POSTMENOPAUSAL CHANGE IN MSCs SENSITIVITY TO TESTOSTERONE, 17β-ESTRADIOL, AND PTH ARE ASSOCIATED WITH IMPAIRED ADIPOGENESIS

Zinoveva AA, Bakhchinian E, Kamenkov SS, Shcherbakova LN, Bugerenko AE, Ogay DS, Voloshin NS, Chechekhina ES ✉, Kulebyakin KYu

Lomonosov Moscow State University, Moscow, Russia

The menopausal transition is accompanied by the decrease in estrogen levels and changes in the estrogen to androgen ratio, resulting in dysregulation of multipotent mesenchymal stem cell (MSCs) differentiation in the subcutaneous adipose tissue, reduction of their adipogenic potential, adipocyte hypertrophy, and metabolic disorder progression. Menopausal hormone therapy (MHT) is used to manage menopausal symptoms. However, the effects of exogenous hormones on MSCs are still poorly understood. The study aimed to assess adipogenic differentiation of the subcutaneous adipose tissue MSCs and their sensitivity to testosterone, 17β-estradiol, and parathyroid hormone (PTH) in postmenopause. A total of six patients with benign gynecological disorders were included in the study, among them two were of reproductive age, one was perimenopausal, and three were postmenopausal. The MSCs adipogenic differentiation was performed throughout 14 days with the addition of testosterone, 17β-estradiol, or PTH, 10 nM each, then the proportion of cells containing lipid droplets was assessed. The adipogenesis level in control samples was 26–30% in patients of childbearing age and 12–42% in postmenopausal ones, with the pronounced interindividual variability. Hormonal stimulation considerably suppressed MSCs adipogenesis in postmenopause: testosterone reduced adipogenesis to 46–56% of control levels, estradiol to 51–84%, PTH to 53–66%, while patients of childbearing age showed a less pronounced effect (65–85%). The obtained data demonstrate a shift in hormonal sensitivity of MSCs from subcutaneous adipose tissue in postmenopause and suggest that MHT may exert an additional inhibiting effect on adipogenesis through suppression of MSCs differentiation.

Keywords: mesenchymal stem cells, testosterone, 17β-estradiol, PTH, adipogenic potential, menopause, menopausal hormone therapy

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Compliance with ethical standards: the study was approved by the Ethics Committee of the Lomonosov Moscow State University (IRB00010587, protocol No. 4 dated 4 June 2018, protocol No. 9 dated 29 October 2018) was conducted in accordance with the principles of the Declaration of Helsinki. All the patients provided informed consent before biomaterial collection.

✉ **Correspondence should be addressed:** Elizaveta S. Chechekhina
Lomonosovsky Prospect 27/1, Moscow, 119192, Russia; voynovaes@my.msu.ru

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ПОСТМЕНОПАУЗАЛЬНОЕ ИЗМЕНЕНИЕ ЧУВСТВИТЕЛЬНОСТИ МСК К ТЕСТОСТЕРОНУ, 17β-ЭСТРАДИОЛУ И ПТГ АССОЦИИРОВАНО С НАРУШЕНИЕМ АДИПОГЕНЕЗА

А. А. Зиновьева, Е. Бахчинян, С. С. Каменков, Л. Н. Щербакова, А. Е. Бугеренко, Д. С. Огай, Н. С. Волошин, Е. С. Чечехина ✉, К. Ю. Кулебякин

Московский государственный университет имени М. В. Ломоносова, Москва, Россия

Менопаузальный переход сопровождается снижением уровня эстрогенов и изменением соотношения эстрогенов и андрогенов, что приводит к дисрегуляции дифференцировки мультипотентных мезенхимных стромальных клеток (МСК) подкожной жировой ткани, снижению их адипогенного потенциала, гипертрофии адипоцитов и прогрессированию метаболических нарушений. Для коррекции менопаузальных расстройств назначается менопаузальная гормональная терапия (МГТ), однако влияние экзогенных гормонов на МСК остается малоизученным. Целью исследования было изучить адипогенную дифференцировку МСК подкожной жировой ткани и их чувствительность к тестостерону, 17β-эстрадиолу и паратиреоидному гормону (ПТГ) в постменопаузе. В исследование включено шесть пациенток с доброкачественной гинекологической патологией, из них две в репродуктивном периоде, одна в перименопаузе и три в постменопаузе. Адипогенную дифференцировку МСК проводили в течение 14 дней с добавлением тестостерона, 17β-эстрадиола или ПТГ по 10 нМ, после чего оценили долю клеток с жировыми каплями. Базовый уровень адипогенеза в контроле составил 26–30% у пациенток репродуктивного возраста и 12–42% в постменопаузе с выраженной межиндивидуальной вариабельностью. Гормональная стимуляция значительно подавляла адипогенез МСК в постменопаузе: тестостерон снизил эффективность до 46–56% от контроля, эстрадиол — до 51–84%, ПТГ — до 53–66%, тогда как в репродуктивном возрасте эффект был умеренным (65–85%). Полученные данные демонстрируют сдвиг гормональной чувствительности МСК подкожной жировой ткани в постменопаузе и свидетельствуют о том, что МГТ может оказывать дополнительное ингибирующее действие на адипогенез через подавление дифференцировки МСК.

