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Postmenopausal Symptoms in Female Veterans with Type 2 Diabetes: Glucose Control and Symptom Severity

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Abstract

Background: While type 2 diabetes mellitus (DM) is a common condition of midlife women, few studies have examined its influence on the symptom features of menopause. To explore this relationship, we conducted a study of symptom patterns of diabetic patients using a random sample of female veterans receiving care in the Veterans Affairs Healthcare system.

Methods: A cross-sectional comparison was conducted with three groups of postmenopausal respondents (ages 45–60 years) to a mailed national survey who also consented to clinical data access: no diabetes ($n=90$), diabetes with better glucose control (hemoglobin A1c [HbA1c] $\leq 7\%$, $n=135$) and diabetes with worse glucose control (HbA1c $>7\%$, $n=102$).

Results: Respondents, on average, were obese (body mass index: 33.9 ± 0.4 kg/m^2), 11.30 ± 0.2 years postmenopause, with more than one chronic illness. Despite higher body mass index and increased comorbidities in women with diabetes compared with nondiabetic women, measures of mental health (anxiety, depressed mood, stress) were similar across groups. The pattern of menopause symptoms did not differ by group. Muscle aches/joint pain was the most prevalent symptom (78.6%), followed by vasomotor symptoms (74.4%). Respondents with elevated HbA1c demonstrated higher total menopausal symptom severity scores (DM-HbA1c >7: 15.4 ± 0.8 vs. DM-HbA1c $\leq 7\%$: 12.2 ± 0.8 vs. No diabetes: 12.3 ± 0.8; $p=0.006$) than the other two groups.

Conclusions: In postmenopausal female veterans with diabetes, glucose control is associated with the severity of those symptoms commonly attributed to menopause. Joint pain is an important part of the postmenopausal symptom complex in this population.

Introduction

Little is known about menopausal symptom patterns in women with type 2 diabetes, an increasingly common chronic health condition during middle age.[1] Prior studies suggest that chronic disease can adversely affect the postmenopausal experience.[2–5] In the case of diabetes, many symptoms overlap with those marking the end of reproductive life. For example, vaginal irritation,[6] urinary incontinence,[7] and disturbed sleep[8] are common features of both diabetes and the menopausal transition.[9] Moreover, the compromised glycemic control of diabetes has been implicated as a mediator of hot flash severity,[10] one of the most troubling postmenopausal complaints.

Despite this prior work, the interaction between diabetes and menopause has not been evaluated in a United States (U.S.) population, where diabetes rates are pronounced. One investigation in Mexico of menopausal symptoms documented higher rates of depressed mood in diabetic women compared with controls, although levels of anxiety and sleep disturbances were similar.[11] A second study from Mexico found no difference in vasomotor symptoms between healthy and diabetic subjects,[12] but neither study carried out a comprehensive symptom assessment or examined the influence of glucose control. Among postmenopausal Ecuadorian women with and without metabolic syndrome, affected participants demonstrated higher physical and psychological symptom scores but similar sexual and vasomotor symptom scores

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compared with healthy controls.[13] However, only a small proportion of those with metabolic syndrome (16%) demonstrated hyperglycemia, making it difficult to determine the relationship between elevated glucose and these symptoms. Finally, in Korea, Lee and colleagues[14] reported a higher prevalence of somatic menopausal symptoms (hot flashes, sleep disturbances, muscle and joint aches) in those postmenopausal subjects with the metabolic syndrome compared with the unaffected controls, but glucose control was not examined as a factor. The purpose of this study was to describe the postmenopausal symptom experience in U.S. women with type 2 diabetes and to examine the association between glucose control and symptom severity.

Materials and Methods

Design and sample

Taking advantage of the well-characterized medical record system used by the Veterans Health Administration (VHA), we conducted a cross-sectional retrospective study of a random sample of female veterans receiving healthcare services from the VHA. The study employed a mailed, self-administered survey and, with consent, the extraction of electronic record data relevant to the study.

