The Cardiovascular Risk Profile of Adolescents with Insulin-dependent Diabetes Mellitus

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Cardiovascular risk factors including blood pressure, lipoprotein concentrations, physical activity, and diet were assessed in 149 diabetic adolescents and 45 nondiabetic siblings. All diabetic subjects had had insulin-dependent diabetes mellitus (IDDM) for a minimum of 2 yr and were currently attending the Children's Hospital of Pittsburgh Diabetes Clinic. For both boys and girls, cardiovascular risk profiles were mildly disturbed among diabetic subjects compared with nondiabetic siblings. These disturbances included higher systolic ($P = 0.002$) and diastolic ($P = 0.024$) blood pressures and higher HDL_3 cholesterol concentrations. The diabetic girls showed higher total cholesterol concentrations during adolescence in contrast to the usual fall seen in nondiabetic adolescents (and evidenced in the siblings studied). In addition, the diabetic girls' mean pulse rate was 12 bpm higher than that of the sibling girls, a finding not seen in the boys. Multiple linear regression analyses showed that neither glycemic control (worse in diabetic girls), diet, nor physical activity were important explanatory variables for any of the lipoprotein or blood pressure measures. These results suggest that the cardiovascular risk profile of diabetic girls may be relatively more disturbed than that of diabetic boys. This difference could not be explained by the slightly higher glycosylated hemoglobin levels in the girls. The loss of the sex differential in the risk for cardiovascular disease experienced by adults with IDDM may partly relate to these adolescent risk factor differences. DIABETES CARE 1985; 8:118–24.

It is generally accepted that diabetic patients have an increased risk of cardiovascular disease. Although a component of this may be related to cardiopathy, the majority of the burden appears to be in the form of accelerated atherosclerosis.[1,2] Much of the data available is based on the experience of non-insulin-dependent diabetic patients, while there is little information concerning insulin-dependent diabetes mellitus (IDDM). Though a large excess risk of cardiovascular disease is reported in the few cohort studies of varying design,[3–7] knowledge of the operation of cardiovascular risk factors in IDDM is extremely limited. Most of the data is cross-sectional in nature, and though many studies have reported lipid concentrations in diabetic children and adolescents[8–15] and a few have reported blood pressure levels,[16,17] we are unaware of any comprehensive description of the cardiovascular risk profile in diabetic children or adolescents.

In the general population, the sex differential in cardiovascular risk factors begins to emerge in adolescence.[18–20] The study of diabetic adolescents is of particular interest, as it would appear that insulin-dependent diabetic patients may show the same lack of a sex differential in cardiovascular mortality as do non-insulin-dependent diabetic patients.[6,7] This is in sharp contrast to the nondiabetic population, where a heavy excess of cardiovascular disease is seen in men. We have therefore studied diabetic adolescents attending the Children's Hospital of Pittsburgh Diabetes Clinic, which previous studies have shown to be fairly representative of the Allegheny County IDDM Registry.[21–23] In this report, we focus on the sex-specific lipoprotein concentrations and blood pressure distributions in the insulin-dependent diabetic population and compare these to a group of nondiabetic siblings of IDDM cases. In addition, the interrelationships of these risk factors, health-related behavior, and glycemic control are explored for the diabetic cases.

METHODS AND SUBJECTS

All Children's Hospital of Pittsburgh Diabetes Clinic patients aged between 9 and 16 yr on 31 December 1981 were eligible

TABLE 1
Mean age in years ± SD by sex and diabetic status

	Boys	Girls
Cases	14.7 ± 2.01 (N = 74)	14.3 ± 2.31 (N = 75)
Siblings	13.9 ± 2.32 (N = 21)	13.7 ± 2.14 (N = 24)

to take part if their diagnosis of diabetes had been made two or more years previously. This was in order to exclude any interference by the honeymoon phase. One hundred and forty-nine IDDM patients participated, which represents 72% of all those eligible. Seventy-four were boys and 75 were girls. In addition, 45 unaffected siblings of IDDM cases were studied, approximately half of whom were related to the diabetic subjects. The remaining unaffected siblings came from other IDDM families in our registry.

