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ACUTE & PERIOPERATIVE PAIN SECTION

Blood Dehydroepiandrosterone and Dehydroepiandrosterone Sulfate as Pathophysiological Correlates of Chronic Pain: Analyses Using a National Sample of Midlife Adults in the United States

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Abstract

Objective. Identifying biomarkers is a priority in translational chronic pain research. Dehydroepiandrosterone (DHEA) and its sulfated form, DHEA-S, are adrenocortical steroids in the blood with neuroprotective properties that also produce sex hormones. They may capture key sex-specific neuroendocrine mechanisms of chronic pain. **Design.** Cross-sectional study. **Methods.** Using data from 1,216 community-dwelling adults aged 34–84 from the Midlife in the United States (MIDUS) cohort, we examined blood DHEA and DHEA-S levels in association with chronic pain in men and women, adjusting for demographics, chronic diseases, medications including opioids, and psychosocial factors. If an association was found, we further explored dose-response relationships by the number of pain locations and the degree of pain interference. **Results.** In women, chronic pain was associated with 0.072 lower (95% confidence interval [CI], –0.127 to –0.017) log10 DHEA-S μg/dL, with pain in one to two locations associated with 0.068 lower (95% CI, –0.131 to –0.006) and in three or more locations 0.071 lower (95% CI, –0.148 to 0.007) log10 DHEA-S (*P* for trend = 0.074). Furthermore for women, low-interference pain was associated with 0.062 lower (95% CI, –0.125 to –0.000), whereas high-interference pain was associated with 0.138 lower (95% CI, –0.233 to –0.043) log10 DHEA-S (*P* for trend = 0.004). Chronic pain was not associated with DHEA or DHEA-S levels in men or DHEA levels in women. **Conclusions.** Chronic pain and its functional interference correspond to lower blood DHEA-S levels in women.

Key Words: DHEA; DHEA-S; Biomarker; Chronic Pain; Neurosteroids; Sex Hormones

Introduction

Chronic pain affects one in five people globally [1] and costs approximately $600 billion in the United States annually [2]. The unsatisfactory treatment efficacy and drug-associated adverse health effects such as opioid overdose [3, 4] have made the development of individualized and mechanism-based chronic pain treatment more urgent. One major challenge for identifying optimal treatment options remains the absence of established biomarkers for chronic pain [5]. Sensory testing, skin punch biopsy, and brain imaging have been identified as promising biomarkers for analgesic randomized controlled trials [5]. However, they primarily target neuropathic pain or are expensive and difficult to analyze and interpret. Currently, there is no consensus regarding acceptable biomarkers for chronic pain in either chronic pain research or clinical practice.

Meanwhile, there may be important correlates of chronic pain from blood panels that capture the specific pathophysiological mechanisms of chronic pain. One major mechanism is central sensitization, which plays an important role in pain sensation, chronic pain occurrence,

and comorbidity [6, 7]. Another major mechanism is abnormal stress responses underlying the emotional aspect of pain that contributes to the transition from acute to chronic pain through neuroendocrine interaction [8]. Studies of blood biomarkers for chronic pain [9–15] have primarily focused on central sensitization, with little consideration for abnormal stress responses. We hypothesize that dehydroepiandrosterone (DHEA) and its sulfated form, DHEA-S, may capture mechanisms underlying both the sensory and emotional components of chronic pain.

DHEA, with its main presence as a sulfate ester (DHEA-S) in blood, is the main product of the adrenal cortex and the most abundant circulating steroid hormone in humans [16]. Blood DHEA and DHEA-S (referred to as DHEA/-S) may be appealing pathophysiological correlates of chronic pain due to their neuroprotective properties, such as their ability to increase neurogenesis [17–20] and protect neurons from neurotoxic effects [21–24]; their potential to reflect adrenocortical function and signal abnormality of the hypothalamic-pituitary-adrenal (HPA) axis [25]; and their ability to modulate inflammatory responses [26, 27]. Lower levels of DHEA/-S in blood may therefore reflect abnormalities in the central nervous system, endocrine system, and immune functions that characterize chronic pain in the human body. In addition, because DHEA/-S serve as prohormones supplying steroids, including androgens and estrogen [16], and given the intimate but complex relationships among estrogen, androgens, and chronic pain [28], as well as the distinct neuroendocrine profiles between men and women, we further expect the association between DHEA/-S and chronic pain to be sex specific.

Although current human evidence suggests an inverse association between chronic pain and blood DHEA/-S levels [29–39], a sex-specific examination has not been conducted. Most studies have been based on highly selected chronic pain patients with limited generalizability or did not control for important confounders such as the use of opioid medication, which decreases DHEA/-S levels and therefore creates spurious associations between chronic pain and DHEA/-S levels. Furthermore, the specificity of blood DHEA/-S levels in indicating chronic pain is unknown due to inadequate adjustment of existing chronic diseases. Therefore, the current study aimed to examine blood DHEA/-S levels as a biomarker for chronic pain in men and women, respectively. We hypothesized that chronic pain would be associated with lower blood levels of DHEA/-S independent of the effect of chronic diseases and medications, including opioids, and that sex would modify the association. We further hypothesized that there would be a monotonic dose-response relationship between chronic pain severity and blood DHEA/-S levels such that chronic pain severity would be negatively associated with DHEA/-S levels. The overall objective was to examine evidence for evaluating DHEA and DHEA-S as blood biomarkers for chronic pain in community-dwelling US adults.

