Diabetologia (1997) 40: 711–717

Diabetologia

Relatively more atherogenic coronary heart disease risk factors in prediabetic women than in prediabetic men

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Summary Men with non-insulin-dependent diabetes mellitus (NIDDM) have a twofold increased risk of coronary heart disease and women with NIDDM have a fourfold increased risk. The reasons for this higher relative risk in NIDDM women than in NIDDM men is not completely understood. Since some studies suggest that duration of clinical diabetes and degree of hyperglycaemia have only a modest effect on coronary heart disease risk, we hypothesized that women who eventually convert to NIDDM might have a more atherogenic pattern of lipids and blood pressure relative to subjects who do not convert than male converters, even in the prediabetic period. We examined this issue in Mexican-American subjects in the 8-year follow-up of the San Antonio Heart Study. Seventy-nine out of 801 men converted to NIDDM compared to 133 out of 1131 women. In both men and women, conversion to NIDDM was significantly associated with increased body mass index, fasting insulin and glucose, higher triglyceride and blood pressure and lower high density lipoprotein (HDL) cholesterol. The relative differences between converters and non-converters was significantly greater for women than for men; this interaction term for gender by conversion status was statistically significant for fasting insulin, triglyceride, HDL cholesterol and diastolic blood pressure. Thus, the higher relative risk for coronary heart disease in women with NIDDM relative to men with NIDDM may be partially due to their greater burden of cardiovascular risk factors even prior to the onset of diabetes. [Diabetologia (1997) 40: 711–717]

Keywords IDDM, prediabetes, lipids, lipoprotein, blood pressure, insulin.

Diabetes mellitus is associated with a marked increase in coronary heart disease (CHD) [1, 2]. In many [1, 3–7] but not all [8–11] studies this excess risk of CHD is relatively higher for female diabetic subjects than for male diabetic subjects. The reasons for the excess risk of CHD in diabetic subjects are multifactorial but include dyslipidaemia, hypertension, and insulin resistance. In some cases, the increase in these risk factors may be relatively greater in female diabetic subjects than in male diabetic subjects. For example, diabetic women have a relatively worse pattern of dyslipidaemia (especially increased low density lipoprotein (LDL) cholesterol and decreased high density lipoprotein (HDL) cholesterol) than diabetic men [12–15].

However, the relatively greater increase in CHD risk for diabetic women than for diabetic men may not depend solely upon greater risk factors for CHD after the development of non-insulin-dependent diabetes mellitus (NIDDM). While the degree and duration of hyperglycaemia are major risk factors for microvascular complications [16, 17], several studies have suggested that these risk factors are not related

Received: 7 November 1996 and in revised form: 11 March 1997

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Abbreviations: CHD, Coronary heart disease; LDL, low density lipoproteins; HDL, high density lipoproteins; NIDDM, non-insulin-dependent diabetes mellitus; IGT, impaired glucose tolerance; NGT, normal glucose tolerance.

or only weakly related to CHD in diabetic subjects [18–21]. However, in some recent European studies, glycaemia has been related to CHD [22, 23]. It is possible that events in the prediabetic state may increase the risk for both NIDDM and CHD. Moreover, hyperinsulinaemia and/or insulin resistance have both been proposed as risk factors for CHD [24]. Whether hyperinsulinaemia is directly atherogenic or is a CHD risk factor by virtue of its correlation with other established CHD risk factors has been controversial [25]. Both insulin resistance [26] and hyperinsulinaemia [27–31] are present in the prediabetic period. In addition, increased cardiovascular risk factors (especially increased blood pressure and triglyceride levels and decreased HDL cholesterol) precede the onset of NIDDM [28, 32–34]. Nevertheless, a number of important issues are unresolved. One is whether female 'prediabetic' subjects have a relatively more atherogenic pattern than male 'prediabetic' subjects and, if so, what are the causes of the increased cardiovascular risk factors in prediabetic subjects. We might expect greater excess in cardiovascular risk factors in female prediabetic subjects than in male prediabetic subjects relative to non-diabetic subjects, since diabetic women have a relatively greater CHD incidence than diabetic men.

