Imaging and Diagnostic Testing

Coronary vascular dysfunction in premenopausal women with diabetes mellitus

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Background Diabetes mellitus abolishes the sex differential in coronary artery disease morbidity and mortality in premenopausal women. This finding is independent of other diabetes-associated risk factors, suggesting that other mechanisms such as impaired coronary vascular function may contribute to the increased cardiovascular risk in women with diabetes. The objective of this study was to investigate the effect of diabetes on coronary vascular function in premenopausal women.

Methods We studied 13 premenopausal women with diabetes (aged 41 ± 10 years) who were free of overt cardiovascular complications, and 21 control women (12 age-matched and 9 postmenopausal [aged 56 ± 8 years]). We used [^{13}N]-ammonia as the flow tracer and positron emission testing to measure myocardial blood flow (MBF) at rest, during maximal hyperemia, and in response to cold pressor testing.

Results Baseline MBF was lower in the postmenopausal controls, reflecting the differences in cardiac work and oxygen demand as assessed by the rate-pressure product. However, baseline MBFs were similar in the 3 groups after normalization for differences in the rate-pressure product. During hyperemia, MBF increased and coronary vascular resistance decreased significantly in the 3 groups. However, the increase (from baseline) in MBF in the women with diabetes (164% ± 58%) was less than in the premenopausal controls (258% ± 81%, $P = .021$), but not significantly different from the postmenopausal control women (204% ± 104%, $P = .51$). Likewise, the increase in MBF in response to cold pressor testing in the women with diabetes (24% ± 19%) was significantly lower than in the premenopausal controls (60% ± 39%, $P = .013$), but similar to that in postmenopausal control women (27% ± 15%, $P = .97$). These differences persisted after adjusting for age and diabetes-associated metabolic abnormalities.

Conclusions These results demonstrate reduced coronary vasodilator function and impaired response of resistance vessels to increased sympathetic stimulation in premenopausal women with diabetes, similar to those observed in healthy postmenopausal women in whom the sex differential in coronary artery disease morbidity and mortality is no longer present. (Am Heart J 2002;144:711-8.)

Coronary artery disease (CAD) is the leading cause of death among women in the Unites States, accounting for 28% of all deaths.[1] The incidence of coronary artery disease is very low among premenopausal women; however, there is a sharp increase with age.[1-3] Among women in their fifth decade, the incidence of CAD is half that of men of the same age. By the sixth decade, however, women and men have the same incidence of CAD.[1,3] The disparity between premenopausal women and men of similar age generally has been ascribed to the cardioprotective effect of female sex hormones.

Evidence that diabetes mellitus abolishes the sex differential in CAD morbidity and mortality in premenopausal women has been consistent.[1,4] Indeed, population-based studies have shown that diabetes imposes a greater risk of CAD in women than in men.[4] Women with diabetes also have a higher incidence of myocardial infarction, and are more likely to die after myocardial infarction, than either men or women without diabetes.[5] Exactly how diabetes mellitus obviates the cardiovascular protective effects of female sex hor-

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Table I. Baseline characteristics of study population

Variable	Premenopausal women with diabetes (n = 13)	Premenopausal control women (n = 12)	Postmenopausal control women (n = 9)
Age (y)	41 ± 10†	40 ± 9*	56 ± 8
Body mass index (kg/m^2)	27 ± 5	24 ± 4	25 ± 2
Type 1/type 2	7:6	–	–
Duration of diabetes (y)	15 ± 14	–	–
Fasting blood glucose (mg/dL)	158 ± 81†	75 ± 15	98 ± 17
Glycohemoglobin (%)*	10.5 ± 3.0	–	–
Total cholesterol (mg/dL)	192 ± 37	164 ± 21	200 ± 22
HDL-cholesterol (mg/dL)	49 ± 11‡	61 ± 11	67 ± 10
LDL-cholesterol (mg/dL)	115 ± 31	86 ± 28	115 ± 21
Cholesterol/HDL-cholesterol	4.1 ± 1.3‡	2.8 ± 0.9	3.0 ± 0.4
Triglycerides (mg/dL)	140 ± 98	85 ± 30	90 ± 26

