Journal of the Endocrine Society, 2024, **8**, bvae099
https://doi.org/10.1210/jendso/bvae099
Advance access publication 3 June 2024
Clinical Research Article

Systemic Inflammatory Indices and Liver Dysfunction in Turner Syndrome Patients: A Retrospective Case-control Study

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Abstract

Context: Liver function abnormalities have been reported in patients with Turner syndrome (TS); however, the pathophysiological mechanisms have not been well elucidated. Low-grade inflammation has been associated with metabolic dysfunction-associated steatotic liver disease.

Objective: We studied systemic inflammatory indices [aspartate transaminase to lymphocyte ratio index (ALRI), aspartate transaminase to platelet ratio index (APRI), gamma-glutamyl transferase to platelet ratio (GPR), neutrophil-lymphocyte-ratio (NLR), and platelet lymphocyte ratio and examined their associations with the hepatic abnormalities observed in these subjects.

Methods: We performed a retrospective analysis of the medical records of 79 patients with TS (mean age 32.5 ± 9.2 SD years) who were treated at the University Hospital of Nancy. Using matched-pair analyses based on age and body mass index (BMI), we compared 66 patients with TS (25.6 ± 7.3 years; BMI 25.9 ± 6.3 kg/m^2) to 66 healthy control participants (24.7 ± 6.8 years; BMI 26 ± 6.7 kg/m^2).

Results: Liver function abnormalities were present in 57% of the patients with TS. The ALRI, APRI, GPR, and NLR were significantly greater in patients with TS who presented with liver dysfunction than in patients with TS who had normal liver function. According to the matched-pair analyses, the ALRI, APRI, and GPR were greater in patients with TS than in healthy control participants. Logistic regression revealed that a diagnosis of TS was significantly associated with ALRI, APRI, and GPR and liver dysfunction.

Conclusion: Noninvasive inflammatory indices (ALRI, APRI, and GPR) might be a promising indicators of liver dysfunction in patients with TS. Future prospective studies are needed to confirm our findings and to explore the clinical significance and prognostic value of systemic inflammatory indices in Turner syndrome.

Key Words: Turner syndrome, inflammatory indices, liver abnormalities, metabolic syndrome

Turner syndrome (TS) occurs in approximately 1:2500 live female births [1]. While 40% to 50% of these patients present a karyotype 45,X, 15-25% have mosaicism with 45,X/46,XX, 20% have an isochromosome, few patients present ring X chromosomes [2], and 10% to 12% of patients with TS have Y chromosome material [2]. In addition to exhibiting characteristic phenotypic features such as growth retardation, dysmorphic signs, ovarian dysgenesis, cardiac and kidney malformation, and endocrine abnormalities, patients with TS have an increased risk of metabolic syndrome compared to the general population [3]. The prevalence of liver abnormalities in patients with TS have been reported to be 20% to 80% depending on age [4-8]. Various associations have been suggested to explain liver dysfunction in TS, including the presence of an X isochromosome (Xq), vascular involvement, age, overweight and obesity, or hyperlipidemia [4-16].

Low-grade inflammation has been associated with metabolic abnormalities such as metabolic dysfunction-associated steatotic liver disease (MASLD) [17, 18]. The ratios of plasma liver enzymes [alanine aminotransferase (ALT), aspartate aminotransferase (AST), or gamma-glutamyl transferase (GGT) to peripheral blood tangible components, such as white blood cells or platelets] have been shown to predict the progression of liver fibrosis [19-21]. Liver biopsy, while considered a reference exam for the diagnosis of MASLD, is not routinely prescribed because of its invasiveness [22]. Current guidelines, such as those from the European Association for the Study of the Liver or the American Association for the Study of Liver Diseases, recommend the use of noninvasive biochemical inflammatory indices to evaluate liver fibrosis [19]. For instance, the AST to platelet ratio index (APRI) and liver fibrosis score based on 4 factors

Received: 7 October 2023. **Editorial Decision:** 16 May 2024. **Corrected and Typeset:** 3 June 2024

(fibrosis-4 index) have been widely used to predict liver fibrosis [19-21]. Several other studies have suggested the use of the APRI score as a marker of fatty liver disease [23, 24]. In addition, the APRI was associated with an increased cardiovascular risk in patients who present with fatty liver disease [25]. Among other noninvasive markers of chronic inflammation, the neutrophil to lymphocyte ratio (NLR) has been identified as the potential contributing factor to the occurrence of diabetes and its complications [26, 27]. Interestingly, endocrine diseases, such as immune-mediated and inflammatory thyroid diseases [28, 29], have been associated with low-grade inflammation.

To identify the potential contributing factors of liver dysfunction in TS that may be applied in clinical practice, we investigated the associations of these aforementioned systemic inflammatory indices with hepatic abnormalities in patients with TS. Second, we investigated the relationships between these indices and the endocrine and metabolic abnormalities observed in patients with TS. We compared the data of patients with TS to those of healthy control participants using a matched-pair analysis based on age and body mass index (BMI).

