

## Thyroid Disorders in Pediatric Patients with Turner Syndrome; A 16 Years' Experience

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### Abstract

#### Background

Turner syndrome patients are more likely to develop autoimmune diseases in contrast to the general population. Many research have had controversial results suggest a possible relation between the cytogenetic findings and development of autoimmune thyroid disease in Turner syndrome. Therefore, we aimed to evaluate the prevalence of thyroid disorders and the possible relationship between thyroid disorders with the cytogenetic findings in these patients.

**Materials and Methods:** The present retrospective study took place in pediatric endocrinology clinic of Imam Reza Hospital (Mashhad, Iran), and every pediatric patient who were younger than 18 years old with the clinical phenotype of Turner syndrome and had complete thyroid function tests enrolled. The medical records of these patients were evaluated and patients were recalled if any further information was needed. The study data including thyroid function tests as well as patients' age, height, weight, and karyotype findings were entered in a check list and the relationship between thyroid functions tests and karyotype findings were evaluated.

**Results:** Among the 79 patients enrolled in the present study, the mean  $\pm$  standard deviation of age was  $10.82 \pm 2.6$  years. The most of the study population had negative anti-TPO results (62 patients, 78%). Among all patients, eight patients (10.1%) had autoimmune hypothyroidism. There was not any significant relationship between thyroid function tests with different cytogenetic findings ( $P > 0.05$ ).

#### Conclusion

Hypothyroidism (26.6%) was the most common thyroid disorder among Turner syndrome patients. Although there was not any significant relationship between thyroid function tests, Z-scores for height and weight with cytogenetic findings; however, our findings highlights the need for more specific screening programs for evaluating the thyroid functions in turner patient.

**Key Words:** Hypothyroidism; Hyperthyroidism, Turner syndrome, Pediatric, Karyotype.

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## 1- INTRODUCTION

Turner syndrome is a genetic disorder with variable chromosomal abnormalities in the X chromosome affecting one in 1893 female live birth (1, 2). Turner syndrome patients are mostly diagnosed because of their short stature, neck, and chest abnormalities in early childhood (3, 4). Cytogenetic techniques make the definite diagnosis of these patients. Turner syndrome's characteristic phenotype is mainly because of an abnormally structured or complete absence of sex chromosomes (5). Although one copy of X chromosomes becomes inactivate in females; however, the inactivation process is not complete, and some genes escape the inactivation process (6).

These genes are mostly located on the X chromosome's short arm and are pseudoautosomal genes (6). Chromosomal abnormalities affecting regions containing these genes result in haploinsufficiency and development of the Turner syndrome phenotype. The short stature homeobox-containing gene (SHOX) is a pseudoautosomal gene located on the X chromosome that is disrupted in Turner syndrome patients because of the haploinsufficiency causing the short stature phenotype (7). Like the SHOX gene, other pseudoautosomal genes on the X chromosome are responsible for most patients' phenotypes. Alongside the typical phenotypic features of turner syndrome patients, it has been reported that these patients are more likely to develop autoimmune diseases (8).

A growing number of microRNAs and X-linked genes have a considerable role in immunity (6, 9). Among these diseases, autoimmune thyroid diseases are a prevalent finding (10). A possible explanation behind the increased frequency of autoimmune diseases is related to the X chromosome's genes (11). Among the autoimmune disorders, autoimmune thyroid disorders are more

prevalent in Turner syndrome patients than the general population (10). It has been demonstrated that Turner syndrome patients with thyroid disorders may not have atypical clinical presentations or biochemical findings and can be diagnosed similarly to other pediatric patients with thyroid disorders (12). The exact mechanism behind the increased prevalence of autoimmune thyroid disorders in Turner syndrome patients is not clearly understood and there are controversial results regarding the relation of different cytogenetic findings and development of thyroid disorders in these patients (8, 13-15). Regarding the controversial results about the autoimmune thyroid disorders in turner patients and the lack of such study in the Iranian population, we aimed to evaluate the prevalence of thyroid disorders and possible relation of cytogenetic findings with the development of thyroid diseases in Iranian Turner syndrome patients.