Subjects were seen in the morning and underwent a standardized examination that involved completion of an administered questionnaire to record family history, the child's medical history, an assessment of physical activity using the Paffenbarger Harvard Alumni Survey,[24] and a previously validated nutrition questionnaire to assess adherence to a low-cholesterol, saturated-fat diet.[25] This interview usually took 15 min, after which four blood pressure and pulse rate measurements were recorded without the subject moving from the sitting position. Both the right and left arms were used, two readings being made with a mercury sphygmomanometer recorded by one of us (T.J.O.) who had been previously trained in blood pressure recordings for epidemiology studies.[26] The other two readings were taken using a BPI 420 automated machine (Medtek Corporation, Princeton, New Jersey), which records systolic and diastolic blood pressures and the pulse rate. The order of arms and methodology was randomly determined. Blood pressures and pulse rates analyzed represent the mean of the second, third, and fourth recordings. Essentially similar patterns were observed using either BPI 420 or mercury sphygmomanometer readings alone. Blood samples were obtained after an overnight fast whenever possible. A brief physical examination with measurement of height and weight, Tanner staging, and assessment of peripheral pulses was made. Because of partial refusals or difficulties in arranging attendance, the number of individuals with data available for any particular analysis varied. In addition, 10 individuals with other major illnesses (e.g., Down's syndrome, a patient with abnormal circulating glucagon molecules, intercurrent illness) were excluded from the lipid and blood pressure data. Only fasted subjects were included in the analyses concerning LDL cholesterol and triglycerides.

TABLE 2
Mean total and LDL serum cholesterol and triglycerides (mg/dl) ± SD by sex and diabetic status (N)

	Boys		Girls	
	Cases (54)	Siblings (20)	Cases (53)	Siblings (21)
Total cholesterol	148 ± 24	145 ± 26	168 ± 31	159 ± 25
LDL cholesterol*	84 ± 22	87 ± 24	97 ± 27	94 ± 22
Triglycerides*	67 ± 21	60 ± 19	79 ± 32	65 ± 17

*LDL cholesterol and triglyceride analyses limited to fasted subjects only, i.e., 29 male cases, 18 male siblings, 32 female cases, 18 female siblings.

TABLE 3
Mean total HDL, HDL_2, and HDL_3 cholesterol serum concentrations (mg/dl) ± SD by sex and diabetic status (N)

	Boys		Girls	
	Cases (54)	Siblings (21)	Cases (53)	Siblings (22)
Total HDL-C	49.6 ± 10.3	45.8 ± 9.3	50.2 ± 9.5	49.3 ± 9.1
HDL_2C	14.3 ± 6.6	13.8 ± 8.4	13.9 ± 6.2	15.8 ± 6.2
HDL_3C	35.3 ± 6.2	32.0 ± 5.7	36.3 ± 5.9	33.5 ± 5.5

LABORATORY METHODS

Serum cholesterol and triglycerides were determined enzymatically[27,28] while HDL cholesterol was measured after precipitation of APO-B-containing lipoproteins with heparin manganese using an adaptation[29] of the Lipid Research Clinics (LRC) method.[30] HDL cholesterol subfractions were also determined after precipitation of HDL_2 with dextran sulfate, enabling HDL_3 to be measured in the supernatant.[31] HDL_2 was calculated by difference (HDL cholesterol − HDL_3 cholesterol). LDL cholesterol was calculated by means of the Friedwald equation.[32] To see if this equation is applicable to IDDM patients, it was compared in a series of 10 patients to ultracentrifuge determination of LDL cholesterol.[30] A strong correlation exists between calculated LDL and measured LDL ($r = 0.99$). It should be noted, however, that the LDL cholesterol concentration is marginally lower when calculated than measured (98.2 versus 106.5 mg/dl, respectively). Glycosylated hemoglobin (GHb) was measured by cation-exchange column chromatography using minicolumns in a water bath (Isolab Inc., Akron, Ohio) after incubation with saline. Normal range is 4.9–7.3%.

Statistical analyses[33] included unpaired Student's *t*-tests (for comparisons of GHb and duration of diabetes between sexes) and two-way analyses of variance (for comparisons of risk factors across the four sex/diabetic groups and for analyses of

TABLE 4
Mean total HDL, HDL_2, and HDL_3 cholesterol serum concentrations (mg/dl) ± SD by sex and diabetic status: Tanner 5 subjects only (N)

	Boys		Girls	
	Cases (28)	Siblings (10)	Cases (23)	Siblings (8)
Total HDL-C	46.5 ± 9.0	40.5 ± 5.6	49.9 ± 10.3	47.6 ± 9.7
HDL_2C	12.9 ± 6.9	9.8 ± 6.1	14.4 ± 6.2	16.6 ± 6.5
HDL_3C	33.6 ± 4.6	30.7 ± 5.2	35.6 ± 6.3	31.0 ± 5.9