Methods

Study Design and Participants

This study was based on biomarker data from the Midlife in the United States (MIDUS) study, a national longitudinal study of healthy aging that recruited 7,108 participants from the 48 contiguous states in the United States at baseline (MIDUS 1) [40]. The MIDUS 2 survey (2004–2006) was conducted among the MIDUS 1 follow-up sample as well as a new African American sample from Milwaukee, WI. Among the MIDUS 2 participants, 1,255 later participated in the MIDUS 2 Biomarker Project. There was an average gap of 25 months between the survey and the biomarker data collection. A detailed description of the study can be found on the MIDUS website [40]. The cross-sectional analyses in this study were based on the MIDUS 2 survey and biomarker data. As this study was based on publicly available secondary data from a national data set, the study is exempt from institutional review board approval. All participants provided informed consent.

Measurement

Dehydroepiandrosterone and Dehydroepiandrosterone Sulfate

Serum DHEA and DHEA-S levels were assessed from blood obtained between 6:00 and 8:00 AM after an overnight fast. Aliquots of 1.0 mL were stored in cryovials at –65°C before DHEA and DHEA-S were assayed. DHEA concentrations were quantified by radioimmunoassay performed using kit DSL8900 from Diagnostic Systems Laboratories (Webster, TX). DHEA-S concentrations were quantified by immunoelectrochemiluminescent with a Roche Modular Analytics E170 analyzer using an Elecsys kit (Roche Diagnostics, Indianapolis, IN). The inter-assay coefficient of variation (CV) was 5.47% and 2.9% for DHEA and DHEA-S, respectively [41], and the intra-assay CV was 2.7–3.8% for DHEA [42] and 0.8–3.8% for DHEA-S [43].

Chronic Pain

In the main MIDUS 2 survey, chronic pain was assessed by the question "Do you have chronic pain—that is, do you have pain that persists beyond the time of normal healing and has lasted anywhere from a few months to many years?" Those who answered "Yes" were classified as having chronic pain. Those with chronic pain were then asked questions about chronic pain locations and interference. We constructed a count variable summing pain locations, including head, neck, back, shoulders, arms and hands, hips, legs and feet, knees, and others, which we examined with both discrete (no pain, one to two locations, and pain in three or more locations) and

continuous approaches. Those with chronic pain were asked to rate from 0 ("did not interfere") to 10 ("completely interfered") how the pain interfered with their general activity, mood, relationship with other people, sleep, and enjoyment of life. In addition to examining the mean score in a continuous way, we categorized those with a mean score of greater than 4 as having high-interference pain and those with a mean score of less than or equal to 4 as having low-interference pain, according to the suggested cutoff value for the Pain Interference subscale [44]. Pain interference data were not available for the Milwaukee, WI, sample.

Covariates

The lag time (in months) between the chronic pain measure and biomarker collection was controlled in the biomarker analysis. Sociodemographic variables included age (years); sex (men vs women); racial and ethnicity group (non-Hispanic White, non-Hispanic African American, and others); and education level (from lowest to highest degree and transformed as a z score). Behavioral variables included body mass index (BMI); smoking status (nonsmoker, past smoker, and current smoker); alcohol consumption (no drinking, moderate drinking, and at-risk drinking based on the National Institute of Alcohol Abuse and Alcoholism guidelines [45]); and physical activity indicated by the metabolic equivalent of task (MET; minutes per week; <500, 500–1,000, and >1,000 representing the thresholds endorsed by the Physical Activity Guidelines Advisory Committee, which suggests that a MET of 500–1,000 per week provides a health benefit [46]). All variables were obtained from the MIDUS 2 Biomarker Project.

Chronic Diseases

Given the need to carefully adjust for chronic diseases associated with both chronic pain and potentially DHEA/-S levels, we pursued a theoretical approach to covariate selection complemented by empirical validation. This involved the following steps:

1. A list of 20 chronic diseases that are medically associated with chronic pain based on current knowledge were generated from the survey and biomarker data, including arthritis; sciatica, lumbago, or backache; migraine; heart disease; circulation problems; stroke or transient ischemic attack (TIA); blood diseases such as anemia; diabetes; chronic obstructive pulmonary disease (COPD) or emphysema; ulcer; cancer; stomach trouble; urinary or bladder problems; constipation; gallbladder trouble; varicose veins; lupus or autoimmune disorder; neurological disorders such as multiple sclerosis or epilepsy; piles or hemorrhoids; and persistent gum, mouth, or teeth trouble.
2. Empirical associations with chronic pain were examined in a logistic regression model with the 20 diseases—adjusting for age, education, and race and ethnicity—and diseases showing effect sizes greater than 0.405 (odds ratio [OR] >1.5) were selected as individual covariates.
3. The remainder of the theoretically related chronic diseases that did not meet this threshold were summed and included as an index covariate. This approach was taken separately by sex to accommodate the possibility that the diseases most associated with chronic pain would be sex specific.

Depression and Anxiety

Diagnoses of major depressive disorder, generalized anxiety disorder, and panic disorder based on the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-III-R*; 1987) [47] during the past 12 months were assessed with the World Mental Health Organization's Composite International Diagnostic Interview Short Form (WHO CIDI-SF) [48, 49]. The WHO CIDI-SF has shown good validity for the full CIDI diagnoses and clinician diagnoses and has been widely used in epidemiological studies [49–51]. Depression and anxiety measures were obtained from the main MIDUS 2 survey.

Medications

The medications currently used were categorized into seven major categories:

1. Antihypertensive (beta-1 selective blockers, beta-2 agonist, calcium channel blocker, angiotensin converting enzyme inhibitors, angiotensin II receptor blocker).
2. Lipid lowering.
3. Antidiabetic.
4. Centrally acting (psychotherapeutic agents, sedative anxiolytics, and sedentary hypnotics).
5. Thyroid hormones.
6. Sex hormones (female sex hormone in women and male sex hormone in men).
7. Opioid medication.

