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ESTROGEN ROUTE REPOSITION DOES NOT AFFECT POSTPRANDIAL LIPEMIA AND INFLAMMATION IN PATIENTS WITH TURNER SYNDROME

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ABSTRACT

Aims: The aim of the present study was to examine the influence of estrogen route reposition on the response of postprandial lipemia and its impact on leukocyte and platelets recruitment, subclinical inflammation and carotid intima-media thickness in patients with Turner syndrome. **Method:** A cross-sectional study was conducted to evaluate the correlation between postprandial lipemia and fasting glycemia, insulin, carotid intima-media thickness, white blood cells and platelets count in 25 Turner syndrome patients. All patients were using oral progesterone, 11 on oral estrogen and 14 on transdermal estrogen. **Results:** The age, carotid intima-media thickness, fasting glucose, insulin and lipid profiles were similar between groups. We did not observe any difference between the oral and transdermal hormone replace therapy with regard to the amount of postprandial triglycerides, the delta value of total white blood cells and neutrophils. The platelets increased significantly only in the oral group of estrogen reposition and there was no difference in the platelets increase between subgroups. There is no correlation between the delta value of triglycerides and the delta values of CRP, platelets, total leukocytes and differential counts or the absolute value of carotid intima-media thickness. **Conclusion:** We conclude that the route of estrogen reposition does not affect the extent of postprandial lipemia and its consequences for leukocyte, platelet recruitment and carotid intima-media thickness.

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INTRODUCTION

Turner syndrome (TS) is associated with a chromosomal defect (monosomy XO, mosaicism or structural abnormality of one of the X chromosomes) that affects roughly 50 in 100,000 newborn girls with a characteristic phenotype of growth retardation and gonadal dysgenesis, in many cases leading to absence of puberty and/or subsequent sterility. Additionally, there is epidemiological evidence for a relatively increased risk of ischemic heart disease and brain vascular diseases in Turner syndrome (Gravholt *et al*., 1998; Morales-Demori, 2017; Kelley, 2017).

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In clinical studies there is evidence of increased levels of serum total cholesterol in children and adolescents (Zaman, 2012), as well as in adults (Zaman, 2012). However, other aspects of lipid metabolism including postprandial triglycerides (TG) levels have not been studied in patients with TS. Postprandial lipemia is recognized as a factor in the atherosclerotic process, and these postprandial triglycerides could be a determinant of coronary heart disease in women (Zaman, 2012; Tanaka, 2004 and Bansal, 2007). In the United States, conjugated oral equine estrogens (CEE) have historically been the most widely used form of estrogen for hormone replace therapy (HRT) in girls with TS (Drobac, 2006). However, transdermal estrogen (TD) is being used more frequently. Theoretical advantages of TD over oral estrogen include a more physiologic mode of delivery, decreased first pass effect and less variability in markers of

hepatic metabolism, IGF-I levels and lipid profile (Jospe, 1995; Vrablik, 2008 and Zaiem, 2017). There are few long-term studies of the effect of combined HRT on lipid metabolism in TS patients or in healthy women of a comparable age (Gravholt, 2004). The present study was designed to evaluate the influence of estrogen route reposition on postprandial lipemia, and the recruitment of WBC, platelets and their impact on subclinical inflammation, evaluated by high-sensitivity C-reactive protein (CRP). In addition, the correlation between the magnitude of postprandial lipemia and carotid intima-media thickness was also verified.

SUBJECTS AND METHODS

Subjects: The study was performed at Clementino Fraga Filho University Hospital, of the UFRJ (Federal Univeristy of Rio de Janeiro), Brazil. After institutional ethics committee approval, 25 patients with TS (45,X and related karyotypes), aged higher than 20 years old, were recruited after obtaining informed written consent. Eleven patients used CEE (Premarin®, Wyeth Medica Ireland, New Bridge, County Kildare, Ireland), 0.625mg/day from the 1st to the 25th day of the month, plus 10mg medroxyprogesterone acetate (MPA) (Provera®, Pharmacia Corporation de Venezuela C.A., Valência, Venezuela) from the 15th to the 25th day, and another group of fourteen patients with TS used the estradiol Estreva® Gel (Laboratoire Theramex, Monaco), 1.5g of Estradiol/day, and medroxyprogesterone acetate in the same manner. Patients used these medicines for a minimum of 1 year. Women with preexisting renal disease, cardiovascular disease and diabetes mellitus were excluded from the study, as well as smokers, patients using aspirin or lipid lowering agents.

