

Association of Urinary Phytoestrogens With Pelvic Organ Prolapse and Fecal Incontinence Symptoms in Postmenopausal Women

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Objectives: The aim of this study was to investigate the association between urinary phytoestrogen levels with symptoms of pelvic organ prolapse (POP) and fecal incontinence (FI) in postmenopausal women.

Methods: This is a cross-sectional study using the National Health and Nutrition Examination Survey database from 2005 to 2010 including postmenopausal women 40 years or older who either had both ovaries removed and/or had no period in the past year due to hysterectomy and/or menopause. Urinary concentrations of 6 phytoestrogens were measured. Pelvic organ prolapse symptoms were defined as a positive response to the question, “Do you see or feel a bulge in the vaginal area?” Fecal incontinence was defined as leakage of mucus, liquid, or solid stool occurring at least monthly. Using appropriate sample weights, prevalence estimates and 95% confidence intervals were calculated. Logistic regression was performed assessing associations between pelvic floor symptoms and log-transformed phytoestrogen levels adjusting for appropriate covariates.

Results: Participants included 1341 postmenopausal women with phytoestrogen data; 1213 with or without POP symptoms and 1221 with or without FI symptoms. Multivariable analysis revealed no association of urinary phytoestrogen levels with POP symptoms. Higher urinary O-desmethylangolensin level was associated with decreased odds of FI symptoms in postmenopausal women (adjusted odds ratio, 0.92; 95% confidence interval, 0.86–0.99).

Conclusions: Increased urinary O-desmethylangolensin level was associated with lower odds of FI. Future research may be warranted to further investigate the potential of specific phytoestrogens as mediators of FI, as well as the role of phytoestrogens on POP symptoms.

Key Words: NHANES, phytoestrogens, pelvic prolapse, fecal incontinence, postmenopausal women

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Symptoms of pelvic floor disorders (PFDs) are common with 17.1% of women in the United States having moderate to severe urinary incontinence (UI), 9.4% with fecal incontinence (FI), and

2.9% with pelvic organ prolapse (POP).¹ In addition, the prevalence of PFDs increases with age and menopausal status, reaching 39% to 50% among women 60 years and older.² Given the association between decreased circulating estrogen levels and increased prevalence of PFDs and the presence of estrogen receptors in the bladder, pelvic floor, and anal sphincter,^{3–7} estrogen has been explored as a mediator of these conditions with mixed clinical results.^{8–13}

Less explored as a potential mediator of or a treatment option for PFDs have been phytoestrogens, also known as plant or dietary estrogens. Phytoestrogens are biochemically similar to estradiol and are present in foods such as nuts, flax seed oil, soy products, cereals, breads, and legumes.¹⁴ There are 3 major classes of phytoestrogens: isoflavones [eg, daidzein, equol, genistein, O-desmethylangolensin (O-DMA)], coumestans (eg, coumestrol), and lignans (eg, enterodiol and enterolactone).¹⁵ A recent review showed that, although the literature is limited, most studies on phytoestrogens and PFDs support potential associations with pathophysiologic mechanisms, symptoms, and treatment for UI and POP, but no data were available reflecting associations with FI.¹⁶

Using the National Health and Nutrition Examination Survey (NHANES), Kreydin et al¹⁷ demonstrated that increasing urine concentration of the phytoestrogen enterodiol was associated with decreased odds of urgency [odds ratio (OR), 0.92; 95% confidence interval (CI), 0.85–0.99], mixed (OR, 0.90; 95% CI, 0.82–0.98), and other (OR, 0.90; 95% CI, 0.81–0.99) UI in postmenopausal women. In addition, increasing urine concentration of the phytoestrogen enterolactone was associated with decreased odds of urgency (OR, 0.92; 95% CI, 0.86–0.99) and mixed (OR, 0.91; 95% CI, 0.84–0.99) UI in women.¹⁷ To expand on information from previous studies, the objective of this study was to use NHANES data to investigate the associations between urinary phytoestrogen levels and symptoms of POP and FI in postmenopausal women.

