

A beneficial effect of estradiol on blood pressure, not on glucose and lipids levels in women with Turner syndrome

Korzystny wpływ estradiolu na ciśnienie tętnicze, nie na stężenia glukozy i lipidów kobiet z zespołem Turnera

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Abstract

Introduction. Turner syndrome (TS) is the form of gonadal malfunction. Arterial hypertension, elevated LDL and glucose and decreased HDL levels are characteristic of TS-women. Hormone therapy is a treatment for short stature and sex hormone deficits. Hormonal replacement therapy (HRT) reduces the risk of cardiovascular diseases. A large percentage of TS-women do not comply with doctors' orders regarding HRT.

The analysis of 17β estradiol (E_2) levels and the assessment of blood pressure, lipid and carbohydrate metabolisms in TS-women it is possible to state whether HRT decreases the risk of cardiovascular diseases?

Material and methods. The group of 95 TS-women, who declared HRT, were investigated. The information about HRT was collected during the anamnesis. E_2 , total cholesterol (TC), high (HDL) and low (LDL) density lipoproteins, triglycerides (TG) and glucose were assessed. Patients were divided into subgroups with $E_2 \geq 110$ pmol/L ($n = 34$) (HE) and < 110 pmol/L ($n = 61$) (LE) respectively.

Results. Arterial hypertension was diagnosed in 26.3%. The groups did not differ in systolic 119 ± 20 versus 118 ± 14 and diastolic 82 ± 13 versus 80 ± 10 mm Hg blood pressure. Despite the higher concentrations of E_2 in HE, no differences were found in weights, lipids and glucose concentrations. Negative correlations between E_2 and body mass ($r = -0.25$, $p = 0.04$) and diastolic blood pressure ($r = -0.28$, $p = 0.02$) as well as positive between E_2 and glucose ($r = 0.24$, $p < 0.05$) were observed only in HE. No correlations between E_2 and lipids were found.

Conclusions. 1. Only 1/3 TS-women, who declare HRT, have a satisfactory level of E_2 .

2. In TS-women HRT does not affect glucose and lipid metabolisms.

3. Negative correlation between E_2 and diastolic blood pressure in TS-women suggest beneficial effect of estrogens in hypertension.

key words: Turner syndrome, arterial hypertension, estradiol, carbohydrates, lipids.

Arterial Hypertens. 2016, vol. 20, no. 4, pages: 206–210

DOI: 10.5603/AH.2016.0023

Streszczenie

Wstęp. Zespół Turnera (ZT) jest formą uszkodzenia gonad. U kobiet z ZT często występują nadciśnienie tętnicze oraz zaburzenia gospodarki węglowodanowej i lipidowej. Terapia hormonalna w ZT służy leczeniu niskorosłości

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i niedoboru hormonów płciowych. Hormonalna terapia zastępcza (HTZ) redukuje ryzyko chorób sercowo-naczyniowych. Duży odsetek kobiet z ZT nie stosuje się do zaleceń lekarskich.

Poprzez pomiar stężenia 17β estradiolu (E_2), ciśnienia tętniczego oraz ocenę metabolizmu lipidowego i węglowodanowego w ZT możemy ocenić, czy HTZ zmniejsza ryzyko chorób układu krążenia?

Material i metody. U 95 kobiet z ZT, które podczas anamnezy deklarowały stosowanie HTZ, zmierzono ciśnienie tętnicze, oznaczono stężenia E_2 , cholesterolu całkowitego (TC), lipoprotein wysokiej (HDL) i niskiej (LDL) gęstości, triglicerydów (TG) oraz glukozy w surowicy. Badane podzielono na podgrupy, w której $E_2 \geq 110$ pmol/l n = 34 (HE) i < 110 pmol/l n = 61 (LE).