After approval by the Institutional Review Boards at the Ann Arbor Veterans Affairs Medical Center and the University of Michigan, Ann Arbor, potential participants, ages 45–60 years, who had received care in the last 2 years were identified from a review of national VHA data sources (laboratory, pharmaceutical, service utilization). Women were classified as having diabetes if they had two or more outpatient visits with a diabetes-related diagnosis code per year in the past 24 months or at least one inpatient hospitalization with a diabetes-related diagnosis code and at least two documented hemoglobin A1c (HbA1c) values in the past 12 months.

Women with diabetes were characterized using their most recent HbA1c value as a measure of glucose control. Optimal or ''better'' glucose control was defined as HbA1c $\leq$ 7% and suboptimal or ''worse'' glucose control was defined as HbA1c $>$ 7%.[15–16] Although the American Diabetes Association[15] and the Veterans Affairs/Department of Defense Diabetes Mellitus Clinical Practice Guideline[16] recommend individualized HbA1c targets, based on patient characteristics (e.g., life expectancy, disease severity, patient preferences), because the study population was fairly young and expected to be relatively healthy, for research purposes, we set the cut-off value for HbA1c at 7%.

Additional selection criteria included the following: no current or past 2 years history of substance abuse, no current or past history of severe psychiatric illness, renal failure, or gynecological cancer; and no current or past 6 months use of hormone products, corticosteroid or anabolic steroids, antipsychotic medications, or more than two classes of psychoactive medications on a daily basis. Postmenopause was defined as amenorrhea for $>$ 12 months or hysterectomy with or without ovariectomy and currently not taking hormones. Reproductive status was determined by self-report on the study survey (having menstrual cycles or amenorrhea for at least 12 months). If participants reported amenorrhea, they were asked to specify the cause: natural menopause, hysterectomy (only the uterus), hysterectomy with removal of the ovaries, other causes.

A stratified, random sample of 900 women meeting the above criteria (300 without diabetes, 300 with diabetes and optimal or better glucose control, and 300 with diabetes and suboptimal or worse glucose control) was selected for the mailed survey. Based on a sample size calculation for 80% power and an alpha significance level of 0.05, 100 subjects were needed per study group. The estimated recruitment pool was multiplied by three to accommodate the anticipated response rate and the loss of participants expected to fail the survey's menopause criteria. Potential participants were mailed an invitation to participate, including a cover letter with an informational brochure, the survey, two copies of the consent form, a stamped return envelope, and a token of appreciation ($10 gift card). The consent form requested permission to examine participant's health record data for two years prior to the study and one year after completing the survey to extract clinical information, such as HbA1c. A reminder letter was sent 2 weeks after the first mailing, followed by a second survey and consent form 2 weeks later. Survey data collection closed 4 weeks after the third mailing.

Measures

The survey collected information about menopause status, the postmenopausal symptom experience, health status, comorbid conditions, diabetes symptoms and self-management behaviors, sociodemographic characteristics, height and weight to calculate body mass index (BMI), and current medication use. Depressive symptoms, anxiety, and perceived stress were also assessed. Glycemic control was measured by serum HbA1c and used to differentiate the groups with diabetes.

Menopause symptom prevalence and severity were measured with the Menopausal Symptom List (MSL).[17] Participants indicated the prevalence and severity of 12 symptoms in the past month. Symptom severity was rated on a four-point scale from 0 (none) to 3 (severe). Individual symptom severity scores were summed to calculate the total MSL severity score (range 0–36).

Respondents prospectively recorded the frequency and severity (mild, moderate, severe) of hot flashes and night sweats for two consecutive days. A hot flash score was calculated using the formula: [number of mild hot flashes] + [2 $\times$ number of moderate hot flashes] + [3 $\times$ number of severe hot flashes], and a mean value for the two days determined. A zero score was recorded for respondents who indicated no symptoms during the two-day period. Perceived health status was assessed using the 12-item Short Form Health Survey.[18] Depressive symptoms were measured using the short form of the Center for Epidemiologic Studies Depression Scale-10,[19] perceived anxiety was measured by the Generalized Anxiety Disorder scale,[20] and the Perceived Stress Scale-10 measured the respondent's appraisal of life stressors.[21]

