**Modulation of Endothelial Function by Walnuts and Sex Hormones**

*To the Editor:*

We read with interest the recent article by Dr Ros and colleagues1 dealing with the relationship between a walnut diet and endothelial function in hypercholesterolemic subjects. The results of their study demonstrated that the walnut diet significantly improved endothelium-dependent vasodilation. The authors indicated that changes of endothelium-dependent vasodilation correlated with those of plasma cholesterol-HDL ratios. They proposed that the improvement of endothelial function might explain the cardiovascular protective effect of walnut intake beyond cholesterol lowering.

Numerous studies have shown that estrogen may also have beneficial effects on cardiovascular functions. One of the mechanisms underlying the protective effect of estrogen may be the enhancement of nitric oxide (NO) production. There is evidence showing that vascular endothelial function is markedly influenced by estrogen and is improved by hormone replacement therapy in postmenopausal women.2 In an in vitro study presented earlier, we demonstrated that 17β-estradiol increased membrane fluidity (a reciprocal value of membrane microviscosity) of erythrocytes and improved the rigidity of cell membranes in postmenopausal women via the NO- and cGMP-dependent mechanism.3 Since abnormalities in membrane microviscosity could cause a disturbance in rheological behavior and microcirculation, these findings suggest that estrogen deficiency might be involved in the pathogenesis of vascular complications in women. Recently, the role of estrogen in male physiology has also become evident, and normal physiological estrogen, which is converted from testosterone by aromatase, may confer cardiovascular benefits for men.4 In this context, we speculate that, because nuts are enriched with arginine,5 changes in NO production by sex hormones might modify the effects of the walnut diet on endothelial function and microcirculation both in men and women. It was demonstrated that the endothelium-walnut interaction may differ among the subjects in the present study of Dr Ros and colleagues. Therefore, we would like to know whether the endogenous sex hormones might be related to the magnitudes of the restored endothelial function by the walnut diet. It would be important to assess more precisely the relationships among nut intake, sex hormone status, and NO production, as well as their contribution to the improvement of endothelial function both in men and women.

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**Response**

Estrogen has a direct effect on relevant endothelial cell biological activities, such as vasomotor function, cell adhesion molecule expression, and angiogenesis through mechanisms that are complex and not always well understood.1,2 As pointed out by Drs Tsuda and Nishio, upregulation of endothelial nitric oxide (NO) production by estrogen may play an important role in its well-known vasodilatory effect. Indeed, attention must be paid to the menstrual cycle when performing endothelial function studies in premenopausal women because estrogen-mediated increases in brachial endothelium-dependent vasodilation occur during the follicular phase.3 A recent report suggests that residual endogenous estrogen in postmenopausal women also influences endothelial function.4 Because walnuts contain significant amounts of l-arginine, the precursor of NO, Drs Tsuda and Nishio speculate that the stimulatory effect of endogenous sex hormones on NO synthesis might be enhanced by increased amounts of substrate. They also wonder whether the estrogen level was related to improved endothelial function during the walnut diet in our study.5 Unfortunately, we did not measure plasma estrogen. Nine out of 10 women in our study were postmenopausal, and none was receiving hormone replacement therapy. As stated, adjustment for sex did not influence the results of endothelial function studies.5 We regret that, like other key questions on the relation of estrogen to vascular health, the question from Drs Tsuda and Nishio remains unanswered. Given the paradox of the lack of clinical benefit (or even harm) of estrogen replacement in women with coronary heart disease in face of the indisputable salutary effects of estrogen on vascular reactivity, this is still an important research field.

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