MATERIALS AND METHODS

The NHANES 2005–2006, 2007–2008, and 2009–2010

The NHANES program consists of cross-sectional, national health surveys conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (<http://www.cdc.gov/nchs/nhanes.htm>). The NHANES provides estimates of the health status of the US population by selecting a representative sample of the noninstitutionalized population using a complex, stratified, multistage, probability cluster design. The NHANES years 2005–2006, 2007–2008, and 2009–2010 were used for this study. The NHANES 2005–2006 oversampled individuals who were 60 years or older; black; Mexican American; and low-income, non-Hispanic white race to provide more reliable estimates for these groups. In the NHANES 2007–2008 and 2009–2010, all Hispanic groups were oversampled, not just Mexican Americans. The NCHS Ethics Review Board approved the protocol, and all participants provided written informed consent.

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TABLE 1. Characteristics of Postmenopausal Women With Phytoestrogen Levels From NHANES

Variable	Prolapse Symptoms, n = 1213		P	FI Symptoms, n = 1221		P
	No	Yes		No	Yes	
Age, % (CI), n, y			0.90			0.18
40–49	1.6% (1.0–2.4), 18	1.5% (0.2–10.3), 1		1.9% (1.3–2.8), 20	0% (0), 0	
50–59	8.5% (6.9–10.6), 98	4.6% (1.4–14.4), 3		8.4% (6.6–10.5), 86	7.7% (4.3–13.6), 15	
60–69	27.3% (24.4–30.3), 313	30.8% (19.7–44.7), 20		28.0% (25.2–31.1), 288	24.2% (18.6–31.0), 47	
70–79	30.1% (27.3–33.2), 346	30.8% (20.5–43.3), 20		30.6% (27.6–33.7), 314	30.4% (23.9–37.9), 59	
≥80	32.2% (29.4–35.2), 370	32.3% (21.1–46.0), 21		30.8% (27.9–33.8), 316	37.6% (31.5–44.2), 73	
Race/ethnicity, % (CI), n			0.45			0.29
Hispanic	93.8% (90.0–96.2), 288	6.2% (3.8–10.0), 19		87.3% (82.7–90.9), 269	12.7% (9.1–17.3), 39	
Non-Hispanic white	94.5% (92.6–95.9), 586	5.5% (4.1–7.4), 34		82.6% (80.0–85.0), 519	17.4% (15.0–20.1), 109	
Black	95.2% (92.1–97.1), 238	4.8% (2.9–7.9), 12		83.5% (77.8–87.9), 212	16.5% (12.1–22.2), 42	
Asian	100% (0), 36	0% (0), 0		87.1% (74.0–94.1), 27	12.9% (5.9–26.0), 4	
Education, % (CI), n			0.34			0.45
<High school	30.9% (27.5–34.4), 354	36.9% (24.7–51.1), 24		30.8% (27.2–34.7), 316	29.9% (22.3–38.8), 58	
High school	26.1% (23.6–28.7), 299	18.5% (11.3–28.8), 12		26.3% (23.9–28.9), 270	22.2% (16.3–29.3), 43	
>High school	43.1% (39.8–46.4), 494	44.6% (32.7–57.1), 29		42.9% (39.6–46.3), 440	47.9% (39.4–56.6), 93	
BMI, % (CI), n, kg/m ²			0.12			0.78
<25.0	26.7% (24.1–29.4), 304	13.9% (6.9–25.9), 9		26.0% (23.2–29.0), 265	24.4% (19.2–30.4), 47	
≥25.0–29.9	31.6% (29.3–34.0), 360	33.9% (21.4–49.1), 2		31.2% (28.9–33.7), 318	33.7% (26.5–41.6), 65	
≥30.0	41.7% (38.5–45.0), 475	52.3% (37.9–66.3), 34		42.8% (39.4–46.3), 436	42.0% (34.3–50.1), 81	
Smoker, % (CI), n			0.17			0.56
Yes	39.7% (36.4–43.1), 455	30.8% (20.6–43.2), 20		39.6% (36.3–42.9), 406	41.8% (35.0–48.8), 81	
Chronic lung disease, % (CI), n			0.59			0.001
Yes	20.7% (18.2–23.3), 237	23.1% (14.9–33.9), 15		19.8% (17.2–22.7), 203	28.4% (22.8–34.7), 55	
Diabetes, % (CI), n			0.71			0.04
Yes	20.4% (18.0–23.0), 234	18.5% (10.6–30.1), 12		18.5% (16.4–20.8), 190	26.8% (18.9–36.5), 52	
Pregnancies	3.8 ± 3.2	4.0 ± 3.2	0.60	3.8 ± 0.1	4.0 ± 0.1	0.62
Vaginal delivery	3.0 ± 0.1	3.0 ± 0.2	0.96	2.9 ± 0.1	3.1 ± 0.2	0.16
Prior hysterectomy, % (CI), n			0.31			0.14
Yes	44.7% (41.7–47.8), 505	52.4% (38.7–65.7), 33		44.7% (41.5–48.0), 451	50.5% (44.0–57.1), 97	
History of hormone use, % (CI), n			0.60			0.004
Yes	35.9% (32.7–39.3), 410	32.3% (20.6–46.8), 21		34.7% (31.4–38.1), 355	45.1% (38.3–52.1), 87	
≥3 chronic diseases, % (CI), n			0.50			0.83
Yes	10.3% (8.9–11.8), 118	7.7% (3.2–17.3), 5		10.2% (8.6–12.1), 105	10.8% (6.9–16.7), 21	
Major depression, % (CI), n			0.05			<0.001
Yes	10.9% (8.9–13.1), 123	18.8% (11.0–30.1), 12		9.5% (7.8–11.5), 97	20.3% (15.1–26.8), 39	