*Glycohemoglobin values in the women with diabetes are average of 4 years.
†$P = .001$ versus postmenopausal women.
‡$P < .05$ versus both groups of controls.

mones in premenopausal women is not well understood. Indeed, the loss of the natural sex advantage in women with diabetes is independent of other diabetes-associated risk factors. After adjusting for differences in hypertension, dyslipidemia, and obesity, the risk of cardiovascular death remains considerably higher in women with diabetes compared with men or women without diabetes.[1,4] This suggests that other mechanisms contribute to the increased cardiovascular risk among women with diabetes. One such mechanism may involve the adverse effect of diabetes on vascular function and, in particular, endothelial function, thereby increasing the potential for coronary vasoconstriction and thrombosis. This study investigated the effect of diabetes on coronary vascular function in premenopausal women. We used positron emission tomographic (PET) imaging to measure myocardial blood flow at rest, during maximal pharmacologic vasodilation, and in response to sympathetic stimulation by the CPT. The blood flow response in premenopausal women with diabetes was compared with that observed in age-matched and postmenopausal healthy women.

Methods

Study population

We studied 13 premenopausal women with type 1 or type 2 diabetes mellitus, aged 24 to 52 years (Table I). The duration of diabetes ranged from 1 to 44 years, averaging 15 ± 14 years. We also studied 2 control populations consisting of 12 age-matched and 9 postmenopausal (56 ± 8 years, not on hormone replacement therapy) women without diabetes. Inclusion criteria for the postmenopausal control women were (1) a serum estradiol level <20 pg/mL, (2) total estrogen level <5 ng/dL, (3) estrone level <4 ng/dL, and (4) cessation of menses for ≥1 year. None of the participants were on hormone replacement therapy. Each subject was evaluated with a careful history and had a normal physical examination and resting echocardiogram. Additionally, the diabetic women were required to have a negative maximal treadmill exercise test and no evidence of regional wall motion abnormalities on stress echocardiography imaging. Exclusion criteria for both the subjects with diabetes and the healthy control volunteers included a history of uncontrolled hypertension, cardiac or pulmonary disease, cerebrovascular or peripheral vascular disease, and serologic evidence of hepatic or renal dysfunction. The women with diabetes did not have evidence of autonomic neuropathy, as assessed by [^{11}C]hydroxyephedrine and PET,[6] nor did they have evidence of left ventricular dysfunction or hypertrophy on 2-dimensional echocardiography. Three of the 6 women with type 2 diabetes were on insulin therapy. Five women with diabetes had mild to moderate diabetic retinopathy. All women with diabetes had normal creatinine and blood urea nitrogen levels, and 2 patients had evidence of microalbuminuria. Two women with diabetes had a history of mild hypertension. None of the subjects were smokers. All women in the study had a low probability of CAD based on the absence of cardiovascular symptoms and a normal resting echocardiogram.

Study protocol

The Human Investigation Committees of Wayne State University and UCLA School of Medicine approved the study protocol, and all participants gave written informed consent. Myocardial blood flow was assessed through the use of a whole-body PET tomograph (Siemens/CTI EXACT HR, Knoxville, Tenn).

All subjects refrained from caffeine-containing beverages or theophylline-containing medications for 24 hours before each hospital visit. Two women with diabetes were receiving a calcium-channel blocker for mild hypertension and 5 patients were receiving a low-dose converting enzyme inhibitor for mild microalbuminuria. All subjects were instructed to stop

these medications for 24 hours before the test. One patient was using contraceptive medication (medroxyprogesterone acetate). All subjects were studied in the fasted state.