Wyniki. Nadciśnienie tętnicze stwierdzono u 26,3%. Obie grupy nie różniły się wartościami ciśnienia tętniczego skurczowego 119 ± 20 v. 118 ± 14 i rozkurczowego 82 ± 13 v. 80 ± 10 mm Hg. Mimo znacznie wyższego stężenia E_2 , w grupie HE nie stwierdzono różnic w masie ciała oraz stężeń lipidów i glukozy. Ujemne korelacje między E_2 i masą ciała ($r = -0,25$; $p = 0,04$) oraz między E_2 i ciśnieniem rozkurczowym ($r = -0,28$; $p = 0,02$) oraz dodatnią między stężeniami E_2 i glukozy ($r = 0,24$; $p < 0,05$) stwierdzono tylko w grupie HE. Nie stwierdzono korelacji między E_2 i stężeniami lipidów.

Wnioski. 1. Tylko 1/3 kobiet z ZT, które deklarują stosowanie HTZ ma zadowalające stężenie estradiolu.

2. Suplementacja estrogenów u kobiet z ZT nie wpływa na stężenie glukozy i lipidów.

3. Ujemna korelacja między E_2 i ciśnieniem rozkurczowym sugeruje korzystny wpływ estrogenów w nadciśnieniu tętniczym.

słowa kluczowe: zespół Turnera, nadciśnienie tętnicze, estradiol, węglowodany, tłuszcze

Arterial Hypertens. 2016, vol. 20, no. 4, pages: 206–210

DOI: 10.5603/AH.2016.0023

Background

Turner syndrome (TS) is named after Dr. Henry Turner, who described the disorder in 1938. TS occurs in women and is characterized by abnormalities in the quantity or structure of sex chromosomes. The syndrome is most frequently characterized by gonadal dysgenesis and somatic disorders, the most important of which, is short stature [1, 2]. Hormonal studies typically reveal the low circulating concentrations of ovarian steroids and the high concentrations of gonadotropins in women aged 14 and over. In very few women with TS, the ovaries show cyclic hormonal activity manifested by the menstrual cycle and even fertility [3]. TS includes a wide range of chromosomal karyotypes and clinical phenotypes [4]. The patients exhibit a wide variety of anomalies and pathologies within different organs. Nevertheless, the clinical features of TS have not been fully resolved [5]. Basic phenotypic abnormalities occur in the tissues of mesodermal origin. TS is characterized by the expression of different phenotypes, and physical stigmata can be mild or absent [6]. TS affects one in every 2500 women. Hence, it can be speculated there are approximately 8000 women with Turner syndrome in Poland of whom 5000 are over 18 years old. Compared to the 'general' population, morbidity and mortality are increased. The risk to die from Turner syndrome among women is four times higher than in the rest of the population [7, 8]. Structural heart defects are found in a quarter to half of the

women with TS. It mainly involves the left side of the heart, including bicuspid aortic valve, aortic arch abnormalities and progressive dilation of the ascending aorta [9, 10]. Aortic dissection sometimes is a fatal complication in Turner syndrome women. The risk of arterial hypertension prevalent in TS women. It is widely known that higher blood pressure, elevated LDL and glucose as well as decreased HDL levels are typical of TS women [11]. Overweight, obesity and a higher percentage of whole-body fat mass increased the risk for both types of diabetes 1 and 2 [12]. Arterial hypertension is reported in 13–58% of adult Turner syndrome patients and confers an increased risk for cerebrovascular disease and aortic dissection, adding significantly to the medical burden of Turner syndrome [13]. The cause of hypertension in Turner syndrome is multi-factorial [14]. Factors involved in the pathogenesis of hypertension and diabetes include inappropriate activation of the renin–angiotensin–aldosterone (RAA) system, oxidative stress, inflammation, impaired insulin-mediated vasodilatation, increased stimulation of sympathetic nervous system (SNS) and abnormal sodium excretion by the kidney [15]. The contribution of both RAA axis and SNS in the pathogenesis of hypertension remains uncertain. SNS is rather over-activated in TS women [16].

