Diabetes, abdominal adiposity, and atherogenic dyslipoproteinemia in women compared to men

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ABSTRACT

*Background:* Atherogenic risk is generally lower for women than men but similar in persons with diabetes.

*Methods and Results:* Measures of cardiovascular risk, body composition, and serum hormones from the baseline examinations of the Insulin Resistance Atherosclerosis Study on 524 non-diabetic women, 258 diabetic women, 421 non-diabetic 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/A1 ratio; non-HDL cholesterol; LDL particle count, small LDL, and IDL by nuclear magnetic resonance (NMR); and c-reactive protein exhibited significant diabetes – gender interaction (p<0.05). ApoB exhibited the most significant interaction (p=0.0005). Age- and ethnicity-adjusted apoB means were lower in non-diabetic women than non-diabetic men (102.4 mg/dl versus 106.8, p<.05) but higher in diabetes (115.7 versus 110.2, p<.01). Plotted against BMI, waist circumference was 6% higher and hip circumference 10 % lower in diabetic than non-diabetic women (both p<0.05) while the circumference measures did not differ conspicuously between diabetic and non-diabetic men.

*Conclusions:* In diabetic women, an elevated level of atherogenic particles, as manifested by apoB and LDL P, which may result from abdominal adiposity, represents a major treatable cardiovascular risk factor.
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 become diabetic compared to men who become diabetic (2-4). Identifying the reasons for this alarming increase in vascular disease in diabetic women is critical. Previous work has established that both genders have higher plasma triglycerides and lower HDL C levels in diabetes (5) and that these differences are more pronounced between non-diabetic and diabetic women than between non-diabetic and diabetic men (6-8). However, the differences, if any, in LDL C 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).

The purpose of this study, therefore, was to characterize the lipoprotein profile in greater detail in larger groups of diabetic and non-diabetic 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 non-diabetic women than between diabetic and non-diabetic 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 in order to obtain approximately equal numbers with diabetes, impaired glucose tolerance, and normal glucose tolerance from each ethnic group and center. A total of 1624 individuals participated in IRAS baseline examinations October 1992 - April 1994. This report includes data on 1423 subjects after excluding 128 subjects who lacked nuclear magnetic resonance (NMR) lipid measures, 63 who did not have an intravenous glucose tolerance test for insulin sensitivity assessment, and 10 without an apo B assay. Serum SHBG, estradiol, and testosterone concentrations were measured using standardized assays from Diagnostic Products Corporation (Siemens). Intra- and inter-assay 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.** Analyses of covariance (ANCOVA) with age, ethnicity (non-Hispanic white, African American, or Hispanic), diabetes, gender, and diabetes-gender interaction 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 gender, 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 2 observations per subject were used to test the difference in slopes versus BMI.

Statistical calculations were performed in SAS version 9.1 (Cary, North Carolina). 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. As well, the proportion of those with impaired glucose regulation did not differ between non-diabetic males and females. As anticipated, age, fasting glucose, 2-hour glucose, fasting insulin, hyperlipidemia treatment rates, and hypertension treatment rates were significantly different in both diabetic groups compared to non-diabetic ones with the exception of hyperlipidemia treatment in men (9% in both male groups). Among non-diabetic subjects, mean 2-hour glucose was higher in women than in men (by t-test, p = 0.023) while the percentage of subjects with impaired glucose regulation was higher in men than in women (by Chi Squared test, p = 0.021) and the percentage on hyperlipidemia treatment was also higher in men (9% versus 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 2A), systolic blood pressure and C-reactive protein were higher in both diabetic men and diabetic women compared to their non-diabetic counterparts. Both of these differences were more than 2 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 non-diabetic women than between diabetic men and non-diabetic men. All four markers of the concentration of atherogenic lipoproteins — apoB, LDL C, non-HDL C, and LDL particle count (LDL P) — were significantly higher in diabetic women compared to non-diabetic women. ApoB and non-HDL C were not significantly different between diabetic and non-diabetic men; LDL C was actually greater in non-diabetic men compared to diabetic men, whereas LDL P was higher in diabetic men compared to non-diabetic men. Non-diabetic men had higher apoB levels than non-diabetic women. However, diabetic women had higher apoB than diabetic men.