Assessment of myocardial blood flow

With [^{13}N]ammonia used as the flow tracer, myocardial blood flow was measured at rest, during adenosine- or dipyridamole-induced hyperemia, and in response to the CPT, as described previously.[7,8] A 20-minute transmission scan was acquired for correction of photon attenuation. Beginning with the intravenous bolus administration of [^{13}N]ammonia (0.286 mCi/kg), serial images were acquired for 20 minutes. Thirty minutes later, adenosine (0.14 mg/kg/min) or dipyridamole (0.56 mg/kg) was infused intravenously for 4 minutes. As shown by Chan et al,[7] the magnitude of hyperemic myocardial blood flow produced by adenosine and by dipyridamole is virtually identical. Two minutes into the adenosine infusion or 4 minutes after dipyridamole administration, a second dose of [^{13}N]ammonia was injected and images were recorded in the same acquisition sequence. Thirty minutes later, a CPT was performed by immersing the patient's hand and forearm in ice water (equal parts of ice and water at 0°C-2°C) for 2 minutes. Forty-five seconds into the CPT, a third dose of [^{13}N]ammonia was injected and images were recorded in the same acquisition sequence. In patients undergoing dipyridamole-stress, the CPT was performed first to avoid the potential interference with the long biological half time of dipyridamole. The heart rate, systemic blood pressure, and 12-lead echocardiogram were recorded at baseline and throughout the infusion of adenosine and the CPT.

Data analysis

To quantify regional myocardial blood flow, sectorial regions of interest encompassing the left anterior descending, circumflex, and right coronary artery territories were automatically assigned to each of 4 mid-ventricular short-axis slices of the [^{13}N]ammonia images, as previously described.[8,9] An additional small circular region of interest was manually placed in the center of the left ventricular blood pool of each image set to obtain the arterial input function. The corresponding regions of interest were then copied to the entire [^{13}N]ammonia image sequence, and regional myocardial tissue and blood pool time-activity curves were obtained. In each vascular territory, a single time-activity curve was obtained by averaging the corresponding [^{13}N]ammonia data in adjacent ventricular planes. Regional myocardial blood flow was then calculated by fitting the [^{13}N]ammonia time-activity curves with a previously validated 2- or 3-compartment tracer kinetic model.[10,11] These 2 tracer kinetic models produce accurate, reproducible, and comparable measurements of myocardial blood flow.[12] An index of coronary vascular resistance was calculated by dividing the mean aortic blood pressure by myocardial blood flow. The coronary vasodilator reserve was defined as the ratio between hyperemic and basal myocardial blood flow.

Laboratory analyses

Venous plasma and serum samples were taken after an overnight fast. Plasma glucose was measured by the glucose oxidase method. Serum cholesterol and triglyceride concentrations were measured through the use of standard enzymatic methods. High-density lipoprotein (HDL) cholesterol was measured with the Equal HDL Direct method and the Technicon DAX System (Bayer Corp, Tarrytown, NY). Low-density lipoprotein (LDL) cholesterol was calculated through the use of the Friedewald formula.[13] Glycohemoglobin level was measured by high-performance liquid chromatography (reference value 4%-8%).

Statistical analysis

Data are presented as mean ± SD. Differences among multiple groups were investigated with repeated measures of analysis of variance, followed by a Tukey test to allow pairwise testing for differences between groups. A multivariate analysis of variance design was used to determine predictors of changes in myocardial blood flow during maximal hyperemia and in response to CPT, and to investigate differences in adjusted myocardial blood flow between groups (SPSS advanced statistics, SPSS Inc, Chicago, Ill). An alpha of 0.05 was used to define statistical significance. P values $<.1$ also are reported, as they were taken to indicate trends toward significance.

Results

Baseline characteristics

Table I summarizes the baseline characteristics of the study patients. As expected, the postmenopausal women were older and the premenopausal women with diabetes had a higher plasma glucose level. Additionally, the women with diabetes had a lower HDL-C and a higher cholesterol/HDL-C ratio compared with both groups of control women.

Systemic hemodynamics

At baseline, the heart rate, systolic blood pressure, and rate-pressure product were slightly higher in the women with diabetes than in both groups of controls. The heart rate and rate-pressure product increased significantly with the CPT and the infusion of adenosine or dipyridamole in the 3 groups studied (Table II). Likewise, systolic and mean aortic blood pressure increased significantly during the CPT but remained unchanged during the infusion of adenosine or dipyridamole in the 3 groups.

