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BRIEF REPORT

Hot Flashes and Cardiovascular Disease Risk Indices Among Women With HIV

Mabel Toribio,[1,a] Evelynne S. Fulda,[1,a] Sarah M. Chu,[1] Zsofia D. Drobni,[2] Magid Awadalla,[2] Madeline Cetlin,[1] Takara L. Stanley,[1] Crystal M. North,[3] Michael D. Nelson,[4] Michael Jerosch-Herold,[5] Lidia S. Szczepaniak,[6] Tricia H. Burdo,[7] Sara E. Looby,[1,8] Tomas G. Neilan,[2,b] and Markella V. Zanni[1,b]

[1]Metabolism Unit, Division of Endocrinology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA, [2]Cardiovascular Imaging Research Center (CIRC), Department of Radiology and Division of Cardiology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA, [3]Division of Pulmonary and Critical Care, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA, [4]Applied Physiology and Advanced Imaging Laboratory, Department of Kinesiology, University of Texas at Arlington, Arlington, Texas, USA, [5]Department of Radiology, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA, [6]MRS Consulting in Biomedical Research, Albuquerque, New Mexico, USA, [7]Department of Neuroscience, Lewis Katz School of Medicine at Temple University, Philadelphia, Pennsylvania, USA, and [8]Yvonne L. Munn Center for Nursing Research, Massachusetts General Hospital, Boston, Massachusetts, USA

Women with HIV (WWH) transitioning through menopause have heightened cardiovascular disease (CVD) risk. In the general population, hot flash burden relates to CVD risk indices. We found higher hot flash burden among women with vs without HIV. Further, among WWH, hot flash burden related to select CVD risk indices.

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Approximately 70% of women in the general population experience hot flashes during the menopausal transition [1]. Hot flash burden relates not only to quality of life measures [2] but also to levels of systemic inflammation and surrogate markers of cardiovascular disease (CVD) risk [1]. Specifically, women with hot flashes (vs women without hot flashes) have greater systemic levels of inflammatory markers [1, 3, 4] and lower flow-mediated dilation [5, 6], a predictor of CVD events [7].

Women with HIV (WWH) vs without have an increased risk of CVD (eg, myocardial infarction [8] and heart failure [9]) in relation to heightened systemic immune activation/inflammation [10]. At least 1 prior study found a higher hot flash frequency among WWH compared with matched women without HIV [11]. The relationship between hot flash frequency and systemic immune activation, as well as subclinical cardiac pathology, among WWH has not been previously investigated. To explore the aforementioned relationships, we leveraged a study in which matched women with vs without HIV underwent questioning regarding reproductive health, detailed immune phenotyping, and cardiovascular imaging including magnetic resonance imaging (MRI) and proton magnetic resonance spectroscopy (^{1}H-MRS).

METHODS

Study Design and Participants

Women (aged 40–75 years) with and without HIV, group-matched based on age and body mass index, were recruited from the Greater Boston area, as previously described [12–14]. Women with a history of CVD, kidney disease, diabetes, and/or standard contraindications to MRI were excluded. A total of 23 WWH on antiretroviral therapy (ART) and 19 women without HIV were enrolled in the study and completed reproductive, immune, and cardiovascular phenotyping assessments. Data on myocardial fibrosis [12], myocardial steatosis [13], and vascular function [14] were previously published. However, data on menopausal symptoms and the relationship between menopausal symptoms and immune/cardiovascular parameters among women in this cohort have not been previously described.

Patient Consent Statement

This study was approved by the Partners HealthCare System Institutional Review Board. All study participants provided written informed consent.

Reproductive Health History

Women were asked questions regarding their menstrual history and reproductive health status. Menopause was defined as no menses in the past year absent an alternative explanation (traditional definition of menopause) [15]. Women also answered questions regarding hot flash presence, frequency, and timing. Details regarding history of prior pregnancies, gynecologic procedures, and current or former use of hormonal or nonhormonal therapies were also obtained.

Laboratory Assessments

Commercial enzyme-linked immunosorbent assay (ELISA) kits were used to measure plasma levels of soluble CD163 (sCD163), soluble CD14 (sCD14), c-c motif ligand 2 (CCL2), and c-x-c

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[a]Co-first authors, equal contribution

[b]Co-senior authors, equal contribution

Correspondence: Markella V. Zanni, MD, Metabolism Unit, Division of Endocrinology, Massachusetts General Hospital and Harvard Medical School, 55 Fruit Street, 5 LON 207, Boston, MA 02114 (mzanni@mgh.harvard.edu).

