Diabetes, Abdominal Adiposity, and Atherogenic Dyslipoproteinemia in Women Compared With Men

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OBJECTIVE—To understand why atherogenic risk differs more between diabetic and nondiabetic women than between diabetic and nondiabetic men.

RESEARCH DESIGN AND METHODS AND RESULTS— Measures of cardiovascular risk, body composition, and serum hormones from the baseline examinations of the Insulin Resistance Atherosclerosis Study on 524 nondiabetic women, 258 diabetic women, 421 nondiabetic men, and 220 diabetic men were compared to detect greater adverse differences in women than in men. Systolic blood pressure; apolipoprotein B (apoB); total cholesterol; apoB–to–apoA-I ratio; non-HDL cholesterol; LDL particle count, small LDL, and intermediate-density lipoprotein by nuclear magnetic resonance; and C-reactive protein exhibited significant diabetes-sex interaction ($P < 0.05$). ApoB exhibited the most significant interaction ($P = 0.0005$). Age- and ethnicity-adjusted apoB means were lower in nondiabetic women than nondiabetic men (102.4 vs. 106.8 mg/dl, $P < 0.05$) but higher in diabetes (115.7 vs. 110.2 mg/dl, $P < 0.01$). Plotted against BMI, waist circumference was 6% higher and hip circumference 10% lower in diabetic than nondiabetic women (both $P < 0.05$), whereas the circumference measures did not differ conspicuously between diabetic and nondiabetic men.

CONCLUSIONS—In diabetic women, an elevated level of atherogenic particles, as manifested by apoB and LDL particle count, which may result from abdominal adiposity, represents a major treatable cardiovascular risk factor. ***Diabetes*** **57:3289–3296, 2008**

Although the gap narrows after menopause, generally the risk of vascular disease is greater in men than in women. In diabetes, by contrast, risk is similar in men and women (1). The equalization of risk is due to the disproportionately greater increase in risk in women who develop diabetes compared with men who develop diabetes (2–4). Identifying the reasons for this alarming increase in vascular disease in diabetic women is critical. Previous work has established that both sexes have higher plasma triglycerides and lower HDL cholesterol levels in diabetes (5) and that these differences are more pronounced between nondiabetic and diabetic women than between nondiabetic and diabetic men (6–8). However, the differences, if any, in LDL cholesterol are much less pronounced and range from slight decreases to slight increases in diabetes (5). Thus, the differences in the conventional lipid profile appear inadequate to explain the differences in clinical risk that have been recorded (2,9).

Because the evidence that apolipoprotein B (apoB) is superior to LDL cholesterol as a marker of atherogenic risk is sufficiently clear (10–14), the American Diabetes Association and the American College of Cardiology have issued a joint consensus statement (15) that apoB should be the final test of the adequacy of LDL-lowering therapy (15,16). Nevertheless, only limited information is available on apoB in diabetic subjects compared with nondiabetic subjects. Two studies have noted that apoB was significantly higher in diabetic compared with nondiabetic women with no significant differences between diabetic and nondiabetic men (17,18). No explanation was offered for this sex difference. Equally important, no mechanism has been suggested that might explain why diabetes in women induces more cardiovascular risk than in men.

The purpose of this study, therefore, was to characterize the lipoprotein profile in greater detail in larger groups of diabetic and nondiabetic men and women than previously examined. We also examined whether the data suggest possible mechanisms that could account for the greater differences in atherogenic risk profile between diabetic and nondiabetic women than between diabetic and nondiabetic men.

RESEARCH DESIGN AND METHODS

The Insulin Resistance Atherosclerosis Study (IRAS) is a multicenter, epidemiological study designed to explore relationships between insulin resistance, cardiovascular risk factors, and disease across different ethnic groups and varying states of glucose tolerance. The IRAS protocol was approved by participating local institutional review committees, and all subjects gave informed consent. Study participants were recruited to obtain approximately equal numbers with diabetes, impaired glucose tolerance, and normal glucose tolerance from each ethnic group and center. A total of 1,624 individuals participated in IRAS baseline examinations from October 1992 to April 1994. This report includes data on 1,423 subjects after excluding 128 subjects who lacked nuclear magnetic resonance (NMR) lipid measurements, 63 who did not have an intravenous glucose tolerance test for insulin sensitivity assessment, and 10 without an apoB assay. Serum sex hormone-binding globulin (SHBG), estradiol, and testosterone concentrations were measured using standardized assays from Diagnostic Products (Siemens). Intra- and interassay coefficients of variation were, respectively, <5.3 and <8.5% for SHBG, <7.0 and <8.1% for estradiol, and <10.0 (values <100 ng/dl) and <7.3% for testosterone. Descriptions of the other measures used in this analysis have been published (19,20).

