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.

Metabolic Interaction Network and Cardiac Abnormalities: A Case Report of Turner Syndrome Complicated by T2DM, Hypertension, Fatty Liver, and Sinus Tachycardia

Liping Zhou
Chongqing Traditional Chinese Medicine Hospital
Zhongpei Chen
Chongqing Traditional Chinese Medicine Hospital
Yuxi Bian
Chongqing Medical University
Chengzhen Jing
Chongqing Medical University
Zhenhan Li
li_zhenhan@126.com

Chongqing Traditional Chinese Medicine Hospital

Case Report

Keywords: Turner syndrome, Metabolic syndrome, Sinus tachycardia, Insulin resistance, Hormone replacement therapy, Multidisciplinary management

Posted Date: September 2nd, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10448670/v1

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

Additional Declarations: No competing interests reported.

Version of Record: A version of this preprint was published at BMC Endocrine Disorders on October 14th, 2026. See the published version at https://doi.org/10.1186/s12902-026-02661-9.

Abstract

Background

Turner syndrome (TS) is a sex chromosome disorder caused by X-chromosome abnormalities, with gonadal dysgenesis, short stature, and clinical heterogeneity. With improved survival rates, adult patients with TS increasingly face a heightened risk of metabolic comorbidities, including insulin resistance and its progression to type 2 diabetes mellitus (T2DM), as well as hypertension and metabolic dysfunction-associated steatotic liver disease (MASLD). However, the interactive mechanisms among these metabolic abnormalities and their early warning signs for progression remain insufficiently explored. This study aims to report a TS case with multiple metabolic complications and analyze the clinical significance of associated cardiac manifestations.

Case presentation

A 30-year-old female TS patient presented with multiple comorbidities. Persistent sinus tachycardia occurred after the initiation of hormone replacement therapy (HRT). Metabolic assessments revealed significant insulin resistance, which was correlated with the development of MASLD and hyperlipidemia. We proposed a metabolic interaction network model to explain the interconnections among these abnormalities and identified sinus tachycardia as a potential early warning signal of metabolic deterioration.

Conclusions

This case highlights the intricate interactions of metabolic abnormalities in TS patients and suggests sinus tachycardia as an early indicator of worsening metabolic disorders. A multidimensional and multidisciplinary management strategy is essential for TS patients with complex metabolic and cardiac comorbidities. Future research should further validate the metabolic interaction network model and explore the diagnostic value of electrocardiographic changes such as sinus tachycardia in the early intervention of TS-related metabolic and cardiovascular complications.

Background

Turner Syndrome (TS) is a common sex chromosome disorder characterized by the complete or partial absence of one X chromosome, with an incidence of approximately 1 in 2000 to 1 in 2500 live female births[1,2]. As a multisystem disorder, TS is associated with a wide range of clinical manifestations, including short stature, gonadal insufficiency, congenital heart defects, and various metabolic abnormalities, which collectively impose significant physical and psychological burdens on affected individuals[3]. While early growth hormone therapy and standardized hormone replacement therapy (HRT) for its classic features (e.g., short stature, gonadal insufficiency) have significantly improved patient

survival, leading to a near-normal life expectancy, the consequent high prevalence of metabolic syndrome has emerged as a central clinical challenge affecting long-term prognosis[2,4]. Current understanding and management of metabolic comorbidities in TS are hampered by significant, interrelated gaps. While X-chromosome abnormalities and estrogen deficiency are recognized as key etiological factors for distinct conditions like insulin resistance, fatty liver, and hyperlipidemia, the overarching systemic network and principal drivers that link these disorders into a coherent clinical phenotype remain poorly defined[5]. X-chromosome abnormalities cause the loss or dysfunction of multiple genes involved in metabolic regulation, and long-term estrogen deficiency resulting from gonadal insufficiency disrupts metabolic pathway balance, jointly increasing the risk of various metabolic disorders[6]. This mechanistic uncertainty is exacerbated by a scarcity of proactive clinical tools, since current research prioritizes manifest complications over validated early-warning indicators (Fig. 1).