Statistical Analysis

Linear regressions estimated log10 DHEA and log10 DHEA-S levels (log transformation to normalize outcome distributions) associated with chronic pain in both men and women, adjusting for the lag time between assessment, age, racial and ethnic group, education level, BMI, physical activity, smoking status, alcohol consumption, the discrete chronic diseases and index of the remaining chronic diseases, depression, anxiety, and the seven types of medications, including opioids. To determine whether coefficients in men and women were significantly different from each, interaction terms between sex and chronic pain were used in a pooled analysis.

To examine the robustness of the association between chronic pain and blood DHEA/-S in men and women, we first examined the impact of opioid medication use by both removing opioid medication as a covariate from the main model and excluding those with opioid medication use from the sample. We expected to see a larger effect size in the former for the association between chronic pain and biomarkers. Second, we further controlled for

nonopioid analgesic use in the main model. We expected to see an attenuated effect size. Third, we added an interaction term of chronic pain × lag time in measurement in the regression model. We expected this to indicate greater relationships of pain to biomarkers with smaller time elapsed between pain and biomarker measurement. Lastly, to eliminate potential residual confounding due to transient mood, recent stress, and trait anxiety, we further added the depressive symptoms score (Center for Epidemiological Studies Depression Inventory [CES-D 20]) [52], stress score (Perceived Stress Scale [PSS-10]) [53], and trait anxiety score (Spielberger Trait Anxiety Inventory) [54] to the main model.

If an inverse association between chronic pain and DHEA/-S was confirmed from the aforementioned main and sensitivity analyses, we further explored the dose-response relationships by regressing log10 DHEA/-S on the number of pain locations and the degree of pain interference using both discrete indicator and continuous (linear and quadratic) approaches. Finally, we calculated Cohen's f^2 for each predictor in the multiple linear regression model to indicate the local effect size for predicting DHEA/-S [55]. Data management and statistical analyses were conducted in SAS version 9.4 (SAS Inc., Cary, NC).

Results

Participants in the Biomarker Project did not differ from the main MIDUS 2 survey participants in age and sex but were more educated. The characteristics of the analytic sample are summarized in Table 1. Among the 1,216 participants with complete data, 691 were women (57%). Thirty-four percent of men and 37% of women reported chronic pain. In men with and without chronic pain, blood DHEA levels were 4.83 ng/mL and 4.79 ng/mL, respectively (P=0.87 on the log scale), and blood DHEA-S levels were 107.7 μg/dL and 110.0 μg/dL, respectively (P=0.74 on the log scale). In women with and without chronic pain, blood DHEA levels were 4.23 ng/mL and 5.04 ng/mL, respectively (P=0.002 on the log scale), and blood DHEA-S levels were 54.6 μg/dL and 68.6 μg/dL, respectively (P<0.001 on the log scale).

In the adjusted models (Table 2), chronic pain was not associated with DHEA/-S levels in men. In women, despite a nonsignificant association for log10 DHEA (β = –0.038; 95% confidence interval [CI], –0.086 to 0.011), chronic pain was associated with 0.072 lower log10 DHEA-S levels (95% CI, –0.127 to –0.017). Interaction terms also revealed that the male-female coefficients differed (for DHEA, interaction β = –0.062, P=0.046; for DHEA-S, interaction β = –0.073, P=0.041). Sensitivity analyses consistently suggested that there was no association between DHEA/-S levels and chronic pain in men. In women, the effect sizes became larger when opioid medication use was not controlled for and slightly smaller when nonopioid analgesic use was further controlled for. When women reporting opioid medication use were excluded, the effect sizes were nearly the same. When the chronic pain × lag time interaction was accounted for, the main effect sizes became larger for DHEA and DHEA-S. In the context of interaction terms, these main effects indicate the association when lag time = 0 (and interaction terms drop out); the sign of the interaction term was positive, indicating that a greater lag time between pain and DHEA/-S assessments attenuated the association. When depressive symptoms, perceived stress, and trait anxiety were added, the effect sizes were nearly the same.

For the number of pain locations for women (Table 2), no obvious monotonic dose-response relationship was detected when modeled discretely for DHEA or DHEA-S. When modeled continuously, nonlinear relationships were detected for log10 DHEA and log10 DHEA-S, both with a negative linear term and a positive quadratic term. When the influential points (Cook's distance > 4/n) were removed, there was no relationship between the number of pain locations and log10 DHEA, whereas the nonlinear relationship remained for DHEA-S (linear term: β=–0.049, P=0.003; quadratic term: β=0.007, P=0.013). There was a monotonic relationship between pain interference and log10 DHEA-S when modeled both discretely (P for trend = 0.004) and continuously (P<0.001), which was not seen in DHEA. The relationships between blood DHEA/-S levels and pain locations as well as pain interference among women are shown in Figure 1.

Table 3 presents the full models with effect sizes for each predictor for the association between chronic pain and blood DHEA/-S among women. Overall, 29.3% and 28.9% of the variance was explained by the models for DHEA and DHEA-S, respectively. Chronic pain was ranked as the fourth most important predictor, secondary to age, racial and ethnic group, and opioid medication use in the model predicting blood DHEA-S levels in women.

Discussion

Based on a study of 1,216 community-dwelling adults aged 35–84 selected throughout the United States, we found an inverse association between chronic pain and blood DHEA-S levels in women as well as a monotonic dose-response relationship associated with chronic pain–related interference, which were independent of chronic diseases and medication use, including opioids. We did not find an association between chronic pain and blood DHEA/-S concentrations in men. The study conducted by Rendina et al. [37], which was also based on the MIDUS data, reported a negative association between DHEA/-S levels and physical vitality and function; chronic pain was examined as the secondary outcome. Pooling across sexes, they found lower blood DHEA and DHEA-S levels in people with chronic pain and in those with more than

