Journal of the American College of Cardiology
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Published by Elsevier Science Inc.

Vol. 36, No. 7, 2000
ISSN 0735-1097/00/$20.00
PII S0735-1097(00)00986-4

The Effect of Type 1 Diabetes Mellitus on the Gender Difference in Coronary Artery Calcification

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OBJECTIVES To examine whether the gender difference in coronary artery calcification, a measure of atherosclerotic plaque burden, is lost in type 1 diabetic patients, and whether abnormalities in established coronary heart disease risk factors explain this.

BACKGROUND Type 1 diabetes abolishes the gender difference in coronary heart disease mortality because it is associated with a greater elevation of coronary disease risk in women than men. The pathophysiological basis of this is not understood.

METHODS Coronary artery calcification and coronary risk factors were compared in 199 type 1 diabetic patients and 201 nondiabetic participants of similar age (30 to 55 years) and gender (50% female) distribution. Only one subject had a history of coronary disease. Calcification was measured with electron beam computed tomography.

RESULTS In nondiabetic participants there was a large gender difference in calcification prevalence (men 54%, women 21%, odds ratio 4.5, $p < 0.001$), half of which was explained by established risk factors (odds ratio after adjustment = 2.2). Diabetes was associated with a greatly increased prevalence of calcification in women (47%), but not men (52%), so that the gender difference in calcification was lost ($p = 0.002$ for the greater effect of diabetes on calcification in women than men). On adjustment for risk factors, diabetes remained associated with a threefold higher odds ratio of calcification in women than men ($p = 0.02$).

CONCLUSIONS In type 1 diabetes coronary artery calcification is greatly increased in women and the gender difference in calcification is lost. Little of this is explained by known coronary risk factors. (J Am Coll Cardiol 2000;36:2160–7) © 2000 by the American College of Cardiology

Patients with type 1 diabetes have greatly elevated risks of coronary heart disease (CHD) (1). The elevation in risk compared to the general population is greater for women than men, so much so that the gender difference in CHD mortality is lost in patients with diabetes (2). Case-fatality rates for myocardial infarction and diabetic cardiomyopathy rates are higher in diabetic women than men but these factors alone are unlikely to explain the loss of the gender difference in CHD mortality (3,4). Whether the gender difference in coronary atherosclerosis itself is lost in diabetes is an important clinical question because strategies for reducing post-infarct mortality are different from those for reducing atherosclerosis. Definitive data on this question are sparse and conflicting. A greater increase in thoracic artery atherosclerosis in young hyperglycemic women than men has been observed at autopsy (5), but the gender difference in carotid intima-medial thickness is apparently preserved in patients with diabetes (6).

The increased risk of CHD in patients with diabetes is in part mediated through an elevation in established coronary risk factors. A possible explanation for the loss of the gender difference in CHD in patients with type 1 diabetes could be that the difference in coronary risk factors between those with and without diabetes is greater for women than men. Alternatively the effect of a given risk factor might be greater in the presence of diabetes in women but not in men. Establishing whether this is the case is important for the appropriate development of CHD prevention and therapeutic strategies in patients with diabetes.

The amount of coronary artery calcification (CAC) has a very high correlation ($r > 0.9$) with coronary atherosclerotic plaque burden, making it a useful measure of the extent of coronary atherosclerosis (7). Coronary artery calcification is accurately quantified by electron beam computerized tomography scanning (EBCT). The objectives of this study were to determine whether diabetes is associated with a loss of the gender difference in coronary artery calcification and, if so, to examine whether this could be explained by established coronary risk factors.

METHODS

Subjects. A random sample of type 1 diabetic men and women aged 30 to 55 years was taken from the diabetes registers of five London hospitals. Type 1 diabetes was defined by age of onset ≤25 years and insulin treatment within one year of diagnosis. A random sample of the general population, stratified to have a similar age and gender distribution to the patients with diabetes, was drawn from the lists of two London general practices. Subjects were included regardless of any history of heart disease. Pregnant women and patients on renal replacement therapy were excluded. Of 1,450 letters sent, 22% were returned as addressee unknown or gone away. Of the remainder, 53% of

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Manuscript received February 28, 2000; revised manuscript received June 2, 2000, accepted July 14, 2000.