In this report, we examine cardiovascular risk factors in Mexican-American female and male prediabetic subjects from a large longitudinal population-based cohort, the San Antonio Heart Study. Mexican Americans have been previously identified as having a threefold increased rate of NIDDM [35], but relatively similar rates of CHD to non-Hispanic whites [36].

Subjects and methods

The San Antonio Heart Study is a population-based study of diabetes and cardiovascular disease in Mexican-Americans and non-Hispanic whites. From 1979 to 1982 (phase I) and from 1984 to 1988 (phase II), we randomly selected households from low-income (barrio), middle-income (transitional), and high-income (suburban) census tracts in San Antonio [35, 37]. All men and non-pregnant women aged 25–64 years who resided in the randomly sampled households were eligible to participate. Only Mexican-Americans were studied in the lower income census tracts. Mexican-Americans were defined as individuals whose ancestry and cultural traditions derived from a Mexican national origin [38]. Detailed descriptions of the two study phases (I and II) have been published previously [35, 37]. This study was approved by the Institutional Review Board of the University of Texas Health Science Center at San Antonio. All subjects gave informed consent.

In October 1987, we began an 8-year follow-up of the phase I cohort to determine the incidence of NIDDM and cardiovascular disease [39]. This follow-up was completed in November 1990. We have reported previously on cardiovascular risk factors prior to the onset of NIDDM in four of six census tracts from phase I [34]. In that report, 43 out of 614 individuals converted to NIDDM. With this small number of subjects, we were not able to examine risk factors for conversion to diabetes separately in the two sexes. Beginning in October 1991, we began a similar 7-year follow-up of the phase II cohort. The results in this report are based on risk factors for the development of NIDDM in all six phase I census tracts for phase I and in the first five of six phase II census tracts (two upper, two lower income and one-middle income). (Data collection is not yet complete in the sixth phase II census tract.) Because of the small numbers of non-Hispanic whites who developed NIDDM (49/1101), this report is restricted to Mexican-Americans. Subjects with diabetes at the baseline examination were also excluded from this report.

At the baseline and follow-up, blood specimens were obtained after a 12- to 14-h fast for determination of serum lipids and lipoproteins. Methods for determination of lipids and lipoproteins and glucose have been described previously [35]. We measured serum insulin with a solid-phase radioimmunoassay (Diagnostic Products Corporation, Los Angeles, Calif., USA) that shows a relatively high degree of cross-reactivity with proinsulin (~ 70–100 %) [37]. A 75-g oral glucose load (Orangedex; Custom Laboratories, Baltimore, Md., USA) was administered, and blood specimens were obtained 1-h and 2-h later for plasma glucose and serum insulin concentrations. At the follow-up examination post-glucose load specimens were obtained only at 2-h. Diabetes was diagnosed according to World Health Organization (WHO) criteria [40]. Subjects who did not meet WHO plasma glucose criteria but who were under treatment with oral antidiabetic agents or insulin were considered to have diabetes.

Anthropometric measurements (height, weight, subscapular and triceps skinfolds) were made after participants had removed their shoes and upper garments and donned an examination gown. Body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters) squared. The ratio of subscapular-to-triceps skinfold (centrality index) was chosen as a measure of central adiposity. (Waist and hip circumferences are not available from the baseline phase I examination.)

The systolic (first phase) and diastolic (fifth phase) blood pressures were measured to the nearest even digit using a random-zero sphygmomanometer (Hawksley-Gelman, Lancing, Sussex, UK). Three readings were recorded for each individual, and the average of the second and third reading was defined as the patient's blood pressure.

Statistical analyses

included analyses of covariance (ANCOVA) performed using SAS statistical software. The principal form of analyses was one-way ANCOVA with conversion to NIDDM as the grouping variable (Tables 1–3). In addition, two-way analyses of covariance were performed with conversion to NIDDM and gender as the main effects; statistical interaction terms of conversion status × gender were computed (Table 4). Triglyceride and insulin levels were log transformed to improve the normality of their distributions. These variables were back transformed for presentation in the Tables.

