Soy Milk Lowers Blood Pressure in Men and Women with Mild to Moderate Essential Hypertension[1]

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ABSTRACT Soy-based diets reduce blood pressure in spontaneously hypertensive rats, but apparently not in hypertensive humans. In the present study, the antihypertensive potential of soy milk (500 mL twice daily) compared with cow's milk was investigated in a 3-mo double-blind randomized study of 40 men and women with mild-to-moderate hypertension. Before initiation of the study, urinary isoflavonoids (measured by HPLC) were undetectable in most cases (for genistein, they were always <100 μmol/L). After 3 mo of soy milk consumption, systolic blood pressure decreased by 18.4 ± 10.7 mmHg compared with 1.4 ± 7.2 mmHg in the cow's milk group ($P < 0.0001$), diastolic blood pressure decreased by 15.9 ± 9.8 mmHg vs. 3.7 ± 5.0 mmHg in the cow's milk group ($P < 0.0001$) and mean blood pressure decreased by 16.7 ± 9.0 mmHg compared with 3.0 ± 4.6 mmHg in the cow's milk group ($P < 0.0001$). Urinary genistein was strongly ($r = -0.588$) and significantly ($P = 0.002$) correlated with the decrease in blood pressure, particularly for diastolic values. In conclusion, chronic soy milk consumption had modest, but significant hypotensive action in essential hypertensive subjects. This hypotensive action was correlated with the urinary excretion of the isoflavonoid genistein. J. Nutr. 132: 1900–1902, 2002.

KEY WORDS: • hypertension • isoflavonoids • genistein • soy milk • equol • humans

The soy isoflavonoids genistein and equol (a metabolite of daidzein) possess natriuretic and vasorelaxant properties in rats (1–4). Nevala et al. (5) found that a soy-based diet attenuated the development of hypertension in spontaneously hypertensive rats and Washburn et al. (6) found that soy protein supplementation significantly reduced diastolic blood pressure (−5 mm Hg) in perimenopausal women. In contrast with the above studies, Hodgson et al. (7) reported that soy isoflavonoids do not reduce blood pressure in hypertensive humans. Therefore, we conducted a randomized, double-blind comparative study of soy milk vs. cow's milk in people with mild-to-moderate hypertension.

SUBJECTS AND METHODS

Subjects. Overall, 40 people with essential hypertension (25 men aged 18–70 y and 15 women aged 50–70 y) were included in the study (no cause of high blood pressure was detected after complete investigation). Patients had hypertension of degree 1 or 2 according to the guidelines of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (8), i.e., in repeated blood pressure measurements (3 d in 3 consecutive weeks), they had systolic blood pressure (SBP)[3] between 140 and 179 mm Hg and diastolic blood pressure (DBP) between 90 and 109 mm Hg. Half of the 40 subjects included were untreated hypertensives (12 took thiazide diuretics, 6 took enalapril and 2 took amlodipine).

Measurement of blood pressure. Blood pressure was measured by sphygnomanometry, according to the recommendations of the American Heart Association (9). In particular, subjects rested for 1 h before blood pressure monitoring began. All measurements were made between 0900 and 1100 h by one observer who was unaware of treatment group. Four recordings were performed in duplicate (in each arm and in recumbent or seated position). When duplicate values showed a difference >5 mm Hg, the measurements were repeated.

Diet protocol. To select a soy preparation for the study, isoflavonoid contents were measured in commercially available preparations, including three different soy milks, soy lecithin and soy germ. Of these, daidzein and genistein contents in the selected soy milk (Calcimel, Santivery s.a., Barcelona, Spain; see **Table 1**) were 2 times higher than in soy lecithin and 10 times higher than in soy germ. Therefore, this soy milk was selected for the study.

Soy milk is often considered superior to cow's milk because of its lower content of saturated fatty acids. Therefore, skimmed cow's milk was given to the placebo control group. Table 1 shows the isoflavonoid concentrations of the two types of milk, and other chemical characteristics. Hypertensive subjects receiving soy milk consumed 63 mg daidzein (334 μmol) and 80 mg genistein (296 μmol), compared with none (undetectable) in the cow's milk group.

