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)

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,

Accepted for publication June 11, 2014.
http://dx.doi.org/10.1016/j.clinthera.2014.06.011
0149-2918/$ - see front matter

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 others[19]; 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.

We included patients age >18 years with a 10-year cardiovascular FRS >6%. We excluded patients who reported any personal history of CVD, defined as prior myocardial infarction or coronary or peripheral revascularization or any current symptom potentially suggestive of angina (chest pain, chest pressure, and chest tightness) or stroke, and patients with chronic renal failure. All individuals provided details of their demographic characteristics, medical history, medication use, current symptoms, and involvement in leisure time physical activity. A history of cigarette smoking was considered present if an individual was a current or former smoker. Patients were considered to have diabetes if they reported using oral hypoglycemic agents, insulin sensitizers, or subcutaneous insulin. Patients were considered to have hypertension if they reported a history of high blood pressure or used antihypertensive medications. Body mass index (BMI) was calculated from height and weight. A family history of premature CVD in parents and siblings was obtained by asking patients whether any member in their immediate family (parents or siblings) experienced a fatal or nonfatal myocardial infarction and/or coronary revascularization before age 55 years for the father and before age 65 years for the mother.

Carotid TPA Determination

Carotid TPA was measured as described previously[20] with a high-resolution duplex ultrasound scanner. Plaque was defined as a local thickening of the IMD >1 mm in thickness. Measurements were made in magnified longitudinal views of each plaque seen in the right and left common, internal, and external carotid arteries. The plane in which the measurement of each plaque was made was chosen by panning around the artery until the view with the largest extent of that plaque was obtained. The image was then frozen and magnified, and the plaque was measured by tracing around the perimeter with a cursor on the screen. The microprocessor in the scanner then displayed the cross-sectional area of the plaque. The operator then moved on to the next plaque and repeated the process until all visible plaques were measured. The sum of cross-sectional areas of all plaques seen between the clavicle and the angle of the jaw was taken as the TPA. To base risk prediction on data from the Tromsø study,[22,23] in which TPA was measured on only one side, TPA was divided by 2, and this value was used for the posttest analysis. Only patients for whom complete data were available were included in the present study. Missing data were due to scheduling issues, patients with physical characteristics that prevent a technically acceptable study, or failure to sign the informed consent form.

FRS Determination

Framingham sex-specific risk equations were used to predict the risk of developing general CVD, CHD, and stroke during the next 10 years as previously described.[24] This traditional risk assessment score was estimated based on the individual's reported smoking, age, and current blood pressure and whether they were receiving antihypertensive therapy. Blood pressure was taken as the mean of 3 measurements performed on the left arm in the sitting position after a 5-minute period of rest (OMRON Hem 705 sphygmomanometer, Vermon Hills, IL).[25]

Statistical Analysis

Continuous variables were summarized as mean (SD). Results were analyzed initially comparing the 2 groups (diabetic and nondiabetic), then by age groups (<40, 40-49, 50-59, and >60 years). We determined the FRS for each patient expressed as the percentage of risk at 10 years.[24] Then, to calculate the posttest probability TPA, we used TPA as a surrogate marker, using data from the Tromsø study[22,23] to relate TPA to cardiovascular risk, estimating the risk of CVD by using the Bayes formula,[26] and calculating the risk with the risk calculator designed by Romanens et al[27] (http://www.scopri.ch/posttestcalculators1.html). Risk was divided into 3 categories: low (≤10% risk of developing a CHD event in the next 10 years), moderate (10.1%–20%), and high risk (>20%). Finally, data were evaluated with the κ coefficient. Statistical significance was set at $P < 0.05$, and the 2-tailed t test, Dunn method ANOVA, and χ^2 test used when appropriate.