Abbreviations and Acronyms

AER = Albumin excretion rate
BMI = body mass index
BP = blood pressure
CAC = coronary artery calcification
CHD = coronary heart disease
CV = coefficient of variation
EBCT = electron beam computerized tomography
HDL = high-density lipoprotein
LDL = low-density lipoprotein

patients with diabetes (57% of men, 49% of women) and 30% of the nondiabetic group (31% of men, 30% of women) agreed to take part. In all, 199 type 1 diabetic patients (95 women) and 201 nondiabetic men and women (107 women) were examined. Ethics Committee approval was obtained. All participants gave fully informed written consent prior to participation, having received full details of the study procedures.

Examination. Participants completed a standardized questionnaire. The average weekly consumption of alcohol units was calculated and smoking exposure was quantified in pack years. The duration and intensity of weekly walking, cycling, sporting and occupational activity was used to define low or high physical activity (below vs. at least 10 MJ energy expenditure per week) (8). Daily insulin dose was also noted. Three supine blood pressure (BP) recordings were made after 5 min rest using an Omron 705c oscillometric device. The mean of the second and third readings was used. Hypertension was defined as having a systolic BP $\geq$140 mm Hg or a diastolic BP $\geq$90 mm Hg or being on antihypertensive drugs. Obesity was defined as a body mass index (BMI) $\geq$30 kg/m^2. Waist and hip circumference were also recorded. The examiners were aware of the diabetic status of the participants.

EBCT scan. An Ultrafast CT scanner (IMATRON C-150XL) was used to quantify coronary calcification. Two sets of 20 transverse tomograms of 3-mm thickness were obtained from the lower margin of the bifurcation of the right branch of the pulmonary artery to the apex of the heart with the subject breathholding. A radiologist placed a region of interest around each potentially calcific lesion (peak density >130 Hounsfield U) within the right coronary, circumflex, left anterior descending and left main coronary arteries. The area and peak density of each lesion was measured. A density score of 1 to 4 was defined based on the peak density of the lesion; calcification score was then calculated as the product of the area of the lesion and its density score as described (9).

To be included in the calcification score a lesion had to have an area of at least 0.51 mm^2, i.e., two contiguous pixels and a peak density of at least 130 Hounsfield U. A total score for each artery and for the entire heart was calculated by summing the lesion scores. The radiation exposure was <1 mSv. All scans were scored by the same radiologist, who was blinded to the gender and the diabetes status of the subject. Based on a small repeatability study (n = 20) the within-observer agreement for the presence of any calcification was high (kappa = 0.84).

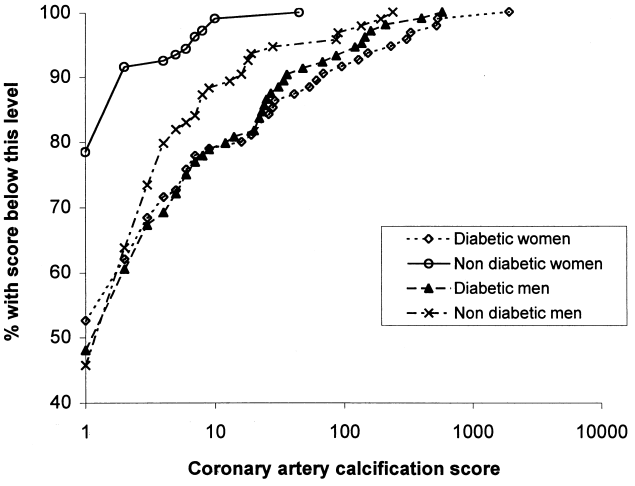

Figure 1. The cumulative frequency of coronary artery calcification score by diabetes status and gender.