Statistical analysis

Analyses were performed using STATA version 10.0 (Stata Corporation, College Station, TX). Descriptive statistics were used to characterize the sample and study groups. Skewed physiologic variables were log-transformed to ensure normality. Group differences in categorical variables were compared using chi-squared tests; group differences in continuous variables were compared by *t*-tests and analysis of variance with post-hoc Bonferroni correction. Associations between glucose control status and menopause symptom severity, controlling for known theoretical and empirical

covariates including BMI, ethnicity, smoking, age of menopause, and type of menopause (natural, induced) were examined using multivariable regression methods. As longitudinal studies demonstrate that women with a history of mood disorder report increased psychological symptoms during the menopausal transition,[22–23] the respondent's self-report of a mental health diagnosis (depression, anxiety, posttraumatic stress disorder [PTSD]) was used in the regression analyses to control for the influence of having a diagnosed mood disturbance (altered mood status). Because the number of years postmenopause and age of menopause are inverse parameters, only age of menopause was included in the regression analyses. Ethnicity was examined as a four-level categorical and a dichotomous variable (white/non-white) in analyses for group differences and to assess associations with the dependent variable. A two-tailed p value of <0.05 was regarded as statistically significant. As the amount of missing data in the major variables was $\leq 6\%$, listwise deletion was used in all analyses.

Results

A total of 537 surveys were returned (59.6%); most respondents ($n=506$; 94%) consented to clinical data access. Upon review of the survey and extracted data, 210 cases were excluded: 112 women were still menstruating and another 98 reported the use of exclusionary medications (e.g., hormone therapy) or clinical conditions (e.g., cancer), or submitted incomplete surveys. The final sample of 327 subjects included: 90 without diabetes, 135 with diabetes and optimal HbA1c values, and 102 with elevated HbA1c values.

Participant characteristics

Participants were on average 55 years of age, obese, and 11.3 years postmenopause. The majority of participants were white (58%), with a range of other ethnic/minority groups represented. Most participants did not smoke ($n=282$; 86%). More than half of the women ($n=178$; 56%) were working full or part-time; most ($n=183$; 59%) household income levels were below the U.S. median.[24]

Table 1 presents the characteristics of the study groups. Women without diabetes were younger, of lower BMI, had fewer self-reported comorbid conditions, and better physical health. Race/ethnicity did not differ across groups whether assessed using four categories (white, black, Hispanic, other) or as white/non-white. Mental health scores and levels of anxiety, perceived stress, and depressive symptoms were similar across the study groups.

Menopause characteristics

Among women with natural cessation of menses, the average age of menopause was 49.2 years, which did not differ by diabetes status. More than half of the respondents (55.1%; $n=179$) reported an induced menopause for surgical or other reasons (trauma, drug exposure) at an early age (mean 39.1 years). Hysterectomy features were similar across all three groups (Table 2).

Menopausal symptom prevalence

For the full sample, muscle and joint aches, hot flashes, and trouble sleeping were the most prevalent symptoms which did not differ by study group (Table 3). Headaches and anxiety were more prevalent in those with elevated HbA1c values.

Menopausal symptom severity

Symptom severity scores were highest for muscle and joint aches followed by hot flashes, and trouble sleeping; headaches received the lowest severity scores (Table 4). Women with worse glucose control demonstrated more severe anxiety and sleep disturbances than those with better glucose control, more severe mood swings than women without diabetes, and more intense headaches compared with both groups. Total MSL severity scores were higher in diabetic women with worse glucose control compared with the other two groups (Table 4).

Factors associated with menopausal symptom severity

In the full sample, cigarette smoking and a diagnosis of altered mood were positively associated with menopause symptom severity after controlling for diabetes status and sociodemographic, clinical, and menopause characteristics (Table 5). Among women with diabetes, worse glucose control ($\beta=0.15$; $p=0.03$), smoking, and a diagnosis of altered mood demonstrated a positive association with perceived menopause symptom severity after adjustment for other covariates.

