Original Article

Prevalence and Predictors of Prediabetes in Adolescents and Young Adults with Turner Syndrome: A Cross-Sectional Study from Eastern India

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Abstract

Background: Individuals with Turner syndrome (TS) have a high risk for prediabetes/type 2 Diabetes Mellitus (T2DM). There is scarce data regarding risk factors for prediabetes in TS, specially from South Asia. **Methods:** We conducted a cross-sectional study on girls with TS aged 12–30 years who had achieved pubertal stage B3 and above—spontaneously or with oestrogen. Anthropometric measurements and biochemical tests were conducted, and medical records were reviewed for details about pubertal onset and progression, growth hormone (GH) and oestrogen therapy. **Results:** Out of 129 patients with TS in our database, 99 met the criteria for inclusion, mean age 18.33+/-3.78 years and mean BMI 20.57+/- 3.71 kg/m^2. Prevalence of prediabetes was 23.23%. Plasma-glucose measured after 75 g-oral-anhydrous-glucose-load (OGTT-PPG) identified five additional prediabetes cases, who had normal fasting plasma glucose (FPG) or HbA1c%. Compared to those without prediabetes, TS with prediabetes (n = 23) had higher mean body weight, BMI, waist circumference (WC) [42.02+/- 5.83 vs 36.22+/-8.07, 22.77+/-2.78 vs 19.91+/- 3.72, 85.26+/- 3.52 vs 81.08+/- 4.59, pall < 0.03], higher median WC-to-height ratio (WHtR) and WC-to-hip ratio (WHR) ((0.64 [0.6–0.69] vs 0.59[0.56- 0.66], 0.9[0.84–1.12] vs 0.85[0.75–1.01], $p_{both} < 0.02$), and higher LDL-cholesterol, triglycerides, and greater prevalence of hepatosteatosis (47.1% vs 21.1%, $P < 0.01$). Among GH recipients (n = 36), those with prediabetes had delayed initiation and shorter duration of GH therapy. There were no differences in cardiometabolic parameters or the prevalence of diabetes between different karyotypic variants of TS. BMI, WC and WHR had significant positive correlation with FBG, OGTT-PPG and HbA1c% ($p_{all} < 0.004$). Delay in oestrogen initiation had a significant correlation with OGTT-PPG (Spearman's-rho = 0.69, $P < 0.004$). BMI, WHR and pubertal status were independent predictors for prediabetes (OR: 1.27 [1.03–1.57]), 1.18 [1.04–1.34]) and 0.09[0.02–0.38], respectively, pall < 0.02), but karyotype was not. BMI had the highest sensitivity [cut-off: 21.04 kg/m^2 (sensitivity: 82.6%, specificity: 62.2%) and WHR had the highest specificity [cut-off: 0.89 (sensitivity: 73.9%, specificity 78.4%)] for predicting prediabetes. **Conclusion:** Indian girls with TS have a high risk for prediabetes, irrespective of underlying karyotype and should be screened with oral glucose challenge to identify prediabetes. Timely intervention against central obesity and early initiation of GH and oestrogen should be ensured in TS. Late presenting girls should be closely monitored for dysglycaemia before and during treatment with GH and/or oestrogen.

Keywords: Growth hormone, prediabetes, Turner syndrome, waist–height ratio, waist–hip ratio

Introduction

Turner syndrome (TS) is a chromosomal disorder of female development characterized by partial or complete deletion of an X chromosome in all or some of the somatic cells.[1] Abnormal glucose metabolism is fairly common in TS patients ranging from impaired fasting glucose (IFG), impaired glucose tolerance (IGT), reduced insulin sensitivity and overt diabetes. According to recent guidelines, the prevalence of glucose intolerance is 15–50% in TS patients and frank type 2 diabetes 10%, but prevalence of type 1 diabetes is unclear.[1] According to a USA-based study, 25% patients did have type 2 diabetes

Access this article online

Quick Response Code:

Website: https://journals.lww.com/indjem/

DOI: 10.4103/ijem.ijem_22_23

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Submitted: 16-Jan-2023 **Revised:** 25-Feb-2023
Accepted: 09-Mar-2023 **Published:** 28-Aug-2023

How to cite this article: Mondal S, Gargari P, Bose C, Chowdhury S, Mukhopadhyay S. Prevalence and predictors of prediabetes in adolescents and young adults with Turner syndrome: A cross-sectional study from Eastern India. Indian J Endocr Metab 2023;27:335-45.

with <0.5% having type 1 diabetes.[2] For this increased prevalence of diabetes in TS, insulin resistance and reduced function of the β-cells have been put forward as possible mechanisms.[3,4] Another study in the USA has demonstrated that 35% of TS patients are diagnosed with prediabetes with significantly reduced insulin sensitivity, β-cell responsiveness and disposition index compared to healthy controls.[5]

Given the vast majority of macrovascular and microvascular complications associated with diabetes as well as even prediabetes, it is imperative to know the burden of dysglycaemia among Indian TS patients of whom the data are relatively scarce. A study from Eastern India comprising 35 TS patients documented two patients of diabetes type 1 and type 2 diabetes, respectively.[6] Another study from Assam documented three patients of diabetes (17.6%); out of 17 TS patients, two of them carrying monosomy X and another one with prediabetes.[7] In this background, the burden of prediabetes in TS with special reference to its risk factors including the role of karyotype, if any, seems to be imperative.

Methods

Study design and study population

We performed a cross-sectional observational study on adolescents and young adults with a karyotype-confirmed diagnosis of TS. The study population included all girls with TS aged between 12 and 30 years who visited the Endocrinology OPD of a tertiary care hospital in Kolkata between 1 September 2016 and 31 August 2019 and who had achieved pubertal status B3 or above, spontaneously or following oestrogen. All the girls underwent clinical evaluation, anthropometric measurements and underwent biochemical tests including screening tests for prediabetes/diabetes mellitus (DM) and other cardiometabolic risk factors. Data about puberty onset, growth hormone (GH) and oestrogen therapy were obtained retrospectively from history obtained from the girls or their caregivers or from available medical records. We excluded patients with DM, overt and uncorrected hypothyroidism or hyperthyroidism, those with celiac disease or inflammatory bowel disease, chronic liver diseases or chronic kidney diseases and those with very rare karyotypic variants like ring chromosome or structural variants of X chromosome. The study was approved by the Institutional Ethics Committee, and informed written consent or assent was obtained from all participants and/or their guardians. The study design is outlined in Figure 1.