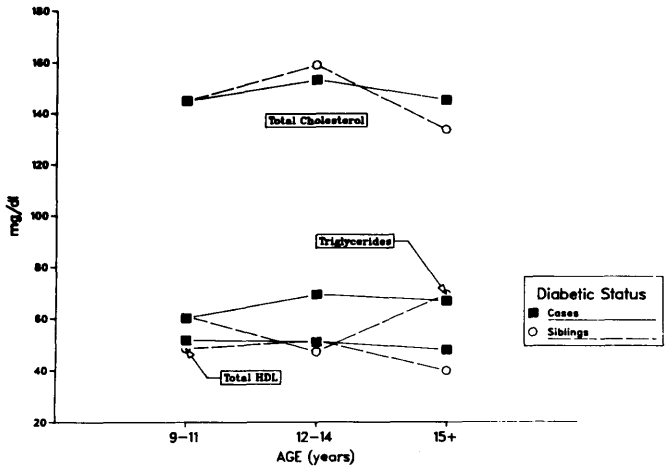

FIG. 1. Mean lipoprotein concentrations for boys by diabetic status and age.

risk factors by age group and diabetic status within sex). Interaction between the two factors (sex/diabetic status or age group/diabetic status) was tested in each analysis but is reported only when significant. Analyses of covariance adjusting for age were performed when indicated (i.e., blood pressure analyses). Multiple linear regression and chi-square analyses were also performed. Because of the non-normal distribution of triglyceride concentrations, these were log transformed before statistical testing.

RESULTS

Table 1 shows the mean age ± standard deviation of the study participants by both sex and diabetic status. No major differences are seen by sex ($F[1,190] = 1.53$, $P = 0.218$), though the cases are a little older ($F[1,190] = 3.75$, $P = 0.054$). The mean duration of diabetes for the boys (mean 7.6 ± 3.4 yr) is similar ($P = 0.3$) to that of the girls (7.0 ± 3.3 yr). The lipid results are presented in Tables 2 and 3. From Table 2, it can be seen that total cholesterol concentrations are generally higher in the girls as compared with boys ($F[1,144] = 16.74$, $P < 0.001$); however, no difference is seen by diabetic status ($F[1,144] = 1.72$, $P = 0.192$). Similarly, a sex difference is noted for calculated LDL cholesterol ($F[1,93] = 4.99$, $P = 0.028$), which is unaffected by diabetic status. Only relatively small sex differences (higher in girls) are seen for triglyceride concentrations ($F[1,93] = 3.791$, $P = 0.054$) and again no major effect of diabetes is seen. These results suggest, therefore, that diabetes per se is not associated with any marked disturbances of these lipoprotein concentrations.

Total HDL cholesterol concentrations (Table 3) do not differ by either sex or diabetic status. However, when examining the HDL subfractions, it is seen that although HDL_2 cholesterol concentrations are similar for all four subgroups, HDL_3 cholesterol concentrations are higher for the cases when compared with the siblings ($F[1,146] = 8.10$, $P = 0.005$). Thus, diabetes may be associated with an increase in HDL_3 cholesterol concentrations.

It should be noted, however, that the normal sex difference in HDL cholesterol concentrations is not fully manifested until late puberty and early adulthood. Therefore, the HDL analyses were repeated after excluding those subjects who had not reached full sexual maturity (i.e., less than Tanner 5). These results are presented in Table 4, where it can be seen that total HDL cholesterol is higher in the girls than the boys ($F[1,65] = 3.91$, $P = 0.052$) irrespective of diabetic status. Though no major differences are noted for HDL_2 cholesterol concentrations by sex ($F[1,65] = 3.255$, $P = 0.076$), and the interaction between sex and diabetic status is statistically insignificant ($P = 0.144$), it can be seen that the diabetic boys' mean HDL_2 cholesterol is 32% higher than that of the sibling boys in contrast to the girls, where the mean of those with diabetes is 13% lower than the siblings. HDL_3 cholesterol concentrations are generally higher in diabetic cases ($F[1,65] = 5.93$, $P = 0.018$), with no sex effect being discernible.