Results

Table 1 shows the age-adjusted clinical and metabolic characteristics at baseline of subjects by conversion status to NIDDM at follow-up separately in men and in women. In both men and women, subjects

Table 1. Baseline characteristics of converters and non-converters to NIDDM by sex in San Antonio Heart Study (adjusted for age)

	Men		*p*-value	Women		*p*-value
	Converters	Non-converters	Conversion status	Converters	Non-converters	Conversion status
n	79	722		133	998	
% IGT at baseline	80 %	8 %	< 0.001	55 %	12 %	< 0.001
BMI (kg/m^2)	30.0 ± 0.5	27.6 ± 0.2	< 0.001	32.0 ± 0.5	27.2 ± 0.2	< 0.001
Fasting insulin (pmol/l)	106 ± 7	57 ± 6	< 0.001	119 ± 6	50 ± 6	< 0.001
Fasting glucose (mmol/l)	5.4 ± 0.1	5.0 ± 0.1	< 0.001	5.4 ± 0.1	4.8 ± 0.1	< 0.001
2-h glucose (mmol/l)	7.6 ± 0.2	5.7 ± 0.1	< 0.001	8.2 ± 0.2	6.1 ± 0.1	< 0.001
Triglycerides (mmol/l)	2.00 ± 0.12	1.59 ± 0.02	0.003	1.89 ± 0.01	1.10 ± 0.01	< 0.001
Total cholesterol (mmol/l)	5.57 ± 0.12	5.47 ± 0.04	0.934	5.29 ± 0.09	5.22 ± 0.03	0.195
HDL cholesterol (mmol/l)	1.03 ± 0.04	1.14 ± 0.01	0.005	1.10 ± 0.03	1.39 ± 0.01	< 0.001
LDL cholesterol (mmol/l)	3.53 ± 0.11	3.52 ± 0.04	0.896	3.22 ± 0.08	3.54 ± 1.06	0.224
Systolic BP (mmHg)	126.1 ± 1.6	119.1 ± 0.5	< 0.001	119.0 ± 1.2	110.5 ± 0.4	< 0.001
Diastolic BP (mmHg)	76.9 ± 1.1	74.7 ± 0.4	0.048	73.7 ± 0.8	69.6 ± 0.3	< 0.001
Skinfolds						
Subscapular (mm)	27.6 ± 1.0	22.33 ± 0.32	< 0.001	32.0 ± 0.9	25.8 ± 0.3	< 0.001
Triceps (mm)	15.0 ± 0.7	14.0 ± 0.22	0.166	27.3 ± 0.7	24.5 ± 0.3	< 0.001
STR	1.78 ± 0.07	1.68 ± 0.02	0.219	1.19 ± 0.03	1.07 ± 0.01	< 0.001
Age[a]	49.9 ± 0.5	43.2 ± 0.2	0.009	47.1 ± 0.4	43.2 ± 0.1	0.004

BP, blood pressure; STR, ratio of subscapular-to-triceps skinfolds
Statistical analysis was done by one-way ANCOVA not adjusted for age

Table 2. Baseline characteristics of converters and non-converters to NIDDM by sex in the San Antonio Heart Study (adjusted for age, BMI, subscapular-to-triceps skinfold ratio and fasting glucose)

	Men		*p*-value	Women		*p*-value
	Converters	Non-converters	Conversion status	Converters	Non-converters	Conversion status
n	79	722		133	998	
Fasting insulin (pmol/l)	90.1 ± 6.5	57.8 ± 6.2	0.004	94.0 ± 6.4	50.6 ± 6.1	< 0.001
Triglycerides (mmol/l)	1.88 ± 0.06	1.61 ± 0.01	0.028	1.72 ± 0.01	1.12 ± 0.01	< 0.001
Total cholesterol (mmol/l)	5.42 ± 0.13	5.98 ± 0.04	0.684	5.27 ± 0.09	5.22 ± 0.03	0.764
HDL cholesterol (mmol/l)	1.07 ± 0.04	1.14 ± 0.10	0.047	1.23 ± 0.03	1.38 ± 0.01	< 0.001
LDL cholesterol (mmol/l)	3.49 ± 0.11	3.52 ± 0.04	0.840	3.25 ± 0.08	3.13 ± 0.02	0.193
Systolic BP (mmHg)	124.2 ± 1.5	119.3 ± 0.5	0.002	115.0 ± 1.2	111.9 ± 0.4	0.015
Diastolic BP (mmHg)	75.2 ± 1.1	74.8 ± 0.3	0.717	71.6 ± 0.8	68.9 ± 0.3	0.028

