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Dietary phytoestrogens and plasma lipids in Dutch postmenopausal women; a cross-sectional study

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Abstract

Objective: Isoflavone supplementation in high doses is associated with plasma lipid, glucose and insulin levels. Little is known about the effects of intake within the range of western diets on these endpoints. *Design:* We conducted a population-based cross-sectional study in 301 women aged 60–75 years. *Methods:* Dietary isoflavone and lignan intake was assessed with a food frequency questionnaire covering habitual diet during the year preceding enrolment. The outcome measures were total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, Lp(a), fasting glucose and insulin levels. Data were analysed using linear regression and logistic regression models. In the analyses we adjusted for a wide range of potential confounders. *Results:* High intake of isoflavones was associated with lower Lp(a) levels (tertile three versus tertile one: odds ratio 0.36, 95% CI 0.16; 0.80). No relation was found between blood levels and the other plasma lipids, glucose or insulin was found. *Conclusion:* The results of this study suggest that an effect of dietary phytoestrogen intake at low levels on plasma lipid levels is of limited magnitude. It is premature to advise postmenopausal women with low phytoestrogen intake to change their diet towards a phytoestrogen rich diet with the sole aim to prevent cardiovascular disease.

Keywords: Phytoestrogens; Diet; Plasma lipids; Menopause; Lignans; Isoflavones

1. Introduction

After menopause, the incidence of cardiovascular disease in women increases, which might be related to the decrease in estrogen levels after menopause. Hormone supplementation therapy (HST) is able to reverse postmenopausal increases in total cholesterol and LDL, and decrease in HDL, at least partially [1]. However, in contrast to the findings in observational studies, recent experimental data revealed an increase in cardiovascular morbidity and mortality with combined estrogen/progesterone regimen [2].

Phyto-estrogens, including isoflavones and lignans, are estrogen-like compounds occurring naturally in plants such as soy, beans and peas, fruits, vegetables, nuts and grains, and could possibly serve as an alternative for hormone supplementation therapy. Phytoestrogens have a high affinity for the estrogen receptor β (ERβ) and less for estrogen receptor α (ERα) [3], and can act both as an agonist and antagonist.

A meta-analysis comprising 38 intervention studies with phytoestrogens from soy found on average a 9.3% decrease in total cholesterol and a 12.9% decrease in LDL cholesterol. Triglycerides decreased by 10.5% and HDL increased by 2.4% but these changes were not statistically significant [4]. In addition to the putative effects on lipids, some recent studies [5–7] have shown a favourable effect of soy on fasting glucose and insulin levels, while others did not find this relation [8].

In Asian countries, where the intake of phytoestrogens through the habitual diet is considerably higher than in the western diet, a relation between dietary phytoestrogens and lipid levels was found [9]. Little is known about the influence of habitual dietary phytoestrogen intake on lipopro-

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teins within the western dietary pattern. The purpose of this cross-sectional study was to investigate whether habitual phytoestrogen consumption at the higher end of the range common in the western diet, results in a favourable lipid profile and a lowering of fasting glucose or insulin levels as compared to low phytoestrogen consumption in postmenopausal women.

2. Subjects and methods

Subjects for this study consisted of 202 women who attended screening and baseline visits for a double blind, randomised placebo-controlled trial assessing the effect of an intervention with phytoestrogens on bone mineral density, cardiovascular disease risk factors, cognitive function, well-being and physical performance. These 202 women were healthy, aged 60–75 years at baseline in 2000 and living in Utrecht or surroundings. They complied with the biannual call for participation in a national screening program for breast cancer in the year prior to the start of our study. All had a normal mammogram in the year prior to enrolment. Exclusion criteria were a history of malignant disease, active renal or liver disease, a history of thromboembolism, current estrogen use or estrogen use in the 6 months prior to enrolment, known allergy for soy or milk protein and endometrial thickness over 4 mm. Only the baseline measurements were used in this cross-sectional study.