Figure 1 shows the mean lipoprotein concentrations for boys by diabetic status and age. For total cholesterol, little overall difference is seen in the pattern, though there is a suggestion of a fall in total cholesterol concentrations in the older siblings (but not for the older diabetic patients) consistent with the pattern described during adolescence in many previous studies.[18–20] Though diabetic boys are shown to have higher triglyceride concentrations in the 12–14-yr-old age group, no age or diabetic differences are significant by analysis of variance. For HDL cholesterol, the cases do not seem to show the usual adolescent fall in HDL cholesterol concentration when plotted against age.[18–20] However, in Figure 2, where the male HDL cholesterol concentrations are plotted against Tanner stage rather than age, it can be seen that the fall is present in both groups ($F[1,68] = 11.00$, $P = 0.001$).

For girls (Figure 3), the usual fall in total cholesterol with age,[18–20] which is seen for the siblings, is not apparent in the

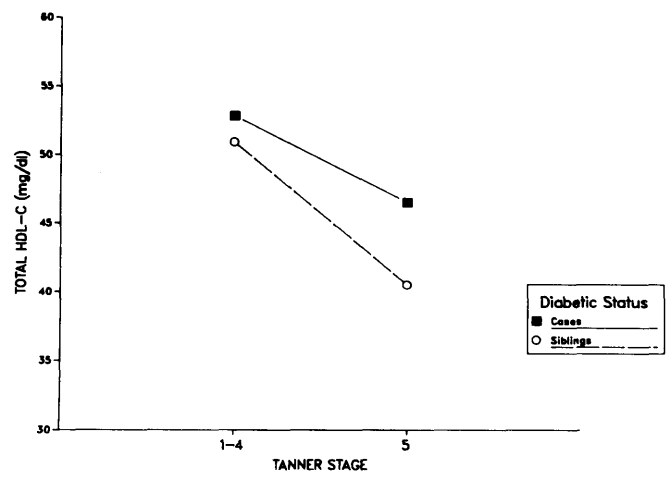

FIG. 2. Mean HDL cholesterol for boys by diabetic status and Tanner stage.

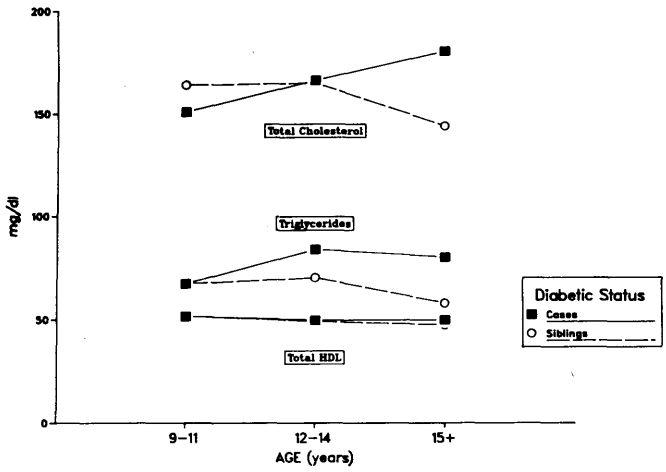

FIG. 3. Mean lipoprotein concentrations for girls by diabetic status and age.

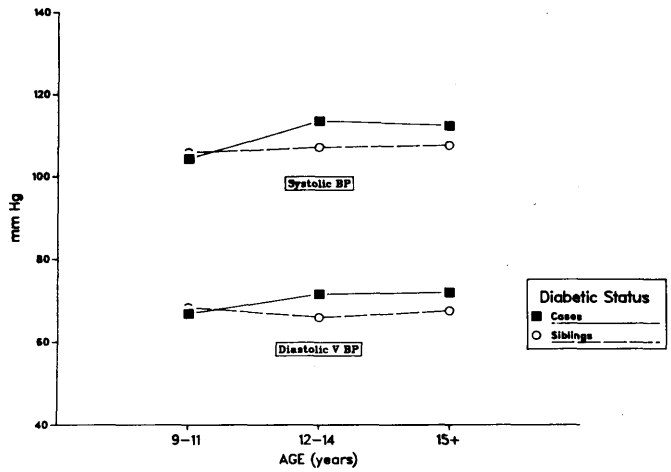

FIG. 5. Mean blood pressure measures for girls by diabetic status and age.

diabetic populations, which shows a rise in total cholesterol. This is confirmed by the analysis of variance, showing a significant interaction between sex and diabetic status ($F[2,68] = 3.34$, $P = 0.041$). No difference in the age pattern is seen for HDL cholesterol by diabetic status. Similarly, the marginally higher triglyceride concentration seen in the cases, when comparing the siblings, is not significant in the analysis of variance.