Statistical analyses. ANCOVA with age, ethnicity (non-Hispanic white, African American, or Hispanic), diabetes, sex, and diabetes-sex interaction

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TABLE 1
Descriptive statistics of the study sample

	Nondiabetic women	Diabetic women*	Nondiabetic men	Diabetic men*
n	524	258	421	220
Age (years)	55 ± 8	57 ± 8	55 ± 9	57 ± 8
Hispanic/black/non-Hispanic white (%)	37/27/36	32/34/34	44/23/33	38/33/29
Impaired glucose regulation (%)†	48	—	56‡	—
Fasting glucose (mg/dl)	96 ± 11	168 ± 58	100 ± 9	172 ± 58
2-h Glucose (mg/dl)	126 ± 33	309 ± 90	121 ± 33‡	302 ± 90
On medication for hyperlipidemia (%)	5	10	9‡	9
On medication for hypertension	23	40	22	35

Data are means ± SD or percent. *Diabetes diagnosed by 1999 World Health Organization criteria: fasting glucose, ≥126 mg/dl; 2-h glucose, ≥200 mg/dl or on hypoglycemic medication. †Fasting glucose ≥100 mg/dl or 2-h glucose ≥140 mg/dl. ‡$P < 0.05$ vs. nondiabetic women.

terms were used to assess whether measures exhibited significant interactions. Cardiovascular risk factors, estimates of body composition, and serum hormones known to be associated with sex, diabetes, and/or cardiovascular risk were included. We then added the risk factor with the most significant interaction to the ANCOVA model for each other risk factor that exhibited significant interaction. Finally, we examined the distributions and conducted ad hoc correlation/regression analyses, including the measures thus selected. Generalized estimating equations with waist and hip circumferences counted in two observations per subject were used to test the difference in slopes versus BMI.

Statistical calculations were performed in SAS version 9.1 (Cary, NC). Log-transformed values were used in analyses of continuous variables which appeared to be more normally distributed with transformation than without. In light of the exploratory nature of these ancillary analyses, *P* values <0.05 were considered statistically significant warranting investigation in other studies.

RESULTS

Table 1 details descriptive statistics for the study subjects. All groups were similar with respect to ethnic composition. Also, the proportion of those with impaired glucose regulation did not differ between nondiabetic men and women. As anticipated, age, fasting glucose, 2-h glucose, fasting insulin, hyperlipidemia treatment rates, and hypertension treatment rates were significantly different in both diabetic groups compared with nondiabetic ones with the exception of hyperlipidemia treatment in men (9% in both male groups). Among nondiabetic subjects, mean 2-h glucose was higher in women than in men (by *t* test, $P = 0.023$), whereas the percentage of subjects with impaired glucose regulation was higher in men than in women (by χ^2 test, $P = 0.021$), and the percentage on hyperlipidemia treatment was also higher in men (9 vs. 5%, $P = 0.014$). There were no significant differences in Table 1 between diabetic women and diabetic men.

Cardiovascular risk factors. With regard to cardiovascular risk factors (Table 2), systolic blood pressure and C-reactive protein (CRP) were higher in both diabetic men and diabetic women compared with their nondiabetic counterparts. Both of these differences were more than two times greater in women than in men and operate to increase risk in diabetic women.

The differences in atherogenic lipoprotein profile were much more striking between diabetic women and nondiabetic women than between diabetic men and nondiabetic men. All four markers of the concentration of atherogenic lipoproteins—apoB, LDL cholesterol, non-HDL cholesterol, and LDL particle count—were significantly higher in diabetic women compared with nondiabetic women. ApoB and non-HDL cholesterol were not significantly different between diabetic and nondiabetic men; LDL cholesterol was actually greater in nondiabetic men compared with diabetic men, whereas LDL particle count was higher in diabetic men compared with nondiabetic men. Nondiabetic men had higher apoB levels than nondiabetic women. However, diabetic women had higher apoB than diabetic men.

These differences in the four major atherogenic lipoprotein indexes are illustrated in Fig. 1. For men, there were only minor differences in the distribution of values for all four indexes between those with and without diabetes. For women, although the average value for LDL cholesterol in diabetic women was 5.6 mg/dl greater than in nondiabetic women ($P < 0.05$), there was no significant difference in the distribution of values of LDL cholesterol between diabetic and nondiabetic women. Moreover, there was no significant increase in the proportion of women with an elevated LDL cholesterol. By contrast, substantial differences were evident for apoB. Not only was the mean difference between the two groups of women greater (13.3 mg/dl, $P < 0.001$) than for LDL cholesterol, the distribution of values in diabetic women was shifted toward higher values with nearly a doubling of the proportion with a markedly elevated level (41 vs. 23%, $P < 0.0001$). All of these findings were confirmed by the differences observed in LDL particle count. Of importance, the differences in non-HDL cholesterol were intermediate between LDL cholesterol and apoB.

Plasma triglycerides were significantly higher in both diabetic groups than nondiabetic groups, but no significant sex-diabetes interaction was observed. However, VLDL and intermediate-density lipoprotein (IDL) particle number were higher only in diabetic women compared with nondiabetic women. LDL particle number was higher in diabetic men compared with their nondiabetic counterparts, but the differences were more marked in women. LDL particle number was similar in both diabetic men and women. As expected from the plasma triglycerides, LDL size was lower in both diabetic groups. Equal percentages of nondiabetic men and women had hypertriglyceridemia (hyperTg)/hyperapobetalipoproteinemia (hyperapoB) (15.8 and 15.7%, respectively). Of the diabetic groups, 24.1% of men vs. 32.8% of women had hyperTg/hyperapoB ($P = 0.036$). Fasting plasma free fatty acids (FFAs) were highest in diabetic women. HDL cholesterol and apoA-I were significantly lower in diabetic women than in nondiabetic women. The difference between the apoB–to–apoA-I ratio was significantly greater between diabetic and nondiabetic women than between the comparable groups of men ($P = 0.0045$), whereas these same differences in total-to-HDL cholesterol ratio were marginally nonsignificant ($P = 0.063$) in this data.