Laboratory methods. After an overnight fast, blood samples were taken from patients and total cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides were measured using standard enzymatic colorimetric methods (intra-assay coefficient of variation [CV] = 1.6%, 2.6% and 2% respectively). HDL cholesterol was measured directly after stabilization of other lipoproteins and low-density lipoprotein (LDL) cholesterol was calculated by the Friedewald equation. HbA_{1c} was measured with a latex enhanced immunoassay (intra-assay CV 1.7%). Urinary albumin excretion was calculated from two timed overnight urine collections. Women who were menstruating were excluded from urinary albumin analyses (n = 54). Urinary albumin was measured with an immunoturbidimetric method (intra-assay CV 2.3%).

Statistical methods. Analyses were carried out with Stata 5. We examined whether there were differences in risk factors between diabetic and nondiabetic participants using multiple linear regression and logistic regression, adjusted for age. We tested whether the difference in risk factors between those with and without diabetes was the same for men and women by including a diabetes-by-gender interaction term in these models. This is equivalent to testing whether the gender difference in risk factors is altered by diabetes. Calcification scores (for the total heart) were positively skewed with a high frequency of zero values (Fig. 1). As data transformation would not have normalized this distribution, we used the nonparametric Mann Whitney *U* test to test for differences in coronary calcification score between those with and without diabetes for each gender. Logistic regression was used to examine the odds of having any calcification (a score >0) associated with diabetes, adjusting for covariates. All covariates were entered into the

Table 1. Sociodemographic and CHD Risk Factors According to Diabetes Status and Gender

	Men		Women	
	Nondiabetic	**Diabetic**	**Nondiabetic**	**Diabetic**
n	94	104	107	95
		Mean (SE)		
Age (yrs)	37.8 (0.04)	38.2 (0.4)	37.9 (0.3)	37.5 (0.5)
Diabetes duration (yrs)	—	23.1 (0.8)	—	23.7 (0.8)
HbA_{1c} % (Gm)§	5.3 (0.04)	8.4 (0.12)‡	5.3 (0.03)	8.9 (0.20)‡
Insulin dose per unit BMI/day		2.3 (0.07)		1.7 (0.05)
BMI kg/m^2	25.0 (0.3)	25.4 (0.3)	25.6 (0.5)	25.3 (0.4)
WHR	0.92 (0.01)	0.91 (0.01)	0.81 (0.01)	0.82 (0.01)
HDL cholesterol mmol/l	1.6 (0.04)	1.7 (0.04)†	1.8 (0.04)	2.0 (0.05)*
LDL cholesterol mmol/l	3.3 (0.11)	3.0 (0.1)*	3.0 (0.08)	2.8 (0.09)
Total cholesterol:HDL ratio	3.8 (0.13)	3.2 (0.1)‡	3.0 (0.09)	2.9 (0.09)
Triglyceride mmol/L (Gm)	1.4 (0.09)	1.2 (0.06)*	0.99 (0.05)	0.95 (0.04)
Systolic BP (mm Hg)	124 (1.3)	129 (1.1)*	111 (1.2)	120 (1.5)‡
Diastolic BP (mm Hg)	76 (1.0)	77 (0.8)	69 (0.8)	72 (0.9)*
		% SE		
% Obese	6 (2)	8 (3)	21 (4)	8 (3)†
% Hypertensive‖	20 (4)	27 (4)	6 (2)	16 (4)*
% AER ≥20 μg/min	4 (2)	22 (4)†	3 (2)	9 (3)
% Ever smoked	56 (5)	50 (5)	48 (5)	45 (5)
% Left school <19 yrs	63 (5)	44 (5)†	65 (5)	54 (5)
% Exercise score <10	73 (5)	82 (4)	86 (4)	85 (4)
% Drinking above 21 U/wk	40 (5)	24 (4)*	7 (3)	11 (3)

*$p < 0.05$; †$p < 0.01$; ‡$p < 0.001$ for the difference between those of the same gender with and without diabetes adjusted for age using regression analysis; §Gm = geometric mean; ‖Hypertension = systolic BP ≥ 140 mm Hg or diastolic BP ≥ 90 mm Hg or on treatment.