The age relationships of blood pressures are shown for boys in Figure 4, where it can be seen that systolic blood pressures are higher in the older age groups ($F[2,70] = 24.72$, $P < 0.001$). Cases have consistently higher systolic blood pressures when compared with the siblings ($F[1,70] = 5.36$, $P = 0.024$), while diastolic (fifth phase) blood pressure shows an effect of age ($F[2,70] = 4.06$, $P = 0.021$) but not diabetes. Likewise, for girls (Figure 5), mean systolic blood pressures are higher in the older age groups ($F[2,72] = 4.66$, $P = 0.012$) and the cases have higher mean pressures than the siblings ($F[1,72] = 4.71$, $P = 0.033$). For diastolic (fifth phase) blood pressure, no age effect is present; however, diabetic status has a marginal effect ($F[1,72] = 3.90$, $P = 0.052$).

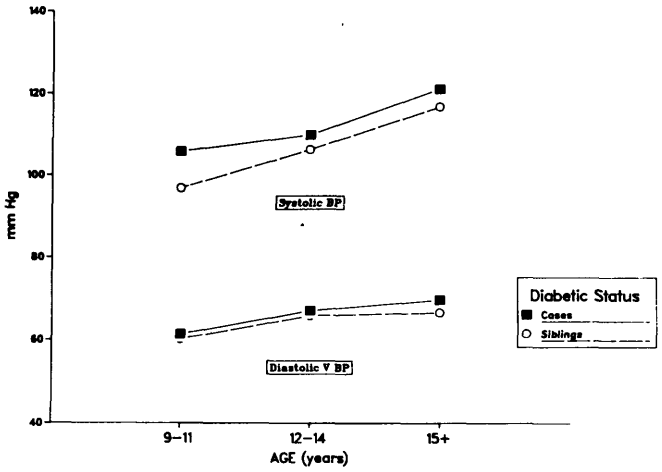

FIG. 4. Mean blood pressure measures for boys by diabetic status and age.

The overall mean blood pressure results are shown in Table 5. Systolic blood pressure is higher in the cases compared with the siblings ($F[1,150] = 10.30$, $P = 0.002$) and in the boys compared with the girls ($F[1,150] = 4.10$, $P = 0.045$), though this latter difference was not significant after age adjustment. Though the differences seen for diastolic fourth phase blood pressures are small, the effect of diabetes ($F[1,147] = 3.12$, $P = 0.08$) and sex ($F[1,147] = 3.87$, $P = 0.051$) border on conventional statistical significance with cases and girls having higher blood pressures. After adjusting for age, the sex effect was significant ($P = 0.017$), although the diabetic effect remained insignificant ($P = 0.14$). Similarly, cases ($F[1,150] = 5.71$, $P = 0.018$) and girls ($F[1,150] = 5.21$, $P = 0.024$) had higher fifth phase blood pressure, the significance of which was unaffected by age adjustment. When examining pulse rate, a clear interaction ($F[1,150] = 6.60$, $P = 0.011$) is seen with the higher pulse rates in cases being largely restricted to the girls.

Three other potential cardiovascular risk factors were evaluated and these are demonstrated in Table 6. Physical activ-

TABLE 5
Mean blood pressure (mm Hg) ± SD and pulse (rate/min) ± SD by sex and diabetic status (N)

	Boys		Girls	
	Cases (55)	Siblings (21)	Cases (55)	Siblings (23)
Systolic	115 ± 10.5	109 ± 10.7	111 ± 8.5	107 ± 6.0
Diastolic IV	75 ± 8.7	73 ± 8.5	78 ± 7.2	75 ± 7.0
Diastolic V	68 ± 8.1	65 ± 8.6	71 ± 7.5	67 ± 6.8
Pulse	74 ± 9.6	72 ± 12.3	83 ± 11.2	71 ± 10.2

TABLE 6
Mean physical activity (kcal/wk), smoking history [% positive (N)], and diet score by sex and diabetic status (N)

	Boys		Girls	
	Cases (70)	Siblings (21)	Cases (70)	Siblings (23)
Physical activity	7515 ± 6085	9048 ± 5885	5000 ± 4493	3320 ± 2521
Smoking	2.8% (2)	4.8% (6)	11.6% (8)	4.2% (1)
Diet*	17.9 ± 3.3	16.2 ± 2.8	18.7 ± 2.4	17.1 ± 2.9

*Diet score represents adherence to a low-saturated-fat diet. High score: good adherence.

ity shows the usual pattern (particularly marked in the siblings) of greater activity in boys as compared with girls ($F[1,180] = 17.69$, $P < 0.001$). However, it should be noted that diabetic status shows no effect. The frequency of smoking was low in all four groups, though 12% of the diabetic girls reported cigarette use. Adherence to a low-saturated-fat diet was greater in the diabetic subjects ($F[1,180] = 10.75$, $P = 0.001$) and in the girls ($F[1,180] = 3.83$, $P = 0.052$).

