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Research Article

Analysis of Metabolic Features and Cardiovascular Risk Factors in a Group of Patients with Turner Syndrome

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Abstract

Objective: Patients with Turner Syndrome (TS) have an unfavorable cardiometabolic profile. It is aimed to determine the cardiometabolic risk factors and the effect of growth hormone therapy on cardiometabolic profile in a group of patients with Turner syndrome.

Methods: A total of 37 TS patients were included in the study. All data were collected from hospital files. Obesity, hypertension, glucose metabolism impairments, insulin resistance and dyslipidemia were obtained as cardiometabolic risk criteria. The effects of Growth Hormone (GH) treatment on cardiometabolic profile were also investigated.

Results: Metabolic impairments were detected in 48% of the studied girls in this cohort. Twenty-one percent of the patients had Impaired Fasting Glucose (IFG) and 20% of the patients had Impaired Glucose Tolerance (IGT). The prevalence of Insulin Resistance (IR) was 20% by OGTT. Dyslipidemia was detected in 27% patients. The Body Mass Index (BMI) in the patients treated with GH over than 3 years and in the patients started GH treatment before 10-years-old was significantly lower (p=0.036, p=0.018, respectively). HDL-C was significantly higher in patients treated with GH over than 3 years (p=0.041).

Conclusions: It is confirmed that cardiometabolic abnormalities are frequent in TS patients and duration of GH treatment (over than 3 years) has protective effect on lipid profile. Metabolic abnormalities should be carefully evaluated during the follow-up of patients with TS.

Keywords: Turner syndrome; Cardiometabolic risk factors; Growth hormone

Introduction

Turner Syndrome (TS) is associated with dyslipidemia, Insulin Resistance (IR), increased incidence of type 2 diabetes (T2DM), Hypertension (HT) and abdominal obesity which all contributes cardiovascular risk factors [1,2]. Epidemiological data indicates that adults with TS have a 2-fold risk of developing coronary artery disease and there is an associated 3-fold risk of mortality from Cardiovascular Diseases (CVDs) in this population [3,4]. Therefore, it is suggested that patients with TS should be followed up intermittently in terms of cardiovascular risk factors because of the increased risk of metabolic abnormalities mentioned above [5].

Since most of the data were collected from adult series, we aimed to investigate the cardiometabolic risk factors such as dyslipidemia, IR, T2DM, HT and obesity in a cohort of children and adolescents with TS to define the modality of onset cardiometabolic co-morbidities. We even investigated the effect of Growth Hormone (GH) treatment on cardiometabolic profile in children with TS.

Methods

Patients and data collection

The files of the 37 patients followed-up with TS were retrospectively scanned. Blood samples were taken following a 12-hour night starvation in all patients to assess the metabolic findings. Fasting Plasma Glucose (FPG), insulin, Total Cholesterol (TC), Low-Density Lipoprotein Cholesterol (LDL-C), High-Density Lipoprotein Cholesterol (HDL-C) and Triglyceride (TG) levels were measured. Dyslipidemia was evaluated according to the recommendations of Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents [6]. According to this high TC was defined as ≥200 mg/dL, high LDL-C as ≥130 mg/dL, high TG as ≥ 150 mg/dL and low HDL-C as <40 mg/dL.

Patients that were older than 10 years underwent a standard 75-g Oral Glucose Tolerance Test (OGTT) to define glucose metabolism impairments. Fasting glucose levels and 2h glucose levels were used for the diagnosis of Diabetes Mellitus (DM), Impaired Glucose Tolerance (IGT), and Impaired Fasting Glycemia (IFG) according to the American Diabetes Association (ADA) criteria [7]. Peak insulin levels above 150 $\mu U/mL$ during OGTT and/or insulin levels more than 75 μU/mL at 120 min of OGTT were assumed IR [8].

Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) were measured with appropriate protocol and HT defined as blood pressure values above the 95th percentile for height, age, and gender [9].