SE = standard error; AER = albumin excretion rate; BMI = body mass index; BP = blood pressure; HDL = high-density cholesterol; LDL = low-density cholesterol.

models simultaneously. We tested whether the odds of any calcification associated with diabetes were the same in men and women by including a diabetes-by-gender interaction term in the model. We examined whether the strength of the association between risk factors and coronary calcification, for a given level of the risk factor, was the same across the four diabetes-gender groups by including a risk factor-by-diabetes-gender category interaction term.

The effect of adjusting for these factors on the diabetes–gender interaction for calcification was also examined. The risk factors considered in these models are shown in Table 1. The correlation between body fat and BMI differs between men and women so that the validity of adjusting gender differences for BMI is debatable. Therefore the effect of adjusting for BMI in the above models is described separately. Risk factors with skewed distributions were normalized by the appropriate transformation before analysis.

RESULTS

Risk factor distribution by diabetes status and gender. One participant (a woman with diabetes) had a history of angina; none had had a myocardial infarction. Men and women with diabetes had higher HDL-cholesterol, lower LDL-cholesterol and lower triglycerides and total:HDL-cholesterol ratios than nondiabetic subjects (Table 1). Exclusion of the three subjects on lipid-lowering drugs did not affect this result. On adjustment for obesity, the differences in lipid profile between those with and without diabetes were unchanged in men but were attenuated to non-significance in women. This difference between men and women in the effect of diabetes was significant for total:HDL-cholesterol ratio ($p = 0.04$) and triglycerides ($p = 0.03$) but not LDL-cholesterol ($p = 0.2$) or HDL-cholesterol ($p = 0.6$). A higher daily insulin dose per unit BMI was observed in men than women (Table 1, $p = 0.001$ for the gender difference). However, a higher insulin dose was associated with a higher total:HDL-cholesterol ratio (correlation coefficient $r = 0.24$, $p < 0.001$). Thus sex differences in insulin dose cannot underlie the observation that diabetes is associated with a lower total:HDL cholesterol ratio in men but not in women.

The difference in BP between those with and without diabetes was greater in women (+8 mm Hg for systolic BP) than in men (+4 mm Hg, $p = 0.08$ for the interaction for systolic BP, $p = 0.02$ for diastolic BP). On adjustment for obesity this difference between men and women in the effect of diabetes on systolic BP was 5 mm Hg ($p = 0.03$ for the interaction). Few subjects were on blood-pressure-lowering drugs (2 nondiabetic men, 13 diabetic men, 3 nondiabetic women, 13 diabetic women). Thus the gender difference in the effect of diabetes on BP is not likely to be an artifact attributable to differential hypertension treatment rates. This was supported by the results of a censored regression analysis in which the diabetes-by-gender interaction for BP was examined with the BP in those on drugs affecting BP

Table 2. Prevalence of Coronary Calcification (Score > 0) by Diabetes Status and Gender

	Prevalence of Calcification		Odds Ratio for Calcification in Diabetic vs. Nondiabetic
	Diabetic	Nondiabetic	
Men	52%	54%	0.9 (0.5–1.6)
Women	47%	21%	3.5 (1.9–6.7)‡
Odds ratio for calcification, men vs. women	1.2 (0.7–2.0)	4.5 (2.4–6.5)‡	

‡$p < 0.001$.

censored to the right ($p = 0.05$ for the interaction for systolic BP, $p = 0.009$ for the interaction for diastolic BP). For the remaining risk factors, the diabetes-associated difference was similar in both genders. Adjustment for educational status, which differed between those with and without diabetes, did not affect any of these results.

CALCIFICATION SCORES. The cumulative frequency of calcification scores is shown in Figure 1. In the nondiabetic group there was a large gender difference in the prevalence of calcification (Table 2). In men diabetes was not associated with a higher prevalence of calcification, although among all men with calcification its severity was greater in those with diabetes ($p = 0.04$ Mann Whitney *U* test). In women diabetes was associated with both a greatly elevated severity of calcification ($p = 0.0001$ Mann Whitney *U* test) and prevalence of calcification (Table 2). Thus the odds ratio for calcification associated with diabetes was 3.9 times higher in women than men, adjusted for age ($p = 0.002$ for this diabetes-by-gender interaction), and as a result the gender difference in calcification prevalence was abolished in diabetic subjects. Adjustment for educational status did not affect this result.