Measurement

Height (cm) was measured using wall-mounted Charder HM200PW stadiometer, and weight (kg) using electronic calibrated scale (Tanita, Japan, ModelHA521) and body mass index [BMI (kg/m^2)] was calculated from height and weight values measured using standard methods.[8,9] Calibrated sphygmomanometer using an appropriately sized cuff was used to measure systolic (SBP) and diastolic blood pressure (DBP), using the average of three separate readings. Pubertal status was determined from Tanner sexual maturity rating (SMR).[10] History regarding spontaneous onset of thelarche, menarche and time of initiation of oestrogen–progestin therapy was retrieved from the subject's hospital records. Waist circumference (WC) was measured at the midpoint between the lowest part of costal margins and the iliac crests and hip circumference at the largest circumference around the buttocks using a non-stretchable measuring tape to the nearest 0.1 cm with the subject wearing minimal clothing without belts and standing straight at minimal respiration. WC–hip ratio (WHR) and WC–height ratio (WHtR) were calculated.[11] All anthropometric measurements were done in fasting state at the same visit. Each measurement was done in triplicate, and the average of the three consecutive measurements values was taken for final input and analysis.

Definitions

Categorization of BMI for those above 18 years of age was done according to Asian-Pacific cut-offs, as underweight (<18.5 kg/m^2), normal weight (18.5–22.9 kg/m^2), overweight (23–24.9 kg/m^2) and obese (> =25 kg/m^2), and standard deviation scores (SDS) for height, weight and BMI were calculated from IAP 2015 percentile charts for those below 18 years of age.[12] Values of WC >80 cm and or >90th percentiles for age-matched Indian girls, and WHR >0.85 and WHtR >0.45 were interpreted as high.[11,13,14] Hypertension was defined as SBP > =130 and/or DBP >=85 mm H g for >16 years and >90th centile of SBP and/or DBP from age-and-height-matched percentile charts for those younger or antihypertensive use.[15] Girls were classified into three groups based on their pubertal onset and progression. Those with spontaneous onset of thelarche before 12 years of age with spontaneous progression to menarche within two years of thelarche were considered to be having spontaneous puberty (SPONTpub). Those with no signs of puberty by age 12 years and raised follicle-stimulating hormone (FSH) were considered to be having absent puberty (ABSpub). Those who had spontaneous thelarche but did not progress to menarche within two years of thelarche or had spontaneous menarche but cessation of menstrual cycles within few years and had raised FSH were considered to be having pubertal arrest (ARRpub). Delayed oestrogen initiation was defined as those with ABSpub (or ARRpub diagnosed before 12 years) in whom oestrogen therapy was not initiated by 12 years of age (DELYDestr). Diabetes and prediabetes were defined using ADA 2017 criteria.[16] Impaired fasting glucose (IFG) was defined as FBG > =100 mg/dl; impaired glucose tolerance (IGT) as OGTT-PPBG > =140 mg/dl and Hba1c% in prediabetes range as Hba1c between 5.7% and 6.5%. Dyslipidaemia was defined as LDL-cholesterol > =130, TG >=150 mg/dl or HDL-cholesterol <50 mg/dl.[17] Hepatic steatosis was defined as the presence of any grade of fatty liver seen on ultrasonography.

Assays

Blood samples were obtained after an 8-h overnight fast for lipid profile, fasting plasma glucose (FPG) and liver function tests (LFT). FPG, post-prandial blood glucose after 2 h of taking 75 g anhydrous glucose orally (OGTT-PPG), LFT and

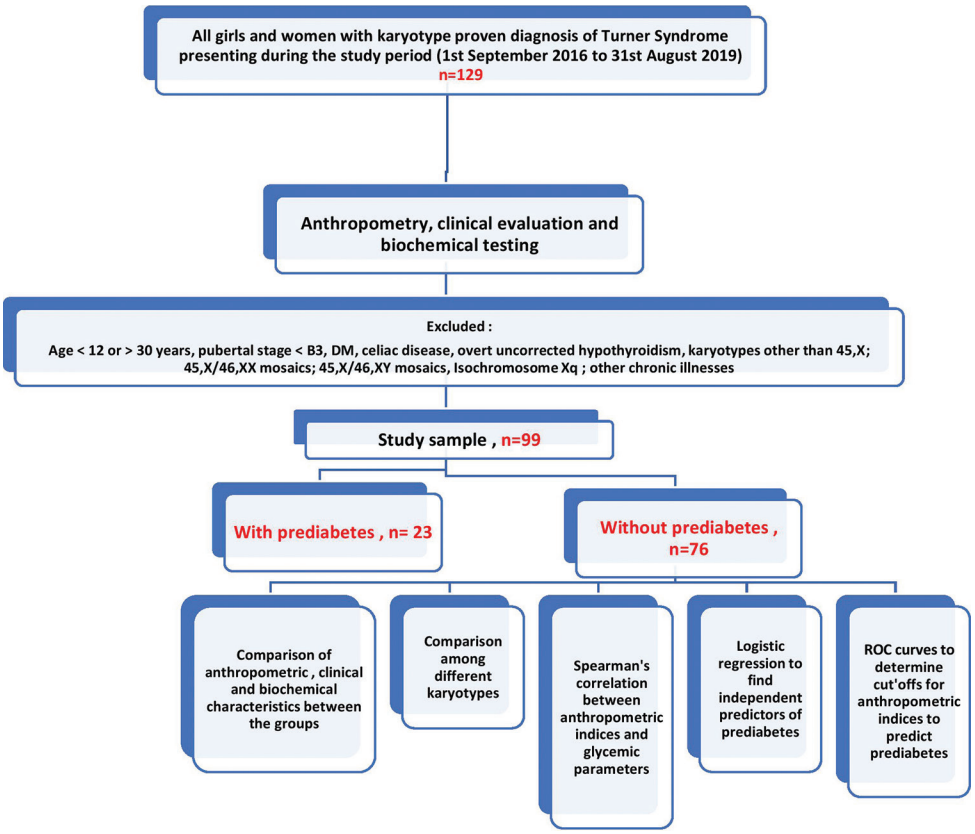

Figure 1: Study design

lipid profile were analysed using commercially available kits with an automated biochemistry analyser Cobas Integra 400 Plus; Roche Diagnostics. HbA1c% was measured using HPLC via BIORAD D10 analyser (BIO-RAD, India, CV: 2.8%). Transabdominal ultrasonography for detecting hepatosteatosis was done using a Philips Affinity 70G model machine, with a 1–8 MHz curvilinear ultrasound probe. Karyotype analysis was performed according to the guidelines from the International System for Human Cytogenetic Nomenclature (ISCN, 2005) on 30 metaphase cells using the GTG banding technique.[1]