Table 1. Characteristics of the analytic sample

Characteristics	Men (n=525), No. (%)/mean ± SD	Women (n=691), No. (%)/mean ± SD
Age, y		
35–49	164 (31.3%)	216 (31.3%)
50–64	229 (43.6%)	304 (44.0%)
≥65	132 (25.2%)	171 (24.7%)
Education		
High school diploma or equivalent	127 (24.2%)	216 (31.3%)
Associate's or vocational degree	149 (28.4%)	211 (30.5%)
Bachelor's degree or above	249 (47.4%)	264 (38.2%)
Race and Ethnicity		
Non-Hispanic White	415 (79.0%)	493 (71.4%)
Non-Hispanic African American	66 (12.6%)	144 (20.8%)
Other	44 (8.4%)	54 (7.8%)
BMI		
<24.9 kg/m^2	91 (17.4%)	202 (29.2%)
25–29.9 kg/m^2	226 (43.0%)	205 (29.7%)
≥30 kg/m^2	208 (39.6%)	284 (41.1%)
Physical Activity—MET/wk, min		
<500	198 (37.7%)	328 (47.5%)
500–1,000	87 (16.6%)	129 (18.7%)
>1,000	240 (45.7%)	234 (33.9%)
Smoking Status		
Nonsmoker	249 (47.4%)	386 (55.9%)
Past smoker	188 (35.8%)	211 (30.5%)
Current smoker	88 (16.8%)	94 (13.6%)
Alcohol Consumption*		
No drinking	152 (28.9%)	275 (39.8%)
Moderate drinking	253 (48.2%)	348 (50.4%)
At-risk drinking	120 (22.9%)	68 (9.8%)
Arthritis	206 (39.2%)	303 (43.8%)
Sciatica, lumbago, or backache	94 (17.9%)	119 (17.2%)
Migraine	24 (4.6%)	83 (12.0%)
Heart disease	82 (15.6%)	56 (8.1%)
Circulation problems	40 (7.6%)	90 (13.0%)
Stroke or TIA	23 (4.4%)	29 (4.2%)
Blood diseases (e.g., anemia)	16 (3.0%)	172 (24.9%)
Diabetes	70 (13.3%)	87 (12.6%)
COPD or emphysema	14 (2.7%)	20 (2.9%)
Ulcer	25(4.8%)	44 (6.4%)
Cancer	61 (11.6%)	103 (14.9%)
Stomach trouble	75 (14.3%)	129 (18.7%)
Urinary or bladder problems	42 (8.0%)	94 (13.6%)
Constipation	14 (2.7%)	49 (7.1%)
Gallbladder trouble	4 (0.8%)	20 (2.9%)
Varicose veins	6 (1.1%)	9 (1.3%)
Lupus or autoimmune disorder	5 (1.0%)	10 (1.4%)
Neurological disorders (e.g., multiple sclerosis, epilepsy)	10 (1.9%)	21 (3.0%)
Piles or hemorrhoids	30 (5.7%)	47 (6.8%)
Persistent gum, mouth, or teeth trouble	48 (9.1%)	67 (9.7%)
Major depressive disorder	36 (6.9%)	108 (15.6%)
Generalized anxiety disorder	9 (1.7%)	21 (3.0%)
Panic disorder	19 (3.6%)	57 (8.2%)
Antihypertensive medication	174 (33.1%)	253 (36.6%)
Lipid-lowering medication	186 (35.4%)	166 (24.0%)
Antidiabetic medication	59 (11.2%)	61 (8.8%)
Centrally acting medication	87 (16.6%)	195 (28.2%)
Thyroid hormone	24 (4.6%)	84 (12.2%)
Sex hormone†	7 (1.3%)	119 (17.2%)
Opioid medication‡	34 (6.5%)	55 (8.0%)
Chronic pain	176 (33.5%)	255 (36.9%)
log10 DHEA, ng/mL	0.681 (±0.260)	0.675 (±0.318)
log10 DHEA-S, μg/dL	2.013 (±0.298)	1.773 (±0.358)

SD = standard deviation; BMI = body mass index; MET = metabolic equivalent of task; TIA = transient ischemic attack; COPD = chronic obstructive pulmonary disease; DHEA = dehydroepiandrosterone; DHEA-S = dehydroepiandrosterone sulfate.

*Alcohol consumption was classified based on the drinking levels defined by the National Institute on Alcohol Abuse and Alcoholism for men and women, respectively.

†Androgen hormones in men and female hormones in women.

‡Among male users, 31 of 34 (91.2%) used one type of opioid medication, and three of 34 (8.8%) used two types; among female users, 48 of 55 (87.3%) used one type of opioid medication, and seven of 55 (12.7%) used two types.

Table 2. Main and secondary analyses of the associations between chronic pain and blood DHEA and DHEA-S levels in men and women

