Diabetes Mellitus and Cardiovascular Disease in Women

James R. Sowers, MD

**Background:** Coronary heart disease (CHD) is the leading cause of morbidity and mortality in women in the United States. Although CHD is less common in premenopausal women than in men, this difference begins to disappear after the onset of menopause, presumably related to reduced levels of female sex hormones.

**Results:** An association between both a postmenopausal increase in blood pressure and CHD that coincide with loss of ovarian function suggests that estrogen and/or progesterone may be protective against hypertension and CHD. Diabetes removes the normal sex difference in the prevalence of CHD. Increased mortality in women with CHD and diabetes compared with women without diabetes has been observed in epidemiological studies.

**Conclusions:** Diabetes appears to obviate the protective effects of female sex hormones. Possible reasons for this catastrophic effect of diabetes in women are discussed.

Arch Intern Med. 1998;158:617-621

While coronary heart disease (CHD) has generally been considered a disease affecting men, the World Health Organization in 1990 reported that heart disease is the leading cause of death for women of all ages in the United States. This disease accounts for nearly 30% of all deaths among women. The incidence of CHD in women rises exponentially with age in industrialized, westernized societies. Below the age of 55 years, the incidence of CHD in women is one third that of men; however, this ratio approaches unity at age 75 years. Indeed, more than a quarter of a million women aged 50 through 79 years die of CHD in the United States each year. As discussed in this article, the rising incidence of CHD parallels increases in the incidence of both hypertension and diabetes with increasing age in the United States. Since, as previously extensively reviewed, the mortality from CHD and myocardial infarction is significantly worse in women than in men, it is important that we better understand the underlying factors that predispose women both to CHD and associated mortality. This article examines those underlying factors with special attention to the important role of diabetes mellitus in promoting CHD and associated mortality in women.

**SEX-SPECIFIC DIFFERENCES IN CHD**

The disparity between the incidence of CHD in premenopausal women and men of the same age suggests that either sex or endogenous sex hormones such as estrogen, progesterone, and/or androgens have a significant influence on the vasculature. There is considerable evidence that estrogen exerts direct effects on the vasculature. There are receptors for estrogen on both vascular endothelial and smooth muscle cells. Estrogen exerts both genomic (gene expression) and nongenomic effects on vascular cells (Figure). Estrogen also exerts indirect effects on the vasculature through its impact on lipoprotein metabolism. Estrogen replacement therapy increases levels of high-density lipoprotein, reduces levels of low-density lipoprotein, and attenuates low-density lipoprotein oxidation. However, multiple regression analysis indicates that no more than 50% of the reduction in CHD with estrogen replacement therapy is attributable to beneficial effects on lipoprotein metabolism.
Cardiovascular Protective Effects of Estrogen

Indirect Effects
1. Increased HDL
2. Reduced LDL
3. Reduction in LDL Oxidation (All Changes Would Be Antiatherogenic)

Genomic
1. Increased Cardiovascular Production of Nitric Oxide: Endothelial Cells Smooth Muscle Cells Myocardial Cells (Increased Endothelial Cell Adhesion, Vascular Contraction, and Growth Proliferation)
2. Inhibition of Vascular Smooth Muscle and Myocardial Growth and Remodeling (Reduced Atherogenesis)
3. Endothelial Cell Proliferation Resulting in Increased Angiogenesis

Nongenomic
1. Increased Platelet Nitric Oxide Production Results in Reduced Platelet Aggregation
2. Increased Endothelial Cell Nitric Oxide Production (Results in Reduced Vascular Contractility and Inhibits Atherosclerosis)
3. Inhibition of L-Channel Calcium Currents (Results in Reduced Vascular Constriction)

Cardiovascular protective effects of estrogen. HDL indicates high-density lipoprotein; LDL, low-density lipoprotein.

Estrogen has been demonstrated to diminish vascular constriction in part by stimulating the release of vasodilators such as nitric oxide and prostacyclin from the vessel wall.14,18-22 (Figure). Since nitric oxide has been shown to attenuate platelet aggregation23 and diminish vascular growth,15,24 this is likely one mechanism by which estrogen exerts its antiatherogenic effects.25-27 Another mechanism by which estrogen may exert antiatherogenic effects is through its influence on vascular smooth muscle cell calcium metabolism.14 An increase in vascular smooth muscle calcium increases cell proliferation,28 and estrogen directly attenuates the entry of calcium through L-channels in these cells.29 Finally, estrogen may inhibit coronary atherosclerosis through its genomic effects30 (Figure).

