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Body fatness and endogenous sex hormones in the menopausal transition

Annamaria Zsakai[a,*], Zsolt Karkus[a], Katinka Utczas[a], Beata Biri[b], Lynnette L. Sievert[c], Eva B. Bodzsar[a]

[a] Department of Biological Anthropology, Eotvos Lorand University, Pazmany P. s. 1/c, 1117 Budapest, Hungary
[b] Department of Biochemistry, Eotvos Lorand University, Pazmany P. s. 1/c, 1117 Budapest, Hungary
[c] Department of Anthropology, UMass Amherst, 217 Machmer Hall, 240 Hicks Way, Amherst, MA 01003, USA

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ABSTRACT

Background: Age at the final menstrual period is of clinical and public health interest because the age at which natural menopause occurs may be a marker of ageing and health, and in general the menopausal transition increases the risk of many diseases, e.g. redistribution in the pattern of adiposity during the menopausal transition may increase risk of metabolic disease. The purpose of this research was to study the relationship between the menopausal status and body fatness.
Subjects and methods: A random sample of 1932Hungarian women was studied. Body composition was estimated by body impedance analysis. In a subsample free estradiol and progesterone levels in saliva were quantified.
Results: Body fat mass increased until the late 50s and then had a decrease through senescence. Premenopausal women who were much older than the median age at menopause had a higher amount of fat than their postmenopausal age-peers, while postmenopausal women, whose menopause occurred much earlier than the median age at menopause, had less fat than their premenopausal age-peers. The body fat mass in premenopausal women with low levels of sex hormones was always below the age-median value of the menopausal status subgroups, while the body fat mass of postmenopausal women with high levels of sex hormone levels was above the age-median values.
Conclusions: The analysis of body fatness in the menopausal transition revealed that (1) the rate of reproductive ageing and the body fat pattern were significantly related, and (2) body fat mass of women with unexpected levels of sex hormones was related more to their hormonal levels than to their menopausal status or their age. Thus future epidemiological screenings of women exposed to higher levels of menopause-related health risks should be expanded beyond the estimation of menopausal status based only on menstrual history to include sex hormone level assessment, as well as body composition analysis.

1. Introduction

Total body mass and the relative mass of tissue components are influenced by genetic and environmental factors (e.g., lifestyle, psychosocial, and sociocultural factors) and their interactions [1]. The body fat content of the human body is regulated by the neuroendocrine system through the whole life span, and can be maintained in a rather stable condition if the control of balance between energy intake and expenditure is appropriate. The neuroendocrine system regulates the energy balance through (1) the activity level of the autonomic nervous system, (2) the secretion of hormones (e.g., growth hormone, thyroid, insulin, sex steroids, leptin, adiponectin, resistin, ghrelin) and (3) physical activity and nutritional behaviours [2–4].

Adipose tissue serves not only as an energy storage site, an insulating layer and a mechanical protective layer, but also serves as an endocrine organ since several hormones (e.g. leptin, adiponectin, resistin, estrogens) are produced by this tissue. Almost all of the health-related changes in the location and amount of adipose tissue by age can be explained by all of these functions of the tissue, e.g. the increased adipose storage during pregnancy serves lactation after pregnancy. Women in different reproductive stages are exposed to different hormonal environments. It is evidenced that, due to the changing sex hormonal levels, the transitions

* Corresponding author.
E-mail addresses: zsakaia@elte.hu (A. Zsakai), karkus@apaczai.elte.hu (Z. Karkus), utczas.katinka@gmail.com (K. Utczas), biri.beata@gmail.com (B. Biri), leidy@anthro.umass.edu (L.L. Sievert), bodzsar@elte.hu (E.B. Bodzsar).

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between these stages are accompanied by significant changes in metabolic status and body structure and, as a consequences of these changes, the transitions are also accompanied by changes in general health status and quality of life as well [5–11]. There is much evidence for the relationship between an increase in overall morbidity and mortality and early or late ages of onset of the menopausal transition, e.g. an association of premature menopause (due to the subsequent oestrogen deficiency) with the increased risk of cardiovascular [11–14] and autoimmune diseases [14,15], osteoporosis [16,17], neurological diseases and psychiatric diseases [18,19] has been confirmed [11,14,15,20–23], while women experiencing menopause at a late age are at a higher risk of breast cancer [24,25] and abdominal obesity [20–23].

Although there is evidence that ageing is associated with reduced energy expenditure (in all of its components, such as physical activity, basal metabolism and adaptive thermogenesis) [26–28], levels of sex hormones decrease dramatically during the menopausal transition, and body fat distribution changes in relation to reproductive ageing due to this change in hormone production in women. However the biological processes that lead to changes in body fat distribution during the menopausal transition, i.e., an increase of total and central body fat (in particular an increase in the accumulation of intra-abdominal fat) and a redistribution of fat from lower body subcutaneous fat toward the abdominal region [29–31] have not been fully explored [32,33]. In addition, the changes in body fat distribution by age and during the menopausal transition cannot be studied independently (the increase in relative body fat mass and the increase in abdominal fat accumulation are the main features of body fatness redistribution by ageing) [29,34–36].