Existing studies have mainly focused on individual metabolic disorders, but the overarching systemic metabolic interaction network that links these disorders into a coherent clinical phenotype remains poorly defined. Notably, cardiac autonomic nerves play a crucial role in regulating systemic metabolism and hemodynamic stability, and their dysfunction may be an important node in the metabolic interaction network of TS[7]. Cardiac autonomic nerve injury can disrupt the regulation of glucose and lipid metabolism, promote insulin resistance, and accelerate the progression of metabolic syndrome[8,9]. More importantly, cardiac autonomic nerve injury often manifests as observable clinical signs, which may serve as an early "warning horn" for the progression of metabolic deterioration in TS[7,10]. The prior case analysis first suggested that persistent sinus tachycardia following HRT, an important manifestation of potential cardiac autonomic nerve dysfunction, may associate with metabolic deterioration and offer a novel angle for identifying early warning signals[11,12]. The role of cardiac autonomic dysfunction within the metabolic interaction network of TS, and the relevance of sinus tachycardia as an early marker, remain incompletely characterized. Drawing on observations from this case, we propose an insulin resistance–centered metabolic interaction framework and suggest sinus tachycardia as a potential early, clinically accessible signal of metabolic deterioration in TS.

Case presentation

An 18-year-old female was admitted on January 19, 2022, with a 7-year history of menstrual irregularity and a 4-year history of hyperglycemia. Menarche occurred at age 11, followed by secondary amenorrhea. Physical examination data from the initial evaluation were unavailable as it was conducted at an outside institution. In 2017 (at age 13), evaluation for amenorrhea included sex hormones, thyroid function, and fasting insulin, with post-treatment reassessment (Fig. 2). Pelvic ultrasound showed an infantile uterus with non-visualized ovaries, and karyotyping revealed 45, X, 9qh+ (Fig. 3), establishing the diagnosis of Turner syndrome with subclinical hypothyroidism. Treatment with levothyroxine and estradiol valerate/cyproterone acetate (Climen) was initiated, with levothyroxine titrated to 50 μg daily based on follow-up results.

In 2018 (4 years prior to admission), the patient developed systemic metabolic disturbances involving both hepatic and glucose metabolism (Fig. 2). Liver function tests showed markedly elevated transaminases, with viral, autoimmune, and infectious etiologies excluded. Abdominal ultrasound demonstrated fatty liver, consistent with MASLD. Hepatoprotective therapy was initiated, and estradiol/dydrogesterone therapy was discontinued. Concurrently, hyperglycemia was identified. OGTT/OGIRT demonstrated marked post-load hyperglycemia with concomitant hyperinsulinemia, and HbA1c was 8%, supporting a diagnosis of diabetes mellitus in the context of insulin resistance. Antidiabetic therapy was initiated with partial glycemic control; however, treatment adherence was poor after discharge. In 2020, liver function partially improved but remained abnormal, requiring ongoing hepatoprotective therapy. At follow-up in 2025, HbA1c remained elevated (7.5%), and despite initiation of saxagliptin, glycemic control remained suboptimal, indicating persistent glycolipid metabolic dysregulation.

On January 19, 2022, the patient was admitted for poorly controlled diabetes. Physical examination showed a temperature of 36.3°C, heart rate 116 bpm, respiratory rate 18 breaths/min, and blood pressure 125/95 mmHg. She had short stature (147 cm) with Turner-related features, including a short/webbed neck, hypertelorism, genu valgum, and underdeveloped secondary sexual characteristics. Cardiac examination revealed tachycardia with a regular rhythm and no murmurs; other systems were unremarkable. Laboratory and imaging findings indicated severe hyperglycemia (HbA1c 11.2%) with hyperinsulinemia and negative diabetes-related autoantibodies, accompanied by ovarian insufficiency, dyslipidemia, hyperuricemia, and persistent liver dysfunction, consistent with systemic glycolipid metabolic disturbance. Electrocardiography and ambulatory monitoring showed sinus tachycardia with reduced heart rate variability, while ambulatory blood pressure monitoring demonstrated elevated diastolic pressure and disrupted circadian rhythm. Imaging revealed fatty liver, reduced bone mineral density, and hypoplastic reproductive organs (Fig. 2). The patient was diagnosed with type 2 diabetes mellitus, Turner syndrome (45,X), grade 1 hypertension (very high risk), sinus tachycardia, MASLD, dyslipidemia, ovarian insufficiency, and osteopenia. Intensive insulin therapy was initiated, combined with metformin and hepatoprotective treatment.

