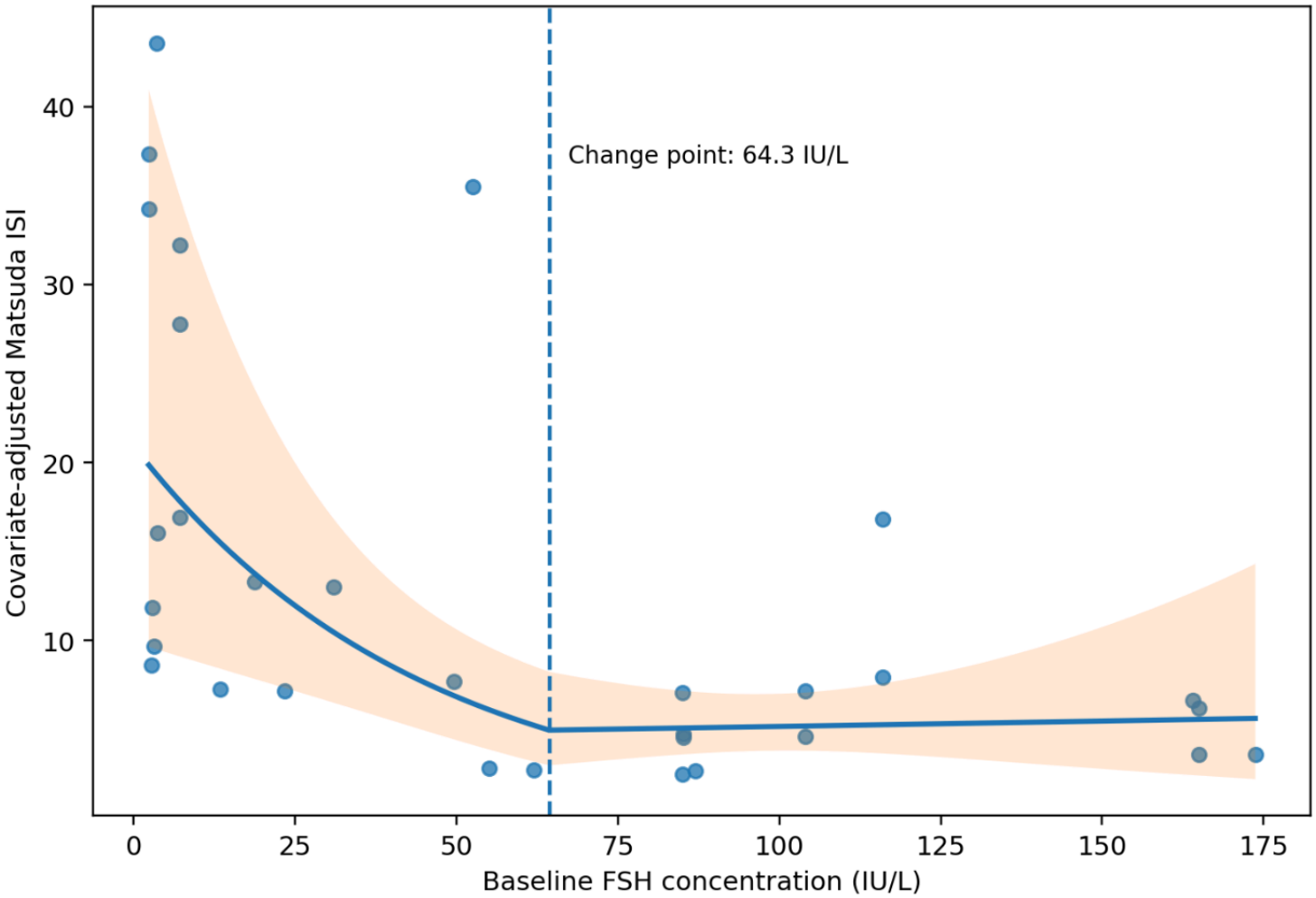


Figure 1

Exploratory segmented association between baseline follicle-stimulating hormone (FSH) concentrations and Matsuda insulin sensitivity index (ISI). Points represent individual Matsuda ISI values standardized to the cohort mean age, a BMI SDS of 0, and no hormone replacement therapy using the fitted covariate effects. The solid line represents the adjusted segmented fit, the shaded area represents the conditional 95% confidence interval, and the dashed vertical line indicates the model-derived change point at 64.3 IU/L. The change point is exploratory and should not be interpreted as a clinical or diagnostic threshold.

Supplementary Files

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