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Short Communication

Influences of the menopause transition and adverse childhood experiences on peripheral basal inflammatory markers

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ABSTRACT

Objective: To characterize the influence of early life stress on peripheral basal inflammatory markers across the menopause transition.

Methods: Participants from the longitudinal Penn Ovarian Aging study were assessed for childhood adversity at study end (14 years) using the Adverse Childhood Experiences (ACE) questionnaire. Responses were categorized as low (0–1) or high (≥2) ACE exposure. The stored blood sample catalogue was reviewed to exclude those samples collected during use of medications that could impact immune status or medications suggestive of infection or allergies. Remaining blood samples (n = 640) from 167 participants were assayed for interleukin-6 (IL-6), interleukin 1-beta (IL-1β), high sensitivity C-reactive protein (hsCRP), and tumor necrosis factor alpha (TNF-α). Menopause staging (premenopause, early transition, late transition, and postmenopause) was determined by questionnaire and menstrual diaries at yearly assessments. Generalized linear models for repeated measures were used to quantify the association between outcomes of interest (i.e., IL-6, IL-1β, hsCRP, and TNF-α) and exposures (i.e., menopause stage, ACE status, their interaction) while controlling for relevant covariates (i.e., BMI, smoking, age at first blood sample, and race). Inflammatory marker levels were log-transformed for modeling.

Results: Log IL-6 levels were higher in the late perimenopause versus premenopause ($p = 0.035$). Menopause stage × ACE interaction was observed for log IL-6, IL-1β, and TNF-α ($p = 0.042$, $p = 0.054$, $p = 0.053$, respectively); for individuals with high (≥2) ACE exposure, IL-6 was higher in the late perimenopause ($p = 0.015$) while IL-1β and TNF-α were lower in the postmenopause versus premenopause ($p = 0.019$ and $p = 0.020$).

Conclusions: Results from this investigation indicate that the late perimenopause stage may be a window of risk for inflammation, particularly for individuals with greater childhood adversity. Prospective studies designed to address childhood stress and inflammation across the menopause transition are needed to confirm these findings. Heightened inflammation, even if transitory, may have negative impact on healthy aging.

1. Introduction

Estradiol modulates cytokines including interleukin-6 (IL-6), interleukin-1β (IL-1β), and tumor necrosis factor alpha (TNF-α) (Pfeilschifter et al., 2002) and estrogen deficiency is associated with sub-optimal immune profiles (Pfeilschifter et al., 2002; Au et al., 2016). Postmenopause is associated with increased, pro-inflammatory serum markers relative to premenopause controls in cross-sectional research (Cioffi et al., 2002; Taleb-Belkadi et al., 2016), with IL-6 levels negatively correlating with estradiol concentrations during the menopause transition (Yasui et al., 2007). Low-dose 17-beta estradiol application significantly decreases C-reactive protein (CRP), a marker of inflammation, relative to placebo (Prestwood et al., 2004). Elevation of pro-inflammatory immune markers (e.g., CRP and IL-6) has implications for cardiac and metabolic health (Kaptoge et al., 2010, 2014; Hotamisligil, 2006), including incident coronary heart disease and cardiovascular event risk for postmenopausal individuals (Pradhan et al., 2002; Ridker, 2000).

Early life stress, including adverse childhood experiences (ACEs), increases risk for age-related and chronic health conditions in human (Felitti et al., 1998) and preclinical (Ruiz et al., 2018) studies. Such stress

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can alter immune system development and functioning, promoting chronic inflammatory response activation and hyperreactivity with lasting consequences for pathology and impaired functioning throughout the life course (Danese and Baldwin, 2017). ACEs are associated with altered adulthood age-related disease biomarkers including elevated inflammatory cytokine levels (Danese et al., 2007; Baumeister et al., 2015). While evidence suggests certain categories, combinations, or degrees of ACE exposure are associated with increased inflammation over midlife in samples of men and women (Lacey et al., 2020; Pereira et al., 2019; Hostinar, 2015), little is known regarding ACEs and immune function during the transition to reproductive senescence despite known effects of estradiol on immune function and health consequences of prolonged inflammation (Matthews et al., 2014; Nguyen and Thurston, 2020).

In the original ACE study, 41% of women were exposed to at least two childhood adversity categories before age 18 (Centers for Disease Control and Prevention, Kaiser Permanente, 2016). Median duration estimates of late menopause transition (i.e., menstrual cycle $\geq$ 60 days to 12 months post final menstrual period) range from 2.15 to 3.42 years, depending on transition onset age (Paramsothy et al., 2017). Identifying high risk individuals for greater inflammation during transition could guide interventions to reduce modifiable risk factors.