RISK FACTORS ASSOCIATED WITH CORONARY CALCIFICATION. The association between risk factors and calcification adjusted for age is shown in Table 3. The strength of the associations of the various risk factors with calcification was similar among the four diabetes-gender groups for most risk factors, though our power to detect small differences in effect was limited. The odds ratios for alcohol consumption and physical activity differed significantly between diabetic women and nondiabetic men. The importance of this is doubtful, as the confidence intervals for these odds ratios were wide.

RISK FACTORS UNDERLYING THE GENDER DIFFERENCE IN CALCIFICATION IN THE NONDIABETIC GROUP. In the nondiabetic group adjustment for systolic BP, total cholesterol: HDL cholesterol, alcohol consumption and smoking reduced the gender difference in calcification by 30%, 18%, 24% and 5%, respectively. On adjustment for these factors simultaneously, men continued to have a twofold odds of calcification compared with women (odds ratio = 2.2 95% CI 1.02–5, $p = 0.04$). Adjustment for BMI increased the odds ratio to 6.3 (95% CI 2.3–17, $p < 0.001$). None of the other risk factors listed in Table 1 contributed to the gender difference in calcification.

CONTRIBUTION OF RISK FACTORS TO THE LOSS OF THE GENDER DIFFERENCE IN CALCIFICATION IN DIABETES. This was explored by examining the effect of adjustment for risk factors on the 3.9-fold higher odds ratio for calcification associated with diabetes in women than men. Adjustment was made for risk factors where the difference between those with and without diabetes was found to differ by gender (i.e., BP, total:HDL-cholesterol ratio, glycemic control). On adjustment, the diabetes-associated odds ratio for calcification remained higher in women than men (threefold higher, $p = 0.02$). On adjustment for BMI, this increased to a sixfold higher odds ratio. Further adjustment for alcohol consumption, physical activity and other risk factors did not change this.

Which risk factors were associated with the much higher odds of calcification in diabetic than nondiabetic women was also examined. Adjusting for systolic BP reduced the odds ratio for calcification in diabetic compared with nondiabetic women from 3.5 to 2.5 (95% CI 2–8, $p < 0.001$). This suggests that BP elevation is part of the explanation for increased calcification in diabetic compared with nondiabetic women. However, adjustment for total: HDL-cholesterol ratio, BMI and educational status increased the odds ratio to 5.6 (95% CI 2.4–13, $p < 0.001$). Further adjustment for other risk factors did not change this odds ratio.

DISCUSSION

Summary of results. This is the first study in which gender differences in both cardiovascular risk factors and a measure of coronary atherosclerosis have been directly compared between young type 1 diabetic patients and the general population. We find that type 1 diabetes abolishes the gender difference in coronary artery calcification and that this is not explained by established CHD risk factors. This study also demonstrates that much of the gender difference in coronary calcification in the general population at this age remains unexplained by established coronary risk factors.

THE GENDER DIFFERENCE IN CALCIFICATION IN NONDIABETIC SUBJECTS. We first examined which factors were important in the gender difference in calcification in the nondiabetic group. The magnitude of the gender difference in calcification in the nondiabetic group is consistent with the 4 to 6-fold risk ratio for CHD mortality in men at this age (10). About half of this gender difference was accounted for by the risk factors measured, mainly BP and lipids. Of course the contribution of known risk factors may be underestimated because of measurement error and because risk factors were only measured on a single occasion (11). However, the magnitude of the remaining difference is such that other risk factors must be involved.