Biochemical analyses

Blood samples were analyzed for glucose, insulin, TC, TG, HDL-C and LDL-C using the standard procedures of the biochemistry

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Table 1: Distribution of the patients according to karyotype (n: 37).

Numeric (N: 25,67%)	Structural (N: 5,14%)	Numeric/structural (N: 7,19%)
45,X	46,X,I (X) (q10)	45,X/46,i (X) (q10)
45,X/46,XX	46,X,del (X) (q21.2)	45,X/46,X,I (Xq)
45,X/47,XXX	46,XX,del (X) (p22-pter)	45,X/46,X,idic (X) (p22.3)

laboratory of our hospital.

Calculations

Body Mass Index (BMI) was calculated by dividing weight (kg) by height squared (m^2). Patients with a BMI between 85-95 percent were defined as overweight and patients with a BMI over 95 percent as obese [10].

Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) index was calculated as the formula [fasting insulin ($\mu U/mL$) x fasting glucose (mg/dL)]/405. IR was assessed according to Turkish standards. HOMA-IR cut-off values were calculated to be 2.22 in the pre-pubertal period and 3.82 in the pubertal period [11].

Cardio metabolic risk criteria

Obesity, HT, IFG, IGT, DM, IR and dyslipidemia were obtained as cardiometabolic risk criteria.

The effects of GH treatment on cardiometabolic profile

Patients received recombinant human GH therapy at a dose of 0.047 mcg/kg per day. GH therapy was started as soon as growth failure had demonstrated and continued until little growth potential observed (growth velocity <2 cm/year) [12]. To compare the relationship between duration of taking GH therapy and cardiometabolic risk factors, patients were divided to two groups: duration of taking GH therapy less than 3 years and over than 3 years. Additionally, to compare the relationship between the age of onset GH treatment and cardiometabolic risk factors, patients were also divided to two groups: onset of GH treatment before 10 years-old and after 10-years-old.

Ethical aspects

The study was approved by the local ethics committee of the hospital and written informed consent was obtained from the participants and/or their family (approval number: 2017/591).

Statistical analysis

In addition to descriptive statistics (mean, standard deviation), Student's t test was used for group comparisons of normally distributed variables. Mann-Whitney U test was used for intergroup comparisons of non-normally distributed variables. Pearson correlation coefficient was used to measure the association between the variables. A P-value of <0.05 was considered statistically significant. Statistical analysis was performed using the program NCSS 2007 (Number Cruncher Statistical System, Kaysville, Utah, USA).

Results

Clinical characteristics and auxological data

The study group consisted of 37 patients with TS, 57% (n:21) with 45, X monosomy, 11% (n:4) with mosaicism, and 32% (n:12) with other karyotypes (Table 1). The mean age at the time of the study was 14.6±4.8 (range was 4.2-23.6) years. Mean age at diagnosis was 9.3±4.1 years with 56% of patients diagnosed after 10 years of age. The mean duration of follow-up in this cohort was 7.2 years. GH therapy was administered in 33 out of 37 patients (89% of the study group). GH treatment was initiated at various ages (between 2.32 and 15.48 years; mean 10.08±3.09 years), depending on the age at diagnosis. Duration of GH treatment ranged between 0.7 and 10.2 years (mean 3.13±1.94).

Table 2: The effect of the duration of GH treatment on cardiometabolic risk factors.