## 2- MATERIALS AND METHODS

### 2-1. Study design and population

The present retrospective study took place in the pediatric endocrinology clinic of Imam Reza Hospital (Mashhad, Iran). From 1999 to 2015, medical records of every patient younger than 18 years of age who had clinical diagnosis of turner syndrome with complete complete thyroid function tests as well as a karyotyping result were included.

### 2-2. Method

The medical records of every patients included in the present study were evaluated by a researcher and the clinical and laboratory data were gathered in checklist for further statistical analysis. The medical records were obtained with permission from the medical record center in Imam Rzea Hospital (Mashhad, Iran). The patients' karyotypes grouped, according to Gravholt et al., study into

seven main categories (16). These groups include 1) 45,XO; 2) 45,X/46,XX; 3) 45,X/47,XXX; 45,X/46,XX/47,XXX; 4) 45,X/46,XY; 5) 46,XX, del(p22.3); 46,X,r(X)/46,XX; 6) 46,X i(Xq); 46,X,idic(Xp), and 7) unbalance X-autosome translocation. The Z-score for patients' height and weight considered in three main groups of <-1, -1 to +1 and >+1. The thyroid profile includes Triiodothyronine (T3), Thyroxine (T4), and Thyrotropin (TSH) performed by Radioimmuno Assay (Gama Counter and Cisbio kit). The anti-thyroid peroxidase (anti-TPO) tests performed by Enzyme Immune Assay (ELISA) method (ELISA Reader device and Orintech kit). The normal ranges of these tests considered as follow (according to the manufacturer's guide), (Table.1).

**Table-1:** The normal ranges of thyroid function tests according to the patients's age.

Variables	1-5 years	6-10 years	11-20 years
TSH ( $\mu$ IU/L)	0.7-6	0.6-4.8	0.5-4.3
T4 ( $\mu$ g/dL)	6-14.7	613.8	5.9-13.2
T3 (ng/dL)	92-248	93-231	91-218

TSH: Thyrotropin; T3: Triiodothyronine; T4: Thyroxine.

### 2-3. Laboratory measurements

There was not any laboratory test provided for the patients.

### 2-4. Intervention

Demographic data from the medical records of patients included in the present study including the patients' age, height and weight as well as their laboratory results including T3, T4, TSH, anti-TPO and karyotype results were gathered by a researcher and entered in a study checklist.

### 2-5. Ethical consideration

The present retrospective study approved by the Mashhad University of Medical Sciences Ethics committee (IR.MUMS.fm.REC.1394.34).