RESULTS

Table I lists the epidemiologic characteristics of the participating women. In total, 1256 women were evaluated (293 with diabetes and 963 controls). As expected, diabetic patients had a larger BMI and a higher prevalence of hypertension ($P < 0.001$) than controls. However, there was no difference in the prevalence of smoking or family history of early

Table I. Baseline characteristics and comparison between groups with and without diabetes mellitus.*

Characteristic	Control Group (n = 963)	Diabetic Group (n = 293)
Age, y	64 (0.4)	63 (0.7)
BMI, kg/m^2	29 (0.2)	32 (0.4)†
SBP/DBP, mm Hg	133 (1)/77(1)	136 (1)†/78(1)
FRS, %	16 (0.4)	35 (1.1)
Posttest-AMI, %	29 (0.7)	49 (1.5)†
Posttest Stroke, %	15 (0.5)	28 (1.1)†
TPA, mm^2	54 (2)	70 (4)†
Smoking, %	19	15
Hypertension, %	53	71†
Family history of early cardiovascular event, %	37	35

AMI = acute myocardial infarction; BMI = body mass index; DBP = diastolic blood pressure; FRS = Framingham risk score; SBP = Systolic blood pressure; TPA = total plaque area.
*Data are presented as mean (SD) unless otherwise indicated.
†$P < 0.05$ vs Control Group.

cardiovascular events. Diabetic participants had higher TPA, resulting in higher posttest risk scores than in controls (Table I, Figure 1, and Figure 2). To assess premenopausal protection, we compared 4 age groups: <40, 40 to 49, 50 to 59, and >60 years.

Diabetic patients age >60 years (Table II) and 50 to 59 years (Table III) had higher weight, systolic blood pressure, and TPA. Thus, FRSs and posttest risk scores for acute myocardial infarction and stroke were higher in the diabetic group of patients. There was no difference in the prevalence of smoking or family history of early cardiovascular events.

Patients age 40 to 49 years were intermediate (Table IV). Although no difference in blood pressure

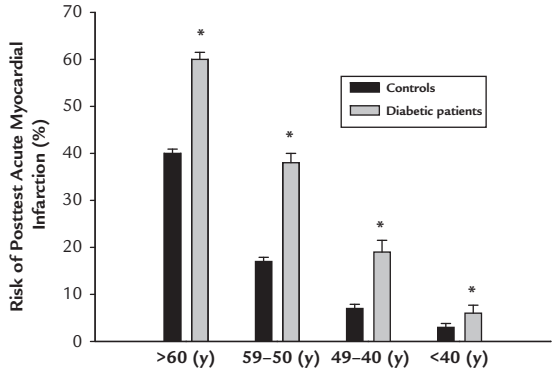

Figure 1. Ten-year risk scores for acute myocardial infarction in diabetic and nondiabetic women. Error bars indicate SDs. *$P < 0.001$.

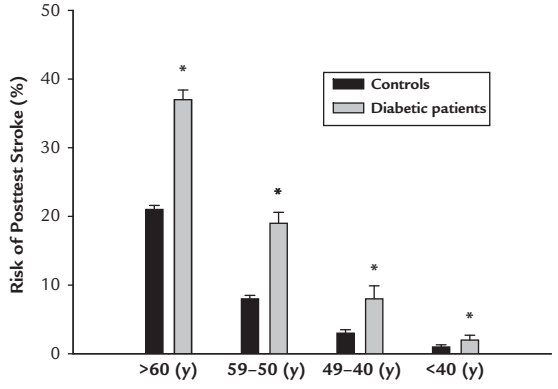

Figure 2. Ten-year risk scores for stroke in diabetic and nondiabetic women. Error bars indicate SDs. *$P < 0.001$.

Table II. Characteristics and comparison between women groups with and without diabetes mellitus, age ≥ 60 years.*

Characteristic	Control Group (n = 614)	Diabetic Group (n = 186)
Age, y	72 (0.3)	70 (0.4)
BMI, kg/m^2	29 (0.2)	32 (0.4)†
SBP/DBP, mm Hg	137 (1)/77 (1)	141 (1)†/78 (1)
FRS, %	22 (0.47)	44 (1.21)†
Posttest-AMI, %	40 (0.9)	60 (1.5)†
Posttest Stroke, %	21 (0.6)	37 (1.4)†
TPA, mm^2	72 (2.7)	87 (6.1)†
Smoking, %	13	11
Hypertension, %	63	77†
Family history of early cardiovascular event, %	37	39

AMI = acute myocardial infarction; BMI = body mass index; DBP = diastolic blood pressure; FRS = Framingham risk score; SBP = Systolic blood pressure; TPA = total plaque area.
*Data are presented as mean (SD) unless otherwise indicated.
†$P < 0.05$ vs Control Group.

was observed, diabetic patients in this age group had a higher BMI and TPA. FRSs and posttest risk scores for acute myocardial infarction and stroke were higher in the diabetic group. Hypertension was more prevalent among diabetic patients.