All analyses were repeated, randomly selecting one individual from each of the 24 families where more than one child took part in the study. This eliminates the problem of nonindependence of subjects, but reduces the sample size. Nonetheless, virtually identical patterns were obtained.

Glycemic control, as measured by glycosylated hemoglobin (GHb), was worse in the diabetic girls compared with boys at the time of examination ($P < 0.05$). However, when considering the mean over the previous 2 yr (based on an average of seven observations per individual), girls had only slightly higher GHbs than the boys (Table 7). Also shown in Table 7 are the significant correlations for cases between GHb and the lipoproteins and blood pressures. No correlations were seen in either sex with LDL and HDL cholesterol. A significant positive correlation was present for GHb at examination with triglycerides in the boys. Significant correlations were seen for each blood pressure measure with the prior 2-yr mean GHb in girls, but not in boys.

Multiple linear regression (MLR) analyses were run for the diabetic subjects using each lipoprotein and blood pressure as the dependent variable. Age, body mass index (BMI), Tanner stage, diet score, physical activity, duration of diabetes, insulin dose/kg, and the two measures of GHb (i.e., at exam and 2-yr mean) were included as independent variables. In boys, 37% of the interindividual variance of LDL cholesterol was explained by Tanner stage, and for triglycerides, 21% was explained by the GHb at examination. No significant explanations were noted for the girls. For HDL cholesterol, again none of the independent variables entered the equation except for log triglyceride in girls (22% of HDL-C and 28% of HDL_2 cholesterol being thereby explained).

Systolic blood pressure variance was largely explained by Tanner stage in both boys (35%) and girls (24%). Diastolic blood pressure (phase V) was partly (17%) explained by age in boys, though in girls Tanner stage (14%) was the only significant variable. As both age and Tanner stage were correlated with mean GHb ($r = 0.25$ and 0.26 in boys, respectively, and 0.33 and 0.28 in girls, respectively), the MLR was repeated without Tanner stage and age as independent variables. Although in these analyses mean GHb now explained some of the variance, the explanation was less than when age and Tanner stage were included (14% of the variance in systolic blood pressure for girls and 11% for diastolic V). For boys, neither mean GHb nor GHb at exam was a significant explanatory variable. These results therefore suggest that although control may partly explain the variance of blood pressure in girls, this is more likely to be a secondary association and that age and/or maturity are the predominant influences rather than vice versa.

DISCUSSION

Though these results are based on fairly small numbers, they do represent, we believe, the first systematic attempt to describe the full cardiovascular risk profile in a well-defined and probably representative group of diabetic adolescents. The response rate of 72% is comparable to most studies of this nature in the general population. Though many studies have reported both lipid concentrations[8–15] and a few blood pressure distributions in childhood and adolescent diabetic populations,[16,17] these are usually based on ill-defined hospital clinic surveys. The Diabetes Clinic at Children's Hospital of Pittsburgh sees approximately 60% of the cases of this age group occurring in Allegheny County.[21–23] The varied results of previous studies of lipids in diabetic youth—some showing increased lipids[8,11,13,14] and some not[12,15]—may reflect the wide range of ages from 2 to 33 yr and failure to account for the changes during adolescence. In addition, some studies did not perform sex-specific analyses.[9–13,15] Ill-defined and loosely matched control subjects represent another problem in a number of these previous studies. Furthermore, some of the earlier studies may be of less current relevance due to the recent shift in dietary recommendations from a diet relatively high in fat to one more restricted in saturated fat and cholesterol. Nonetheless, our choice of comparison group, siblings of cases with IDDM, is open to question, for it is conceivable that such families might share a predisposition to both glucose and lipoprotein metabolic abnormalities and/or such siblings might have early

TABLE 7
Mean GHb (%) ± SD by sex, and correlations of GHb with CVD risk factors (cases only)

