Effect of Diabetes Mellitus on Liporpotein Triglyceride and Cholesterol Concentrations Related to Sex

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We studied sex differences in the serum lipid abnormalities associated with diabetes mellitus in 111 patients with insulin-dependent diabetes and 270 patients with non-insulin-dependent diabetes, who were compared with 586 nondiabetic controls. Relative to control levels, the increases in triglycerides were 17 to 34 mg per deciliter greater in diabetic women than in diabetic men. The median low-density-lipoprotein cholesterol concentration in non-insulin-dependent diabetics was 1 to 4mg per deciliter lower than the control level in women and 16 to 22mg per deciliter lower in men, and was 30 mg per deciliter higher than control in insulin-dependent diabetic women and similar to control in insulin-dependent diabetic men. The decrease in median high-density-lipoprotein cholesterol in non-insulin-dependent diabetics was 2 to 7 mg per deciliter greater in women than in men, and the increase in high-density-lipoprotein cholesterol in insulin-dependent diabetics was 3 mg per deciliter less in women than in men. We conclude that diabetes has a greater adverse effect on triglyceride and lipoprotein cholesterol concentrations in diabetic women than in diabetic men, and that this may explain the greater increase in risk of anteriosclerosis in diabetic women.

Key words: Lipoprotein triglyceride, diabetes mellitus,

Diabetes is frequently associated with elevated concentrations of total plasma triglyceride and low-density-lipoprotein (LDL) cholesterol and reduced concentrations of high-density-lipoprotein (HDL) cholesterol.[1-5] Both coronary and peripheral arterial atherosclerosis appear to be associated with these lipoprotein abnormalities in diabetics.[4,6-8] Whereas normal women usually have less arteriosclerotic vascular disease than men, diabetic women lose this protection and have prevalence rates of arteriosclerotic disease that approach or equal those of men.[9-11] It is not known whether lipid abnormalities are greater in diabetic women than in men, or whether these abnormalities may explain the difference in the risk of arteriosclerosis.

Recent studies have distinguished the lipoprotein and lipid changes observed in Type I, or insulin-dependent, diabetes (IDDM) from those in type II, or non-insulin-dependent, diabetes (NIDDM). There is general agreement that the level of HDL, cholesterol is higher than normal in IDDM[2,5,12,13] and normal or lower in NIDDM.[6,14] In contrast, changes in LDL cholesterol are not consistently seen. Some workers have reported elevations of LDL cholesterol in IDDM[3,4] and NIDDM,[5,6] but no LDL elevations were observed in the primarily NIDDM group studied in Framingham[15] or in studies by Eckel et al[12] and Lisch and Sailer.[11] Recent evidence indicates that concentrations of LDL cholesterol are lower in patients with better diabetic control[3,16] and that insulin administration over a period of hours to weeks improves lipoprotein and lipid levels in diabetics.[16,17] Thus, the level of glycemic control may explain some of the differences among studies. These observations suggest that it is essential to consider the mode of therapy, the level of glycemic control, and they type of diabetes when any cross-sectional analysis of hyperlipidemia in a diabetic population is directed at evaluating difference due to sex.

We measured whole plasma and lipoprotein lipids in 381 adults with IDMM or NIDDM who were classified by mode of hypoglycemic therapy and by sex, and compared the results with those in nondiabetic controls matched for age and sex. This report analyzes three questions: Do sex differences exist in lipoprotein abnormalities induced by diabetes, is LDL cholesterol revated in NIDDM and IDDM, and are lipoprotein lipids affected by the mode of therapy.

Methods

Subject recruitment and classification

Diabetic subjects from PMRC Centre, Fatima Jinnah Medical Center for study were recruited. 507 diabetics who were at least 20 years of age, we exclude from the analyses, 31 women taking steroid sex hormones, 13 subjects taking lipid-altering medications and 7 persons over the age of 79. The lipid measurements of 8 persons who had fasted for less than 12 hours before blood was drawn were also excluded, as were an additional 25 diabetics on treatment regimens of both oral antihyperglycemic drugs and insulin. The remaining 381 subjects were divided into four classifications, three groups of subjects with NIDDM treated by diet, or insulin, and all subjects with IDDM. These classifications are based on the recommendation of the National Diabetes Data Group[18] and have been described previously[7]

Two similarly aged non-diabetics control groups were used in the analysis - one for comparison with the order subjects with NIDDM and one for the younger subjects with IDDM. Controls for the patients with NIDDM were friends of the patients and of similar age, but had no family or personal history of diabetes. Controls were excluded if they were taking lipid-altering medications, had fasted for less than 12 hours before blood was drawn, or were women taking steroid sex hormones

leaving 54 men and 40 women.

