

The Cutoff of Gonadotropins for Close Evaluation of Cardiometabolic Risk Factors in Turner Syndrome

Abstract

Background: Turner syndrome is a common genetic disorder in females. It is a disorder characterized by variable number of clinical features, so it needs a multidisciplinary approach for care. Therefore, we aimed to define the cutoff of gonadotropins for close evaluation of cardiometabolic risk factors in Turner syndrome. **Methods:** This is a case-control study on 31 patients with Turner syndrome and 31 healthy individuals. Clinical examination including blood pressure measurement and systems evaluation was performed. Laboratory testing, which included 12-h fasting, assessed lipid profile, glucose, and serum gonadotropin. **Results:** Turner syndrome had a higher BMI, systolic, and diastolic blood pressure than the normal group ($P < 0.001$). Patients with Turner syndrome had significantly higher total cholesterol, low-density lipoprotein, triglyceride, and TG-to-high-density lipoprotein ratio compared to the healthy individuals ($P < 0.05$). With increasing LH and FSH, BMI values, systolic blood pressure, and total cholesterol increased significantly ($P < 0.001$). Serum TG levels in Turner syndrome were only positively correlated with LH and not correlated with FSH. The cutoff point of LH and FSH for triglyceride in upper 75 percentile were 31 (sensitivity = 38.1%, specificity = 80%) and 48 (sensitivity = 61.9%, specificity = 70%), respectively. **Conclusions:** Based on dyslipidemia and lower level of ejection fraction, considering cardiometabolic risk factors in lower age groups in Turner syndrome can be recommended.

Keywords: Child, gonadotropins, Turner syndrome

Introduction

Turner syndrome (TS) is a common genetic disorder in females. It occurs 1 in 2500 live-born females.^[1] Multiple defects such as dysmorphic stigmata, short stature, sexual infantilism, and renal, cardiac, skeletal, endocrine, and metabolic abnormalities are involved in TS through all stages of their lives.^[2] It is caused by complete or partial loss of one X chromosome, often in mosaic karyotypes.^[3]

It is assumed that TS may increase the occurrence of cardiometabolic morbidities and mortalities compared to the general population which may be due to its multifactorial characteristics such as lifestyle, epigenetics, genetics, hypogonadism, and medications^[4] Girls with TS in comparison with other girls are at a greater risk of decreased β -cell dysfunction and cardiovascular diseases.^[2] Moreover, increased systolic and diastolic blood pressures were seen significantly in late adolescence and early adulthood

in TS.^[5] A cluster of risk factors such as insulin resistance and dyslipidemia which may lead to the development of type 2 diabetes mellitus and cardiovascular diseases are probably the most common metabolic abnormalities found in adult patients with TS.^[4,6] According to cardiometabolic complications of TS, if this complication is predicted based on gonadotropin, clinicians may be more alert and can prevent this complication with controlling BMI and blood pressure. TS is a disorder characterized by various clinical features, so it needs a multidisciplinary approach for care. Therefore, we aimed to define the cutoff of gonadotropins for close evaluation of cardiometabolic risk factors in TS.

Methods

This is a case-control study on 31 patients with TS based on karyotype. They were on regular follow-up at 17 Shahrivar Children Hospital (Guilan University of Medical Science, Iran). Thirty-one healthy children with comparable age and sex distribution

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were enrolled as controls. All participants with blood pressure treatment, history of aortic coarctation, renal or cardiac diseases, and diabetes mellitus were excluded.

For all eligible children (patients and controls), demographic characteristics were recorded. Clinical examination including blood pressure measurement and systems evaluation was performed. By automatic oscillometry, blood pressure was measured on the right upper arm, after 3–5 min short rest in a seated position by the American Heart Association method.^[7] Laboratory testing which included 12-h fasting assessed lipid profile, glucose, and serum gonadotropin. Lipid profile was performed by the endpoint method (enzymatic method) and included serum triglyceride (TG), total serum cholesterol, high-density lipoprotein-cholesterol (HDL), and low-density lipoprotein-cholesterol (LDL). Very low-density lipoprotein-cholesterol was estimated using the calculation of TG/5. Abdominal sonography was performed and heart echocardiography was done by Samsung ultrasound EKO 7 device for all patients.

Ethical considerations

The study protocol was approved by the ethics committee of Guilan University of medical sciences (number: IR.GUMS.REC.1399.061 date: 2020-05-06) and written informed consent was taken from parents or participants.