2.1. Additional recruits

To increase the power of the study, we additionally recruited 99 women from an ongoing cohort study, fulfilling the same inclusion and exclusion criteria as the participants who were recruited via the trial. The ongoing cohort study is one of two Dutch contributions to the European Prospective Study into Nutrition and Cancer, the Prospect-EPIC cohort [10]. This cohort consists of 17.357 women recruited between 1993 and 1997 through the regional breast cancer-screening program. At baseline (1993–1997) women filled in a food frequency questionnaire (FFQ). Usual phytoestrogen intake was calculated from this questionnaire [11].

To ensure a wide range of intake levels, there was a relative over-sampling of women with a low intake of phytoestrogens. In total, the study population consisted of 301 postmenopausal women, aged 60–75 years.

All women underwent the same measurements, including the administration of a new FFQ to calculate the phytoestrogen intake at time of the measurements of our endpoints of interest. The measurements took place from March 2000 to September 2001.

The Institutional Review Board of the University Medical Center Utrecht approved the study protocol and all participants gave written informed consent.

3. Measurements

3.1. General

At the physical examination we measured height, without shoes, to the nearest 0.5 cm and weight to the nearest 0.5 kg. Blood pressure and heart rate were assessed by a Critikon Dynamap at the right arm. Subjects were in sitting position and were still fasting. Hypertension was defined as use of antihypertensives, systolic blood pressure $\geq$ 160 mmHg or diastolic blood pressure $\geq$ 90 mmHg. Also waist circumference, just above the iliac crest, and hip circumference at the trochanter major (in cm) were measured to obtain a measure of upper body adiposity. Body mass index (BMI) was calculated by dividing weight (in kg) by height squared (in m^2). From the health questionnaire, we obtained information about age at menarche, age at menopause, history of oral contraceptive use, use of hormone replacement therapy, cholesterol lowering and antihypertensive medication and smoking history. Physical activity was determined through the validated questionnaire on mobility in elderly [12].

3.2. Dietary measurements

Data on nutrient intake in the year prior to enrolment were derived from a two-step dietary assessment comprising a simple self-administered questionnaire, followed by a structured interview with trained dieticians. The FFQ was validated previously [13] and slightly modified to capture dietary estrogen intake.

From the FFQ we calculated average intake of alcohol, saturated fat, mono unsaturated fat, polyunsaturated fat, fibre, fruit, vegetable and vitamin C by using national Dutch food composition data. Phytoestrogen intake was calculated as follows. Through medical (Medline) and agricultural (Agricola) scientific literature and contacts with several experts in the field of phytoestrogens we retrieved laboratory analysis data for the phytoestrogen content of food items. We searched for data on measurements of the phytoestrogens daidzein, genistein, formononetin, biochanin A, coumestrol, matairesinol and secoisolariciresinol in foods. Subsequently phytoestrogen intake was scored as described in detail previously [14]. Briefly, we calculated and assigned for each food-item in the FFQ values for the isoflavones daidzein, genistein, formononetin, biochanin A, and for the lignans matairesinol and secoisolariciresinol. Each phytoestrogen content of a food-item was then scored in seven categories. We multiplied the score of each food item by the daily consumption of that food (in grams) and then summed across foods to get the total individual intake of each phytoestrogen.

All nutrient values were adjusted for total energy intake by means of the regression residual method [15].

3.3. Laboratory measurements

Venous blood samples were collected after an overnight fast. Glucose levels were assessed using a GlucoTouch reflectometer (LifeScan, Inc., Benelux), a reagent-strip glucose oxidase method. Venous whole blood was immediately applied to the test strip. After the samples were prepared by centrifugation, 8 ml plasma and 6 ml serum were stored at −80 °C for future testing. After completion of the study lipids (total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides and lipoprotein (a)) and insulin were determined. All laboratory measurements were done in an independent laboratory where technicians were not aware of the research hypothesis.

Cholesterol was assessed by an enzymatic method with Cholesterol Reagent (Synchron LX Systems; Beckman Coulter). HDL-cholesterol was assessed using a direct HDL-cholesterol assay with a timed endpoint method. Triglycerides were also determined with a timed endpoint method (Synchron LX Systems; Beckman Coulter). Finally Immulite 2000 (DPC) was used to measure insulin levels.