Statistical methods

Statistical analyses were done using SPSS Statistics v. 28. Quantitative variables were expressed as mean (SD) or median (minimum–maximum). Categorical variables were expressed in terms of frequency. Comparison between two groups was done using student's t test or Mann-Whitney U test for normally or non-normally distributed quantitative variables respectively, and using Chi-square test for categorical variables. ANOVA or Kruskal–Wallis with *post hoc* comparison using Tukey's method was done for comparing multiple karyotype groups. Correlations were analysed using Spearman's rho. Multiple logistic regression to identify the independent predictors of prediabetes was done in two steps—univariate analysis (step 1) followed by multivariate analysis using independent variables which were found to be significant ($P < 0.05$) or suggestive of significance ($P < 0.100$) in step 1. P value less than 0.05 was considered as significant. ROC curves were constructed, and cut-offs were determined using Youden's index in conjunction with ROC analysis. AUC >=0.5 was considered significant.

Ethical Clearance Statement

The current study is approved by the Institutional Ethics Committee of IPGME&R, Kolkata held on 28/01/2017, memo no IPGME&R/IEC/2017/098 dated 06/02/2017. Written informed consent was obtained for participation in the study and use of the patient data for research and educational purposes from the participants and/or their parents and assent was obtained for those below 18 years of age and hat the procedures follow the guidelines laid down in Declaration of Helsinki (1964).

Results

Clinical and biochemical characteristics of the study cohort

Out of 129 girls with TS that visited Endocrinology OPD during the study period, a total of n = 99 girls aged were finally included after application of inclusion and exclusion criteria. The mean age of the girls was 18.33+/- 3.78 years. Prediabetes was seen in 23 patients, thus the prevalence of prediabetes among adolescents and young adults with TS in our cohort was 23.23%. Out of the 129 girls, six girls had DM and were excluded from the current study. Dyslipidaemia was seen in n = 72,72.7% and hepatic steatosis in n = 27,27.3%.

The mean body weight was 37.57+/- 7.97 kg, and mean BMI was 20.57+/- 3.71 kg/m^2. The median height-SDS, weight-SDS and BMI-SDS were -3.31 [-5.05 to -1.79], 1.28 [1.24 to 3] and -0.03 [-2.52 to 3.01], respectively. Median WHR was 0.87[0.75 to 1.12], and median WHtR was 0.63[0.53 to 0.69]. Majority (n = 54, 54.5%) had normal BMI, n = 16,16.2% were overweight, n = 15,15.2% were obese, whereas n = 14,14.1% were underweight for age. High WC was seen in n = 64,64.6% of the girls, high WHR in n = 56, 56.6%, while high WHtR was seen in all (100%) the patients.

Out of the 23 girls with TS and prediabetes, n = 10 (43.4%) had abnormality in two out of the three parameters (eight had IGT and Hba1c% in prediabetes range, one each had IFG + IGT and IFG + Hba1c% in prediabetes range). Another ten girls had abnormality detected in any one of the three parameters. OGTT-PPG alone could detect n = 5 cases, FPG alone was abnormal in n = 3 cases, and Hba1c% alone was abnormal in n = 2 cases. Out of the eighteen girls with IGT, thirteen had isolated IGT (iIGT (IGT + normal FBG), whereas four had IGT + IFG. Abnormality in all three parameters (FBG, OGTT-PPBG and Hba1c%) was seen in three cases.

Comparison of TS girls with and without prediabetes

Compared to those without prediabetes (n = 76), those with prediabetes (n = 23) had higher mean of body weight (kg), BMI (kg/m^2) and WC in cm (42.02+/- 5.83 vs 36.22+/-8.07, 22.77+/- 2.78 vs 19.91+/- 3.72, 85.26+/- 3.52 vs 81.08+/- 4.59 for TS with and without prediabetes, respectively, $p_{all} < 0.003$). TS with prediabetes had higher median BMI-SDS (median[IQR] 0.5[0.9] vs -0.34[1.27], $P < 0.001$) and weight-SDS (median[IQR] 0.99[0.66] vs 1.48[0.9], $P < 0.001$) than those without prediabetes though HT-SDS was similar in both. Those with prediabetes had higher median WHtR and waist–hip ratio WHR (0.64 [0.6–0.69] vs 0.59[0.56–0.66], 0.9[0.84–1.12] vs 0.85[0.75–1.01] for those with and without prediabetes, respectively, $p_{both} < 0.001$). Those with prediabetes had significantly higher FPG (mg/dl), OGTT-PPG (mg/dl), HbA1c%, LDL-c, triglycerides, higher prevalence of hepatic steatosis and lower HDL-c compared to those without prediabetes (pall < 0.03, Table 1). There were no differences in the karyotype distribution, prevalence of hypertension, thyroid dysfunction, family history of diabetes, duration of oestrogen therapy prior to metabolic evaluation or proportion of girls having received GH therapy between the two groups.