Statistical analysis

Data were analyzed using SPSS 18.0 for windows (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean \pm SD. Categorical variables were expressed as number (percent). Continuous variables were checked using the Shapiro–Wilk test for normality. To compare the normally distributed variables, an independent Student's *t*-test was used. While to compare non-normally distributed variables, the Mann–Whitney *U* test was used between two groups. Categorical variables were compared by using the Chi-square test (χ^2). To assess the relationship between normally distributed and non-normally distributed variables, Pearson's correlation coefficient and Spearman's rank correlation were used, respectively. To define the diagnostic profile of serum luteinizing hormone (LH) and follicle stimulating hormone (FSH) in identifying abnormal cholesterol and TG among patients with TS, the ROC curve was designated.

All tests were two-sided, and $P < 0.05$ was considered statistically significant.

Results

Thirty-one patients with TS and 31 healthy individuals were included in the study. There was no significant difference between groups regarding age and sex. TS had a higher BMI, systolic, and diastolic blood pressure than the normal group ($P < 0.001$) [Table 1].

Patients with TS had significantly higher total cholesterol, LDL, HDL, TG, and TG-to-HDL ratio compared to the healthy individuals. Serum gonadotropins were significantly higher in TS ($P < 0.001$). Ejection fraction (EF) of Turner patients was also significantly lower than the control group ($P < 0.001$).

Of the Turner population studied in this study, 22 patients had hormone replacement therapy (HRT), while 9 patients were not treated with HRT. The mean age of the Turner patients who had HRT was significantly higher than controls ($P < 0.001$). Also, BMI, systolic, and diastolic blood pressures were significantly higher in treated than untreated patients ($P < 0.001$).

Total cholesterol ($P = 0.02$) and TGs ($P = 0.023$) were significantly higher in HRT-treated Turner patients than in the untreated Turner group. However, there was no significant difference between groups regarding LDL and HDL ($P > 0.05$). LH ($P < 0.001$) and FSH ($P = 0.02$) were also higher in HRT-treated Turners than in untreated Turners [Figure 1].

There was no significant difference between the HRT-treated and untreated Turners in terms of EF ($P > 0.05$). In this study, investigators examined the correlation between quantitative variables with serum gonadotropin levels in women with TS. Based on this study, BMI, systolic blood pressure, and total cholesterol had a significant positive correlation with both LH and FSH values. With increasing LH and FSH, BMI values, systolic blood pressure, and total cholesterol also increased significantly ($P < 0.001$). Serum TG levels in TS were only positively correlated with LH and not correlated with FSH [Table 2].

The area under the curve (AUC) of LH and FSH for cholesterol in upper 75 percentile was 0.991 and 0.954, respectively. The cutoff point of LH and FSH for cholesterol in upper 75 percentile were 37.5 (sensitivity = 38.1%, specificity = 80%) and 96.5 (sensitivity = 100%, specificity = 92.6%), respectively [Figure 2].

The AUC of LH and FSH for TG in the upper 75 percentile was 0.764 and 0.726, respectively. The cutoff

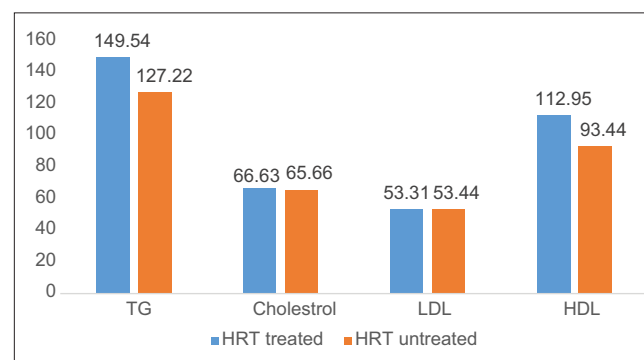


Figure 1: The Comparison of lipid profiles in HRT-treated and untreated patients with TS

