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Macrophage subsets in the adipose tissue could be modified by sex and the reproductive age of women

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ABSTRACT

The presence of proinflammatory monocytes/macrophages (CD14+CD16+) has been documented in conditions of inflammation, such as atherosclerosis. We analysed the proportion of proinflammatory monocytes/macrophages in perirenal and perivascular fat in healthy living kidney donors with regard to sex and age reflecting reproductive status in women; therefore, women were further divided to younger and older group (younger and older than 51 years) reflecting potential age of menopause. Monocyte/macrophages were identified as CD14+ mononuclear cells and divided into subpopulations based on the co-expression of CD16. We found no differences in the monocyte/macrophage content between men (n = 15) and women (n = 28). Conversely, we observed a higher proportion of double positive CD14+CD16+ monocytes/macrophages in older women (n = 14) compared to younger women (n = 14). In addition, a strong correlation was found between the monocyte/macrophage content in fat and age only in older women. Therefore, proinflammatory monocytes/macrophages (CD14+CD16+) should be evaluated according to the sex and age.

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1. Introduction

Cardiovascular disease caused by atherosclerosis is rare in premenopausal women. However, its incidence increases rapidly after menopause. In our previous work, we detected a high prevalence of metabolic cardiovascular risk factors in women before menopause [1,2]. In addition, postmenopausal status is a strong risk factor for developing hypertension, which is potentially mediated through the increased body mass index immediately after menopause [3]. One emerging risk factor, especially in women approaching menopause, is an improper amount, distribution and malfunction of fat. An increase in the volume of adipose tissue leads to its infiltration by monocytes and macrophages [4,5], which are very potent inductors and accelerators of inflammatory status [6]. The presence of proinflammatory monocytes/macrophages co-expressing in addition to CD14 also CD16 marker (CD14+CD16+) in circulation and in inflamed tissue has been documented in several inflammation conditions as bacterial sepsis [7], Crohn disease [8], and coronary heart disease [9]. It was also proved that this subset of cells exhibits a distinct cytokine secretion pattern with high production of proinflammatory cytokines [10] and also has higher potency of phagocytosis and antigen presentation compared to classical CD14+CD16− blood monocytes [11].

The frequency of one of the most important risk factors for subclinical inflammation—obesity—in the Czech population is increasing and is currently approximately 30% in both sexes [12]. However, there are no data on the monocytes/macrophages phenotype in adipose tissue with respect to sex differences and the reproductive status in women. In our previous work, we detected the impact of saturated fatty acids on circulating inflammatory markers in postmenopausal women, which was found to have a positive relationship with weight gain [13]. We also found that the relationship of C-reactive protein was continuously increasing with age from 25 to 65 years in men, but in women it started to increase only after menopause [14]. These two phases of proinflammatory status in women might play a role in the increase of the risk after menopause. In younger women after standardized exercise we also

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detected substantially greater decrease of visceral compared to subcutaneous fat measured by magnetic resonance imaging [15]. The aim of the present study was to analyse the proportion of proinflammatory monocytes/macrophages in perirenal and perivascular fat as potential inflammatory mediators and to detect whether there are any differences between men and women and between women of premenopausal and postmenopausal ages.

2. Methods

Samples of perirenal and renal perivascular (surrounding the arteria renalis) tissue were obtained during the isolation of kidneys in living donors. The design of the study was approved by the Ethics Committee of the Institute. All participants were fully informed about the study and signed informed consent forms. All participants were interviewed with regard to their medical history and main cardiovascular risk factors. Samples of adipose tissue were collected during hand-assisted laparoscopic nephrectomy, cooled and immediately transferred to the laboratory. After visible blood vessels and connective tissues were removed, each tissue sample was dissected to generate small samples, exposed to collagenase and then repeatedly filtered and purified; finally, the stroma vascular fraction (SVF) was eluted from the sample. SVF was analysed on the same day using a flow cytometry analyser, CyAn (Beckman Coulter), and different monoclonal antibodies and fluorochromes (CD14− Phycoerythrin-Cyanine 7, PC7, CD16−Phycoerythrin-Texas Red-X, ECD, CD163 Phycoerythrin, PE/clone RM3/1) were used to define different subsets of monocytes/macrophages. The cells of the monocyte/macrophage lineage were identified as CD14+ mononuclear cells, and based on the co-expression of CD16, two subsets were identified. Flow cytometry data were analysed using Kaluza software (Beckman Coulter). The characteristics under study were analysed separately in men ($n = 15$) and women ($n = 28$). Women were, according to the approximate mean age of menopause, further divided into younger (younger than 51 years, $n = 14$) and older age groups (older than 51 years, $n = 14$).