Subjects were asked not to change dietary habits (Mediterranean diet) during the study, particularly the consumption of salt, fruit, vegetables and fat [for influence of dietary habits on blood pressure see (10)].

Ethical aspects. Subjects were informed about objectives, methods, potential benefits and/or disadvantages of the trial and a written informed consent was obtained before inclusion in the study. Subjects were free to decide about their inclusion in the study or to stop at any time.

Study protocol. A 4-wk washout period, without medication (antihypertensive or other), was scheduled. Then, subjects were given 500 mL soy or cow's milk twice daily for 3 mo. The allocation of the diet, soy or cow's milk, was made at random. A twice-a-day administration was used on the basis of previous pharmacokinetic data for isoflavonoids (11) showing a plasma half-life of ~6 h.

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[3] Abbreviations used: DBP, diastolic blood pressure; MBP, mean blood pressure; SBP, systolic blood pressure.

TABLE 1

Isoflavonoid concentrations and other chemical characteristics of soy milk and skimmed cows milk[1]

Variable	Soy milk	Cow's milk
Genistein, *mg aglycone equivalent/L*	80 ± 8	ND
Daidzein, *mg aglycone equivalent/L*	63 ± 9	ND
Equol, *mg aglycone equivalent/L*	ND	ND
Protein, *g/L*	18	15.5
Carbohydrates, *g/L*	13.5	25
Lipids, *g/L*	10.5	1.5
Calcium, *mg/L*	600	600
Energy, *kJ/L*	220	175

[1] Values are means ± SD, $n = 8$; ND, below detection limit. Soy milk was Calcime1 (Santivery s.a., Barcelone, Spain). Cow's milk was Leche Pascual desnatada (Spain).

The trial as well as the statistical analysis of the results was carried out without awareness of treatment group assignment. The primary criterion of efficacy was a reduction in blood pressure due to treatment. Isoflavonoid concentrations were measured in milk and urine by HPLC (12).

Statistical analysis. Statistical analysis was performed using a StatView program (version 4.02, Abacus Concept, Inc., Berkeley, CA). The following tests were conducted: χ^2 test for comparison of qualitative variables; nonpaired bilateral Student's *t* tests for comparison of quantitative variables (variances were firstly compared by Fisher's *F*-test to show a lack of significant differences); and correlation/covariance analysis by using Fisher's *r*-to-Z transform. A difference was considered significant when the level of significance of the bilateral test was ≤ 0.05.

Distribution of qualitative variables was expressed as the frequency of the different observed values. Distribution of quantitative variables was expressed as mean ± SD.

RESULTS

At the beginning of the study, the soy milk and cow's milk groups did not differ in blood pressure (SBP, 155 ± 12.5 vs. 151.7 ± 13.8 mm Hg and DBP, 100.3 ± 8.8 vs. 99.2 ± 5.4 mm Hg), age (47.5 ± 10.4 vs. 49.4 ± 10.8 y), sex (14 men/6 women vs. 11 men/9 women) or any other variable measured (weight, body mass index, plasma lipids, ions and hormones and renal function). Moreover, urinary excretions of equol, daidzein and genistein were undetectable in most cases. For genistein, they were always <100 μmol/L (urinary genistein > 100 μmol/L was an exclusion criteria).

Effects on blood pressure of soy milk vs. cow's milk. Soy milk decreased blood pressure significantly and more than cow's milk ($P < 0.001$, **Fig. 1**). SBP, DBP and MBP decreased by 18.4 ± 10.7, 15.9 ± 9.8 and 16.7 ± 9.0 mm Hg, in the soy milk group, respectively, and by 1.4 ± 7.2, 3.7 ± 5.0 and 3.0 ± 4.6 in the cow's milk group.