Ключевые слова: мультипотентные мезенхимные стромальные клетки, тестостерон, 17β-эстрадиол, ПТГ, адипогенный потенциал, менопауза, менопаузальная гормональная терапия

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Вклад авторов: А. А. Зиновьева, Е. Бахчинян — эксперименты по дифференцировке МСК, обработка результатов; С. С. Каменков — выделение и культивирование МСК, статистическая обработка данных, написание рукописи; Л. Н. Щербакова — организация клинического этапа, получение биологического материала, интерпретация результатов, редактирование рукописи; А. Е. Бугеренко, Д. С. Огай — организация клинического этапа, получение биологического материала; Н. С. Волошин — количественная оценка адипогенной дифференцировки; Е. С. Чечехина — концепция и дизайн исследования, выделение и культивирование МСК, интерпретация результатов, написание рукописи; К. Ю. Кулебякин — концепция и дизайн исследования, интерпретация результатов, редактирование рукописи.

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✉ **Для корреспонденции:** Елизавета Сергеевна Чечехина
Ломоносовский проспект, д. 27, корпус 1, г. Москва, 119192, Россия; voynovaes@my.msu.ru

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The menopausal transition represents a unique stage of a woman's life, when sudden rearrangement of neuroendocrine regulation leads to the profound change of both the function of classic hormone-dependent target organs and the behavior of multipotent mesenchymal stem cells (MSCs) of adipose and bone tissues [1, 2]. MSCs represent a key element of mesodermal tissue regeneration and have a unique ability to differentiate in different directions (adipogenic, osteogenic, and chondrogenic) [3]. The MSCs activity is under strict neuroendocrine control to ensure timely adjustment to the body's current demands [4]. In particular, in the female body, 17β-estradiol signaling is involved in the stromal tissue morphology and energy balance regulation during the menstrual cycle [5]. After menopause, the decrease in 17β-estradiol levels and changes in the estrogen to androgen ratio lead to the dysregulation of MSCs differentiation, as well as to changes in sensitivity to homeostatic hormones, such as parathyroid hormone (PTH) [6, 7]. Simultaneously, the MSCs senescent phenotype is formed, which results in the reduced MSC functional activity and worse tissue regeneration capacity [8–11]. An interplay between these processes leads to gender-specific manifestations of aging, including changes in the adipose tissue distribution, osteoporosis, and increased cardiometabolic risk [12, 13].

Traditionally, symptoms are alleviated by prescribing the menopausal hormone therapy (MHT) aimed mainly at replenishing estrogen (primarily 17β-estradiol) deficiency. MHT has a complex effect on adipose and bone tissues. It is well known that transdermal 17β-estradiol administration enhances the adipogenic potential of MSCs in the adipose tissue of the femoral depot without any considerable effect on abdominal cells [14]. As for the bone tissue, MHT slows down weight loss, stimulates MSCs osteogenic differentiation, suppresses osteoclast activity, and reduces bone resorption, thereby contributing to lower risk of osteoporosis [15]. Despite all the benefits, MHT prescription has several contraindications and is associated with some risk factors (thrombosis, cancer). Furthermore, it is not recommended to use MHT for adjustment of age-associated metabolic disorders and prevention of cardiovascular disorders [16]. In a number of countries, androgen-based drugs are prescribed to adjust vulvovaginal atrophy and increase libido, along with conventional MHT [17]. No testosterone-based drugs for treatment of menopausal symptoms have been registered in the Russian Federation. Furthemore, it is not recommended to prescribe testosterone-based drugs to women with cognitive impairment, cardiovascular and metabolic disorders [16, 18]. With respect to the existing limitations of systemic hormone therapy, the development of targeted methods based on the use of MSCs itself or their secretome (bioactive factors capable of locally modulating the MSCs differentiation processes without any systemic hormonal load) is becoming a promising area [19, 20]. In-depth knowledge of the mechanisms underlying the hormone-dependent MSCs differentiation in both young and elderly women will open new areas for personalized therapeutic approaches to adjustment of metabolic disorders in postmenopausal women in the future.