TABLE 2
Age- and ethnicity-adjusted selected measures by sex and diabetes status

Measure	Nondiabetic women	Diabetic women	Nondiabetic men	Diabetic men	DW-NW	DM-NM	Interaction *P* value*	DM-DW	NM-NW
Cardiovascular risk factors									
Systolic blood pressure (mmHg)	122.3 ± 0.70	129.7 ± 1.00	123.6 ± 0.78	127.1 ± 1.08	7.34†	3.58‡	0.037	−2.53	1.24
Diastolic blood pressure (mmHg)	76.6 ± 0.41	77.5 ± 0.58	79.6 ± 0.45	79.6 ± 0.63	0.91	−0.05	0.36	2.06§	3.03†
ApoB (mg/dl)	102.4 ± 1.1	115.7 ± 1.6	106.8 ± 1.2	110.2 ± 1.7	13.3†	3.4	0.0005	−5.4§	4.5‡
ApoA-I (mg/dl)	139.4 ± 1.11	130.5 ± 1.61	121.3 ± 1.24	113.9 ± 1.73	−8.86†	−7.41†	0.61	−16.61†	−18.06†
LDL cholesterol (mg/dl)	140.8 ± 1.5	146.4 ± 2.2	143.1 ± 1.7	134.8 ± 2.4	5.6§	−8.3‡	0.0006	−11.6†	2.3
HDL cholesterol (mg/dl)¶	49.4 ± 0.6	42.2 ± 0.7	40.1 ± 0.5	34.9 ± 0.7	−7.2†	−5.2†	0.53	−7.3†	−9.4†
Total cholesterol (mg/dl)	212.5 ± 1.86	219.3 ± 2.67	211.3 ± 2.08	207.0 ± 2.87	6.81§	−4.22	0.022	−12.28‡	−1.25
ApoB–to–apoA-I ratio	0.73 ± 0.01	0.87 ± 0.02	0.87 ± 0.01	0.95 ± 0.02	0.15†	0.08‡	0.0045	0.08‡	0.15†
Total-to-HDL cholesterol ratio	4.23 ± 0.06	5.10 ± 0.10	5.17 ± 0.08	5.82 ± 0.13	0.87†	0.65†	0.063	0.72†	0.94†
Non-HDL cholesterol (mg/dl)¶	156.3 ± 1.7	170.1 ± 2.7	164.0 ± 2.0	165.5 ± 2.8	13.8†	1.5	0.0071	−4.6	7.7‡
Triglycerides (mg/dl)¶	107.0 ± 2.5	150.2 ± 5.1	122.0 ± 3.2	160.7 ± 5.9	43.2†	38.7†	0.30	10.5	15.0†
LDL particles by NMR (nmol/l)¶	1,063.7 ± 14.6	1,260.6 ± 24.9	1,173.8 ± 18.1	1,243.5 ± 26.6	196.9†	69.7§	0.0015	−17.1	110.1†
Small LDL by NMR (nmol/l)¶	375.5 ± 14.4	618.5 ± 34.1	563.6 ± 24.1	754.2 ± 45.1	243.0†	190.6†	0.032	135.7§	188.0†
LDL size by gel (angstroms)	262.3 ± 0.4	259.0 ± 0.6	259.3 ± 0.5	255.2 ± 0.6	−3.3†	−4.1†	0.46	−3.8†	−3.0†
VLDL particles by NMR (nmol/l)	59.0 ± 1.3	65.0 ± 1.9	72.0 ± 1.5	71.8 ± 2.0	6.0‡	−0.1	0.070	6.8§	12.9†
IDL by NMR (nmol/l)	45.3 ± 1.1	52.6 ± 1.6	42.4 ± 1.3	41.7 ± 1.7	7.2†	−0.7	0.006	−10.9†	−2.9
C-reactive protein (mg/l)¶	2.2 ± 0.1	4.3 ± 0.3	1.4 ± 0.1	2.0 ± 0.2	2.1†	0.7†	0.022	−2.3†	−0.8†
Fasting FFAs (mg/dl)	0.51 ± 0.01	0.64 ± 0.01	0.43 ± 0.01	0.53 ± 0.01	0.13†	0.10†	0.17	−0.11†	−0.08†
Body composition									
Waist circumference (cm)#	87.0 ± 0.53	97.3 ± 0.76	94.8 ± 0.60	101.3 ± 0.83	10.26†	6.43†	0.0054	3.96†	7.79†
Hip circumference (cm)#	107.6 ± 0.51	112.0 ± 0.72	102.4 ± 0.56	105.5 ± 0.78	4.40†	3.12‡	0.32	−6.52†	−5.25†
100 × WHR#	80.8 ± 0.3	87.0 ± 0.4	92.6 ± 0.3	96.0 ± 0.4	6.2†	3.4†	0.0001	9.1†	11.8†
BMI (kg/m^2)	28.9 ± 0.2	32.5 ± 0.3	27.6 ± 0.3	30.2 ± 0.4	3.6†	2.5†	0.099	−2.3†	−1.3†
Serum hormones									
Fasting insulin (pmol/l)¶**	12.6 ± 0.4	19.7 ± 0.8	12.8 ± 0.4	19.2 ± 0.8	7.1†	6.4†	0.58	−0.5	0.2
SHBG (nmol/l)¶**	36.5 ± 1.2	18.0 ± 0.9	19.4 ± 0.8	13.4 ± 0.7	−18.5†	−6.1†	0.0002	−4.7†	−17.1†
Total testosterone (pg/ml)¶**	21.8 ± 0.6	24.5 ± 1.0	475.2 ± 14.9	383.6 ± 17.3	2.7§	−91.6†	<0.0001	359.0†	453.4†
Estradiol (pg/ml)¶	56.3 ± 4.9	53.6 ± 8.0	26.4 ± 1.3	26.5 ± 2.0	−2.7	0.1	0.77	−27.1†	−29.9†