Table 3. Age-Adjusted Odds Ratio (95% CI) for the Association Between Each Risk Factor and Coronary Calcification by Gender and Diabetes Status

	Nondiabetic Men	Nondiabetic Women	Nondiabetic Men and Women Adjusted for Gender	Diabetic Men	Diabetic Women	Diabetic Men and Women Adjusted for Gender	All Subjects Adjusted for Age, Diabetes and Gender
n	94	107	201	104	95	199	
Age (5 yrs)	1.6 (0.9–2.9)	1.8 (1–3.4)	1.7 (1.1–2.6)*	1 (0.6–1.6)	1.6 (1–2.5)	1.3 (0.9–1.8)	1.4 (1.1–1.9)†
HbA_{1c} %	1.0 (0.3–2.8)	2.8 (0.9–8.6)	1.6 (0.8–3.5)	1.2 (0.2–1.7)	1.0 (0.8–1.2)	1.1 (0.9–1.3)	1.1 (0.9–1.3)
HbA_{1c} in top quartile	—	—	—	1.6 (0.6–4.0)	0.5 (0.2–1.2)	0.8 (0.4–1.5)	—
Diabetes duration (5 yrs)	—	—	—	1.4 (1.06–2.0)*	1.4 (1.0–1.9)	1.4 (1.1–1.8)†	—
Insulin dose per unit BMI/day				1.4 (0.8–2.4)	0.5 (0.2–1.4)	1.1 (0.7–1.7)	—
Body mass index (kg/m^2)	1.3 (1.1–1.6)†	1.2 (1.1–1.4)‡	1.3 (1.2–1.4)‡	1.2 (1.1–1.4)†	1.4 (1.2–1.6)‡	1.3 (1.2–1.4)‡	1.3 (1.2–1.4)‡
HDL cholesterol (mmol/l)	0.7 (0.2–1.9)	0.2 (0.05–0.9)†	0.4 (0.2–0.9)*	0.7 (0.2–1.8)	0.4 (0.2–1.1)	0.5 (0.3–1.0)	0.5 (0.3–0.8)†
LDL cholesterol (mmol/l)	1.1 (0.7–1.6)	1.2 (0.7–2.2)	1.1 (0.8–1.5)	1.5 (0.9–2.5)	1.5 (0.9–2.5)	1.4 (1.0–2.0)*	1.2 (0.98–1.6)
Total cholesterol:HDL-C ratio	1.3 (0.9–1.8)	1.8 (1.1–3.1)*	1.4 (1.1–1.9)*	1.6 (1.1–2.2)*	1.6 (0.99–2.7)	1.6 (1.1–2.2)†	1.5 (1.2–1.9)‡
Triglycerides (mmol/l)	1.4 (0.9–2.0)	2.4 (1.1–5.4)*	1.6 (1.1–2.3)*	1.4 (0.8–2.4)	1.4 (0.6–2.9)	1.4 (0.9–2.1)	1.5 (1.1–2.0)*
Systolic BP (mm Hg)	1.03 (1–1.1)	1.03 (1–1.1)	1.03 (1.0–1.06)*	1.03 (1.0–1.1)	1.06 (1–1.1)*	1.05 (1.02–1.07)‡	1.04 (1.02–1.06)‡
Waist-hip ratio (× 100)	1.1 (1–1.2)*	1.04 (0.97–1.1)	1.06 (1.0–1.1)*	1.0 (0.9–1.1)	1.08 (1–1.12)*	1.04 (1.0–1.1)*	1.05 (1.02–1.06)†
Albumin excretion rate ≥20 μg/min	3.0 (0.3–31)	3.0 (0.2–53)	3 (0.5–18)	3.1 (1.1–9)*	1.1 (0.2–6.1)	2.3 (0.9–6)	2.5 (1.1–5.5)†
Smoking (10 pack-yrs)	1.5 (0.9–2.5)	1.4 (0.9–2.2)	1.5 (1.4–2.0)*	1.4 (0.9–2.1)	1.1 (0.6–1.8)	1.3 (0.9–1.7)	1.3 (1.1–1.7)†
Left school before age 19 yrs	1.9 (0.8–4.6)	2.3 (0.8–7.0)	2 (1–4)*	1.7 (0.8–3.6)	2.2 (1.0–5)	1.9 (1.1–3.4)*	2.0 (1.3–3)
Drinking above 21 U/wk	2.9 (1.2–7.0)*	1.5 (0.3–8.0)	2.5 (1.2–5.4)*	0.9 (0.3–2.2)	13 (1.5–109)	1.8 (0.8–3.8)	2.1 (1.2–3.6)‡
Exercise score >10	2.2 (0.8–6.2)	0.23 (0.02–1.9)	1.2 (0.5–2.7)	0.6 (0.2–1.7)	0.2 (0.04–0.8)*	0.4 (0.2–0.9)*	0.7 (0.4–1.2)