These differences in the four major atherogenic lipoprotein indices are illustrated in Figure 1. For men, there were only minor differences in the distribution of values for all four indices between those with and without diabetes. For women, although the average value for LDL C in diabetic women was 5.6 mg/dL greater than in non-diabetic women (p<0.05), there was no significant difference.
in the distribution of values of LDL C between diabetic and non-diabetic women. Moreover there was no significant increase in the proportion of women with an elevated LDL C. 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 C, the distribution of values in diabetic women was shifted towards higher values with nearly a doubling of the proportion with a markedly elevated level (41% versus 23%, p<0.0001). All these findings were confirmed by the differences observed in LDL P. Of importance the differences in non-HDL C were intermediate between LDL C and apoB.

Plasma triglycerides were significantly higher in both diabetic groups than non-diabetic groups but no significant gender-diabetes interaction was observed. However, VLDL and IDL particle number were higher only in diabetic women compared to non-diabetic women. LDL particle number was higher in diabetic men compared to their non-diabetic counterparts but the differences were more marked in females. LDL particle number was similar in both diabetic male and female subjects. As expected from the plasma triglycerides, LDL size was lower in both diabetic groups. Equal percentages of non-diabetic males and females had hyperTg/hyperapoB (15.8 and 15.7% respectively). Of the diabetic groups, 24.1% of men versus 32.8% of women had hyperTg/hyperapoB (p=0.036). Fasting plasma FFA were highest in diabetic women. HDL C and apoA-I were significantly lower in both diabetic groups compared to their non-diabetic counterparts. Both diabetic groups were more obese than the non-diabetic 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 waist hip ratio (WHR) and waist circumference in diabetic compared to non-diabetic women was significantly greater than the difference between diabetic and non-diabetic men. As well, waist circumference for diabetic women was significantly greater than for non-diabetic men (p<0.001).

Finally, apoB appeared to be the key measure characterizing the cardiovascular risk factor interactions. As shown in Table 3A, further adjustment for apoB abolished the significance of the gender-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 non-significant (p=0.092) 3.04 mmHg interaction effect in Table 3. Also the interaction effect of LDL C changes from a highly significant (p=0.0006) 13.9 mg/dl to a marginally non-significant (p=0.076) 5.7 mg/dl. Adjusting for apoB attenuated the magnitude of the other interactions by at least 48% and all were more than marginally non-significant (p>0.10).

Body Composition. Table 2B lists the principal results for all the major groups. All four measures — waist circumference, hip circumference, waist/hip ratio and BMI — were significantly higher in both diabetic groups compared to their non-diabetic counterparts. Both diabetic groups were more obese than the non-diabetic 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 waist hip ratio (WHR) and waist circumference in diabetic compared to non-diabetic women was significantly greater than the difference between diabetic and non-diabetic men. As well, waist circumference for diabetic women was significantly greater than for non-diabetic 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 non-diabetic subjects in each gender. Panel 2A and 2B 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 (Panel 2C) 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 (Panel 2D) at any given BMI, waist circumference was 6% greater (p<0.001) in diabetic compared to non-diabetic women. On the other hand, hip circumference was 10% lower at any given BMI in diabetic compared to non-diabetic women. Thus comparing diabetic to non-diabetic subjects, expansion of lower body adipose tissue mass was considerably more constrained in women while expansion of upper body abdominal tissue mass was considerably more pronounced.

**Serum Hormones.** With regard to serum hormones (Table 2C), as expected, serum fasting insulin was higher in both genders in diabetic subjects compared to non-diabetic subjects, total testosterone levels were approximately 20 times higher in men than women whereas estradiol levels in women were double that in men. Sex hormone-binding globulin (SHBG) levels were markedly lower in diabetic compared to non-diabetic 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 non-diabetic men. Diabetic men had significantly lower levels of testosterone than non-diabetic men while diabetic women had significantly higher testosterone than non-diabetic women.