Data are means ± SE. DW-NW, diabetic women–nondiabetic women; DM-NM, diabetic men–nondiabetic men; DM-DW, diabetic men–diabetic women; NM-NW, nondiabetic men–nondiabetic women. *Null hypothesis for interaction *P* value: DW-NW = DM-NM (equivalent to DM-DW = NM-NW). †$P < 0.001$; ‡$P < 0.01$; §$P < 0.05$. ¶Log-transformed for analysis and back-transformed for presentation. #Excluded four subjects missing waist or hip circumference measurements. **Excluded 266 subjects missing testosterone and SHBG measurements.

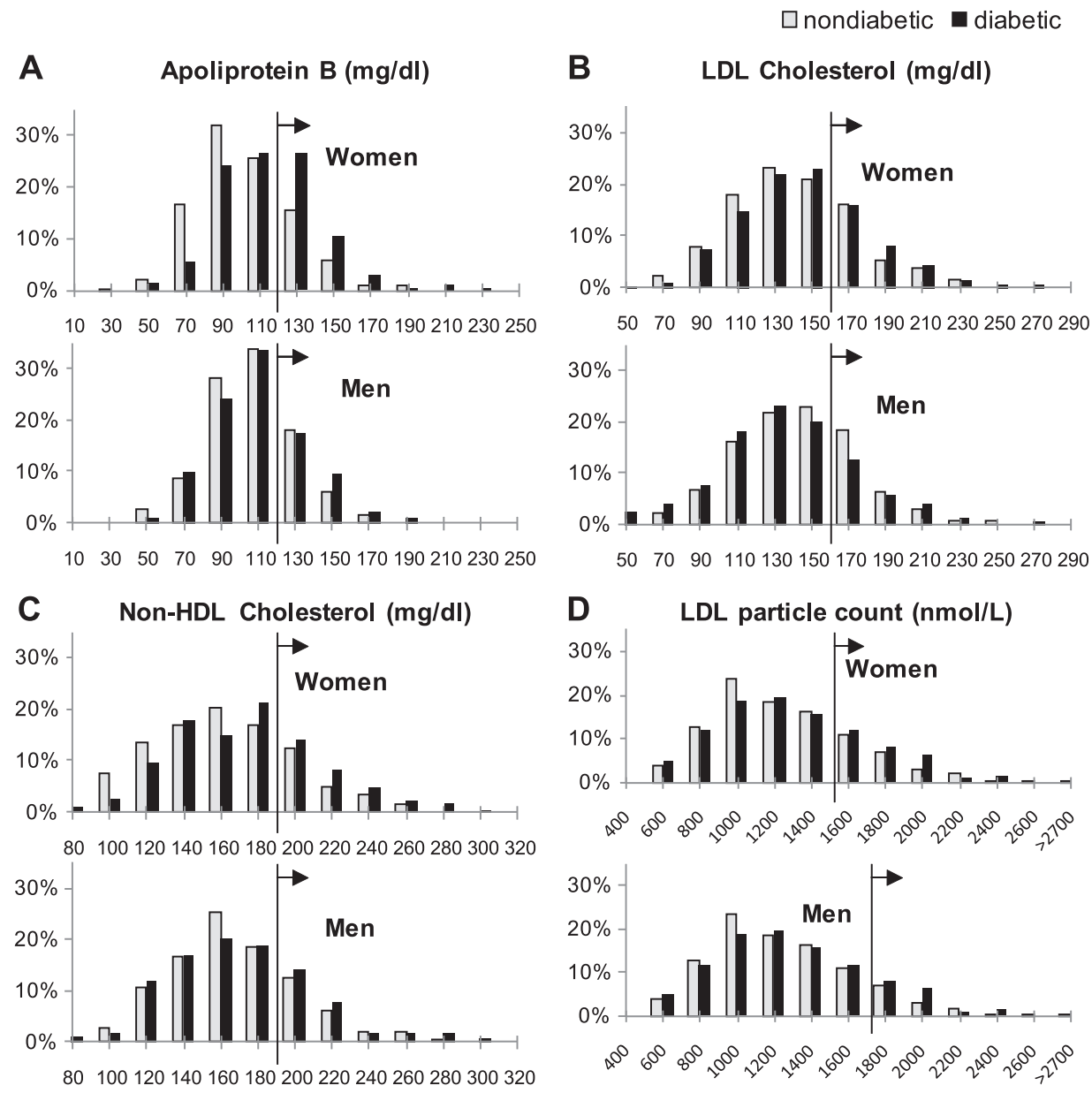

FIG. 1. Histograms of apoB (*A*), LDL cholesterol (*B*), non-HDL cholesterol (*C*), and LDL particle count (*D*) by sex and diabetes status. χ^2 comparisons of the proportions above selected risk thresholds among diabetic versus nondiabetic subjects were as follows. *A*: Of diabetic women, 41% had apoB >120 mg/dl vs. 23% of nondiabetic women, $P < 0.0001$; 30% of diabetic vs. 26% of nondiabetic men, $P = 0.22$. *B*: Of diabetic women, 31% had LDL cholesterol >160 mg/dl vs. 27% of nondiabetic women, $P = 0.19$; 24% of diabetic vs. 29% of nondiabetic men, $P = 0.14$. *C*: Of diabetic women, 32% had non-HDL cholesterol >190 mg/dl vs. 23% of nondiabetic women, $P = 0.003$; 29% of diabetic vs. 24% of diabetic men, $P = 0.16$. *D*: Of diabetic women, 20% had LDL particle count >1,617 nmol/l vs. 10% of nondiabetic women, $P = 0.0002$; 12% of diabetic vs. 10% of nondiabetic men, $P = 0.28$.