Discussion

Little is known about menopausal symptom patterns in women with type 2 diabetes, which is increasingly prevalent[1] and has many symptoms that may overlap with those marking the end of reproductive life.[6–8] This study describes the menopause history and symptom experience of women with and without type 2 diabetes receiving care in the VHA system. Our results suggest that despite higher BMI and increased disease-related comorbidities, women with diabetes experienced natural and induced menopause at the same age and reported similar postmenopausal symptoms as their nondiabetic peers. Muscle and joint aches, hot flashes, and trouble sleeping were the most common postmenopausal complaints, consistent with results from cohort studies of healthy and ethnically diverse women.[25–30]

The rate of surgical menopause in our sample (approximately 50%) was higher than estimates reported (between 33% and 45%) for the general population[31–32] and could be related to the presence of risk factors such as low socioeconomic status and minority ethnicity.[33–34] Our findings are congruent with a study of hysterectomy prevalence in female veterans,[35] which documented that rates varied by age, increasing from 12% in 18–39 year olds to 35% among 40–49 year olds and 57% in women aged 50 years or older.[35] Predictors included older age, multiparity, marital status, health conditions, and PTSD. Coupled with our findings, these data suggest that veterans using VHA services may have increased hysterectomy prevalence compared with the general population and further investigations are warranted.

The mean age of menopause was 39 years among women with induced menopause and 49 years in those with natural menopause, which is earlier than the mean age of 51 years among North American women.[9] Respondent characteristics

Table 1. Clinical and Demographic Characteristics by Study Groups

	Women without diabetes (n = *90*)	*Women with diabetes (HbA1c ≤ 7%)* (n = *135*)	*Women with diabetes (HbA1c > 7%)* (n = *102*)	p
Age in years	53.6 ± 0.5[a]	55.5 ± 0.4	55.5 ± 0.5	0.003
Age of menopause	44.8 ± 0.8	43.9 ± 0.7	42.5 ± 0.9	0.13
Years postmenopause	8.9 ± 0.8[b]	11.6 ± 0.8	13.0 ± 0.9	0.007
BMI (kg/m^2)[c]	30.8 ± 0.6[d]	34.8 ± 0.6	35.9 ± 0.7	< 0.001
Ethnicity				0.47
White	57 (65)	80 (60.2)	50 (50)	
Black	24 (27)	36 (27)	32 (32)	
Hispanic	4 (5)	9 (6.8)	9 (9)	
Other[e]	3 (3)	8 (6)	9 (9)	
Medical conditions	2.8 ± 0.2[d]	5.3 ± 0.2	5.5 ± 0.3	< 0.001
Altered mood diagnosis	22 (25%)	48 (36%)	36 (37%)	0.14
Neuropathy diagnosis[f]	11 (12%)	34 (26%)	38 (39%)	< 0.001
Tobacco use[f]	15 (17)	11 (8)	19 (19)	0.04
HbA_{1c} (%)[c,g]		6.4 ± 0.05	8.9 ± 0.2	< 0.001
Age of diabetes diagnosis[g]		49.8 ± 0.5	45.4 ± 0.8	< 0.001
Diabetes duration in years[g]		5.7 ± 0.5	10.1 ± 0.7	< 0.001
Perceived Stress Scale–10 score	14.8 ± 0.8	14.6 ± 0.7	16.4 ± 0.8	0.21
Generalized anxiety disorder–7 score	5.2 ± 0.6	5.0 ± 0.5	5.4 ± 0.5	0.86
CESD–10 score	9.0 ± 0.7	9.5 ± 0.6	10.8 ± 0.7	0.14
Physical health score	43.3 ± 1.3[h]	38.6 ± 1.1	39.1 ± 1.2	0.012
Mental health score	43.8 ± 1.2	44.9 ± 1.0	41.7 ± 1.2	0.12
SSRI, SNRI or gabapentin use[f]	18 (20%)	43 (32%)	33 (32%)	0.04

Values are mean ± standard error of the mean (SEM) or *n* (%).
[a]ANOVA with post hoc Bonferroni: $p = 0.005$ vs. women with better glucose control (HbA1c ≤ 7%); $p = 0.012$ vs. women with worse glucose control (HbA1c > 7%).
[b]ANOVA with post hoc Bonferroni: $p = 0.005$ vs. women with worse glucose control (HbA1c > 7%).
[c]Normality ensured by logarithmic transformation.
[d]ANOVA with post hoc Bonferroni: $p < 0.001$ vs. women with better glucose control (HbA1c ≤ 7%); $p < 0.001$ vs. women with worse glucose control (HbA1c > 7%).
[e]Other: Native American Indian ($n = 4$); Asian ($n = 2$); Hawaiian Pacific Islander ($n = 1$); multiracial women ($n = 14$, 10 of whom identified as Native American Indian).
[f]Chi-squared with Fisher exact test.
[g]*t*-Test.
[h]ANOVA with post hoc Bonferroni: $p = 0.014$ vs. women with better glucose control (HbA1c ≤ 7%); $p = 0.06$ vs. women with worse glucose control (HbA1c > 7%).
ANOVA, analysis of variance; BMI, body mass index; CESD-10, Center for Epidemiologic Studies Short Depression Scale; HbA_{1c}, hemoglobin A1c; SNRI, selective norepinephrine receptor inhibitor; SSRI, selective serotonin receptor inhibitor.