Predictors of changes in myocardial blood flow in multivariable analysis

Because there were differences in baseline characteristics between the groups, a multivariable analysis was performed to determine independent predictors of the change (from baseline) in myocardial blood flow during maximal hyperemia and in response to the CPT. Variables considered in the model were age, fasting blood glucose, HDL-C, and cholesterol/HDL-C ratio. In the final model, only age ($F = 6.26$, $P = .004$), and fasting blood glucose ($F = 3.32$, $P = .036$) were inde-

Table II. Systemic hemodynamics in the women with diabetes and in the healthy controls

Hemodynamic measure	Baseline	CPT	Peak hyperemia
Women with diabetes (n = 13)			
Heart rate (beats/min)	76 ± 10	85 ± 7*	106 ± 12*
Blood pressure (mm Hg)			
Systolic	133 ± 21†	149 ± 28*	132 ± 32
Mean aortic	91 ± 13	100 ± 14*	86 ± 16
Rate-pressure product	10.2 ± 0.24†	12.8 ± 0.27*†	14.2 ± 0.42*
Premenopausal controls (n = 12)			
Heart rate (beats/min)	69 ± 7	76 ± 16*	99 ± 9*
Blood pressure (mm Hg)			
Systolic	116 ± 20	132 ± 26*	113 ± 15
Mean aortic	81 ± 14	96 ± 19*	80 ± 11
Rate-pressure product	0.80 ± 0.15	10.1 ± 0.30*	11.3 ± 0.20*
Postmenopausal controls (n = 19)			
Heart rate (beats/min)	65 ± 8	76 ± 12*	92 ± 10*
Blood pressure (mm Hg)			
Systolic	107 ± 7	149 ± 18*	106 ± 20
Mean aortic	78 ± 5	104 ± 8*	78 ± 11
Rate-pressure product	0.70 ± 0.10	11.2 ± 0.16*	0.97 ± 0.18*

*$P < .05$ versus corresponding value at baseline.
†$P < .05$ versus both groups of controls.

pendent predictors of the changes in myocardial blood flow. Cholesterol/HDL-C ratio (F = 2.09, $P = .131$) and HDL-C (F = 0.87, $P = .588$) were not significant predictors of the changes in myocardial blood flow. Accordingly, myocardial blood flows during maximal hyperemia and in response to the CPT were adjusted for the baseline differences in age and blood glucose between the groups.

Regional myocardial blood flow and coronary vascular resistance

Baseline. The baseline blood flow was regionally homogeneous in the women with diabetes and in both groups of controls. Baseline blood flow was lower in the postmenopausal women without diabetes, reflecting the differences in cardiac work and oxygen demand as assessed by the rate-pressure product. However, baseline blood flow was similar in the 3 groups studied after adjusting for differences in the rate-pressure product, age, and fasting blood glucose (Table III).

Blood flow response to adenosine or dipyridamole infusion. During hyperemia, blood flow was regionally homogeneous (ie, no regional perfusion defects) in the women with diabetes and in both groups of controls, a finding that argues against flow-limiting coronary stenoses. Myocardial blood flow increased and coronary vascular resistance decreased significantly in the 3 groups studied (Table III). However, peak myocardial blood flow was lower in the women with diabetes and in the postmenopausal women than in the premenopausal control women (Table III). Coronary vasodilator reserve was lower in the women with diabetes than in the premenopausal controls (Figure 1). These differences persisted after adjusting for age and fasting blood glucose. However, these differences were not significantly affected by the duration of diabetes ($P = .99$). A post hoc analysis demonstrated a 61% power to detect a difference in means across the 3 groups studied.

Blood flow response to the CPT. During the CPT, myocardial blood flow was regionally homogeneous and increased significantly in the 3 groups studied (Table III). However, the magnitude of flow increase was significantly lower in the women with diabetes (24% ± 19%) and in the postmenopausal women (27% ± 15%) than in the premenopausal control women (60% ± 39%) ($P < .05$ vs both groups) (Figure 2). The coronary vascular resistance index fell only in the premenopausal control women. These differences persisted after adjusting for age and fasting blood glucose. However, these differences were not significantly affected by the duration of diabetes ($P = .87$). A post hoc analysis demonstrated a 76% power to detect a difference in means across the 3 groups studied.