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motif chemokine ligand 10 (CXCL10), as previously described [12]. Levels of anti-Müllerian hormone (AMH), a biomarker of ovarian reserve [16], were also measured via ELISA (Ansh Laboratories, Webster, TX, USA).

Cardiovascular Proton Magnetic Resonance Spectroscopy and Magnetic Resonance Imaging

Cardiovascular MRI was performed on a 3T MRI (Skyra; Siemens Healthcare, Erlangen, Germany) to assess cardiac and vascular structure and function, and cardiovascular ^{1}H-MRS was performed on a second 3T MRI system (Tim Trio; Siemens, Erlangen, Germany) to quantify intramyocardial triglyceride content. Detailed procedural methods are as previously described [12–14].

Statistical Analysis

Between-group differences in variables were calculated using the Student *t* test for normally distributed variables, the Wilcoxon rank-sum test for non–normally distributed variables, and the Fisher exact test for categorical variables. Bivariate analyses were calculated using Spearman's correlation coefficient. A multivariable regression model with days per week with hot flashes as the dependent variable and HIV status and race as covariates was performed. Statistical analyses were performed using JMP Pro software (versions 14.0 and 15.0; SAS Institute).

RESULTS

Baseline Characteristics

There were no baseline demographic differences between groups (Table 1). WWH had significantly higher systemic levels of sCD14, sCD163, and CCL2, as previously reported [12].

Reproductive Aging Parameters

The percentage of women with no menses in the past year absent an alternative explanation did not differ significantly between groups (WWH vs women without HIV: 69.6% vs 57.9%; $P = .52$), nor did the percentage of women with undetectable levels of AMH (77.3% vs 83.3%; $P = .71$) (Table 2). No participants were currently on estrogen and/or progesterone therapy, and there was no difference between groups

Table 1. Baseline Demographic Parameters Among Women With and Without HIV

	Whole Group (n = 42)	Women With HIV (n = 23)	Women Without HIV (n = 19)	*P* Value
Demographic parameters				
Age, y	52 ± 5	51 ± 5	52 ± 6	.79
Race, %				.18
White	52.4	39.1 (9/23)	68.4 (13/19)	
Black	33.3	43.5 (10/23)	21.1 (4/19)	
Other	14.3	17.4 (4/23)	10.5 (2/19)	
Ethnicity, Hispanic, %	11.9	8.7 (2/23)	15.8 (3/19)	.64
BMI, kg/m^2	32 ± 7	32 ± 8 (n = 22)	31 ± 7 (n = 19)	.71
Current smoking, %	47.6	52.2 (12/23)	42.1 (8/19)	.55
Former smoking, %	20.0	27.3 (6/22)	11.1 (2/18)	.26
Current cocaine use, %	2.4	0.0 (0/23)	5.3 (1/19)	.45
Total cholesterol, mg/dL	198 ± 36	200 ± 40 (n = 21)	196 ± 30 (n = 16)	.78
LDL-C, mg/dL	111 ± 29	114 ± 32 (n = 21)	106 ± 24 (n = 15)	.40
Triglycerides, mg/dL	103 (85–157)	107 (91–173) (n = 21)	92 (67–136) (n = 16)	.14
10-y ASCVD risk score, %	2.5 (1.3–4.5)	3.6 (1.2–4.7) (n = 21)	1.9 (1.3–3.7) (n = 16)	.70
WHR	0.9 ± 0.1	0.9 ± 0.1 (n = 21)	0.9 ± 0.1 (n = 15)	.52
Immune parameters				
CCL2, pg/mL	192.7 ± 48.0	210.4 ± 42.8 (n = 20)	167.4 ± 44.8 (n = 14)	**.009**
CXCL10, pg/mL	124.4 (98.0–189.1)	152.0 (100.2–206.5) (n = 20)	106.7 (97.4–134.5) (n = 14)	.10
sCD14, ng/mL	1755.8 ± 453.4	1925.1 ± 488.6 (n = 20)	1513.9 ± 256.7 (n = 14)	**.003**
sCD163, ng/mL	1127.4 ± 336.0	1260.3 ± 293.1 (n = 20)	937.5 ± 308.4 (n = 14)	**.005**
HIV-specific parameters				
Duration since HIV diagnosis, y	—	19.2 ± 7.7	—	—
Duration of ART, y	—	16.7 (8.9–21.4) (n = 18)	—	—
CD4+ T-cell count, cells/mm^3	—	872 (574–1147)	—	—
Nadir CD4+ T-cell count, cells/mm^3	—	113 (19–255) (n = 20)	—	—
HIV viral load, copies/mL[a]	—	19 (19–19) (n = 20)	—	—

There were no significant differences in baseline demographic parameters among women with and without HIV. Select immune markers, including CCL2, sCD14, and sCD163, were significantly higher among women with HIV. Normally distributed variables are presented as mean ± SD; non–normally distributed data are presented as median (interquartile range). *P* values <.05 were considered statistically significant and are presented in boldface.