After discharge, the patient underwent regular follow-up with serial biochemical assessments (Fig. 2). In the early post-discharge period (February–March 2022), liver function and lipid parameters showed partial improvement; however, hyperglycemia persisted, requiring intensification of antidiabetic therapy. During longer-term follow-up, glycemic control showed transient improvement (HbA1c 7.0% in January 2023) but remained unstable thereafter, with recurrent deterioration (up to 12.2% in December 2023 and 10.8% in December 2025). Liver enzymes and lipid profiles exhibited a similar fluctuating pattern, indicating sustained glycolipid metabolic dysregulation. In January 2026, cardiovascular autonomic function testing demonstrated borderline orthostatic systolic blood pressure response and impaired handgrip-induced blood pressure modulation, with a total Ewing score of 1.5, consistent with early or atypical autonomic neuropathy. Concurrent lower limb arterial Doppler and ankle-brachial index (ABI) assessment revealed normal bilateral ABI (L 1.07, R 1.17) but early evidence of increased peripheral vascular resistance. Electrocardiography showed sinus tachycardia. Peripheral neuropathy evaluation

was largely unremarkable except for absent ankle reflexes. Key autonomic and cardiovascular findings are summarized in Fig. 3. In the absence of structural cardiac abnormalities, the interval emergence of sinus tachycardia during follow-up, together with objective evidence of early autonomic dysfunction, supports a temporal association with long-standing metabolic dysregulation, and raises the possibility that it represents an early clinical expression within the metabolic–cardiac interaction continuum.

Discussion and conclusions

This case describes a patient with TS and a 45, X, 9qh+ karyotype who, over the disease course, developed a spectrum of interconnected clinical phenotypes, including ovarian insufficiency, insulin resistance, T2DM, MASLD, dyslipidemia, reduced bone mineral density, hypertension, and persistent sinus tachycardia. Rather than representing isolated, organ-specific complications, these manifestations evolved sequentially and in parallel, forming a coherent pattern of multi-system involvement[13]. Notably, the emergence of sinus tachycardia and subsequent evidence of early autonomic dysfunction occurred in the context of long-standing and fluctuating metabolic disturbances, in the absence of structural cardiac abnormalities, suggesting a temporal and pathophysiological linkage between metabolic dysregulation and cardiac autonomic alterations[14,15]. Current international clinical practice guidelines emphasize that TS is a complex, lifelong, multi-system disorder extending beyond growth and gonadal dysfunction, with cardiovascular disease as a major determinant of morbidity and mortality[16,17]. In this context, the present case raises the possibility that the diverse clinical manifestations observed in TS may be better understood within an integrated framework of metabolic–cardiac interactions.

From a pathophysiological perspective, this case reflects a progressive endocrine, metabolic continuum driven by ovarian failure, related estrogen deficiency, in which insulin resistance acts as a central pathogenic hub linking glucose and lipid metabolic disturbances, hepatic steatosis, and bone metabolic impairment[18]. Congenital gonadal dysgenesis resulting from the X-chromosome abnormality is the initiating link in this entire pathological chain[13]. Chronic estrogen deficiency not only impacts reproductive system development but also drives metabolic disturbances by modulating insulin receptor sensitivity and bone metabolism signaling pathways[19]. Insulin resistance, as a central hub, triggers TS-related T2DM and participates in the pathogenesis of MASLD and hyperlipidemia by promoting hepatic lipid synthesis, forming a metabolic vicious cycle[20,21]. The patient exhibited elevated fasting insulin levels, progressive MASLD, T2DM, and dyslipidemia (peak triglyceride level of 35.42 mmol/L), which typify this metabolic cycle[22]. Meanwhile, estrogen deficiency and insulin resistance jointly impair bone metabolism, with the patient's lumbar spine T-score (-1.7 to -2.1) exemplifying their combined effect, reflecting the same metabolic-endocrine imbalance in different target organs[23]. At a deeper level, these metabolic and endocrine disturbances likely represent downstream effects of X chromosome haploinsufficiency–driven transcriptional and epigenetic dysregulation, disrupting gene networks involved in energy metabolism, organ development, and tissue homeostasis, thereby shaping the systemic and heterogeneous manifestations of TS[24].