We aimed to determine whether ACEs impacted inflammatory marker change across transition from pre-to postmenopause among Penn Ovarian Aging Study (POAS (Hollander et al., 2001)) participants using secondary analyses. We focused on direct and interactive effects of menopause stage, as hormonal milieus (Harlow et al., 2012) (e.g., decreasing but variable estradiol in perimenopause (Genazzani et al., 2005)) and symptoms (e.g., depression symptoms (Freeman et al., 2014), sleep disturbances (Kravitz et al., 2008), hot flushes (Freeman et al., 2011)) differ by menopause stage. First, we assessed whether menopause stage predicted basal peripheral inflammatory marker levels, hypothesizing that advancing stage would be associated with greater levels of inflammation markers relative to premenopause. Then, we determined whether menopause stage and ACE exposure individually or interactively predicted inflammatory marker levels. We hypothesized those with higher ACE exposure would have greater inflammatory marker levels and, for these women, advancing stage would be associated with greater inflammation relative to premenopause levels. Across all aims, we controlled for potential confounders of BMI, smoking, age at first blood sample, and race.

2. Methods

2.1. Cohort description

One hundred sixty-seven (n = 167) longitudinal POAS Cohort (described in detail elsewhere (Hollander et al., 2001)) participants completed the ACE Questionnaire (ACE-Q) (Felitti et al., 1998) and had unused blood samples appropriate for inflammatory marker assays. Samples were considered for assaying if participants did not report a cold or infection and were not using antibiotics, corticosteroids, over-the-counter cold or allergy medications, or psychotropic medications potentially impacting inflammatory marker levels at time of collection.

POAS cohort enrollment eligibility criteria included age between 35 and 47 years, premenopausal with regular, normal-range menstrual cycles, and presence of a uterus and at least one ovary. Exclusion criteria included recent drug or alcohol abuse, psychotropic drug use, hormonal contraception use, or history of health problems affecting hormone function (e.g., diabetes, breast cancer). The cohort was identified through random number dialing to Philadelphia County, Pennsylvania residences between 1996 and 1997 and designed to include equal numbers of Caucasian and African American participants. All participants provided written informed consent at study enrollment and verbally assented to completing the ACE-Q. The University of Pennsylvania institutional review board approved study procedures.

2.2. Assessment periods for the POAS cohort

Data were collected approximately yearly and included demographics, menstrual cycle dates, reproductive history, general health status and behaviors, and menopausal symptom information. Interviewers obtained participant height, weight, and blood samples at each assessment period. ACE history was obtained at study end, 14 years post-enrollment.

2.3. Study variables

2.3.1. Menopausal status

Menopause stage groupings were adapted from the initial staging system for reproductive aging in women (Soules et al., 2001) resulting in four stages: premenopause (i.e., regular 22–35 day menstrual cycles or $\geq$7 day cycle length change from baseline), early transition (i.e., $\geq$7 day cycle length change for $\geq$ 2 consecutive cycles or 60 days amenorrhea), late transition (i.e., >60 days-11 months amenorrhea), and postmenopause (i.e., $\geq$12 months amenorrhea without hysterectomy).

2.3.2. Adverse childhood experiences

ACEs were assessed using the ACE-Q (Felitti et al., 1998), a 10-item self-report scale assessing exposure to 10 categories of early life adversity before age 18. Three items queried exposure to abuse, 2 regarding neglect, and 5 regarding household dysfunction (i.e., exposure to domestic violence, divorce/separation from parent, parent with mental health condition, parent with substance abuse, family member imprisoned). Studies demonstrate a graded adverse effect of ACEs on health outcomes (e.g. (Felitti et al., 1998; Chapman et al., 2004),). For analysis, we defined ACE as low (0–1 ACE) or high ($\geq$2 ACEs).

