Type 1 Diabetes Accelerates Progression of Coronary Artery Calcium Over the Menopausal Transition: The CACTI Study

Amena Keshawarz,[1,2] Laura Pyle,[2,3] Amy Alman,[4] Caprice Sassano,[2] Elizabeth Westfeldt,[2] Rachel Sippl,[2] and Janet Snell-Bergeon[1,2]

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OBJECTIVE

Type 1 diabetes is associated with a higher risk of cardiovascular disease (CVD) in women. Although menopause increases risk of CVD, it is uncertain how menopause affects risk of CVD in women with type 1 diabetes. We examined whether risk of CVD changes differentially in women with and those without type 1 diabetes over the transition through menopause.

RESEARCH DESIGN AND METHODS

Premenopausal women with type 1 diabetes ($n = 311$) and premenopausal women without diabetes ($n = 325$) enrolled in the Coronary Artery Calcification in Type 1 Diabetes (CACTI) study and attended up to four study visits over 18 years. Coronary artery calcium (CAC) volume was measured from computed tomography scans obtained at each visit. Longitudinal repeated-measures modeling estimated the effect of diabetes on CAC volume over time and the effect of menopause on the diabetes-CAC relationship.

RESULTS

CAC volume was higher at baseline and increased more over time in women with type 1 diabetes than in women without diabetes. A significant diabetes-by-menopause interaction was found ($P < 0.0001$): postmenopausal women with type 1 diabetes had significantly higher CAC volumes than premenopausal women (5.14 ± 0.30 vs. 2.91 ± 0.18 mm^3), while there was no difference in women without diabetes (1.78 ± 0.26 vs. 1.78 ± 0.17 mm^3). This interaction remained significant after adjusting for CVD risk factors.

CONCLUSIONS

Type 1 diabetes was associated with higher CAC volume and accelerated progression of CAC over time. Menopause increased CAC progression more in women with diabetes than in women without diabetes independent of age and other CVD risk factors known to worsen with menopause.

Cardiovascular disease (CVD) is the leading cause of mortality in the U.S., but the risk of developing CVD varies significantly between men and women. On average, women have a lower risk of developing CVD than men of similar ages. Women tend to be diagnosed with CVD up to 10 years later than men, and as they undergo menopause and cease producing ovarian estrogen, their risk of CVD increases independently of age and other cardiovascular risk factors (1,2).

[1]Department of Epidemiology, Colorado School of Public Health, University of Colorado Anschutz Medical Campus, Aurora, CO
[2]Barbara Davis Center for Diabetes, Aurora, CO
[3]Department of Biostatistics, Colorado School of Public Health, University of Colorado Anschutz Medical Campus, Aurora, CO
[4]Department of Epidemiology & Biostatistics, University of South Florida, Tampa, FL

Corresponding author: Amena Keshawarz, amena.keshawarz@cuanschutz.edu

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Type 1 diabetes is associated with an increased risk of CVD; adults with type 1 diabetes have more coronary artery calcium (CAC) than adults without diabetes (3), which in turn predicts higher rates of incident CVD and diabetes complications (4–6). The increase in cardiovascular risk differs by sex: women with type 1 diabetes see a greater increase in CAC and their overall cardiovascular risk than do men with type 1 diabetes (7–9). Specifically, women with type 1 diabetes have a risk for CVD up to nine times higher than that of women without diabetes, whereas men with type 1 diabetes are at four times higher risk than men without diabetes (7).

Proatherogenic changes in the lipid profile due to reduced estrogen contribute to increased cardiovascular risk across menopause (10); however, few studies have followed women with type 1 diabetes as they transition through menopause. It is important to understand the effects of this transition on CVD risk because of the increasing incidence of type 1 diabetes and lower rates of diabetes-related mortality, which have the combined effect of increasing the number of older women with type 1 diabetes. Type 1 diabetes is associated with increased incidence of hypertension and atherosclerosis (11), and the relationship between diabetes and CVD risk factors differs by sex. Women with type 1 diabetes shift more toward atherogenic lipoprotein distribution (12), are more insulin resistant (13), and have less favorable changes to their fat distribution (8) than men with type 1 diabetes. Menopause is further associated with worsening of these risk factors (14,15), although little is known about how type 1 diabetes and menopause may interact to modify the risk of CVD in women. We examined the change in cardiovascular risk, as measured by CAC and by other cardiovascular risk factors, in premenopausal women with and in premenopausal women without type 1 diabetes as they underwent menopause.

RESEARCH DESIGN AND METHODS

Study Population

The Coronary Artery Calcification in Type 1 Diabetes (CACTI) study enrolled 680 men and 736 women, either with or without type 1 diabetes, who were between the ages of 19 and 56 years at the baseline visit. Participants completed up to four visits over the course of 18 years, between 2000 and 2018. All participants provided written informed consent at each study visit.

