METABOLISM CLINICAL AND EXPERIMENTAL XX (2013) XXX–XXX

Available online at www.sciencedirect.com

Metabolism

www.metabolismjournal.com

Estrogen receptor protein content is different in abdominal than gluteal subcutaneous adipose tissue of overweight-to-obese premenopausal women☆

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ARTICLE INFO

Article history:
Received 1 November 2012
Accepted 25 February 2013

Keywords:
Body fat distribution
Sex steroid receptors
Estradiol
Caucasian
African American

ABSTRACT

Objective. Premenopausal women demonstrate a distinctive gynoid body fat distribution and circulating estrogen status is associated with the maintenance of this adiposity patterning. Estrogen's role in modulation of regional adiposity may occur through estrogen receptors (ERs), which are present in human adipose tissue. The purpose of this study was to determine regional differences in the protein content of ERα, ERβ, and the G protein-coupled estrogen receptor (GPER) between the abdominal (AB) and gluteal (GL) subcutaneous adipose tissue of overweight-to-obese premenopausal women.

Materials/Methods. Biopsies of the subcutaneous AB and GL adipose tissue were performed in 15 premenopausal women (7 Caucasian/8 African American, 25.1 ± 1.8 years, BMI 29.5 ± 0.5 kg/m^2). Adipose tissue protein content was measured by western blot analysis and correlation analyses were conducted to assess the relationship between ER protein content and anthropometric indices/body composition measurements.

Results. We found that ERα protein was higher in AB than GL (AB 1.0 ± 0.2 vs GL 0.67 ± 0.1 arbitrary units [AU], $P = 0.02$), ERβ protein was higher in GL than AB (AB 0.78 ± 0.12 vs GL 1.3 ± 0.2 AU, $P = 0.002$), ERα/ERβ ratio was higher in AB than GL (AB 1.9 ± 0.4 vs GL 0.58 ± 0.08 AU, $P = 0.007$), and GPER protein content was similar in AB and GL ($P = 0.80$) subcutaneous adipose tissue. Waist-to-hip ratio was inversely related to gluteal ERβ ($r^2 = 0.315$, $P = 0.03$) and positively related to gluteal ERα/ERβ ratio ($r^2 = 0.406$, $P = 0.01$).

Abbreviations: AB, abdominal; BMI, body mass index; DERKO, double ERα/ERβ knockout mouse; DHEA-S, dehydroepiandrosterone sulfate; DXA, dual-energy x-ray absorptiometry; ERα, estrogen receptor alpha; ERβ, estrogen receptor beta; GL, gluteal; GPER, G protein-coupled estrogen receptor; HDL, high-density-lipoprotein cholesterol; HOMA-IR, Homeostasis model assessment of insulin resistance; LDL, low-density-lipoprotein cholesterol; SAT, subcutaneous adipose tissue; SHBG, sex hormone-binding globulin; TC, total cholesterol; TG, triglycerides; WHR, waist-to-hip ratio; αERKO, Estrogen Receptor α knockout mouse; βERKO, Estrogen Receptor β knockout mouse.

☆ Disclosure Summary: The authors have nothing to disclose.

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http://dx.doi.org/10.1016/j.metabol.2013.02.010

Conclusions. These results indicate that depot specific ER content may be an important underlying determinant of regional effects of estrogen in upper and lower body adipose tissue of overweight-to-obese premenopausal women.

1. Introduction

Excess weight increases the risk of multiple disease states, including heart disease, hypertension, Type 2 diabetes, certain cancers (e.g. colon and breast) and stroke [1–4]. Recent body composition studies emphasize the importance of regional adiposity compared to overall adiposity in assessing disease risk [1–5]. The hypothesis that the localization of body fat, and not merely total fat mass, holds high importance in the elevated health risks associated with obesity is not a new idea; J. Vague first suggested that the relative amount of upper- versus lower-body obesity was important [6].

Premenopausal women demonstrate a distinctive gluteal–femoral body fat distribution [7–9]. Although evolutionary reasoning behind this pattern of adiposity is not definitive, one hypothesis is that women accumulate energy reserves in the lower body in preparation for increased energy utilization and adipose mobilization from this depot during pregnancy and lactation [10–12]. Sequestration of fat in the lower body region is associated with decreased risk for cardiovascular and metabolic disease versus accumulation of central adiposity [9,13–17]. Therefore, a full understanding of the physiology behind why, and by what mechanisms, adipose tissue accumulates in specific depots is important in efforts of obesity and chronic disease prevention.