Patients in the <40 year age group were in their mid-30s (Table V). Despite no difference between

Table III. Characteristics and comparison between women groups with and without diabetes mellitus, age 50 to 59 years.*

Characteristic	Control Group (n = 232)	Diabetic Group (n = 71)
Age, y	56 (0.2)	56 (0.3)
BMI, kg/m^2	29 (0.4)	34 (0.8)†
SBP/DBP, mm Hg	128 (1)/78 (1)	134 (2)†/80 (1)
FRS, %	10 (0.4)	25 (1.2)
Posttest-AMI, %	17 (0.9)	38 (2.0)
Posttest Stroke, %	8 (0.5)	19 (1.6)†
TPA, mm^2	35 (3.0)	54 (6.5)†
Smoking, %	32	22
Hypertension, %	39	63
Family history of early cardiovascular event, %	42	28†

AMI = acute myocardial infarction; BMI = body mass index; DBP = diastolic blood pressure; FRS = Framingham risk score; SBP = Systolic blood pressure; TPA = total plaque area.
*Data are presented as mean (SD) unless otherwise indicated.
†$P < 0.05$ vs Control Group.

Table IV. Characteristics and comparison between women groups with and without diabetes mellitus, age 40 to 49 years.*

Characteristic	Control Group (n = 90)	Diabetic Group (n = 26)
Age, y	47 (0.3)	46 (0.6)
BMI, kg/m^2	30 (0.7)	36 (1.3)†
SBP/DBP, mm Hg	125 (1)/78 (1)	127 (3)/80 (2)
FRS, %	6 (0.4)	13 (1.2)†
Posttest-AMI, %	7 (0.9)	19 (2.5)†
Posttest Stroke, %	3 (0.5)	8 (1.9)†
TPA, mm^2	14 (1.7)	27 (6.6)†
Smoking, %	20	23
Hypertension, %	31	57†
Family history of early cardiovascular event, %	26	42

AMI = acute myocardial infarction; BMI = body mass index; DBP = diastolic blood pressure; FRS = Framingham risk score; SBP = Systolic blood pressure; TPA = total plaque area?
*Data are presented as mean (SD) unless otherwise indicated.
†$P < 0.05$ vs Control Group.

diabetic patients and controls with regard to BMI and blood pressure, as in older groups, TPA was 75% higher in diabetic women. Although the prevalence of hypertension and family history of early cardiovascular events was the same, the FRS and posttest risk scores for acute myocardial

Table V. Characteristics and Comparison Between Women Groups With and Without Diabetes Mellitus, <40 years.*

Characteristic	Control Group (n = 27)	Diabetic Group (n = 10)
Age, y	34 (1)	35 (1)
BMI, kg/m^2	30 (1.4)	29 (2.0)
SBP/DBP, mm Hg	125 (3)/78 (2)	124 (5)/78 (4)
FRS, %	3 (0.4)	6 (1.4)†
Posttest-AMI, %	3 (0.8)	6 (1.7)†
Posttest Stroke, %	1 (0.3)	2 (0.7)†
TPA, mm^2	4 (1.3)	11 (3.8)†
Smoking, %	14	10†
Hypertension, %	22	30
Family history of early cardiovascular event, %	40	20

AMI = acute myocardial infarction; BMI = body mass index; DBP =diastolic blood pressure; FRS = Framingham risk score; SBP = Systolic blood pressure; TPA = total plaque area.
*Data are presented as mean (SD) unless otherwise indicated.
†$P < 0.05$ vs Control Group.

infarction and stroke were also elevated in the youngest diabetic group.