Study protocol: After a 12-hour overnight fast, an intravenous catheter was inserted into the forearm vein for blood sampling. Each participant was given a test meal containing 50g fat/m^2 body surface area. The meal consisted of whole milk, chocolate, milk cream, coconut milk, butter and salted crackers. Composition of the meal was 61.7% fat, 29.6% carbohydrates, and 8.7% protein. After the meal, subjects were not allowed to eat for the next 4 hours but were given free access to water. Blood samples were drawn before the meal and every 2 hours after the meal over a 4-hour period. The plasma was separated immediately after blood collection by centrifugation. The blood samples were collected in fasting state, as well as two and four hours after the fat overload to measure glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides (TG), leucocytes, platelets, and insulin. CRP was measured in fasting state and four hours after the fat overload. TG, total and HDL cholesterol, glucose, leucocytes and platelets were measured by standard laboratory techniques. LDL cholesterol was calculated with Friedewald's formula (Friedewald, 1972). Determination of insulin levels was carried out by the chemiluminescence method using double antibodies, specific to human insulin. The reference values range from 3 to 16 μUI/mL, the intra-assay coefficient of variation (CV) was 3.9% and the inter-assay CV 8.1%. CRP levels were measured by high-sensitivity immunonephelometry with lower detection limit of 0.1mg/L, the intra-assay and inter-assay variation coefficients were 3.1% to 4.0% and 2.5% to 3.8%, respectively.

Measurement of carotid intima-media Thickness (IMT): IMT of the common carotid artery was calculated by the same examiner using high-resolution ultrasound imaging (Acuson Aspen Advanced model, 10mH linear probe, USA), as described by Soares *et al.,* (2005). The common carotid arteries were scanned at the level of the bifurcation on both the right and left sides. Subsequently, IMT was measured in the far wall of the arteries at the sites of most advanced atherosclerotic lesions, identified as diffuse and continuous projections with the greatest distance between the lumen-intimal interface and the media-adventitial interface, but without atherosclerotic plaques. The mean value was calculated. Plaques were excluded from measurement.

Statistical analyses: Statistical analyses were performed using the SAS 6.04 System statistical software (SAS Inc., Cary NC, USA). To compare the numeric continuous variables (glucose, insulin levels, HOMA index, baseline lipid profile) between the two subgroups, the Student's *t* or the Mann-Whitney tests were used. The ANOVA for repeated measures was executed to evaluate the three moments of the triglycerides in each group and between groups. The Wilcoxon marked position test was applied to evaluate the variation of CRP between the baseline and post-4 hours. Spearman's coefficient was used to evaluate the correlation between glucose, HOMA-IR index, the delta value of WBC, neutrophils, CRP and platelets with the absolute delta value of TG. The criterion adopted for determining significance was the 5% level ($p<0.05$).

RESULTS

Baseline characteristics of the study participants are shown in Table 1.

Table 1. Baseline Clinical characteristics of oral group (n=11) and transdermal group (n=14) of estrogen reposition in TS patients

	Group	Mean	SD	*p value*
Age	Transdermal	24.9	5.2	0.46
	Oral	26.5	4.9	
Glucose	Transdermal	78.2	11.2	0.51
	Oral	76.1	3.2	
Insulin	Transdermal	5.07	5.71	0.32
	Oral	5.52	3.21	
HOMA-IR	Transdermal	1.067	1.395	0.25
	Oral	1.031	0.593	
Total Cholesterol	Transdermal	171.3	28.6	0.12
	Oral	193.1	40.1	
HDL	Transdermal	51.6	9.9	0.066
	Oral	59.2	9.5	
LDL	Transdermal	104.2	23.2	0.64
	Oral	115.6	40.8	
TG	Transdermal	76.6	27.4	0.21
	Oral	91.8	32.3	
CRP	Transdermal	2.9	2.5	0.44
	Oral	13.2	23.1	
Platelets	Transdermal	304.9	102.0	0.13
	Oral	255.1	51.1	
WBC	Transdermal	6642.9	2888.1	0.76
	Oral	5754.5	908.1	
Neutrophils	Transdermal	4008.5	2091.6	0.93
	Oral	3468.9	657.4	
IMT	Transdermal	0.49	0.08	0.52
	Oral	0.51	0.10	

