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A total of 2,194 lipid measurements were available from 895 subjects; the mean ± SD number of measurements per patient was 2.5 ± 1.0 and the median 3 (range 1–5). A total of 183 subjects had only one measurement, 254 had two measurements, 333 had three measurements, 121 had four measurements, and only 4 subjects had five measurements.

**A1C**

Samples were analyzed centrally on a Tosoh G7 analyzer, using high-performance liquid chromatography and absorbance change detection and Diabetes Control and Complications Trial (DCCT)-aligned methods. The normal range for A1C was 4.9–6.3%, and the coefficient of variation (CV) was 4.8 and 6.6% at a level of 5.5 and 10.1%, respectively.

**Lipids**

All samples were assayed centrally. Measurements of total cholesterol, HDL cholesterol, and TG were performed enzymatically on a Dimension Rxl system (Dade Behring) using reagents and calibrants supplied by the manufacturer. Between-run CVs were for total cholesterol 1.3% at 3.2 mmol/l and 1.2% at 7.5 mmol/l, for TG 3.2% at 1.0 mmol/l and 1.1% at 2.2 mmol/l, and for HDL cholesterol 3.3% at 0.6 mmol/l and 2.1% at 1.5 mmol/l.

LDL cholesterol was calculated with Friedwald’s formula: LDL = total cholesterol − HDL cholesterol − TG/2.2.

Because our samples were collected in nonfasting conditions, non-HDL cholesterol (total cholesterol minus HDL cholesterol) was also assessed.

**Urinary albumin and creatinine**

All urine samples were stored at −70°C before the centralized analysis in a single reference laboratory. Albumin was measured by a double antibody enzyme-linked immunosorbent assay method. The within and in-between assay CVs were 6 and 12%, respectively. Creatinine was measured using a modified Jaffe method (Unimate 7, Roche Diagnostic Systems, Basel, Switzerland) on a Cobas Mira (Roche Diagnostic Systems) automated spectrophotometer. The CV was 2% at 2.2 mmol/l.

**Calculations**

BMI was calculated as weight/height$^2$. SD scores for BMI were calculated using the British 1990 Growth Reference and Cole’s LMS method.

**Statistical analysis**

Data are summarized as means ± SD or median (range) for continuous variables and as cell frequencies and percentages for categorical variables. Non–normally distributed variables (A1C and TG) were log transformed before analysis. Comparisons between different groups were performed by unpaired t tests. Comparisons across categories were made using χ² or Fisher’s exact test. Correlations between variables of interest were performed by Pearson correlation. General linear models were used to assess longitudinal associations between variables, which are expressed as B coefficient ± SE.

**RESULTS** — The baseline characteristics of the study population are shown in Table 1. Age, duration of diabetes, and age at diagnosis were similar between male (n = 490) and female (n = 405) subjects. No significant differences were found in glycemic control between sexes, whereas BMI SD scores were significantly higher in females than in males. Levels of
Lipids and microalbuminuria in youth with diabetes

**Table 1—Baseline characteristics**

| Category                        | All      | Male    | Female  |
|---------------------------------|----------|---------|---------|
| Total cholesterol (mmol/l)      | 4.5      | 4.3     | 4.7     |
| HDL cholesterol (mmol/l)        | 1.6      | 1.5     | 1.7     |
| LDL cholesterol (mmol/l)        | 2.3      | 2.2     | 2.5     |
| TG (mmol/l)                     | 1.0      | 1.0     | 1.0     |
| Non-HDL cholesterol (mmol/l)    | 2.9      | 2.7     | 3.1     |

Data are medians (range) and means ± SD. *P < 0.01 for females vs. males.

**Changes in lipids and albumin excretion**

We examined whether lipid parameters predicted trends in albumin excretion during follow-up. Table 3 shows the results of this analysis, before and after adjusting for age, sex, duration, BMI SD score, and A1C. Total cholesterol and non-HDL cholesterol were independently related to changes in log ACR during follow-up.

During follow-up, 115 (13%) subjects developed microalbuminuria (28 persistent and 87 transient microalbuminuria). Age-related changes in total cholesterol and non-HDL cholesterol, and specifically the rise in their levels after the age of 15–16 years, were particularly marked in subjects with persistent microalbuminuria when compared with individuals with transient microalbuminuria and normoalbuminuria (Fig. 1).