BP, blood pressure; STR, ratio of subscapular-to-triceps skinfolds.
Statistical analysis was done by one-way ANCOVA

who converted to NIDDM had significantly higher BMI, fasting insulin, fasting and 2 h glucose levels, percentage with impaired glucose tolerance at baseline, triglyceride, systolic and diastolic blood pressure and subscapular skinfold than subjects who remained non-diabetic. Converters also had lower HDL cholesterol. In neither men nor women was there a significant difference in total or LDL cholesterol between converters and non-converters to NIDDM. Triceps skinfolds and subscapular-to-triceps skinfold ratio were associated with conversion to NIDDM in women, but not in men.

Since impaired glucose tolerance at baseline is associated with conversion to NIDDM at follow-up, we performed a two-way analyses of variance with impaired/normal glucose tolerance (IGT/NGT) status at baseline as one main effect and conversion to NIDDM at follow-up as the other main effect (data not shown). IGT was associated with increased BMI, fasting insulin, higher triglyceride, systolic and diastolic blood pressure and lower HDL cholesterol relative to NGT. However, after adjustment for glucose tolerance status at baseline, both male and female converters to NIDDM had a higher BMI, fasting insulin, triglyceride, systolic and diastolic blood pressure and lower HDL cholesterol than subjects who did not convert to NIDDM. In the remainder of this report (Tables 2 and 3), we adjust for fasting glucose at baseline to control for the effect of baseline glycaemia.

Table 2 shows characteristics of subjects at baseline according to conversion status adjusted for age, BMI, ratio of subscapular-to-triceps skinfolds and fasting glucose. In general, both male and female converters to NIDDM continued to have significantly higher blood pressure, fasting insulin, triglyceride and lower HDL cholesterol than non-converters, although the magnitude of these differences was considerably attenuated compared to the unadjusted analyses (Table 1). (Stepwise linear regression

Table 3. Baseline characteristics of converters and non-converters to NIDDM by sex in the San Antonio Heart Study (adjusted for age, STR, BMI, fasting glucose and fasting insulin)

	Men		*p*-value	Women		*p*-value
	Converters	Non-converters	Conversion status	Converters	Non-converters	Conversion status
n	79	722		133	998	
Triglycerides (mmol/l)	1.74 ± 0.01	1.62 ± 0.12	0.338	1.5 ± 0.02	1.25 ± 0.01	< 0.001
Total cholesterol (mmol/l)	2.29 ± 0.06	2.36 ± 0.03	0.234	5.10 ± 0.10	5.24 ± 0.03	0.162
HDL cholesterol (mmol/l)	1.08 ± 0.04	1.14 ± 0.11	0.116	1.25 ± 0.03	1.34 ± 0.10	0.001
LDL cholesterol (mmol/l)	3.42 ± 0.12	3.51 ± 0.04	0.493	3.06 ± 0.09	3.26 ± 0.03	0.071
Systolic BP (mmHg)	119.2 ± 0.12	120.4 ± 0.5	0.070	116.1 ± 1.3	112.0 ± 0.4	0.002
Diastolic BP (mmHg)	74.9 ± 1.1	75.0 ± 0.3	0.983	71.1 ± 0.8	70.0 ± 0.3	0.190

BP, blood pressure; STR, ratio of subscapular-to-triceps skinfolds
Statistical analysis was done by one-way ANCOVA

Table 4. Baseline differences between converters and non-converters to NIDDM by gender