We assumed that there is a shift in the MSCs sensitivity to hormones in peri- and postmenopause, due to which testosterone, 17β-estradiol, and PTH have a more pronounced anti-adipogenic effect, than in women of childbearing age.

The study aimed to assess the features of adipogenic differentiation of the subcutaneous adipose tissue MSCs in women of childbearing age, peri- and postmenopausal women, as well as to assess changes in the MSCs sensitivity to testosterone, 17β-estradiol, and PTH in postmenopause.

METHODS

Patient characteristics

A total of six patients, who underwent elective surgery due to benign gynecological disorders, were included in the study. Two patients of childbearing age underwent diagnostic laparoscopy aimed to rule out tubal factor infertility; one patient, who were through perimenopausal transition, underwent hysterectomy due to multiple fibroids; three patients, who were in their late postmenopause (postmenopausal for more than 20 years), underwent surgery due to pelvic organ prolapse.

Inclusion criteria: elective laparoscopic surgery due to benign gynecological disorders. Patients of childbearing age (under 45), perimenopausal and postmenopausal patients were included. Exclusion criteria: malignant neoplasms, acute inflammatory disorders at the time of surgery, diabetes mellitus. Clinical characteristics of the patients included in the study are provided in Table 1.

MSCs isolation from the subcutaneous adipose tissue

The subcutaneous adipose tissue samples were obtained during laparoscopic gynecological surgery. Samples were collected from the umbilical area (first trocar insertion site); the sample volume was about 1 cm^3. Samples were transported in sterile containers with the Hanks' Balanced Salt Solution (PanEco, Russia) supplemented with 5% penicillin/streptomycin (Gibco, USA) at a temperature of 4 °C and processed within 2 hours after collection.

The subcutaneous adipose tissue samples were placed in a Petri dish and washed three times with the cooled sterile

Table 1. Clinical characteristics of patients

ID	Age, years	BMI, kg/m^2	Reproductive aging stage (Straw classification)	Extent of surgery	Somatic diseases
1	35	25.5	-4	Diagnostic laparoscopy, chromopertubation	Migraine
2	25	22.3	-4	Diagnostic laparoscopy, chromopertubation	Not detected
3	45	20.1	-1	Laparoscopic hysterectomy due to multiple fibroids	Hashimoto's thyroiditis
4*	71	25.3	2	Laparoscopic sacral colpopexy	Grade 3 hypertension, Cardiovascular risk class 3
5	69	24.3	2	Laparoscopic sacral colpopexy	Not detected
6	71	40.6	2	Laparoscopic sacral colpopexy	Grade 3 hypertension, Cardiovascular risk class 4. CAD: angina pectoris

Note: * — the patient had a history of using topical estrogens.