Our results indicate that TPA increased with age in both diabetic ($P < 0.05$) and nondiabetic women ($P < 0.05$). To evaluate restratification of risk in our participating women, we compared CVD risk estimated by FRS and posttest risk incorporating posttest probability TPA of the diabetic patients versus controls, divided into 2 age groups (age >50 and <50 years). Among the younger diabetic patients, 55.2% migrated to a higher risk category (mean [SE] $\kappa = 0.274$ [0.91]), whereas among older diabetic women, 13.7% migrated to a higher risk stratum (mean [SE] $\kappa = 0.196$ [0.06]).

DISCUSSION

To our knowledge, this is the first study reporting subclinical atherosclerosis in young, premenopausal, diabetic women using TPA determination, a powerful predictor of cardiovascular risk. We found an unexpectedly high prevalence of atherosclerosis and elevated cardiovascular risk among premenopausal diabetic women. In our population, diabetic women age >50 years had the classic phenotype: obesity, higher blood pressure, higher incidence of hypertension, and larger TPA. These characteristics put them in a higher degree of cardiovascular risk compared with the nondiabetic patients.

The evaluation of subclinical atherosclerosis is a recent approach incorporated to determine cardiovascular risk. Previously, most studies used carotid IMT or coronary artery calcium (CAC) to determine subclinical atherosclerosis, but these techniques have some limitations. In meta-analysis, IMT is a weak predictor of cardiovascular risk,[28] and progression of IMT does not predict risk.[29] Although coronary calcium is a stronger predictor of cardiovascular risk, there are concerns about radiation,[30] particularly for long-term exposure among patients with CAD.[31,32] In contrast to IMT, carotid plaque burden is highly correlated with CAC[33] and has several important advantages[34]: progression of TPA strongly predicts risk,[20] progression can be measured within individuals in clinically meaningful timeframes, and measurement of TPA can be used to manage patients.[35,36]

Importance of Risk Score Determination

Determination of cardiovascular risk should be the centerpiece of initial evaluation for any patient in primary care because physicians will treat them according to their risk.

For practical purposes, any patient who has a CHD event is at increased risk of a subsequent event, whereas patients with a >20% risk for a CHD event based on the FRS are considered to be at equivalent risk to those with established CHD and should be receiving preventive therapy, including statins.[37] Current guidelines and many clinical studies consider diabetes as a CHD risk equivalent (>20% risk during 10 years) in setting targets for LDL-C and non–HDL-C levels.[38–40]

Although many diabetic patients are not CHD risk equivalent based on models such as the United Kingdom Prospective Diabetes Study risk engine,[41] risk calculation ensures that high-risk diabetic patients are treated intensively. However, few premenopausal women are treated intensively, perhaps because age dominates risk prediction.

Subclinical Atherosclerosis During Premenopause

Several studies have examined the association among endogenous sex hormones and atherosclerosis,[42–44] CVD,[45,46] and mortality[47–49] in postmenopausal women, with conflicting results. Although some studies found that higher levels of androgens and sex hormone–binding globulin were associated with a reduced level of atherosclerosis,[43,45] others found a positive association between testosterone and CVD risk.[45,46]

Agrinier et al[50] investigated the effect of menopause on various CHD risk factors and on the global risk of CHD in a population-based sample of women, making the difference between menopause and age-related effects. They found no association between elapsed time since menopause and lipid levels and no differences of age-adjusted lipid levels between the perimenopausal and postmenopausal groups, indicating that changes in lipid profile occur in the perimenopausal period. Other longitudinal studies about the effect of menopause on lipids in Northern American,[51] Northern European,[52] Chinese,[53] and Japanese[54] population-based samples of women reported similar results.

These results are consistent with our observations because TPA increased significantly in both groups with age; as serum estrogen levels decrease, serum lipids may increase. Estrogens induce an early increase of LDL receptors, which are responsible for the uptake of plasma lipoproteins, and decrease 3-hydroxy-3-methylglutaryl-coenzyme A reductase

activity,[55] the key enzyme of the biosynthetic pathway. Moreover, estrogens enhance biliary secretion of cholesterol.[56] All these results suggest that estrogens may contribute to decrease serum LDL-C levels, providing cardiovascular protection. However, this effect is limited in diabetic women. Bertoni et al[57] investigated the presence of subclinical atherosclerosis in patients with metabolic syndrome. They measured CAC and carotid IMT in 5810 patients in the Multi-Ethnic Study of Atherosclerosis (age 45–84 years) without prior CVD; they found that the homeostasis model assessment–estimated insulin resistance (HOMA-IR) index was associated with increased IMT after adjustment for demographic characteristics (age, site, and educational level), smoking, and LDL-C level in each ethnic group, except in Hispanic individuals, and in both men and women. After further adjusting for nonglucose metabolic syndrome components, HOMA-IR was not associated with increased IMT.