Common stool types, % (CI), n		<0.001
1	3.1% (2.2–4.3), 31	1.1% (0.3–4.3), 2
2	5.7% (4.3–7.4), 57	4.7% (2.4–8.9), 9
3	18.4% (16.0–21.0), 185	17.3% (12.6–23.2), 33
4	56.6% (53.2–59.9), 569	41.9% (34.9–49.2), 80
5	8.0% (6.5–10.0), 80	12.6% (8.5–18.2), 24
6	7.3% (5.9–8.9), 73	16.8% (11.3–24.2), 32
7	1.1% (0.6–2.1), 11	5.8% (3.2–10.2), 11

N, number; %, percentage; CI, confidence interval; SE, standard error.

Procedures and Participants

Participants were interviewed in their homes and underwent standardized physical examination, including measured height and weight, and further questioning in a mobile examination center (MEC). Trained interviewers asked questions about FI among women 20 years and older in a private MEC interview. Women answered questions regarding POP symptoms along with questions on reproductive health. For this study, the sample was limited to postmenopausal women who were 40 years or older who either had both ovaries removed and/or had no period in the past year due to hysterectomy and/or menopause.

Fecal Incontinence and POP Assessment

To define FI and POP, a similar methodology from a previous publication using NHANES data from 2005–2006 was used.¹⁸ To evaluate for the occurrence of monthly FI, the Fecal Incontinence Severity Index, which asks about the frequency of leakage of gas, mucus, liquid, and/or solid stool with the following categories: “never,” “2 or more times per day,” “once per day,” “2 or more times per week,” “once a week,” to “1 to 3 times per month,” was used.¹⁹ Fecal incontinence was defined as leakage of mucus, liquid, or solid stool occurring at least monthly on the Fecal Incontinence Severity Index. Women were asked about POP using the previously validated question, “Do you see or feel a bulge in the vaginal area.”²⁰ The responses were dichotomized, and POP was defined as a positive response.

Urinary Phytoestrogen Assessment

Urinary concentrations of 6 phytoestrogens (isoflavones: daidzein, equol, genistein, and O-DMA; lignans: enterodiol and enterolactone) were measured using either high-performance liquid chromatography–atmospheric pressure photoionization–tandem mass spectrometry (HPLC-APPI-MS/MS) or liquid chromatography electrospray ionization mass spectrometry (LC-ESI-MS/MS). Cross-over studies comparing samples analyzed by HPLC-APPI-MS/MS and LC-APPI-MS/MS showed similar spectrometric readings.²¹

Associated Risk and Protective Factors

Women self-reported their race/ethnicity, which was then categorized as non-Hispanic white, non-Hispanic black, Hispanic (including Mexican American), and Asian. Age was categorized in 10-year increments from 40 years of age to age 79, with women 80 years and older in the same category. Education was categorized as at least some level of high school education (general education development or equivalent) or more than high school. Body mass index (BMI) was calculated as kg/m² and categorized as less than 25.0 (underweight/normal weight), 25.0 to 29.9 (overweight), and 30.0 or more (obese). Smoking status was based on the question, “Smoked at least 100 cigarettes in your lifetime?” with an affirmative response resulting in the designation as “smoker.”