Hypotensive efficacy of soy milk and urinary isoflavonoid content. Correlation/covariance analysis of the decrease in blood pressure as a function of daily urinary isoflavonoid excretion showed that urinary genistein, but not daidzein was strongly correlated, particularly for the diastolic values. The decreases in diastolic blood pressure were negatively correlated ($r = -0.588$, $P = 0.002$) with urinary genistein excretion at the end of the study (**Fig. 2**). Urinary equol excretion tended to be negatively correlated ($r = -0.279$, $P = 0.189$) with the decrease in systolic blood pressure.

The hypotensive responses to the soy milk diet by the hypertensive subjects were highly variable (Fig. 2). Thus, 12 of the 20 patients

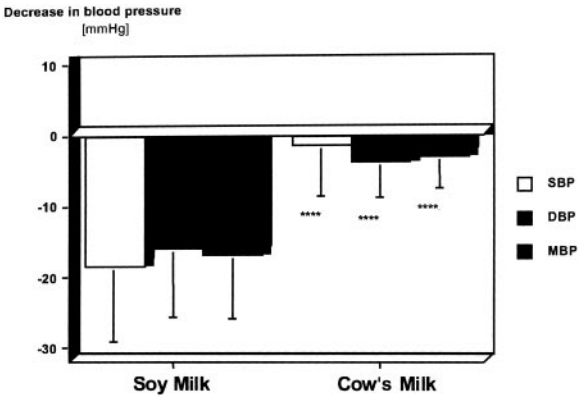

FIGURE 1 Change in blood pressure in men and women who consumed a soy milk or cow's milk-based diet for 3 mo. Values are means ± SD, $n = 20$. SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure. ****Different from soy milk, $P < 0.0001$.

(60%) showed a hypotensive response > 9 mm Hg (lower limit including 90% of control patients receiving cow's milk).

DISCUSSION

A 3-mo soy milk diet had modest, but significant hypotensive action in essential hypertensive patients. Moreover, urinary genistein excretion was strongly and significantly correlated with the decrease in blood pressure, particularly diastolic blood pressure.

Our study confirms and extends to human hypertension previous observations by Nevala et al. (5) showing that a soy-based diet attenuates the development of hypertension in spontaneously hypertensive rats [see also (13)] and those of Washburn et al. (6) that soy protein supplementation (isocaloric supplements containing 34 mg of phytoestrogens) significantly reduced diastolic blood pressure in perimenopausal women. As expected, the soy-based diet lowered diastolic blood pressure more in subjects with mild-to-moderate essential hypertension (−16 mm Hg) than in healthy perimenopausal women (−5 mm Hg).

In contrast with the above observations, Hodgson et al. (7)

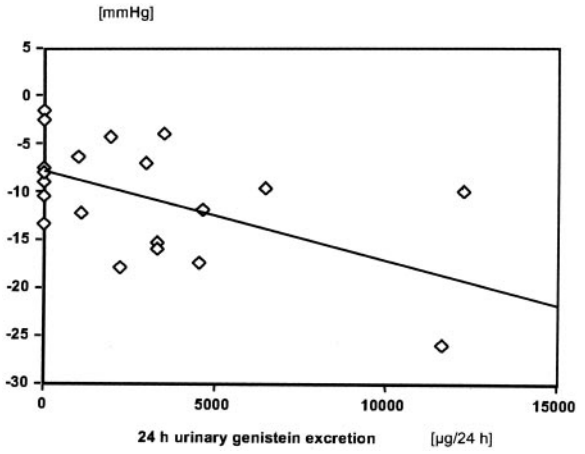

FIGURE 2 Inverse correlation between changes in diastolic blood pressure and daily urinary genistein excretion in men and women who consumed a soy milk–based diet for 3 mo. Urinary genistein was negatively correlated ($r = -0.588$, $P = 0.002$) with the decrease in diastolic blood pressure.

reported that one tablet containing 55 mg isoflavonoids (30 mg genistein, 16 mg biochanin A, 1 mg of daidzein and 8 mg of formononetin), taken daily for 8 wk had no significant hypotensive action in essential hypertensive patients. Differences from our present results may have had several explanations, including the greater amount of isoflavonoids given here with the natural soy milk (80 mg genistein + 63 mg daidzein/d), the short half-life of genistein in humans (11,14), allowing a better 24-h blood pressure control with twice-a-day treatment in the present study and in the study of Washburn et al. (6) (vs. once-a-day tablets in Hodgson's study) and finally, soy proteins were lacking in the tablets and can contribute to the hypotensive action of soy-based diets.