Methods

This was a single-center retrospective study conducted in the Department of Endocrinology of the University Hospital of Nancy, which is one of the referral centers for TS in the Grand Est Region of France. All the data were collected retrospectively from the medical records obtained during regular follow-up visits. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines [30] (Supplementary Table S1) [31].

Study Population

All subjects included in the present study regularly visited the endocrinology department of the University Hospital of Nancy for routine consultations. The University Hospital of Nancy is a regional center of competence for TS within the French rare diseases network FIRENDO (Filière Maladies Rares Endocriniennes). Clinical care is provided by a multidisciplinary team, including nutrition specialists and psychiatrists. At the time of the study (March 2022), our TS cohort comprised 83 genetically confirmed patients with TS according to a karyotype analysis (in a 12-cell cytogenetic analysis in the context of prenatal cytogenetics; a minimum of 15 cells in the context of postnatal cytogenetics, with at least 3 karyotypes established, and at least 50 cells for a targeted search for a mosaic in relation to a particular phenotype) [32]. The mean duration of the follow-up of the patients with TS was 6.5 +/− 2 years. The follow-up was performed according to the national protocol of care for patients with TS [33], which is regularly updated. Data for a cross-sectional analysis were collected over a period of time between January 2019 and March 2022 as part of annual care of the patients with TS. The inclusion criteria were as follows: (1) aged between 18 years and 56 years, the latter being an average age of hormone replacement therapy (HRT) discontinuation in patients with TS followed in our department; and (2) had genetically confirmed TS. We included patients aged 18 years, as a transition period between pediatric and adult age can represent a bias in relation to modifications in growth hormone treatment regimens. We did not include subjects older than 56 years because of metabolic and hormonal changes related to aging. This could represent a potential bias in the evaluation. The exclusion criteria were as follows: (1) the presence of other genetic or chromosomal abnormalities other than Turner syndrome; (2) serious medical or psychiatric conditions; (3) drug- or alcohol-related health problems; and (4) the use of antiplatelet, anticoagulant, or anti-inflammatory medication.

The control cohort comprised age- and BMI-matched female subjects aged between 18 and 56 years who underwent an initial health assessment for gender dysphoria before any medical treatment. The University Hospital of Nancy is a regional referral center for gender dysphoria. Clinical care has been provided since the 1990s. The initial screening as part of the standard care in our department included a specific psychiatric and endocrinological evaluation comprising a complete examination of past medical history and check-ups of hormonal, metabolic, and cardiovascular status according to international guidelines that are regularly updated [34]. Underlying psychiatric disorders were stabilized, and parallel routine psychiatric follow-ups were included as necessary surveys. Clinical records were discussed by a multidisciplinary team before any hormonal treatment was initiated. Data were collected between January 2019 and March 2022. The exclusion criteria were as follows: (1) presence of endocrine or other somatic abnormalities; (2) serious medical and psychiatric conditions; (3) drug- or alcohol- related health problems; and (4) contraception, antiplatelet, or anticoagulant or anti-inflammatory medication use.

Clinical and Morphological Data

BMI was calculated for all subjects as body weight in kilograms divided by height in meters squared (kg/m^2). Overweight was defined as a BMI > 25 kg/m^2, and obesity was defined as a BMI > 30 kg/m^2. For all subjects, medical records were reviewed to retrieve relevant details about their medical history. Bone densitometry was measured with dual-energy X-ray absorptiometry (Hologic®) to evaluate the bone mineral density of the lumbar spine (L1-L4) and femoral neck. Osteoporosis was defined as a T score below −2.5 SD, osteopenia was defined as a T score between −1 and −2.5 SD, and normal bone density was defined as a T score greater than −1 SD [35].

In patients with TS, the presence of the following medical conditions was recorded: cardiac malformations (bicuspid valve, aortic dilatation, coarctation of the aorta or aortic dissection), renal malformations, ear-nose-throat malformations, endocrine diseases, diabetes, gastrointestinal diseases, and other autoimmune diseases. Details regarding GH treatment, HRT (estrogens + progesterone/progestogen), treatment for thyroid disease, and hepatic dysfunction were recorded.

Biochemical Analyses

Annual follow-up on clinical biochemical parameters for patients with TS was performed in accordance with the recommendations of the French National Authority for Health [32] in the Department of Biochemistry of the University Hospital of Nancy. In patients with TS, TSH was evaluated annually or in the presence of suggestive symptoms or positivity of thyroid peroxidase antibodies. Hypothyroidism was defined as elevated TSH (confirmed with a second independent sample) and/or a history of hypothyroidism that was appropriately treated. Glucose metabolism abnormalities were