such as chronic illness,[36] obesity,[37] and African American and Hispanic ethnicity[38] have been associated with early menopause and may have contributed to this finding.

Symptom prevalence rates in our sample were higher than rates documented in cohort studies of healthy women. Approximately 69% of our respondents had trouble sleeping, compared with rates ranging from 43% to 50% in other postmenopausal cohorts.[25–26,30] Muscle and joint aches, hot flashes, and sad mood were reported at rates up to 79%, 75%, and 61% in this study compared with rates of 55%, 49%, and 22%,

Table 2. Type of Menopause by Study Group

	Entire sample (n = *325*)	*Women without diabetes* (n = *90*)	*Women with diabetes HbA1c ≤ 7%* (n = *133*)	*Women with diabetes HbA1c > 7%* (n = *102*)	p[a]
Type of menopause					0.75
Natural	146 (44.9)	43 (47.8)	60 (45.1)	43 (42.2)	
Induced[b]	179 (55.1)	47 (52.2)	73 (54.9)	59 (57.8)	
Surgical causes					0.09
Hysterectomy with ovariectomy	89 (51.7)	25 (54.3)	41 (59.4)	23 (40.4)	
Hysterectomy	83 (48.3)	21 (45.7)	28 (40.6)	34 (59.6)	

Values are *n* (%).
[a]Chi-squared with Fisher's exact test.
[b]Includes surgical procedures (hysterectomy with ovariectomy, hysterectomy; $n = 172$, 52.9%) and other causes (trauma, clinical conditions, medications; $n = 7$, 2.2%).

Table 3. Menopause Symptom Prevalence by Study Groups

	Entire sample (n = 313)	*Women without diabetes (n = 87)*	*Women with diabetes (HbA1c ≤ 7%) (n = 129)*	*Women with diabetes (HbA1c > 7%) (n = 97)*	p
Muscle/joint aches	245 (78.6)	68 (78.2)	100 (77.5)	77 (80.2)	0.91
Hot flashes	233 (74.4)	66 (75.9)	90 (70.0)	77 (79.4)	0.25
Trouble sleeping	214 (68.6)	60 (69.0)	81 (62.3)	73 (76.0)	0.11
Memory	203 (65.0)	57 (65.5)	76 (58.9)	70 (72.9)	0.10
Irritable	199 (64.2)	55 (63.2)	79 (61.7)	65 (68.4)	0.56
Sad or blue	191 (61.2)	50 (57.5)	78 (60.5)	63 (65.7)	0.52
Decreased libido	178 (58.4)	52 (60.5)	66 (52.0)	60 (65.2)	0.13
Leaking urine	179 (57.2)	45 (51.7)	71 (55.0)	63 (65.0)	0.16
Mood swings	169 (54.2)	44 (50.6)	66 (51.2)	59 (61.2)	0.23
Anxiety	165 (52.9)	48 (55.2)	58 (45.0)	59 (61.5)	0.05
Headaches	147 (47.0)	37 (42.5)	52 (40.3)	58 (59.8)	0.01
Vaginal dryness	141 (45.2)	42 (48.3)	52 (40.3)	47 (50.0)	0.35

Values are *n* (%).
Chi-squared with Fisher exact test.

respectively, in the postmenopausal subsample of the multiethnic Study of Women Across the Nation (SWAN).[22,26,38]