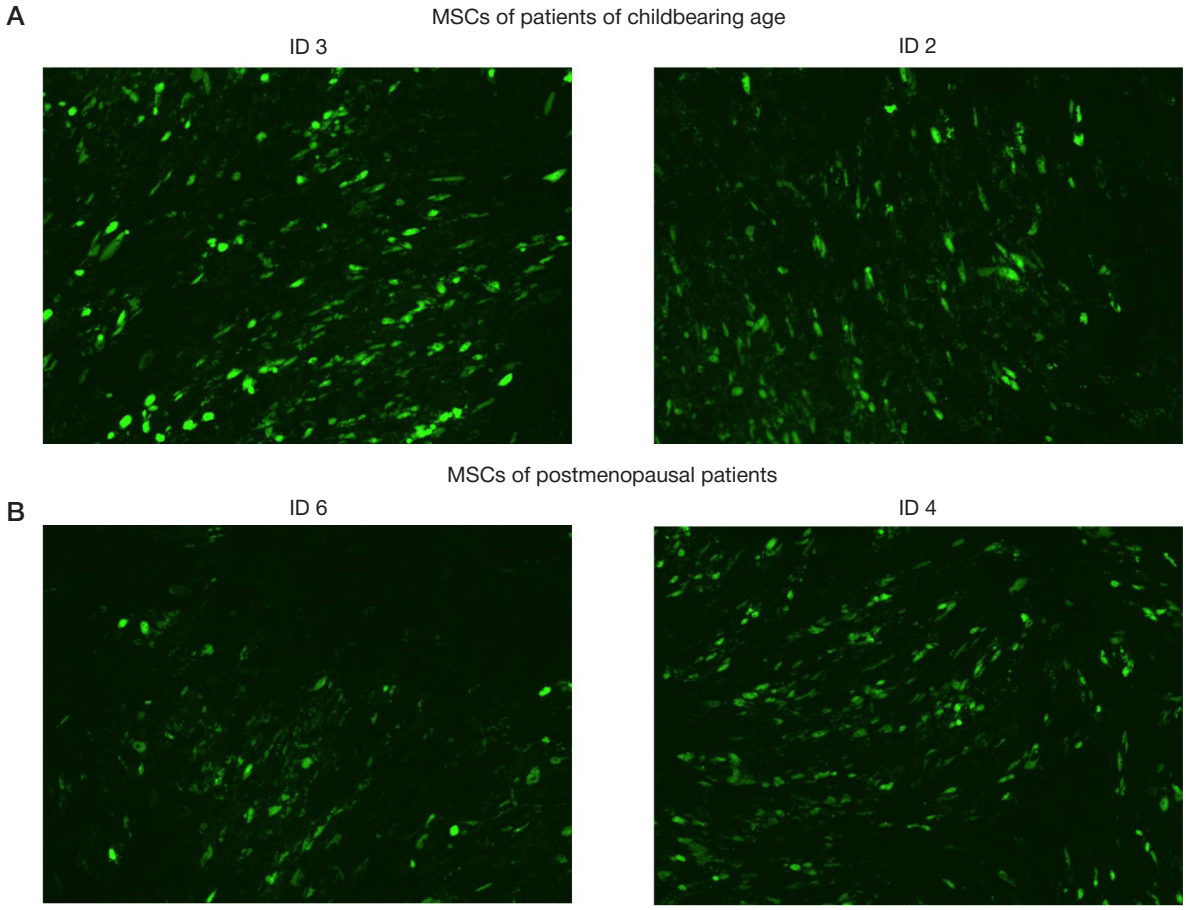

Fig. 1. Adipogenic differentiation of the MSCs obtained from patients of childbearing age and postmenopausal patients in the control differentiation medium. **A**. Images of the MSCs obtained from patients of childbearing age at the differentiation endpoint (day 14) with the Nile Red stained lipid droplets. **B**. Images of the MSCs obtained from postmenopausal patients at the differentiation endpoint (day 14) with the Nile Red stained lipid droplets

phosphate-buffered saline (PanEco, Russia) to eliminate remnants of blood and tissue fluid. Then the tissue washed was thoroughly minced using a sterile scalpel for 5–10 min until a homogeneous suspension was obtained. The processed material was transferred to the sterile 50 mL test tube and mixed with type I collagenase (Worthington, USA) in a concentration of 1.5 mg/mL dissolved in the Hanks' Balanced Salt Solution. The collagenase volume was calculated based on the ratio 1 : 2 by weight of tissue. Incubation was done at 37 °C in the 5% CO_2 atmosphere for 50–60 min, with regular stirring (every 10 min).

The resulting suspension was centrifuged at 180 g for 10 min at 4 °C. Centrifugation yielded three layers: the upper layer comprising the floating mature adipocytes and lipids, intermediate layer, and the lower layer comprising the stromal vascular fraction (SVF) in the form of the dark red sediment. The upper two layers were carefully removed using a pipette. The lower layer comprising SVF was resuspended in the Hanks' Balanced Salt Solution. The resulting suspension was filtered through a 100 μm nylon mesh in order to remove the intact tissue fragments trapped in the sediment. The filtrate was transferred into clean test tubes. The filtered suspension was centrifuged at 180 g for 10 min. Then the resulting sediment was resuspended in 3–5 mL of the complete culture medium, mixed thoroughly, and transferred to Petri dishes.

MSCs culturing

The cells were passaged in the DMEM medium with the low glucose content (PanEco, Russia) supplemented with the 10% fetal bovine serum (Gibco, USA) and 1% penicillin/streptomycin (Gibco, USA). The cells were passaged, when the 100% confluency was reached. The medium was collected from the culture dish, washed three times with the Versene solution (PanEco, Russia), then added a small amount of the 0.25% trypsin solution (PanEco, Russia), distributed evenly across the bottom of the dish, and incubated at 37 °C for 3–5 min. After the rounded detached cells appeared (this was controlled using the inverted microscope), the suspension was added the complete culture medium to the working volume, pipetted carefully to obtain a homogenous suspension, and transferred into the new Petri dish.