Our analyses of the menopausal transition and CAC included all women who were enrolled in the CACTI study who were premenopausal at baseline, completed computed tomography (CT) scans for use in quantifying CAC, and provided complete information on their menopausal status at one or more follow-up study visits ($n = 636$). We excluded women who were postmenopausal at baseline ($n = 83$) or whose menopausal status was uncertain based on our definitions ($n = 17$) (see REPRODUCTIVE HISTORY AND MENOPAUSE STATUS). Of the 83 women who were postmenopausal at baseline, 37 had undergone a hysterectomy. Therefore, the final sample for the longitudinal analyses consisted of 311 women (49%) with type 1 diabetes and 325 women (51%) without diabetes.

Data Collection

Participants completed a baseline study visit followed by study visits at 3, 6, and 14 years. During study visits, clinical anthropometric measurements were taken, a fasting blood sample was collected, electrocardiography was performed, and a cardiac CT scan was obtained to measure CAC. The Colorado Multiple Institutional Review Board reviewed and approved the study protocol and all study procedures.

Reproductive History and Menopause Status

All women enrolled in the CACTI study completed a reproductive history questionnaire in which they provided information about their menstrual cycle, reproductive surgery, pregnancy, and menopause. Women who reported ever having amenorrhea or irregular menstrual cycles were defined as having a history of ovarian dysfunction. Women were asked whether they had undergone a hysterectomy, oophorectomy (unilateral or bilateral), or natural menopause. They were classified as postmenopausal if they had undergone a hysterectomy with bilateral oophorectomy or if it had been >1 year since their last menstrual cycle but not because of pregnancy, breastfeeding, or use of birth control. We excluded women who had undergone a hysterectomy but had had only one or neither ovary removed, as their menopausal status was uncertain. Women were classified as premenopausal if they indicated they were not postmenopausal, had not undergone a hysterectomy, or had menstruated within 1 year of their visit date.

CAC Measurement

Cardiac CT scans were performed at all study visits. Participants underwent electron beam CT at the first three study visits and spiral CT at the fourth study visit. One cardiologist oversaw the scoring of all electron beam CT scans by one technician, and that cardiologist reviewed and scored the spiral CT scans completed at the fourth visit.

Statistical Analyses

Details of our statistical approach are available in the Supplementary Data. We compared, by diabetes status, premenopausal women's demographic characteristics, measures of cardiovascular risk, anthropometric measures, clinical measures, and laboratory results at baseline. We also examined the women's demographic, menopausal, and cardiovascular characteristics at their final study visit.

Because of the longitudinal cohort design of the CACTI study, we anticipated that loss to follow-up could potentially bias our results. To examine whether differential loss to follow-up occurred, we compared the baseline characteristics of women who completed four study visits with those of women who completed fewer than four visits.

To examine CAC as an outcome, we applied a square root transformation to CAC volume to account for interscan variability, as described previously (16). To determine whether CAC differed by diabetes status and menopause status over time, we used a repeated-measures model examining square root–transformed CAC volume and testing two interactions: the interaction between diabetes and visit, and the interaction between diabetes and menopause. We adjusted the base model for time-varying age and baseline CAC volume.

We then tested cardiovascular risk factors (adiposity, blood pressure, lipids) to determine their relationships with diabetes status and menopause status. We adjusted all models for age, visit,

menopause status, and diabetes status; baseline values of the risk factor of interest; the interaction between diabetes and visit; and the interaction between diabetes and menopause.

We finally retested the base model, including all risk factors that had a significant statistical interaction between diabetes and menopause, and a variable for ovarian dysfunction. Women with type 1 diabetes have previously reported higher prevalences of amenorrhea and irregular menstrual cycles than women without diabetes (17), and we explored whether accounting for the risk factors that are known to change with menopause and for ovarian dysfunction changed the relationship between diabetes, menopause, and CAC.

All analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC). *P* values <0.05 were considered significant.

RESULTS

Participant Characteristics

Comparisons of baseline characteristics by diabetes are shown in Table 1. Women with type 1 diabetes were younger and had higher CAC volume, higher systolic and diastolic blood pressures, higher pulse pressure, and about a twofold higher 10-year risk of experiencing a cardiovascular event, as calculated by the atherosclerotic cardiovascular disease (ASCVD) risk estimator (18). A total of 26% of women with type 1 diabetes had CAC scores greater than zero; 11% of women without diabetes had scores greater than zero. Women with type 1 diabetes reported a higher prevalence of both amenorrhea and menstrual irregularity. They also had higher adiposity and lower LDL cholesterol, total cholesterol, and triglycerides than women who did not have diabetes.