Data on disease status were ascertained through the question, “Has a doctor or other health professional told you that you had [disease]?” In addition to hypertension, the following were disease types also examined and categorized as positive by self-report: arthritis, cerebrovascular accident, chronic lower respiratory tract disease, coronary heart disease, congestive heart failure, liver disease, thyroid disease, cancer (other than skin), and diabetes mellitus.²² Chronic lower respiratory tract disease included self-reported emphysema, chronic bronchitis, or asthma; coronary heart disease included coronary heart disease, angina, or a myocardial infarction. Diabetes included participants who also were taking insulin and/or oral medication for diabetes mellitus. The cumulative number of positive responses to these disease types was divided into 5

categories: 0, 1, 2, 3, and 4 or more. Women self-reported number of pregnancies, vaginal deliveries, cesarean deliveries, having had a hysterectomy with or without oophorectomy, and prior hormone use.

Depression was assessed in a private interview in the MECs using the validated Patient Health Questionnaire-9. The Patient Health Questionnaire-9 yields scores from 0 to 27, and scores 10 or higher are used to define major depression with a sensitivity of 88% and a specificity of 88%.²³

Stool consistency was assessed using the Bristol Stool Form Scale (color picture card with pictures and written descriptors of the 7 stool types) and the following written question: "Please look at this card and tell me the number that corresponds with your usual or most common stool type."²⁴ Stool types vary from type 1 (separate hard lumps, like nuts), type 2 (sausage like, but lumpy), type 3 (like a sausage, cracks), type 4 (like a sausage, smooth), type 5 (soft blobs with edges), type 6 (mushy stool), and type 7 (entirely liquid), as in other NHANES publications.²⁵

Statistical Analysis

The NHANES 2005–2006 (n = 2638), 2007–2008 (n = 2718), and 2009–2010 (n = 2941) data were combined to provide robust sample sizes for women with phytoestrogen data. Prevalence estimates and 95% CIs were calculated by using STATA 12.1 (STATA Corp College Station, TX), which incorporates the design effect, appropriate sample weights, and the stratification and clustering of the complex NHANES sample design. The sample weights were adjusted for unequal probabilities of selection and nonresponse. The Pearson χ^2 test was used to assess the association between having FI or POP and risk and protective factors. Multivariable logistic regression models were adjusted for age, race, BMI of 30 or higher, parity, hysterectomy status, smoking status, diabetes, chronic lung disease, depression, and hormone use to assess the association between pelvic floor symptoms (POP and FI) and log-transformed phytoestrogen levels. Prevalence ORs and 95% CIs were reported from the multivariable models, using the appropriate sampling weights, with the level of statistical significance set at $P < 0.05$.

RESULTS

Phytoestrogens and POP Symptoms

Characteristics of women with POP symptoms are shown in Table 1. Among 8270 women with phytoestrogen data, 1341

(16.2%) were postmenopausal. Of these women, 1213 reported data on the presence or absence of POP symptoms (90.5%). Overall, 5.4% of postmenopausal women had POP symptoms (95% CI, 4.2%–6.9%). Women with and without POP symptoms had a mean age (\pm SD) of 63.5 years (\pm 11.3 years). No differences existed in POP symptoms by mean age ($P = 0.91$) or by racial/ethnic groups ($P = 0.45$): white (5.5%; 95% CI, 4.1–7.4) compared with Latina (6.2%; 95% CI, 3.8–10.0), black (4.8%; 95% CI, 2.9–7.9), and Asian (0%; 95% CI, 0–0) women. Women with POP symptoms were more likely to have depressive symptoms compared with women without prolapse symptoms (18.8% vs 10.9%; $P = 0.05$). The results of the multivariable analysis (Table 2) revealed that there was no association of POP symptoms with urinary phytoestrogens.