Table 1: Demographic characteristics of participants in two groups

Variable	Group status	TS		Healthy individuals		Sum		Statistical estimate
		n	%	n	%	n	%	
Age (years)	<10	8	25.8	12	38.7	20	32.3	0.416
	>10	23	74.2	19	61.3	42	67.7	
Age (years) Mean±SD		4.13±13.41		3.82±12.38		3.98±12.9		0.312
BMI	<18.5	0	0	2	6.5	2	3.2	0.490
	>18.5	31	100	29	93.5	60	96.8	
BMI Mean±SD		1.78±22.07		19.72±0.86		1.82±20.9		0.0001
Systolic blood pressure (mmHg) Mean±SD		16.34±97.96		11.22±79.29		16.79±88.62		0.0001
Diastolic blood pressure (mmHg)		10.47±60.41		2.38±50.96		8.91±55.69		0.0001
Total cholesterol		24.74±143.05		16.70±104.29				0.0001
LDL		5.75±66.35		6.09±51.25				0.0001
HDL		4.57±53.35		9.97±65.45				0.0001
TG		22.16±107.29		8.62±91.9				0.0010
TG-to-HDL ratio		0.43±2.02		0.21±1.42				0.0001
LH		15.97±19.62		9.97±10.76				0.0001
FSH		37.45±54.77		10.04±13.98				0.0001
Ejection fraction		2.88±65.06		2.37±69.8				0.0001

LDL=Low-density lipoprotein; HDL=High-density lipoprotein; TG=Triglyceride

Table 2: Correlation between quantitative variables with serum gonadotropins (LH and FSH) in women with TS

Variable	LH values	Values FSH
BMI		
Pearson correlation coefficient	0.825	0.721
P	0.0001	0.0001
Correlation type	Positive correlation	Positive correlation
Systolic blood pressure		
Pearson correlation coefficient	0.890	0.798
P	0.0001	0.0001
Correlation type	Positive correlation	Positive correlation
Total cholesterol		
Pearson correlation coefficient	0.646	0.612
P	0.0001	0.0001
Correlation type	Positive correlation	Positive correlation
LDL		
Pearson correlation coefficient	-0.067	-0.047
P	0.718	0.802
Correlation type	Without correlation	Without correlation
HDL		
Pearson correlation coefficient	-0.046	0.022
P	0.808	0.906
Correlation type	Without correlation	Without correlation
TG		
Pearson correlation coefficient	0.474	0.308
P	0.007	0.092
Correlation type	Without correlation	Without correlation
EF%		
Pearson correlation coefficient	-0.144	0.010
P	0.440	0.959
Correlation type	Without correlation	Without correlation

LDL=Low-density lipoprotein; HDL=High-density lipoprotein; TG=Triglyceride; EF=Ejection fraction

point of LH and FSH for TG in upper 75 percentile (sensitivity = 61.9%, specificity = 70%), respectively were 31 (sensitivity = 38.1%, specificity = 80%) and 48 [Figure 3].

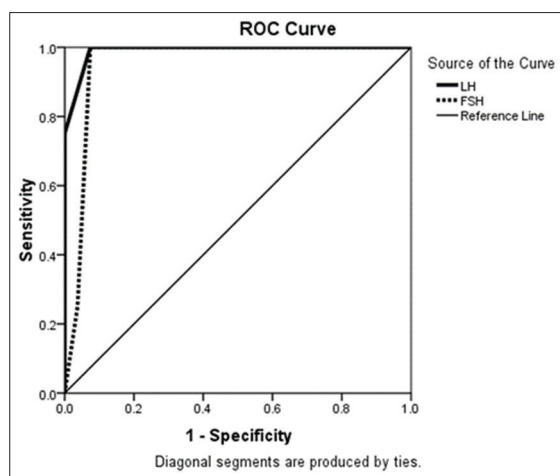


Figure 2: Roc curve of LH and FSH based on cholesterol

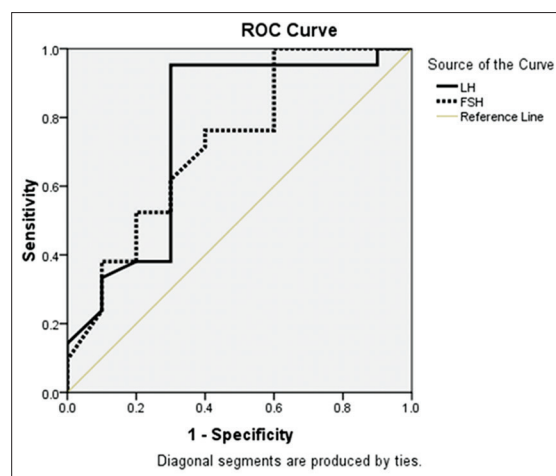


Figure 3: Roc curve of LH and FSH based on cholesterol

Discussion

In this study, cardiometabolic risk factors were compared in patients with TS with those in the normal population. Also, the effect of serum gonadotropins on biochemical factors affecting the cardiometabolic health of cholesterol and TG was assessed to indicate a cutoff for it as a novelty of this study. Previous investigations assessed primarily the actions of estrogens as the female sex hormone on insulin resistance because it has been shown that estradiol has direct actions for increasing skeletal muscle and adipocytes glucose uptake plus anti-inflammatory and antioxidant effects. It indirectly develops insulin receptor function and may have cardiometabolic effects.^[8,9] Therefore, in these patients, high levels of LH and FSH were noted as a result of a low level of estrogen.