We compared participant characteristics at the last visit by diabetes status and menopause status; these results are presented in Supplementary Table 1. At the end of the follow-up, 24% of women with type 1 diabetes ($n = 75$) had gone through menopause (84% natural vs. 16% surgical menopause), and 30% of women without diabetes ($n = 97$) had done so (80% natural vs. 20% surgical menopause). The mean ± SD age at natural menopause was 50 ± 6 years among women with type 1 diabetes, and 50 ± 8 years among women without diabetes. Similar to baseline values, more women with type 1 diabetes had CAC scores greater than zero, regardless of menopause status, when compared with women without diabetes.

Of the 636 women included in our analyses, 414 completed all four study visits and 222 completed fewer than four study visits. A comparison of baseline characteristics by follow-up time is presented in Supplementary Table 2. On average, women who were lost to follow-up were slightly younger at baseline (33 ± 8 vs. 36 ± 8 years), but we found no other notable clinical differences at baseline.

Table 1—Baseline characteristics of all premenopausal study participants ($n = 636$)

	Women with diabetes ($n = 311$)	Women without diabetes ($n = 325$)	*P* value
Demographics			
Age (years)	34 ± 8	36 ± 8	0.01
Diabetes duration (years)	22 ± 8	—	—
Measures of ovarian dysfunction*			
Irregular menstrual cycles	58 (18)	37 (11)	0.04
Amenorrhea	45 (14)	18 (5)	0.0009
Measures of cardiovascular risk			
CAC score (Agatston units)	25.10 ± 102.00	1.37 ± 7.88	<0.0001
0†	232 (75)	289 (89)	<0.0001
1–100	61 (20)	36 (11)	
101–300	11 (4)	0 (0)	
>300	7 (2)	0 (0)	
ASCVD risk (%)	1.3 ± 2.4	0.6 ± 1.2	<0.0001
Anthropometry			
BMI (kg/m^2)	26.1 ± 4.8	25.0 ± 5.3	0.0008
Waist circumference (cm)	80.8 ± 12.0	77.6 ± 12.4	0.0009
Waist-to-hip ratio	0.78 ± 0.06	0.76 ± 0.06	0.03
Clinical information			
Systolic blood pressure (mmHg)	112 ± 12	110 ± 12	0.0009
Diastolic blood pressure (mmHg)	76 ± 8	75 ± 8	0.99
Pulse pressure (mmHg)	36 ± 10	34 ± 8	<0.0001
Laboratory results			
Fasting glucose (mmol/L)	10.4 ± 5.0	4.8 ± 0.5	<0.0001
HbA_{1c} (% [mmol/mol])	8.0 ± 1.4 (64 ± 15.3)	5.4 ± 0.4 (36 ± 4.4)	<0.0001
HDL cholesterol (mmol/L)	1.5 ± 0.4	1.5 ± 0.4	0.10
LDL cholesterol (mmol/L)	2.6 ± 0.7	2.7 ± 0.8	0.003
Triglycerides (mmol/L), median (IQR)	0.85 (0.69, 1.15)	0.97 (0.72, 1.32)	0.02
Total cholesterol (mmol/L)	4.6 ± 0.9	4.7 ± 0.9	0.01
Estimated insulin sensitivity (mg/dL)	7.2 ± 3.1	20.4 ± 8.6	<0.0001
eGFR (mL/min/1.73 m^2)	106.5 ± 27.1	107.6 ± 21.1	0.58

Data are mean ± SD or *n* (%) unless otherwise indicated. eGFR, estimated glomerular filtration rate; IQR, interquartile range. *Measures of ovarian dysfunction are based on participant responses at visit 2, not at baseline. For this reason, we included 271 premenopausal women with diabetes, 27 postmenopausal women with diabetes, 279 premenopausal women without diabetes, and 46 postmenopausal women without diabetes. †Because of rounding, percentages may not add up to 100%.

Change in CAC Over Time

After adjusting for age and baseline CAC, we found significant interactions between diabetes and visit and between diabetes and menopause ($P < 0.0001$ for both) on CAC. The effect of diabetes increased over time and with the transition through menopause. Least squares mean square root–transformed CAC volumes by diabetes status and menopause status at each follow-up visit are presented in Fig. 1. CAC volume increased more over time in women with diabetes than in women without diabetes. Furthermore, women who became postmenopausal also had greater increases in their CAC volume, even when models were adjusted for age;

