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ORIGINAL ARTICLE

Effects of high-dose phytoestrogens on circulating cellular microparticles and coagulation function in postmenopausal women

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coagulation factors;
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Background/Purpose: Estrogen in hormone replacement therapy causes homeostatic changes. However, little is known regarding the safety of high-dose phytoestrogen on coagulation and hematological parameters in healthy postmenopausal women. This study evaluated the effects of high-dose soy isoflavone (300 mg/day) on blood pressure, hematological parameters, and coagulation functions including circulating microparticles in healthy postmenopausal women.

Conflicts of interest: The authors have no conflicts of interest relevant to this article.

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postmenopausal women

Methods: The original study is a 2-year prospective, double-blind, placebo-controlled study. In total, 431 postmenopausal women (from 3 medical centers) were randomly assigned to receive either high-dose isoflavone or placebo for 2 years. At baseline, 6 months, 1 year, and 2 years after treatment, blood pressure, body weight, liver function tests, hematological parameters, and lipid profiles were measured. The 1st year blood specimens of 85 cases of 144 eligible participants (from one of the three centers) were analyzed as D-dimer, von Willebrand factor antigen, factor VII, plasminogen activator inhibitor type 1, and circulating cellular microparticles, including the measurement of monocyte, platelet, and endothelial microparticles.

Results: In the isoflavone group, after 1 year, the changes in liver function tests, hematological parameters, and coagulation tests were not different from those of the control. Triglyceride levels were significantly lower after 6 months of isoflavone treatment than the placebo group, but the difference did not persist after 1 year. Endothelial microparticles increased steadily in both groups during the 1-year period but the trend was not affected by treatment.

Conclusion: The results of the present study indicate that high-dose isoflavone treatment (300 mg/day) does not cause hematological abnormalities or activate coagulation factors.
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Introduction

Ever since hormone replacement therapy was reported to cause early adverse effects on cardiovascular risk,[1,2] much research has been directed towards developing new treatments that show cardiovascular safety in postmenopausal women.

Phytoestrogens are a diverse group of non-steroidal plant-derived compounds that are structurally similar to estradiol and have a weak affinity on estrogen receptors.[3] Many kinds of food contain phytoestrogens. Soybeans, one of the most common sources of plant estrogens, are particularly rich in isoflavones (the main effective compounds of phytoestrogens). Soy proteins have been reported to have beneficial effects on cardiovascular and skeletal health in postmenopausal women.[3]

Despite the reported benefits of phytoestrogens, there are still safety concerns about their long-term usage.[4,5] One of the concerns is subclinical lymphocytopenia. A multicenter study showed that around 13% of postmenopausal women who daily received 600 mg ipriflavone, a synthetic isoflavone, for 3 years developed lymphocytopenia (lymphocyte counts $< 500 \times 10^6$/L).[6] A similar observation was reported by Agnusdei and Bufalino[7] that 2 years of ipriflavone supplementation caused approximately 3% of participants to have subclinical low lymphocyte counts. Although a subsequent study showed that soy protein supplementation, unlike synthetic isoflavone, did not cause lymphocytopenia in postmenopausal women, the dose used in that study was about 10% of the former two.[8]

Another concern is about the estrogenic effect of phytoestrogen. Estrogen therapy has been found to cause increased early risk of coronary heart disease, as well as an increased risk of stroke and venous thromboembolism.[1,2,9] Given the structural similarity of isoflavones to estrogen and the potential importance of the prothrombotic effects of estrogen, the effect of isoflavones on hemostasis is also of interest.

The traditional dosage for isoflavone intervention ranges from 20 mg to 90 mg, that is, <100 mg.[10–12] However, according to the comparison that estrogenic activity of 200 mg isoflavone is approximately equivalent to 0.4–2.0 mg of estradiol,[13,14] so the phytoestrogen dosage used in the previous studies on protective effect of bone may be suboptimal. Besides, the optimal dose of isoflavone as hormone replacement therapy in postmenopausal women is still uncertain, and the safety of high-dose (250–300 mg/day) isoflavone has not adequately addressed previously.

Circulating cellular microparticles are intact vesicles shed from cell membranes, ranging in size from 0.2 μm to 2.0 μm in diameter.[15–17] They arise mainly through cell membrane activation processes, and through apoptosis. Microparticles originating from platelets, endothelial cells, and monocytes have been most extensively studied in various clinical settings, such as cardiovascular disease, inflammation, and metabolic syndromes.[16,18] Only recently have they been proposed in postmenopausal women as a predictive factor for premature coronary calcification.[19]

In this study, we investigated the effects of phytoestrogen on coagulation function, by giving the participants, a 12-month treatment of isoflavone and determining the effects on homeostatic factors, hematological parameters and cellular microparticles. The pharmacological dose of isoflavone (300 mg/day) used in this study was higher than previous studies,[10–12] and would provide more informative data about its safety profile in clinical practice. Participants in this study were originally enrolled in the Taiwan Isoflavones Multicenter Study (TIMS).[20]

Materials and methods

The TIMS was a 2-year prospective, double-blinded clinical trial conducted at three medical centers in Taiwan: the National Taiwan University Hospital, Changhua Christian Hospital, and National Cheng Kung University Hospital, from which 144, 142, and 145 (total, 431) participants were recruited, respectively.

Participants were aged 45–65 years (mean ± standard deviation 57.6 ± 3.0 years). All participants' final menstruation was between 12 months and 10 years prior to the study. Their baseline follicle stimulating hormone levels were ≥40 mIU/mL. The bone mineral density of the second to fourth lumbar vertebrae was 1 standard deviation below the

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