Phytoestrogens and FI Symptoms

Characteristics of women with FI symptoms are also included in Table 1. Among the 1341 postmenopausal women with phytoestrogen data, 1221 (91.1%) reported on FI symptoms. Overall, 15.9% (95% CI, 14.2%–17.7%) reported at least monthly FI symptoms. Postmenopausal women with and without FI symptoms had a mean age of 63.2 years (\pm 11.3 years) without differences by mean age ($P = 0.18$) or among racial groups ($P = 0.23$). Compared with women without FI symptoms, women with FI symptoms were more likely to report diabetes (26.8% vs 18.5%; $P = 0.04$), chronic lung disease (28.9% vs 19.4%; $P = 0.001$), and depressive symptoms (20.3% vs 9.5%; $P < 0.001$). Women with FI symptoms were also more likely to report using female hormones compared with women without FI symptoms (45.1% vs 34.7%; $P = 0.004$). The most common Bristol stool type was type 4 (normal; smooth and soft consistency: 41.9% (95% CI, 34.9–49.2) in women with FI symptoms and 56.6% (95% CI, 53.2–59.9) without FI symptoms ($P < 0.001$). After adjusting for potential confounding covariates including age, race, BMI of 30 or higher, parity, hysterectomy status, smoking status, diabetes, chronic lung disease, depression, and hormone use, increased level of urinary O-DMA was associated with decreased odds of FI symptoms [adjusted OR (aOR), 0.92; 95% CI, 0.86–0.99] (Table 2).

DISCUSSION

Analysis of a US population-based survey revealed that increased urinary phytoestrogen concentrations were not associated

TABLE 2. Multivariable Association Between Urinary Phytoestrogen Levels and Symptoms of POP and FI in Postmenopausal Women From NHANES

Phytoestrogens	Prolapse Symptoms* aOR (95% CI) n = 1092		FI Symptoms† aOR (95% CI) n = 1092	
Isoflavone				
Daidzein	0.95 (0.86–1.06)	$P = 0.37$	0.95 (0.87–1.03)	$P = 0.20$
O-DMA	0.99 (0.91–1.08)	$P = 0.40$	0.92 (0.86–0.99)	$P = 0.02$
Equol	0.95 (0.79–1.13)	$P = 0.43$	0.95 (0.87–1.05)	$P = 0.30$
Genistein	0.96 (0.88–1.05)	$P = 0.34$	0.99 (0.92–1.06)	$P = 0.75$
Lignan				
Enterodiol	0.85 (0.71–1.03)	$P = 0.31$	1.00 (0.89–1.13)	$P = 1.00$
Enterolactone	1.05 (0.88–1.25)	$P = 0.42$	0.88 (0.77–1.01)	$P = 0.07$

*Model adjusted for age, race, BMI greater than 30, parity, hysterectomy status, and smoking status.

†Model adjusted for age, race, BMI greater than 30, parity, hysterectomy status, smoking status, diabetes, chronic lung disease, depression, and hormone use.

with POP symptoms; however, a higher level of O-DMA appeared to be associated with a protective effect for FI symptoms. The current data are similar to other NHANES data that reported decreased odds of urgency and mixed UI symptoms among postmenopausal women with increased specific urinary phytoestrogen levels (enterodiol and enterolactone).¹⁷ Perhaps, women with increased exposure to certain phytoestrogens share similar protective effects with regard to UI and FI symptoms.

