

Sex Hormones and Asymmetric Dimethylarginine in Transplant Arteriosclerosis

To the Editor:

We read with interest the recent article by Dr Weis and colleagues¹ dealing with the role of asymmetric dimethylarginine (ADMA), the endogenous inhibitor of NO synthase, in arteriosclerosis in heart transplant recipients. The results of their study demonstrated that plasma ADMA is elevated in cardiac transplant recipients. In addition, the authors indicated that transplant recipients who are actively infected with cytomegalovirus have higher plasma ADMA levels and are at greater risk of transplant arteriosclerosis, because, in an in vitro study, endothelial cells infected by cytomegalovirus elaborated more ADMA and manifested an impairment of NO activity. The authors proposed that ADMA-induced endothelial dysfunction may play an important role in the altered vascular function and structure observed in the coronary arteries of cardiac transplant recipients.

There is evidence that sex hormones might have a role in the ADMA-mediated regulation of cardiovascular functions. Holden et al² showed that hormone replacement therapy significantly decreased plasma ADMA levels in postmenopausal women. They also observed that estrogen increased the activity of dimethylarginine dimethylaminohydrolase (DDAH) activity in endothelial cells and proposed that estrogen can alter the catabolism and release of ADMA. It was demonstrated that inhibition of NO bioavailability by ADMA and a subsequent reduction in endothelial function might contribute to the increase in blood pressure during salt intake in normotensive postmenopausal women not receiving estrogen.³

In a previous study, we showed that estrogen-induced improvement of membrane fluidity (a reciprocal value of membrane microviscosity) of erythrocytes is mediated by NO production, which is counteracted by ADMA in postmenopausal women.⁴ The finding suggests that, because abnormalities in membrane microviscosity could cause a disturbance in rheological behavior and microcirculation, estrogen deficiency with a concomitant increase in plasma ADMA levels 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.⁵ In this context, we speculate that changes in sex hormones might modify the ADMA levels and cardiovascular complications in transplant recipients. Therefore, it would be important to assess more precisely the relationship among sex hormones, ADMA, and arteriosclerosis in transplant recipients.

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Response

We thank Drs Tsuda and Nishio for their interest in our paper describing the effects of cytomegalovirus (CMV) infection on the endothelial NO synthase pathway.¹ We demonstrated that CMV infection in endothelial cells increased oxidative stress, which impaired dimethylarginine dimethylaminohydrolase (DDAH) activity, and thereby increased accumulation of asymmetric dimethylarginine (ADMA). In heart transplant patients, CMV infection was associated with higher ADMA elevation and more severe transplant atherosclerosis.¹ Drs Tsuda and Nishio are speculating that changes in sex hormones might modify the ADMA levels and cardiovascular complications after heart transplantation. Our study was not designed to examine the effects of endogenous sex hormones on ADMA metabolism or transplant vasculopathy. However, it has been shown that estradiol administration impaired graft survival by increasing acute rejection episodes in murine cardiac allografts.² In contrast, estrogen prevented transplant arteriosclerosis in experimental cardiac allografts, at least in part by abolishing major histocompatibility complex class II antigen expression in the coronary arteries and by decreasing vascular invasion of macrophages.³ Moreover, conjugated estrogens acutely abolished abnormal endothelium-dependent vasodilatation after human heart transplantation.⁴ Intriguingly, grafts from female donors seem to be slightly less likely to develop angiographic transplant vasculopathy (International Society for Heart and Lung Transplantation, annual report 2003). In attempting to link these observations (and respond to the letter of Drs Tsuda and Nishio), we note that estrogen has been shown to enhance DDAH activity and to stimulate the metabolism of ADMA.⁵

Accordingly, we agree with Drs Tsuda and Nishio that it would be of interest to conduct additional studies to delineate the interaction of gender differences or hormonal status on ADMA metabolism and allograft vasculopathy after human heart transplantation.

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