		log10 DHEA, ng/mL				log10 DHEA-S, μg/dL			
Predictor	n	*β*	SE	95% CI	*P*	*β*	SE	95% CI	*P*
Men, N=525									
Main analysis*	525	0.011	0.022	–0.031 to 0.054	0.61	0.009	0.026	–0.041 to 0.060	0.72
Secondary Analyses†									
Not adjust for opioid medication	525	0.008	0.021	–0.035 to 0.050	0.72	0.001	0.026	–0.049 to 0.051	0.97
Exclude opioid medication user	491	0.006	0.022	–0.037 to 0.049	0.78	0.002	0.026	–0.049 to 0.053	0.94
Add nonopioid analgesic use	525	0.011	0.022	–0.032 to 0.053	0.62	0.009	0.026	–0.041 to 0.060	0.72
Add lag time × chronic pain	525	–0.023	0.042	–0.105 to 0.059	0.58	0.026	0.050	–0.071 to 0.124	0.60
Add depressive symptoms, perceived stress, and trait anxiety	523	0.011	0.022	–0.031 to 0.054	0.60	0.010	0.026	–0.040 to 0.061	0.69
Women, N=691									
Main analysis‡	691	–0.038	0.025	–0.086 to 0.011	0.13	–0.072	0.028	–0.127 to –0.017	0.010
Secondary Analyses†									
Not adjust for opioid medication	691	–0.047	0.025	–0.096 to 0.002	0.058	–0.081	0.028	–0.136 to –0.026	0.004
Exclude opioid medication user	636	–0.040	0.025	–0.090 to 0.009	0.11	–0.071	0.029	–0.127 to –0.015	0.014
Add nonopioid analgesic use	691	–0.037	0.025	–0.085 to 0.012	0.14	–0.068	0.028	–0.123 to –0.013	0.015
Add lag time × chronic pain	691	–0.058	0.049	–0.154 to 0.037	0.23	–0.092	0.055	–0.200 to 0.015	0.093
Add depressive symptoms, perceived stress, and trait anxiety	682	–0.039	0.025	–0.088 to 0.010	0.11	–0.076	0.028	–0.132 to –0.021	0.007
Dose-Response Relationship in Women: Number of Chronic Pain Locations, n=691									
Discrete									
No chronic pain, n=441		Ref	Ref	Ref		Ref	Ref	Ref	
Pain in one to two locations, n=139		–0.055	0.028	–0.110 to 0.000	0.74	–0.068	0.032	–0.131 to –0.006	0.073
Pain in three or more locations, n=111		–0.012	0.035	–0.080 to 0.057		–0.071	0.039	–0.148 to 0.007	
Continuous§									
Linear term		–0.046	0.016	–0.078 to –0.014	0.005	–0.059	0.019	–0.095 to –0.022	0.002
Quadratic term		0.009	0.003	0.004 to 0.014	<0.001	0.009	0.003	0.003 to 0.015	0.002
Dose-Response Relationship in Women: Degree of Chronic Pain Interference, n=557									
Discrete									
No chronic pain, n=341		Ref	Ref	Ref		Ref	Ref	Ref	
Low-interference pain, n=146		–0.050	0.029	–0.106 to 0.007	0.14	–0.062	0.032	–0.125 to 0.000	0.004
High-interference pain, n=70		–0.065	0.043	–0.149 to 0.020		–0.138	0.048	–0.233 to –0.043	
Continuous¶									
Linear term		–0.014	0.007	–0.027 to –0.001	0.034	–0.026	0.007	–0.041 to –0.012	<0.001

DHEA = dehydroepiandrosterone; DHEA-S = dehydroepiandrosterone sulfate; SE = standard error; CI = confidence interval; Ref = Reference.

Results from linear regressions; n=1,216.

*Adjusted for lag time; age; education; racial and ethnic group; body mass index (BMI); metabolic equivalent of task (MET) per week; smoking status; alcohol consumption; arthritis; sciatica, lumbago, or backache; circulation problems; ulcer; constipation; gallbladder trouble; lupus or autoimmune disorder; the number of chronic diseases; depression; anxiety; antihypertensive drug; lipid-lowering drug; antidiabetic drug; centrally acting medication; thyroid hormone; male hormone; and opioid medication use.

†Opioid medication use was excluded from the multivariable linear regression model. Those reporting opioid medication use were excluded from the analysis. Nonopioid analgesic use was additionally controlled for in the multivariable linear regression model. An interaction term between chronic pain and lag time was added to the multivariable linear regression model. Depressive symptoms, perceived stress, and trait anxiety were additionally controlled for in the multivariable linear regression model.

‡Adjusted for lag time; age; education; racial and ethnic group; BMI; MET per week; smoking status; alcohol consumption; arthritis; sciatica, lumbago, or backache; migraine; circulation problems; urinary or bladder problems; constipation; varicose veins; lupus; the number of chronic diseases; depression; anxiety; antihypertensive drug; lipid-lowering drug; antidiabetic drug; centrally acting medication; thyroid hormone; female hormone; and opioid medication use.

§Both the linear and quadratic terms were needed.

¶Only the linear term was needed.

three tender points compared with those without tender points. Our findings indicate that these associations are sex specific.

The association detected between chronic pain and blood DHEA-S levels in women is based on a conservative approach, including a rigorous adjustment for existing chronic diseases, as well as adjustment of comprehensive medication types, with a particular focus on opioid medication. As chronic pain is increasingly recognized as a disease by itself, any exploration of biomarkers for chronic pain should target specific biomarkers independent of existing chronic diseases. Our method of controlling both the discrete and the cumulative measures of pain-related chronic diseases makes it less likely that the proposed biomarkers are merely proxies of existing disease rather than unique indicators of