In the present case, sinus tachycardia is better interpreted not as an isolated electrocardiographic abnormality, but as a clinically relevant manifestation arising within the metabolic interaction network of Turner syndrome. Although cardiovascular evaluation in TS has traditionally focused on congenital heart disease, aortic pathology, and hypertension, increasing evidence indicates that autonomic dysfunction and altered heart rate dynamics also contribute to the cardiovascular phenotype[25]. The coexistence of persistent sinus tachycardia, reduced heart rate variability, documented autonomic dysfunction, T2DM, hypertension, and MASLD in this case suggests that cardiac abnormalities in TS may reflect the combined effects of metabolic burden and autonomic dysregulation, rather than structural abnormalities alone. This case therefore underscores that cardiac manifestations in TS should be interpreted within a systemic metabolic interaction network, providing a rationale for earlier recognition and integrated long-term management in patients with complex multisystem involvement.

Abbreviations

ABI
Ankle-brachial index
HRT
Hormone replacement therapy
TS
Turner syndrome
T2DM
Type 2 diabetes mellitus
MASLD
Metabolic dysfunction-associated steatotic liver disease

Declarations

Ethics approval and consent to participate

Ethical approval was not required for this case report in accordance with local regulations.

Consent for publication

Written informed consent for publication was obtained from the patient.

Author Contribution

L. Z. conceived the case report, collected and organized the clinical data, performed the literature review, and drafted the manuscript. Z. C. contributed to the collection and interpretation of the clinical data and revised the manuscript. Y. B. assisted with data analysis, literature review, and the preparation of tables and figures. C. J. contributed to the clinical assessment and interpretation of the findings. Z. L.

supervised the study, contributed to the conception and clinical interpretation of the case, and critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

References

1. Gravholt CH, Andersen NH, Christin-Maitre S, et al. Clinical practice guidelines for the care of girls and women with Turner syndrome. Eur J Endocrinol. 2024;190(6):G53–151. 10.1093/ejendo/lvae050.
2. Gravholt CH, Viuff M, Just J, et al. The Changing Face of Turner Syndrome. Endocr Rev. 2023;44(1):33–69. 10.1210/endrev/bnac016.
3. Yoon SH, Kim GY, Choi GT, Do JT. Organ Abnormalities Caused by Turner Syndrome. Cells. 2023;12(10):1365. 10.3390/cells12101365.
4. Gravholt CH, Viuff MH, Brun S, Stochholm K, Andersen NH. Turner syndrome: mechanisms and management. Nat Rev Endocrinol. 2019;15(10):601–14. 10.1038/s41574-019-0224-4.
5. Viuff MH, Just J, Brun S, et al. Women With Turner Syndrome Are Both Estrogen and Androgen Deficient: The Impact of Hormone Replacement Therapy. J Clin Endocrinol Metab. 2022;107(7):1983–93. 10.1210/clinem/dgac167.
6. Galian-Gay L, Rodriguez-Palomares JF. Turner syndrome and aortic complications: more benign than previously thought. Heart. 2022;109(2):82–3. 10.1136/heartjnl-2022-321330.
7. de Groote K, Patel SR, Mortensen KH, et al. Management of Cardiovascular Health Issues in Turner Syndrome: Expert Insights and Expanded Recommendations From the 2024 Guideline Development Team. Am J Med Genet C Semin Med Genet. 2025;199(2):51–71. 10.1002/ajmg.c.32139.
8. Mondal S, Gargari P, Bose C, Garg MK, Chowdhury S, Mukhopadhyay S. Abnormal Body Composition Increases the Cardiometabolic Risk in Adolescents and Young Adults With Turner Syndrome. Endocr Pract. 2024;30(3):259–69. 10.1016/j.eprac.2023.11.013.
9. Zhou Z, Xiao S, Guo X, et al. Metabolic profiles of Turner syndrome: A real-world cohort study. Med Clin (Barc). 2025;165(4):107061. 10.1016/j.medcli.2025.107061.
10. Stefil M, Kotalczyk A, Blair JC, Lip GYH. Cardiovascular considerations in management of patients with Turner syndrome. Trends Cardiovasc Med. 2023;33(3):150–8. 10.1016/j.tcm.2021.12.002.
11. Alam S, Claxton JS, Mortillo M, et al. Thirty-Year Survival after Cardiac Surgery for Patients with Turner Syndrome. J Pediatr. 2021;239:187–e1921. 10.1016/j.jpeds.2021.08.034.
12. van der Coelen S, Hagen CP, Nadesapillai S, et al. Minipuberty in girls with Turner syndrome provides insight into reproductive potential-a prospective cohort study. Fertil Steril. 2025;124(6):1314–23. 10.1016/j.fertnstert.2025.07.003.
13. Bakalov VK, Cheng C, Zhou J, Bondy CA. X-chromosome gene dosage and the risk of diabetes in Turner syndrome. J Clin Endocrinol Metab. 2009;94(9):3289–96. 10.1210/jc.2009-0384.