Finally, apoB appeared to be the key measure characterizing the cardiovascular risk factor interactions. As shown in Table 3, further adjustment for apoB abolished the significance of the sex-diabetes interaction of each of the other cardiovascular risk measures. Of note in this regard is that adjustment for apoB attenuated the interaction of systolic blood pressure from a marginally significant ($P = 0.037$) 3.76-mmHg interaction effect (difference in the differences) in Table 2 to a marginally nonsignificant ($P = 0.092$) 3.04-mmHg interaction effect in Table 3. Also, the interaction effect of LDL cholesterol changes from a highly significant 13.9 mg/dl ($P = 0.0006$) to a marginally nonsignificant 5.7 mg/dl ($P = 0.076$). Adjusting for apoB attenuated the magnitude of the other interactions by at least 48%, and all were more than marginally nonsignificant ($P > 0.10$).

Body composition. Table 2 lists the principal results for all of the major groups. All four measures—waist circumference, hip circumference, waist-to-hip ratio (WHR), and BMI—were significantly higher in both diabetic groups compared with their nondiabetic counterparts. Both diabetic groups were more obese than the nondiabetic ones, and the increase in adipose tissue mass was generalized but more accentuated in the abdominal region. It is noteworthy that the difference in the WHR and waist circumference in diabetic compared with nondiabetic women was significantly greater than the difference between diabetic and nondiabetic men. Also, waist circumference for diabetic women was significantly greater than for nondiabetic men ($P < 0.001$).

Figure 2 contrasts the differences in body composition expressed as a ratio of waist or hip circumference at the

lowest quintile of BMI in nondiabetic subjects in each sex. Fig. 2*A* and *B* demonstrate that as BMI increased, upper body tissue mass (as measured by waist circumference) increased more than lower body mass (hip circumference) in all groups ($P < 0.001$). The trend was more pronounced in women than in men ($P < 0.001$). In men (Fig. 2*C*), there was little difference in the slopes and intercepts of either waist or hip circumference between the two groups at any given BMI. By contrast in women (Fig. 2*D*) at any given BMI, waist circumference was 6% greater ($P < 0.001$) in diabetic compared with nondiabetic women. On the other hand, hip circumference was 10% lower at any given BMI in diabetic compared with nondiabetic women. Thus, comparing diabetic with nondiabetic subjects, expansion of lower body adipose tissue mass was considerably more constrained in women, whereas expansion of upper body abdominal tissue mass was considerably more pronounced.

Serum hormones. With regard to serum hormones (Table 2), as expected, serum fasting insulin was higher in both sexes in diabetic subjects compared with nondiabetic subjects, total testosterone levels were ~20 times higher in men than women, whereas estradiol levels in women were double that in men. SHBG levels were markedly lower in diabetic compared with nondiabetic women with a smaller, although still significant, difference noted between the two groups of men. As a result, diabetic women SHBG levels did not differ significantly from nondiabetic men. Diabetic men had significantly lower levels of testosterone than nondiabetic men while diabetic women had significantly higher testosterone than nondiabetic women.

Although the diabetes-sex interaction of fasting insulin was not significant, there was a significant sex interaction ($P < 0.0001$) in the association between waist circumference and insulin (Fig. 3): The difference in waist between men and women in the highest quintile of insulin was less than one-half the same difference in the lowest insulin quintile. When SHBG was added to this association with waist circumference, sex-SHBG interaction was nonsignificant ($P = 0.74$). However, the range of SHBG for women (1–206 nmol/l) was nearly double that of men (1–109 nmol/l), albeit with considerable overlap. As a result, although the effect on waist per absolute SHBG increment was similar, the differences in waist between the highest and lowest SHBG tertiles did differ significantly by sex (7.0 ± 1.2 cm for men vs. 13.6 ± 1.1 cm for women, $P < 0.0001$). Finally, when both WHR and SHBG were added to the apoB ANCOVA model (Table 3), the sex-diabetes interaction became marginally nonsignificant ($P = 0.053$).

Ethnic heterogeneity. In each of the IRAS ethnic groups (Hispanics, African Americans, and non-Hispanic whites), the differences between diabetic and nondiabetic subjects were higher in women than men for apoB and WHR and lower for SHBG (data not shown).