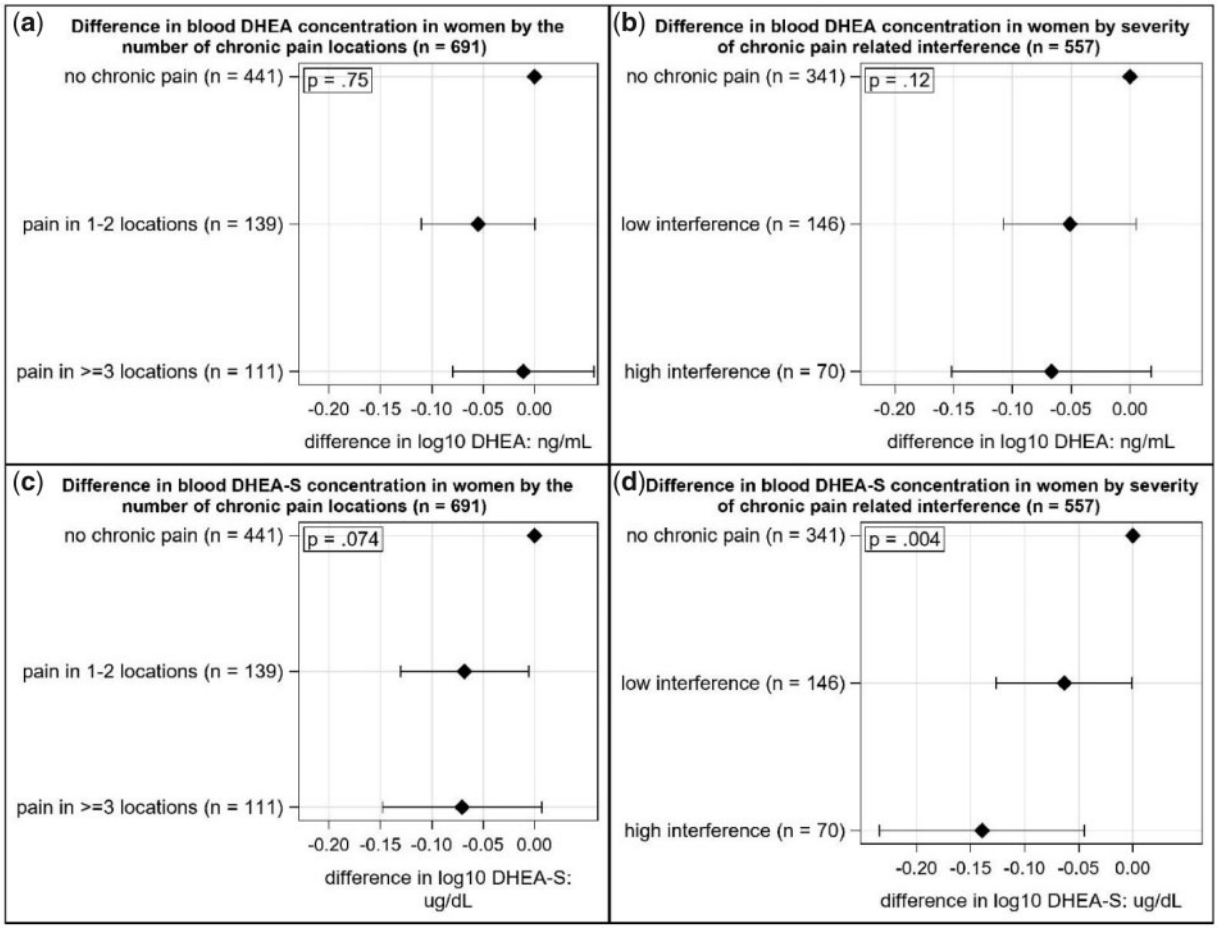

Figure 1. Dose-response relationships among blood DHEA and DHEA-S (DHEA/-S) levels, the number of chronic pain locations, and the degree of chronic pain interference among women. DHEA = dehydroepiandrosterone; DHEA-S = dehydroepiandrosterone sulfate.

chronic pain. Furthermore, as opioid medication is strongly correlated with chronic pain and also directly decreases gonadal hormone levels and weakens endocrine functions [56, 57], an association between chronic pain and lower DHEA-S levels in women independent of opioid medication use accentuates the connection between the two.

The sex difference in our findings might be due to the effect of sex hormones. Emerging evidence suggests that both estrogen and androgens contribute to the marked sex differences in the occurrence of some chronic pain conditions, with testosterone mainly associated with lower pain sensitivity and estrogen having more complex associations with chronic pain [28]. It has been reported that a low-estradiol, low-progesterone condition is associated with a pain vulnerability state by reducing endogenous opioid system function in women, possibly through β-endorphin–mediated mechanisms [58]. This may suggest a reduced endogenous pain inhibition in women with lower estradiol levels. DHEA and DHEA-S are important precursors of both estradiol and testosterone in men and women [17], and in women in particular, the majority of androgens are converted from DHEA/-S [59]. Therefore, lower levels of DHEA/-S may be a more salient predictor for chronic pain in women due to the impact on restricted production of both estradiol and testosterone. In an additional analysis, we did not find differences in the association among premenopausal and postmenopausal women, suggesting that the correspondence between lower blood DHEA-S levels and chronic pain in women may apply to a wide age range. The null association between blood DHEA levels and chronic pain in women in our study should be cautiously interpreted, given the much lower concentrations and stability of DHEA compared with DHEA-S.

Three possible explanations for the association between chronic pain and DHEA-S levels in women are worth noting. First, chronic pain, as chronic stress itself, could suppress HPA axis functioning, which results in reduced production of DHEA/-S by the adrenal cortex. It has been suggested that DHEA-S levels are a more sensitive marker than cortisol levels for adrenal insufficiency

Table 3. Contribution of each predictor in the main model to the blood DHEA and DHEA-S levels in women