This high level of symptom reporting may be related to characteristics of the sample. As a group, the respondents were obese, with a third reporting a diagnosis of altered mood. Collectively, these clinical factors, along with the high rates of hysterectomy, have been linked to higher rates of vasomotor, sleep, somatic, genitourinary, and mood symptoms in the postmenopause.[23,26,39–42,45] Increased symptom reporting has also been associated with African American and Hispanic ethnicity,[26,39,43–44] groups well represented in this sample. Traumatic life events are another correlate of menopause symptoms,[46] and although not assessed in this investigation, female veterans are often considered a trauma-exposed group[47] and potentially vulnerable to a magnified symptom response. Lastly, other studies[48–49] have documented that veterans report more symptoms compared with the general population, with increased symptom rates observed in females compared with males.[49]

These symptom prevalence rates are consistent with rates observed in the few postmenopausal studies of women with chronic illness. Two-thirds of the participants had diabetes as part of a set of five chronic health conditions; the nondiabetic women reported two to three comorbid conditions. In addition to diabetes, the most prevalent comorbidities were hypertension ($n = 234$; 73%), hyperlipidemia ($n = 208$; 65%), and osteoarthritis ($n = 155$; 48%). Among post-polio survivors, Kalpakjian et al.[5] demonstrated postmenopausal symptom prevalence rates in the 80% range for vasomotor, sleep, mood, sexual, and cognitive symptoms. In HIV-infected women,[2]

Table 4. Menopause Symptom Severity by Study Group

	Women without diabetes (n = 87)	*Women with diabetes (HbA1c ≤ 7%) (n = 129)*	*Women with diabetes (HbA1c > 7%) (n = 97)*	p
Muscle/joint aches	1.6 ± 0.1	1.7 ± 0.07	1.7 ± 0.07	0.65
Hot flashes	1.3 ± 0.1	1.2 ± 0.07	1.4 ± 0.07	0.34
Trouble sleeping	1.4 ± 0.1	1.3 ± 0.08	1.7 ± 0.08[a]	0.05
Decreased libido	1.2 ± 0.1	1.2 ± 0.09	1.5 ± 0.09	0.14
Irritable	1.0 ± 0.1	1.0 ± 0.07	1.2 ± 0.07	0.29
Memory	0.9 ± 0.09	0.9 ± 0.06	1.1 ± 0.06	0.31
Leaking urine	0.9 ± 0.1	0.9 ± 0.07	1.1 ± 0.07	0.15
Sad or blue	0.9 ± 0.1	1.0 ± 0.07	1.2 ± 0.07	0.11
Mood swings	0.8 ± 0.1	0.9 ± 0.07	1.1 ± 0.07[b]	0.03
Anxiety	0.8 ± 0.09	0.7 ± 0.07	1.1 ± 0.07[c]	0.03
Vaginal dryness	0.9 ± 0.1	0.7 ± 0.06	0.9 ± 0.06	0.29
Headaches	0.7 ± 0.1	0.7 ± 0.07	1.0 ± 0.07[d,e]	0.009
Total MSL score	12.3 ± 0.8	12.2 ± 0.8	15.4 ± 0.8[b,f]	0.006
Hot flash score	10.5 ± 1.4	9.6 ± 0.9	9.5 ± 0.9	0.85

Values are mean ± SEM; data were analyzed using ANOVA with post hoc Bonferroni.
[a] $p = 0.05$ vs. women with better glucose control (HbA1c ≤ 7%).
[b] $p = 0.03$ vs. women without diabetes.
[c] $p = 0.04$ vs. women with better glucose control (HbA1c ≤ 7%).
[d] $p = 0.016$ vs. women with better glucose control (HbA1c ≤ 7%).
[e] $p = 0.04$ vs. women without diabetes.
[f] $p = 0.009$ vs. women with better glucose control (HbA1c ≤ 7%).
MSL, Menopause Symptom List.