Differences between women with type 1 and type 2 diabetes

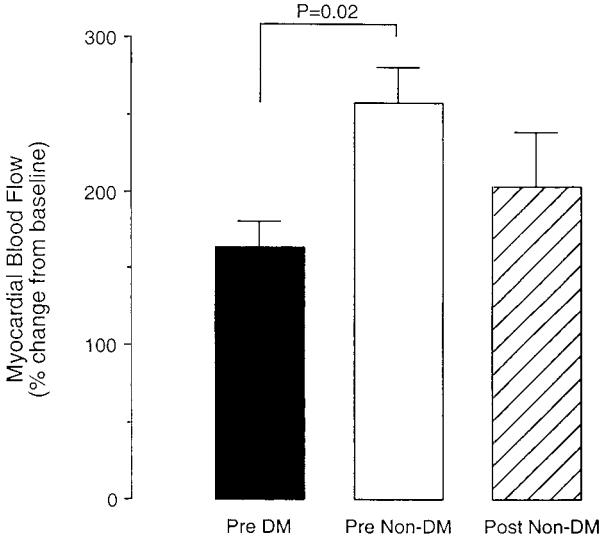
Table IV summarizes the comparison between the women with type 1 and type 2 diabetes. As expected, women with type 1 diabetes were younger and had a longer duration of the disease than those with type 2

Table III. Myocardial blood flow and coronary vascular resistance in the women with diabetes and in the healthy controls

Variable	Premenopausal women with diabetes (n = 13)	Premenopausal control women (n = 12)	Postmenopausal control women (n = 9)
Myocardial blood flow (ml/min/g)			
Baseline	1.02 ± 0.13	0.94 ± 0.15	0.75 ± 0.14*
Baseline corrected	1.02 ± 0.22	1.21 ± 0.28	1.09 ± 0.19
Cold pressor test	1.25 ± 0.28†	1.49 ± 0.42†	0.95 ± 0.15
Peak hyperemia	2.64 ± 0.52†	3.27 ± 0.43†‡	2.22 ± 0.56†
Coronary flow reserve	2.60 ± 0.62	3.58 ± 0.81§	3.08 ± 1.08
Coronary vascular resistance (mm Hg/ml/min/g)			
Baseline	92 ± 14	88 ± 17	107 ± 21
Cold pressor test	85 ± 23¶§	69 ± 14*	112 ± 16
Peak hyperemia	35 ± 11†¶	26 ± 6†	37 ± 11

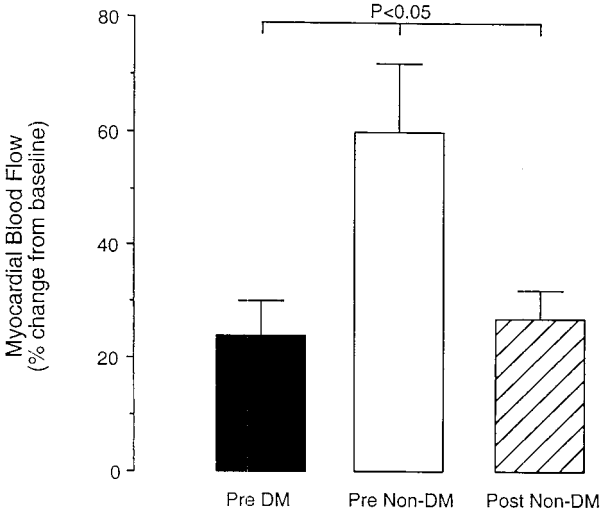
*$P < .05$ versus both groups of premenopausal women.
†$P < .05$ versus corresponding value at baseline.
‡$P < .05$ versus premenopausal women with diabetes and postmenopausal controls.
§$P < .05$ versus premenopausal women with diabetes.
¶$P < .05$ versus both groups of controls.

Figure 1



Bar graph showing the changes in MBF in response to the infusion of adenosine or dipyridamole in the women with diabetes and the control women.

Figure 2



Bar graph showing the changes in MBF in response to the CPT in the women with diabetes and the control women.

diabetes, whereas women with type 2 diabetes had a higher body mass index than those with type 1 diabetes. Glycemic control was comparable in both groups of diabetics. Additionally, LDL-C and cholesterol/HDL-C ratio were higher in the subjects with type 2 diabetes. However, resting blood flow was similar in the 2 groups (1.01 ± 0.18 vs 1.02 ± 0.07 mL/min/g in type 1 and type 2 diabetics respectively, $P = .83$), as was its change during adenosine (177% ± 54% vs 150% ± 64% in type 1 and type 2 diabetics respectively, $P = .45$) and the CPT (34% ± 16% vs 22% ± 6% in type 1 and type 2 diabetics respectively, $P = .16$).