defined according to the standard criteria [36] as a fasting plasma glucose ≥ 126 mg/dL (7.0 mmol/L) or a random plasma glucose ≥ 200 mg/dL (11.1 mmol/L) in a patient with classic symptoms of hyperglycemia. Fasting serum total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride levels were assessed by enzymatic methods at the Laboratory of Biochemistry of the University Hospital of Nancy by enzymatic methods. Low-density lipoprotein cholesterol was calculated according to Friedewald's formula. Lipid profile abnormalities were defined as follows: low-density lipoprotein > = 1.6 g/L, total cholesterol > = 2.0 g/L, HDL < 0.35 g/L or > 0.9 g/L, and triglyceride > = 1.5 g/L. Liver dysfunction was defined as a persistent increase in plasma levels of the following hepatic enzymes on consecutive annual tests: ALT > 35 IU/L, AST > 35 IU/L, GGT > 38 IU/L, or ALP > 120 IU/L [37, 38]. All patients with liver dysfunction were referred for further diagnostic evaluation and follow-up in the Department of Hepatology of the University Hospital of Nancy. Hepatic panel analyses (including viral serology and markers of autoimmunity) [37] were obtained for all participants to exclude common causes of hepatic dysfunction. The fibrosis-4 index [FIB-4 = (age × AST)/(platelets × $\sqrt{}$[ALT])] was used to estimate the presence of hepatic fibrosis [4]. FIB-4 was categorized as low (<1.30), indetermediate (1.30-2.67), or high (>2.67) risk of fibrosis using cut-offs previously shown to be associated with advanced fibrosis and in alignment with clinical guidelines [19, 38]. The following components of the blood count correspond to the generally accepted threshold values: platelets (150-450 G/L), neutrophils (1500-7000 G/L), and lymphocytes (1000-4000 G/L). C-reactive protein (CRP) was assessed with a positivity threshold of > 4.0 mg/L. Inflammatory indices were assessed as previously shown: aspartate transaminase to lymphocyte ratio index (ALRI) [39], APRI [20, 25], GPR, gamma-glutamyl transferase to platelet ratio (GPR) [40], NLR [26, 27], and platelet to lymphocyte ratio [41]. MASLD was defined as hepatic steatosis detected by imaging or biopsy, plus at least 1 of the following signs: (1) BMI ≥ 25 kg/m2; (2) fasting plasma glucose ≥ 100 mg/dL (≥ 5.6 mmol/L); (3) plasma triglycerides ≥ 150 mg/dL (≥ 1.70 mmol/L); or (4) plasma HDL cholesterol < 50 mg/dL (< 1.3 mmol/L) [42, 43].

Statistical Analysis

Continuous variables are expressed as the means ± SDs, medians and interquartile ranges, categorical variables expressed as frequencies (percentages), and odd ratios are expressed as estimates and 95% confidence intervals. Comparisons of baseline characteristics between the population patients with TS and liver dysfunction and the population of patients with TS without liver dysfunction were carried out using Student's *t*-test and the χ^2 test as needed. To compare the population of patients with TS and healthy control participants, the data were matched using the match R function according to age ± 4 years and BMI ± 3 kg/m^2. Comparisons of baseline characteristics (based on medical history of HRT, thyroid dysfunction, and GH treatment) for matched data were carried out using a paired *t*-test (continuous variables) and McNemar's tests (binominal variables). Comparisons of clinical characteristics and inflammatory indices were performed between patients with and without liver dysfunction. Inflammatory indices were also compared between patients with and without thyroid dysfunction. Further, patients with TS with and without medical history of GH were compared regarding endocrinopathies and inflammatory indices. The association between the presence of TS and clinical characteristics was analyzed by conditional logistic regression models, taking into account the matched nature of the data with TS patients/control participants as the explained variable or outcome, the following characteristics as explanatory variables, and the matched pairs as strata. The logistic model was used to measure the association between the presence of TS as an event (binary explained variable Y) and a number of explanatory variables × (characteristics or variables). Continuous variables such as the inflammatory indices (ALRI, APRI, GPR, NLR, and platelet to lymphocyte ratio) were categorized according to the median to satisfy some of the properties of logistic regression models (log-linearity). Log-linearity was verified by the restricted cubic splines method. Regression models included diagnosis (TS or control), inflammatory indices, hypothyroidism as a marker of autoimmunity, low bone mineral density (osteopenia or osteoporosis; based on the literature data suggesting the association between metabolic syndrome and low bone mineral density) [44], liver dysfunction, dyslipidemia and interactions between diagnosis, and the other variables. All analyses were performed using the commercially available software SAS version 9.3 (SAS Institute Inc., Cary, NC, USA) and the R software (The R Foundation for Statistical Computing). The two-tailed significance level was set at $P < .05$. A *P*-value of the comparison of each characteristic between patients with normal liver function and with liver dysfunction was corrected for a false discovery rate using the Benjamini–Hochberg method.

Ethical Approval

The study was approved by the Institutional Review Board (no. 344). It is registered at ClinicalTrials.gov (NCT05473091) and at the French National Commission for Data Protection and Liberties (no. 2021PI189-219). Before inclusion, all subjects received written information regarding the study objectives, voluntary participation, and assurance of confidentiality. All the data were anonymized before the start of the analysis.