Table 5. Multivariate Analysis: Menopause Symptom Severity Score

Variable	*Unstandardized beta (95% CI)*	*Standardized beta*	p	R^2
Model 1, all women			<0.001	0.15
Diabetes HbA1c >7%	2.10 (−0.34–4.55)	0.12	0.09	
Diabetes HbA1c ≤7%	−0.45 (−2.63–1.74)	−0.028	0.68	
Altered mood disorder	4.53 (2.51–6.50)	0.27	<0.001	
Tobacco use	3.61 (0.96–6.21)	0.16	0.008	
Age of menopause	−0.13 (−0.28–0.024)	−0.13	0.08	
Ethnicity, Black	0.41 (−1.70–2.51)	0.02	0.64	
Ethnicity, Hispanic	1.60 (−1.74–4.93)	0.06	0.35	
Ethnicity, other[a]	3.13 (−0.33–6.60)	0.10	0.08	
BMI[b]	1.27 (−3.34–5.80)	0.03	0.61	
Type of menopause (natural, induced)	0.09 (−2.21–2.40)	0.005	0.94	
Model 2, women with diabetes			<0.001	0.14
Diabetes HbA1c >7%	2.43 (0.21–4.66)	0.15	0.03	
Altered mood disorder	4.11 (1.82–6.40)	0.25	<0.001	
Tobacco use	4.30 (1.05–7.53)	0.18	0.01	
Age of menopause	−0.11 (−0.30–0.061)	−0.11	0.19	
Ethnicity, Black	0.64 (−1.93–3.21)	0.04	0.63	
Ethnicity, Hispanic	1.71 (−2.14–5.60)	0.06	0.38	
Ethnicity, other[a]	2.94 (−0.99–6.90)	0.10	0.14	
BMI[b]	1.74 (−3.80–7.29)	0.04	0.53	
Type of menopause (natural, induced)	0.35 (−2.42–3.13)	0.02	0.80	

[a]Other: Native American Indian ($n=4$); Asian ($n=2$); Hawaiian Pacific Islander ($n=1$); multiracial women ($n=14$, 10 of whom identified as Native American Indian).
[b]BMI: log transformed to ensure normality.

high rates (>70%) of psychological and genitourinary symptoms were noted, while elevated rates (>80%) of decreased libido, muscle and joint stiffness, and cognitive symptoms were described in postmenopausal women with the metabolic syndrome.[50] These data suggest that comorbid, chronic conditions may be an important contributor to increased symptom reporting with menopause.

We also report for the first time that glucose control was a key correlate of menopause symptom severity in women with diabetes, independent of the well-described influence of obesity and ethnicity. Women with worse glucose control had higher symptom severity scores than their peers with better control who were of similar body size, years post menopause, and psychological status. Moreover, menopause symptom severity scores were similar between diabetic women with optimal glucose control and the nondiabetic cohort, despite differences in BMI and disease-related comorbidities. These data suggest that interventions targeting glucose control may improve the postmenopausal symptom experience for women with diabetes.

The increased severity of anxiety and mood symptoms among diabetic women with worse glucose control is not surprising. Depressed mood occurs in 25%–45% of adults with diabetes,[51–52] and up to 40% of diabetic patients experience anxiety,[53] with women more affected than men.[52–53] Both conditions (anxiety, depression) have been associated with poor glycemic control.[52,54–56] While the association of these symptoms with diabetes is well documented, few studies have specifically examined them in diabetic midlife women, much less in the context of the postmenopause.[57] With only cross-sectional data, it is difficult to determine if the greater severity of psychological symptoms observed here is related to menopause, diabetes, or an interaction between both conditions.

Symptoms of diabetes and depression can be interconnected and difficult to disentangle, which may be especially true in the context of the postmenopause. For example, somatic symptoms such as fatigue, cognitive complaints of impaired concentration and psychological concerns of emotional lability are symptoms associated with all three conditions. Evidence from meta-analyses is conflicting, showing that depression increases diabetes risk and worsens glucose control,[58] and likewise diabetes increases risk for depression.[59] In another meta-analysis, a differential impact of these conditions was observed: depressed mood imposed a 60% increased risk for type 2 diabetes, while diabetes incurred a 15% rise in depression risk.[60] Future longitudinal studies that characterize women using the stages of reproductive aging[61] would help clarify these relationships.

Vasomotor symptoms were similar across the study groups and corroborate some,[12,13] but not all,[14] findings from international studies in women with diabetes or the metabolic syndrome. Although a hypothetical link has been proposed,[10,62] there is little data describing the relationship between vasomotor symptoms with glucose and insulin parameters even in healthy cohorts. One investigation of nondiabetic Swedish women showed no relationship between vasomotor symptoms and glucose values,[63] while a longitudinal study of multi-ethnic U.S. women demonstrated that hot flashes were associated with insulin resistance.[62] Given the emerging evidence that vasomotor symptoms may be a surrogate marker for cardiovascular disease risk,[64] more studies are needed.