	Men	Women	*p*-value	
	Difference (converters-non-converters)	Difference (converters-non-converters)	Conversion status	Conversion status × gender
Adjusted for age				
BMI (kg/m^2)	2.4	4.8	0.001	0.032
Fasting insulin (pmol/l)	49.0	69.0	0.001	0.004
Fasting glucose (mmol/l)	0.40	0.61	0.001	0.064
2-h glucose (mmol/l)	1.89	2.10	0.001	0.516
Triglycerides (mmol/l)	0.41	0.79	0.001	0.002
Total cholesterol (mmol/l)	0.50	0.09	0.599	0.636
HDL cholesterol (mmol/l)	–0.13	–0.24	0.001	0.008
LDL cholesterol (mg/dl)	0.01	0.08	0.454	0.738
Systolic BP (mmHg)	7.00	8.84	0.001	0.431
Diastolic BP (mmHg)	2.26	4.09	0.001	0.032
STR	0.10	0.12	0.002	0.967
Adjusted for age, BMI, STR and fasting glucose				
Fasting insulin (pmol/l)	32.3	43.4	0.001	0.042
Triglycerides (mmol/l)	0.27	0.60	0.001	0.032
Total cholesterol (mmol/l)	–0.06	0.05	0.501	0.680
HDL cholesterol (mmol/l)	–0.07	–0.15	0.001	0.042
LDL cholesterol (mg/dl)	–0.03	–0.12	0.322	0.872
Systolic BP (mmHg)	6.12	8.22	0.001	0.327
Diastolic BP (mmHg)	1.62	4.11	0.001	0.087
Adjusted for age, BMI, STR, fasting glucose and insulin				
Triglycerides (mmol/l)	0.12	0.25	0.001	0.188
Total cholesterol (mmol/l)	–0.07	–0.1	0.322	0.695
HDL cholesterol (mmol/l)	–0.06	–0.09	0.003	0.485
LDL cholesterol (mg/dl)	–0.09	0.26	0.122	0.613
Systolic BP (mmHg)	1.49	4.13	0.001	0.888
Diastolic BP (mmHg)	0.03	1.11	0.512	0.630

BP, blood pressure; STR, ratio of subscapular-to-triceps skinfolds
Statistical analysis was done by two-way ANCOVA with gender and conversion status as main effects

showed that most of the attenuation was due to differences in BMI (data not shown).)

Table 3 shows metabolic characteristics after further adjustment for fasting insulin level. In men, conversion to NIDDM was no longer significantly related to lipids and lipoproteins or blood pressure, whereas in women conversion to NIDDM continued to be significantly related to higher triglyceride and systolic blood pressure and to lower HDL cholesterol.

Since our study included more women than men, it is possible that the continuing statistically significant association between NIDDM conversion and cardiovascular risk factors in women may have been due to greater statistical power in women. To test this hypothesis we computed a two-way analysis of variance with main effects of gender and conversion status and an interaction terms of gender × conversion status (Table 4). Generally, the risk factor differences between converters and non-converters were larger for women than for men. The interaction term for conversion status × gender was statistically significant for BMI, triglyceride, HDL cholesterol and fasting insulin. After adjustment for age, BMI, the ratio of

subscapular-to-triceps skinfold and fasting glucose, the conversion status × gender interaction remained statistically significant for fasting insulin, triglycerides and HDL cholesterol. However, after further statistical adjustment for fasting insulin, the conversion status × gender interaction term became non-significant for triglyceride and HDL cholesterol.