Adipogenic differentiation

MSCs were seeded onto 6-well plates (at 90–100% confluence) and incubated for 14 days in the complete culture medium supplemented with the reduced adipogenic cocktail (10 μg/mL insulin (Merck Millipore, Germany), 1 μM dexamethasone (Abcam, UK), 0.5 mM IBMX (Abcam, UK)). One hormone was added to certain wells: 10 nM 17β-estradiol (Tocris Bioscience, UK), 10 nM testosterone (Cloud-Clone Corp., USA), or 10 nM PTH (Tocris Bioscience, UK), other conditions remained the same.

To visualize lipid droplets in the differentiated adipocytes, the cells were stained with Nile Red (Merck, Germany), the lipophilic fluorescent dye showing high specificity and luminescence intensity when bound to neutral lipids, on day 14 of differentiation. Then the cells were imaged using the Nikon Eclipse Ti2 microscope (Nikon; Japan) with the Nikon Plan Fluor 10x/0.3 lens and Kinetix camera (Teledyne Photometrics, USA). The quantitative analysis was performed

Table 2. Absolute adipogenic differentiation efficiency values (proportion of cells with lipid droplets) in patients of various age groups

ID	Age, years	Reproductive aging stage (Straw classification)	Adipogenic differentiation, control	Adipogenic differentiation + testosterone	Adipogenic differentiation + 17β-estradiol	Adipogenic differentiation + PTH
1	35	–4	26.23%	18.77%	21.84%	19.68%
2	25	–4	29.85%	22.22%	25.25%	19.49%
3	45	–1	19.78%	11.35%	11.15%	10.66%
4	71	2	41.90%	23.56%	35.09%	27.80%
5	69	2	21.48%	11.24%	10.97%	11.28%
6	71	2	12.30%	5.63%	8.06%	6.55%

using the AI module for automated image assessment being part of the NIS-Elements 5.42.02 software (Nikon, Japan). All the cells in each image were segmented using the Segment Objects.ai model. Then each cell was tested for the presence of lipid droplets in it. The overall adipogenic differentiation efficiency was estimated as a percentage of cells with lipid droplets relative to the total number of cells. The analysis was performed on a number of randomly selected fields of view from different wells of the plate, which ensured the sample representativeness.

Statistical analysis

Statistical analysis of the results was performed using the SigmaPlot 11.0 software package (Systat Software Inc., San Jose, California, USA). The data distribution was tested for normality using the Shapiro–Wilk test. Independent groups were compared using the Student's t-test (for the normally distributed data) and Mann–Whitney *U*-test (for the non-normally distributed data). The differences were considered significant at $p < 0.05$. The values are presented as the mean ± standard error of the mean (mean ± SEM).