14. Noordman ID, Fejzic Z, Bos M, et al. Cardiac abnormalities in girls with Turner syndrome: ECG abnormalities, myocardial strain imaging, and karyotype-phenotype associations. Am J Med Genet A. 2021;185(8):2399–408. 10.1002/ajmg.a.62259.
15. Donadille B, Christin-Maitre S. Heart and Turner syndrome. Ann Endocrinol (Paris). 2021;82(3–4):135–40. 10.1016/j.ando.2020.12.004.
16. Birjiniuk A, Weisman AG, Laternser C, et al. Cardiovascular Manifestations of Turner Syndrome: Phenotypic Differences Between Karyotype Subtypes. Pediatr Cardiol. 2024;45(7):1407–14. 10.1007/s00246-023-03159-0.
17. McCarrison S, Carr A, Wong SC, Mason A. The prevalence of hypertension in paediatric Turner syndrome: a systematic review and meta-analysis. J Hum Hypertens. 2023;37(8):675–88. 10.1038/s41371-022-00777-8.
18. Donadille B, Valent A, Amemiya K, et al. Aortic Tissue Analysis in Turner Syndrome. J Am Coll Cardiol. 2022;80(13):1284–5. 10.1016/j.jacc.2022.07.017.
19. Szybiak W, Kujawa B, Miedziaszczyk M, Lacka K. Effect of Growth Hormone and Estrogen Replacement Therapy on Bone Mineral Density in Women with Turner Syndrome: A Meta-Analysis and Systematic Review. Pharmaceuticals (Basel). 2023;16(9):1320. 10.3390/ph16091320.
20. Bakalov VK, Cooley MM, Quon MJ, et al. Impaired insulin secretion in the Turner metabolic syndrome. J Clin Endocrinol Metab. 2004;89(7):3516–20. 10.1210/jc.2004-0122.
21. Singh I, Noel G, Barker JM, et al. Hepatic abnormalities in youth with Turner syndrome. Liver Int. 2022;42(10):2237–46. 10.1111/liv.15358.
22. Hjerrild BE, Holst JJ, Juhl CB, Christiansen JS, Schmitz O, Gravholt CH. Delayed β-cell response and glucose intolerance in young women with Turner syndrome. BMC Endocr Disord. 2011;11:6. 10.1186/1472-6823-11-6.
23. Ikegawa K, Hasegawa Y. Fracture risk, underlying pathophysiology, and bone quality assessment in patients with Turner syndrome. Front Endocrinol (Lausanne). 2022;13:967857. 10.3389/fendo.2022.967857.
24. Viuff M, Skakkebaek A, Nielsen MM, Chang S, Gravholt CH. Epigenetics and genomics in Turner syndrome. Am J Med Genet C Semin Med Genet. 2019;181(1):68–75. 10.1002/ajmg.c.31683.
25. Zuckerman-Levin N, Zinder O, Greenberg A, Levin M, Jacob G, Hochberg Z. Physiological and catecholamine response to sympathetic stimulation in turner syndrome. Clin Endocrinol (Oxf). 2006;64(4):410–5. 10.1111/j.1365-2265.2006.02483.x.