Discussion

In this report we have shown that prediabetic subjects not only have hyperinsulinaemia, but also increased cardiovascular risk factors including increased triglyceride and blood pressure and decreased HDL cholesterol. This has been shown previously in middle-aged Mexican-Americans [34], elderly Americans [32], middle-aged Israeli men [33] and elderly Finnish subjects [28]. In earlier studies, investigators have not studied whether the excess in atherogenic risk factors in prediabetic women was relatively greater than the excess in prediabetic men [28, 32, 33]. Such a pattern might be expected, given the greater relative risk of CHD in women than in men with clinical diabetes [1, 3–7]. We examined this issue in our previous report [34] but found no evidence for a gender × conversion status interaction probably because of the lesser number of prediabetic subjects in that study. (Forty-three subjects had converted to NIDDM out of 614 non-diabetic subjects at baseline in our earlier report, compared with 212 out of 1932 in the present report.) The present data suggest that the greater excess in cardiovascular risk factors in diabetic women compared to diabetic men described in earlier reports [12–15] actually precedes the onset of the diabetic state. This greater atherogenicity for women may be partially due to hyperinsulinaemia, since after adjustment for this variable the gender × conversion status interaction term ceases to be statistically significant. A possible explanation is that the sex difference in risk factors is considerably reduced in prediabetic subjects as compared to subjects who do not convert to NIDDM. We cannot, however, exclude the possibility that other factors such as differences in small dense LDL or oxidized LDL could also explain differences between prediabetic subjects and those subjects who remain normoglycaemic.

Most [16, 18–21], but not all, studies [22, 23] show that duration of diabetes and hyperglycaemia are only weakly related to the development of CHD in diabetic subjects. In the Wisconsin study of diabetic retinopathy, Klein [41] has shown that a 1 % increase in glycated haemoglobin is significantly associated with a 10 % rise in ischaemic heart disease as opposed to a 70 % increase in proliferative retinopathy. These results suggest that glycaemic control would be associated with improvements in both macrovascular disease as well as microvascular disease, although the effect would be much greater for the latter endpoint. It is likely, therefore, that tight control of hyperglycaemia will only decrease macrovascular disease to a minor degree, whereas it is likely to markedly decrease microvascular disease. To fully prevent the excess risk of CHD in NIDDM one would need either to prevent NIDDM itself or aggressively treat established cardiovascular risk factors (e. g. blood pressure, dyslipidaemia and smoking cessation] in the prediabetic phase.

An additional strategy to reduce the risk of CHD in NIDDM would be to aggressively treat cardiovascular risk factors. The National Cholesterol Education Program [42] has recommended that treatment of increased LDL cholesterol in NIDDM subjects should be as aggressive as in subjects with established CHD (i. e. target for LDL cholesterol < 2.6 mmol/l). Our data suggest that perhaps these recommendations should extend to prediabetic subjects as well. However, no prospective data exist on the various lipoprotein fractions predicting CHD in prediabetic subjects. Reduction of LDL cholesterol with simvastatin in diabetic subjects who had a prior myocardial infarction led to a 55 % reduction in CHD (which was statistically significant) in the 4S study [43] suggesting the importance of lowering LDL, at least in diabetic subjects with a prior myocardial infarction.

Our study has a number of strengths. The data are population-based and the study uses standardized criteria for the diagnosis of diabetes. Because of the high rate of conversion to NIDDM, we have accumulated a large number of prediabetic subjects. Our study also has some weaknesses. We lack information on whether prediabetic subjects have an increased incidence of CHD relative to normoglycaemic subjects because our population is middle-aged and thus has a relatively low rate of CHD events. We did not use definitive measures of either insulin resistance or insulin secretion; however, fasting insulin correlates well with more sophisticated measures of insulin resistance such as the euglycaemic clamp ($r = -0.6$) [44, 45]. These more sophisticated approaches are difficult to apply in epidemiological studies because of expense and patient acceptance.

In conclusion, we have shown increased cardiovascular risk factors in both male and female prediabetic subjects; the relative excess of CHD risk factors is greater in prediabetic women than in prediabetic men which is consistent with their greater relative risk of CHD in most studies. The increased cardiovascular risk factors in prediabetic women are most dependent on their greater adiposity and especially hyperinsulinaemia. Interventions to fully reduce the excess risk of CHD in NIDDM subjects should focus not only on subjects with clinical diabetes but also on prevention of NIDDM and aggressive treatment of cardiovascular risk factors in prediabetic subjects.

These interventions are particularly important for women.

Acknowledgements. This work was presented in part at the 56th annual meeting of the Scientific Sessions of the American Diabetes Association. San Francisco, Calif., USA, 8–11 June 1996 This work was supported by grants R01 HL24799 and R37 HL36820 from the National Heart, Lung and Blood Institute.

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