Considerable experimental evidence indicates that estrogen exerts its cardiovascular protective effects by acting through binding to its receptor on vascular tissue.27 Estrogen receptor expression has also been shown in cytoplasmic and nuclear regions of human aorta. Heterogeneity of estrogen receptor distribution has been demonstrated among various vascular beds, between female and male animals, and between normal and atherosclerotic vascular tissue.28-31 In primates, the estrogen receptor quantity of cytoplasmic extracts of aorta of proestrous females is greater than that of males.32 In humans, atherosclerotic coronary arteries of premenopausal women demonstrate significantly diminished expression of estrogen receptors compared with normal arteries of premenopausal women.33 These investigations suggest that the antiatherogenic effects of estradiol are in part mediated through cardiovascular estrogen receptors, and that atherosclerosis is associated with decreased estrogen receptor expression.28,31,32

GENERAL RISK FACTORS FOR CHD IN WOMEN

As previously noted, age-related increases in hypertension parallel increases in CHD in the United States and other industrialized nations. Following adolescence, men have a considerably greater prevalence of hypertension than women until 50 to 60 years of age, at which time the prevalence is similar in men and women.3 The absolute number of women with hypertension in the United States is greater than that for men as a result of greater longevity of women.3 Dyslipidemia is likely a predisposing factor for CHD in women as well as men. It has been reported that women with angiographically documented CHD had higher mean cholesterol levels than women without CHD.33,34 The Framingham data35,36 have clearly documented obesity as an independent risk factor for CHD in women as well as men. Other long-term follow-up studies37,38 have documented that weight gain in adulthood as well as obesity per se increase the risk of CHD in women as well as men. Despite the fact that risk factors for CHD are similar in both sexes, relatively few large, controlled, interventional studies that assess CHD risk factors, such as lipid levels and blood pressure, have been conducted in women. Exceptions include prospective clinical trials such as the Systolic Hypertension in the Elderly Program,39 the Treatment of Mild Hypertension Study Trial,40 and the ongoing AntiHypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial.41 These trials have included premenopausal and postmenopausal women, but precise hormonal status has not been delineated. Sex-specific analysis of the Systolic Hypertension in the Elderly Program and the Treatment of Mild Hypertension Study trials demonstrated equivalent benefits between men and women treated for hypertension. A meta-analysis examining trials of lipid therapy in women42 demonstrated that there is currently no evidence from primary prevention trials that lowering cholesterol levels decreases mortality in women; however, treatment of hypercholesterolemia in women with known CHD appears to decrease mortality.43,44 Hopefully, the AntiHypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial and other large interventional trials will supply us with additional information regarding the impact of reducing known CHD risk factors in women.

IMPACT OF DIABETES ON CHD IN WOMEN

Diabetes mellitus removes the normal sex-related differences in the prevalence of CHD4,43-45 and end-stage renal disease.46 In the Framingham Study,43 for individuals aged 50 to 59 years, diabetes mellitus was a greater risk factor for CHD in women than in men. Even when corrected for diabetes-associated hypertension, dyslipidemia, and obesity, the risk of coronary events in women with diabetes was double that of women without diabetes.45 Increased mortality in women with CHD and diabetes (mostly type 2 diabetes) compared with women without diabetes was observed in an epidemiological study from Rancho Bernardo, Calif.45-47 When adjusted for other CHD risk factors, the risk ratio was 3.5 for women with diabetes compared with 2.4 for men with diabetes.45-47 Moreover, women with diabetes are more likely to die following myocardial infarction than women without diabetes or men.4,48-49 Thus, the existence of diabetes in women appears to abrogate the cardiovascular protective effects of endogenous estrogen.4
The mechanisms by which diabetes obviates the cardiovascular protective effects of female sex hormones in premenopausal women are not well understood. However, data are emerging suggesting potential mechanisms involved in this process. Increased cardiovascular disease in individuals with diabetes mellitus appears to be related to a number of factors. Pathological factors include enhanced platelet aggregation, 48,49 relatively greater coagulation and decreased fibrinolytic activity, 10,50 lipoprotein abnormalities, 51 endothelial dysfunction, 52-54 enhanced oxidative stress, 10,55 vascular protein glycation, 10,56 and enhanced growth factor stimulation. 10,56 Thus, diabetes mellitus, associated hyperglycemia, and other attendant metabolic abnormalities may obviate the cardiovascular protective effects of estradiol through one or more of these mechanisms. One possible mechanism involves the interaction between hyperglycemia and estradiol in regulation of cardiovascular nitric oxide production. It has recently been reported that hyperglycemia decreases estradiol-mediated nitric oxide production from cultured endothelial cells. 50 Thus, it appears that hyperglycemia may negate the protective effects of estradiol in part by decreasing vascular and perhaps platelet nitric oxide production. Since nitric oxide production reduces vascular tone, platelet aggregation, 23 and vascular growth, 21,22 this hyperglycemia-related abnormality may help explain why premenopausal women with diabetes mellitus have a high prevalence of hypertension, platelet abnormalities, and premature atherosclerosis.