*$p < 0.05$; †$p < 0.01$; ‡$p < 0.001$ for the association between the risk factor and calcification adjusted for age.
BP = blood pressure; BMI = body mass index; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

ROLE OF RISK FACTORS IN THE LOSS OF THE GENDER DIFFERENCE IN CAC IN PATIENTS WITH DIABETES. That diabetes has a greater effect on calcification in women than men suggests that diabetes may be associated with a greater risk factor disturbance in women than men relative to the general population. The obvious candidates are those risk factors that are important in the gender difference in the general population. We found that diabetes was associated with a lower total:HDL-cholesterol ratio and triglycerides in men but not in women. We also found that type 1 diabetes was also associated with a significantly greater difference in BP in women than in men, despite a greater prevalence of albuminuria in men. However, the greater effect of diabetes on calcification in women than men was not explained by these risk factors. Neither was it explained by diabetes modifying the risk ratio associated with a given level of a risk factor in women.

OTHER POSSIBLE EXPLANATIONS FOR THE LOSS OF THE GENDER DIFFERENCE IN CALCIFICATION IN PATIENTS WITH DIABETES. Other explanations must therefore be sought for the dramatic difference in the effect of diabetes on calcification in women compared with men. The total cholesterol:HDL-cholesterol data suggest that investigation of the role of more subtle alterations in lipids and lipoproteins, particularly related to triglyceride metabolism, such as lipoprotein particle size, is warranted. Whether there is a more profound adverse effect of diabetes on endothelial function in women than men is also of interest and would be consistent with our BP data. This is plausible because gender differences in endothelial function (12), perhaps mediated by estrogen, may contribute to the gender difference in atherosclerosis and because defective endothelial function has been reported in uncomplicated type 1 diabetes (13). It is also possible that data on these risk factors, e.g., glycemia, over a longer period might explain more of the loss of the gender difference. Further studies are now underway to test these hypotheses.

IMPORTANT DIFFERENCES BETWEEN TYPE 1 AND TYPE 2 DIABETES. In patients with type 2 diabetes there is also an unexplained reduction in the gender difference in CHD risk, but this study cautions against assuming that the reasons will prove common to both types of diabetes. In type 2 diabetes HDL cholesterol is reduced and the gender difference is attenuated (14,15). We found that the gender difference in HDL cholesterol was maintained and indeed, consistent with other studies, HDL cholesterol was higher in type 1 diabetic than nondiabetic patients. The higher HDL cholesterol in type 1 diabetic patients may be related to increased lipoprotein lipase activity, possibly secondary to insulin therapy (16). In type 2 diabetes there is a greater elevation in central obesity in women than in men compared with the nondiabetic population (15). We did not find any attenuation of the gender difference in waist–hip ratio in patients with type 1 diabetes, and diabetes was associated with a lower prevalence of obesity in women but not in men.