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; ASCVD, atherosclerotic cardiovascular disease; CCL2, c-c motif chemokine ligand 2; CD4, cluster of differentiation 4; CXCL10, c-x-c motif chemokine ligand 10; LDL-C, low-density lipoprotein cholesterol; sCD14, soluble CD14; sCD163, soluble CD163; WHR, waist-to-hip ratio.

[a]The lower limit of detection for the HIV viral load assay employed was 20 copies/mL. Values of 19 copies/mL were imputed when the viral load was undetectable.

Table 2. Reproductive Health Parameters Among Women With and Without HIV

	Whole Group (n = 42)	Women With HIV (n = 23)	Women Without HIV (n = 19)	*P* Value
Absence of menses within the past year, %	64.3	69.6 (16/23)	57.9 (11/19)	.52
Undetectable AMH, %	80.0	77.3 (17/22)	83.3 (15/18)	.71
Presence of hot flashes, %	45.2	56.5 (13/23)	31.6 (6/19)	.13
Average number of days per week with hot flashes	2.8 (0.6–7.0)	7.0 (1.3–7.0) (n = 12)	0.8 (0.0–2.1) (n = 6)	**.01**
Duration of hot flashes, y	5.0 (1.7–9.0)	5.0 (1.8–12.0) (n = 11)	5.0 (1.3–8.0) (n = 7)	.86
Current hormone therapy use, %	0.0	0.0 (0/23)	0.0 (0/19)	—
Current nonhormonal therapy use for menopause symptoms, %	5.0	9.5 (2/21)	0.0 (0/19)	.49

Reproductive health parameters such as the percentage of participants with no menstrual cycle within the past year and the percentage of participants with an undetectable AMH did not differ significantly between women with vs without HIV. Women with HIV had a significantly higher number of days per week with hot flashes. None of the women in the study were currently on hormonal therapy with estrogen and/or progesterone. Normally distributed variables are presented as mean ± SD; non–normally distributed data are presented as median (interquartile range). *P* values <.05 were considered statistically significant and are presented in boldface.

Abbreviation: AMH, anti-Müllerian hormone.

in current use of nonhormonal therapies for menopausal symptoms (Table 2).

WWH had a significantly increased frequency of hot flashes (days per week with hot flashes) compared with women without HIV (median [IQR], 7.0 [1.3–7.0] vs 0.8 [0.0–2.1]; $P = .01$) (Table 2). Further, among the whole group, after controlling for race, HIV status remained an independent predictor of days per week with hot flashes (overall model $R^2 = .52$; $P = .01$; HIV status, $P = .003$). In sensitivity analyses excluding either women with menses in the past year or women with detectable AMH, WWH still reported a higher number of days per week with hot flashes (median [IQR], 7.0 [6.3–7.0] vs 0.4 [0.0–2.3]; $P = .007$; and median [IQR], 7.0 [2.4–7.0] vs 0.8 [0.0–2.1]; $P = .01$; respectively). Among WWH, age and duration since HIV diagnosis were not significantly higher among women experiencing (vs not experiencing) hot flashes in the past year (data not shown). Among WWH experiencing hot flashes in the past year, longer duration of ART use was noted (median [IQR], 21.2 [16.0–22.7] vs 9.3 [3.3–16.0] years; $P = .03$).

Hot Flash Burden and Associations With Key Immune and Cardiovascular Parameters

Among the whole group and among WWH (but not among women without HIV), women with >1 hot flash per day had higher levels of sCD14 compared with women with ≤1 hot flash per day ($P = .004$ and $P = .02$, respectively). Increased levels of sCD163, CCL2, or CXCL10 were not observed among women with >1 vs ≤1 hot flash per day among the whole group or among subgroups stratified by HIV status (data not shown). Among WWH, years since onset of hot flashes related directly to increased intramyocardial triglyceride content ($\rho = 0.80$; $P = .02$) and inversely to left atrial passive ejection fraction, a measure of diastolic function ($\rho = -0.70$; $P = .03$). Notably, years since onset of hot flashes did not relate to aortic pulse wave velocity, a measure of large vessel vascular function, either in the whole group or among subgroups (data not shown).