Subjects selected as controls for this investigations were the randomly sampled adults 20 years of age and older who were free of diabetes according to the medical history and who had fasted for at least 12 hours before blood was drawn. Women taking steroid sex hormones and persons taking lipid-altering medications were excluded, leaving 312 men and 171 women as controls for the patients with IDDM.

Laboratory Procedures

Lipoprotein cholesterol and triglyceride were measured with previously described methods.[20] Cholesterol was measured by HDL enzymatic method and triglycerides by the method of Kessler, using the Auto Analyzer system.[20] Levels of very-low-density lipoprotein (VLDL) were calculated as the difference between lipid concentrations in total plasma and those in the density 1.006 infranatant after ultracentrifugation at 40,000 rpm (105,000xg) for 18 hours at 10oC. HDL lipids were measured after heparin-manganese chloride precipitation of VLDL and LDL. LDL lipids were calculated cholesterol = T-cholesterol-Triglycerides/5-HDL.

Nonlipid blood-chemistry studies included measurement, of glucose and creatinine. Clinical chemistry measurements in the diabetes and the controls for subjects with NIDDM were performed at Pakistan Medical Research Council (PMRC) and Postgraduate Medical Institute (PGMI). Plasma glucose was measured by the glucose oxidase method, and creatinine by the alkaline-picrate method. Clinical-chemistry measurements in the controls for subjects with IDDM were performed. Plasma glucose was measured on the ABA-100 by a hexokinase method.[21] Creatinine was measured by the Jaffe reaction.[22]

Plasma and Liporpotein Triglyceride

Table shows the mean (ñSD) and median values for plasma and lipoprotein-triglyceride concentrations for each diabetic and control group. Positive skewing apparent from a comparison of the mean with the median values. Differences in median values between diabetics and controls are plotted in figure. The median plasma triglyceride level was significantly higher in diet-treated men and women with NIDDM than in controls. Sulfonylurea-treated diabetics of both sexes and higher triglyceride levels than controls, but the differences were not significant because of the small sample sizes. Triglyceride levels in insulin-treated men with NIDDM were almost identical to those in controls - significantly lower than in diet-treated men and lower, but no significantly lower than in sulfonylurea-treated men. A similar trend toward a lower triglyceride level was observed in insulin-treated women with NIDDM, as compared with diet-treated and sulfonylurea-treated women, but in contrast to the results in men, the level remained 32 mg per deciliter (0.36 mmol per liter) higher than the control value. In men and women with IDDM, total triglyceride levels were significantly higher than control levels, but women had greater elevations than men. The respective triglyceride levels in men and women with IDDM were somewhat lower than those in insulin-treated men and women with NIDDM. Across all categories of NIDDM and in IDDM, women had consistently higher triglyceride values than men relative to controls, with elevations ranging from 33 to 58 percent in women and -2 to 27 percent in men.

Elevations in VLDL-triglyceride concentrations showed trends similar to those observed in total triglyceride. There were statistically significant differences between diet-treated and insulin-treated men with NIDDM and between women and IDDM and controls. Like the increases in total triglyceride, the increases in VLDL triglyceride were consistently greater in women than in men, with relative differences from control values ranging from 21 to 84 percent in women as compared with -3 to 45 percent in men.

