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# Sex differences in the pathogenesis of type 2 diabetes may explain the stronger impact of diabetes on atherosclerotic heart disease in women

Extensive clinical evidence shows that women of reproductive age are less prone to atherosclerotic heart disease than men. Women have a nearly decade-long delay in first myocardial infarction compared to men.[1,2] Furthermore, at any given age, women have a lower risk of cardiovascular disease relative to men.[3,4] However, in reproductive-age women, the presence of diabetes totally negates this protection from atherosclerotic heart disease, and diabetic women are more severely affected than men.[5–8] For example, the INTERHEART study reported that diabetic women had a threefold to fourfold increased risk of developing atherosclerotic heart disease compared to men.[9] The mechanisms by which diabetes becomes a "coronary heart disease equivalent" and accelerates atherosclerotic heart disease in women are poorly understood. Several hypotheses have been proposed that do not exclude one another.

Some of the excess risk may be the result of a sex difference in the management and treatment of diabetes,[10] but this is unlikely to play a major role. The fact that hyperglycemia is observed in both type 1 and type 2 diabetes suggests that it may play a role in the acceleration of vascular events in diabetic women. A meta-analysis of data from more than 200,000 men and women with type 1 diabetes reported that women with type 1 diabetes have twice the excess risk of fatal and nonfatal vascular events than men with type 1 diabetes.[11] In fact, women are believed to exhibit an overall greater cumulative lifetime exposure to hyperglycemia because of poorer glycemic control compared to men.[12] This could be partially attributed to greater insulin resistance during puberty in young women with type 1 diabetes.[13]

Accumulating evidence suggests that this loss of protection from atherosclerotic heart disease in diabetic women is related to the disparity in type 2 diabetes pathogenesis between men and women. A meta-analysis including almost 900,000 individuals reported a 40% greater risk of incident coronary artery disease in diabetic women compared to men with diabetes.[14] The authors concluded that a greater deterioration in and more prolonged exposure to cardiovascular risk factors among prediabetic women compared with men, possibly driven by greater levels of adiposity, may be responsible for the excess risk of diabetes-related coronary artery disease in women. Consistent with this possibility, accumulating evidence supports the hypothesis that for women to become diabetic, their metabolic and cardiovascular risk factor profile must deteriorate to a greater extent than men's. In fact, in a cross-sectional study of older adults from the UK (aged 60–79 years), non-diabetic women tended to have more favorable risk factors and were less insulin resistant than non-diabetic men.[15] However, this difference was blunted in the diabetic state. Levels of abdominal adiposity, inflammation (white blood cell count), insulin resistance, diastolic blood pressure, atherogenic lipids (low HDL-cholesterol), endothelial dysfunction (tissue plasminogen activator) and coagulation (factor VIII) deteriorated to a greater extent between diabetic and non-diabetic women than between diabetic and non-diabetic men. This is consistent with the notion that, because they are more insulin sensitive than men, women must experience a greater overall metabolic deterioration, accumulate more fat, and experience greater insulin resistance and related risk factors in order to evolve from normoglycemia to diabetes.[16]

A recent study including over 1500 participants from the Bogalusa Heart Study and spanning 33 years from childhood to adulthood sheds new light on the timing of the development of type 2 diabetes in women.[17] In childhood, boys and girls in whom diabetes did and did not develop at follow-up exhibited similar levels of cardiometabolic risk factors. Yet, over time, during the transition from normoglycemia to diabetes, women experienced greater deterioration in body weight, total cholesterol, LDL cholesterol, and fasting plasma glucose (FPG). Importantly, this metabolic dysregulation was observed as early as 23 years of age on average and persisted throughout adulthood, up to the age of the diagnosis of diabetes. Therefore, during the transition from childhood to midlife, women who will develop diabetes are exposed to faster metabolic alterations and higher burden of exposure to increased adiposity, LDL cholesterol, and fasting hyperglycemia than men who will develop diabetes.[17]

Thus, accumulating evidence suggests that the excess risk of diabetes-related atherosclerotic heart disease in women is rooted in the biological sex differences between men and women. Specifically, in the transition from normoglycemia to overt diabetes, there is an earlier, greater and more prolonged decline in metabolic homeostasis leading to a deleterious burden of cardiometabolic risk factors in women compared to men. The combined effect of these multiple cardiometabolic risk factors in diabetic women may explain the stronger impact of diabetes on cardiovascular events in women as compared to men rather than the effect of diabetes per se. This reinforces the necessity of early screening for at-risk women in young adulthood for sex-based preventive intervention.

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