Differences in pubertal status and oestrogen therapy between TS with and without prediabetes

Those with prediabetes had higher prevalence of absent puberty (ABSpub) compared to those without prediabetes (87% vs 40.8% for TS with and without prediabetes, $P < 0.001$). None of those with prediabetes had spontaneous puberty, while n = 15, 19.7% of those without prediabetes had spontaneous onset and progression of puberty (SPONTpub). A total of 13% of those with prediabetes and 39.5% of those without prediabetes had pubertal arrest (ARRpub). The median age of initiation of oestrogen in those with ABSpub (n = 51) was 16 years (12–17). Among the girls with prediabetes who had ABSpub (n = 20), all had delayed oestrogen initiation beyond 12 years (DELYDestr, n = 20,100%). This was significantly higher than the proportion of DELYDestr among those without prediabetes (n = 8, 28.6%). The median delay in the age of oestrogen initiation in those with prediabetes was significantly higher than those without prediabetes (4[2–5] vs 1[0–2] in those with and without prediabetes, $P = 0.03$).

Subgroup analysis by age group

We categorized the study population into three age groups, adolescents (aged between 12 and 18 years, n = 56,56.6%), young adults (18.1–25 years, n = 40, 40.4%) and adults (25.1–30 years, n = 3,3%).The prevalence of prediabetes was slightly higher among young adults (n = 13,32.5%) and adults (n = 1,33.4%) with TS compared to adolescents (n = 9, 16.1%); however, these differences were not statistically significant ($P = 0.16$). There were no differences in the prevalence of prediabetes identified by IFG (n = 5,4 and 0), IGT (n = 7,10 and 0) or Hba1c% criteria (n = 6,7 and 1) (pall > 0.4) among the three age groups.

Subgroup analysis by GH therapy

A total of 36 girls had received GH therapy, of whom n = 11 (30.56%) had prediabetes. The prevalence of prediabetes among GH recipients was not significantly different from those who did not receive GH (n = 12/63,19%) ($P = 0.221$). Among those having received GH (n = 36), GH initiation was at a significantly later age in those with prediabetes (n = 11,30.56%) than those without prediabetes (n = 25,69.445) (13.5[11–15] vs 7.9[7–8], $P = 0.001$). The duration of GH therapy prior to metabolic evaluation was also shorter in those with prediabetes (2[0.2–6.5] vs 5[3–7], $P = 0.003$).

We found no differences in the mean height or in median height-SDS between those who received GH and those who did not (134.19+/- 6.05 vs 135.14+/- 5.19. and -3.3 [-4.87 to -2.19] vs -3.32 [-5.05 to -1.79] for GH recipients vs non-recipients, $p_{both} > 0.5$). However, in our cohort, the girls on GH were younger than those who were not (16.96+- 3.64 vs 19.1+- 3.68, $P = 0.02$). The median age of GH initiation was 9 [5–15], and the median duration of GH therapy was 4.5 years [0.25–8]. Height measurement for the current study was done only once which means that the girls were at different points of time during GH therapy and in different stages of puberty at the time when the height was measured.

Subgroup analysis by karyotype

The karyotype distribution of our cohort was n = 45, for 45, X; n = 30 for 45, X/46, XX; n = 20 for isochromosome Xq (n = 7 for 46, X, iXq and n = 13 for 45, X/46, X, iXq) and n = 4, for 45, X/46, XY. We had excluded cases with structural aberrations of X like ring chromosome and Xp deletion from our study. Upon ANOVA analysis, we found no differences in age,

Table 1: Comparison of girls with Turner syndrome with and without prediabetes

Parameter	Prediabetes (*n*=23)	Without prediabetes/ diabetes mellitus (*n*=76)	Whole group (*n*=99)
Age (years)	19.52 (4.33)	18.01 (3.61)	18.33 (3.75)
Height (cm)	135.78 (5.31)	134.49 (5.56)	134.79 (5.51)
Height-SDS[$]	-3.07[-4.5 to - 1.79]	-3.45 [-5.01 to -1.91]	
Body weight (kg)*	42.02 (5.83)	36.22 (8.07)	37.57 (7.97)
Body weight SDS[$]	0.99 [-0.35 to 1.81]	1.48 [-1.24 to 3]	
BMI (kg/m^2)*	22.77 (2.78)	19.91 (3.72)	20.57 (3.71)
BMI-SDS[$]	0.5 [-0.89 to 2.61]	-0.33 [-2.5 to 3]	
Waist circumference (cm)*	85.26 (3.52)	81.08 (4.59)	82.05 (4.70)
Waist–hip ratio[$]*	0.9[0.84–1.12]	0.85[0.75–1.01]	0.87[0.75–1.12]
Waist–height ratio[$]*	0.64[0.6–0.69]	0.59[0.56–0.66]	0.63[0.53–0.69]
Karyotype			
45, X	13 (56.5%)	32 (42.1%)	45 (45.45%)
45, X/46, XX	5 (21.7%)	25 (32.9%)	30 (30.3%)
Isochromosome Xq	5 (21.7%)	15 (19.7%)	20 (20.2%)
45, X/46, XY	0	4 (5.3%)	4 (4.4%)
Pubertal status[#]			
Absent puberty (ABSpub)	20 (87%)	31 (40.8%)	51 (51.5%)
Spontaneous onset with pubertal arrest (ARRpub)	3 (13%)	30 (39.5%)	33 (33.33%)
Spontaneous onset and progression of puberty (SPONTpub)	0	15 (19.7%)	15 (15.15%)
Delay in oestrogen initiation beyond 12 years* (among those with ABSpub, *n*=51)	20 (100%)	8 (28.6%)	28 (28.28%)
Duration of oestrogen therapy prior to metabolic evaluation[$]*	2.35 (1.92)	1.97 (1.22)	2.16 (1.08)
FPG (mg/dl)*	89.86 (14.53)	81.21 (7.99)	83.22 (10.48)
PPG (mg/dl)*	146.56 (16.99)	104.92 (15.92)	114.36 (23.59)
Hba1c%*	5.65 (0.41)	5.07 (0.26)	5.21 (0.39)
Hypertension	3 (13%)	6 (7.9%)	9 (9.09%)
Dyslipidaemia*	23 (100%)	49 (64.5%)	76 (76.76%)
Thyroid dysfunction			
Family h/o diabetes	8 (34.8%)	19 (25%)	27 (27.3%)
Nil	8 (34.8%)	31 (40.8%)	39 (39.39%)
Overt hypothyroidism, on LT4	7 (30.4%)	15 (19.7%)	22 (2.22%)
Subclinical hypothyroidism, on LT4	5 (21.7%)	14 (18.4%)	19 (19.19%)
Subclinical hypothyroidism, not on LT4	3 (13%)	15 (19.7%)	18 (18.18%)
Hyperthyroidism, in remission	0	1 (1.3%)	1 (1.01%)
LDL-cholesterol*	147.03 (40.22)	117.39 (32.86)	124.27 (36.72)
HDL-cholesterol*	41.83 (9.98)	50.07 (13.64)	48.15 (13.30)
Triglycerides*	199.52 (50.41)	127.92 (50.44)	144.56 (58.66)
Hepatic steatosis*	11 (47.8%)	16 (21.1%)	27 (27.27%)
Grade 1*	2 (8.7%)	11 (14.4%)	13 (13.1%)
Grade 2*	7 (30.4%)	4 (5.3%)	11 (11.1%)
Grade 3*	2 (8.7%)	1 (1.3%)	3 (3%)
ALT (U/L)*	81.85 (35.09)	31.07 (19.21)	41.55 (30.97)
AST (U/L)*	83 (36.97)	35.72 (17.70)	46.32 (30.42)
Received GH	11 (47.8%)	25 (32.9%)	36 (36.36%)
Age of initiation of GH[$]*	13.5[11–15]	7.9[7–9]	9[5–15]
Duration of GH therapy prior to metabolic evaluation[$]*	2[0.2–6.5]	5[3–7]	4.5[0.2–8]