DISCUSSION

Our objective was to understand why atherogenic risk differs more between diabetic and nondiabetic women than between diabetic and nondiabetic men. Our analysis focused on differences in cardiovascular risk profiles to assess whether they might explain, at least in part, the alarmingly higher risk in diabetic women. In the IRAS database, compared with nondiabetic women, diabetic women have a more atherogenic lipoprotein profile, a

TABLE 3
Baseline measures with significant demographically adjusted interaction by sex and diabetes status additionally adjusted as indicated

Measure	Nondiabetic women	Diabetic women	Nondiabetic men	Diabetic men	DW-NW	DM-NM	Interaction *P* value*	DM-DW	NM-NW
CVD risk factors additionally adjusted for apoB									
Systolic blood pressure (mmHg)	122.7 ± 0.70	129.0 ± 1.01	123.6 ± 0.78	126.9 ± 1.08	6.34†	3.30‡	0.092	−2.13	0.91
LDL cholesterol (mg/dl)	145.0 ± 1.2	139.3 ± 1.8	143.4 ± 1.4	132.0 ± 1.9	−5.7§	−11.4†	0.076	−7.3§	−1.6
Total cholesterol (mg/dl)	217.7 ± 1.47	210.7 ± 2.12	211.7 ± 1.64	203.9 ± 2.26	−6.94§	−7.82§	0.82	−6.82‡	−5.94§
ApoB–to–apoA-I ratio	0.76 ± 0.01	0.81 ± 0.01	0.88 ± 0.01	0.92 ± 0.01	0.05†	0.05§	0.70	0.11†	0.11†
Non-HDL cholesterol (mg/dl)¶	161.8 ± 1.2	160.5 ± 1.8	164.5 ± 1.4	162.1 ± 1.9	−1.3	−2.4	0.74	1.6	2.7
LDL particles by NMR (nmol/l)¶	1,111.3 ± 10.8	1,170.9 ± 16.4	1,178.9 ± 12.8	1,211.8 ± 18.2	59.6§	32.9	0.32	40.9	67.5†
Small LDL by NMR(nmol/l)¶	402.9 ± 14.1	549.5 ± 27.8	567.5 ± 22.1	723.5 ± 39.3	146.6†	156.1†	0.45	174.1†	164.6†
IDL by NMR (nmol/l)	47.3 ± 1.1	49.3 ± 1.5	42.6 ± 1.2	40.5 ± 1.6	2.0	−2.1	0.13	−8.7†	−4.7§
ApoB adjusted for demographics, WHR, and SHBG (mg/dl)									
ApoB (mg/dl)	108.9 ± 1.4	113.7 ± 1.7	101.7 ± 1.4	100.6 ± 2.1	4.8‡	−1.1	0.053	−13.0†	−7.2§

Data are means ± SE. DW-NW, diabetic women–nondiabetic women; DM-NM, diabetic men–nondiabetic men; DM-DW, diabetic men–diabetic women; NM-NW, nondiabetic men–nondiabetic women. *Null hypothesis for interaction *P* value: DW-NW = DM-NM (equivalent to DM-DW = NM-NW). †$P < 0.001$; ‡$P < 0.05$; §$P < 0.01$. ¶Log-transformed for analysis and back-transformed for presentation.