DISCUSSION

Findings relating to hot flash burden, select immune markers, and CVD parameters are presented here among a group of women with and without HIV, yielding 3 key hypothesis-generating insights. First, WWH had increased hot flash frequency compared with women without HIV. Second, among both WWH and the whole group, women who experienced >1 hot flash per day had higher levels of a key marker of monocyte activation, sCD14. Third, among WWH, years since onset of hot flashes related to cardiac pathology by cardiovascular MRI/MRS, namely increased myocardial steatosis (measured by intramyocardial triglyceride content) and decreased diastolic function (measured by left atrial passive ejection fraction). Together, these insights suggest a potential link between hot flash burden and CVD risk among WWH, which will need to be confirmed in larger studies.

In our study, WWH had a higher number of days per week with hot flashes compared with women without HIV. This finding dovetails with observations by Looby et al. suggesting increased frequency and severity of hot flashes among women with vs without HIV [11]. The mechanistic explanations as to why WWH experience more frequent and severe hot flashes remain unknown. Our finding that among WWH duration of ART use was significantly longer among women experiencing hot flashes in the last year suggests a potential relationship between prolonged ART exposure and vasomotor instability.

Among our whole group and among WWH, women with >1 hot flash per day exhibited higher systemic levels of sCD14, a predictor of atherosclerosis and mortality among people with HIV [17, 18]. This novel finding suggests a possible link between monocyte activation and hot flash burden among WWH. General population studies also point to a possible link between systemic and vascular inflammation and hot flash burden [3, 4, 19]. For example, Huang et al. found that systemic levels of the pro-inflammatory cytokines interleukin-8 and tumor necrosis factor–α were higher among postmenopausal women experiencing more severe hot flashes [3]. Additional studies

among WWH are needed to better understand the relationship between systemic immune activation and hot flash burden and whether this relationship affects CVD risk among WWH during menopause.

Our finding that among WWH the number of years since onset of hot flashes relates both to abnormal cardiac structure (myocardial steatosis) and function (diastolic dysfunction) highlights a potential link between hot flash frequency and years since onset of hot flashes and CVD risk in this population. In the general population [20, 21] and among WWH [13], myocardial steatosis relates to diastolic dysfunction. In population studies, diastolic dysfunction is a key intermediary in the path to development of heart failure [22]. Whether hot flash burden relates to heart failure risks and adverse heart failure outcomes among WWH remains unknown. This question is of primary interest, as prior work by our group has demonstrated that women with vs without HIV have increased heart failure risks and worse heart failure outcomes [9].

Our study was characterized by limitations. First, the small sample size and recruitment from 1 geographic region limit generalizability; however, the racial and ethnic diversity of our participants reflects that of WWH in the United States. Second, the cross-sectional study design precludes inferences regarding causality. Additionally, women with and without HIV were not matched based on reproductive aging stage, and potential effects of older ART agents on hot flash symptomatology among WWH were not assessed. Nevertheless, the study is strengthened by the synthesis of data on reproductive health history with deep cardiovascular and immune phenotypic data. Lastly, while our data ascertainment pertaining to hot flash burden was based on interview and therefore may be affected by recall bias, physiologic assessments of vasomotor instability [23] could provide complementary information with which to evaluate the relationship between reproductive aging, hot flashes, and CVD risk among WWH.

Among women in the general population, menopause has been associated with increased CVD risk [24]. Given that WWH have increased CVD risk as well as evidence of advanced reproductive aging [10], there are strong imperatives to determine how menopause may affect CVD risk among WWH. Our findings relating hot flash burden to surrogate markers of CVD risk such as monocyte activation and diastolic dysfunction among WWH provide a foundation for future studies in this field. Moreover, given that hot flashes may affect adherence to ART among menopausal WWH [25], addressing hot flash burden clinically among WWH has important implications for control of HIV viremia and attendant inflammation in this at-risk population. Additional research is required to improve our understanding of the mechanisms underlying the relationship between hot flashes and CVD risk indices among WWH and to determine if hot flashes represent a sex-specific risk factor for CVD in WWH.

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