

How many eventually develop hypothyroidism? A 5-year follow-up of Turner syndrome

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Abstract. We studied the prevalence and incidence of hypothyroidism in 171 women with Turner syndrome (TS) during a period of 5 years. At the mean age of 33 years, 19% were treated for hypothyroidism and another 11% had newly detected disease, i.e. 30% had hypothyroidism, evenly distributed among the karyotypes. Elevated thyroid peroxidase antibody titer (TPO) was present in 30% of all TS and in 37% of those with hypothyroidism. After a 5-year follow-up, another 15% developed hypothyroidism giving an annual incidence of 3%. Altogether, 45% had hypothyroidism at the mean age of 38 years. In TS above 50 years of age 47% had hypothyroidism. In conclusion, almost every second TS woman will most probably develop hypothyroidism and those with elevated TPO levels are at highest risk. © 2006 Elsevier B.V. All rights reserved.

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1. Introduction

Hypothyroidism of autoimmune origin is common among Turner syndrome (TS) women (20–30%) [1,2]. Tiredness is a common symptom leading the patient to the doctor [3]. However, hypothyroidism is also the most common hormonal dysfunction in women of the general population, (2–5%) [2,4]. A positive family history increases the risk for hypothyroidism in women [5]. A positive family history has been documented in

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TS by Wilson who found elevated thyroid peroxidase antibodies (TPO) in both TS patients and their mothers [6]. It has been suggested that there might be a causal relationship between aberrations of the X-chromosome and the risk of autoimmune hypothyroidism [6]. In a previous study we reported from 92 TS women whose karyotype had been complemented with Fluorescence In Situ Hybridization (FISH) analyses and we found no correlation between hypothyroidism and the chromosomal status [2]. Controlled studies regarding the prevalence and incidence of hypothyroidism in TS are sparse. Thus, the present aim was to study the number of patients with hypothyroidism and the frequency of TPO in a large cohort of TS from western and southern Sweden in comparison with a random population of women of similar age from the same region. Furthermore, the incidence of hypothyroidism in TS during a 5-year follow-up was studied.

2. Materials and methods

During the period 1995–2003, 171 women, aged 16–71 years, with TS were studied at the University clinics of Internal Medicine and Obstetrics and Gynecology in Göteborg and Malmö, Sweden. All TS women participated in a program including examinations regarding endocrinology, gynecology, audiogram, echocardiography, bone measurement with a Dual Energy X-ray Absorptiometry and blood sampling at the first visit at the adult clinic and at every 5th-year follow-up (Fig. 1). The TS women were compared with randomly selected controls, *n*=228, aged 25–64 years from the WHO MONICA (World Health Organization, MONItoring of trends and determinants in CARDiovascular diseases) Project in 1995 in Göteborg [7] including cardiovascular risk factor screening in 38 countries around the world.

Estrogen hormone replacement therapy (HRT) (17β-estradiol 2 mg) was currently given to 95% of the TS women. Of the controls, 31% were taking oral contraceptives and 16% above 45 years of age were taking HRT (17β-estradiol, 2 mg).

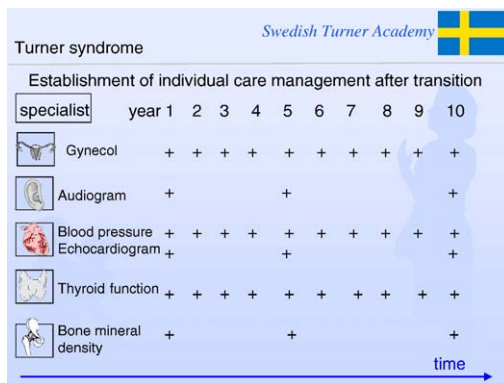


Fig. 1. Schedule for the transition from the pediatric to the adult clinic and follow-up of girls and women with Turner syndrome in the Swedish Turner Academy at all University Hospitals in Sweden.

Data on a family history of thyroid disease among TS women were asked for during the investigation. A sibling, mother, father, aunt, uncle, grandmother or grandfather with a thyroid disease was registered as a positive family history of thyroid disease. Concentrations of serum-free thyroxin (T4) and thyroid stimulating hormone (TSH) were measured with an immunometric method with luminometry (Johnson and Johnson, USA) and TPO concentrations were determined with the BRAHMS luminometric test anti-TPO (Henning, Berlin, Germany). The chromosomal findings were based on medical records. The karyotype was defined after the analysis of 30 cells.

The study was approved by the Ethics Committees at Göteborg and Lund Universities and all the participants gave their informed consent.

Differences between the patients and the controls were tested with Student's *t*-test and differences between non-continuous variables among TS women were tested with Mantel–Haentzel's chi-squared test. Differences within TS subjects after follow-up were tested with Wilcoxon's signed rank test. A *p*-value of <0.05 (two-sided test) was considered statistically significant.