Table:2 Whole plasma and lipoprotein triglyceride concentrations in men and women with NIDDM or IDDM and in nondiabetic controls

Category & treatment	No. of subject	Total Triglycerides		Lipoprotein Triglyceride					
Median				VLDL		LDL		HDL	
		Mean±SD	Median	Mean±SD	Median	Mean±SD	Median	Mean±SD	Median
Men with NIDDM									
Controls	54	133±66.7	121	87±60.6	76	32±12.3	30	11±4.7	11
Diet	43	215±176.1	154	167±170.8	110	33±9.1	31	15±4.6	14
Sulfonylurea	38	230±260.1	147	181±250.7	91	34±11.6	32	15±5.0	14
Insulin	79	196±450.8	119	148±445.5	70	32±11.5	33	16±7.2	14
Men with IDDM									
Controls	312	116±88.3	94	85±83.0	64	19±9.7	17	12±5.1	11
Insulin	63	118±78.3	96	76±70.1	62	28ñ12.2	25	14±7.4	13
Controls	40	119±60.6	98	72±48.9	58	34±12.6	32	14±4.4	13
Women with NIDDM									
Diet	39	265±426.7	148	204±418.3	94	42±19.6	36	19±7.4	19
Sulfonylurea	25	198±170.4	155	142±162.0	107	38ñ14.5	33	18±7.7	16
Insulin	46	299±641.8	130	244±632.0	70	38±20.4	34	18±7.3	15
Women with IDDM									
Controls	171	73±35.5	66	44±29.2	38	17±8.6	16	12±5.1	12
Insulin	48	121±73.2	97	72±66.2	46	32±11.1	31	17±6.3	16

LDL-triglyceride concentrations were similar among all NIDDM treatment groups and controls, for both men and women. Men and women with IDDM, however, had LDL-triglyceride values significantly higher than controls. Increments from control values were similar in men and women with NIDDM, as were the percentage increments (3 to 10 percent and 3 to 12 percent, respectively). Women with IDDM had greater absolute and relative increases from control values (15mg per deciliter and 94 percent, respectively) than did men with IDDM (8mg per deciliter and 47 percent).

HDL-triglyceride concentrations were significantly higher than control values in all groups of diabetic men and in women with insulin-treated NIDDM or IDDM. Diet-treated women with NIDDM or IDDM had significantly higher HDL-triglyceride concentrations than men. The increments above control were greater in women (2 to 6 mg per deciliter or a relative difference of 15 to 46 percent) than in men (2 to 3 mg per deciliter or a relative difference of 18 to 27 percent).

Plasma and Lipoprotein Cholesterol

The mean (±SD) and median values for plasma and lipoprotein cholesterol in each diabetic and control group are shown in Table. The differences in median values between the diabetic groups and their respective controls are plotted in figure. Total plasma cholesterol levels in men with NIDDM were lower than in controls, although the difference was not statistically significant. The median values for women with NIDDM were above those of controls, but again the differences were not significant. Subjects with IDDM, regardless of sex, had total cholesterol values significantly higher than controls, but the elevation above the control value was live times greater in women than in men.

The level of VLDL cholesterol was consistently higher in men and women with NIDDM than in controls. The elevations were significant for men treated with diet or sulfonylureas and for all three treatment groups of women with NIDDM. The value for VLDL cholesterol in men with IDDM was slightly but not significantly lower than the control value, whereas women with IDDM had a significantly higher value than control. Elevations in VLDL cholesterol above control were slightly greater in women than in men. The relative differences from control were more dissimilar; 25 to 118 percent above control in women, as compared with 15 percent below control and 80 percent above control in men.

The LDL cholesterol concentrations in the NIDDM groups were generally below those of controls, with absolute reductions from control greater in men than in women. The median LDL cholesterol value was not different from control in men with IDDM, but it was significantly above control (by 30mg per deciliter) in women. Expressed as percentages, the reductions in LDL cholesterol from control were greater in men with NIDDM (-10 to -14 percent) than in women (-1 to -3 percent). Women with IDDM had a greater increment above control (25 percent), than men with IDDM (1 percent).

The HDL-cholesterol value was significantly lower in the diet-treated and sulfonylurea-treated men with NIDDM than in controls or insulin-treated men with NIDDM. Among the women with NIDDM, the HDL cholesterol value was significantly below control levels in the sulfonylurea and insulin groups. The decrements from control in all women with NIDDM were greater than in men. In subjects with IDDM, the HDL-cholesterol values were significantly higher than control, with the increment greater in men than women. Nonetheless, absolute concentrations of HDL cholesterol were higher in women across all diabetic categories than they were in men. Expressed as a percentage, the decrement from control in NIDDM was greater in women than in men, resulting in relative inductions of 13 to 26 percent in women and 2 to 17 percent in men. The relative increase in IDDM as greater in men (12 percent) than in women (4 percent).