4. Data analysis

The energy adjusted dietary intake of lignans and isoflavones was divided into tertiles. Because of the skewed distribution of isoflavone and lignan intake we report the median and interquartile range per tertile of intake. The distribution of triglycerides was skewed to the right and log transformed. We evaluated the relation between isoflavone and lignan intake and our endpoints, the plasma lipids, glucose and insulin levels using linear regression, after adjusting for potential confounders. Potential confounders included in the regression model were age (in years), cholesterol lowering medication (yes/no), use of antihypertensives (yes/no), BMI (kg/m^2), waist/hip ratio, smoking (no/past/current), physical activity (Voorrips score), total energy intake (kj/day), alcohol intake (g/day), saturated fat (g/day), mono unsaturated fat(g/day), polyunsaturated fat(g/day), time postmenopausal (years), fibre intake (g/day), fruit intake (g/day) vegetable intake (g/day) and vitamin C intake (mg/day). Lp(a) had a skewed distribution to the right with a peak at the lower detection limit. We divided Lp(a) by the median in two groups; high and low Lp(a). Logistic regression models were used to investigate the association between lignan and isoflavone intake and Lp(a).

Women on cholesterol lowering drug treatment ($N = 45$) were excluded from the analyses on blood lipids (cholesterol, LDL, HDL, triglycerides and Lp(a)), and, likewise, women on insulin treatment for diabetes mellitus ($N = 7$) were excluded from the analyses on insulin and glucose.

The associations of cardiovascular risk factors with isoflavones and lignans were also estimated in the following predetermined subgroups; ever smokers/never smokers, BMI < 25/BMI > 25, short (≤17 years)/long (>17years) menopausal To test statistical significance of the subgroup effects, interaction terms of phytoestrogen intake with smoking, BMI, menopause, respectively, were added to the regression model.

5. Results

The median intake of isoflavones in the lowest tertile was 0.2 mg/day and in the highest tertile 11.4 mg/day. For the lignan intake the differences were less extreme, 0.8 mg/day and 2.2 mg/day, respectively (see Table 3). General characteristics of the study population are reported in Tables 1 and 2.

The women with high isoflavone intake were somewhat younger and more physically active, consumed more vegetables and fruits, but less fat and used somewhat more alcohol (Table 3).

Table 1
Baseline characteristics

	Mean	S.D.
Age (years)	66.6	4.5
BMI (kg/cm2)	26.5	4.0
Waist-to-hip ratio	0.8	0.1
Years postmenopausal (years)	17.9	7.1
Systolic blood pressure (mmHg)	145.6	21.7
Diastolic blood pressure (mmHg)	77.6	13.8
Cholesterol (mmol/l)	6.2	1.0
LDL (mmol/l)	4.1	0.9
HDL (mmol/l)	1.5	0.4
Triglycerides (mmol/l)	1.4	0.9
Lp(a) (pmol/l)	0.3	0.3
Fasting glucose (mmol/l)	5.6	1.3
Fasting insulin (mmol/l)	9.9	8.0
Physical activity (Voorrips score)	14.7	8.1
	N	Percentage
Smoking		
current	54	17.9
past	97	32.2
Insulin treatment	7	2.3
Cholesterol lowering medication	45	14.9

Table 2
Dietary characteristics

	Mean	S.D.
Energy (kcal/day)	2037.1	450.8
Protein (g/day)	94.8	24.0
Plant protein (g/day)	36.6	11.5
Total fat (g/day)	75.2	23.6
Saturated fat (g/day)	31.1	11.3
Mono unsaturated fat (g/day)	27.4	9.3
Poly unsaturated fat (g/day)	16.1	6.5
Dietary fibre (g/day)	34.8	10.6
Vitamin C (mg/day)	133.2	62.7
Alcohol (g/day)	9.2	10.7
Fruit (g/day)	289.6	172.0
Vegetables (g/day)	222.6	102.7

Table 3
Average daily intake of phytoestrogens

	Median intake[a] (mg/day)	Range (25–75%)
Isoflavone intake		
Low isoflavone tertile	0.20	0.15; 0.24
Middle isoflavone tertile	0.76	0.40; 1.77
High isoflavone tertile	11.43	7.59; 19.63
Lignan intake		
Low lignan tertile	0.75	0.53; 1.14
Middle lignan tertile	1.63	1.51; 1.74
High lignan tertile	2.21	2.02; 2.53

[a] Energy adjusted.