Study validity. The response rate of 30% in the nondiabetic group and 53% in the diabetic group raises the possibility of selection bias. Our true response rate is probably considerably higher than this, as it is likely that many of the addresses from which there was no response at all were no longer valid. In any case, the main conclusion of the abolition of the gender difference in diabetes would only be affected if the difference in response rates between the diabetic and nondiabetic group differed by gender. This was not the case. Furthermore, the distribution of risk factors in the nondiabetic group was similar to that of the same age-gender bands of the general population in the Health Survey for England, which is consistent with the nondiabetic sample being representative of the general population in terms of CHD risk (17). Among the diabetic group the prevalence of hypertension and albuminuria was similar to that found in the United Kingdom patients in the EURODIAB IDDM Complications Study (18). Observer bias is also unlikely, as the examiners were blinded to the diabetic status of participants for the EBCT scan scoring. Reverse causation bias, which arises when there are changes in risk factor levels following diagnosis of disease, is also unlikely. Although we sampled people without regard to their cardiovascular disease history, only one person had a clinical diagnosis of angina and few had nephropathy.

THE VALIDITY OF CORONARY CALCIFICATION AS A MEASURE OF CORONARY ATHEROSCLEROSIS. Our data demonstrate unequivocally that there is a loss in the gender difference in coronary artery calcification in diabetes. The usefulness of EBCT defined CAC as a measure of atherosclerosis burden in the general population is well established (19). Autopsy studies have demonstrated the amount of calcification increases with the amount of atherosclerosis (7,20). For example, the total calcium volume in the coronary arteries was highly correlated with total plaque volume ($r = 0.87$, $p < 0.0001$) (7). In vivo studies are of course restricted to angiographic studies of symptomatic patients. These have also shown that CAC score is associated with the extent of luminal stenoses, though slightly less strongly than with atherosclerotic plaque burden in autopsy studies (19). However, luminal stenosis is itself not perfectly correlated with atherosclerosis burden, probably because diseased vessels enlarge to preserve lumen size (21), so that the autopsy data are more relevant than the angiography data to the validity of our study. Consistent with its being a good marker of the amount of atherosclerotic plaque, EBCT-defined CAC score is also an important predictor of clinical events (22,23).

CALCIFICATION IS SIMILARLY RELATED TO ATHEROSCLEROSIS IN MEN AND WOMEN. For our data to imply a loss in the gender difference in coronary atherosclerosis requires that coronary calcification be similarly related to coronary atherosclerosis in women and men and in diabetic and nondiabetic subjects. Importantly, a given calcification score predicts a similar burden of plaque in male and female

hearts at autopsy (24–26). Although one study concluded that CAC score related differently to angiographic stenosis in men than women, the comparison was made at the same age rather than at the same degree of plaque (27).

THE RELATIONSHIP OF CALCIFICATION TO ATHEROSCLEROSIS IN DIABETES. There are fewer data on whether EBCT-defined CAC has the same association with atherosclerosis in diabetic and nondiabetic subjects. At autopsy, plaques in type 1 diabetic subjects were found to have a similar calcium content for a given amount of plaque as in nondiabetic subjects (28). Of particular importance is that type 1 diabetes is associated with medial calcification of the peripheral vessels, raising the question of whether the calcification we have observed in the coronary vessels could be medial. However non-atherosclerotic medial calcification is not common in the coronary tree (29). Those sporadic reports of extensive medial coronary calcification have been in patients with renal failure (30,31). Therefore it seems likely that the CAC in these young diabetic patients without renal failure is intimal and indicative of atherosclerosis. This is further supported by the similar strength of the association of CHD risk factors with CAC in the diabetic and nondiabetic subjects in this study.

In summary, we have found that type 1 diabetes abolishes the gender difference in coronary calcification which likely reflects atherosclerosis. An important clinical implication is that interventions aimed solely at reducing post-infarct mortality in diabetic women are likely to have little impact on the greater elevation of CHD mortality in diabetic women than men. Strategies to prevent coronary atherosclerosis are needed and the high prevalence of coronary calcification despite the young age of our study participants demonstrates that prevention must be instigated at an early age. Reductions in BP, lipids and other established coronary risk factors are important for reducing CHD in diabetic patients. However, greater progress in our understanding of the pathogenesis of atherosclerosis in diabetic women is necessary for its effective prevention.

Acknowledgments

The authors are grateful to the fieldwork team and the radiographers at the Harefield and Royal Brompton and Harefield NHS Hospital Trust. We also wish to thank the patients and volunteers who took part and their physicians.

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