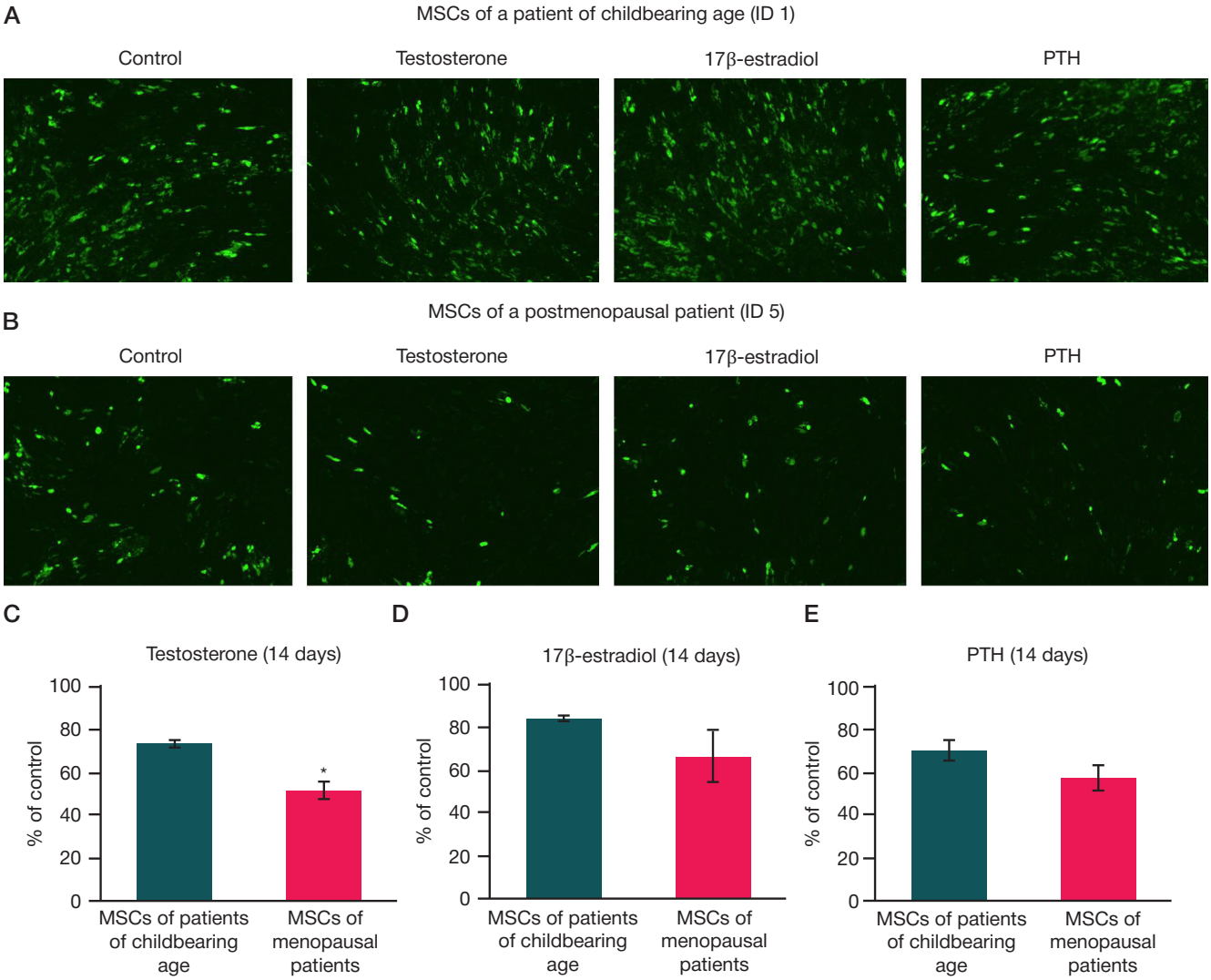

Fig. 2. Adipogenic differentiation of the MSCs obtained from patients of childbearing age and postmenopausal patients in the control differentiation medium, as well as in the differentiation medium supplemented with testosterone, 17β-estradiol, and PTH. **A**. Images of the MSCs obtained from patients of childbearing age at the differentiation endpoint (day 14) with the Nile Red stained lipid droplets. B. Images of the MSCs obtained from postmenopausal patients at the differentiation endpoint (day 14) with the Nile Red stained lipid droplets. **C**–**E**. Results of quantification of adipogenic differentiation in the presene of testosterone (**C**), 17β-estradiol (**D**), and PTH (**E**) normalized to the control differentiation conditions (n = 2,3; * — $p < 0.05$; t-test).

Table 3. Changes in adipogenic differentiation efficiency depending on testosterone, 17β-estradiol, and PTH supplementation in patients of various age groups

ID	Age, years	Reproductive aging stage (Straw classification)	Adipogenic differentiation + testosterone, % of control differentiation	Adipogenic differentiation + 17β-estradiol, % of control differentiation	Adipogenic differentiation + PTH, % of control differentiation
1	35	–4	72%	83%	75%
2	25	–4	74%	85%	65%
3	45	–1	57%	56%	54%
4	71	2	56%	84%	66%
5	69	2	52%	51%	53%
6	71	2	46%	66%	53%

RESULTS

Adipogenesis visual and quantitative characteristics in control conditions

Images of the fluorescence stained MSCs cultures obtained from patients of childbearing age (25–35 years, STRAW –4) showed high differentiation efficiency: lipid droplets occupying a large part of the cytoplasm were found in a large proportion of cells, which suggested active terminal phase of adipogenesis (Fig. 1A). In contrast, there were a considerably lower number of such cells in the MSCs cultures obtained from postmenopausal patients (69–71 years, STRAW +2) (Fig. 1B). The baseline proportion of Nile Red+ cells in the control was 26–30% in patients of childbearing age and 12–42% in postmenopausal patients, with the marked interindividual variability in the latter (Fig. 1B, Table 2).

We should also mention the detected discrepancy between age and the control values of adipogenic MSCs differentiation in two patients. Thus, patient 4 (71 years, postmenopause for more than 20 years) showed a relatively high adipogenesis level in the control (41.9%) (Fig. 1B; Table 2), which was much higher compared to the values of other patients of the same age. One possible explanation of this phenomenon can be personal clinical features of the patient: she received topical estriol for 1 month during the postoperative period, which could positively affect MSCs and their differentiation capacity. In contrast, patient 3 (45 years, late menopausal transition) showed a low level of adipogenic differentiation in the control (about 20%) (Table 2), which suggests the decrease in the cells' functional sensitivity already during the menopausal transition, which is characterized by unstable hormone levels with the preserved menstrual cycle. The data obtained emphasize considerable heterogeneity of the age-related MSCs alterations resulting from both baseline hormone levels and clinical factors, which should be taken into account when interpreting the MSCs differentiation results and developing the drugs for adjustment of metabolic disorders based on MSCs and their secretome.