Table 4
Multiple adjusted differences between the lowest and highest tertile of isoflavone intake

	Confidence (95%)			
	Difference	*P*-value	Interval	*P* for trend
Cholesterol (mmol/l)	−0.13	0.49	−0.49; 0.24	0.48
LDL-cholesterol (mmol/l)	−0.06	0.74	−0.39; 0.28	0.72
HDL-cholesterol (mmol/l)	−0.08	0.19	−0.20; 0.04	0.22
Triglycerides (mmol/l)	0.00	0.99	−0.10; 0.12	0.92
High Lp(a) (odds ratio)	0.36	0.01	0.16; 0.80	0.01
Glucose (mmol/l)	0.10	0.42	−0.15; 0.36	0.48
Insuline (pmol/l)	−0.77	0.33	−2.32; 0.77	0.31

No significant differences were found for total cholesterol, LDL-cholesterol, HDL-cholesterol triglycerides, fasting glucose and insulin levels between the different levels of isoflavone and lignan intake (Tables 4 and 5). The prevalence of a high Lp(a) was significantly lower in women with high isoflavone intake (Table 4). After adjustment for confounders this difference remained present (odds ratio: 0.39, $P = 0.02$) for the difference between the lowest and the highest tertile of isoflavone intake. For the lignans no difference in Lp(a) was seen across categories of intake (Table 5).

Analyses in the predetermined subgroups did not change the results materially.

6. Discussion

This study showed significantly lower Lp(a) levels with higher habitual isoflavone intake, which remained after adjustment for known confounders. Groups of high and low isoflavone intake or lignan intake showed no significant differences for any of the other endpoints.

Lp(a) has shown to be a strong and independent risk factor for atherosclerotic heart disease. In both men and women it has been associated with premature cardiovascular disease although the mechanism involved remains to be elucidated [16].

Table 5
Multiple adjusted differences between the lowest and highest tertile of lignan intake

	Confidence (95%)			
	Difference*	*P*-value	Interval	*P* for trend
Cholesterol (mmol/l)	−0.21	0.39	−0.69; 0.27	0.40
LDL-cholesterol (mmol/l)	−0.21	0.35	−0.65; 0.23	0.35
HDL-cholesterol (mmol/l)	0.01	0.88	−0.15; 0.17	0.76
Triglycerides (mmol/l)	−0.03	0.78	−0.14; 0.13	0.78
High Lp(a) (odds ratio)	0.47	0.15	0.17; 1.31	0.18
Glucose (mmol/l)	0.08	0.64	−0.25; 0.40	0.57
Insuline (pmol/l)	0.42	0.68	−1.57; 2.41	0.64

* Adjusted for age (in years); cholesterol lowering medication (yes/no); use of antihypertensives (yes/no); BMI (kg/m^2); waist/hip ratio; smoking (no/past/current); physical activity (voorrips score); total energy intake (kj/day); alcohol intake (g/day); saturated fat (g/day); mono unsaturated fat (g/day); polyunsaturated fat (g/day); time postmenopausal (years); fibre intake (g/day); fruit intake (g/day); vegetable intake (g/day); and vitamin C intake (mg/day).

To appreciate the results of our study some strengths and limitations have to be addressed. Although this study had an observational design, with the resulting potential for confounding, we were able to adjust for other cardiovascular risk factors and dietary factors.

In the analysis of our data we adjusted for fibre intake as fibre is associated with lignan intake as well as with cardiovascular disease. Furthermore we adjusted for age, BMI, waist/hip ratio, smoking, physical activity, time postmenopausal, total energy intake, intake of alcohol, saturated fat, mono unsaturated fat, polyunsaturated fat, fruit, vegetable and vitamin C in an attempt to control for confounding caused by a healthy lifestyle.

Assessment of phytoestrogen intake with a FFQ allowed us to estimate phytoestrogen intake during the year preceding the study. This is particularly important given the fact that foods containing high amounts of phytoestrogens, especially isoflavones, are most likely to be consumed weekly or monthly instead of on daily basis in western diets. Several days diaries or 24-h recall interviews may give more accurate estimates of frequently consumed food items but are less useful with infrequently consumed items, like soy, being of importance.