*Denotes significant differences between those with and without prediabetes, $P<0.05$. [$]Denotes median [range] values for parameters, [#]all girls had pubertal status B3 and above, spontaneously or with oestrogen, LT4=levothyroxine, GH=growth hormone

anthropometric parameters and metabolic parameters among the four karyotype groups [Table 2]. Spontaneous puberty was significantly higher among 45, X/46, XX mosaics (n = 9,30%) followed by isochromosomes (n = 3,15%) and 45, X (n = 3, 6.67%). All of the four girls with 45, X/46, XY mosaicism had absent puberty.

Prevalence of hepatic steatosis and comparison of parameters between those with and without hepatic steatosis

Out of the n = 27 cases of liver steatosis seen on USG, majority had grade 1 fatty liver (n = 13,13.1%) followed by grade 2 steatosis (n = 11,11.1%). Three girls had grade 3 steatosis.

Table 2: Comparison of anthropometric and biochemical parameters among the different karyotypes of Turner syndrome

	45, X (*n*=45)	45, X/46, XX (*n*=30)	Isochromosome Xq 46, X, iXq or 45, X/46, X, iXq (*n*=20)	45, X/46, XY (*n*=4)
Age (years)	18.36 (4.12)	18.01 (3.81)	19 (3.04)	17 (3.92)
Height (cm)	134.29 (5.47)	134.61 (6.09)	135.79 (4.32)	136.75 (7.64)
Weight (kg)	37.55 (7.71)	36.59 (9.54)	39.18 (6.22)	37.12 (7.28)
BMI (kg/m^2)	20.71 (3.47)	20.09 (4.7)	21.18 (2.76)	19.68 (2.37)
Waist circumference (cm)	81.73 (4.75)	82.23 (4.45)	82.75 (5.02)	80.75 (5.56)
Waist–height ratio[$]	0.61[0.56–0.69]	0.6[0.56–0.66]	0.62[0.56–0.68]	0.6 (0.57–0.61)
Waist–hip ratio[$]	0.86 (0.07)	0.86 (0.05)	0.86 (0.07)	0.82 (0.02)
Prediabetes[$]	13 (28.9%)	5 (16.7%)	5 (25%)	0
Pubertal status[#]*				
Absent puberty	25 (55.56%)	13 (43.33%)	9 (45%)	4 (100%)
Spontaneous onset with pubertal arrest	17 (37.78%)	8 (26.67%)	8 (40%)	0
Spontaneous onset and progression of puberty	3 (6.67%)	9 (30%)	3 (15%)	0
Delay in oestrogen initiation beyond 12 years (among those with ABSpub, *n*=51)	3[0–5]	5[1–5]	4[1–5]	0
FPG (mg/dl)	84.3 (10.75)	82.94 (17.82)	80.86 (11.7)	85 (10.68)
Plasma glucose (mg/dl) after 75 g glucose	114.08 (25.35)	116.43 (23.97)	113.44 (20.88)	106.5 (17.46)
Hba1c%	5.22 (0.44)	5.14 (0.32)	5.31 (0.38)	5.03 (0.13)
Hypertension	3 (33.3%)	2 (22.2%)	3 (33.3%)	1 (11.1%)
Thyroid dysfunction				
Nil	20 (44.4%)	14 (46.7%)	3 (15%)	2 (50%)
Overt hypothyroidism, on LT4	10 (22.2%)	3 (10%)	9 (45%)	0
Subclinical hypothyroidism, on LT4	9 (20%)	6 (20%)	3 (15%)	1 (5.3%)
Subclinical hypothyroidism, not on LT4	6 (13.3%)	6 (20%)	5 (25%)	1 (25%)
Hyperthyroidism, in remission	0	1	0	0
LDL-c	118.56 (35.94)	127.37 (39.36)	136.2 (31.27)	105.75 (43.7)
HDL-c	49.45 (14.47)	46.47 (10.55)	46.55 (15.36)	54.25 (4.03)
Triglycerides	144.05 (62.32)	147.83 (60.2)	147.6 (51.61)	110.5 (42.91)
Hepatic steatosis	12 (26.7%)	6 (20%)	8 (40%)	1 (25%)
Received GH	19 (42.2%)	10 (33.3%)	5 (25%)	2 (50%)

*Denotes significant differences among the four groups on Chi-square or ANOVA. Parameters are expressed as mean (SD) or median (minimum–maximum) for parametric and non-parametric quantitative parameters, respectively, or as *n* (%) for categorical variables

Grade 2 steatosis was significantly higher in those with prediabetes (30.4% vs 5.3%, $P < 0.001$), who also had higher ALT and AST levels than those without prediabetes.