### 2-6. Inclusion and exclusion criteria

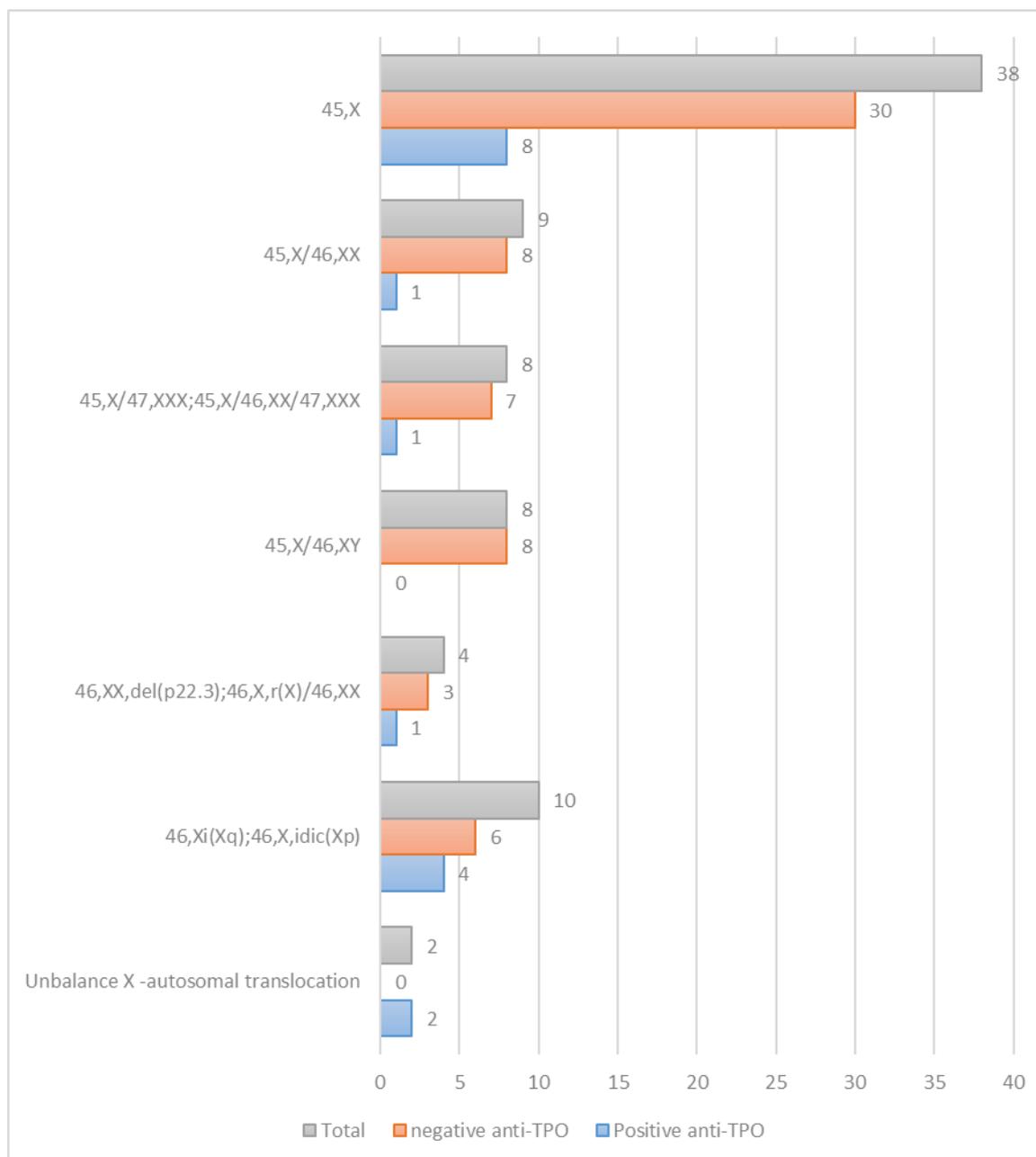
Every patient who was younger than 18 years old and had clinical phenotype suggesting of turner syndrome with a complete medical records containing age, height, weight, thyroid function tests (including T3, T4, TSH and anti-TPO) and a karyotype test result were included in the present study. Those patients who did not have an informed consent form indicating their willingness to participate in research projects were not included.

### 2-7. Data Analyses

The study data analyzed by SPSS software (version 20). The Chi- square tests used to evaluation of the relation between karyotype findings and autoimmune thyroid disorders. The ANOVA test used to determine the association between thyroid function and the Kruskal-Wallis test to determine the relationship between patients' weight and height according to their karyotype findings.

## 3- RESULTS

Among the 79 patients enrolled in the present study, the mean  $\pm$  standard deviation of age was  $10.82 \pm 2.6$  years old. The mean  $\pm$  standard deviation of height and weight were  $123 \pm 19.93$  centimeter and  $32 \pm 14.02$  kilograms, respectively. Most of the patients (38 patients, 35.4%) were diagnosed to have turner syndrome when they were aged between 11 and 15 years old. The prevalence of different cytogenetic findings of the peripheral blood karyotype are summarized in **Figure.1**.



**Fig.1:** Distribution of anti-TPO results and autoimmune disorders according to the patients' karyotypes. TPO: anti-thyroid peroxidase.