Estrogen status is related to the maintenance of a gynoid body fat distribution [18]. The loss of circulating estrogen over the menopausal transition is associated with increases in central adiposity, a pattern of adiposity linked to increased cardio-metabolic disease risk [19–22]. The expression of estrogen receptor alpha (ERα) [23,24], estrogen receptor beta (ERβ) [25–28], and the G protein-coupled estrogen receptor (GPER) [29] within human adipose tissue indicates estrogen has direct effects within adipose tissue [30]. Taken together, a shift toward increased central adiposity with decreases in circulating estrogen status and the presence of ERs within the adipose tissue present a strong case for modulation of adipose accumulation via estrogen, potentially in a region specific manner.

There have been few investigations into regional differences in estrogen receptor expression in human adipose tissue, with most of those focusing on differences in estrogen receptor gene expression between subcutaneous and visceral abdominal adipose tissue [28,31]. To our knowledge studies are lacking which characterize the protein content of all three estrogen receptors in upper and lower body adipose tissue in overweight or moderately obese women. There is limited evidence that ERβ mRNA expression is higher in gluteal than abdominal subcutaneous adipose tissue (SAT) from overweight premenopausal women [25], supporting the hypothesis that regional differences in ER expression may be a mechanism behind regional differences in adipose accumulation and/or mobilization. Importantly, ERα and ERβ are reported to have distinct actions and ERβ may even oppose the actions of ERα [25,28,32,33], highlighting the need for a clear representation of the relative ERα to ERβ ratio in each adipose depot. Therefore, the primary purpose of this study was to determine if there are regional differences in the protein content of ERα, ERβ, and GPER between the abdominal (AB) and gluteal (GL) SAT of overweight-to-obese premenopausal women demonstrating a gluteal–femoral body fat distribution (defined as a waist-to-hip ratio < 0.85).

African American women tend to be more obese than Caucasian women [34] and for a given amount of total body adiposity Caucasian and African American women are reported to have different body fat distributions. African American women have less visceral adipose tissue for a similar age and BMI [35–37], and/or have greater amounts of SAT even after adjustment for total body fat [36,38,39]. If these racial differences in regional adiposity are related to local adipose tissue actions of estrogens is unknown. Therefore, as a secondary aim, subgroup analyses were conducted to investigate racial (Caucasian and African American) differences in regional ER protein content. Establishing regional SAT ER protein content is an important step towards understanding how estrogen may affect adipose depots in the upper and lower body differently, potentially playing a modulatory role in regional adipose tissue accumulation.

2. Methods

2.1. Participants

Fifteen overweight/obese premenopausal women, (7 Caucasian/8 African American, 25.1 ± 1.8 years, 81.3 ± 2.5 kg, BMI 29.5 ± 0.5 kg/m^2) between 18 and 39 years old were studied (Table 1). Participants were eumenorrheic (average cycle length 30 ± 1 days), not taking hormonal contraceptives (no use in ≥ 6 months at study entry), weight stable (< 3 kg weight change in previous 6 months) and not regularly active (< 30 min/day of exercise, < 2 days/week). Exclusion criteria included: trying to get pregnant, currently pregnant or lactating, smoking, history of metabolic or cardiovascular disease, taking any medications known to alter lipid metabolism or blood flow. Participants were informed verbally and in writing of the purpose, risks, and benefits of the research and provided informed consent prior to enrollment in the study. This study was approved by the Medical Center Institutional Review Board at East Carolina University.

2.2. Body composition

Participants were weighed on an electronic scale with weight recorded to the nearest 0.1 kg and height was measured with a standard stadiometer to the nearest centimeter (cm). Minimal

Please cite this article as: Gavin KM, et al, Estrogen receptor protein content is different in abdominal than gluteal subcutaneous adipose tissue of overweight-to-obese..., Metabolism (2013), http://dx.doi.org/10.1016/j.metabol.2013.02.010