Compared to those without liver steatosis, those with steatosis (n = 27) had higher body weight (41.91+/- 6.18 vs 35.04+/- 7.99), HbA1c% (5.41% +/- 0.48 vs 5.13% +/- 0.32), higher prevalence of prediabetes (40.7% vs 16.7%) and a significantly later age of starting GH (11.2+/- 3.23 vs 9.30+/- 2.24 years) (pall < 0.03) apart from having higher ALT (66.08+/- 30.64 vs 24.31+/- 16.12) and AST (70.19+/- 29.65 vs 26.92+/- 11.21) levels (U/L). However, there were no differences with regard to the percentage of girls on oestrogen or GH, the pubertal status or the delay in oestrogen initiation between those with and without liver steatosis.

Correlation

There was a significant correlation of FPG, OGTT-PPG and Hba1c% with body weight (Spearman's rho = 0.29, 0.42 and 0.52, respectively, $p_{all} < 0.03$), BMI (Spearman's rho = 0.27, 0.39 and 0.49, respectively, $p_{all} < 0.003$), WC (Spearman's rho = 0.34, 0.46 and 0.33, respectively, $p_{all} < 0.004$) and WHR (Spearman's rho = 0.32,0.42 and 0.29, respectively, $p_{all} < 0.004$). FPG and OGTT-PPG also correlated with WHtR (Spearman's rho = 0.22 and 0.3, respectively, $p_{both} < 0.03$). There was a correlation of the delay in oestrogen initiation with OGTT-PPG and serum triglycerides (Spearman's rho = 0.69 and 0.52, respectively, $p_{both} < 0.004$).

Logistic regression

After multiple logistic regression, in a model using age, karyotype, pubertal status, BMI and WHR as independent variables, we found three independent predictors for prediabetes in TS, namely BMI, WHR and pubertal status. BMI (OR: 1.27[1.03–1.57]) and WHR (OR: 1.18 [1.04–1.34])], pboth < 0.02) were positive predictors, whereas spontaneous puberty (SPONTpub) was a negative predictor (OR: 0.0[0.02–0.38], $P = 0.001$) for the occurrence of prediabetes.

ROC analysis

ROC curves were drawn for BMI, WC and WHR [Figure 2 and Table 3]. The AUROC was the highest for WHR (0.81,0.72–0.89) followed by WC (0.76, 0.66–0.86) and BMI (0.73, 0.63–0.84) and WHtR (0.70, 0.57–0.82) in predicting prediabetes. BMI had the highest sensitivity [cut-off:

Table 3: AUROC with C.I. and cut-offs of different anthropometric parameters in predicting prediabetes in Turner syndrome*

Parameter	AUROC (%)	C.I.	*P*	Cut-off	Sensitivity	Specificity
BMI (kg/m^2)	73.1	62.5–83.6	0.001	21.04	82.6	62.2
Waist circumference (cm)	75.7	65.5–86	<0.001	83.5	73.9	67.6
Waist–hip ratio	80.7	71.9–89.4	<0.001	0.89	73.9	78.4
Waist–height ratio	69.6	57.1–82.2	0.005	0.62	69.6	64.9

*AUROC=area under receiver operating characteristic curve, C.I. = confidence interval

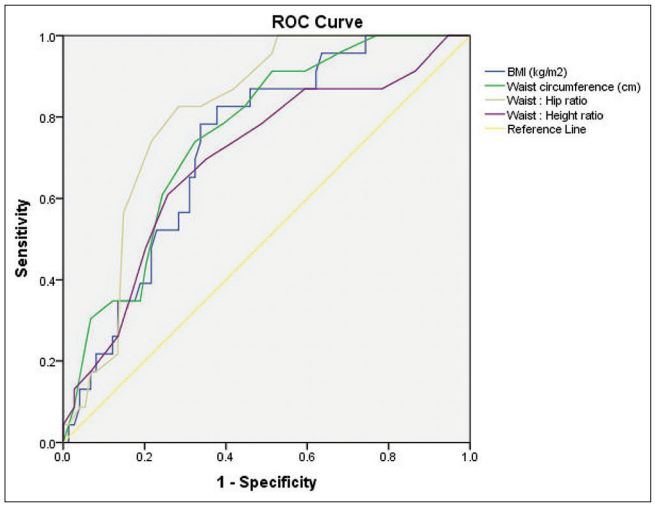

Figure 2: ROC curves for different anthropometric indices for predicting prediabetes in Turner syndrome

21.04 kg/m^2 (sensitivity: 82.6%, specificity: 62.2%)], and WHR had the highest specificity [cut-off: 0.89 (sensitivity: 73.9%, specificity 78.4%)] in predicting prediabetes.

Discussion

In the current study, out of 129 girls and women with TS, we studied 99 girls and women aged between 12 and 30 years who had achieved pubertal status of at least B3 and did not have DM. TS has been found to increase not only the risk of T2DM but also T1DM, albeit to a lesser extent than T2DM.[18] However, several clinical studies in adult population have shown gradually progressive, adult-onset glucose intolerance in TS.[18-20] Studies have reported abnormal glucose metabolism in up to 70% of girls with TS. The prevalence of diabetes has been reported to be anywhere between 5 and 25% in different studies.[19,21] We had excluded TS with DM from our study; however, we encountered six patients with T2DM out of 129 patients, which corroborates with the existing literature.

There is lesser data on the prevalence of prediabetes in TS. The prevalence of prediabetes in our cohort was 23.23%. This is higher than the previously reported prevalence of prediabetes among Indian adolescent girls, ranging between 6 and 12%.[22-24] The prevalence of prediabetes among young and middle-aged adults in India conducted using a large-scale demographic and health survey in 2015–2016 was 5.57%. In the same survey, the prevalence of prediabetes among those aged 18–25 years was 4.56%.[25] In our study, there was a slightly higher prevalence of prediabetes among young adults (32.5%) and adults (33.3%) compared to adolescents (16.1%) with TS, but the differences were not statistically significant. We did not find any differences in the prevalence of prediabetes identified by IFG, IGT or Hba1c% among the different age groups. We also did not find age to be an independent predictor for prediabetes in TS. The study by Cicognani *et al*. found that measures of carbohydrate tolerance improved between 12 and 16 years which the authors attributed to lack of oestrogen release.[26] Another longitudinal study by Lebenthal *et al*. found age to be associated with evolution of hypertension, impaired glucose tolerance and abnormal lipid profile and a significant change in BMI percentiles over time.[27] We did not have longitudinal follow-up data of our patients, and the numbers were small when categorized into the different age groups, specially adults over 25 years. Also, the girls in our study were started on oestrogen if they failed to have spontaneous onset of puberty by 12–13 years of age, following current guidelines, except those presenting later to us. Thus, the effects of lack of oestrogen release were not prominently seen.