Discussion

Numerous studies have described lipid and lipoprotein abnormalities associated with diabetes mellitus,[1-17] however, the findings have not always been resistant. Some of the inconsistencies may be due to differences in the classification of diabetics, failure to distinguish among different treatment regimens, differences in the degree of diabetic control, or variations control populations. Consideration of treatment is articularly important because improved metabolic control of plasma and lipoprotein lipid concentrations has been reported with better diabetic control.[16,17] Most studies have focused on total lipids or lipoprotein cholesterol, with few including measurements of the lipoprotein cholesterol and triglyceride. Finally, various studies have not identified consistent male to female differences in lipoproteins associated with diabetes. This report presents total and lipoprotein cholesterol and triglyceride measurements in subjects in defined categories of diabetes and treatment, compares them with nondiabetic subjects, and comments on the question of male to female differences.

Perhaps the most interesting result of this study is one consistently greater degree of lipoprotein abnormalities in female as compared with male diabetics in both NIDDM and IDDM. Regardless of treatment category or type of diabetes, women had consistently higher median total and VLDL-triglyceride and LDL-cholesterol levels and lower HDL-cholesterol levels than control subjects or diabetic men (Fig. I). previous studies distinguished between male and female diabetics in reporting total and lipoprotein lipid concentrations, but specific differences between men and women as compared with a control population have been noted only rarely. In examining previous studies, trends toward greater elevations above control in women than in men are seen for total cholesterol and LDL cholesterol in the data of Nikkila[2] and Hormila[6], Reckless et al, and Barett- Connor et al[16] Brown et al. Found trends toward a greater rise in triglycerides, a lesser reduction in LDL cholesterol, and a greater reduction in HDL cholesterol in women with NIDDM as compared with men.[17] A lesser

increase in the HDL2 subfraction was observed in insulin-treated women diabetics as compared with men in a study by Mattock et al[5]

The observed differences between male and female diabetics in the present study may be due to several factors: the number of subjects was larger than in most other studies, the controls were closely comparable, lipoprotein levels were adjusted for age and body mass index, and all measurements were made in a laboratory using highly standardized methods. Median values rather than means were used for comparisons, since means are often skewed by outliers, as is apparent in Tables 2 and 3. Finally, it is the difference between diabetics and controls that is most informative in speaking of male-female differences, since the absolute concentrations in plasma are strongly influenced by sex and age. Since all lipoprotein abnormalities in diabetes are imroved by diabetic control,[3,16,17] a consistent bias toward better diabetic control in all the male diabetics, as compared with the female diabetics, cannot be ruled out. However there is no reason to believe that such a consistent bias might operate in favor of men. The effects of different treatment methods on glycosylated hemoglobin were not assessed in this study. However, the similarities in median glucose concentrations in corresponding categories of male and female diabetics provide evidence against any bias associated with diabetic control. Finally, the consistency with which the male-female difference was maintained across all categories of NIDDM and IDDM reinforces the credibility of the observation.

Table: Whole plasma and lipoprotein cholesterol concentratiosn in diabetic and control subjects.