Mean concentrations of total cholesterol (4.7 ± 1.2 vs. 4.5 ± 0.8 mmol/l, P = 0.04) and non-HDL cholesterol (3.2 ± 1.5 vs. 2.9 ± 0.8 mmol/l, P = 0.03) were higher in subjects developing microalbuminuria when compared with individuals with normoalbuminuria (see Table A1 in the online appendix). However, these dif-

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**Table 2—Independent predictors of lipid levels during follow-up**

| Predictor              | B ± SE | P     |
|------------------------|--------|-------|
| Total cholesterol      |        |       |
| Age (years)            | 0.042 ± 0.014 | 0.004 |
| A1C (%)                | 0.161 ± 0.016 | <0.001|
| BMI SD score           | 0.077 ± 0.043 | NS    |
| Log TG                 |        |       |
| Age (years)            | 0.018 ± 0.005 | <0.001|
| A1C (%)                | 0.045 ± 0.005 | <0.001|
| BMI SD score           | 0.062 ± 0.014 | <0.001|
| HDL cholesterol        |        |       |
| Age (years)            | −0.038 ± 0.006 | <0.001|
| A1C (%)                | 0.001 ± 0.007 | NS    |
| BMI SD score           | −0.06 ± 0.019 | 0.001 |
| LDL cholesterol        |        |       |
| Age (years)            | 0.050 ± 0.011 | 0.013 |
| A1C (%)                | 0.072 ± 0.013 | <0.001|
| BMI SD score           | 0.079 ± 0.03  | 0.025 |
| Non-HDL cholesterol    |        |       |
| Age (years)            | 0.080 ± 0.013 | <0.001|
| A1C (%)                | 0.160 ± 0.015 | <0.001|
| BMI SD score           | 0.138 ± 0.040 | 0.001 |

Data are from 712 subjects with more than one lipid measurement and are adjusted for repeated measurements and sex.
ferences disappeared after adjusting for A1C. Microalbuminuria-positive subjects also presented a high percentage of abnormal lipid levels, specifically total cholesterol and LDL cholesterol, when compared with normoalbuminuric subjects.

**CONCLUSIONS** — In the present study, we found a high prevalence of lipid abnormalities in an adolescent population with type 1 diabetes, diagnosed during childhood and followed longitudinally during puberty. Lipid levels were significantly influenced by age, duration of diabetes, BMI, and glycemetic control. In addition, we found that total cholesterol and non-HDL cholesterol were significantly related to albumin excretion during the study period.

In our study, the mean frequency of high and borderline total cholesterol during follow-up was 18.6 and 34.8%, respectively. A large proportion of subjects had high non-HDL cholesterol (23.9%), whereas the frequency of low HDL cholesterol was not particularly high (2.5%), similar to findings from previous studies (9). A high proportion of subjects had abnormal levels of TG and LDL cholesterol, even though these parameters are less reliable, given that blood samples were collected in nonfasting conditions.

Few data are available on lipid levels in young people with type 1 diabetes, and the majority of studies have been cross-sectional (7,8,16,17), with only a few being longitudinal with short-term follow-up or a retrospective design (9,18,19). In the SEARCH study (16), one of five children with type 1 diabetes presented total cholesterol >5.2 mmol/l, similar to our results. Data from the Oxford Regional Prospective Study showed that 15.3% subjects had total cholesterol >5.2 mmol/l and 17.9% TG above 1.7 mmol/l (12). Similar data have been reported in a study from the U.S. where 15.2% of children had high total cholesterol (7) and from a German study where 28.6% of patients had dyslipidemia (8). Therefore, in line with these studies, we confirmed a high prevalence of dyslipidemia in youth with type 1 diabetes, and this is potentially clinically significant, given the well-known relationship of dyslipidemia with cardiovascular events (1) and the fact that lipid levels frequently track from childhood to adulthood (20).

An overall increase in lipid parameters with age was found in the present study, and this was particularly evident in male subjects. However, our study shows also a small but identifiable fall in cholesterol around the age of 15–16 years, followed by an increase thereafter. In healthy adolescents, there is a decline of ~10–20% in cholesterol levels during puberty (21). This decline has been consistently reported in boys, whereas in girls, the picture has been more controversial, since some studies have not shown any pubertal decline in total cholesterol (22). However, an influence of age and puberty on lipid levels has not always been reported in children and adolescents with type 1 diabetes, and this is probably related to differences in the age range across different studies (9,10,12). Lipid levels, except TG, were higher in type 1 diabetic girls than in boys. This is in line with previous data (8,23), and it might be related to different degrees of insulin resistance between the two sexes or to a direct effect of the hormonal status on one or more enzymes implicated in lipoprotein metabolism (23).