Results showed that BMI and systolic and diastolic blood pressure were higher in TS versus the control group. These factors can be noted as independent risk factors for cardiovascular events and cardiometabolic defects. Consistent with current results, O’Gorman *et al.*, Hanew *et al.*, and Álvarez-Nava *et al.* mentioned higher BMI in patients with TS than the normal population.^[10-12] However, studies have shown that in addition to the short stature, other causes, such as dyslipidemia and some other metabolic mechanisms, may influence this increase in BMI. On the other hand, it has been suggested that increasing BMI increases the chance of cardiovascular events. Therefore, by increased BMI in patients with TS, cardiovascular events are also expected to have a higher chance.^[13] Generally, higher incidence of hypertension especially essential hypertension was noted in TS versus normal population. Causes including increased activity of the renin–angiotensin–aldosterone system and sympathetic system hyperactivity are factors that may increase the occurrence of hypertension in patients with TS.^[14]

In this study, patients with TS had significantly higher total cholesterol, LDL, TG, TG-to-HDL ratio, and lower

EF than the control group. Although these disturbances in lipid profiles are not a new result, previous studies not only mentioned a higher level of these factors, they even assessed metabolic syndrome risk factors as well.^[10,12] In previous investigations, the high prevalence of hypercholesterolemia (27%)^[6,12] or lower HDL^[4] was also noted. Further studies also mentioned increased carotid intima-media thickness in women with TS and noted atherosclerosis was associated with increased LDL and decreased HDL levels.^[15] It seems that based on the current study which was conducted on patients with the mean age of 13 years and a higher level of dyslipidemia and lower level of EF, considering cardiometabolic risk factors in younger age groups in TS can be recommended.

Assessing the relationship between serum gonadotropins and serum levels of metabolic factors affecting cardiovascular health, results showed that both gonadotropins (LH and FSH) were positively correlated with BMI, systolic blood pressure, and total cholesterol. However, TG had a positive correlation only with LH. Therefore, it seems that in the case of higher FSH and LH in younger patients, clinicians should consider early cardiometabolic risk factors in this age group. As a novel assessment, the cutoff for gonadotropins was reported in this study. The cutoff point of LH and FSH for cholesterol in upper 75 percentile were 37.5 (sensitivity = 38.1%, specificity = 80%) and 96.5 (sensitivity = 100%, specificity = 92.6%), respectively. The AUC of LH and FSH for TG in the upper 75 percentile were 0.764 and 0.726, respectively. The cutoff point of LH and FSH for TG in upper 75 percentile were 31 (sensitivity = 38.1%, specificity = 80%) and 48 (sensitivity = 61.9%, specificity = 70%), respectively. Therefore, it seems that clinicians should pay enough attention to patients with these cutoffs of gonadotropins.

In subgroup analysis, Turner patients treated with HRT had higher total cholesterol and TG than the untreated group, but there was no difference between groups regarding other lipid profiles including LDL and HDL. Furthermore, those

treated with HRT had significantly higher BMI, systolic, and diastolic blood pressure than the other group. A study by al-Sheikh *et al.* reported that there was no significant difference between the two groups in those treated with HRT and those not treated in terms of BMI, serum lipids, systolic, and diastolic blood pressure. This study stated that HRT has no effect on the lipid profile of patients.^[16] In a study published by Irzyniec *et al.* (2014),^[17] it was also reported that there was no significant difference in serum lipid levels between the two groups of patients treated and untreated with HRT.^[15] Comparing current and previous studies showed that the higher level of cholesterol and TG in this study may occur because HRT is used at the beginning of treatment and this study was conducted on younger participants, which would be decreased gradually and have no effect on lipid profiles including LDL and HDL finally.

