Journal of Affective Disorders 156 (2014) 200–205

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research report

Urinary phytoestrogens and depression in perimenopausal US women: NHANES 2005–2008

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A R T I C L E I N F O

Article history:
Received 2 September 2013
Received in revised form
20 December 2013
Accepted 20 December 2013
Available online 30 December 2013

Keywords:
Lignans
Isoflavones
Depression
Perimenopause
Cross-sectional study

A B S T R A C T

Background: Fluctuating hormonal levels observed during the menopausal transition may increase vulnerability to depression in susceptible women. Thus, it is of interest to examine the effect of natural estrogens such as phytoestrogens on the risk of depression in perimenopausal women.

Methods: Our analysis included 193 perimenopausal women of the National Health and Nutrition Survey (NHANES) 2005–2008 aged 45–55 years. Urinary concentrations of phytoestrogens (isoflavones and lignans) were measured by HPLC-APPI-MS/MS. Depression was assessed using the Patient Health Questionnaire-9 (PHQ-9). Logistic regression models examined the association of phytoestrogens concentrations (creatinine-standardized and log-transformed) with depression (yes/no).

Results: Unadjusted odds ratios (OR) of the associations between urinary phytoestrogen concentrations and perimenopausal depression were below 1; however, only lignans were significantly inversely associated with depression. The latter findings were not attenuated in multivariate analysis including age, race, body mass index, poverty income ratio, smoking, alcohol consumption, cancer, diabetes, and cardiovascular disease (lignans: OR=0.66; 95% confidence intervals (CI) 0.50–0.87, enterodiol: OR=0.63; 95% CI 0.51–0.78, enterolactone: OR=0.75; 95% CI 0.60–0.93).

Limitations: Our cross-sectional study design does not allow for causal inferences. Because information to precisely assess perimenopausal symptoms was missing, we defined perimenopause based on women's age.

Conclusions: Lower lignans but not isoflavones concentrations were statistically significantly associated with an increased risk of depression in perimenopausal women. Because of medical risks associated with the use of hormone therapy, further investigation on the effect of lignans on the risk of depression in perimenopausal women is warranted.

1. Introduction

Depression is a major public health problem worldwide (Murray and Lopez, 1997). Women are at higher risk than men to experience depressive episodes. One of the hypotheses to explain this difference between men and women is the contribution of sex hormones (e.g. estrogens) to the development of depressive symptoms (Bromberger et al., 2010). At times of hormonal fluctuations, such as the transition phase of the puberty and the premenstrual, postnatal and perimenopausal periods, women are particularly prone to depression (Bromberger et al., 2007; Cohen et al., 2006; Freeman et al., 2006; Gibbs et al., 2012; Jolley et al., 2007; Studd, 2011; Thapar et al., 2012).

Depression results from a complex interaction of genetic, psychological, and environmental factors (Bagdy et al., 2012) and is characterized by depressed mood, loss of interest in pleasurable activities, feelings of guilt and low self-esteem, sleep and appetite disturbance, tiredness, and diminished ability to concentrate (Kennedy, 2008). The principal types are major depression, dysthymia, and bipolar disease (manic-depressive disease) (Baune et al., 2006).

The current analysis focuses on perimenopausal depression. Perimenopause is an imprecisely described period in middle-aged women. It can be defined as the period between the moment the

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0165-0327/$ - see front matter © 2014 Published by Elsevier B.V.
http://dx.doi.org/10.1016/j.jad.2013.12.029

first changes in the menstrual cycle occur and the 12 months following the definitive cessation of menstruation (Mendoza et al., 2013). The median age of menopause among white women from western countries ranges between 50 and 52 years of age, and about two years earlier for African, American and Latino women (Gold, 2011). For our ethnically mixed population this could mean that the median age of menopause would be around 49–50 years. Findings from cross-sectional studies indicate that first endocrine changes of perimenopause start at about the age of 45 (Trevoux et al., 1986).

Estrogens may act on depression by selectively binding to the beta-estrogenic receptors (ERβ) in the brain (Bodo and Rissman, 2006) thereby interacting with the dopaminergic, serotonergic and cholinergic neurotransmitter systems, which regulate cognitive function and mood (Craig and Murphy, 2007; Lipovac et al., 2010). There is some evidence that hormone therapy (HT) improves psychological well-being of menopausal women (Haines et al., 2003). Soares et al. found that the transdermal oestradiol therapy had a significant antidepressant effect in perimenopausal women, whereas Pearce et al. observed that HT did not affect depression or anxiety (Pearce et al., 1997; Soares et al., 2001).

To prevent potential medical risks associated with the use of HT, it may be of interest to evaluate the effect of natural estrogens such as phytoestrogens on the risk of depression in perimenopausal women. Phytoestrogens are found in many plant foods (e.g. soy, flaxseeds, legumes). The main groups of phytoestrogens are lignans, isoflavones, and coumestans (Branca and Lorenzetti, 2005; Humfrey, 1998). They may act as weak estrogens (Humfrey, 1998). However, they can also act as antioxidants and anti-inflammatory agents (Patisaul and Jefferson, 2010). Accordingly, phytoestrogens increase the activity and expression of antioxidant defense enzymes (such as glutathione peroxidase, glutathione reductase and superoxide dismutase). These effects on oxidative stress are similar to the effects of estrogens. Additionally, phytoestrogens may inhibit tyrosine kinase, lower cholesterol, and inhibit cell proliferation and DNA synthesis (Sumien et al., 2012).