3. Results

At baseline, 19% TS women were treated for hypothyroidism and elevated serum TSH was found in another 11%. As a result, hypothyroidism was more common in TS, 30%, than in controls, 2% ($p < 0.001$). Serum-free T4 was lower ($p < 0.001$) and serum TSH higher ($p < 0.001$) in TS than in age-matched controls. Of all TS with hypothyroidism, 37% had an elevated TPO titer vs. 22% of those without hypothyroidism ($p < 0.05$), evenly distributed between the karyotype 45,X and non-45, X. A high body mass index, but not a family history or blood lipids, was associated with hypothyroidism in TS. After the 5-year follow-up, a further 15% developed hypothyroidism, of whom 36% had elevated TPO. Altogether, 45% TS women had hypothyroidism after the 5-year follow-up (Table 1, Fig. 2). The annual incidence of hypothyroidism after age 33 years was 3% in TS. Treated hyperthyroidism was found in 2% of TS women compared to <1% in the controls and no new cases during the follow-up period for TS.

During follow-up there was a continuous increase in serum TSH (within the normal range) in 55% TS women who neither had hypothyroidism at the start nor after 5 years. Of these, 19% had positive TPO.

Table 1

Prevalence of elevated thyroid peroxidase antibodies (TPO) and hypothyroidism in Turner syndrome patients of different ages in studies during the recent years

	<i>N</i>	Mean age, years	Elevated TPO %	Hypothyroidism %	Hypoth+TPO %
Livadas et al., 2005 [10]	84	10	42	24	63
Elsheikh et al., 2001 [1]	145	26	41	21	–
El-Mansoury et al., 2005 [2]	92	38	25	25	43
" 5-year follow-up	92	43	26	40	44
Present study, 2006	171	33	30	30	37
" 5-year follow-up	171	38	34	45	36

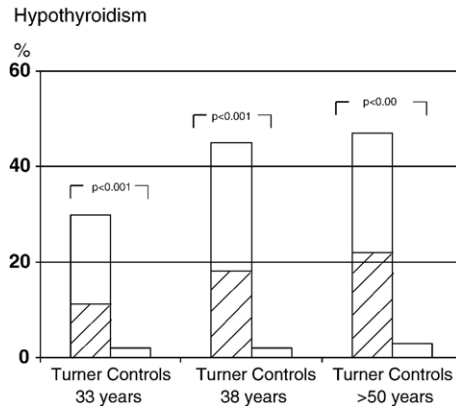


Fig. 2. The prevalence and incidence of hypothyroidism in women with Turner syndrome at age 33 years ($n=171$) and at 5-year follow-up with an annual incidence of 3% (age 38 years), and in TS women >50 years of age ($n=34$) compared with a random population sample of age-matched women, the WHO MONICA Project, Göteborg ($n=228$). The percentage of TS women with elevated thyroid peroxidase antibody titer (TPO) is given in each bar (striped area).

The age of TS women with hypothyroidism was 36 ± 11 years and of TS women without hypothyroidism, 40 ± 11 years. There were 34 TS women above 50 years of age at follow-up. Of these, 16/34 developed hypothyroidism (47% vs. 45% in all TS) and 18/34 did not develop hypothyroidism (53% vs. 55% in all TS). Of those above 50 years with hypothyroidism, 7/16 (44%) had elevated TPO (Fig. 2), and of those without hypothyroidism, 4/18 (20%) had elevated TPO and were 45,X.

There were no correlations between age and TSH, T4 or TPO, respectively. TPO correlated to TSH, ($r=0.16$; $p<0.05$).

4. Discussion

Hypothyroidism was common in this large cohort of women with TS. Almost every second TS woman will most probably develop hypothyroidism during their lifetime. It is hard to predict who, but those with elevated TPO are at the highest risk. The prevalence of elevated TPO in a general female European population was 7% [8] and 11% in US women [4] and doubled in women with a positive family history for hypothyroidism, 27% [5]. Furthermore, 86% in those with the overt disease had positive TPO [5], (Table 2). We did not find any significant family history for hypothyroidism in TS with hypothyroidism compared with those without disease in the present study. A positive family history has been found in TS with elevated TPO in both TS patients and their mothers [6]. The prevalence of TPO differs between studies in adult TS, 25–41% [1,2] and can be high already during childhood, 42–52% [9,10], (Table 1). Interestingly, the prevalence of hypothyroidism in TS was quite similar in these studies, 21–25%. Hyperthyroidism was uncommon in TS, 2%, but more frequent than in the general population in this study, $<1\%$, and in the US population, 1% [4].

Table 2

Prevalence of elevated thyroid peroxidase antibody titer (TPO) and hypothyroidism in women in the general population [4], in women with a positive family history for hypothyroidism [5] and in Turner syndrome [2] with and without a positive family history for hypothyroidism

	TPO %	Hypothyroidism %
Female population [4]	15	2
Positive family history [5]	27	4
Positive family history+hypothyroidism [5]	86	
Turner population [2]	25	25
Turner+positive family history [2]	14	7
Turner+hypothyroidism [2]	43	

Serum TSH increased with time, still within the normal range, in TS women who were not hypothyroid at the start or after the 5-year follow-up, which supports a further increase in incidence of hypothyroidism.

Elevated TPO concentrations were evenly distributed between the different karyotype variants. Therefore, the risk of developing hypothyroidism appears to be high for all TS women, independent of karyotype.

In conclusion, almost every 2nd TS woman will probably develop hypothyroidism and those with elevated TPO are at the highest risk. The annual incidence of hypothyroidism was 3% in TS. Thyroid function must be checked regularly in women with TS.

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