The correlation between the blood pressure–lowering effect of soy milk and urinary genistein excretion (and to a lesser extent with urinary equol excretion) suggests that isoflavonoids can mediate, at least in part, the hypotensive actions of a soy diet. Indeed, some of us previously found that genistein possesses a similar salidiuretic profile and compares well with furosemide in the isolated, perfused rat kidney and is also natriuretic by the subcutaneous route in rats (2). Moreover, equol also compared well with furosemide as a natriuretic agent in the isolated, perfused rat kidney (3). However, natriuresis by oral equol in rats was only 18% of that obtained with furosemide (3), probably due to protein binding and extensive glucuro-conjugation. The same should be true for genistein, which is also extensively sulfo- and glucuro-conjugated in humans (14). On the other hand, no attempt was made here to investigate potential natriuretic actions of the soy milk diet. In addition to natriuresis, genistein and equol possess vasorelaxant properties in animal models (1,3,4), which can also play a role in the antihypertensive action of soy diets. Finally, Duarte et al. (15) recently reported that the flavonoid quercetin (a chemical analog of genistein) possesses antihypertensive effects in spontaneously hypertensive rats due to its antioxidant properties.

In addition to isoflavonoids, protein or other components of soy milk may also contribute to its blood pressure–lowering action. Soy diets have modestly, but significantly higher contents of arginine (a precursor of nitric oxide) than casein diets (16). Therefore, the extent to which the modest natriuretic and vasorelaxant actions of genistein and equol contribute to the beneficial action of the soy diet in hypertension remains as an open question.

The blood pressure–lowering action of a 3-mo soy milk diet was significant, but modest (−16 mm Hg in DBP vs. −4 mm Hg in the cow's milk group). This investigation was performed in mild-to-moderate hypertensives and, to our knowledge, nothing is known concerning the magnitude of potential hypotensive actions in more severely hypertensive patients. Moreover, mild-to-moderate hypertension is the most frequent form of hypertension, and subjects can readily benefit from a modest diet-dependent reduction in blood pressure.

The above considerations raise an important public health concern. Indeed, after a very large number of reports showing beneficial aspects of a soy-based diet in cancer, osteoporosis and atherosclerosis [for a recent review see (17)], others have recently expressed concern about reduction of mineral and vitamin intestinal absorption (due to soy's phytic acid) and disorders in thyroid function [see, for example (18)]. It is perhaps too early to place the antihypertensive actions of a soy-based diet in this debate. Indeed, our study had some possible flaws, i.e., the difference in taste between soy milk and cow's milk can be recognized by the patients, and soy milk and cow's milk were substantially different in fat and carbohydrate composition (Table 1), warranting a crossover design. Therefore, our study can be considered as preliminary, requiring subsequent trials for validation.

A final aspect of our results is whether genistein and/or daidzein can explain the blood pressure–lowering action of a vegetarian diet [for a recent review see (19)]. In this respect, it is important to stress that the amount of isoflavonoids in a vegetarian diet is highly variable, strongly depending on soy product consumption. On the other hand, a comparison of our results with those of Hodgson et al. (7) suggests that only a soy-rich diet, containing large amounts of isoflavonoids, is required to obtain a blood pressure–lowering action. Therefore, isoflavonoids should be only modest contributors to the blood pressure–lowering action of a vegetarian diet (19).

In conclusion, chronic soy milk consumption had modest, but significant hypotensive action in essential hypertensive patients. This hypotensive action was correlated with the urinay excretion of the isoflavonoid genistein. Further investigation is required to determine the relative contribution of isoflavonoids and soy proteins in the hypotensive actions of soy-based diets.

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