The most common cytogenetic finding regardless of the thyroid function tests were 45,XO (38 patients, 48.1%) following 45,XO/46,XX (9 patients, 11.3%). Most of the study population had negative anti-TPO results patients (62 patients, 78%). The distribution of the anti-TPO results according to the cytogenetic findings is demonstrated in **Figure.1**. The ANOVA test did not reveal any significant

relationship between the anti-TPO results and different cytogenetic findings ( $P>0.05$ ). Eight patients (10.1%) of all patients had autoimmune hypothyroidism and the Chi-square test did not reveal any significant relationship between autoimmune hypothyroidism and cytogenetic findings ( $P>0.05$ ); while most of the Turner patients with autoimmune thyroid disorder had 45,XO karyotype.

The thyroid function tests were normal in most of the patients (57 patients, 72.2%) (Figure.2). Twenty-one patients (26.6%) had hypothyroidism, and the others (1.3%) had hyperthyroidism. Thyroid function tests were not related to the cytogenetic findings ( $P>0.05$ ). The distribution of the

thyroid function results according to the cytogenetic findings demonstrated in Figure.2. Characteristics of the participants' height and weight based on their Z-score illustrated in Figures 3 and 4.

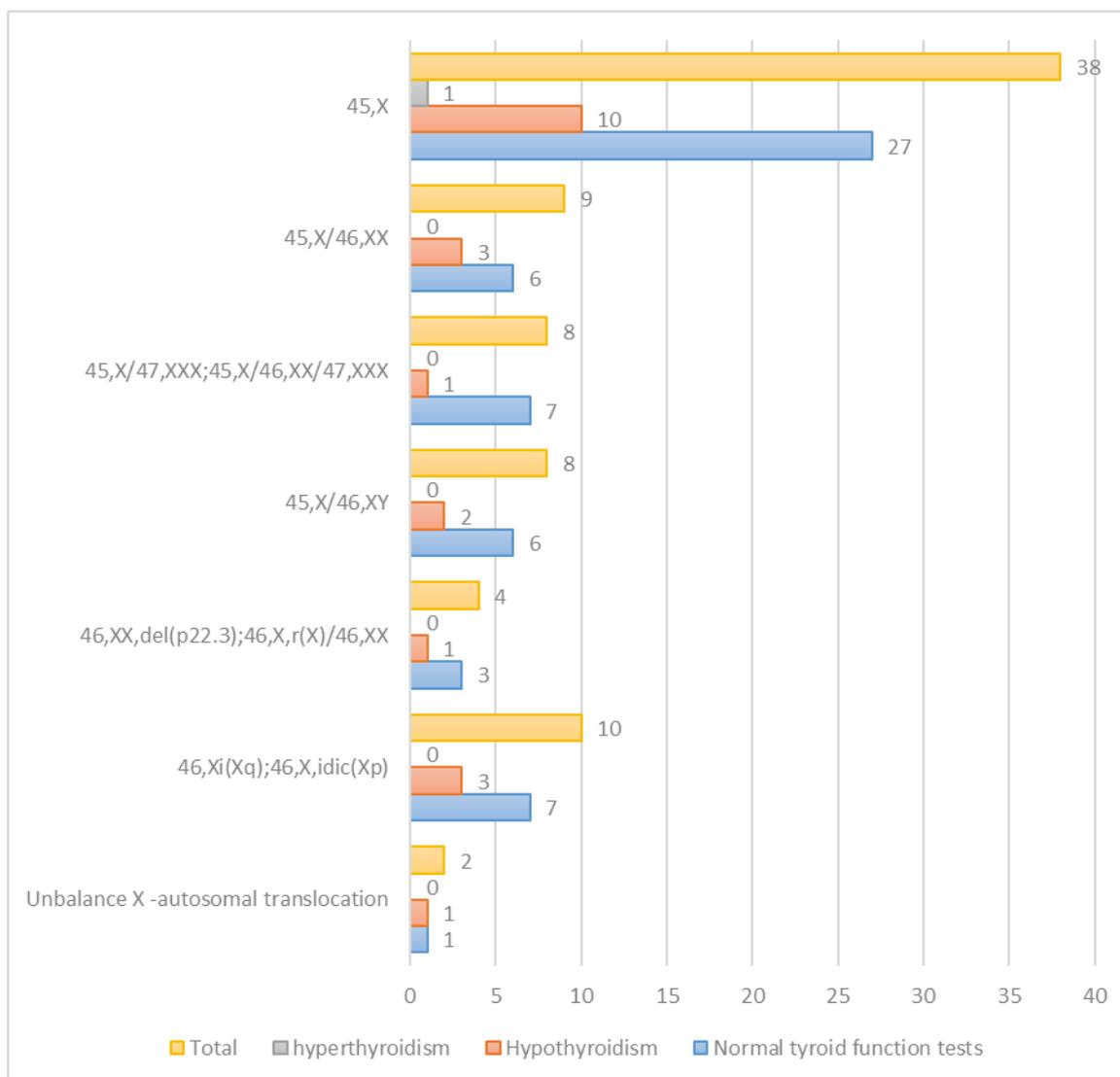
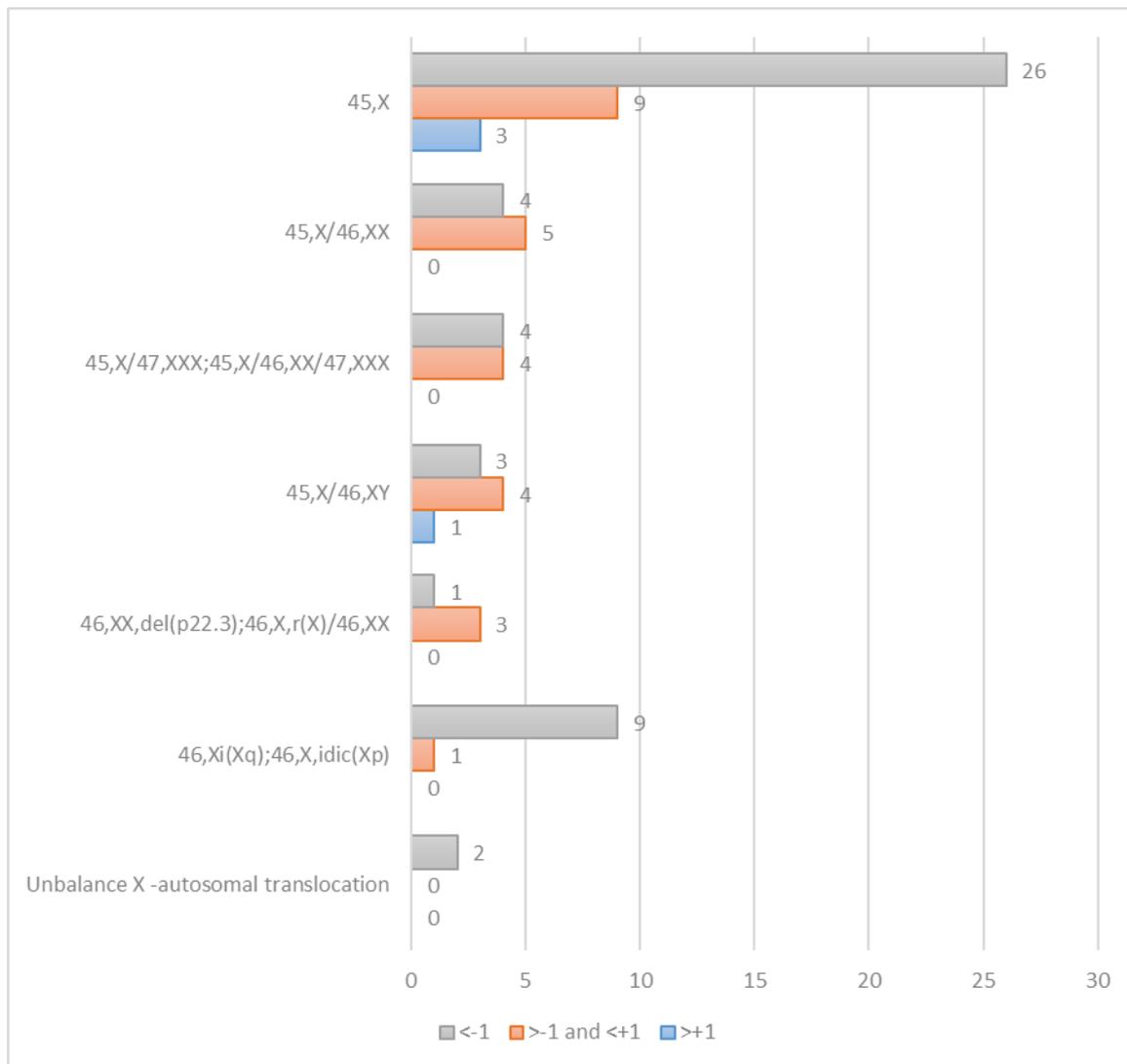
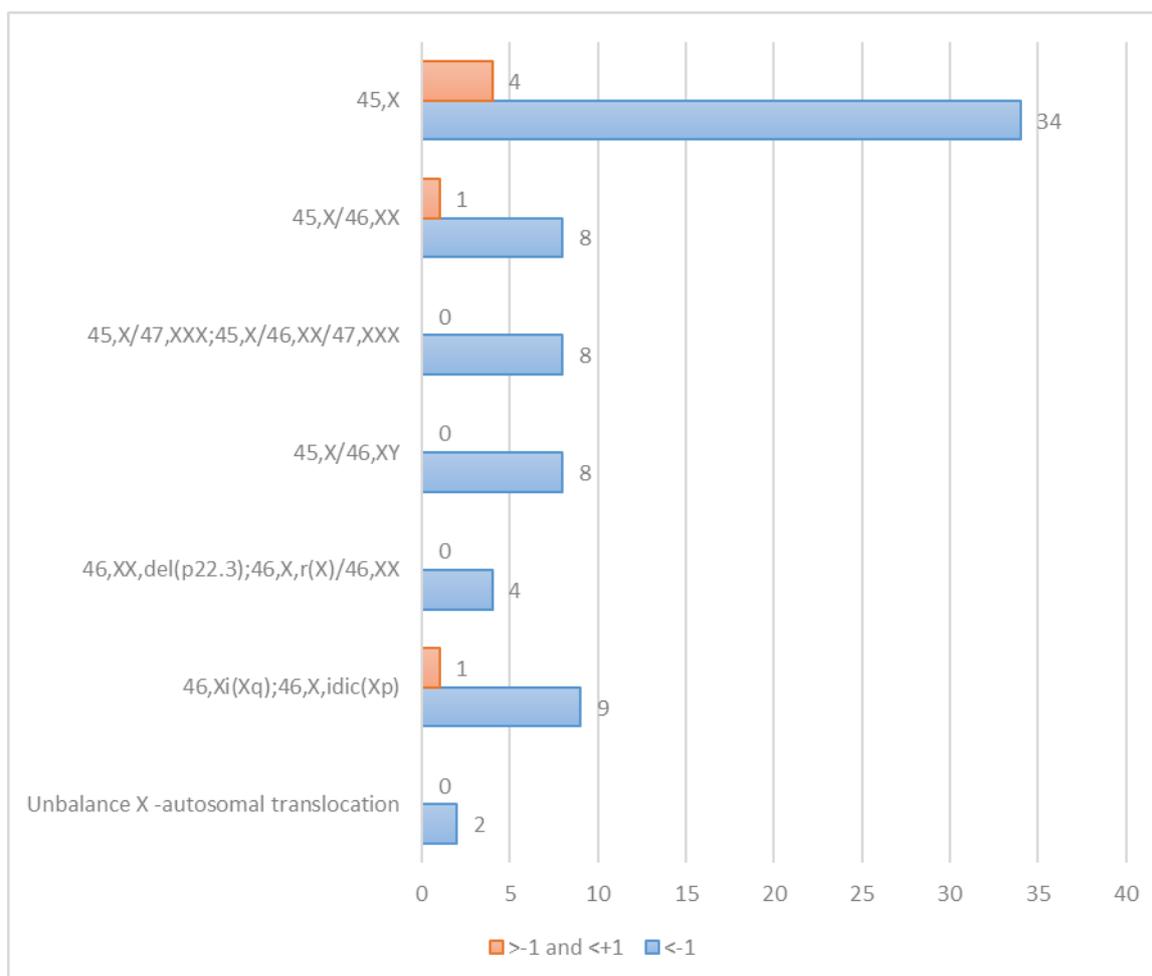