Figures

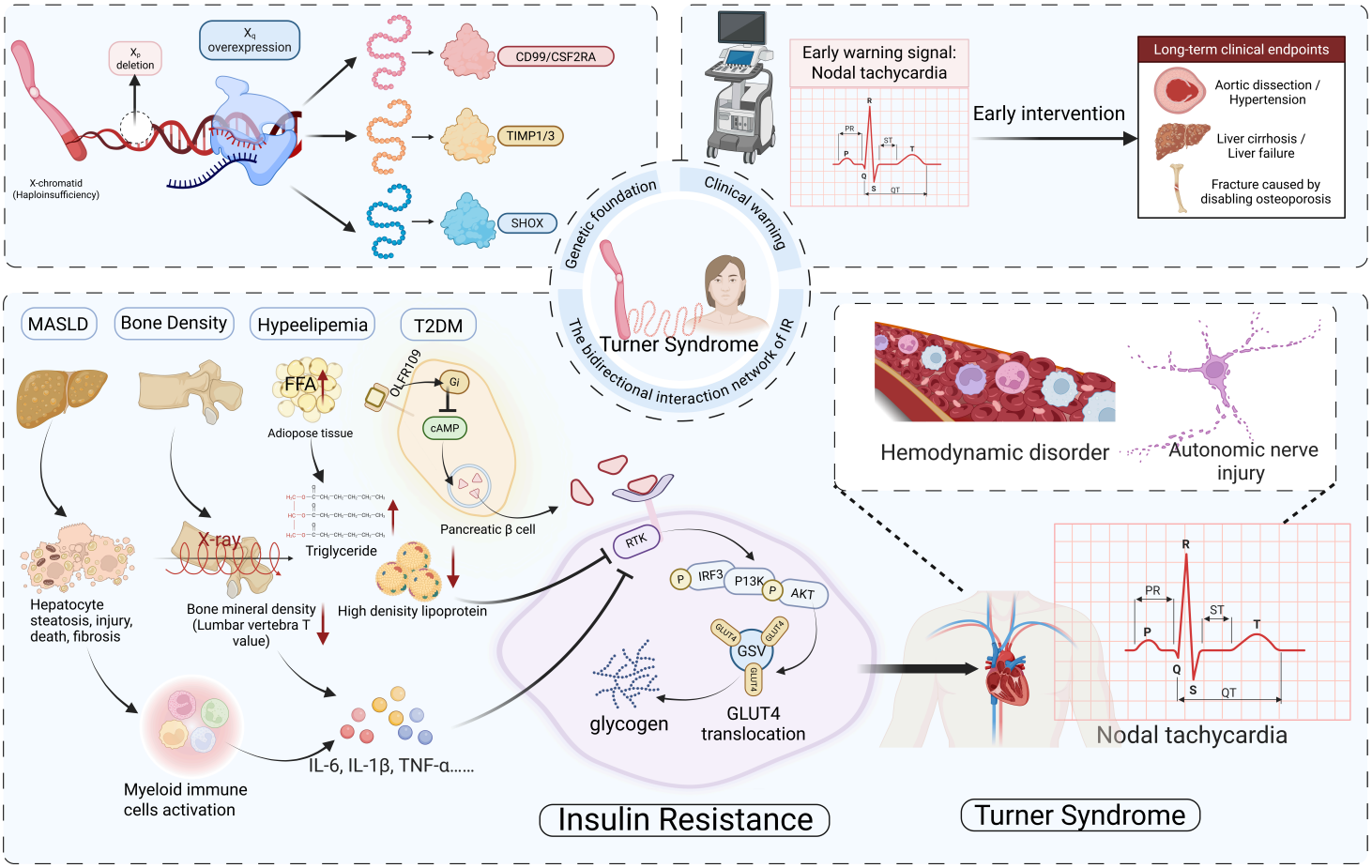


Figure 1

Conceptual diagram.

Metabolic interaction network and cardiac abnormalities in Turner syndrome.

