Cardiovascular Risk Factors and Urinary Albumin: Vive la Petite Difference

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It has been known for a long time that cardiovascular events are more frequent in men than in women, at least before menopause. The community-based cross-sectional PREVEND study, published in this issue of JASN by Verhave et al. (1), provides welcome novel information that further addresses this issue and allows formulation of interesting and novel hypotheses. In a large sample of 7841 citizens of the Dutch city of Groningen, a number of classical risk factors such as age, systolic and diastolic BP, body mass index, waist-hip ratio, fasting glucose, cholesterol, creatinine clearance, and administration of oral antidiabetic agents (as a surrogate marker for type 2 diabetes), as well as use of antihypertensive and lipid-lowering treatment, were associated with increased levels of urinary albumin excretion (UAE). Men had higher UAE values, consistent with the notion (perhaps politically incorrect) that men are disadvantaged by nature. Nothing new here. What is new is the documentation that there was interaction between risk factors and gender. In other words, for a given increment in age, BMI, and plasma glucose, the increment in UAE was greater in male than in female subjects. Unfortunately we do not have information on menopausal status, and this very important confounder will have to be investigated in future analyses.

It is a plausible, but not proven, hypothesis that UAE is a valid surrogate marker for impaired endothelial cell function. If one accepts this tenet, the finding may be interpreted to suggest that men are more susceptible to the deleterious vascular effects of the above risk factors. Several pieces in the puzzle are still lacking. First of all is the issue of whether the above risk factor profile will indeed reliably predict future cardiovascular events in prospective studies. Second, although it is universally accepted that UAE is a predictor of cardiovascular events, whether a given UAE is similarly deleterious in predicting cardiovascular events in men as it is in women is not known. This is an important consideration if one intends to establish gender-specific risk factor assessment and indications for preventive measures. Third, the question is unresolved whether hidden confounders, for instance lifestyle differences between male and female subjects, that had not been incorporated into the multivariate model account for the difference between the genders in the above study. Fourth, and most important, we remain ignorant about the mechanisms underlying this difference between men and women. Is it that estrogens are protective? The authors correctly argue that this hypothesis is not supported by recent intervention studies such as the HERS trial (2) and the Women Health Study (3); on the other hand, because of several limitations, these studies do not disprove this possibility either. One can also not definitely exclude that androgens are deleterious — a hypothesis that the authors apparently do not consider to be likely. Androgens for instance activate the renal angiotensin system, and they might cause endothelial cell injury by this and other mechanisms. Perhaps nature demands a price for the advantage (or disadvantage) of being male.

According to the Steno hypothesis (4), microalbuminuria is an index of endothelial cell dysfunction. It is rewarding to consider what is known about gender or sex hormones, respectively, and endothelial cell function (5). The available information makes it difficult to decide whether estrogens are beneficial, whether androgens are deleterious, or whether both alternatives play a role in different contexts. Estrogen, progesterone, and testosterone receptors have been identified in the plasmalemma, the cytosol, and the nuclear compartments of vascular cells. Furthermore, both rapid onset of non-genomic and delayed genomic vascular effects have been seen after administration of sex hormones, further increasing the complexity of the issue. Presumably the best-established gender difference with respect to endothelial cell function is the effect of nitric oxide (6–10). NO release from the endothelium is higher in arteries of women compared with men. There is good evidence that estrogens are responsible for the gender difference. Gender differences in the regulation of endothelial cell cytosolic Ca2+ concentration are related to direct or indirect effects of estrogens (9,11), possibly related to differences in eNOS activity on the one hand (12) and differences in antioxidant defenses on the other hand (13). The issue is rendered even more complex by the recent recognition that there are two types of estrogen receptors, alpha and beta. Studies in beta receptor knockout mice show that the vascular wall becomes suprasensitive to relaxation by 17-beta-estradiol. Compared with knockout mice, estrogen attenuates vasoconstriction by a beta receptor–mediated increase in inducible NOS expression in wild-type mice (14,15).

The idea that estrogens are the main modulators of endothelial cell function, as postulated by Verhave et al. (1), finds
support in observations, such as the one of Robert et al. (16), that in female rats with metabolic syndrome, the protective effect of female gender was abrogated by ovariectomy and restored by estrogens, whereas orchidectomy did not confer protection.

Clinical studies on this issue are more difficult to come by, but the study of Virdis et al. (17) strongly suggests that premenopausal normotensive women are protected against the deleterious effect of aging of endothelial cell function via preservation of NO availability by activating the l-arginine NO pathway and by inhibiting oxidative stress. Not all observations go in the direction of a lesser cardiovascular risk profile in women, such as the greater increase of homocystein after l-methionin loading in women compared with men (18).

A very interesting model is provided by studies of transsexuals addressing the change in vascular function after male-to-female changeover using ethinyl estradiol and cyproterone acetate on the one hand and female-to-male changeover using testosterone on the other hand (19). Apparently aging and the impact on vascular function are more aggressive in males, as shown by the observation that telomere length is better preserved in women compared with men (20) — a sad thought suggesting that nature apparently does not care very much about males once they have completed their reproductive function.

As all good studies, the present report of Verhave et al. raises more questions than it answers, but it will certainly not fail to stimulate future research in this still murky and unresolved area of cardiovascular research.

References