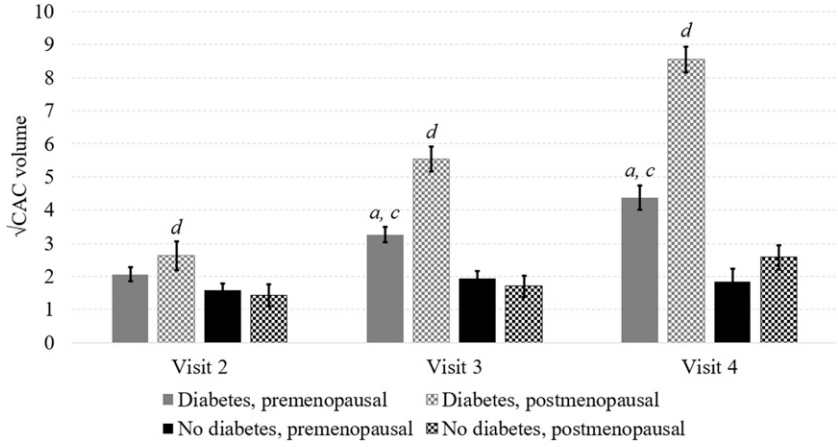

Figure 1—Least squares mean CAC volumes by diabetes status, menopause status, and follow-up visit after adjusting for age and baseline CAC ($n = 636$ women). [a]$P < 0.05$, premenopausal vs. postmenopausal women, diabetes only; [c]$P < 0.05$, diabetes status in premenopausal women only; [d]$P < 0.05$, diabetes status in postmenopausal women only; no significant relationship for postmenopausal vs. premenopausal women without diabetes.

this effect was greatest among women with type 1 diabetes.

Effect of Menopause on Cardiovascular Risk Factors

Least squares mean values of each cardiovascular risk factor are presented in Table 2, as are the *P* values for the diabetes-menopause interaction term. We found a significant interaction between diabetes status and menopause status for ASCVD risk score ($P = 0.0001$), systolic blood pressure ($P = 0.005$), and diastolic blood pressure ($P = 0.001$).

Because we were most concerned with the risk factors that changed with menopause, we included in a final model those that had a significant diabetes-by-menopause interaction to determine whether these risk factors explain the difference in CAC volume by diabetes status and menopause status. We added to the base model ASCVD risk score, systolic and diastolic blood pressures, antihypertensive medication use, and the presence of ovarian dysfunction. Inclusion of these covariates did not appreciably change the least squares mean CAC volume for each group over time (Fig. 2), and a significant diabetes-by-menopause interaction remained after we adjusted for these variables ($P < 0.0001$).

CONCLUSIONS

To our knowledge, this is the first article to report the association between the menopausal transition and subclinical atherosclerosis in women with type 1 diabetes and in women without diabetes. We found that not only do women with type 1 diabetes have higher CAC volumes than women without diabetes, but differences in CAC volume by diabetes status increase over time and as women transition through menopause.

It is well known that cardiovascular risk increases in women after menopause; this increase is potentially attributable to atherogenic changes in factors such as lipids, blood pressure, and adiposity over the menopausal transition (15,19–21). For example, in a cross-sectional analysis of CVD risk factors by age, total cholesterol, LDL cholesterol, and systolic blood pressure, all were significantly higher in postmenopausal women than in premenopausal women of the same age, whereas BMI was higher in women with surgical menopause than in premenopausal women (21). In our study, however, changes in these CVD risk factors did not account for the difference in the effect of menopause by diabetes status. Women with type 1 diabetes had faster increases in the extent of subclinical atherosclerosis associated with menopause, despite lower atherogenic lipid levels at baseline and no difference in lipid changes across the menopausal transition, than did those without diabetes.

Furthermore, systolic and diastolic blood pressures had significant diabetes-by-menopause interactions, such that the increases expected during menopause did not occur in women with type 1 diabetes as they did in women without diabetes. People with type 1 diabetes are more likely to be receiving antihypertensive treatment and to be prescribed statin medications; this potentially explains why blood pressure and lipids did not increase with menopause in women with type 1 diabetes. Although we did adjust for medication use in our models, statistical adjustment may not fully capture this complex relationship. Even if more frequent treatment with antihypertensive medications and statins explains the lack of increases in lipids and blood pressure with menopause in women with type 1 diabetes, a worsening of traditional CVD risk factors does not seem to explain the differential effect of menopause on the progression of subclinical atherosclerosis by diabetes status.

In addition to diabetes-associated changes in cardiovascular risk, women with type 1 diabetes are more likely than those without diabetes to have adverse female-specific risk factors that affect their overall cardiovascular health. Women with type 1 diabetes have more ovarian dysfunction—including delayed menarche and irregular menstrual cycles—than women without diabetes (22). Delayed menarche and irregular menstrual cycles persisted in our cohort and are associated with an increased risk of CVD (17,23). Nevertheless, our results showed that although menstrual irregularity and amenorrhea are more prevalent among women with type 1 diabetes, these measures of ovarian dysfunction did not mitigate the interaction between diabetes and menopause.