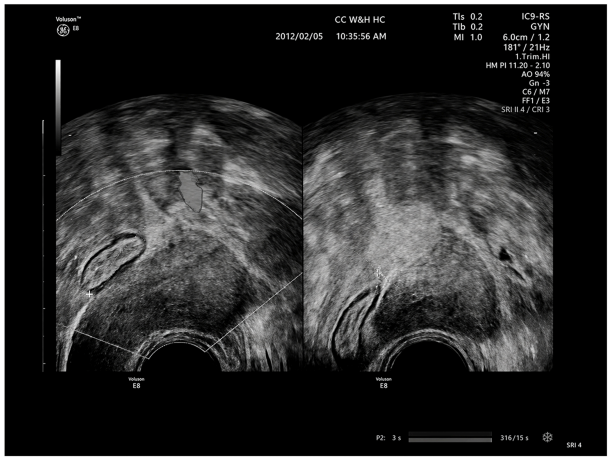
A

Test Item (Abbreviation), Unit	Test Result	Reference Range
ALT, U/L	231.30 ↑	0–45
AST, U/L	150.60 ↑	0–40
CHE, U/L	12178 ↑	5000–12000
ALP, U/L	124.00	35–135
TBA, umol/L	2.10	0–10
GGT, U/L	63.00 ↑	7–52
TP, g/L	81.80	65–85
ALB, g/L	45.40	35–54

B

Test Item (Abbreviation), Unit	Test Result	Reference Range
hTSH, mIU/L	4.91	0.35–4.94 (nonpregnant)
FSH, mIU/mL	7.12	3.03–8.08 (follicular phase)
E2, pmol/L	47.71 ↓	77.07–921.17 (follicular phase)
INS(0h), pmol/L	79.20	30.12–124.92

C



D

Test Item (Abbreviation), Unit	Test Result	Reference Range	Test Item (Abbreviation), Unit	Test Result	Reference Range
ALT, U/L	231.30 ↑	0–45	GLU, mmol/L	8.05 ↑	3.8–6.1
AST, U/L	150.60 ↑	0–40	UREA, mmol/L	3.80	2.6–8.0
CHE, U/L	12178 ↑	5000–12000	CREA, umol/L	45.00	40–110
ALP, U/L	124.00	35–135	UA, umol/L	500 ↑	135–425
TBA, umol/L	2.10	0–10	Ca, mmol/L	2.35	2.1–2.7
GGT, U/L	63.00 ↑	7–52	K, mmol/L	4.00	3.5–5.3
TP, g/L	81.80	65–85	Na, mmol/L	142.90	137–145
ALB, g/L	45.40	35–54	Cl, mmol/L	108.60	99–110
GLB, g/L	36.40	20–40	AMS, U/L	95.00	28–100
A/G, N/A	1.20	1.2–2.4	COcp, mmol/L	12.00 ↓	21–29
TBIL, umol/L	7.50	2–23	Cys-C, mg/L	1.02	0.1–1.2
DBIL, umol/L	3.10	0–7	PAlb, mg/L	245.30	200–400
IBIL, umol/L	4.40	0–16	AFU, U/L	27.60	0–40

Figure 2

Summary of clinical course.

A. In 2017 (age 13), evaluation for amenorrhea including sex hormones, thyroid function, and fasting insulin, with post-treatment reassessment performed.

B. In 2018 (four years prior to admission), onset of systemic metabolic disturbances affecting hepatic and glucose metabolism.

C. On January 19, 2022 (admission), imaging revealed fatty liver, reduced bone mineral density, and hypoplastic reproductive organs.

D. After discharge, the patient underwent regular follow-up with serial biochemical assessments and monitoring of metabolic parameters.