Fig.2: Distribution of patients' thyroid function based on their karyotype results.



**Fig.3:** Distribution of patients Z-scores of weight based on their karyotype results.



**Fig.4:** Distribution of patients Z-scores for height based on their karyotype results.

Patients Z-score for weight and height were not related to the cytogenetic findings ( $P>0.05$ ). Distribution of patients' weight

and height according to their age summarized in **Table.2**.

**Table-2:** Distribution of patients' weight, height and autoimmune thyroid disorder according to their age.

Z-score of height	Age (year)							
	1-5		6-10		11-15		16-20	
	N.	%	N.	%	N.	%	N.	%
<-1	10	76.9	22	84.6	28	100	12	100
-1 to +1	3	23	4	15.3	0	0	0	0
Z-score of weight								
<-1	10	77	15	53.5	20	71.4	6	50
-1 to +1	3	23	9	32.1	8	28.5	4	33.3
>+1	0	0	2	7.1	0	0	2	16.6
Autoimmune thyroid disorder								
Positive	1	7.6	2	7.6	3	10.7	1	8.3
Negative	12	92.3	24	92.3	25	89.2	11	91.6

Among the 21 hypothyroid patients, 19 (90.4%) had Z-score <-1, and none of them had Z-score>+1 for height (**Table.3**).

Most of the participants who had Z-score<-1 of weight had normal thyroid function (**Table.3**).

**Table-3:** Distribution of patients' weight and height according to their thyroid function.

Thyroid function	Z-score of weight						Z-score of height			
	<-1		-1 to +1		>+1		<-1		-1 to +1	
	N.	%	N.	%	N.	%	N.	%	N.	%
Hypothyroidism	15	71.42	5	23.8	1	4.7	19	90.4	2	9.5
Normal	35	61.4	19	33.33	3	5.26	52	91.2	5	8.7
Hyperthyroidism	1	100	0	0	0	0	1	100	0	0

#### 4- DISCUSSION

The present study demonstrated that among pediatric patients with Turner syndrome phenotype, different cytogenetic abnormalities were not related to abnormal thyroid function tests or autoimmune thyroid disorders. Most of the study population had negative anti-TPO results patients and thyroid function tests were normal in most of the patients with suggestive phenotypes of Turner syndrome. Turner syndrome is a genetic disease with a highly variable phenotype affecting female patients. Various studies demonstrated that these patients are at higher risk of developing autoimmune disorders than the general population. The underlying mechanism behind the increased prevalence of autoimmune hypothyroidism and other clinical conditions, including celiac disease, is controversial. Defective regulatory T lymphocytes failing to inhibit effector T lymphocytes is one of these controversial explanations behind the increased autoimmunity in Turner syndrome patients that is demonstrated in some studies and refute in others (17, 18). Turner syndrome patients with autoimmune thyroid disorders may develop physical and mental developmental delays or signs and symptoms of thyroid gland dysfunction, including weight loss, tachycardia, and sleep disorders (19, 20). Early diagnosis and treating autoimmune thyroid disorders

after diagnosis may resolve the patients' symptoms. Although the prevalence of thyroid disorders and their related complications are widely studied in the general population; however, in turner syndrome patients, thyroid disorders are among the neglected conditions (19). The pooled data from 18 studies demonstrated that the prevalence of autoimmune thyroid disorders in turner patients is 38.6% (10). The prevalence of hypothyroidism and hyperthyroidism reported being 12.7% and 2.6% of Turner syndrome patients, respectively (10). To the best of our knowledge, our present study is the first report about the prevalence of autoimmune thyroid disorders in patients with suggestive phenotype of Turner syndrome in Iran. According to our results, 22% of patients with turner syndrome phenotype had positive anti-TPO. The prevalence of autoimmune thyroid disorders in turner patients varies among different studies, from 1.6% to 64% in diverse populations (13, 15, 21-24). Other studies, including Wikiera et al., and Yu et al., reported approximately similar results to our research, indicating that 33% and 25% of their polish and Chinese patients had positive anti-TPO results, respectively (25, 26). The rest of studies, including Elsheikh et al., Fleming et al., and Hamza et al. reported a higher prevalence of anti-TPO results among their patients as 41%, 48%, and 67.5%, respectively (13, 14, 27) while some studies, including Bettendorf et al.,