With the known influence of the selective serotonin and norepinephrine receptor inhibitors and gabapentin on the relief of vasomotor symptoms,[65–67] it is possible that the higher use rates of these medications in women with diabetes (Table 1) may have masked potentially higher rates of

vasomotor symptoms in these women. Further, the women with diabetes had higher rates of neuropathy that may have diminished peripheral sensitivity. Future studies in diabetic women using skin conductance devices to measure vasomotor events paired with glucose monitoring would more accurately characterize these symptoms.

Muscle and joint aches were reported with the greatest prevalence and severity by the entire sample. Musculoskeletal complaints are common and emerge differentially across the menopause transition, reported by 20%–80% of women.[25,30,68–69,71] An accumulating body of evidence from cross-sectional and longitudinal studies has demonstrated a relationship between menopause and the complaints of joint pain/stiffness, independent of aging [30,68,71] and obesity.[30,68–69] Retrospective surveys in women with pain complaints also indicate migraine headache and back pain improved or disappeared in menopause, while osteoarticular pain and tension headache presented or worsened.[72–73]

Female gender has also been repeatedly associated with an increased risk for osteoarthritis, especially around the age of 50.[70,74,77,84] In the Framingham cohort, the prevalence of symptomatic degenerative changes of the knee and hand were more prevalent in women than men.[75–76] Further, greater physical function limitations were observed in postmenopausal women compared with premenopausal SWAN participants independent of aging, BMI and depressive symptoms.[78] Moreover, hormone therapy trials demonstrate evidence that exogenous estrogen improves muscle and joint symptoms. In the Women's Health Initiative (WHI), treatment with estrogen plus progestin reduced joint pain and stiffness and prevented the onset of musculoskeletal complaints in participants who were asymptomatic at baseline.[79] Likewise, among WHI post-hysterectomy participants who received estrogen alone, there was improvement in joint pain compared with controls.[80]

The age, obesity, and military history features of our sample may also contribute to the rates of muscle and joint pain symptoms. Several reviews have documented the independent effect of elevated BMI and age on the risk for osteoarthritis of the knee,[81–84] hip,[82,83] and hand[83] among both women and men. Prospective cohort investigations and retrospective case control studies have repeatedly demonstrated that BMI is an independent risk factor for osteoarthritis with incremental impact; as BMI progresses from normal-weight to obese, osteoarthritis risk increases.[83] Similarly, in the Framingham study,[75] participants at baseline without knee osteoarthritis had increased risk for this condition if they had higher baseline BMI. Increasing age has also been associated with a 10-fold increase in degenerative changes in the hand, knee, and hip.[82]

Military service is a characteristic of our sample that may have influenced musculoskeletal symptom severity. Musculoskeletal injuries are a major concern among military personnel[85] and the leading cause of disability.[86] Military women have twice the injury rates of men; almost half sustain a musculoskeletal injury in initial training.[87] Without longitudinal data, it is difficult to determine if the prevalence and severity of muscle and joint symptoms are a function of menopause, comorbid obesity, or military service.

Strengths of the study included access to an ethnically diverse national sample and electronic health record data to accurately evaluate clinical features of diabetes. The cross-sectional design precluded assessment of the temporal relationship of symptoms with menopause or diabetes, and generalizability is limited to women veterans using VHA services. The retrospective self-report of symptoms and age of menopause are prone to bias. Without data regarding the military service experience, or a detailed gynecological history, we cannot account for the impact of these respondent characteristics on the menopause symptom experience.

Conclusions

In summary, a number of high-risk health conditions (obesity, hypertension, depression, induced menopause) were reported by postmenopausal women using the VHA for health care. Although women with type 2 diabetes experience similar symptoms, including joint pain, as their nonaffected peers, glucose control was a key independent correlate of menopause symptom severity along with the covariates of altered mood and tobacco use. These findings substantiate the importance of addressing postmenopausal symptoms in the clinical management of female veterans with diabetes receiving VHA services. The data also suggest that interventions targeting glucose control may improve the postmenopausal experience of women with diabetes.

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Author Disclosure Statement

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