Accordingly, it has been suggested that phytoestrogens have preventive effects on various diseases such as osteoporosis, metabolic syndrome, hormone-related cancers, and cardiovascular diseases (Patisaul and Jefferson, 2010). In addition, several studies on the effects of soy isoflavones extracts on the symptoms of the climacteric syndrome have been published (Bolanos et al., 2010). Furthermore, there are a few studies related to the potential influence of phytoestrogens intake on cognition (Sumien et al., 2012) and depressive symptoms (de Sousa-Munoz and Filizola, 2009; Ishiwata et al., 2009; Nagata et al., 2000).

So far, health effects of phytoestrogens were evaluated by assessing the consumption of these plant constituents by study participants. This does not take into account inter-individual differences in the metabolism of phytoestrogens, i.e. the individual ability to produce the isoflavones equol and *O*-desmethylangolensin (*O*-DMA) and the lignans enterolactone and enterodiol from phytoestrogen precursors by the gut microflora (Humfrey, 1998). In contrast, measuring the concentration of phytoestrogens in urine takes these inter-individual variations in microbial synthesis into consideration (Lampe et al., 2006). Therefore, the main purpose of the present study was to determine whether lower concentrations of isoflavones, lignans, genistein, daidzein, equol, *O*-DMA, enterolactone, and enterodiol are associated with an increased risk of depression in women aged 45–55 years using data from the National Health and Nutrition Survey (NHANES) 2005–2008. To our knowledge, this is the first study to investigate the association between these urinary phytoestrogen levels and depression in perimenopausal women.

2. Methods

2.1. Study population

The present study used data of the 2005–2006 and 2007–2008 NHANES cycles. These cycles comprised data of 20,497 people. We restricted the analysis to women aged 45–55 years (n=875), i.e. perimenopausal women. Because information to precisely assess perimenopausal symptoms such as irregular menstrual cycle or hot flushes, sleep disorders, 12 months of amenorrhea is not available in the NHANES cycles 2005–2008 (Mendoza et al., 2013; Wiacek et al., 2011), we defined perimenopause based on the women′s age. There were no pregnant women to exclude. Eight hundred women completed the depression questionnaire (PHQ-9). Further participants were excluded due to missing information on urinary phytoestrogen levels (phytoestrogens were measured only in a representative one-third sub-sample of NHANES), leaving a sample of 258 women. Additional women were excluded from the analyses if they had bilateral ovariectomy, had a hysterectomy or had taken birth control pills at the time of the study (n=64). After excluding HT users (n=1), the final analytic sample included 193 women.

The NHANES study protocols were approved by National Center for Health Statistics (NCHS) Research Ethics Review Board (ERB) and informed consent was obtained from all participants.

2.2. Measurements

Spot urine samples were collected at NHANES mobile examination centers (MEC). They were processed, stored, and shipped to the Division of Environmental Health Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention for analysis (for details see NHANES Laboratory/Medical Technologists Procedures Manual). Urinary concentrations of phytoestrogens were separated by reverse-phase HPLC, detected by APPI-MS/MS by the Nutritional Biomarkers Branch, and quantified by isotope dilution.

Urinary phytoestrogens were creatinine-standardized to correct for urine dilution and creatinine was measured using Beckman Synchron CX3 Clinical Analyzer at the University of Minnesota.

Depressive symptoms were assessed in the Mobile Examination Center (MEC) using the Patient Health Questionnaire (PHQ-9), a short screening questionnaire often used in practice and research, a reliable and valid diagnostic tool for detecting depression (Kroenke et al., 2001; Manea et al., 2012; Spitzer et al., 1999). The self-reported PHQ-9 included nine DSM-IV based symptom criteria for depression that are scored in a four-point Likert scale ranging from "0" (not at all) to "3" (nearly every day). The resulting total score ranged from 0 to 27 (Kroenke et al., 2001; Manea et al., 2012; Spitzer et al., 1999). Participants were asked how often they were bothered by these symptoms over the past two weeks. A PHQ-9 score ≥ 10 was considered as moderate to severe depression, whereas a score below 10 was considered as no or mild depression. This cut-off point (≥ 10) had a sensitivity of 88% and a specificity of 88% for the diagnosis of major depression (Kroenke et al., 2001; Manea et al., 2012). Thus, we dichotomized a participant′s PHQ-9 score into <10 (no depression) and ≥ 10 (depression). Potential confounders in our analyses were weight and height, which were measured by trained personnel. Body mass index (BMI) was calculated as weight in kg divided by squared height in meter. Self-reported data of the participants were obtained by household interviews and included information on age, race/ethnicity, poverty income ratio (PIR, calculated as a proportion of the self-reported family income to the United States census-based poverty threshold value for each calendar year adjusted for inflation and the age of the family reference person),