Effect of glycemic control on myocardial blood flow

To determine the effect of glycemic control on the myocardial blood flow responses to the CPT and adenosine, the diabetic subjects were divided into 2 groups, based on their glycohemoglobin levels. Group

Table IV. Comparison between women with type 1 and type 2 diabetes

Variable	Type 1 diabetics (n = 7)	Type 2 diabetics (n = 6)
Age (y)	36 ± 11	44 ± 5
Body mass index (kg/m^2)	27 ± 10	35 ± 8
Duration of diabetes (y)	22 ± 14*	6 ± 5
Fasting blood glucose (mg/dL)*	142 ± 57	177 ± 105
Glycohemoglobin (%)*	10 ± 4	10 ± 1
Total cholesterol (mg/dL)	175 ± 30	211 ± 36
HDL-cholesterol (mg/dL)	51 ± 14	46 ± 5
LDL-cholesterol (mg/dL)	99 ± 20†	133 ± 33
Cholesterol/HDL-cholesterol	3.7 ± 1.5	4.5 ± 1.0
Triglycerides (mg/dL)	124 ± 126	156 ± 55
Creatinine (md/dL)	0.8 ± 0.4	0.7 ± 0.2
BUN (md/dL)	13 ± 3	12 ± 4
Urine albumin (μg/mg)	30 ± 41	8 ± 2
vWF antigen (%)	141 ± 67	125 ± 49

*P = .028 versus type 2.
†P = .04 versus type 2.

1 consisted of 6 patients with a glycohemoglobin level >10% (reference value 4%-8%), and Group 2 was composed of 7 patients with a glycohemoglobin level ≤10%. The 10% cutoff was chosen based on the fact that it represented the mean glycohemoglobin level for the entire group of diabetics. Table V summarizes these results. Overall, diabetic patients showed a significantly impaired response to the CPT compared with the premenopausal controls (F = 3.6, P = .02). The flow response to CPT was significantly lower among diabetics with poorer glycemic control than in the premenopausal controls (20% ± 8% vs 60% ± 39%, P = .04). The flow response to cold was higher in the diabetics with relatively "good" glycemic control than in those with "poorly" controlled diabetes, but the difference did not reach statistical significance (29% ± 7% vs 20% ± 8%, P = .09). In contrast, our preliminary findings suggest that the degree of glucose control does not appear to significantly affect the flow response to adenosine (Table V).

Discussion

Premenopausal women are at lower risk of coronary artery disease than are men of similar age.[3,14] Diabetes mellitus abolishes the sex differential in coronary artery disease morbidity and mortality.[1,4] Indeed, women with diabetes have a 2- to 4-fold increased risk of coronary artery disease than men, a finding that is independent of other diabetes-associated risk factors.[4] This suggests that other mechanisms contribute to the increased cardiovascular risk among women with diabetes. One such mechanism may involve the deleterious effect of diabetes on vascular function and, in particular, endothelial function,[6,15] thereby increasing the potential for coronary vasoconstriction and thrombosis.

Our findings provide direct evidence that premenopausal women with diabetes have a significantly impaired regulation of coronary vascular tone. In this study, coronary vasodilator reserve (reflecting primarily endothelium-independent coronary vasodilation) in premenopausal women with diabetes was decreased by 35% compared with premenopausal controls. Likewise, the magnitude of flow increase in response to the CPT (reflecting primarily endothelium-dependent coronary vasomotion) in premenopausal women with diabetes was decreased by 60% compared with premenopausal control women. The impaired blood flow response to the CPT in the women with diabetes was nearly identical to that observed in healthy postmenopausal women, in whom the sex differential is no longer present. Most importantly, the observed differences in myocardial blood flow were evident even after adjusting for baseline differences in age and diabetes-associated metabolic abnormalities.