	Boys		Girls	
	At exam	$\bar{X}$ Prior 2 yr	At exam	$\bar{X}$ Prior 2 yr
GHb	10.6 ± 1.6*	10.5 ± 1.4	11.3 ± 1.5*	10.9 ± 1.2
Ln triglyceride	+0.45*	+0.26	+0.14	+0.09
Systolic	+0.18	+0.08	+0.25	+0.34*
Diastolic IV	+0.26	+0.28	+0.13	+0.30*
Diastolic V	+0.19	+0.13	+0.21	+0.34*

*$P < 0.05$.

diabetes. However, none of the 45 siblings studied had abnormal glucose tolerance tests and our repeated analyses, using only one subject from each family, had the same results. In addition, the choice of siblings has the advantage that they are probably similar to the diabetic subjects in terms of social class, diet, and other unmeasurable factors, thus permitting a more powerful study of the effects of diabetes per se.

Of further interest is the finding concerning HDL subfractions. The well-reported paradox of increased or normal HDL cholesterol concentrations in IDDM patients despite increased cardiovascular risk[34] could be explained, in part, if this increase is primarily due to an increase in HDL_3 concentrations, which is probably not the subfraction related to cardiovascular risk.[35] Though two recent reports have suggested that IDDM patients may have increases in HDL_2,[36,37] in one of these studies,[36] this suggestion was by inference only (i.e., increased apoprotein A_I/A_{II} ratios) and in the other,[37] increases in HDL_3 were also seen, though these did not reach statistical significance. This latter study of adults found higher HDL_2 cholesterol in the male but not in the female subjects. Although not significant statistically, a similar pattern is seen in our study for Tanner 5 subjects. Thus, it would seem probable that, given a larger sample of mature subjects, we would have similarly shown higher HDL_2 cholesterol in male but not female patients. The finding of an increased HDL_3 cholesterol in our diabetic subjects is consistent with a previous report.[38] Furthermore, we have previously shown that in nondiabetic women, serum insulin levels are much more strongly correlated with the HDL_3 subfraction than with HDL_2.[39] If higher HDL cholesterol concentrations in this study reflect the large doses of insulin used in IDDM therapy, one would predict a greater increase in HDL_3 rather than HDL_2 as noted. We fail to show any relationship between glycemic control and HDL cholesterol—in common with some[13,24,40,41] but not all studies.[14,42–44] It is possible that, given a large sample size, the negative correlations seen in this study (up to $r = -0.20$ for HDL_2 cholesterol with GHb at exam) in boys would be significant.

Despite the increased risk of cardiovascular disease that diabetic patients experience, it should be noted that adolescent cardiovascular risk profiles, both male and female, are not greatly disturbed in this study. This may reflect, in part, the attempt to foster good dietary habits in these diabetic subjects. Nonetheless, cardiovascular risk profile disturbances are noted particularly for female patients who show higher total cholesterol concentrations during adolescence in contrast to the usual nondiabetic fall evidenced by the siblings. In addition, diastolic (fifth phase) blood pressure is generally higher for the female cases but not for the males when compared with siblings. Furthermore, a remarkable sex-specific effect of diabetes on pulse rate is seen, which is unlikely to result from any sex-specific subject/observer interaction. We suspect, therefore, that this is a real finding that merits further investigation, for example, as to whether it reflects early autonomic neuropathy. This finding is particularly interesting in the light of recent reports[45,46] suggesting that heart rate may affect the progression of atherosclerosis in monkeys. This higher pulse rate does not appear to relate to the girls' poorer glycemic control, for no correlation was found between pulse and GHb. Indeed, the effects of glycemic control and of the measured health-related behaviors on the lipoproteins and blood pressure measures also appear relatively small. Apart from triglycerides in boys, GHb does not feature as a significant explanatory variable for any of the lipoproteins or blood pressures, whereas age and/or maturation (but not diet or physical activity) are important.

We would thus conclude that the cardiovascular risk profile of diabetic adolescents is mildly disturbed and is largely independent of glycemic control and health-related behavior, and when such disturbances vary by sex, it is the girls who show the more "adverse" pattern. Though this is consistent with the loss of the sex differential in cardiovascular disease mortality in diabetes, prospective studies, which also consider other risk factors (e.g., clotting and platelet abnormalities), are now needed to further determine the reasons for the accelerated development of atherosclerotic disease in diabetes.

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