Although the diabetes-gender interaction of fasting insulin was not significant, there was a significant gender interaction (p<0.0001) in the association between waist circumference and insulin (Figure 3): the difference in waist between men and women in the highest quintile of insulin was less than half the same difference in the lowest insulin quintile. When SHBG was added to this association with waist circumference, gender-SHBG interaction was non-significant (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, though 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 gender (7.0±1.2 cm for men versus 13.6±1.1 cm for women, p<0.0001). Finally when both WHR and SHBG were added to the apoB ANCOVA model (Table 3B), the gender-diabetes interaction became marginally non-significant (p=0.053).

**Ethnic heterogeneity.** In each of the IRAS ethnic groups (Hispanics, African Americans, and non-Hispanic whites) the differences between diabetic and non-diabetic 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 non-diabetic women than between diabetic and non-diabetic 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 to non-diabetic women, diabetic women have a more atherogenic lipoprotein profile, a higher systolic blood pressure, and a more pro-inflammatory profile. While many of these differences exist between diabetic and non-diabetic men, all are less pronounced, some are non-significant, and indeed one, LDL C, was lower in diabetic than non-diabetic men. Of importance, the key findings were consistent across the three different ethnic groups in IRAS.

Our data indicate that gender is a critical determinant of atherogenic lipoprotein levels in diabetes. As evidenced both by apoB and
LDL P, differences in atherogenic particle number were much more pronounced between diabetic and non-diabetic women than between diabetic and non-diabetic men. It is important to note that the differences in apoB and LDL P were more pronounced than differences in LDL C or non-HDL C. Our data extend earlier reports of gender-related differences of apoB between diabetic and non-diabetic subjects (17,18). Not only was the average apoB highest in diabetic women, almost half of diabetic women had a markedly elevated apoB. Indeed, 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 due principally to more small dense LDL, explaining why LDL C 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/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 C-reactive protein 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 gender-diabetes interaction of each of the other cardiovascular risk factors. Despite this result, we believe a more complete explanation of the gender-diabetes-cardiovascular risk interaction is likely multifactorial with apoB being a key factor. It is possible that apoB’s greater cross-sectional diabetes-gender interaction may be offset by another measure’s greater longitudinal association 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 standard deviation of apoB than of LDL C or Non-HDL C.

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 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 since 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 non-diabetic men. Moreover, at any given BMI, the relative distribution of upper and lower body adipose tissue was similar between diabetic and non-diabetic men. By contrast, at any given BMI, waist circumference was greater in diabetic women compared to non-diabetic women whereas hip circumference was less. Thus, while 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 non-diabetic 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 non-diabetic subjects, differences, which were particularly pronounced in women? We propose that this report’s cross-sectional data 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 non-diabetic women is more pronounced than between diabetic and non-diabetic men. In this report, the most striking differences involve elevations of plasma apoB, CRP, and systolic BP. Since 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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Figure 1. Histograms of (A) Apolipoprotein B (ApoB), (B) low density lipoprotein cholesterol (LDLC), (C) non high density cholesterol (NonHDL C), and (D) low density lipoprotein particle count (LDLP) by gender and diabetes status. Chi Square comparisons of the proportions above selected risk thresholds among diabetic versus non-diabetic subjects were:

(A) 41% of diabetic women had apoB > 120 mg/dl versus 23% of non-diabetic women, p<0.0001; 30% of diabetic versus 26% of non-diabetic men, p=0.22.
(B) 31% of diabetic women had LDLC > 160 mg/dl versus 27% of non-diabetic women, p=0.19; 24% of diabetic versus 29% of non-diabetic men, p=0.14.
(C) 32% of diabetic versus 23% of non-diabetic women had NonHDL C > 190 mg/dl, p=0.003; 29% of diabetic versus 24% of diabetic men, p=0.16.
(D) 20% of diabetic versus 10% of non-diabetic women had LDLP > 1617 nmol/L, p=0.0002; 12% of diabetic versus 10% of non-diabetic men, p=0.28.
Figure 2. Waist and hip circumferences by BMI quintile for non-diabetic men (NM), diabetic men (DM), non-diabetic women (NW), and diabetic women (DW). Both measures are indexed by dividing by the mean circumference for the lowest BMI quintile of non-diabetic 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 noted in each panel.
Figure 3. Mean waist circumferences plotted against mean fasting insulin (FI) by gender-specific FI quintile for 640 men and 777 women in the Insulin Resistance Atherosclerosis Study (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. All parameters, the main effect of gender (75.5 versus 62.7), and gender interaction (0.091 versus 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 FI quintile ranged from 115 to 140 in men and 144 to 175 in women.
### Table 1. Descriptive statistics of the study sample

|                        | Non-diabetic Women (NW) | Diabetic* Women (DW) | Non-diabetic Men (NM) | Diabetic* Men (DM) |
|------------------------|-------------------------|----------------------|-----------------------|-------------------|
| N                      | 524                     | 258                  | 421                   | 220               |
| Age, mean (SD), y      | 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, mean (SD), (mg/dL) | 96 (11)                | 168 (58)             | 100 (9)               | 172 (58)          |
| 2-hr Glucose, mean (SD), (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                |

*Diabetes diagnosed by 1999 World Health Organization criteria: Fasting glucose > 126 mg/dl, 2-hr glucose > 200 mg/dl, or on hypoglycemic medication

† Fasting glucose > 100 mg/dl or 2-hr glucose > 140 mg/dl.

‡ p< 0.05 versus non-diabetic women.
| Measure                                      | Non-diabetic Women(NW) | Diabetic Women(DW) | Non-diabetic Men(NM) | Diabetic Men(DM) | DW-NW | DM-NM | Interaction p-value† | DM-DW | NM-NW |
|----------------------------------------------|-------------------------|--------------------|----------------------|------------------|-------|-------|----------------------|-------|-------|
| 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***|
| Apolipoprotein B (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** |
| Apolipoprotein A1 (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             | 39.4±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 |
| Apolipoprotein B/A1 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/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)#                       | 207.0±2.87              | 219.3±2.67         | 211.3±2.08           | 207.0±2.87       | 6.81* | -4.22 | 0.022               | -12.28**| -1.25 |
| LDL size by gel (angstroms)                  | 262.3±0.4               | 259.0±0.6          | 253.9±0.5            | 252.0±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 free fatty acids (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***|

† Null hypothesis for interaction p-value: DW-NW = DM-NM (equivalent to DM-DW = NM-NW).

# Log-transformed for analysis and back-transformed for presentation; * p<0.05; **p<0.01; ***p<0.001; †excluded 266 missing testosterone and sex binding hormone globulin (SHBG) measurements; § excluded 4 missing waist or hip circumference
Table 3. Means ± standard errors of baseline measures with significant demographically adjusted interaction by gender and diabetes status additionally adjusted as indicated

| Measure                                      | Non-diabetic Women(NW) | Diabetic Women(DW) | Non-diabetic Men(NM) | Diabetic Men(DM) | DW-NW | DM-NM | Interaction p-value† | DM-DW | NM-NW |
|----------------------------------------------|------------------------|--------------------|----------------------|------------------|-------|-------|---------------------|-------|-------|
| **A. CVD risk factors additionally adjusted for apolipoprotein B** |                        |                    |                      |                  |       |       |                     |       |       |
| 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**|
| Apolipoprotein B/A1 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)#               | 1111.3±10.8            | 1170.9±16.4        | 1178.9±12.8          | 1211.8±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**|
| **B. Apolipoprotein B (mg/dl) adjusted for demographics, waist/hip ratio, and SHBG** |                        |                    |                      |                  |       |       |                     |       |       |
| Apolipoprotein B (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**|

† Null hypothesis for interaction p-value: DW-NW = DM-NM (equivalent to DM-DW = NM-NW).
# Log-transformed for analysis and back-transformed for presentation;
* p< 0.05; **p<0.01; ***p<0.001