HDL, high density lipoprotein; LDL, Low density lipoprotein; TG, triglycerides; CRP, high-sensitivity C-reactive protein; WBC, Total white blood cells; IMT, Intima-media carotid thickness. p value significant < 0.05

There were no statistically significant differences between groups with regard to age, total cholesterol and fractions, triglycerides, HOMA-IR index, glucose, insulin levels, IMT, CRP, platelets, total white blood cells (WBC) and differential count. After the fat overload, TG ($p=0.0001$ for both subgroups) (Figure 1), total WBC ($p=0.0006$ in the transdermal group and $p=0.003$ in the oral group) and

Table 2. Leukocytes, neutrophils, platelets and CRP behavior over time and between oral and transdermal group of estrogen reposition

	Basal	2 hours	4 hours	*p value*[a]	*p value*[b]
	Mean±SD	Mean±SD	Mean±SD		
Leukocytes					
Transdermal	6642±2888	7700±3906	8085±3205	0.0006	0.95
Oral	5754±908	6781±1447	7245±1167	0.003	
Neutrophils					
Transdermal	4008±2091	5301± 3461	5398±2905	0.0001	0.96
Oral	3468±657	4534±1410	4664±1292	0.019	
Platelets					
Transdermal	304.9±102	311.2±111.6	320.6±103.2	0.34	0.38
Oral	255.1±51.1	268.5±43.3	288.6±49.5	0.003	
CRP					
Transdermal	2.9±2.5	-	3.1±2.7	0.15[c]	0.5[d]
Oral	13.2±23.1	-	12.4±20.2	0.41[c]	

SD, Standard Deviation; CRP, highsensitivity C-reactive protein
[a] ANOVA for repeated measures in each subgroup
[b] ANOVA for repeated measures between the two subgroups
[c] Wilcoxon marked position test to evaluate the variation between baseline and 4 hours
[d] Mann-Whitney test to compare the delta value between groups
p value significant < 0.05

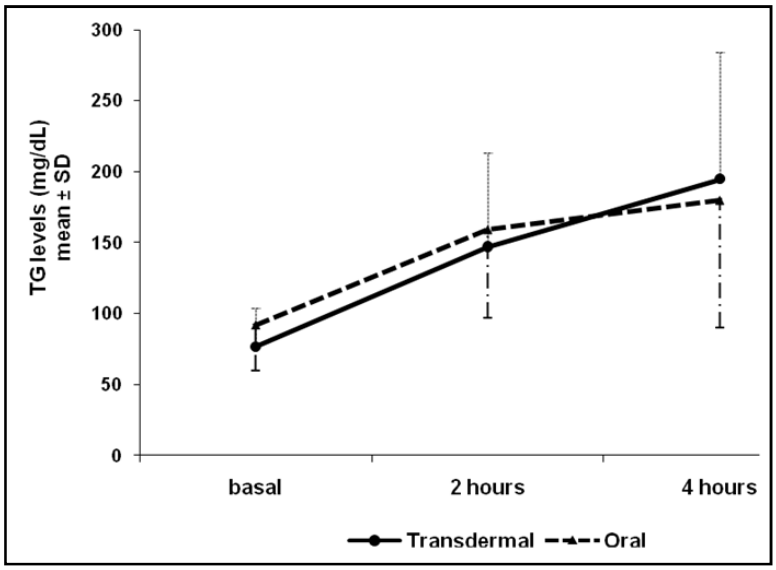

Figure 1. Schematic representation of postprandial TG response of the two main groups (Trandermal and Oral group of estrogen reposition). The ANOVA for repeated measures between the two subgroups presented a p=0.17

neutrophils (p=0.0001 in the transdermal group and p=0.016 in the oral group) increased significantly in comparison with the baseline values in both subgroups of estrogen reposition. But these increases were similar in both subgroups. The platelets increased significantly only in the oral group (p= 0.003) of reposition, and there was no difference between the subgroups (Table 2). CRP did not change over time between subgroups (p=0.15 in the transdermal group and 0.41 in the oral group) (Table 2). There was no correlation between the delta value of triglycerides with glucose, HOMA-IR index and IMT, as well as with the delta values of CRP, platelets, total leukocytes and neutrophils.