FFQs depend on reported intakes of participants. Biomarkers of dietary phytoestrogen, e.g. urinary excretion or blood levels, could provide a more objective alternative. Unfortunately, biomarkers only reflect intake in the 24 h prior to collection of the sample [17].

Bias in data collection was no serious threat to the validity of our study. Women were not informed of the study

hypotheses, and the subgroup with low phytoestrogen intake was not aware of this selection criterion. Furthermore, all blood samples were analysed in one batch and the laboratory technicians were not informed about the study hypothesis.

To avoid the suggestion of a degree of precision for which the data are too limited we scored the phytoestrogen content found in the literature into seven categories instead of reporting the exact contents. Based on these scores we divided the participants in three groups of intake, low, median and high isoflavone and lignan intake respectively. The differences in phytoestrogen content between different brands and in different countries are often not known and the use of categories rather than absolute contents reduces the measurement error, although it also reduces the power to detect an association.

After menopause total cholesterol, LDL, Lp(a) and triglyceride levels increase and HDL levels slightly decrease. Hormone supplementation therapy (HST) is able to reverse these changes at least partially. In contrast to our findings, a meta analysis comprising 38 studies showed a decrease in total cholesterol and LDL with supplementation of phytoestrogens [4]. In this meta-analysis people with high baseline LDL-levels had the largest reduction in LDL and total cholesterol levels. However, in our study we cannot study this, as we did not measure change in LDL-level over time. The major difference with our study is the dose of phytoestrogens. We focussed on habitual intake in a Western population; the levels of phytoestrogen intake in our study were therefore considerably lower than can be achieved in an experimental setting. Furthermore, the meta-analysis combined studies in both males and females and did not discriminate between pre- and postmenopausal women. After publication of the meta-analysis several trials aiming specifically at postmenopausal women found, in contrast to the meta-analysis, no significant effect on cholesterol, LDL or HDL [18–23] except for two studies [24,25]. Effects of phytoestrogens might be different in pre- and postmenopausal women. In post menopausal women the main source of endogenous estrogens are aromatised androgens from fatty tissue and phytoestrogens inhibit the aromatisation of androgens through several enzymes [26], thereby decreasing the endogenous estrogen levels and counteracting the increase in total estrogen activity caused by the phytoestrogen [27].

Studies on habitual dietary intake of phytoestrogens are scarce. Two studies in Asian populations did find a positive effect of phytoestrogen intake on total cholesterol and LDL but the levels of intake are several fold higher in the Asian population as compared to western populations. In western postmenopausal women some positive effects of dietary phytoestrogens on plasma lipids were reported [28]. Our results are not consistent with these findings, but confounding by unmeasured factors could have caused the discrepancy. Our findings are consistent with the recent negative trial findings in postmenopausal women. It seems questionable whether the positive influence of phytoestrogen supplementation on serum lipids as shown in the meta-analyses applies to postmenopausal women and whether it can be extrapolated to long-term low dose exposure to phytoestrogens.

Data regarding Lp(a) and phytoestrogens is inconsistent, three trials reported an increase in Lp(a), one a decrease [18,22,25], while studies on HST show decreases of Lp(a) [29]. As far as we know we are the first to look at Lp(a) levels in relation to dietary phytoestrogens. The present study provides evidence for a positive effect of phytoestrogens on Lp(a) levels, although a chance finding can not be ruled out. Confirmation has to be awaited.

With respect to fasting glucose and insulin, estrogens are known to increase the sensitivity of the pancreas for glucose and decrease insulin resistance in the peripheral tissue but two small studies did not find an effect of soy isoflavones on fasting insulin [30]. A study comparable to the present study, investigating the association between fasting glucose and dietary phytoestrogen in postmenopausal American women found the same null result for fasting glucose but did report lower insulin levels both fasting and post glucose challenge [31].

In conclusion, the results of this study support the presence of a beneficial effect of higher dietary phytoestrogen intake on Lp(a), even at low overall levels of intake. However, in view of the limited magnitude of the effect and the absence of effects on the other lipids, glucose and insulin, it is premature to advise postmenopausal women with low phytoestrogen intake to change their diet towards a phytoestrogen rich diet with the aim to prevent cardiovascular disease.

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