Hormone therapy in TS patients is not only a treatment for short stature (growth hormone) and the compensation for sex hormone deficit (sex hormones), but also the counteraction to the deficit

effects, including the reduction in the risk of cardiovascular diseases. Oestrogens not only contribute to the normal autonomous regulation. They also regulate vascular function by modulation cascades RAA system and endothelin, by their antioxidant activity [17], and reduction of inflammation with an increased C-reactive protein, positively influence dyslipidaemia with an unfavourable atherogenic profile. Not all the effects of oestrogens are documented in TS patients. In our previous study we recognize that TS-women, who receive HRT, use this method of treatment insufficiently [18]. A large percentage of women with TS do not comply with doctors' orders regarding hormonal treatment. Therefore by analysing gonadal hormones concentrations and assessing the risk factors of cardiovascular diseases we can venture to answer the question: whether HRT decreases the risk of occurrence of cardiovascular diseases in TS women or not?

The aim of this study was to assess the lipid and carbohydrate metabolisms as well as blood pressure in TS women who declared using HRT in the context of the blood concentration of 17β estradiol (E_2).

Material and methods

Investigations were conducted since 1995 year. Clinical subjects counted 176 women with Turner syndrome at the age ranging from 18 to 53 years, mean 24.6 ± 7.7 , height 145 ± 7.1 (123–172) cm, and weight 50 ± 9.8 (28.8–80) kg, BMI 23.8 ± 4.2 (14.2–36.2) kg/m^2 . Blood pressure was measured in office. Hypertension was defined as systolic blood pressure ≥ 140 and diastolic blood pressure ≥ 90 mm Hg. Some patients were under antihypertensive treatment. They were also counted as hypertensives. The number of hypertensive TS women was 46 (26.1%). Only 95 women with TS, who declared using hormonal replacement therapy (HRT) (25 ± 8 years) were included in the study. The information about the application of HRT was collected during

the anamnesis. In all TS women the concentration of 17β estradiol (E_2) was measured. The total cholesterol (TC), high and low density lipoprotein (HDL and LDL), triglycerides (TG) and glucose blood serum concentrations were also assessed. Turner syndrome was diagnosed in each of the examined women and confirmed by karyotyping [6]. This group of patients was divided into two subgroups in which $E_2 \geq 110$ pmol/L ($n = 34$) — HE and the second group with $E_2 < 110$ pmol/L ($n = 61$) — LE. The collected research material was statistically computed with the use of the program STATISTICA 12 (data analysis software system), StatSoft, Inc. Results were introduced as a mean value \pm standard deviation. To compare the given results we used U Mann-Whitney-Test. Correlation analyses were conducted using the τ Kendall test. Relevance level was assumed as $\alpha = 0.05$.

Results

Arterial hypertension was diagnosed in 25 TS women (26.3%). In group HE 8 (23.5%) and LE 17 (27.9%). Both groups did not differ also in systolic 119 ± 20 vs 118 ± 14 mm Hg and diastolic 82 ± 13 vs 80 ± 10 mm Hg blood pressure. The mean values of body mass, lipid metabolism and glucose parameters in TS patients with low and normal estradiol levels are presented in table I.

In HE group despite the significantly higher concentrations of E_2 , we did not find differences in weights, the lipid metabolism parameters and glucose concentrations as compared to LE group. No correlations between E_2 and analyzed lipid metabolism parameters were found in both groups of TS women. Negative correlations between E_2 and body mass ($\tau = -0.25$, $p = 0.04$) as well as between E_2 and diastolic blood pressure ($\tau = -0.28$, $p = 0.02$) were found only in the HE group. This group is also characterized by the positive correlation between the E_2 and glucose levels ($r = 0.24$, $p < 0.05$).