We had used FPG, OGTT-PPG as well as Hba1c% to screen our patients for prediabetes/DM. Majority of the cases of prediabetes had abnormality in more than one of the three parameters. However, ten cases had an abnormality in only one of the parameters. OGTT-PPG alone detected an additional five cases of prediabetes who had normal FPG and Hba1c% values. Choi *et al*. had used OGTT and insulin sensitivity indices in their study and reported eighteen cases with impaired glucose tolerance (IGT) in their cohort of 118 patients.[20] Current guidelines recommend annual assessment of BMI and FPG testing starting from 10 years of age.[1] We found OGTT-PPG to detect several additional cases of prediabetes who had normal FPG and HbA1c% values. In the recent meta-analysis by Liu *et al.*, the authors found that on long-term follow-up, the incidence of type 2 diabetes was lower in prediabetes with isolated—IGT (IGT with normal FBG) than those with IGT along with IFG, both of which were higher than in the normoglycaemic group.[28] We found thirteen girls with IGT with normal FBG and four girls with IGT + IFG. While we plan their longitudinal follow-up, it would be interesting to note if these two groups of girls with TS and prediabetes follow different trajectories for the development of DM.

In our study, we found that while majority of the girls with prediabetes showed abnormalities in two or more of the three glycaemic parameters, ten cases had abnormality in only one out of the three. Five out of these ten girls had abnormal

OGTT-PPG, and Hba1c% alone was abnormal in only two cases. In a recent study by Sheanon *et al.*, TS girls had increased prevalence of impaired fasting glucose and impaired glucose but similar Hba1c as healthy controls. However, in spite of having similar Hba1c, girls with TS had poorer results on studies of β cell function.[5] Current guidelines recommend measuring FBG and Hba1c% to screen for dysglycaemia in TS.[1] Given the high cost of Hba1c%, it might be prudent to monitor FBG and OGTT-PPBG rather than HbA1c% to screen for prediabetes/diabetes in TS in resource-constrained settings, like most centres in India.

We found girls with prediabetes to be having higher BMI and also BMI-SDS compared to those without prediabetes. There has been a suggestion that in smaller samples, BMI-SDS, being adjusted for age might be a better parameter for comparison between groups, and prior studies on children and adolescents with TS had compared them to age and BMI-SDS matched healthy girls and found higher cardiometabolic risk and reduced beta cell function in TS.[29] Majority of our girls had normal BMI as per age-specific BMI charts for Indian girls, and the prevalence of overweight-obesity was only 31.4.%. All the girls in our study are from India or Bangladesh. South-East Asians are known to run a high risk for insulin resistance and cardiometabolic risk, even in those who are non-obese, and therefore, belonging to a high-risk ethnicity could be an additive factor to the adverse metabolic risks imparted due to TS.[30,31]

Those with prediabetes had significantly higher BMI and markers of central obesity, including waist circumference, waist–height ratio and waist–hip ratio. All these parameters had significant association with prediabetes on univariate analysis. BMI had the highest sensitivity for predicting prediabetes, and the cut-off for predicting prediabetes was 21.04 kg/m^2. While South Asian cut-offs for BMI to define overweight or obesity are lower than Caucasians, our BMI cut-off to predict prediabetes in TS among South Asians is even lower than the South Asian cut-off. Most of the girls with normal or low BMI had WC, WHR and WHtR higher than the South Asian cut-offs for central obesity and high cardiometabolic risk.[11,13,32] This fact has also been seen in other studies focusing on anthropometric variables in TS.[33] Thus, girls with TS are predisposed to have high incidence of central obesity, insulin resistance and cardiometabolic risk.

Interestingly, although our BMI cut-off was lower, the cut-offs for waist circumference (83.5 cm), waist–hip ratio (0.89) and waist–height ratio (0.62) in predicting prediabetes in TS were higher than the cut-offs for those without TS. Possible reasons behind this could be the altered skeletal structure, scoliosis and sometimes lymphedema of girls with TS that could contribute to high values for WC as also shorter height in women with TS. Studies focusing on the body composition in girls and women with TS are warranted for a better understanding of the association between anthropometric parameters and cardiometabolic risk in women with TS.

We found waist–hip ratio to have the highest AUROC to predict prediabetes in TS, followed by waist circumference and BMI. Waist–hip ratio had the highest specificity for predicting prediabetes in TS, while the sensitivity was the highest for BMI. Waist–height ratio had the lowest sensitivity and specificity among the anthropometric indices. In a study from Central America, WHtR was found to be the best predictor for metabolic syndrome in adult women with TS.[33] Our cohort had included many post-pubertal girls who were yet to achieve their final height. Whether ethnic differences may contribute to our findings and whether a combination of anthropometric parameters of central obesity could improve the detection of high metabolic risk in TS remains an area for research. Nevertheless, our findings highlight the importance of frequent anthropometric measurements and testing for dysglycaemia in those with TS. Early intervention to prevent weight gain or central obesity is important in girls and women with TS.