Previous studies have suggested that premenopausal women with type 1 diabetes may have fewer available ovarian follicles than women without diabetes. Data conflict regarding ovarian reserve as measured by serum anti-Müllerian hormone: whereas several studies reported lower levels of serum anti-Müllerian hormone in women with diabetes than in those without type 1 diabetes (24,25), others found no difference by diabetes status (26,27). It is possible that women with type 1 diabetes experience a more rapid decline in ovarian reserve before menopause (24), which could lead to the discrepancies seen in the literature. It is also possible that the hormonal mechanisms contributing to ovarian aging in type 1 diabetes are related to the mechanism by which CAC accumulates.

Table 2—Least squares means for each cardiovascular risk factor examined over four study visits, by diabetes status and ultimate menopause status

	With diabetes		Without diabetes		
	Premenopausal women (n = 236)	Postmenopausal women (n = 75)	Premenopausal women (n = 228)	Postmenopausal women (n = 97)	P value*
Measures of cardiovascular risk					
√CAC volume (mm^3)	2.91 ± 0.18	5.14 ± 0.30	1.78 ± 0.17	1.78 ± 0.26	<0.0001
ASCVD risk (%)	1.5 ± 0.1	2.7 ± 0.1	1.3 ± 0.1	1.7 ± 0.1	0.0001
Anthropometry					
BMI (kg/m^2)	26.3 ± 0.1	25.5 ± 0.2	26.2 ± 0.1	26.0 ± 0.2	0.06
Waist circumference (cm)	82.0 ± 0.3	81.2 ± 0.6	81.5 ± 0.3	81.6 ± 0.5	0.36
Waist-to-hip ratio	0.78 ± 0.002	0.77 ± 0.005	0.77 ± 0.002	0.77 ± 0.004	0.14
Clinical information					
Systolic blood pressure (mmHg)	113.7 ± 0.4	112.1 ± 0.8	111.5 ± 0.4	113.4 ± 0.7	0.005
Diastolic blood pressure (mmHg)	72.7 ± 0.3	71.8 ± 0.6	74.2 ± 0.3	76.1 ± 0.5	0.001
Pulse pressure (mmHg)	41.0 ± 0.3	41.0 ± 0.7	37.2 ± 0.3	37.0 ± 0.6	0.77
Laboratory results					
HDL cholesterol (mmol/L)	1.62 ± 0.01	1.62 ± 0.03	1.59 ± 0.01	1.60 ± 0.02	0.70
LDL cholesterol (mmol/L)	2.58 ± 0.02	2.52 ± 0.05	2.63 ± 0.02	2.67 ± 0.04	0.14
Triglycerides (mmol/L)	0.89 ± 0.02	0.99 ± 0.03	0.99 ± 0.02	1.01 ± 0.03	0.13
Total cholesterol (mmol/L)	4.54 ± 0.03	4.51 ± 0.06	4.72 ± 0.03	4.82 ± 0.05	0.11
Estimated insulin sensitivity (mg/dL)	11.5 ± 0.2	11.3 ± 0.3	14.0 ± 0.2	13.4 ± 0.3	0.44
eGFR ($mL/min/1.73\ m^2$)	95.5 ± 0.5	98.4 ± 1.1	96.6 ± 0.6	97.3 ± 1.0	0.17

All models were adjusted for age, visit number, menopause status, diabetes, baseline values of the outcome of interest, the interaction between diabetes and visit, and the interaction between diabetes and menopause. All clinical information models were further adjusted for use of antihypertensive medications. The model examining LDL cholesterol was adjusted further for use of lipid-lowering medications. eGFR, estimated glomerular filtration rate. *For diabetes∗menopause interaction.

Indeed, a hypothesized mechanism for the diabetes-menopause interaction is the promotion of ovarian maturation by exogenous insulin, which may contribute to greater ovarian dysfunction and the potential early ovarian aging in type 1 diabetes (22,28).

This potential earlier ovarian aging probably does not manifest as premature menopause in type 1 diabetes, because age at menopause does not seem to differ by diabetes status. A recent comparison of 140 postmenopausal women with type 1 diabetes with 5,426 women without diabetes in the Ovarian Ageing in Type 1 Diabetes Mellitus (OVADIA) study found no difference in the mean ± SD age at natural menopause: 49.8 ± 4.7 years in women with type 1 diabetes versus 49.8 ± 4.1 years in women without diabetes (29). These data are consistent with our finding of no difference in age at natural menopause among women in our study cohort, and the ages at menopause reported in the OVADIA study are very similar to our findings in both women with type 1 diabetes (50 ± 6 years) and women without diabetes (50 ± 8 years). It therefore seems unlikely that the interaction between type 1 diabetes and menopause can be explained by earlier menopause.