2.1. Statistical analyses

Data are presented as the means with standard deviations for continuous variables and percentages with standard deviations for categorical variables. Between-group comparison of continuous variables was performed using unpaired t-test. The χ^2 test was applied for discrete variables. Linear regression was used for modelling the relation between the proportion of macrophages under study and age. Regarding the difference between correlation coefficients, the test of equality of slopes was not used because of the low number of participants. In all tests, p values less than 0.05 were considered statistically significant.

3. Results

The mean age of men was 42.8 ± 12.9 years, and the mean age of all women was 50.3 ± 7.9 years. The difference between the two groups was significant ($p = 0.02$). In all patients, no history of cardiovascular disease, hypertension or diabetes mellitus was reported; two women of older age displayed dyslipidaemia. Six men, 4 women of younger age and 3 women of older age were smokers. The mean body mass index in the entire group was 25.4 (±3.3) kg^*m^{-2}. The mean body mass index in men was 25.9 (±3.3); in women of younger age, it was 24.7 (±3.6); and in women of older age, it was 25.7 (±3.3) kg^*m^{-2}. No statistically significant differences among these groups were detected.

Regarding the monocyte/macrophage characteristics, there were no significant differences between men and women. Subsequently, women were analysed with respect to age. The data focused separately on men and on two predefined subgroups of women, as shown in Table 1. In the perirenal adipose tissue, there were no significant differences in the number of total monocytes/macrophages among men, and women of younger and older age. In contrast, a higher proportion of proinflammatory double positive CD14+CD16+ monocytes/macrophages was observed in older women than in younger women ($p < 0.01$). The main proinflammatory parameter, the ratio of CD14+CD16+/CD14+CD16− macrophages, was also higher in older women than in younger women ($p < 0.02$). There were no significant differences observed between men and either of the subgroups of women. An identical pattern of differences was also found in renal perivascular fat (with the exception of the total number of CD14+macrophages). As CD14+CD16−macrophages were mostly (96 ± 4%) CD163 positive, the data of the CD14+CD16−CD163+ population mirrored those of CD14+CD16+. The proportion of anti-inflammatory CD14+CD16−CD163+ macrophages in perirenal fat was higher (55 ± 17 vs. 37 ± 9%; $p < 0.01$) in women of premenopausal age than in women of postmenopausal age. In addition, a significant positive correlation ($p < 0.01$) with age was found in the entire group of women.

In addition, we studied the association of monocytes/macrophages with age (Fig. 1). The correlation between monocytes/macrophages CD14+CD16+/CD14+CD16− ratio and age in perirenal adipose tissue was strong and in the entire group of women (Fig 1A) but not in men (Fig 1B). When this ratio was analysed according to age in women, no effect of age on the proportion of proinflammatory monocytes/macrophages was found in younger women; however, a significant correlation was observed in older women (Fig 1A). In the entire group of men and women, there was no significant correlation between total monocytes/macrophages content and age in either type of adipose tissue (data not shown). Similarly, there were no significant associations between monocyte/macrophage characteristics and body mass index observed in the groups under study (data not shown).

4. Discussion

We found no differences in the monocyte/macrophage content between men and women, healthy non-obese kidney donors, in perirenal and renal perivascular fat. However, when women were divided according to their age reflecting approximate menopausal status, we found a higher proportion of double positive CD14+CD16+ monocytes/macrophages in older women compared to younger women. In addition, a strong correlation was only observed between the monocyte/macrophage content and age in older women.

The majority of results documenting a direct relationship between adipose tissue and atherosclerosis have been obtained in experimental studies in animal transgene models [16–18]. The only study assessing the proportion of CD16 positive macrophages in human adipose tissue was reported by Bourlier [19]; in this study, only human subcutaneous tissue was analysed. It was repeatedly shown that chronic, low-grade inflammation in adipose tissue, mediated by immune cells, primarily macrophages, is closely associated with obesity-related metabolic diseases, mainly insulin resistance [20]. In our study, which was limited to non-obese individuals, we found no significant correlation between the body mass index and content of monocytes/macrophages, which indicates that within normal physiological ranges/physiological values, there is no significant association between these inflammatory mechanisms and the body mass index. The potential unfavourable impact of perivascular adipose tissue on vascular health has already been confirmed by experimental, clinical and

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