The current exploratory analysis reveals that increased levels of ingested estrogen or estrogen-like compounds may share potentially similar mechanisms for decreased UI and FI symptoms in postmenopausal women. Aside from providing estrogen replacement in menopause, the biologic activities of ingested estrogens (phytoestrogens) and exogenous estrogens are complex. Before this study, there have been no previously published studies on phytoestrogens and FI. Although urinary levels of the phytoestrogen enterolactone were not associated with FI symptoms in this study, another study showed that enterolactone activates specific estrogen receptors (estrogen receptor alpha) in mouse uterus and vagina, whereas having little or no activity in bone.²⁶ In addition, more estrogen receptor- α receptors are distributed throughout the female urinary tract, compared with the less consistent estrogen receptor- β receptors present in the urethra and bladder.²⁶ Although estrogen receptors are present in the anal sphincter complex and have not been found in the rectal mucosa,⁴ less is known about the activation of the estrogen receptors in the external anal sphincter.⁵ Interestingly, according to one study, lignans, such as enterolactone, preferentially bind to estrogen receptor- α receptors compared with isoflavones, such as O-DMA, that preferentially bind to estrogen receptor- β receptors.²⁷ Unfortunately, none of these studies sufficiently explain the physiology as to why increased urinary levels of O-DMA (isoflavone) are associated with decreased FI symptoms in postmenopausal women and why there is no association between urinary levels of enterolactone (lignan) and FI symptoms in these women. Other studies evaluating the role of exogenous estrogen on FI symptoms have shown inconclusive results.^{10,11} More studies, especially in vitro and translational, are needed to further investigate the physiologic mechanism by which phytoestrogens may be protective regarding UI and FI symptom development in postmenopausal women.

In contrast, estrogen taken as part of menopausal replacement therapy (MRT) has been shown to be associated with increased FI symptoms in women.⁹ In the Nurses' Health Study, the authors reported that women who had used MRT in the past had an increased hazard ratio for FI of 1.32 (95% CI, 1.20–1.45) compared with women who had never used MRT.⁹ Women who took oral combined estrogen and progestin MRT also had an increased risk of FI (hazard ratio, 1.37; 95% CI, 1.10–1.70) compared with women who used estrogen-only MRT.⁹ Of note, in the current study, women who reported FI symptoms reported higher rates of "ever" using hormones compared with women without FI symptoms.

Although the literature on the role of phytoestrogens in the prevention and treatment of PFDs is limited, a review article on phytoestrogens and their associations with PFDs presented evidence from in vitro studies on type I collagen production and oxytocin expression, suggesting that phytoestrogens may have a role in POP development, which is not supported by this current study's finding.^{16,28,29} Whether these in vitro studies translate to a decreased risk of the development of POP is unknown.³⁰ In another study, the phytoestrogen puerarin was associated with decreased POP symptoms in postmenopausal women with stage II–IV prolapse and increased expression of elastin and collagen I/III.³¹ In the current study, perhaps the amount of phytoestrogens ingested by the postmenopausal participants was too low to demonstrate positive clinical effects on their POP symptoms. Given

the current paucity of data in the literature, more prospective studies are needed to further evaluate the role of phytoestrogens on POP symptoms.

The strengths of this study include the population-based study design and large sample size. Validated questions were used to assess both POP and FI symptoms. In addition, this is the first study to assess the association between phytoestrogens and FI symptoms in postmenopausal women. The limitations of this study include the cross-sectional nature of the NHANES data set and therefore the inability to prove causality between phytoestrogens and FI symptoms. Given the definition of "postmenopause" used in this analysis, the study sample may not reflect an accurate representation of the general postmenopausal population (eg, premenopausal women status post-hysterectomy but with intact ovaries could have been included). We used this definition of menopause based on a previous NHANES publication.¹⁷ Reassuringly, after running a sensitivity analysis that defined postmenopause as women aged 50 years or more, the association and magnitude of the association between O-DMA and FI do not change. The sample size, however, is much smaller. Furthermore, although there is a significant association between urinary O-DMA and FI symptoms on multivariable analysis, the aOR is 0.92. Although controlling for potential confounding factors, there may be other confounding variables that influence this outcome, including the amount of time that the women may have ingested these compounds and other factors that may be involved in maintaining stool continence such as diet, stool consistency, and pelvic floor innervation, vascularity, and coordinated muscle function. Because of the study design, this study is unable to explain the physiologic mechanism as to how O-DMA may be protective against FI symptoms in postmenopausal women.

In conclusion, increased urinary O-DMA level was associated with decreased FI symptoms in postmenopausal women but was not associated with POP symptoms. Further investigation is warranted to explore the relationships between phytoestrogens and the development of PFDs in postmenopausal women.

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