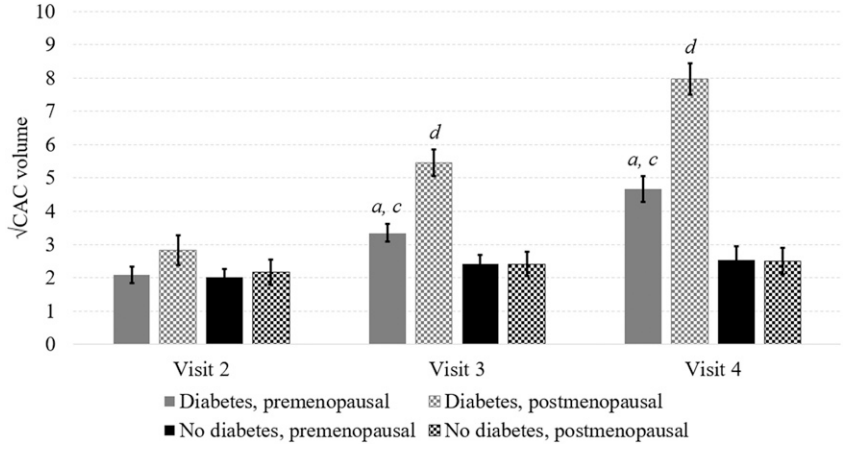

Figure 2—Least squares mean CAC volumes by diabetes status, menopause status, and follow-up visit after adjusting for age, baseline CAC, blood pressure, ASCVD risk score, use of antihypertensive medications, and self-reported ovarian dysfunction (n = 636 women). [a]$P < 0.05$, premenopausal vs. postmenopausal women, diabetes only; [c]$P < 0.05$, diabetes status in premenopausal women only; [d]$P < 0.05$, diabetes status in postmenopausal women only; no significant relationship for postmenopausal vs. premenopausal women without diabetes.

Before age 40, women with type 1 diabetes have a reported 40-fold higher risk of death from CVD than women without diabetes, largely because of the extremely low risk of CVD-related mortality in women without diabetes who are under age 40 (7). The CACTI study enrolled relatively young women at baseline, with the mean ± SD age of premenopausal women with diabetes being 34 ± 8 years and of those without diabetes, 36 ± 8 years. Because CAC becomes detectable only as the subclinical atherosclerosis process progresses and more complex lesions develop, it is likely that the low CAC levels among nondiabetic women in the CACTI study will increase over time as the cohort ages and women in the earlier stages of atherosclerosis develop calcified lesions.

This study has several limitations that should be noted when interpreting the

results. First, menstrual history, menopause status, and age at menopause were self-reported. This may lead to some misclassification, although it is unlikely to differ by diabetes status. Second, loss to follow-up occurred during the study period, and although the use of repeated-measures modeling allows for the inclusion of study participants who are missing visit-level data, baseline characteristics could have been associated with subsequent loss to follow-up. However, our comparison of women who completed all four study visits with those who completed fewer than four study visits revealed few differences between the two groups.

Changes over time in the study protocol and in assays used to measure cardiovascular biomarkers limited the availability of several risk factors that would have been useful to examine in the context of menopause and subclinical atherosclerosis. Specifically, we were unable to examine hs-CRP, adiponectin, or circulating white blood cell count in our models, as these assays were not completed at all study visits. These biomarkers indicate inflammation and are associated with both coronary artery disease (30) and CAC (31), although we previously showed that hs-CRP was not associated with CAC progression in the CACTI study (32).

Finally, although CAC is a proxy for the burden of subclinical atherosclerosis, it may not fully reflect the underlying burden of soft plaque. Nevertheless, CAC has predicted future cardiovascular events and adverse outcomes in a number of populations (33,34), including people with type 1 diabetes (5,6,35).

In addition to these limitations, this study has a number of strengths. This cohort includes a contemporaneous control group of women without diabetes, allowing for comparisons over time by diabetes status. The cohort is well characterized and has had excellent follow-up. Further, the age range of the participants in this study and the follow-up duration has allowed for a longitudinal examination of cardiovascular risk factors across the menopausal transition, in contrast to many studies that have relied on a cross-sectional comparison of premenopausal and postmenopausal women.

It has already been established that premenopausal women with type 1 diabetes lose the cardiovascular protection that women without diabetes have, and the CACTI study provides evidence that menopause increases CVD risk more in women with type 1 diabetes than in women without diabetes. This increase in risk is not explained by changes to traditional cardiovascular risk factors. Given that type 1 diabetes incidence is increasing globally by 3–5% per year (36–39), and that improved treatment has increased longevity (40), a growing number of women with type 1 diabetes are living through menopause and into older age. It is imperative to examine how diabetes and sex-specific risk factors may interact to affect cardiovascular risk in this growing population, and how treatments could modify this risk.