Evidence exists for a role for high levels of insulin as a potential cause for the high rate of atherosclerotic CHD among women with diabetes. In a 16-year follow-up study of the Framingham population, the insulin therapy was associated with greater cardiovascular-related mortality in women with diabetes compared with men with diabetes. Indeed, the role of insulin and sex hormones in coronary disease in individuals with or without diabetes was considered to be of sufficient importance to warrant a workshop sponsored by the National Heart, Lung, and Blood Institute. Insulin may negate the antiatherogenic effects of estradiol through its influence on vascular smooth muscle cell proliferation as well as other less understood mechanisms.

### Table 1. Abnormalities of Platelet Function in Diabetes Mellitus

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Commentary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased platelet adhesiveness</td>
<td></td>
</tr>
<tr>
<td>Increased platelet aggregation</td>
<td></td>
</tr>
<tr>
<td>Decreased platelet survival</td>
<td></td>
</tr>
<tr>
<td>Increased platelet generation of vasoconstrictor prostaglandins</td>
<td></td>
</tr>
<tr>
<td>Reduced platelet generation of prostacyclin and other vasodilator prostaglandins</td>
<td></td>
</tr>
<tr>
<td>Altered platelet divalent cation homeostasis (i.e., decreased Mg^{2+}, and increased Ca^{2+})</td>
<td></td>
</tr>
<tr>
<td>Increased nonenzymatic glycosylation of platelet proteins</td>
<td></td>
</tr>
<tr>
<td>Decreased platelet polyphosphoinositide content</td>
<td></td>
</tr>
<tr>
<td>Decreased platelet nitric oxide production that contributes to increased aggregation and adhesion to endothelial cells</td>
<td></td>
</tr>
</tbody>
</table>

*Mg^{2+}, indicates intracellular magnesium; Ca^{2+}, calcium.*

### Table 2. Coagulation and Lipoprotein Abnormalities Seen in Individuals With Diabetes Mellitus

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Commentary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated plasma levels of VLDL, LDL, and lipoprotein(a)</td>
<td></td>
</tr>
<tr>
<td>Decreased plasma HDL cholesterol</td>
<td></td>
</tr>
<tr>
<td>Elevated plasma triglyceride levels</td>
<td></td>
</tr>
<tr>
<td>Increased lipoprotein oxidation</td>
<td></td>
</tr>
<tr>
<td>Increased lipoprotein glycation</td>
<td></td>
</tr>
<tr>
<td>Increased small, sense LDL cholesterol products</td>
<td></td>
</tr>
<tr>
<td>Decreased lipoprotein lipase activity</td>
<td></td>
</tr>
<tr>
<td>Increased fibrinogen and PAI-1</td>
<td></td>
</tr>
<tr>
<td>Decreased fibrinolytic activity</td>
<td></td>
</tr>
<tr>
<td>Increased antithrombin III, protein C and S levels</td>
<td></td>
</tr>
</tbody>
</table>

*VLDL indicates very low-density lipoprotein; LDL, low-density lipoprotein; HDL, high-density lipoprotein; and PAI-1, plasminogen activator inhibitor-1.*