Table I. Body mass, 17β estradiol (E_2), the total cholesterol (TC), high and low density lipoproteins (HDL and LDL), triglycerides (TG) and glucose blood serum concentrations of 95 women with Turner syndrome with low (LE) and normal (HE) estradiol levels, who declared using HRT. Means \pm SD; * $p < 0.001$

Tabela I. Masa ciała, stężenie 17β -estradiolu (E_2), cholesterolu całkowitego (TC), lipoprotein wysokiej (HDL) i niskiej (LDL) gęstości, trójglicerydów (TG) i glukozy w surowicy krwi u 95 kobiet z zespołem Turnera, z niskim (LE) i prawidłowym stężeniem estradiolu, które deklarywały stosowanie HTZ. Wartości średnie \pm SD; * $p < 0,001$

	Mass [kg]	E_2 [pmol/L]	TC [mmol/L]	HDL [mmol/L]	LDL [mmol/L]	TG [g/L]	Glucose [mmol/L]
HE (n = 34)	49 ± 8	$284 \pm 163^*$	4.9 ± 0.9	1.5 ± 0.4	3.2 ± 0.8	0.9 ± 0.4	5.1 ± 0.7
LE (n = 61)	50 ± 9	53 ± 10	4.9 ± 0.9	1.4 ± 0.4	3.3 ± 0.9	1.1 ± 0.6	5 ± 0.7

Discussion

Arterial hypertension is observed in 13–58% TS women. The reported prevalence of hypertension can partially be attributed to the varying definitions of hypertension [13]. In our study, blood pressure was measured in office. In our group of women with Turner syndrome, elevated blood pressure and hypertension were diagnosed in 25 TS women (26.3%). Elevated blood pressure adds to the increased morbidity and mortality of Turner syndrome. Arterial hypertension should be carefully diagnosed and rigorously treated. An important role, as a cause of high blood pressure, plays the activity of the sympathetic nervous system. Oestrogen deficiency due to gonadal malfunction contributes to the problem, both by stimulating sympathetic activity and promoting a metabolic syndrome. The impact of oestrogens on metabolism of lipids is well established. Oestrogens diminish lipids oxidation and increase the synthesis of triglycerides. Changes in the content of serum lipids explain the increase in HDL concentrations and the slight decrease in LDL and TC levels. The TG concentration and the storage of lipids also increase [19]. However, the application of HRT does not affect the lipid metabolism in women with Turner syndrome [11]. Perhaps the dose of HRT in TS women is too low? To this moment the optimal dose of HRT and form of application in the substitutive treatment of women with TS has not been established so far [20]. On the other hand a large percentage of women with TS does not comply with doctors' orders regarding hormonal treatment. In our material only half of patients (54%) declared using HRT [18]. However, only 1/3 TS women who declared using HRT have a satisfactory level of estradiol.

In our study, we did not observe any differences in lipid metabolism parameters in women who use HRT compared to those who do not. The timing, duration, and compliance with HRT treatment among the HRT-treated subjects were sometimes difficult to establish. Nevertheless, our finding that HRT-treated TS women with estradiol concentrations either above or below 110 pmol/L had no differences in lipid parameters supports the hypothesis that HRT does not have a beneficial impact on the lipids. However, we cannot exclude that HRT has a positive effect on blood pressure. The results of the correlation analysis indicate a positive correlation between E_2 and glucose concentrations, which is well known. The negative correlation between the E_2 concentration and body mass as well as between

E_2 and diastolic blood pressure in TS women with E_2 concentration ≥ 110 pmol/L indicates a beneficial effect of estradiol on the above mentioned parameters.

Conclusions

1. In TS women who declared using HRT only 1/3 have a satisfactory level of estradiol.
2. The hormone replacement therapy in women with TS does not affect significantly the glucose and lipid metabolism.
3. The negative correlations between E_2 and body mass and diastolic blood pressure in TS women suggests beneficial effect of estrogens in the treatment of arterial hypertension.

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