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Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. A.K. conducted all analyses and wrote the manuscript. A.K., C.S., E.W., and R.S. recruited study participants, collected data, and checked data quality. L.P. designed the analytic plan and interpreted data. A.A. measured, analyzed, and interpreted data. J.S.-B. conceived and directed the study and wrote and reviewed the manuscript. All authors reviewed and approved the final manuscript. J.S.-B. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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References

1. Groban L, Lindsey SH, Wang H, Alencar AK. Sex and gender differences in cardiovascular disease. In *Sex Differences in Physiology*. Neigh G, Mitzelfelt M, Eds. Academic Press (Elsevier), London, U.K., 2016, p. 61–87
2. Maas AH, Appelman YEA. Gender differences in coronary heart disease. Neth Heart J 2010;18:598–602
3. Snell-Bergeon JK, Hokanson JE, Jensen L, et al. Progression of coronary artery calcification in type 1 diabetes: the importance of glycemic control. Diabetes Care 2003;26:2923–2928
4. Budoff M, Backlund JC, Bluemke DA, et al.; DCCT/EDIC Research Group. The association of coronary artery calcification with subsequent incidence of cardiovascular disease in type 1 diabetes: the DCCT/EDIC trials. JACC Cardiovasc Imaging 2019;12:1341–1349
5. Guo J, Erqou SA, Miller RG, Edmundowicz D, Orchard TJ, Costacou T. The role of coronary artery calcification testing in incident coronary artery disease risk prediction in type 1 diabetes. Diabetologia 2019;62:259–268
6. Lovshin JA, Bjornstad P, Lovblom LE, et al. Atherosclerosis and microvascular complications: results from the Canadian Study of Longevity in Type 1 Diabetes. Diabetes Care 2018;41:2570–2578
7. Laing SP, Swerdlow AJ, Slater SD, et al. Mortality from heart disease in a cohort of 23,000 patients with insulin-treated diabetes. Diabetologia 2003;46:760–765
8. Dabelea D, Kinney G, Snell-Bergeon JK, et al.; Coronary Artery Calcification in Type 1 Diabetes Study. Effect of type 1 diabetes on the gender difference in coronary artery calcification: a role for insulin resistance? The Coronary Artery Calcification in Type 1 Diabetes (CACTI) Study [published correction appears in Diabetes 2004;53:2177]. Diabetes 2003;52:2833–2839
9. Colhoun HM, Rubens MB, Underwood SR, Fuller JH. The effect of type 1 diabetes mellitus on the gender difference in coronary artery calcification. J Am Coll Cardiol 2000;36:2160–2167
10. Matthews KA, Kuller LH, Sutton-Tyrrell K, Chang YF. Changes in cardiovascular risk factors during the perimenopause and postmenopause and carotid artery atherosclerosis in healthy women. Stroke 2001;32:1104–1111
11. de Ferranti SD, de Boer IH, Fonseca V, et al. Type 1 diabetes mellitus and cardiovascular disease: a scientific statement from the American Heart Association and American Diabetes Association. Circulation 2014;130:1110–1130
12. Maahs DM, Hokanson JE, Wang H, et al. Lipoprotein subfraction cholesterol distribution is proatherogenic in women with type 1 diabetes and insulin resistance. Diabetes 2010;59:1771–1779
13. Millstein RJ, Pyle LL, Bergman BC, et al. Sex-specific differences in insulin resistance in type 1 diabetes: the CACTI cohort. J Diabetes Complications 2018;32:418–423
14. Derby CA, Crawford SL, Pasternak RC, Sowers M, Sternfeld B, Matthews KA. Lipid changes during the menopause transition in relation to age and weight: the Study of Women's Health Across the Nation. Am J Epidemiol 2009;169:1352–1361
15. Matthews KA, Crawford SL, Chae CU, et al. Are changes in cardiovascular disease risk factors in midlife women due to chronological aging or to the menopausal transition? J Am Coll Cardiol 2009;54:2366–2373
16. Hokanson JE, MacKenzie T, Kinney G, et al. Evaluating changes in coronary artery calcium: an analytic method that accounts for interscan variability. AJR Am J Roentgenol 2004;182:1327–1332