### PLATELET AND COAGULATION ABNORMALITIES IN WOMEN WITH DIABETES MELLITUS

Platelet adhesion and platelet aggregation are often enhanced in diabetes mellitus (Table 1). The precise cause of enhanced platelet reactivity and other functional abnormalities of the platelet in diabetes mellitus is complex, but it appears that abnormalities in platelet intracellular divalent cation metabolism may play an integral role. Platelet intracellular calcium has been reported to be high and magnesium to be low in platelets from individuals with diabetes. High intracellular calcium and low intracellular magnesium both increase platelet aggregation. Nitric oxide produced by platelets, as well as vascular tissue, inhibits platelet aggregation and platelet adhesion to endothelial cells. In diabetes mellitus there is reduced nitric oxide production and/or increased nitric oxide destruction, which contributes to enhanced platelet aggregation. In this regard, observations that hyperglycemia attenuates nitric oxide production provides a possible mechanism by which women with diabetes may lose the protection afforded by estrogen.

In individuals with diabetes mellitus the balance between coagulation and fibrinolytic activities in the circulation is affected in a number of ways (Table 2). A procoagulant state in diabetes appears to be mediated in part by higher than normal levels of a number of coagulation factors. For example, an increase in the endothelium–derived von Willebrand factor occurs in diabetes mellitus, particularly in association with endothelial cell injury. Microvascular and macrovascular damage, and poor diabetic control. High concentrations of factor VIII, related to hyperglycemia, accelerate the rate of thrombin formation, and this may contribute to occlusive vascular disease in patients with diabetes. Levels of fibrinogen, factor VII, and thrombin-antithrombin complexes have also been reported to be elevated in patients with diabetes. Elevated levels of these coagulation factors, particularly fibrinogen, are important for increasing the survival of the provisional clot matrix at the site of injured endothelium. Increased levels of thrombin-antithrombin complexes have been observed in patients with diabetes in association with en-
hanced thrombin generation. High plasminogen activator inhibitor-1 levels have also been observed in patients with diabetes mellitus. Elevated levels of plasminogen activator inhibitor-1 also appear to be associated with elevated serum levels of insulin and triglycerides. Indeed, insulin has been shown to stimulate plasminogen activator inhibitor-1 synthesis in hepatocytes. Thus, it appears that both hyperinsulinemia and hyperglycemia contribute to an abnormal balance between coagulation and fibrinolysis in individuals with diabetes (Table 2).

### ENDOTHELIAL DYSFUNCTION IN DIABETES

A number of anatomical and functional abnormalities of the vascular endothelium are associated with diabetes mellitus (Table 3). In diabetes mellitus, endothelial cell lipoprotein lipase activity is decreased, as is the conversion of cholesterol ester–enriched very low-density lipoprotein to low-density lipoprotein. The resulting large and abnormal cholesterol ester–enriched very low-density lipoprotein level is injurious to endothelial cells after receptor-mediated uptake. Hyperglycemia appears to contribute to endothelial dysfunction through several mechanisms. Hyperglycemia attenuates the ability of estrogen to stimulate endothelial cell nitric oxide production. Further metabolic factors may contribute to endothelial cell matrix production, which may contribute to basement membrane thickening. Hyperglycemia increases endothelial cell collagen and fibrinogen synthesis. Hyperglycemia also delays cell replication and increases endothelial cell death in part by enhancing oxidation and glycation.

Additional metabolic factors may contribute to endothelial dysfunction in women with diabetes. Hypercholesterolemia and hypertriglyceridemia impair endothelial-dependent relaxation. Therefore, it is reasonable to assume that careful control of metabolic abnormalities (both hyperglycemia and dyslipidemia) may lessen the burden of cardiovascular disease in women with diabetes mellitus. Prospective clinical trials are needed to test this possibility.

This article summarizes available information regarding the disproportionate burden of diabetes on CHD in women. Considerable in vitro and in vivo animal data suggest that hyperglycemia, and perhaps hyperinsulinemia-insulin resistance undermine the cardiovascular protective effects of estrogen. Recent data suggest that hyperglycemia attenuates the ability of estrogen to stimulate endothelial cell production of nitric oxide. Local (paracrine-autocrine) production of nitric oxide by endothelial cells, vascular smooth muscle cells, cardiac myocytes, and platelets exerts a braking effect on platelet aggregation, vascular constriction, and cardiovascular growth and remodeling. Thus, hyperglycemia attenuates the cardiovascular protective effects afforded by estrogen stimulation of nitric oxide production. Hyperinsulinemia, as exists in type 2 diabetes, appears to interact with estrogen to have detrimental cardiovascular effects. Further clinical studies should address the potential ability of anti-oxidant therapy and the use of angiotensin-converting enzyme and angiotensin antagonists, and possibly arginine, to improve the cardiovascular and platelet production of nitric oxide in this patient population. Another potentially exciting therapeutic tool is afforded by the recent clinical availability of insulin-sensitizing drugs such as thiazolidinediones (Troglitazone) in attenuation of the degree of hyperinsulinemia and thus potentially adverse cardiovascular effects related to estrogen hyperinsulinemia interactions in women with type 2 diabetes mellitus.