reported a considerably lower prevalence of anti-TPO among their population (28). A possible explanation behind the different prevalence of positive anti-TPO results may be related to the patients' age. Turner syndrome patients as young as one year to over 60 years of age enrolled in these studies (13, 14, 27). However, Wikiera et al. and Yu et al. reported slightly similar positive anti-TPO, had a similar mean age of turner syndrome patients to our population (25, 26). Most of the turner syndrome in our study has 45, XO phenotype, which is in line with similar studies (14, 16, 27-29). While our research failed to establish a relationship between karyotype findings and the development of autoimmune diseases, further studies, including Kucharska et al. and Hamza et al. reported a significant relationship in their population (13, 23). Similar to our research, Bettendorf et al., Yu et al., Francisco et al., and Livades et al. studies did not demonstrate a significant relationship between patient's karyotypes and the development of autoimmune thyroid diseases (26, 28-30). Although we could not find a significant relation between karyotype findings and autoimmune thyroid disorders; however, we demonstrated that one patient among the three patients with 46,XX,del(p22.3);46,X,r(X)/46,XX had autoimmune diseases. Hamza et al. study demonstrated that 57.9% of turner patients with Isochromosome Xq and 33.3% of turner patients with 45,X/46,XX had autoimmune diseases (13). In contrast to Hamza et al. study, Bakalov et al. and Elsheikh et al. reported that 58.3% and 71% of their patients with autoimmune thyroid disorder had Isochromosome Xq (14, 15). Most of the turner patients had normal thyroid function (72.2%) and 26.6% had hypothyroidism. While the prevalence of hypothyroidism among our population was similar to the Elsheikh et al., Wikiera et al., and Kucharska et al. studies, Yu et al. and Hamza et al. studies

reported higher rates of hypothyroidism among their populations (13, 14, 23, 25, 26). Only one patient in our population had graves' disease. The graves diseases is not a common finding among turner patients and only Hamza et al. reported a case of graves' disease in their population (13, 15, 22, 23). As same as the possible effect of turner syndrome patients on the aniti-TPO results, the similar relation may be present for hyper- or hypothyroidism as well. Some studies including Bettendorf et al. study demonstrated that as turner patients become older, the frequency of hypothyroidism also increases; however, our study failed to demonstrate such relation and demonstrated patients aging from 16 to 20 years shows the highest frequencies for hypothyroidism (28). Moreover, another explanation behind the controversial results of the thyroid function tests in different studies could be their ethnicity. A recent meta-analysis reported that autoimmune thyroid disorders are more prevalent among Turner syndrome patients from Asian regions in contrast to the European regions (10).

#### **4-1. Study Limitations**

The present study had some limitations that should be addressed for future researches. The retrospective nature of the course was the main limitation. Moreover, the limited sample size made it difficult to compare different age groups. According to their ages, normalization of the turner patients may provide more specific results regarding the relationship between the developments of autoimmune thyroid diseases in turner patients.

#### **5- CONCLUSION**

Among the pediatric patients with clinical phenotype suggestive for Turner syndrome, 26.6% had hypothyroidism and 22% of our study population had positive anti-TPO results. This finding highlights the need for more specific screening

programs for evaluating the thyroid functions in Turner patients. Our study demonstrated that patients with Turner syndrome phenotype ageing between 16 and 20 years develops thyroid disorders more common than other age groups, and screening programs should pay more attention to this group. Although our study demonstrated that the prevalence of thyroid disorders is different among patients with abnormal cytogenetic findings; however, there was not any significant relationship between these variables among our population. Therefore, relying on the cytogenetic findings to screen patients for autoimmune disorders may not be the right choice.

## 6- ACKNOWLEDGMENTS

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**7- CONFLICT OF INTEREST:** None.

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