17. Snell-Bergeon JK, Dabelea D, Ogden LG, et al. Reproductive history and hormonal birth control use are associated with coronary calcium progression in women with type 1 diabetes mellitus. J Clin Endocrinol Metab 2008;93: 2142–2148
18. Goff DC Jr, Lloyd-Jones DM, Bennett G, et al.; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [published correction appears in Circulation 2014;129(Suppl. 2): S74–S75]. Circulation 2014;129(Suppl. 2):S49–S73
19. Rosano GMC, Vitale C, Marazzi G, Volterrani M. Menopause and cardiovascular disease: the evidence. Climacteric 2007;10(Suppl. 1):19–24
20. Woodard GA, Brooks MM, Barinas-Mitchell E, Mackey RH, Matthews KA, Sutton-Tyrrell K. Lipids, menopause, and early atherosclerosis in Study of Women's Health Across the Nation Heart women. Menopause 2011;18:376–384
21. de Kat AC, Dam V, Onland-Moret NC, Eijkemans MJC, Broekmans FJM, van der Schouw YT. Unraveling the associations of age and menopause with cardiovascular risk factors in a large population-based study. BMC Med 2017;15:2
22. Wellons MF, Matthews JJ, Kim C. Ovarian aging in women with diabetes: an overview. Maturitas 2017;96:109–113
23. Solomon CG, Hu FB, Dunaif A, et al. Menstrual cycle irregularity and risk for future cardiovascular disease. J Clin Endocrinol Metab 2002;87:2013–2017
24. Soto N, Iñiguez G, López P, et al. Anti-Mullerian hormone and inhibin B levels as markers of premature ovarian aging and transition to menopause in type 1 diabetes mellitus. Hum Reprod 2009;24:2838–2844
25. Kim C, Karvonen-Gutierrez C, Kong S, et al. Antimüllerian hormone among women with and without type 1 diabetes: the Epidemiology of Diabetes Interventions and Complications Study and the Michigan Bone Health and Metabolism Study. Fertil Steril 2016;106:1446–1452
26. de Kat AC, Gremmels H, Verhaar MC, Broekmans FJM, Yarde F. Early vascular damage in young women with DM-1 and its relation to anti-Müllerian hormone: a cross-sectional study. Int J Endocrinol 2016;2016:1487051
27. Yarde F, Spiering W, Franx A, et al.; OVADIA Study Group. Association between vascular health and ovarian ageing in type 1 diabetes mellitus. Hum Reprod 2016;31:1354–1362
28. Kim C, Cleary PA, Cowie CC, et al.; DCCT/EDIC Research Group. Effect of glycemic treatment and microvascular complications on menopause in women with type 1 diabetes in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) cohort. Diabetes Care 2014;37: 701–708
29. Yarde F, van der Schouw YT, de Valk HW, et al.; OVADIA Study Group. Age at menopause in women with type 1 diabetes mellitus: the OVADIA study. Hum Reprod 2015;30:441–446
30. Pai JK, Pischon T, Ma J, et al. Inflammatory markers and the risk of coronary heart disease in men and women. N Engl J Med 2004;351:2599–2610
31. Maahs DM, Ogden LG, Kinney GL, et al. Low plasma adiponectin levels predict progression of coronary artery calcification. Circulation 2005; 111:747–753
32. Alman AC, Kinney GL, Tracy RP, et al. Prospective association between inflammatory markers and progression of coronary artery calcification in adults with and without type 1 diabetes. Diabetes Care 2013;36:1967–1973
33. Gepner AD, Young R, Delaney JA, et al. Comparison of carotid plaque score and coronary artery calcium score for predicting cardiovascular disease events: the Multi-Ethnic Study of Atherosclerosis. J Am Heart Assoc 2017;6:e005179
34. Carr JJ, Jacobs DRJ Jr, Terry JG, et al. Association of coronary artery calcium in adults aged 32 to 46 years with incident coronary heart disease and death. JAMA Cardiol 2017;2:391–399
35. Guo J, Nunley KA, Costacou T, et al. Greater progression of coronary artery calcification is associated with clinically relevant cognitive impairment in type 1 diabetes. Atherosclerosis 2019;280:58–65
36. Mayer-Davis EJ, Lawrence JM, Dabelea D, et al.; SEARCH for Diabetes in Youth Study. Incidence trends of type 1 and type 2 diabetes among youths, 2002-2012. N Engl J Med 2017; 376:1419–1429
37. Negrato CA, Lauris JRP, Saggioro IB, et al. Increasing incidence of type 1 diabetes between 1986 and 2015 in Bauru, Brazil. Diabetes Res Clin Pract 2017;127:198–204
38. Onda Y, Sugihara S, Ogata T, Yokoya S, Yokoyama T, Tajima N; Type 1 Diabetes (T1D) Study Group. Incidence and prevalence of childhood-onset type 1 diabetes in Japan: the T1D study. Diabet Med 2017;34:909–915
39. Fox DA, Islam N, Sutherland J, Reimer K, Amed S. Type 1 diabetes incidence and prevalence trends in a cohort of Canadian children and youth. Pediatr Diabetes 2018;19:501–505
40. Miller RG, Secrest AM, Sharma RK, Songer TJ, Orchard TJ. Improvements in the life expectancy of type 1 diabetes: the Pittsburgh Epidemiology of Diabetes Complications study cohort. Diabetes 2012;61:2987–2992