Category & treatment Median	No. of subject	Total Triglycerides		Lipoprotein Triglyceride					
				VLDL		LDL		HDL	
		Mean±SD	Median	Mean±SD	Median	Mean±SD	Median	Mean±SD	Median
Men with NIDDM									
Controls	54	225±33.4	226	19±13.2	15	156±33.5	158	50±12.1	48
Diet	43	218±34.8	210	35±26.9	27	142±31.6	139	41±12.7	40
Sulfonylurea	38	220±47.4	217	40±43.0	26	141±42.0	142	40±12.5	40
Insulin	79	218±62.1	209	33±65.4	19	137±43.2	136	48±16.8	47
Men with IDD									
Controls	312	195±34.3	190	24±18.6	20	126±31.0	125	44±10.9	43
Insulin	63	204±55.8	196	21±18.4	17	133±51.7	126	50±15.3	48
Women with NIDDM									
Controls	40	235±31.1	226	15±11.4	11	155±30.3	150	66±16.5	62
Diet	39	248±67.7	238	47±73.0	24	147±43.4	149	55±19.1	52
Sulfonylurea	25	242±53.1	235	33±31.6	21	158±43.9	146	51±18.5	46
Insulin	46	250±79.2	233	43±81.6	19	148±53.5	148	59±23.2	54
Women with IDDM									
Controls	171	180±32.6	174	15±9.7	12	112±29.9	109	54±11.3	52
Insulin	48	219±40.8	212	20±14.6	15	139±38.3	139	60±16.5	54

The observed results may explain the higher prevalence of arteriosclerosis in diabetic women. Both LDL cholesterol and HDL cholesterol are strongly related to cardiovascular disease in diabetic men and women,[7,15] and there is no indication that these risk factors are less important in the development of cardiovascular disease in diabetics then in nondiabetics.[9] Finally, the increase in the risk of cardiovascular disease associated with diabetes is greater in women than in men[9,11]. The consistently greater lipoprotein abnormalities in diabetic women may explain this greater predisposition. In the light of a recent report showing that coronary heart disease can be prevented by lowering cholesterol, the data suggest that lowering LDL cholesterol in diabetic women may be a particularly important therapeutic objective. Obviously, both groups would also benefit from maximal glycemic control, weight loss if appropriate, and removal of other risk factors for arteriosclerotic vascular disease, especially smoking and hypertension.[10,11,29] One explanation for the greater increase in the risk of arteriosclerosis in diabetic women might be a negration of the anti-related difference in HDL cholesterol seen in the general population persists between diabetic men and women (Table 2); thus, it is difficult to argue that diabetic women are endocrinologically different from nondiabetic women. The data suggest nonetheless that the impact of the diabetic state on lipoprotein homeostasis is proportionally greater in women.

The greater adverse effect of diabetes on lipoprotein concentrations in women may be related to a greater rate of entry of VLDL into the circulation in women which is suggested from studies of animal models estrogen treatment, and pregnancy. A greater generation of HDL and LDL would be likely to result from such an increase in VLDL entry. Because of these differences, an equivalent reduction in insulin action on lipoprotein lipase-mediated removal of VLDL triglyceride from the circulation, among other possible effects, may result in greater lipoprotein abnormalities in women than in men. Further studies are required to verify this hypothesis and may lead to more rational treatments.

In conclusion, these studies provide evidence for a consistently greater adverse effect of diabetes on whole plasma triglyceride and lipoprotein-cholesterol concentrations in all categories of female diabetics as compared with male diabetics. The elevation in LDL cholesterol in women with IDDM was particularly notable, as were the relatively low total and VLDL triglyceride levels in insulin-treated men and women with NIDDM. These results suggest several mechanisms by which lipid metabolism may induce atherogenesis in diabetes. Measures to reverse these effects may deserve a high priority in the treatment of diabetics, especially diabetic women.

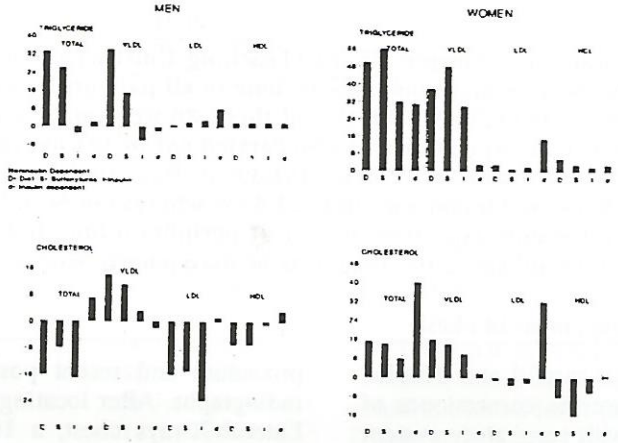

Fig. Differences between median values for total & lipoprotein triglyceride & cholesterol in diabetic and control subjects.

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