2.3.3. Inflammatory marker assessments

Participants provided 2.5 oz blood samples from the non-dominant arm into a vacutainer serum separator tube with separator gel and clot activator at each in-home assessment. Menstruating participants provided blood samples between days 2–6 of two consecutive cycles, whereas non-menstruating participants provided 2 blood samples one month apart. Blood samples were centrifuged for 10 min, frozen, and stored in aliquots using polypropylene containers at −80°C. Blood samples were initially collected for hormone assays (see, e.g. (Epperson et al., 2017)), then remaining samples (with above caveats) were assessed for serum levels of high sensitivity (hs)CRP by Immunonephelometry (Siemens, BNII Malvern PA). hsCRP was measured in singlicate on BNII. hsIL-6, hsIL-1β, and hsTNF-α were assessed using Human High Sensitivity TNFa, IL-1b and IL-6 Cytokine premixed magnetic Luminex performance assay (R&D Systems). Multiple samples for individual participants were appropriately blocked and quantified together. IL-6, IL-1β, and TNF-α assays were run in duplicate and repeated if duplicate values differed by > 20%. Intra- and inter-assay coefficients of variation were 5.2% and 9.6% (IL-6), 5.3% and 12.8% (IL-1β), and 5.2% and 9.6% (TNF-α), respectively, and are not available for hsCRP. Sensitivity thresholds were 0.16 mg/mL (hsCRP), 0.14 pg/mL (IL-6), 0.08 pg/mL (IL-1β), and 0.29 pg/mL (TNF-α).

2.3.4. Statistical analysis

Differences between low and high ACE participants were compared using two-sample *t* tests and Fisher's exact tests, due to small sample sizes in some cells. Inflammatory marker levels were compared after natural log transformation to meet assumptions for linear models. A general linear mixed model with an exchangeable correlation structure to account for repeated measures was used to estimate associations of interest between outcomes of interest (i.e., inflammatory marker levels) and exposures (i.e., menopause stage, ACE status, their interaction) while controlling for covariates. Robust variances were assumed using Generalized Estimating Equations (GEE) framework. Two-sided p-values <0.05 were considered statistically significant. Total ACE-Q was dichotomized

as low ACE (0–1 ACEs) versus high ACE (≥2 ACEs) groups; two or more ACEs increased risk for depression among POAS cohort (Epperson et al., 2017) and ACE study women participants (Chapman et al., 2004). Relevant covariates were determined *a priori* based on previous literature and included BMI (continuous), and smoking status (current smoker or non-smoker), race (African American or Caucasian), and age at first blood sample (<40; 40–44.99; ≥45). Menopause stage was categorized into premenopause, early transition, late transition, and postmenopause. Analyses were conducted using R version 3.6.3.

3. Results

3.1. Participants, assessments, and menopause stage

Inflammatory marker assays were conducted using 640 blood samples from participants (n = 167). Supplementary Table 1 includes baseline demographic and inflammatory marker levels and comparisons between low and high ACE groups. Race and smoking status differed between participants with high and low ACEs ($p = 0.044$ and 0.047, respectively), with a greater proportion of participants who identified as African American and participants who smoked in the high ACE group.

Half (56.29%; 94/167) the sample was observed from pre- to post-menopause stages. Supplementary Table 2 contains average time spent and blood samples provided in each menopause stage.

3.2. Early life adversity

Approximately 16.8%, 30.5%, and 52.7% of the sample endorsed experiencing 0, 1, or ≥2 ACES, respectively. Supplementary Table 3 includes ACE frequencies. At baseline, a greater proportion of high ACE individuals endorsed a previous diagnosis of depression given by a doctor ($p = 0.012$, Supplementary Table 4).

3.3. Relationship between menopause stage on inflammation

In models adjusted for BMI, smoking status, race, and age at first sample (Supplementary Tables 5A and 5B), log IL-6 was higher in late transition than premenopause ($p = 0.035$) and we observed a non-significant trend that advancing menopause stage was associated with log IL-6 ($p = 0.094$). Similarly, non-significant trends indicated log TNF-α was higher in late transition than premenopause ($p = 0.088$). Menopause stage was not significantly associated with log IL-1β ($p = 0.341$) or log hsCRP ($p = 0.336$).

3.4. Relationship between menopause stage and early life adversity on inflammation

In models that included menopause stage, ACE status (low versus high), and their interaction (Supplementary Tables 6A and 6B), menopause stage interacted significantly with ACE exposure on log IL-6 ($p = 0.042$) and at trend level for log IL-1β and log TNF-α ($p = 0.054$ and $p = 0.053$, respectively). Log IL-6 was significantly higher in late transition for the high versus low ACE group ($p = 0.015$), as were log IL-1β and log TNF-α at trend levels ($p = 0.077$, and $p = 0.099$, respectively). Log IL-1β and log TNF-α were significantly lower for those with higher ACE exposure in the postmenopause ($p = 0.019$ and $p = 0.020$).