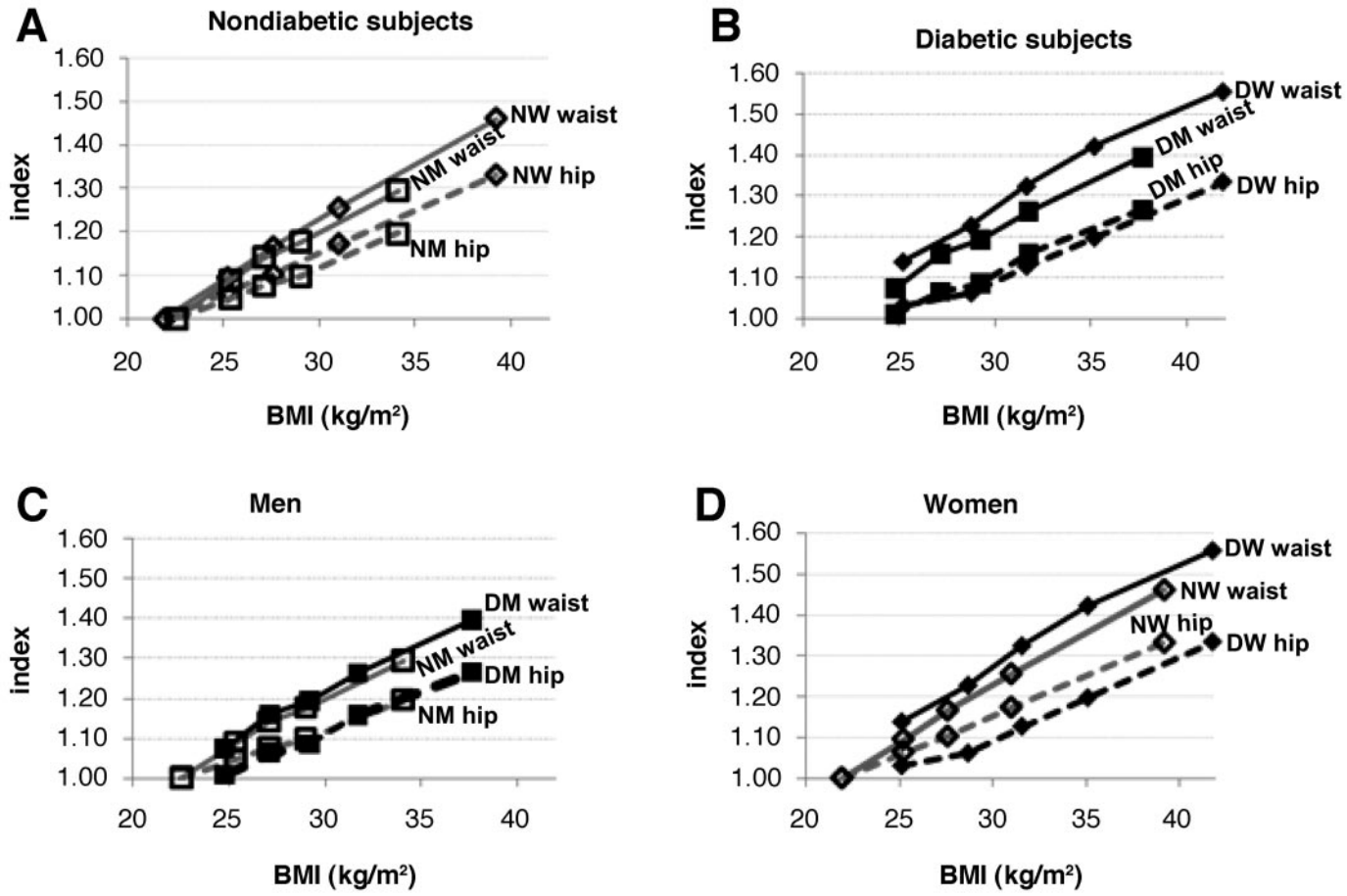

FIG. 2. Waist and hip circumferences by BMI quintile for nondiabetic men (NM), diabetic men (DM), nondiabetic women (NW), and diabetic women (DW). Both measures are indexed by dividing by the mean circumference for the lowest BMI quintile of nondiabetic subjects. For each group, the slope for waist circumference differs significantly from the slope for hip circumference ($P < 0.001$). Significant differences in intercept and slope ($P < 0.05$) are as follows. *A*: All intercepts set = 1; waist slope, NW > NM. *B*: Waist intercept, DW 0.07 > DM. *C*: Waist intercept, DM 0.002 > NM; hip intercept, DM 0.06 < NM; hip slope, DM > NM. *D*: Waist intercept, DW 0.06 > NW; hip intercept, DM 0.10 < NM.

higher systolic blood pressure, and a more proinflammatory profile. Although many of these differences exist between diabetic and nondiabetic men, all are less pronounced, some are nonsignificant, and one, LDL cholesterol, was lower in diabetic than nondiabetic men. Of importance, the key findings were consistent across the three different ethnic groups in IRAS.

Our data indicate that sex is a critical determinant of atherogenic lipoprotein levels in diabetes. As evidenced both by apoB and LDL particle count, differences in atherogenic particle number were much more pronounced between diabetic and nondiabetic women than between diabetic and nondiabetic men. It is important to note that the differences in apoB and LDL particle count were more pronounced than differences in LDL cholesterol or non-HDL cholesterol. Our data extend earlier reports of sex-related differences of apoB between diabetic and nondiabetic subjects (17,18). Not only was the average apoB highest in diabetic women, almost one-half of diabetic women had a markedly elevated apoB. ApoB was significantly higher in diabetic women than in diabetic men. Our results also demonstrate that each class of apoB lipoprotein particles—VLDL, IDL, and LDL—was significantly higher in diabetic women. The higher total LDL particle number was principally due to more small dense LDL, explaining why LDL cholesterol inadequately estimated the differences in LDL. That the overall balance of the atherogenic lipoproteins was substantially altered in diabetic women is evident from the apoB–to–apoA-I ratio.

These data are the most complete characterization of the plasma lipoproteins in these groups to date. Our findings concerning apoB plus the higher systolic blood pressure and CRP go far to explain the markedly higher risk of vascular disease in diabetic women. The differences in apoB are particularly striking. Adjusting for apoB abolished the significance of the sex-diabetes interaction of each of the other cardiovascular risk factors. Despite this result, we believe a more complete explanation of the sex–diabetes–cardiovascular risk interaction is likely multifactorial with apoB being a key factor. It is possible that the greater cross-sectional diabetes-sex interaction of apoB may be offset by the greater longitudinal association of another measure with cardiovascular events. However, this does not appear to be the case in Framingham and INTERHEART reports (13,21) that have shown a greater increase in risk per SD of apoB than of LDL cholesterol or non-HDL cholesterol.

Given how clinically important the differences in apoB appear to be, we have tried to uncover possible pathophysiological mechanisms. HyperTg/hyperapoB (22) was the dominant atherogenic dyslipoproteinemia in the diabetic women and is characterized by higher VLDL and LDL particle numbers with predominantly small, dense LDL due to increased secretion of apoB lipoprotein particles by the liver (23,24). The mechanism of increased secretion of