In general, this study noted a novel cutoff point of gonadotropins for cardiometabolic risk factors. This study had some limitations. A low sample size which was absolutely shown in subgroup analysis may induce no significant power to show the differences between groups. On the other hand, the sample size of untreated patients with HRT was not enough to determine the independent effect of TS on cardiometabolic factors. Moreover, the lower age of patients with TS can have a significant impact on these factors. Therefore, further case-control or cohort studies with a larger sample size are recommended. Based on dyslipidemia and lower level of EF in these patients, considering cardiometabolic risk factors in lower age groups in TS can be recommended.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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References

- Hall JG, Gilchrist DM. Turner syndrome and its variants. *Pediatr Clin North Am* 1990;37:1421-40.
- Gravholt CH, Andersen NH, Conway GS, Dekkers OM, Geffner ME, Klein KO, *et al.* Clinical practice guidelines for the care of girls and women with turner syndrome: Proceedings from the 2016 Cincinnati international turner syndrome meeting. *Eur J Endocrinol* 2017;177:G1-G70.
- Gravholt CH, Viuff MH, Brun S, Stochholm K, Andersen NH. Turner syndrome: mechanisms and management. *Nat Rev Endocrinol* 2019;15:601-14.
- Davis SM, Geffner ME. Cardiometabolic health in Turner syndrome. *American Journal of Medical Genetics* 2019;181:60-66.
- Brun S, Cleemann L, Holm K, Salskov G, Erlandsen M, Berglund A, *et al.* Five-year randomized study demonstrates blood pressure increases in young women with Turner syndrome regardless of estradiol dose. *Hypertension* 2019;73:242-8.
- Lebenthal Y, Levy S, Sofrin-Drucker E, Nagelberg N, Weintrob N, Shalitin S, *et al.* The natural history of metabolic comorbidities in turner syndrome from childhood to early adulthood: Comparison between 45, X monosomy and other karyotypes. *Front Endocrinol* 2018;9:27.
- Pickering TG, Hall JE, Appel LJ, Falkner BE, Graves J, Hill MN, *et al.* Subcommittee of professional and public education of the American heart association council on high blood pressure research. Recommendations for blood pressure measurement in humans and experimental animals: Part 1: Blood pressure measurement in humans: A statement for professionals from the subcommittee of professional and public education of the American heart association council on high blood pressure research. *Hypertension* 2005;45:142-161.
- Gupte AA, Pownall HJ, Hamilton DJ. Estrogen: An emerging regulator of insulin action and mitochondrial function. *J Diabetes Res* 2015;2015:916585.
- Mauvais-Jarvis F. Menopause, estrogens, and glucose homeostasis in women. *Adv Exp Med Biol* 2017;1043:217-25.
- O'Gorman CS, Syme C, Lang J, Bradley TJ, Wells GD, Hamilton JK. An evaluation of early cardiometabolic risk factors in children and adolescents with Turner syndrome. *Clin Endocrinol (Oxf)* 2013;78:907-13.
- Hanew K, Tanaka T, Horikawa R, Hasegawa T, Fujita K, Yokoya S. Women with Turner syndrome are at high risk of lifestyle-related disease -From questionnaire surveys by the Foundation for growth science in Japan. *Endocr J* 2016;63:449-56.
- Álvarez-Nava F, Racines M, Witt J, Guarderas J, Estévez M, Lanes R. Anthropometric variables as cardiovascular risk predictors in a cohort of adult subjects with Turner syndrome. *Diabetes Metab Syndr Obes* 2019;12:1795-809.
- Los E, Quezada E, Chen Z, Lapidus J, Silberbach M. Pilot study of blood pressure in girls with Turner syndrome: An awareness gap, clinical associations, and new hypotheses. *Hypertension* 2016;68:133-6.
- Elsheikh M, Conway GS. The impact of obesity on cardiovascular risk factors in Turner's syndrome. *Clin Endocrinol (Oxf)* 1998;49:447-50.
- Pirgon Ö, Atabek ME, Oran B, Güçlü R. Atherogenic lipid profile and systolic blood pressure are associated with carotid artery intima-media thickness in children with Turner syndrome. *J Clin Res Pediatr Endocrinol* 2008;1:62-71.
- Elsheikh M, Bird R, Casadei B, Conway G, Wass J. The effect of hormone replacement therapy on cardiovascular hemodynamics in women with Turner's syndrome. *J Clin Endocrinol Metab* 2000;85:614-8.
- Irzyniec TJ, Jeż W. The influence of hormonal replacement and growth hormone treatment on the lipids in Turner syndrome. *Gynecol Endocrinol* 2014;30:250-3.