Hormone-dependent effects on adipogenic differentiation

Testosterone supplementation caused the most pronounced adipogenesis suppression in the MSCs obtained from postmenopausal patients. Relative adipogenesis efficiency decreased to 46–56% compared to the control values (ID 4–6), while patients of childbearing age showed a moderate effect (72–74%) (Fig. 2A–C; Table 3). 17β-estradiol and PTH also inhibited differentiation in the late postmenopausal women (51–84% and 53–66% of the control, respectively) (Fig. 2 A–B, D–E; Table 3).

On the group of postmenopausal patients, patient 4 with the history of topical estradiol therapy having an abnomally high basal adipogenesis value turned out to be especially insensitive to the effects of 17β-estradiol and PTH (Fig. 1B; Table 3). In patient 3, all the hormones reduced relative differentiation efficiency to postmenopausal levels (54–57%), which confirms the data on the premature shift in MSC sensitivity to hormonal stimuli (Table 3).

Based on the data obtained we can conclude that the MSCs adipogenic differentiation depends on both women's age and hormone levels. High adipogenic differentiation efficiency is observed in the childbearing age, while in postmenopause (without systemic or topical hormone therapy) it is significantly decreased. High adipogenic activity in the 71-year-old postmenopausal patient, who received topical estriol therapy and, conversely, low differentiation level in a younger patient (ID 3; 45 years), being through her menopausal transition, suggest that the hormonal status can have a more pronounced effect on the MSCs functional state, than chronological age, and should be taken into account when interpreting experimental data and developing targeted therapeutic approaches.

Hormonal stimulation has fundamentally different effects on the MSCs obtained from patients of childbearing age and postmenopausal patients. It is clear that MSCs from postmenopausal patients demonstrate a pronounced decrease in adipogenesis efficiency in response to testosterone, estrogen, and PTH exposure. However, no similar anti-adipogenic effect is observed in the MSCs of younger patients. Thus, our findings suggest that there is a shift in the MSCs sensitivity to hormones in peri- and postmenopause.

DISCUSSION

The menopause represents a critical phase of a woman's life, associated with significant changes in the levels of circulating hormones. It is characterized by the decrease in estrogen levels and the increase in the androgen to estrogen ratio. In postmenopause, estrogens are predominantly synthesized in the adipose tissue from androgen precursors generated in the adrenal glands and ovaries. Androgen and estrogen concentrations in the adipose tissue are higher compared to circulating levels, reflecting the role of the adipose tissue as a critical reservoir and a site for the sex steroid metabolism [21]. The changes that occur during menopause are exacerbated by the overall aging of the body. The age-related and menopausal processes directly affect both terminally differentiated cells and stem cells, reducing their proliferation and differentiation potential.

In our study we have shown that the menopausal transition has a pronounced effect on the adipose tissue MSCs functions. MSCs of postmenopausal women demonstrate the decrease in adipogenic potential compared to MSCs of women of childbearing age [14, 22, 23]. The MSCs differentiation potential decrease in postmenopause can have a direct effect on the adipose tissue structure and functions. Since MSCs

represent the source of new adipocytes, disturbances of their differentiation lead to reduction of the pool of young functional adipocytes, hypertrophy of the existing cells, and accumulation of excess lipid droplets in the cells.

Earlier it has been shown that in premenopause the adipose tissue is characterized by high estrogen metabolism enzyme activity and estrogen concentrations significantly exceeding the serum levels. Following the onset of menopause, there is a significant decrease in both estrogen levels and the activity of appropriate enzymes. Furthermore, comparative analysis of the estrogen metabolism enzyme mRNA expression in the adipose tissue revealed similar patterns, regardless of the menopausal status, which suggests the key role of post-transcription mechanisms in reducing the tissue enzyme activity [24].

The results of our study provide a possible explanation of the mechanisms underlying such post-transcriptional alterations. Reduction of the subcutaneous MSCs adipogenic potential in postmenopausal women can be the first event initiating the cascade of changes in the adipose tissue. The lack of young functional adipocytes resulting from the decreased MSCs differentiation disturbs the adipose tissue normal architecture and cellular composition. This leads to accumulation of hypertrophic adipocytes showing the significantly decreased synthetic activity in the adipose tissue, which, in turn, decreases its overall enzyme activity.