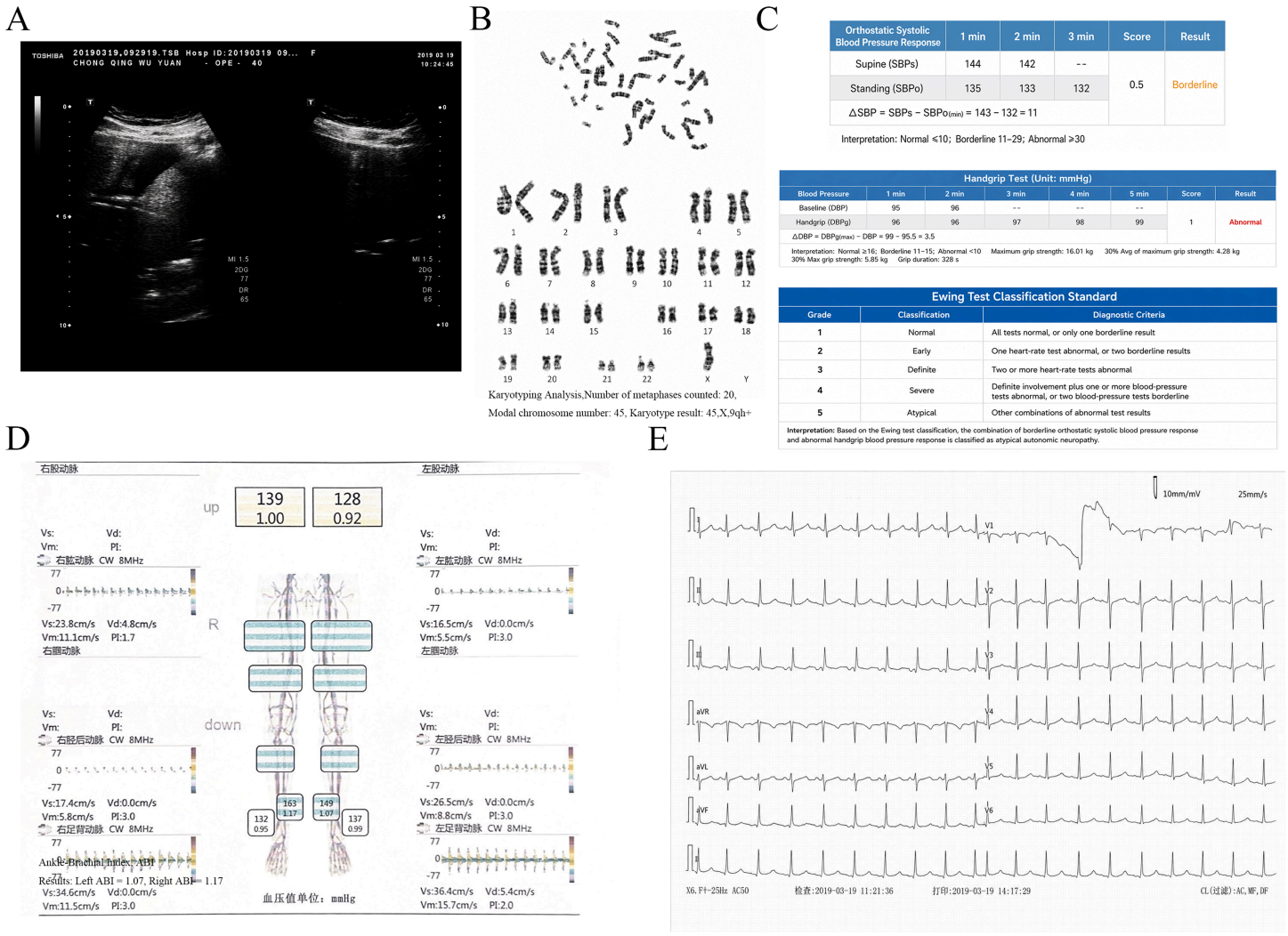


Figure 3

Diagnostic findings and autonomic summary.

A. Pelvic ultrasound demonstrating an infantile uterus with non-visualized ovaries.

B. Karyotyping revealed 45, X, 9qh+, consistent with a diagnosis of Turner syndrome.

C. Cardiac autonomic function testing showing borderline systolic blood pressure response during supine-to-standing and abnormal handgrip responses, with a total Ewing score of 1.5, indicative of atypical autonomic neuropathy.

D. Lower limb arterial Doppler and ankle-brachial index (ABI) assessment showing normal bilateral ABI (L 1.07, R 1.17) with early signs of increased peripheral vascular resistance.

E. Electrocardiography demonstrating sinus tachycardia.

Supplementary Files

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

- CAREchecklist.pdf