4. Discussion

This study contributes longitudinal evidence that menopause status impacts several inflammatory markers. We examined menopause stage influence on basal peripheral inflammatory markers—and the degree to which menopause stage interacted with ACE exposure level to influence these markers—in a longitudinal study of healthy participants premenopausal at study start. Findings indicated changes inherent to the menopause transition, including hormonal changes, may impact inflammatory markers, as IL-6 was significantly higher in late transition relative to premenopause. Evidence also suggested that relatively greater exposure to childhood adversity may amplify inflammatory changes during certain stages, as IL-6 increased significantly more among high ACE participants during late transition. IL-1β and TNF-α exhibited estimated effects in the same direction, though non-significant.

These pilot findings suggest the menopause transition may be an important window of risk for inflammation and its adverse effects that differentially affects women with high ACEs. Our participants spent 2.05 years in late transition, on average; exposure to elevated inflammation for this time may be associated with poor health outcomes. For high ACE participants, those years were associated with even higher degrees of inflammation relative to women with little or no ACE exposure.

Our results extend previous work. Longitudinal studies examining inflammation during menopause transition have focused primarily on CRP, finding no association between stage or final menstrual period and CRP (Lee et al., 2009; Matthews et al., 2009; Wang et al., 2018; Razmjou et al., 2016). Razmjou and colleagues (Razmjou et al., 2016) further reported peri- and postmenopause increases in soluble TNF-α receptors 1 and 2 relative to premenopause levels, but no increases in IL-6 or IL-1β. Our finding signaling late transition increases in IL-6 coheres with cross-sectional findings of higher IL-6 later in the menopause transition (i.e., postmenopause) relative to premenopause controls (Cioffi et al., 2002), though others found no differences (Yasui et al., 2007; Sites et al., 2002). While marginal, TNF-α and IL-1β increased during late transition relative to premenopause in our work. TNF-α was higher in postmenopause versus premenopause participants in multiple (Taleb-Belkadi et al., 2016; Sites et al., 2002; Vural et al., 2006a, 2006b) but not all (Cioffi et al., 2002; Yasui et al., 2007) cross-sectional studies, as was IL-1β in one (Vural et al., 2006a) but not another (Yasui et al., 2007) cross-sectional study.

We did not observe higher inflammatory marker levels in postmenopause versus premenopause, contrary to predictions. Significantly lower IL-1β and TNF-α levels for high ACE individuals in postmenopause compared to low ACE individuals were unexpected. Our study had relatively fewer participants with post-menopause versus early or late transition data. Future studies should examine these patterns using a larger postmenopause cohort.

As the first study examining ACE impact on inflammation in a longitudinal sample with a uniform premenopause baseline, this study represents a novel contribution to literature suggesting exposure to adversity early in development confers risk for negative health markers and outcomes during menopause transition (Epperson et al., 2017), including elevated inflammation (Matthews et al., 2014; Nguyen and Thurston, 2020). In cross-sectional research, childhood emotional abuse was significantly associated with higher IL-6, but not CRP, in late transition and postmenopause (n = 304) (Nguyen and Thurston, 2020). To our knowledge, the only other longitudinal work examining ACES and inflammation (i.e., CRP) in the menopause transition found childhood sexual abuse, emotional abuse and neglect, physical neglect, and the number of categories of childhood adversity exposure predicted higher CRP levels over 8-year follow-up, controlling for menopause stage (Matthews et al., 2014).

Study strengths included a longitudinal design with all participants enrolling during premenopause and observed over multiple stages of the transition, measurement of four inflammatory markers, and examination of interactive effects of menopause stage with ACE exposure on inflammatory markers. This short communication is based upon statistically significant ($p < 0.05$) and trend findings to inform future research. Limitations included blood sample collection at non-uniform times of day and settings (i.e., participants' homes). Moreover, ACE-Q sum scores provide limited detail regarding early adversity frequency and intensity. These data indicate the importance of continued research to identify individuals at risk for extended periods of inflammation during aging.

5. Conclusions

The late perimenopause transition is associated with increased inflammation. Importantly, childhood adversity—which can be readily assessed using the ACE-Q—is associated with risk for greater inflammation during the late transition. This stage may be an opportune time for inflammation-reducing interventions (e.g., stress reduction, mindfulness, diet, exercise), particularly for those with significant childhood adversity.

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Declaration of competing interest

CAM, RLJ, MDS, and EWF have nothing to disclose. CNE serves on the Advisory Board for Sage Therapeutics and Asarina Pharma, from which she receives consulting fees. She receives research grant support from Sage Therapeutics. Portions of this manuscript were presented as a poster abstract at the 2020 Annual Meeting of the North American Menopause Society.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2021.100280.

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