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Pain sensitivity among women with low estrogen levels

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Abstract

The purpose of study is to investigate estrogen influence on sensitivity of pain among menopausal women with estrogen deficiency, suffering from low back pain (LBP). Patients (n=108) completed questionnaires to identify pain severity, anxiety and life satisfaction. The data collected included socio-demographic characteristics and plasma estrogen level (PEL) measurements, health and reproductive status. Significant differences were observed with severity of LBP between women with low estrogen and women with normal PEL. There was a significant, negative association between PEL and anxiety. A conclusion suggests that in women PEL as a hormonal and reproductive factor is associated with LBP.

Keywords: Pain sensitivity, women, low back pain, estrogen, menopause.

1. Introduction

There are many evidences that estrogen have a significant role in modulating endogenous opioid neurotransmission and associated psychophysical responses to a pain stressor in humans (Smith et al., 2006). Estrogens seem to play an important role in inducing antinociception in animals in conditions of experiment (DawsonBasoa & Gintzler, 1998). These analgesic effects can be related to the fact that estrogens regulate the transcriptional control of opioid synthesis and of delta and kappaopioid receptors in lamina II of the spinal cord (Amandusson & Blomqvist, 2001) On the other hand the present findings suggest that the decrease in pain sensitivity induced by estradiol could not be explained by its effect on opioid receptors. The previously reported effects of estradiol on brain levels of **β**-endorphin and met-enkephalin may contribute to the analgesic effect of this steroid (Gordon & Soliman, 1996). Administration of estrogen in women increases paininduced **μ**-opioid receptor binding in the brain, suggesting that exogenous estrogen enhances functioning of the endogenous opioid system (Smith et al., 2006). In addition to their antinociception role, estrogens also seem to play a role in inducing hyperalgesia and pain (Dao & LeResche, 2000; Lanlua et al., 2001).

It has become increasingly apparent that women suffer a disproportionate amount of pain during their lifetime compared to men (Leveille et al., 2005; Craft, 2007). Women reported higher rates of chronic pain conditions and

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depression and higher pain severity than men. Depression and chronic pain conditions represent significant sources of disability, especially for women (Munce & Stewart, 2007). According to Rousseau & Gottlieb (2004) back and spine impairments are more common in women than men (73.3 versus 57.7 per 1000 population). But only in women, factors associated with pain included depressive symptoms, and moreover men and women differ in the factors associated with musculoskeletal pain in older ages (Leveile et al., 2005; Sievert & Goode-Null, 2005). Several recent studies have found that women are more sensitive to pain during periods of low estrogen. Pain perception varies according to the menstrual cycle phases in women with chronic pain (Hellstrom & Anderberg, 2003; LeResche et al., 2003) The researchers found that the affective component of pain may be enhanced during the low-estrogen phase of the menstrual cycle in healthy women (Craft, 2007). Postmenopausal women experiences greater pain symptoms than premenopausal women (Dugan et al., 2006). On the other hand hormonal and reproductive estrogen-related factors were associated with chronic low back pain (LBP) in women (Wijnhoven et al, 2006). There are many data that the prevalence rate of LBP increases in middle-aged women. Likewise, the investigators (Wijnhoven et al, 2006; Finset et al., 2004) also found that the prevalence of LBP peaks in women at menopausal transition. Twice as many postmenopausal women suffer LBP compared to pre-menopausal women (Yip et al., 2002, Adera et al., 1994). Women in this age also experience increasing socio-psychological stress due to menopause, changing family situations and the need to adopt multiple roles (Toriizuka et al., 2000; Freeman et al., 2007). Low back disability increases rapidly in 44-55 year old women (Finset et al., 2004). This greatly affects an individual's social and family life, employment opportunities and overall quality of life (Yip et al., 2002).

The purpose of study is to investigate the relationship between estrogen on one hand and psychological distress and LBP on the other during the menopause.