	log10 DHEA, ng/mL				log10 DHEA-S, μg/dL			
Predictor	β	SE	P	Cohen's f^2*	β	SE	P	Cohen's f^2*
Lag time in pain and biomarker assessment, mo	0.000	0.001	0.636	0.000	–0.001	0.001	0.183	0.003
Age, y	–0.010	0.001	<0.001	0.128	–0.010	0.001	<0.001	0.088
Race and Ethnicity			0.003	0.018			0.002	0.020
Non-Hispanic White	Ref	Ref	Ref		Ref	Ref	Ref	
African American	–0.094	0.030	0.002		–0.108	0.034	0.001	
Other	0.032	0.041	0.437		0.048	0.046	0.299	
Normalized education level	–0.010	0.011	0.367	0.001	0.012	0.013	0.363	0.001
BMI, kg/m^2	0.003	0.002	0.117	0.004	0.003	0.002	0.164	0.003
Physical Activity—MET/wk, min			0.787	0.000			0.819	0.001
<500	–0.015	0.030	0.609		0.021	0.034	0.538	
500–1,000	Ref	Ref	Ref		Ref	Ref	Ref	
>1,000	–0.010	0.031	0.753		0.011	0.035	0.758	
Smoking Status			0.470	0.002			0.229	0.004
Never smoker	Ref	Ref	Ref		Ref	Ref	Ref	
Past smoker	0.030	0.025	0.241		0.021	0.028	0.463	
Current smoker	0.024	0.035	0.486		0.067	0.040	0.089	
Alcohol Consumption			0.655	0.001			0.096	0.007
No drinking	Ref	Ref	Ref		Ref	Ref	Ref	
Moderate drinking†	0.011	0.023	0.646		0.057	0.026	0.030	
At-risk drinking‡	0.036	0.039	0.362		0.037	0.044	0.404	
Arthritis	–0.026	0.024	0.291	0.002	–0.038	0.027	0.161	0.003
Sciatica, lumbago, or backache	0.023	0.030	0.439	0.001	0.051	0.034	0.136	0.003
Migraine	0.044	0.034	0.192	0.003	0.054	0.038	0.156	0.003
Circulation problems	0.020	0.033	0.540	0.001	–0.012	0.038	0.749	0.000
Urinary or bladder problems	–0.007	0.032	0.831	0.000	–0.031	0.036	0.383	0.001
Constipation	–0.083	0.042	0.050	0.006	–0.004	0.048	0.941	0.000
Varicose veins	–0.122	0.095	0.199	0.003	–0.052	0.107	0.626	0.000
Lupus or autoimmune disorder	–0.142	0.091	0.117	0.004	–0.228	0.102	0.026	0.008
Count of residual chronic diseases	–0.016	0.011	0.149	0.003	–0.014	0.012	0.244	0.002
Major depressive disorder	0.009	0.033	0.789	0.000	0.035	0.037	0.341	0.001
Anxiety disorder	0.025	0.037	0.506	0.001	0.048	0.042	0.259	0.002
Antihypertensive medication	–0.044	0.025	0.086	0.004	–0.066	0.029	0.022	0.008
Lipid-lowering medication	–0.067	0.027	0.013	0.009	–0.057	0.030	0.059	0.005
Antidiabetic medication	0.036	0.041	0.386	0.001	0.097	0.047	0.039	0.006
Centrally acting medication	–0.033	0.026	0.204	0.002	–0.032	0.029	0.268	0.002
Thyroid hormone	–0.058	0.033	0.080	0.005	–0.092	0.037	0.014	0.009
Current female hormone use	–0.047	0.029	0.106	0.004	–0.083	0.033	0.013	0.010
Opioid medication	–0.149	0.042	<0.001	0.019	–0.145	0.047	0.002	0.014
Presence of chronic pain	–0.038	0.025	0.129	0.004	–0.072	0.028	0.010	0.010
Total variance explained			0.293				0.289	

DHEA = dehydroepiandrosterone; DHEA-S = dehydroepiandrosterone sulfate; SE = standard error; Ref = Reference; BMI = body mass index; MET = metabolic equivalent of task.

n=669.

*For each variable, Cohen's f^2 was calculated as the added proportion of variance contributed by the variable of interest on account of the rest of covariates, divided by the residual variance of the full model.

†Moderate drinking for women is defined as up to one drink per day during the past month.

‡At-risk drinking for women is defined as more than eight drinks in a week or four or more drinks on any day during the past month.

[25]. Given the lack of association found between chronic pain and DHEA-S levels in men, this mechanism may not be the major one. Alternatively, lower blood levels of DHEA-S may contribute to pain centralization through the impaired inhibition of pain signals at the periphery and the central nervous system, either directly or indirectly through sex hormone–mediated pathways [60–62]. This may provide a better explanation for the sex-specific association found in our study. The third explanation is the existence of a predisposing compromised stress response system that contributes to both lower DHEA-S levels and chronic pain. In each scenario, DHEA-S in the blood has the potential to correlate with chronic pain. With further literature review [58, 60–68], we proposed potential pathways linking chronic pain state, DHEA/-S, sex hormone production, long-term opioid medication use, and pain centralization mechanisms, as shown in Figure 2.

The negative monotonic dose-response relationship in women between DHEA-S concentrations and the degree of chronic pain interference, as well as a less obvious dose-response relationship for the number of chronic