Results

General Characteristics of the Study Population

Data of 87 patients with TS and 101 control participants who were eligible to participate were retrieved from the database of the Department of Endocrinology. After excluding 3 patients with TS who did not give their written consent to participate, 5 patients with TS without confirmed written genetic analysis, and 1 control participant who did not give his/her written consent to participate, a total of 79 patients with TS and 100 control participants were included in the present study. The majority of study participants were White; 5 participants were African. In total, 10 patients with TS and hepatic dysfunction were overweight, and 12 patients with TS were obese. For a matched-pair analysis, 66 patients with TS and 66 control participants were matched according to age and BMI. The remaining subjects (13 patients with TS and 35 control participants) could not be included because of missing data or because they did not fulfill the matching criteria. Figure 1 shows the flowchart of the selection process for the study population. Among the 79 patients with TS, 40 (50.6%) had a monosomy of chromosome X, 23 (29%) had

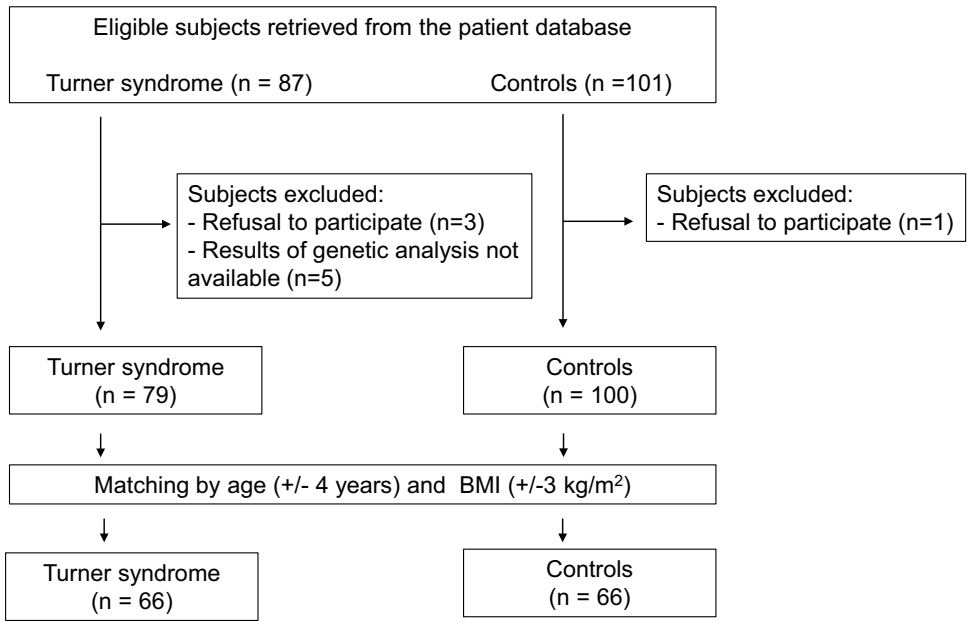

Figure 1. Flow chart illustrating the selection process of the study population.

structural abnormalities of the X chromosome, 13 (16.5%) had mosaicism, and 3 (3.8%) had the presence of the Y chromosome. The clinical characteristics of the subjects with TS with and without liver dysfunction are presented in Table 1. A total of 45 patients with TS presented with liver dysfunction. The prevalence of liver dysfunction ($P = .0006$) and dyslipidemia ($P = .0009$) increased with age (Supplementary Table S2) [31].

Inflammatory Indices in Patients With TS

Several inflammatory indices (ALRI, APRI, GPR, and NLR) were significantly greater in patients with TS presenting with liver dysfunction than in patients with TS without liver dysfunction (Table 2). However, no significant difference in these inflammatory indices was noted between the subgroup of patients with TS with hypothyroidism and the subgroup of patients with TS with normal thyroid function (Supplementary Table S3) [31]. There was no difference in inflammatory indices between patients with TS with a history of GH treatment and those without a history of GH therapy (Supplementary Table S4) [31]. The data concerning the role of HRT in liver dysfunction in patients with TS are inconclusive, given the small sample size.

In addition, all patients with TS had a CRP level less than 4 mg/L, except for 10 subjects who had a CRP value between 4 and 12 mg/L. These 10 subjects were overweight or obese and had a normal FIB-4. None of the patients had leukocytosis or other biological abnormalities that suggested underlying infection.

Matched-pair Analysis Including Patients With TS and Control Subjects

Sixty-six patients with TS and 66 healthy control participants were included in the age- and BMI-matched paired analysis. The characteristics of the study subjects are detailed in Table 3. Systemic inflammatory indices (ALRI, APRI, and GPR) were greater in patients with TS than in control participants (Table 4). The final outcomes of the multiple regression models examining the associations of clinical and biological variables with TS are detailed in Table 5. The results revealed that several inflammatory indices (ALRI, APRI, and GPR) were significantly associated with a diagnosis of TS. The data further showed significant associations between the diagnosis of TS and the following variables: liver dysfunction, low bone mineral density, and a history of hypothyroidism.