Our results agree with those of recent investigations demonstrating impaired forearm and leg arterial vasoreactivity in premenopausal women with type 2 diabetes. Using Doppler flowmetry, Lim et al[16] showed impaired cutaneous vasodilation in response to acetylcholine (endothelium-dependent) and sodium nitroprusside (endothelium-independent). They reported that the magnitude of endothelium-dependent forearm vasodilation in premenopausal women with diabetes was reduced by 52% compared with healthy premenopausal women, but it was similar to the vasodilator response in healthy postmenopausal women (not on hormone replacement therapy). Additionally, they showed a 30% reduction in endothelium-independent vasodilation in the premenopausal women with diabetes compared with the healthy premenopausal controls. In keeping with these findings, Steinberg et al[17] demonstrated an even more dramatic reduction (~70%) in endothelium-dependent femoral artery vasodilation in premenopausal women with diabetes compared with healthy premenopausal women. However, they reported no differences in endothelium-independent femoral artery dilation between premenopausal women with diabetes and control women. Thus, our findings confirm and extend these observations in an important way by demonstrating similar abnormalities in vascular function in the coronary circulation of premenopausal women with diabetes.

The mechanisms by which diabetes removes the natural protective effects of female sex hormones on the coronary circulation in premenopausal women are not well understood. Estrogen, the predominant female sex hormone, facilitates coronary vasodilation by several mechanisms, including direct[18] and indirect[19] actions on vascular endothelial and smooth muscle cells

Table V. Effect of glycemic control on the myocardial blood flow responses to CPT and adenosine

Condition	Diabetics with GlycoHb >10% (n = 6)	Diabetics with GlycoHb ≤10% (n = 7)	Premenopausal controls (n = 12)	Postmenopausal controls (n = 9)
CPT (%)	20 ± 8*	29 ± 7	60 ± 39	27 ± 15†
Adenosine (%)	164 ± 80	163 ± 33	258 ± 81	204 ± 103

GlycoHb, Glycated hemoglobin.
*P = .04 versus premenopausal controls.
†P = .065 versus premenopausal controls.

that appear to result from the activation of estrogen receptors in the vessel wall.[20] Diabetes-associated hyperglycemia and other attendant metabolic abnormalities may interfere with one or more of these mechanisms. For example, hyperglycemia decreases estradiol-mediated nitric oxide production from cultured endothelial cells.[21] Additionally, hyperglycemia leads to increased formation of oxygen-derived free radicals that inactivate endothelium-derived NO[22,23] and, thus, interfere with endothelium-dependent vasodilation.[24] Insulin resistance and its associated hyperinsulinemia may also contribute to vascular dysfunction, especially among women with type 2 diabetes.[25,26]

In this study, we included women with type 1 and type 2 diabetes. Hyperglycemia is the hallmark of diabetes, but the defect underlying this metabolic abnormality differs in subjects with type 1 (ie, insulin deficient) and type 2 (ie, insulin resistant) diabetes. Despite this fundamental difference between subjects with type 1 and type 2 diabetes, the current data, as well as preliminary data from our laboratory in a larger number of patients with diabetes, including men, suggest that coronary blood flow abnormalities in these patients are similar even after adjusting known baseline metabolic differences.[27] Together, these data suggest that the presence of coronary vascular dysfunction in these patients is independent from the diabetes type. Thus, the similarities in coronary vascular dysfunction between the 2 groups would provide further support for a key role of hyperglycemia in the pathogenesis of vascular dysfunction in diabetes.

Study limitation

It is possible that occult atherosclerosis in the women with diabetes might have attenuated the maximal flow response to adenosine. However, we deliberately studied young asymptomatic women with diabetes, all of whom had normal maximal stress echocardiography, and none showed regional defects on rest-stress perfusion imaging. These findings argue against flow-limiting epicardial coronary stenoses in our healthy controls and in the subjects with diabetes.[28]

Conclusions

We have demonstrated that premenopausal women with diabetes show reduced coronary vasodilator function and significantly impaired response of resistance vessels to increased sympathetic stimulation. The impaired myocardial blood flow response to cold suggests an abnormality in endothelial function. More importantly, this vascular dysfunction in premenopausal women with diabetes is similar to that observed in healthy postmenopausal women in whom the sex differential is no longer present. This microvascular dysfunction may contribute to the pathogenesis of myocardial ischemia and to adverse cardiovascular events in women with diabetes.

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