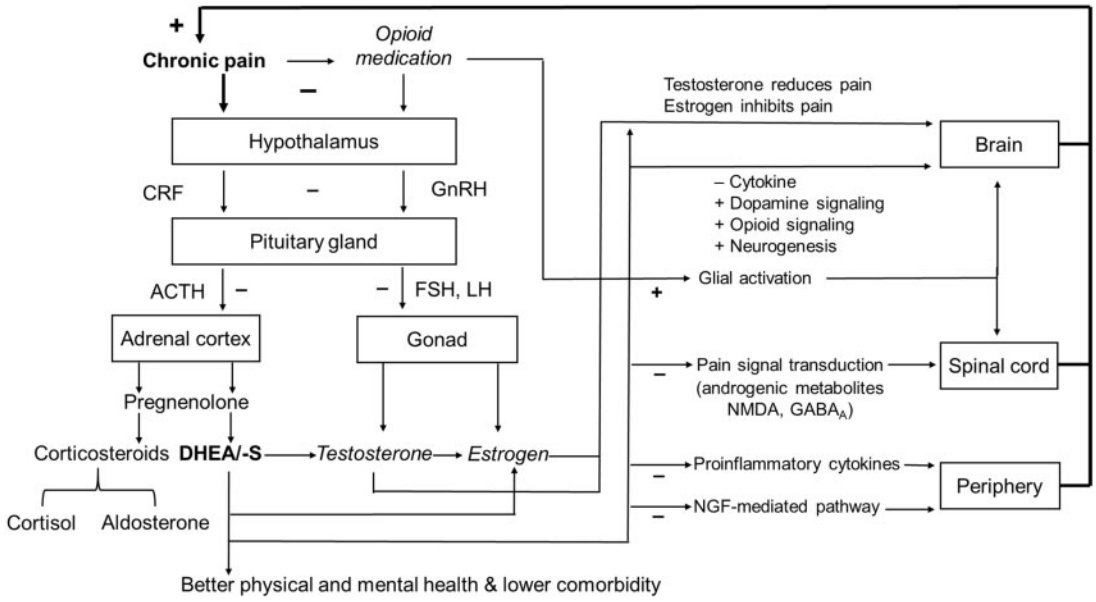

Figure 2. Potential integrated pathways linking chronic pain, long-term opioid medication use, DHEA and DHEA-S (DHEA/-S), sex hormone production, and pain centralization mechanisms. Chronic pain, as a chronic stress, suppresses the function of the hypothalamus in releasing corticotropin-releasing factor which, in turn, suppresses the function of the pituitary gland in releasing adrenocorticotropic hormone (ACTH) which, in turn, suppresses the adrenal production of pregnenolone; corticosteroids, including cortisol and aldosterone; and DHEA/-S. Meanwhile, long-term opioid medication, for managing pain, suppresses the hypothalamus in releasing gonadotropin-releasing hormone (GnRH) which, in turn, suppresses the pituitary gland in releasing sex hormones, including follicle-stimulating hormone and luteinizing hormone, which, respectively, suppress the testes and ovaries in releasing testosterone and estrogen. DHEA/-S are precursors for producing both testosterone and estrogen, and testosterone can further be metabolized into estrogen. Biologically, DHEA/-S may act locally and centrally to reduce pain signals and protect against pain centralization. At periphery, DHEA/-S may inhibit proinflammatory cytokines and suppress the nerve growth factor (NGF)–mediated pathway, impeding signal transmission from nociceptors. At the dorsal horn of the spinal cord, DHEA/-S may suppress pain signal transduction through androgenic metabolism and complex effects on N-Methyl-D-aspartic acid and γ-Aminobutyric acid type A ($GABA_A$) receptors. Blood DHEA/-S can further cross the blood-brain barrier and exert neuroprotective function through suppressing cytokines, activating dopamine signaling and opioid signaling, and promoting neurogenesis in certain brain areas. DHEA/-S can be metabolized into testosterone and estrogen in the brain which, together with the sex hormones produced by the gonads, act to reduce pain perceptions and strengthen descending pain inhibition. Meanwhile, long-term opioid medication use can induce hyperalgesia by enhancing glial activation at the spinal cord and in the brain. Overall, the state of chronic pain suppresses the adrenal production of DHEA/-S which, in turn, perpetuate the status of chronic pain. Administration of DHEA/-S may be beneficial in reducing pain in women, as DHEA/-S are the main sources for androgen production in women.

pain locations, warrants further examination. Because pain interference is a result of more comprehensive and complex central processing, one possibility could be that DHEA-S levels are more reflective of the adrenal insufficiency and stress response dysfunction that either contribute to or are a consequence of chronic pain. The nonlinear relationship between the number of pain locations and blood DHEA-S levels suggests that lower DHEA-S levels may better capture the mechanisms of regional chronic pain than widespread pain conditions such as fibromyalgia, which is consistent with the finding by Sturgeon et al. [69] of no association between DHEA-S and fibromyalgia. Widespread pain in women may be associated with distinct neuroendocrine and hormonal profiles compared with more common chronic pain conditions. However, studies specifically examining blood DHEA/-S levels and widespread pain conditions in women are needed to confirm our speculation.

Our results must be cautiously interpreted considering the following limitations. First, the cross-sectional association between chronic pain and blood DHEA-S concentrations prevents causal interpretation. Although a gap between chronic pain and DHEA/-S measurement makes it tempting to construe the findings as longitudinal, this time lag was not intended for prospective interpretations, and both measurements were designed to occur within the same wave of the study. Second, reduced DHEA/-S levels have been associated with aging. Although age was controlled in our analyses, it is important to further examine the relationship between DHEA/-S and chronic pain throughout the life span. Third, chronic pain assessment was based on one question. Although single-item pain measurement is common, measurement error is also inevitable. However, such exposure misclassification is most likely nondifferential with respect to the outcomes, which would lead to an underestimation of the

association between chronic pain and DHEA/-S. Fourth, we do not have more detailed information such as the types of sex hormones and the dose and frequency of opioid medication used by the participants, which results in residual confounding. Finally, because it is unknown when the biomarker data were collected with respect to women's menstrual cycles, the influence of female reproductive hormones, as well as dysmenorrhea-associated analgesic use, on the association between chronic pain and DHEA/-S levels is unknown.

Despite these limitations, our study provides an important clue as to whether blood-based DHEA and DHEA-S could be considered chronic pain markers. The sex difference in our results adds to a growing body of results on the discrepancy in chronic pain in men and women and associated biomarkers. The dose-response relationship found for pain interference is also consistent with the underlying mechanisms that lower blood DHEA-S levels could represent. A further translational step should be to examine any preventive or therapeutic effect brought about by supplementing DHEA/-S in managing chronic pain conditions in women. Long-term administration of DHEA has been reported to increase pain threshold in rats [70]. Recently, DHEA-S has been found to improve stress-induced visceral changes and be beneficial for irritable bowel syndrome (IBS) treatment in animal IBS models [61]. Intravaginal prasterone, the synthetic equivalent to endogenous DHEA, has been approved by the US Food and Drug Administration for the treatment of moderate to severe dyspareunia [71]. Most recently, pregnenolone, which is the precursor for both corticosteroids and DHEA/-S, has been proven effective for alleviating chronic low back pain in veterans, although the majority of the participants were male [72]. It remains to be seen whether DHEA/-S has therapeutic value across other types of chronic pain conditions in women and, furthermore, whether supplementation of DHEA/-S protects against the transition into chronic pain.

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