Table 1. Clinical characteristics of patients with Turner syndrome

	Normal liver function (n = 34)	Liver dysfunction (n = 45)	
Clinical parameters			*P*-value
Age (years)	24.9 ± 8.5	32.1 ± 9.5	.0004
BMI (kg/m^2)	25.2 ± 5.0	26.8 ± 6.8	.41
Cardiac malformation (%)	8 (24.2)	19 (42.2)	.15
Kidney malformation (%)	4 (12.1)	8 (17.8)	.54
Spontaneous puberty (%)	10 (33.3)	5 (11.9)	.04
GH treatment (%)	21 (75.0)	24 (72.7)	1.00
HRT (%)	22 (66.7)	36 (80.0)	.20
History of hypothyroidism (%)	14 (42.4)	19 (42.2)	1.00
Overweight (%)	13 (39.4)	23 (52.3)	.36
Obesity (%)	4 (12.1)	12 (27.3)	.16
Diabetes (%)	2 (6.1)	3 (6.7)	1.00
Karyotype			
Structural abnormalities of X chromosome (%)	9 (26.5)	14 (31.1)	.19
45X/46XY (%)	2 (5.9)	1 (2.2)	
Homogeneous 45X (%)	15 (44.1)	25 (55.6)	
Mosaicism 45X/46XX (%)	8 (23.5)	5 (11.1)	

Values are expressed as frequencies (percentages) for categorical variables and mean ± SD for continuous variables.
Abbreviations: BMI, body mass index; ENT, ear-nose-throat; HRT, hormone replacement therapy.

Table 2. Inflammatory indices in patients with Turner syndrome

	Normal liver function (n = 34)		Liver dysfunction (n = 45)			
Inflammatory indices	**Mean (± SD)**	**Median (Q1-Q3)**	**Mean (± SD)**	**Median (Q1-Q3)**	***P*-value**	***P*-value (FDR)**
NLR	1.84 (± 0.77)	1.79 (1.28-2.31)	2.72 (± 2.15)	2.09 (1.61-2.78)	.03	.056
PLR	146.17 (± 69.49)	144.58 (89.38-172.90)	167.49 (± 76.02)	148.40 (113.91-195.93)	.26	.30
APRI	0.09 (± 0.04)	0.09 (0.06-0.12)	0.14 (± 0.07)	0.12 (0.09-0.17)	.0004	.0015
ALRI	11.66 (± 5.09)	10.48 (8.52-13.86)	22.98 (± 16.87)	20.26 (11.28-24.64)	< .0001	<.0001
GPR	0.07 (± 0.03)	0.07 (0.04-0.08)	0.44 (± 0.50)	0.26 (0.19-0.57)	< .0001	<.0001

Variables are expressed as means ± SD, median, and interquartile range.
Abbreviations: ALRI, aspartate transaminase to lymphocyte ratio index; APRI, aspartate transaminase to platelet ratio index; FDR, false discovery rate; GPR, gamma-glutamyl transferase to platelet ratio; NLR, neutrophil to lymphocyte-ratio; PLR, platelet to lymphocyte ratio.

Table 3. Characteristics of study subjects included in a matched-pair analysis

	Turner syndrome n = 66	**Controls n = 66**	***P*-value**
Anthropometric data			
Age (years)	25.6 ± 7.3	24.7 ± 6.8	.44
Height (cm)	152.11 ± 7.00	164.41 ± 6.38	< .0001
Weight (kg)	59.97 ± 16.06	70.56 ± 19.23	< .0001
BMI (kg/m^2)	25.9 ± 6.3	26.0 ± 6.7	.97
History of GH treatment (%)	45 (78.9)	0	
HRT (%)	50 (78.9)	0	
HbA1c (%)	5.42 ± 0.72	5.48 ± 0.42	.5
Fasting glucose (mmol/L)	0.90 ± 0.19	0.86 ± 0.09	.56
TSH (mIU/L)	2.57 ± 1.47	2.18 ± 1.28	.04
TG (mmol/L)	0.94 ± 0.56	0.89 ± 0.62	.09
TC (mmol/L)	1.87 ± 0.45	1.63 ± 0.51	< .0001
HDL (mmol/L)	0.65 ± 0.19	0.51 ± 0.17	< .0001
LDL (mmol/L)	1.05 ± 0.37	1.06 ± 0.56	.14
Liver enzymes			
ALT (IU/L)	31.83 ± 20.98	22.18 ± 15.80	.0002
AST (IU/L)	28.31 ± 12.09	20.30 ± 7.15	< .0001
GGT (IU/L)	60.31 ± 69.23	21.62 ± 20.67	< .0001
ALP (IU/L)	86.33 ± 47.15	68.14 ± 21.57	.02

Variables expressed as means ± SD; categorical variables as frequencies (percentages).
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; ENT, ear-nose-throat; GGT, gamma-glutamyl transferase; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; HRT, hormone replacement therapy; LDL, low-density lipoprotein; TC, total cholesterol; TG, triglycerides.