We did not find any differences in the prevalence of prediabetes or its risk factors among the different karyotypes. Some studies have implicated certain karyotypes to have a higher risk for prediabetes or metabolic syndrome. Few studies have found that those with isochromosome Xq have a higher risk for diabetes and based on their gene expression profile, attributed this risk to haploinsufficiency of Xp and excess dosage of Xq- genes.[2,34] We have previously described a high prevalence of isochromosomes in our cohort of Turner syndrome from East India.[35] However, in our current study, we did not find any differences in the prevalence of prediabetes among classic TS, 45, X/46, XX mosaic TS or isochromosomes. GAD 65 Ab and anti-IA2 Ab were measured for those with DM, who were not included in the current study, and were found to be negative in all. The high risk for autoimmunity among isochromosomes is well-established.[36,37] Although TS has been associated with a higher risk for T1DM in addition to T2DM, but anti-islet cell antibodies have not been isolated at a higher frequency in TS compared to the general population.[38] An UK-based registry reported a higher prevalence of prediabetes in those with ring chromosomes.[39] Due to very small numbers in our cohort (n = 2), we excluded TS with ring chromosomes from our current study on glycaemic profile in TS. Some studies have shown a higher prevalence of obesity and clustering of metabolic risk factors among classic TS compared to other karyotypes.[27] We found a high prevalence of overweight-obesity and increased central obesity indices in all TS, irrespective of the underlying karyotype.

We found a higher prevalence of USG detected liver steatosis in those with prediabetes (47.8%) compared to those without prediabetes (21.1%). The prevalence of grade 2 liver steatosis and the values of ALT and AST were particularly higher in those with prediabetes. Up to 20–25% of girls and 40% of adult women with TS have transaminitis usually in the absence of signs and symptoms of liver disease.[40,41] The exact aetiology is unknown, though fatty liver disease, autoimmune hepatitis and abnormalities in hepatic microvasculature have all been proposed. In our study, we found a high prevalence of hepatic

steatosis with elevated liver enzymes, especially in those with prediabetes. Majority had grade 1 fatty liver. Turner syndrome is a rare cause of liver cirrhosis though prevalence higher than the general population has been noticed.[42] Those with steatosis had higher HbA1c% levels and delayed GH initiation, but we did not find any differences in oestrogen use or pubertal status between those with and without liver steatosis. Although pharmacologic oestrogen use has been associated with liver enzyme elevations, but over the long term, oestrogen treatment normalizes hepatic enzymes. We did not have pre-oestrogen therapy values for liver enzymes or longitudinal follow-up data of those with steatosis or transaminitis. Since we did not have gamma glutamyl transaminase (GGT) and platelet values of all the girls with TS, we could not calculate indices or risk scores for steatosis or fibrosis. We had used USG for the detection of fatty liver which, however, has its own drawbacks, including poor sensitivity at low levels of steatosis <20%–30% steatosis and in very obese patients.[43,44] Additionally, semi-quantitative grades of fatty liver seen on USG are fraught with inter-observer differences and errors, and we did not use validated quantitative USG scores like Hamaguchi index or US-Fatty Liver Index. Future systematic studies focusing on hepatic steatosis, steatohepatitis and liver cirrhosis are warranted to throw more light on non-alcoholic fatty liver disease (NAFLD) in TS.

In our study, among recipients of GH (n = 36), the prevalence of prediabetes was 30.56%, and this was marginally higher than that in those who had never received GH. The impact of GH therapy on glycaemic profile in TS remains unclear, with different studies reporting negative, neutral and positive effects on insulin sensitivity and glucose tolerance.[45-47] Interestingly, we found that among recipients of GH who had prediabetes, the initiation of GH was significantly delayed (age at GH start was 13.5 vs 7.9 years in those with and without prediabetes) and for a shorter duration (2 years vs 5 years) compared to those who had normoglycaemia. A prior study showed that while GH therapy reduces insulin sensitivity in the initial few months, it stabilizes later on, and with prolonged therapy, there is a relative improvement in insulin sensitivity due to favourable changes in body composition.[48] Thus, early initiation and prolonged GH therapy could have a favourable effect on the glycaemic profile of girls and women with TS. Since the age of presentation of TS is often late in our country, if a decision to initiate GH at a later age is taken, close monitoring of the glycaemic status becomes necessary.

In our cohort, none of the girls with prediabetes had spontaneous onset and progression of puberty. All of them either had ovarian failure demonstrated by either the absence of pubertal onset or spontaneous onset of puberty with pubertal arrest within few years. The prevalence of absence of pubertal onset was significantly higher than those without prediabetes. Also, among those with absent puberty, the age of oestrogen initiation was significantly delayed in those having prediabetes. Animal models have demonstrated antiapoptotic action of oestrogen on β-cells.[49] In humans, a protective effect of hormone replacement therapy with oestrogen on the development of DM has been demonstrated in postmenopausal women.[50] Several studies have shown that oestrogen therapy does not impact glucose tolerance in patients with TS.[51,52] In a study by Gravholt *et al.*, the authors suggested that delayed initiation of oestrogen in their study might explain the lack of demonstration of oestrogens on glucose tolerance in women with TS.[53] In our country, delayed presentation and a concurrent delay in oestrogen are common problems.[37] Apart from psychological consequences and effects on bone, this could have adverse metabolic consequences as well.

To the best of our knowledge, this is the largest study of metabolic profile in TS in the country. One important limitation is that we did not study a group of age and pubertal status matched healthy Indian girls who could serve as controls for the girls with TS. Effects of GH and oestrogen on the glycaemic and metabolic profile of girls with TS remain controversial and need systematic longitudinal studies. Our study was limited in being cross-sectional in design with anthropometric and glycaemic parameters measured only once during this study. Longitudinal studies focusing on changes in metabolic parameters of girls before and after GH and oestrogen therapy form an important area for future research in TS. Other important limitations of our study include lack of data on indices of insulin sensitivity, beta cell function and body composition analysis of the girls with TS.

TS has a high prevalence of prediabetes, irrespective of the underlying karyotype, and the risk might be higher in South Asian girls with TS. It is necessary to assess anthropometric markers for central obesity like waist circumference and waist–hip ratio, in addition to BMI, of all adolescents and adults with TS. Screening for prediabetes/DM in TS should include not only fasting but also plasma glucose after oral glucose challenge tests and Hba1c%. Hepatic steatosis is common in girls with TS and prediabetes. Delay in GH and oestrogen initiation may increase the risk for prediabetes in TS. Those with delayed presentation should be closely monitored for dysglycaemia when started on GH and/or oestrogen.

Acknowledgement

Chiranjit Bose wants to acknowledge the Department of Science and Technologies, India, for his fellowship.

Financial support and sponsorship

Endocrine Society, Bengal for research grant.

Conflicts of interest

There are no conflicts of interest.

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