2. Methods

2.1. Subject

One-hundred fifty women who reported LBP with recovery within a month or recurrent or continuous pain during the preceding 12 months were invited to participate in study, and 108 women signed up for the study. Those women who satisfied the inclusion criteria were included in the study. The following categories were used in this study: premenopausal – with regular menstrual cycles in the 22–35-day range and normal plasma estrogen levels (PEL) and postmenopausal (12 months or more amenorrhea with low estrogen levels). At enrollment in the cohort, the ages of the participants were 31 to 54 years, 49 (age 31 to 38 years) participants were premenopausal as defined by regular menstrual cycles in normal range (22–35 days) for the past three cycles, had an intact uterus and at least one ovary. 59 (age 41 to 54 years) were postmenopausal as defined by 12 months or more amenorrhea (Freeman et al., 2005; Gracia et al., 2005). Exclusion criteria for cohort enrollment included current use of psychotropic or hormonal medications, pregnancy, serious health problems known to compromise ovarian function (eg, diabetes mellitus, and breast or endometrial cancer), and alcohol or drug abuse within the past year. All participants gave written consent to participate.

2.2. Procedures

The data were collected in 2 assessment periods between 2008 and 2009. Periods were at 9-month intervals, after the previous assessment, for a total of 1 year per participant. Each assessment period included two visits, scheduled in the first 6 days of two consecutive menstrual cycles or 1 month apart in noncycling women to obtain blood samples for the hormone assessments.

There were anthropomorphic measurements done on all the subjects according to the recommendations of the World Health Organization: Body Mass (in kg), Height (in cm), Body Mass Index (BMI) in $\kappa g/m^2$ (Table1).

Table 1. Participant Characteristics at Baseline

Variable	Premenopausal women with normal PEL Mean (SD)	Postmenopausal women with low PEL Mean (SD)
Age	35.3 (5.5)	48.1 (4.8)
Body mass index	26.1 (8.0)	29.5 (6.0)

Trained research interviewers obtained all data in individual in-person interviews at the participants' homes. The study was described to the participants as a general women's health study. The structured interview questionnaire focused on overall health and included demographic background information, menstrual cycle dates, reproductive experience, general health and neurological status, current medications, and health behaviors including smoking and alcohol use. Patients, women suffer from LBP completed questionnaires to identify pain intensity and anxiety.

2.3. Measures

2.3.1. Hormone analysis.

Nonfasting blood samples for hormone assays were collected at each study visit. The samples from women with identifiable menstrual cycles were collected within the first 6 days of bleeding, with a mean cycle day of 3.5 for the samples in this report. Assays of estradiol were conducted using commercially available kits (ACS®Estradiol-6II. Bayer Corporation, NY). All inter-assay and intra-assay coefficients were less than 5%.

2.3.2. Pain intensity

Pain intensity was assessed on an 11-point Numerical rating scale (NRS) ranging from 0 to 10 in which 0 represents "no pain" and 10 "pain as bad as you can imagine." Patients were asked to indicate present pain intensity, average pain intensity in the past 24 hours, and worst pain intensity. The NRS has been demonstrated to be a reliable and valid measure of pain intensity (Jensen et al., 1986).

2.3.3. State-Trait Anxiety Inventory

The inventory is based on the distinction between state anxiety and trait anxiety. State anxiety is defined as a transitory, emotional condition characterized by subjective feelings of tension and apprehension. Trait anxiety is defined as anxiety-proneness - that is an individual's tendency to respond to stressful situations with raised state anxiety. The STAI consists of two questionnaires, each of 20 items, designed for the self reported assessment of the intensity of feelings. As such, the STAI adopts a psychological reasoning approach - that is, I feel (Cox & Ferguson, 1991).