Etiology of Liver Abnormalities in Patients With TS

An etiological diagnosis of hepatic dysfunction was established in 13 patients out of 45. Nine patients with TS had MASLD. In 4 other patients, a liver biopsy was needed to establish a final diagnosis: 2 patients had primary sclerosing cholangitis, 1 patient had autoimmune hepatitis, and 1 patient had MASLD. In 32 patients with TS, a precise diagnosis was not determined. A total of 43 patients with TS had FIB-4s lower than 1.45. In 2 patients with TS, the FIB-4 score was between 1.45 and 4. Elastography was performed in 19 patients with TS, with a median score of 5.95 kPa (interquartile range 4.4-6.1). Among the 7 patients with pathological elastography results, all had a normal FIB-4.

Discussion

The noninvasive inflammatory indices ALRI, APRI, GPR, and NLR were significantly greater in patients with TS presenting with liver dysfunction than in patients with TS without liver dysfunction. The major results of the matched-pair analysis further revealed that ALRI, APRI, and GPR were significantly greater in patients with TS than in healthy control participants. To our knowledge, there are no studies in which these markers were assessed in subjects with TS.

Our results further revealed a significant association between the diagnosis of TS and autoimmune thyroiditis and between the diagnosis of TS and low bone mineral density. Both conditions (autoimmune thyroiditis and low bone mineral density) are characterized by disturbed immune homeostasis and have been associated with metabolic syndrome [44]. Taking together, these observations suggest that chronic inflammation may be an underlying feature of endocrine and metabolic abnormalities in patients with TS.

Noninvasive markers, such as FIB-4 and APRI, have been recommended as alternative tools to assess the presence of liver fibrosis given the invasiveness and financial costs of liver biopsy [19, 22, 45]. They are used more broadly to define cardiometabolic risk, given their role in liver, lipid, and glucose metabolism [46, 47]. For instance, the APRI has been shown to predict cardiometabolic risk in individuals with metabolic syndrome without a previous liver dysfunction [25]. In a cross-sectional study, De Matteis et al [25] assessed the potential role of APRI in predicting cardiovascular risk using subjects from the Framingham Heart Study: 540 subjects with metabolic syndrome and 685 without metabolic syndrome or a previous diagnosis of chronic hepatitis C. The authors showed that an APRI > 0.5 indicated an increase in cardiovascular risk in all age categories. For the age group between 18 and 50 years, women with elevated APRIs had the same cardiovascular risk as men. The authors concluded that an APRI > 0.5 was associated with a 3-fold greater incidence of cardiovascular disease in patients with metabolic syndrome than in nonmetabolic subjects of both sexes.

The diagnostic value of the APRI in patients with TS remains to be established. The majority of our patients with TS with liver dysfunction had hepatic steatosis and

Table 4. Clinical and biological parameters included in the matched-pair analysis

Parameter	Control	Turner syndrome	*P*-value
	Mean ± SD / n (%)	Mean ± SD / n (%)	
ALRI	10.05 ± 7.71	16.4 ± 9.79	<.0001
APRI	0.07 ± 0.03	0.11 ± 0.05	<.0001
GPR	0.08 ± 0.07	0.23 ± 0.27	.0002
NLR	1.79 ± 1.25	2.01 ± 1.05	.11
ALRI > median[a]	15 (25.9)	44 (73.3)	<.0001
APRI > median[a]	19 (32.2)	41 (66.1)	.0003
GPR > median[a]	18 (32.7)	35 (67.3)	.0005
NLR > median[a]	24 (42.1)	34 (56.7)	.14
Liver dysfunction	9 (13.6)	33 (53.2)	<.0001
Dyslipidemia	19 (30.6)	29 (46.8)	.1
Low bone mineral density[b]	8 (14.5)	25 (43.1)	.0009
History of hypothyroidism	3 (4.5)	29 (43.9)	<.0001

Continuous variables expressed as means ± SD; categorical variables as frequencies (percentages).
Abbreviations: ALRI, aspartate transaminase to lymphocyte ratio index; ALT, alanine aminotransferase; APRI, aspartate transaminase to platelet ratio index; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; GPR, gamma-glutamyl transferase to platelet ratio; NLR, neutrophil to lymphocyte-ratio; PLR, platelet to lymphocyte-ratio; PLT, platelets.
[a]Continuous variables were categorized according to the median to satisfy the properties of logistic regression models (log-linearity). The log linearity was verified by the restricted cubic splines method.
[b]Low bone mineral density = osteopenia and/or osteoporosis.