Duration of GH treatment	<3 years (n)	≥3 years (n)	*P*
BMI, kg/m^2	24.3±3.71	21.2±5.3	0.036
Fasting glucose, mg/dL	96.6±9.4	99.1±11.9	0,972
Fasting insulin, *μIU/mL*	10.4±10.1	11.9±9.5	0.570
HOMA-İR	2.59±2.64	3.05±2.62	0.693
TC, mg/dL	175.8±33.1	161.6±31	0.495
TG, mg/dL	100.5±49.4	73.2±21.0	0.154
LDL-C, mg/dL	107.6±32.2	87±21.3	0.100
HDL-C, mg/dL	48.9±10.4	60.0±15.1	0.041
SBP, mmHg	110.36±13.11	116±8.5	0.245
DBP, mmHg	72.45±11.26	77.36±7.97	0.252

GH: Growth Hormone; BMI: Body Mass Index; HOMA-IR: Homeostasis Model Assessment of Insulin Resistance; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; TC: Total Cholesterol; TG: Triglyceride; LDL-C: Low-Density Lipoprotein Cholesterol; HDL-C: High-Density Lipoprotein Cholesterol.

Cardiometabolic risk factors

Carbohydrate metabolism and findings from OGTT: Among 37 patients evaluated for impaired carbohydrate metabolism, 8 (21%) patients had IFG and only 3 (8%) patients were insulin resistant according to HOMA-IR. A total of 25 patients underwent an OGTT. In 7 (28%) patients IGT were detected. Four of them had also IFG. All the other patients had Normal Glucose Tolerance (NGT). When the results of OGTT were evaluated for IR, five (20%) patients were insulin resistant according to OGTT.

Lipid metabolism: Among 37 patients evaluated for dyslipidemia 27% had the disease. Five (13%) patients had high TC, high TG, high LDL-C and low HDL-C simultaneously. One (3%) patient had both high TC and low HDL-C. Four (11%) patients had solely low HDL-C.

Hypertension

Hypertension was not detected in any patient.

Metabolic comorbidities

Metabolic impairments were detected in 48% of the studied girls in this cohort. Four (11%) patients had obesity and 6 (16%) patients were overweight. 5 (13%) patients had both dyslipidemia and IGT. They were more overweight compared to those without metabolic abnormalities.

The effect of the duration of GH treatment on cardiometabolic risk factors

Duration of taking GH therapy was 3.13±1.94 years (ranged from 0.7 to 10 years). Eighteen patients were receiving GH treatment for 3 years and over. The BMI in the patients treated with GH over than three years was significantly lower than the patients treated with GH less than three years (p=0.036). These patients also had higher HDL-C

Table 3: The effect of the age at onset GH treatment on cardiometabolic risk factors.

Age at Onset GH Treatment	<10 years-old	≥10 years-old	*P*
BMI, kg/m^2	21.8±5.7	23.6±4.7	0.018
Fasting glucose, mg/dL	97.8±14.1	96.0±10.1	0.551
Fasting insulin, *µIU/mL*	10.1±12.4	10.8±9.2	0.496
HOMA-İR	3.12±3,24	2.34±1,88	0.491
TC, mg/dL	167.5±26.9	172.6±33	0.824
TG, mg/dL	82.3±45.8	88.1±40	0.394
LDL-C, mg/dL	98.5±27.3	103.2±29.6	0.738
HDL-C, mg/dL	56.3±13.3	51.5±13.8	0.738
SBP, mmHg	106.09±9.45	115.07±12.45	0.047
DBP, mmHg	67.82±10.15	78.47±6.45	0.003

GH: Growth Hormone; BMI: Body Mass Index; HOMA-IR: Homeostasis Model Assessment of Insulin Resistance; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; TC: Total Cholesterol; TG: Triglyceride; LDL-C: Low-Density Lipoprotein Cholesterol; HDL-C: High-Density Lipoprotein Cholesterol.

levels (Table 2). BMI was negatively correlated with the time of GH treatment (r=0,470, p<0,05), SBP and DBP were positively correlated with the time of GH treatment (r=0.422, r=0.461, p<0.05 for all, respectively), and there was no correlation between the lipid profile and the time of GH treatment in the entire cohort.