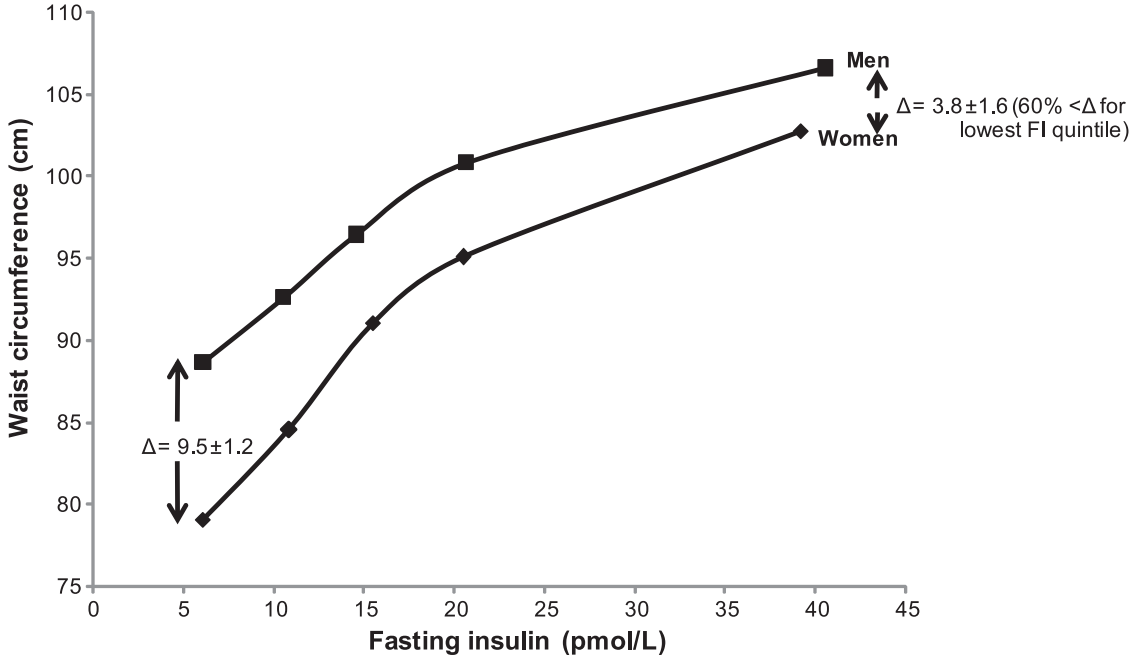

FIG. 3. Mean waist circumferences plotted against mean fasting insulin (FI) by sex-specific fasting insulin quintile for 640 men and 777 women in the IRAS. Regression fit with all variables log-transformed for men: waist = $75.5*FI^{0.091}$ with $R^2 = 0.296$; for women: waist = $62.7*FI^{0.132}$ with $R^2 = 0.336$. For all parameters, the main effect of sex (75.5 vs. 62.7) and sex interaction (0.091 vs. 0.132) were highly significant ($P < 0.0001$). The means (range) for the first through fifth quintiles, respectively, were 6.1 (1–8), 10.5 (9–12), 14.6 (13–17), 20.7 (18–24), and 40.6 (25–255) for men and 6.1 (1–8), 10.4 (9–12), 15.1 (13–17), 20.5 (18–24), and 39.2 (25–171) for women. The number of subjects per fasting insulin quintile ranged from 115 to 140 in men and 144 to 175 in women.

apoB particles is multifactorial, but increased fatty acid flux to the liver is one of the key components (25). In this regard, the differences in body composition of the two groups of women are striking, particularly because efflux of fatty acids from adipose tissue is the major determinant of fatty acid flux to the liver (26).

The absolute differences in measures of body composition were greater between the two groups of women than between the two groups of men. Not only were the differences in body composition less marked between the two groups of men, but abdominal obesity was already a prominent feature in nondiabetic men. Moreover, at any given BMI, the relative distribution of upper and lower body adipose tissue was similar between diabetic and nondiabetic men. By contrast, at any given BMI, waist circumference was greater in diabetic women compared with nondiabetic women, whereas hip circumference was less. Thus, although there was little difference in regional adipose tissue between the two groups of men, there were clear differences in the degree of regional expansion between the two groups of women.

Expansion of visceral and deep subcutaneous adipose tissue compartments is associated with high transmembrane adipocyte fatty fluxes, which was evidenced in our study by higher plasma FFA levels (26,27). Higher plasma FFA are necessarily associated with increased hepatic fatty acid flux and therefore with increased hepatic apoB secretion (25,26). All of our observations are therefore consistent with *1*) the smaller gap in apoB between the two groups of men, *2*) the higher apoB in both male groups than in nondiabetic women, and *3*) the greater apoB in diabetic women than in any of the other groups. It therefore seems reasonable to suggest that the atherogenic transformation of the lipoprotein profile within diabetic women was due to the marked expansion and transformation of the distribution of adipose tissue. Differences in the distribution of body fat may also account for the diabetes-related CRP difference that was selective for women (28,29).

What then could explain the differences in adipose tissue between diabetic and nondiabetic subjects, which were particularly pronounced in women? We propose that the cross-sectional data of this study be used to generate prospective hypotheses for longitudinal testing. As adipocytes form and mature, they accumulate and sequester dietary triglycerides. Consequently, energy intake must increase to meet essential metabolic demands. Multiple in vitro studies have established that insulin is a potent stimulant of adipogenesis (30–32), and plasma insulin has been correlated with subsequent visceral obesity (33). Elevated insulin levels could be a consequence of obesity, but alternatively, based on our results, we query whether sustained elevation of plasma insulin, as part of a complex hormonal interaction, might play a role in producing an expansion of abdominal adipose tissue, which is particularly pronounced in diabetic women.

In summary, our data demonstrate that for multiple variables, the difference in atherogenic profile between diabetic and nondiabetic women is more pronounced than between diabetic and nondiabetic men. In this report, the most striking differences involve elevations of plasma apoB, C-reactive protein, and systolic blood pressure. Because these are modifiable risk factors, our observations point to the potential to ameliorate the loss of cardiovascular protection in diabetic women.

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