Table 5. Final outcomes of multiple regression models examining the association of clinical and biological variables with Turner syndrome

Variable	OR (95% CI)	*P*-value
ALRI > median[a]	13.50 (3.21-56.77)	.0004
APRI > median[a]	4.00 (1.64-9.79)	.002
GPR > median[a]	3.80 (1.42-10.18)	.008
NLR > median[a]	1.62 (0.67-3.92)	.28
PLR > median[a]	2.12 (0.92-4.92)	.08
Liver dysfunction	5.00 (2.08-12.01)	.0003
Dyslipidemia	2.29 (0.94-5.56)	.07
Low bone mineral density[b]	8.00 (1.84-34.79)	.006
History of hypothyroidism	14.00 (3.34-58.77)	.0003

Abbreviations: ALRI, aspartate transaminase to lymphocyte ratio index; ALT, alanine aminotransferase; APRI, aspartate transaminase to platelet ratio index; AST, aspartate aminotransferase; CI, confidence interval; GPR, gamma-glutamyl transferase to platelet ratio; GGT, gamma-glutamyl transferase; NLR, neutrophil to lymphocyte-ratio; OR, odd ratio; PLR, platelet to lymphocyte-ratio; PLT, platelets.
[a]Continuous variables were categorized according to the median to satisfy the properties of logistic regression models (log-linearity). The log linearity was verified by the restricted cubic splines method.
[b]Low bone mineral density = osteopenia and/or osteoporosis.

overweight or obesity status. Metabolic syndrome and overweight status have been reported to be among the causes of hepatic steatosis in patients with TS [3] and may contribute to the development of obesity-related conditions such as MASLD [48]. In addition, obesity is known to be associated with immune system dysregulation and liver complications [49]. The FIB-4 was lower than 1.45 in 97% of our population of patients with TS with liver dysfunction, despite the presence of pathological values from hepatic elastography. Therefore, the FIB-4 seems less appropriate for detecting liver dysfunction in our patients. Interestingly, literature data indicate a limited diagnostic accuracy of FIB-4 in the early stages of liver fibrosis [50, 51]. Among other serum markers, we observed high ALRI and GPR in our patients with TS and liver dysfunction. The ALRI has been identified as a promising prognostic factor for hepatocellular carcinoma [52], and the GPR has been identified as a marker of liver fibrosis and cirrhosis in patients with chronic hepatitis B infection [40].

In line with other reports [4, 8, 13], the results of the present study indicate that the prevalence of liver dysfunction in patients with TS increases with age. In parallel, we observed an increased frequency of dyslipidemia but not of endocrinopathies or diabetes in patients in the same age categories. As the patients were on HRT, the effect of estrogen decline is rather unlikely. Generally, the amount of adipose tissue increases with age in relation to a positive caloric balance, decreased physical activity, and decreased basal metabolism [53]. Similar to previous studies [54, 55], we did not observe any significant difference in inflammatory indices in the population of our patients with TS with a history of estrogen therapy or GH treatment compared to those without GH therapy. Regarding the effects of HRT on liver function, the literature data are inconclusive [7, 16]. In a recent study [8] including 2145 young patients with TS (0 to 25 years) and 8580 age-matched healthy female control participants, 58% of patients with TS had increased liver enzymes and had increased odds of any liver diagnosis (liver disease, hepatitis, cirrhosis/fibrosis, or liver tumor). Age, BMI, and the presence of cardiovascular disease or diabetes but not thyroid disease or estrogen therapy significantly increased the odds of elevated liver enzymes in girls with TS. The median age at the onset of abnormalities was 12 years.

Contrary to the literature [1, 4, 6, 9], we did not observe any significant relationship between the karyotype and liver dysfunction. Taken together, the available data are mostly based on single reports or small retrospective studies (Fig. 2) [4-16]. Histological and pathophysiological studies of liver damage in patients with TS are rare. One study [10] reported 3 main categories of lesions: (1) MASLD; (2) biliary lesions such as sclerosing cholangitis, primary biliary cirrhosis, and biliary atresia; and (3) other less frequent abnormalities of hepatic architecture that can lead to more serious complications such as cirrhosis and portal hypertension [4-16].

Future research is warranted to confirm our results while controlling for potential biases such as lifestyle and environmental factors. It is important to explore inflammatory scores in patients with TS with and without liver disease, both before puberty and in adulthood, to evaluate the potential influences of X-linked genes and sex steroids on proinflammatory indices throughout life. Notably, some studies have reported the presence of an inflammatory state in TS patients with TS during the prepubertal stage [54, 55].

