

Original Research

Risk of Vascular Disease in Premenopausal Women With Diabetes Mellitus

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ABSTRACT

Purpose: The aims of this study were (1) to estimate the prevalence of cardiovascular disease risk factors among premenopausal and menopausal Argentinean women with and without type 2 diabetes mellitus and (2) to assess the contribution of total plaque area (TPA) to risk stratification when added to Framingham risk scores.

Methods: A descriptive cross-sectional study in primary prevention in 1257 women (ages 19-84 years) from Argentina. TPA was measured by ultrasonography. Framingham sex-specific risk equations were used to predict the risk of developing cardiovascular disease, coronary heart disease, and stroke during the next 10 years. Patients were divided into diabetic (n = 293) and control groups (n = 964), and then each group was divided according to age (>40, 40-49, 50-59, and ≥60 years).

Findings: No difference was observed between diabetic and control groups in the incidence of smoking or the presence of early family cardiovascular event. Overall, diabetic patients had higher body mass index, blood pressure, and TPA versus the control group. The Framingham risk score was higher in the diabetic group in all age groups. The mean (SD) coronary heart disease scores for the diabetic group at <40, 40 to 49, 50 to 59, and ≥60 were 6% (1.7%), 19% (2.5%), 38% (2.0%), and 60% (1.5%), respectively, whereas the scores in the control group

3% (0.8%), 7% (0.9%), 17% (0.9%), and 40% (0.9%), respectively. The stroke score was also enhanced in diabetic women, independent of their age. These data indicate that diabetic women in the premenopausal age or the early years of menopause age (40-50 years) are at intermediate or higher risk of developing a cardiovascular event.

Implications: Premenopausal diabetic women should be considered at possibly high risk of cardiovascular events compared with nondiabetic women. Direct assessment of atherosclerotic burden, such as TPA, should be used early in this population instead of relying on traditional risk scores. (*Clin Ther.* 2014;36:1924-1934) © 2014 Elsevier HS Journals, Inc. All rights reserved.

Key words: subclinical atherosclerosis, imaging, cardiovascular disease, women.

INTRODUCTION

Atherosclerosis is the primary cause of cardiovascular disease (CVD) in industrialized countries in both women and men. Coronary artery disease (CAD) causes 23% of all deaths in women.¹ There is compelling evidence that women with CAD experience worse outcomes than men, irrespective of age.^{2,3} Stroke is the third-leading cause of death for women, who are more likely to be living alone and widowed before stroke, are more often institutionalized after stroke,

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and have poorer recovery from stroke than men.⁴ The same is true for other cardiovascular events.²

Women differ from men in important ways, including genetic differences in immunity,^{5,6} coagulation,⁷ hormonal factors,⁸ reproductive factors (including pregnancy and childbirth), and social factors,^{9,10} all of which can influence risk of cardiovascular events and their outcomes. In diabetic women, the risk of coronary mortality is increased 3- to 7-fold compared with the 2- to 3-fold increase observed in diabetic men. Diabetes mellitus definitely increases the effects of the other risk factors and modifies the protective effect by estrogens.¹¹

In women, determination of cardiovascular risk is not intense, and investigators have applied the term “bikini medicine” to actual preventive medicine practice in women,¹² referring to a focus on the breasts and the reproductive system during premenopausal years, with cardiovascular prevention considered only after menopause.

Currently, global risk assessment calculated from a the Reynolds Risk Score,¹³ Framingham risk equation,¹⁴ or other such scales is used to identify women at increased risk; however, they are still not detected early enough to decrease their rate of cardiovascular events. One problem may be overestimation of premenopausal protection; another may be overestimation of the sensitivity of risk scores.

In women, as well in men, CAD events are the result of a complex interaction of multiple risk factors. These factors include arterial hypertension, smoking, hypercholesterolemia, and diabetes.¹⁴ However, for women, up to 20% of all coronary events occur in the absence of these major risk factors,¹⁵ whereas many women with traditional risk factors do not experience coronary events, indicating that the algorithm used is not sensitive enough to prevent most of the cardiovascular events. In addition, physicians and other health care practitioners continue to underestimate cardiovascular risk in women, with consequent underuse of preventive therapies.^{16,17} Furthermore, women present with more advanced disease, owing to lack of early recognition and management.² Accurate risk assessment may represent the first step toward improving the outcome for women at risk.

Diabetes accelerates the development of atherosclerosis, such that women with diabetes are at a 2- to 4-fold increased risk of CVD compared with age-matched patients without diabetes.² Coronary heart

disease (CHD) constitutes more than two-thirds of all deaths in older patients with diabetes. This has stimulated interest in reducing CHD- and CVD-related morbidity and mortality through primary prevention among such patients.¹⁸

Despite this changing view of pathophysiology, variables included in current risk algorithms for women are largely unchanged from those recommended 40 years ago. Additional risk markers that have been proposed include alternative lipid measures, inflammatory biomarkers, markers of glycemic control, and others¹⁹; however, data are inconclusive, and the event rates are still elevated. Recently, the measurement of atherosclerosis burden as a predictor of cardiovascular events has been proposed, using the determination of total plaque area (TPA).²⁰

Atherosclerosis develops silently for decades before symptoms occur. Thus, there is an opportunity for timely detection and personalized prevention. However, the period preceding development of symptoms (preclinical atherosclerosis) is not efficiently used to prevent events or to categorize the risk of patients in primary care. Subclinical atherosclerosis can be detected accurately and noninvasively by means of the determination of carotid TPA by ultrasonography.²⁰ This well-developed technique can be used at the patient's first visit and at follow-up visits to determine the effectiveness of different therapies. A recent meta-analysis found that TPA was a stronger predictor of cardiovascular risk than the more widely used carotid intima-media thickness (IMT).²¹ The objectives of this study were (1) to estimate the prevalence of CVD risk factors among premenopausal and menopausal Argentinean women with and without type 2 diabetes and (2) to assess the contribution of TPA to risk stratification when added to a Framingham risk score (FRS).

METHODS

Study Participants

This was a cross-sectional study conducted in a consecutive sample of women referred by their primary care physician to an atherosclerosis prevention program (LifeQualityA), conducted by Blossom DMO Argentina and Instituto de Investigaciones en Ciencias de la Salud. All participants gave written informed consent to participate in a protocol approved by the Blossom DMO Argentina Ethics Committee.

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