The effect of the age of onset GH treatment on cardiometabolic risk factors

Comparison of the age of onset GH treatment before and after 10 years old and cardiometabolic risk factors presented in (Table 3). The mean age of onset of GH therapy was 10.08±3.1 years. In 16 patients GH treatment started before 10-years-old. The BMI in the patients started GH treatment before 10-years-old was significantly lower than the patients started GH treatment after 10-years-old (p=0.018). Additionally SBP and DBP were significantly lower in patients started GH treatment before 10-years-old (p=0.047, p=0.030 respectively). In Spearman's correlation analysis only HDL-C levels were positively correlated with age of onset GH treatment (r=0.545, p=0.007).

Discussion

TS is associated with a number of abnormalities in glucose metabolism including IR, IFG, IGT, and T2DM [2]. Although the exact prevalence is unknown, the overall risk of developing T2DM appears to be frequent [13]. In a recent study, Ibarra-Gasparini et al. also confirmed the high prevalence of DM in adult TS patients [14]. In our study, although two patients were diabetic according to OGTT, patients were considered as having IGT because of the lack of the symptoms of diabetes and having less than 6.5% of HbA1c. Thus, in this present study, IGT prevalence was 28%, which is higher than previous studies [14-15].

It is also described a higher occurrence of IR in patients with TS than controls [16]. Although the molecular basis of IR in TS remains incompletely understood, an impaired insulin secretion and a defect of insulin action have been implicated in previous studies [13,17]. In our cohort, IR was 8% according to HOMA-IR, however when patients were evaluated by OGTT, IR was detected in 20% of the patients. Interestingly, those who have IR with HOMA-IR do not have IR with OGTT. According to this result, we suggest that the use of HOMA-IR to assess IR in TS patients may not be confidential, since an early insufficient insulin secretion is considered in these patients. But considerably more comprehensive studies are needed to highlight the mechanism of insulin secretion and action in TS patients.

TS patients also have an abnormal lipid profile. But lipid profile observed in TS patients noticeably varied between studies. While elevated TC is the most common pattern, higher TG and LDL-C were also described [18,19]. In the entire cohort, the prevalence of dyslipidemia established as 27% based on the defined features of dyslipidemia. Decreased HDL-C was the most the prevalent component that levels assumed to play an essential role in pathogenesis of atherosclerosis [20].

In the evaluation the effect of GH therapy on glucose tolerance in TS patients, some studies have shown no effect [21], while others have found increased insulin resistance in long-term GH therapy [22,23]. In our study, we found that duration of GH treatment and age at onset GH treatment did not affect glucose, insulin and HOMA-IR. Studies even demonstrated the beneficial effects of GH therapy on BMI in patients with TS [23,24]. Our study confirms that GH therapy reduces BMI (Table 2 and 3). We found that both receiving GH treatment more than 3 years and the onset of GH therapy before the age of 10 years have a mitigating effect on BMI. These observations are consistent with the observation of Danda et al. in which displayed a possible beneficial effect on BMI [24].

In a recent study Kohno demonstrated a favorable impact of GH therapy on atherogenic risk in TS patients [25]. In this study the increasing levels of TC with age in prepubertal TS girls were improved during 3 year of GH therapy. Weibin et al. also showed an obvious improvement on lipid metabolism of patients who underwent GH therapy [26]. They detected significantly increased plasma HDL-C, as shown in our study, and decreased plasma LDL-C as well. In our study population, we showed a significant increase in plasma HDL-C in the patients that received GH treatment more than 3 years.

There are some limitations of this current study that needs to be addressed. Although, the majority of TS subjects took one or more prescription medications, in our study, we only investigated the cardio-metabolic variables of the TS patients, and did not take into account the current use of medication such as Hormone Replacement Therapy (HRT) and l-thyroxin, which may have additional modest confounding effects on cardio-metabolic risk factors. In conclusion, despite the limitations, our study suggests that metabolic alterations appears very early in the natural history of TS. We report that the majority of individuals with TS suffer from abnormal carbohydrate and lipid metabolisms. This study reinforces the need for routine screening of glucose and lipid metabolism over time in TS patients.

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