Glycemic control significantly influenced changes in lipid levels during follow-up. The only parameter not related to A1C was HDL cholesterol, similarly to previous findings in adults (24). The lack of a relationship between A1C and HDL cholesterol could be due to opposite effects of glycemia on different HDL sub-classes, which cannot be detected by simply assessing total HDL cholesterol (24). A strong relationship between other lipid parameters and A1C was detected in the DCCT as well as in studies more specifically targeting children and adolescents with type 1 diabetes (7,9,10). The adverse effect of glycemic control could be due to glycation of lipoproteins, with consequent reduction of their catabolism, and to stimulation of transfer of cholesterol to HDL to apolipoprotein B–containing lipoproteins (2). The strong relationship between lipid levels and A1C underlines the role of good management of diabetes in controlling dyslipidemia. This is confirmed by data from the DCCT, where intensive treatment was associated with a significant reduction in lipid levels (24). However, it is important to acknowledge that, despite attempts to improve glycemic control, the present study and previous studies indicate that the prevalence of lipid abnormalities is high and persistent over time in youth with type 1 diabetes (8,9), therefore suggesting the possible need of additional interventions with lipid-lowering drugs.

In the present study, BMI was another important determinant of lipid levels. Previously, a similar association between overweight and an adverse lipid profile was documented in subjects with type 1 diabetes (7,9). In the DCCT cohort, excessive weight gain was related to dyslipidemia and declines in A1C were associated with improvements in lipid levels only in subjects with the least weight gain during the intervention period (25). These observations have been related to a state of insulin resistance/hyperinsulinemia associated with increased body weight (23).

The relationship between microalbuminuria and dyslipidemia has not been extensively investigated in young people with type 1 diabetes. In adult populations, increased total cholesterol and/or TG have been associated with microalbuminuria (6), although associations with lipid abnormalities were found to be more marked in patients with macroalbuminuria (6,23). With respect to the pediatric populations with diabetes, data from the Oxford Regional Prospective Study showed that the prevalence of microalbuminuria increased across tertiles of total cholesterol (12), and a recent German study has shown a predictive value of both LDL cholesterol and TG on the development of persistent microalbuminuria (11). In the present study, we examined lipid levels in relation to changes in albumin excretion, as a continuous variable, and the development of microalbuminuria. Increased total cholesterol and non-HDL cholesterol levels were independently related to ACR during follow-up.

### Table 3—Relationship between lipid parameters and ACR

| Parameter          | B ± SE* | P* | B ± SE† | P† |
|--------------------|---------|----|---------|----|
| Total cholesterol  | 0.041 ± 0.011 | <0.001 | 0.033 ± 0.013 | 0.009 |
| Log TG             | 0.12 ± 0.033 | <0.001 | 0.072 ± 0.037 | NS |
| HDL cholesterol    | −0.006 ± 0.026 | NS | 0.03 ± 0.007 | NS |
| LDL cholesterol    | 0.007 ± 0.015 | NS | −0.002 ± 0.016 | NS |
| Non-HDL cholesterol| 0.47 ± 0.012 | <0.001 | 0.32 ± 0.014 | 0.02 |

The dependent variable is log ACR. Regression coefficients B are for each 1 mmol/l increase in lipid levels.

*Unadjusted values. †Adjusted values for age, sex, duration, BMI SD score, and A1C.
even after adjusting for glycemic control and other confounding factors. In addition, the changes in lipid levels with age in subjects with persistent microalbuminuria were remarkable when compared with those with transient microalbuminuria or normoalbuminuria. Both total cholesterol and non-HDL cholesterol showed a marked increase from the age of about 15 years in

Figure 1—Longitudinal changes in total cholesterol and non-HDL cholesterol with age in subjects with normoalbuminuria (MA−) and in individuals with transient and persistent microalbuminuria (MA).
individuals developing persistent microalbuminuria. It is interesting that in our study population the mean age at microalbuminuria onset was 15 years, therefore providing further support for a potential relationship between lipid levels and microalbuminuria. Overall, lipid levels were higher in subjects developing microalbuminuria when compared with normoalbuminuric subjects. However, these differences were probably related to the worse glycemic control in subjects with microalbuminuria, since they disappeared when adjusting for A1C.

In this longitudinal study of young people with type 1 diabetes, we found that lipid levels varied with age and were higher in females than in males. Lipid levels were independently related to BMI, and all parameters, except HDL cholesterol, were also influenced by glycemic control. A significant number of subjects presented high and borderline lipid levels that persisted over time. Total cholesterol and non-HDL cholesterol were closely related to albumin excretion during follow-up, suggesting a potential role in the pathogenesis of diabetic nephropathy. These results highlight the need of screening for dyslipidemia in adolescents with type 1 diabetes to identify early subjects at risk for complications, who need more intensive follow-up and perhaps other therapeutic interventions.

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