2.3.4. Beck Depression Inventory

The Beck Depression Inventory is a 21-item instrument with emphasis on cognitive symptoms of depression (Beck, 1961). The response format is from 0 to 3, giving a theoretical range of 0 to 63 points. Its reliability and validity have been studied, and strong support for the psychometric quality of the questionnaire has been provided (Beck et al., 1988).

2.4. Statistics

Pearson's correlation test was used to compute the relationship between hormone values and symptoms (psychological distress and musculo-skeletal pain. $P<.05$ was chosen as the criterion for statistical significance, but some findings of borderline significance, defined as $p<.10$, are also reported. Multiple linear regression analyses were used to analyze whether hormone values contributed to the prediction of symptoms and vice versa.

SPSS version 11.0 for Windows was used for statistical analyses.

3. Results

Significant differences were observed with severity of LBP between women with low estrogen and women with normal PEL. There was a significant, negative association between PEL and anxiety (R=.39 P<.001).

Moderate or severe pain intensity, and depressed mood (P<.002) were significantly associated with menopausal stages in bivariable analysis. Anxiety was significantly associated with menopausal stages (P<.001). Age was associated only with the pain intensity (P<.001). The significant associations of age with this symptom were observed only in age groups 45 years or older.

There was a significant trend (P<.0005) of increased scores of pain intensity and depressed mood, and anxiety with an increasing age and decreasing levels of estrogens (Table 2). The results of the univariate analysis indicated a significant correlation (p<.0005) between a high symptom score higher BMI and high levels on the NRS score.

Table 2. Intensity of pain , Depression and anxiety among women with normal and law PEL

Variable	Premenopausal women with normal PEL Mean (SD)	Postmenopausal women with low PEL Mean (SD)
Pain intensity	3.2 (1.8)	4.6 (2.1)
Depression	12.9 (3.8)	14.7 (3.1)
Anxiety	32.8 (5.1)	36.4 (6.1)

The mean and standard deviation of the participant's hormone measures were calculated at each of the two study groups. The association of these measures with each symptom adjusted for menopausal stage was then estimated. Lower mean levels of estradiol were associated with pain intensity (P<.001) and higher levels of anxiety (P<.04). Estradiol levels were not significantly associated with depression, in the group of premenopausal women.

We then estimated the association between menopausal stage in the postmenopausal group and symptom severity adjusted for other risk factors of the study: age, depression, current smoking, BMI, anxiety. Estimates were obtained for each symptom using the same set of covariates, and each variable was adjusted for all other variables in the model. Menopausal stage was associated with pain intensity (P<.001), and depressed mood (P<.002) after adjusting for other risk factors. The risk of anxiety increased throughout the menopausal transition and was greatest in the postmenopausal group (odds ratio [OR] 2.87, 95% confidence interval [CI] 1.76–4.67, P<.001). The risk of depressed mood was greatest in the late premenopausal stage compared with the premenopausal group (OR 1.48, 95% CI 1.11–1.99, P<.009). Depressed mood decreased postmenopause (OR 0.64, 95% CI 0.41–1.00), P<.05).

Obese postmenopausal women have been found to have an increased pain intensity compared to non-obese women. Some investigators have reported that women with low weight/BMI had higher scores on depression at the time of the menopause but others have found the opposite correlation (Erlik, 1982). A higher BMI was correlated with a higher anxiety and depression in the present study. Overweight might be viewed as a lifestyle factor, with less concern about health and lower self-esteem in psychosocial terms. Obesity is further correlated to several illnesses, such as non-insulin dependent diabetes mellitus, and hypertension.

4. Conclusions

This study demonstrates that reports of pain intensity, anxiety, and depressed mood significantly increase in the transition to menopause. The association of these symptoms with menopausal stage was independent of age and other known risk factors such as body mass. In women PEL as a hormonal and reproductive factor is associated with LBP. Estrogens modulate responses to a pain stressor and anxiety in women.

Factors related to increased estrogen levels may specifically decrease the risk of chronic LBP and stress in women with low estrogen levels.

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