A strength of the present study is the matched-pair analysis with the use of 1:1 nearest neighbor matching, which provides an efficient comparison [56]. In addition, we followed the French national protocol for the diagnosis and care of patients with TS [33]. This limits the heterogeneity of our population from the entire population of patients with TS. Liver dysfunction was observed in 57% patients with TS, which is comparable to the data in the literature [5, 6, 8]. We excluded common

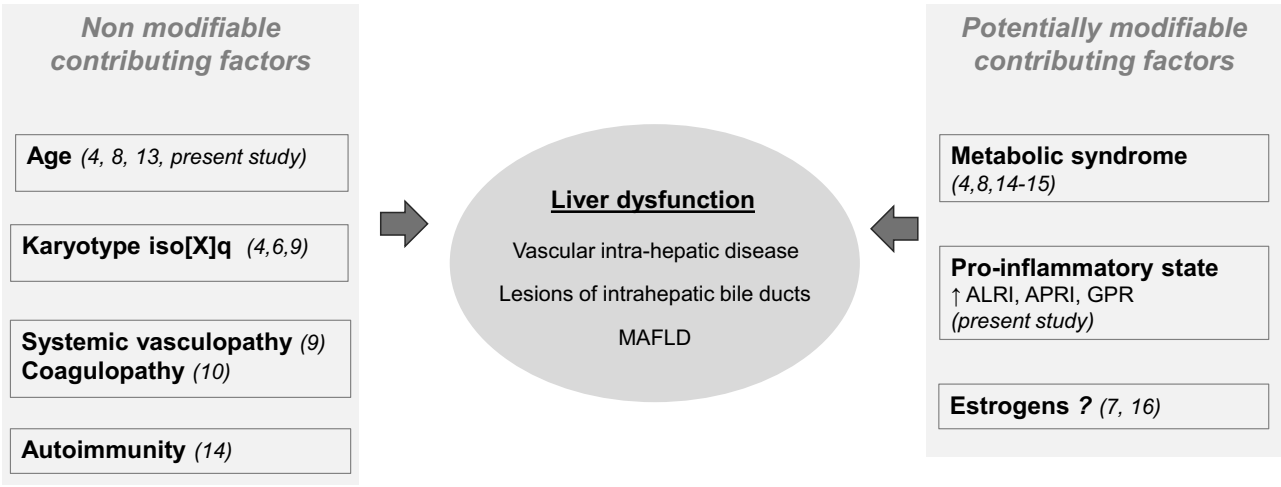

Figure 2. Factors contributing to liver dysfunction in patients with TS. Thus far, available data suggest that liver dysfunction in TS is a multifactorial process. The prevalence of liver dysfunction in patients with TS seems to increase with age (4, 8, 13, present study). Data are inconsistent regarding the association between karyotype and liver dysfunction [4, 6, 9]. Few histologic studies [9, 10] have identified biliary lesions and abnormalities of the hepatic architecture leading to cirrhosis and portal hypertension. Immune dysregulation and metabolic syndrome have been described in several reports [4, 8, 14, 15]. Data are inconclusive regarding estrogen or hormone replacement therapy [7, 16]. The present study revealed that the inflammatory indices ALRI, APRI, and GPR were significantly greater in patients with TS indicating the existence of a proinflammatory state. Abbreviations: ALRI, aspartate transaminase to lymphocyte ratio index; APRI, aspartate transaminase to platelet ratio index; GPR, gamma-glutamyl transferase to platelet ratio; MASLD, metabolic dysfunction-associated steatotic liver disease; metabolic syndrome, abdominal obesity, high blood pressure, impaired fasting glucose, dyslipidemia; TS, Turner syndrome.

causes of hepatic dysfunction, including viral serology and autoimmunity. We also eliminated situations in which liver enzyme elevations were secondary to transient acute illness.

Among the limitations of this study that need to be acknowledged here are the use of a single-center approach and retrospective design, which may limit the generalizability of the results. We also recognize the possibility of recall bias, as information that was based on medical records was collected after the events occurred. Histological data and liver imaging data were not available for all patients. Given the small sample size, we could not evaluate the role of HRT. Finally, we acknowledge the problem of multiple comparisons with the need for further validation and exploration.

Conclusion

The results of the present study suggest that a systemic inflammatory state is among the factors contributing to hepatic dysfunction in patients with TS. Noninvasive biochemical indices (ALRI, APRI, and GPR) might be valuable indicators of liver dysfunction in patients with TS and assist physicians in their clinical practice. Future large multicentric longitudinal prospective studies with a population of control participants are needed to confirm our findings and explore the prognostic value of systemic inflammatory indices in this population. It is important to explore inflammatory scores in patients with TS with and without liver disease, both before puberty and in adulthood, to evaluate the potential influences of X-linked genes and sex steroids on proinflammatory indices throughout life.

Funding

This research did not receive any specific grants from funding agencies in the public, commercial, or not-for-profit sectors.

Author Contributions

E.F. (ORCID ID: 0000-0002-5434-7320) made substantial contributions to this work by playing a leading role in the design and conceptualization of the study, data collection and analyses, and drafting and revision of the manuscript; N.Z. searched the data; contributed to the analysis and interpretation of the data; and drafted, reviewed, and edited the manuscript; B.R. contributed to the conceptualization of the study and collection of the data; S.B.H. contributed to the interpretation of the data and reviewed and edited the manuscript; and Z.L. had a significant role in the statistical analyses and interpretation of the data. All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Disclosures

The authors have nothing to disclose.

Data Availability

The additional data are available from the corresponding author upon reasonable request.

Clinical Trial Information

This study is registered at ClinicalTrials.gov (NCT05473091).

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