Accepted for publication July 1, 1997.

Reprints: James R. Sowers, MD, Division of Endocrinology, Metabolism and Hypertension, Wayne State University School of Medicine, 4201 St Antoine, UHC–4H, Detroit, MI 48201 (e-mail: sowers@oncgate.roe.wayne.edu).

### REFERENCES

17. Weiner GP, Lizzasin I, Baylis SA, Knowles RG, Charles IG, Moncada S. Induc-


19. Williams JK, Adams MR, Klopfenstein HS. Estrogen modulates responses of ath-

20. Walsh BW, Schiff I, Rosner B, Grienberg L, Ravnikar V, Sacks F. Effects of post-

21. Hong MK, Romm JA, Reaag K, Green CE, Rackley CE. Effects of estrogen-


25. The Writing Group for the PEPI Trial. Effects of estrogen or estrogen/progesterone regimens on heart disease risk factors in postmenopausal women: The Post-


29. Lin AL, Gonzalez R, Carey KD, Shain SA. Gender and baboon aortic steroid hor-


32. Lin AL, Gonzalez R, Carey KD, Shain SA. Gender and baboon aortic steroid hor-

33. Gillum RF. The association of body fat distribution with hypertension, hyperten-

34. Lapidus L, Bengtsson C, Larsson B, Pennett K, Rybo E, Sjostrom L. Distribution of adipose tissue and risk of cardiovascular disease and death: a 12-year fol-

35. Gillom RF. Association of body fat distribution with hypertension, hyperten-

36. Levin CE, Grandits GA, Fack J, McDonnell R, Elmer PJ. Efficacy and tolerance of antihypertensive treatment in men and women with stage 1 diastolic hyper-

37. Davis BR, Cutler JA, Gordon DJ, et al, for the ALLHAT Research Group. Ratio-

38. Davis BR, Cutler JA, Gordon DJ, et al, for the ALLHAT Research Group. Ration-


42. Ford I, Singh TP, Kitchen S, Makris M, Ward JD, Preston FD. Activation of coa-


44. Ramirez LC, Arauz-Pacheco C, Lacker C, Albritton B, Adams BW, Raskin P. Li-


49. Standley PR, Ali S, Bapna C, Sowers JR. Increased platelet cytosolic calcium re-

50. Carmassi F, Morale M, Puccetti R, et al. Coagulation and fibrinolytic system im-

51. Oppenheimer MJ, Sundquist K, Bierman EL. Down-regulation of high-density li-


54. Johnson PK, Colerajmar DS, Yue DK, et al. Endothelial dysfunction in insulin-


56. Sowers JR. Insulin and insulin-like growth factor in normal and pathological car-


58. Capron L, Jarnet J, Kusandjian S, Honsait E. Growth promoting effects of dia-


60. Lewis CE, Grandits GA, Kim EA, Jekanowski J, Isner JM. Effect of estrogen on tissue plasminogen activator (PAI-1) in hypertension are related to metabolic risk factors for cardio-


62. Ford I, Singh TP, Kitchen S, Makris M, Ward JD, Preston FD. Activation of coa-


64. Carmassi F, Morale M, Puccetti R, et al. Coagulation and fibrinolytic system im-


66. Ramirez LC, Arauz-Pacheco C, Lacker C, Albritton B, Adams BW, Raskin P. Li-

67. Landin K, Tengbom L, Smith U. Elevated fibrinogen and plasminogen activator inhibitor (PAI-1) in hypertension are related to metabolic risk factors for cardio-

68. Sowers JR, Tuck M, Sowers DK. Plasma antithrombin III and thrombin genera-

69. Ramirez LC, Arauz-Pacheco C, Lacker C, Albritton B, Adams BW, Raskin P. Li-

70. Bucala R, Makita Z, Koschinsky T, Gerami A, Vlassara H. Lipid advanced glyco-