We have shown that adding 17β-estradiol, PTH and especially testosterone significantly inhibits adipogenic differentiation of MSCs in postmenopausal patients, reducing the efficiency to 46–84% of the control, while young women show only a moderate effect. This change in sensitivity is of particular importance when prescribing MHT. It is well known that the adipose tissue of patients receiving MHT maintains high local estrogen concentrations and remains capable of active sex steroid metabolism, which prevents the development of visceral obesity typical for postmenopausal women [25]. Despite the fact that the mechanisms of the adipose tissue distribution hormonal regulation are complex and involve effects on the lipolysis, lipogenesis, and insulin sensitivity, our data suggest one more previously undescribed mechanism: the MHT-associated adipose tissue redistribution slowdown occurs not only due to the direct metabolic effects of estrogens, but also indirectly through the inhibition of the MSCs adipogenic differentiation by sex steroids.

Our study has shown the pronounced individual variability of the MSCs adipogenic potential in postmenopause. Such variability is determined not only by age and the time of onset of menopause, but also by the individual history of hormone therapy. The best example is patient 4, in whom, despite short-term use of topical estriol, relatively high basal adipogenesis was maintained, comparable with the values of younger patients. Such individual variability emphasizes the need to consider medical history data, including the history of using hormonal drugs, when interpreting the MSCs functional properties and developing personalized approaches to adjustment of postmenopausal disorders.

Our study fits well into modern concepts of the clinical and molecular mechanisms underlying the female body aging and changing balance of estrogens and androgens with the ovarian function loss [12, 26]. The data obtained are well correlated with the available data on the impact of estrogen deficiency on metabolic processes, tissue regeneration, and pathogenesis of postmenopausal disorders [27–30]. The approach involving the use of MSCs or their secretome for targeted therapy can open new promising methods for adjustment of postmenopausal disorders without systemic hormonal load [19, 20].

At the same time, the detected considerable interindividual variability of the MSCs functional properties requires further investigation of the mechanisms underlying regulation of MSCs differentiation and senescence considering the hormonal status, genetic and epigenetic context of each patient. This emphasizes the need for a comprehensive personalized approach to both selection of conventional menopausal hormone therapy and development of new MSC-based biotechnological methods for treatment of postmenopausal women.

Study limitations and the direction of future research

Small sample size (n = 2–3) significantly limits the study statistical power and reduces the possibility of extrapolating the results to a wider population of menopausal women. The perimenopause group is represented by only one patient (ID 3), which makes it impossible to assess the dynamic changes during the transition period. The data obtained suggest the potentially premature adipogenesis decrease. However, this conclusion needs to be confirmed in the larger cohort.

In the future it is planned to expand the sample of patients to increase the statistical power, reduce the effect of interindividual variability, and validate the results. Considerable basal adipogenesis variability (12–42% in postmenopausal patients) can be associated with individual differences in the hormonal status, concomitant disorders (hypertension, CAD), and therapy features (such as the use of topical estriol in patient 4). These factors make it difficult to distinguish between the effects directly related to menopause and the influence of individual patient characteristics.

Moreover, the study is based solely on the abdominal subcutaneous adipose tissue samples, which makes it impossible to assess the impact of hormonal factors on the visceral adipose tissue. In the future it is planned to include various adipose tissue types in the studies for more comprehensive assessment of the impact of menopause on the adipogenic potential.

CONCLUSIONS

It has been shown that the menopausal transition reduces the subcutaneous adipose tissue multipotent mesenchymal stem cell (MSCs) adipogenic differentiation capability. This triggers the cascade of changes in the adipose tissue: reduction of the proportion of young adipocytes, hypertrophy of mature cells, and the decrease in the local estrogen metabolism activity. Sex steroids (17β-estradiol, testosterone) and PTH enhance adipogenesis inhibition in postmenopausal women compared to women of childbearing age, which suggests the shift in the MSCs sensitivity to hormones following the ovarian failure. This mechanism can explain the adipose tissue redistribution slowdown associated with MHT not only by the direct metabolic effects of estrogens, but also through the MSCs differentiation modulation. To gain a deeper understanding of the mechanisms that determine the shift in hormonal sensitivity of MSCs in postmenopause, further study of the post-transcriptional regulation and senescence of these cells, considering genetic and epigenetic factors, is recommended. The results of such analysis can be used when developing the MSCs secretome-based cell preparations for adjustment of postmenopausal metabolic disorders.

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