In the same study, individuals in the highest quintile of HOMA-IR had an elevated prevalence of CAC in each ethnic group and both sexes, after adjustment for demographic characteristics, smoking, and LDL-C level but not after further adjustment for nonglucose metabolic syndrome components. Among those with detectable CAC, there was no significant association between HOMA-IR and the amount of CAC. These data do not contradict our results because CAC only detects calcified tissue, whereas TPA detects early lesions of atherosclerosis.

The same investigator also reported an association between physical activity and IMT.[58] The authors assessed physical activity and walking pace via questionnaire among 6482 US adults ages 45 to 84 years without prior clinical CVD participating in the Multi-Ethnic Study of Atherosclerosis from 2000 to 2002. Subclinical atherosclerosis was assessed by the ankle-brachial index, CAC, and IMT. In this article, they do not report specifically the presence of atherosclerosis in the young, mild, and older diabetic age groups. They concluded that after adjustment for age, race/ethnicity, clinic site, educational level, income, and smoking, increasing total, moderate and vigorous, and intentional-exercise physical activity were associated with increased ankle-brachial index ($P < 0.05$) in women only.

Gestational diabetes and the association with subclinical atherosclerosis have been also evaluated. In a study of young women with previous gestational diabetes, a population at high risk for type 2 diabetes and metabolic syndrome, the investigators found that carotid IMT was increased.[59]

Gunderson et al[60] evaluated whether gestational diabetes increases the risk of early atherosclerosis independent of prepregnancy obesity and subsequent metabolic disease. They studied 898 women free of diabetes and heart disease at baseline, who delivered ≥ 1 postbaseline births, reported a history of gestational diabetes, and had common carotid IMT measured. They concluded that history of gestational diabetes may be a marker for early atherosclerosis independent of prepregnancy obesity among women who have not developed type 2 diabetes or the metabolic syndrome. [60]

Finally, we found that posttest probability TPA reclassified only 13% of the older diabetic patients to a higher level of risk, whereas the effect of incorporating TPA into risk prediction was much greater in young diabetic women: 37% were reclassified as high risk, suggesting that they should be treated more intensively. Using this improved risk score determination (posttest probability TPA), we expect to prevent more CHD compared with the traditional FRS.

Our study has several positive aspects. First, this study focused on diabetic women across a wide range of age, thus enhancing generalizability of our findings. Second, we quantified carotid plaque burden in a well-characterized cohort of women. Third, we controlled for classic CVD risk factors without the need for laboratory determinations to indicate the enhanced cardiovascular risk observed in young diabetic women. Finally, our results are based on age associated with fertility instead of estrogen levels, and this design turned out to be a practical approach to evaluate the cardiovascular risk of any diabetic woman. A limitation of this approach was that we did not have hormonal levels to define menopause; instead, we based determination of menopause on age. This age classification was based on local data in which menopause is present at age <40 years in $<20\%$, at age 40 to 49 years in $<50\%$, and at age 50 to 59 years in $>50\%$.[61] Similar frequencies may apply to most countries.

CONCLUSION

In our population, after age 40 years diabetic women should be considered at possibly high risk of cardiovascular events compared with a nondiabetic group.

To accurately define risk, direct assessment of atherosclerotic burden, such as TPA, should be used early in this population, even before menopause, instead of relying on traditional risk scores. This study was supported by an unrestricted institutional grant from Blossom DMO Argentina.

CONFLICTS OF INTEREST

Drs Pérez and García have no conflicts of interest with regard to the content of this article. Drs Spence and Armando are principals in Vascularis Inc. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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