The main purpose of the present study was to analyze the changes in body fat mass in relation to age and menopausal status. The menopausal status of subjects was estimated on the basis of menstrual history parameters. In addition, free estradiol and progesterone levels in saliva were quantified in a subsample of subjects. Serum samples cannot be usually collected in epidemiological surveys. That is why the salivary level of the studied sex hormones has not been analysed in a larger sample. To achieve the main purpose of the study (1) body fatness (fat mass and fat distribution) of women was described by ageing and menopausal status, and (2) body fatness of subjects whose sex hormone levels were out of the normal interval of their menopausal status category were analysed.

2. Subjects and methods

2.1. Sample

After anthropometric, body composition and osteometric examinations, women (n: 1932, aged 35+ years; Table 1) were interviewed by questionnaires concerning their reproductive and menstrual history, socio-demographic background, lifestyle (habitual physical activity and nutrition), health conditions and subjective health. The subsample of women who participated in the saliva estradiol and progesterone estimation consisted of 173 subjects (Table 1). The presented cross-sectional survey was carried out between 2011 and 2014. Sample selection was done by considering the recommendations of the Sampling and Methodology Section of the Hungarian Central Statistical Office, which were based on the population statistics of the administrative territories and design-statistical regions.

Women who had any diseases or were taking any medications known to affect body composition, or who were hysterectomized or ovariectomized, were not included in the analysis. Only those women who had not used hormonal contraceptives or other sex hormones in the last year were asked to collect saliva samples for sex hormone level estimations.

All subjects were asked to give their informed consent to participate in the study. All participants were provided with detailed information on the main purposes of the study and on all examinations before their approval. The participation was voluntary and anonymous. The research objectives, the research methodology and the questionnaires were approved by the National Human Research Ethics Committee (108/2011) and the Hungarian Scientific Research Fund (EIK-1001/2011).

2.2. Methods

Subjects were divided into premenopausal, early and late perimenopausal and postmenopausal subgroups on the basis of their *menstrual cycle characteristics* (the occurrence of irregular periods and the age of last menstrual period; Table 1):

- premenopausal status: menstrual period in the past 3 months and no decreased predictability,
- early perimenopausal status: menstrual period in the past 3 months but less predictability in the preceding 12 months,
- late perimenopausal status: menstrual bleeding in the past 12 months but not in the past 3 months, and.
- postmenopausal status: amenorrheic for the past 12 months and no hysterectomy.

The age of natural menopause was estimated retrospectively by considering the age at the last menstrual cycle in the postmenopausal subgroup (median age at menopause was 51.60 years, 95% confidence interval: 50.78–52.40 years, probit analysis) [37]. Subjects were divided into 10-year long birth cohorts. Subjects were divided into “too early,” “normal” and “too late” menopause on the basis of the age at normal menopause. Premature menopause was diagnosed by the cessation of menstruation before the age of 40 years, in accord with the scientific literature, while “too late” menopause was defined as when the final menstruation period occurred after the age of 60 years [38,39].

The subjects in the subgroup selected for hormonal level estimations were categorized on the basis of their sex hormone levels. Due to the financial conditions of the study, saliva samples could be collected from altogether 200 subjects. The subjects in this subgroup were selected randomly, to achieve an adequate distribution of the subgroup by age and menopausal status. Finally sex hormone level estimation could be made in 173 women. In the other 27 women, the saliva was not the appropriate amount, consistency or colour, or an impossible menstruation status assessment excluded the collected sample from the hormone level estimation.

It is obvious that the levels of female sex hormones show cyclic fluctuations during reproductive life, and only one estimation of hormonal levels is not enough to divide subjects into menopausal status subgroups even in the context of the average length of menstrual cycle and date of the last menstruation. Our aim was only to identify those subjects whose hormonal levels were unexpected for their menstrual status determined on the basis of menstrual cycle patterns, i.e. premenopausal women (n: 12) whose hormonal levels were too low or postmenopausal women (n: 26) whose hormonal levels were too high for their menopausal status.

The levels of free estradiol and free progesterone were estimated by the 17β-Estradiol (RE52601) and Progesterone (RE52281) Saliva ELISA kits of IBL (Hamburg, Germany). Saliva samples were collected with commercially available equipment. Subjects were asked to avoid eating, drinking, chewing gum or brushing their teeth for 30 min before sampling. Saliva samples were collected between 10.00 and 12.00 in the morning, stored at −20 °C (no longer than 2 months before the assays), warmed up to room tem-