DISCUSSION

A large number of TS patients present estrogen deficiency, which results in loss of the cardioprotective effects of estrogen during menacme. The necessity for estrogen replacement has been recognized ever since the description of the syndrome by Henry Turner. However, there is no consensus regarding the ideal dosage and form of estrogen administration in these patients, nor for its use in adolescence and adult life (Shankar, 2018). It is known that low-density lipoprotein (LDL) particle size is heterogeneous, and the proatherogenic action of small dense LDL particles (sd-LDL) has been well documented (Gravholt, 2016 and Allaire, 2017). The proportion of these particularly harmful sd-LDL increase with higher levels of plasma triglycerides (TGs); and thus, sd-LDL accompanies conditions characterized by normal higher fasting TG levels and conditions associated with higher postprandial TG levels without fasting hypertriglyceridemia (Masuda, 2017 and Orem, 2017). In the present study, the route of estrogen reposition did not affect the magnitude of postprandial lipemia. Most individuals are at postprandial state for most of the day, and it is known that postprandial hypertriglyceridemia is related to coronary heart disease (CHD) (Kats, 2017; Perez-Martinez, 2016 and Nakamura, 2016). This could be because of trans-endothelial migration of TG-rich particles (Proctor, 2003), but also via postprandial recruitment and activation of circulating leukocytes attributing to endothelial cell activation (Van Oostrom, 2004). Supporting this theory, van Oostrom and colleagues have shown that postprandial recruitment of neutrophils may contribute to endothelium dysfunction (van Oostrom, 2003). Additional in vitro and ex vivo studies have suggested a direct relation between TG and leukocyte activation (Wanten, 2001). With the present study we have confirmed earlier reports that when TG increases in the postprandial phase there is a fat specific temporary increase in

neutrophils (van Oostrom, 2003; Van Oostrom, 2003; de Vries, 2015). These sd-LDL particles easily penetrate into the vascular wall, and they are more susceptible to oxidation and other modifications that predispose them to interact with the macrophage scavenger receptors, thus forming foam cells and promoting atherosclerosis (Bjornheden, 1996; Tani, 2011 and Gardner, 1996). Moreover, to assess early stages of atherosclerosis, ultrasound measurement of IMT of the common carotid artery is used. Several basic observations justify the use of this surrogate measurement. Comparison between IMT measured by B-mode ultrasound and by light microscopy demonstrates a good correspondence (Iwakiri, 2012). IMT also correlates with many established risk factors for atherosclerotic disease, such as smoking, hypertension, hypercholesterolemia, and increasing age (Ravani, 2015). Furthermore, carotid IMT reflects the severity of atherosclerotic disease in coronary arteries (Zhang, 2018 and Amato, 2017) and predicts future cardiac events (Sillesen, 2017). In our study, no difference between IMT was observed in the two groups, possibly because the fasting and postprandial lipid profiles in these groups were similar.

In our study, the elevation of platelets was only significant in the oral group of reposition. That platelets increase after a fat overload remains controversial. As we saw in the transdermal group, Kälsch and colleagues did not observe any increase in the number of platelets after the fat overload (Kalsch, 1989). However, van Oostrom and colleagues have shown that postprandial hypertriglyceridemia can increase platelets and this phenomenon can be blunted by rosuvastatin (de Vries, 2015). Despite the uncertainty in the increasing the number of platelets, most authors agree that the postprandial phase can lead to an activation of platelets, and this can be responsible for postprandial angina pectoris with myocardial infarction (Kalsch, 1998; Broijersen, 2009; Elmas, 2007). Although specific studies on the role of inflammation in regulation of plasma lipids are lacking, there are a few studies that suggest a link between inflammation and fasting or postprandial lipid profiles (Lanes, 2004 and Bradescu, 2005 and Chung, 2007). Interleukin-6 (IL6), tumor necrosis factor (TNF)-α and C-reactive protein (CRP) are associated with fasting triglycerides (Chung, 2007) while CRP in some studies was also associated with postprandial lipemia (Lanes, 2004 and Bradescu, 2005), probably through down-regulation of lipoprotein lipase activity (Borba, 2006). Recent reports show that CRP could be a biomarker for atherosclerosis in the general population (Singh, 2017). In our study, postprandial lipemia did not increase CRP levels in both subgroups. We conclude that the route of estrogen reposition does not affect postprandial lipemia and its relation to leukocyte and platelet recruitment, or to subclinical inflammation in patients with Turner syndrome.

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