Dietary Fats Do Not Contribute to Hyperlipidemia in Children and Adolescents With Type 1 Diabetes

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OBJECTIVE — To determine the relative influence of diet, metabolic control, and familial factors on lipids in children with type 1 diabetes and control subjects.

RESEARCH DESIGN AND METHODS — We assessed fasting serum cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, lipoprotein(a), apolipoprotein (apo)-A1, and apoB in 79 children and adolescents with type 1 diabetes and 61 age- and sex-matched control subjects, together with dietary intakes using a quantitative food frequency questionnaire.

RESULTS — Total cholesterol, LDL cholesterol, apoB, HDL cholesterol, and apoA1 were significantly higher in children with diabetes. Children with diabetes had higher percentage energy intake from complex carbohydrates ($P = 0.001$) and fiber intake ($P = 0.02$), and they had lower intake of refined sugar ($P < 0.001$) and percentage energy from saturated fat ($P = 0.045$) than control subjects. Total cholesterol ($\beta = 0.43$, $P < 0.001$), LDL cholesterol ($\beta = 0.4$, $P < 0.001$), and apoB ($\beta = 0.32$, $P = 0.006$) correlated independently with HbA_{1c} but not dietary intake. HDL cholesterol ($\beta = 0.24$, $P = 0.05$) and apoA1 ($\beta = 0.32$, $P = 0.004$) correlated independently with HbA_{1c}, and HDL cholesterol ($\beta = -0.34$, $P = 0.009$) correlated with percentage energy intake from complex carbohydrates. Triglycerides correlated independently with percentage energy intake from complex carbohydrates ($\beta = 0.33$, $P = 0.01$) and insulin dose ($\beta = 0.26$, $P = 0.04$). Subjects with diabetes and elevated LDL (>3.35 mmol/l, >130 mg/dl), for whom dietary therapy would be recommended, had significantly higher HbA_{1c} ($P = 0.007$), but they had higher intake of complex carbohydrates than subjects with LDL cholesterol <3.35 mmol/l.

CONCLUSIONS — Lipid abnormalities remain common in children and adolescents with type 1 diabetes who adhere to current dietary recommendations, and they relate to metabolic control but not dietary intake.

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Abnormal lipid metabolism is well documented in children with type 1 diabetes, but the contribution of dietary factors to lipid abnormalities in these children has not been studied in detail. Newly diagnosed children with type 1 diabetes have severe hyperlipidemia, which resolves on initiation of insulin (1). LDL and total cholesterol are higher in children with type 1 diabetes than their siblings (2) and control subjects (3), and they relate to metabolic control in some (2–5) but not all (6) studies. Familial factors are also important (4). In adults with type 1 diabetes, there are associations between lipid abnormalities and HbA_{1c}, as well as with smoking, central obesity, and physical activity (7). None of these studies have specifically investigated the contribution of diet to lipid abnormalities.

Early studies assessing diet and lipids in children with type 1 diabetes have shown an improvement in cholesterol levels with a diet reduced in saturated fat (8), and over time between the 1971 and 1979 Joslin diabetes camps (9). However, the baseline fat intake in both studies was high, and dietary recommendations have changed significantly since the 1970s, from higher- to lower-fat diets (10,11), so these results are no longer applicable to children with type 1 diabetes. At entry into the Diabetes Control and Complications Trial (DCCT), subjects with diabetes were found to have lipid levels similar to an equivalent nondiabetic population, although lower HDL cholesterol and higher triglycerides and total and LDL cholesterol were seen in adolescents (12). In this group, triglycerides and total and LDL cholesterol were independently associated with HbA_{1c} (12). A recent large study in adults with type 1 diabetes, comparing Southern European with Northern, Western, and Eastern European patients, found an association between the glycemic index of foods and both HbA_{1c} and HDL cholesterol, but it did not report intake of fats (13).

Because of the paucity of data relating dietary factors to serum lipids in children and adolescents with type 1 diabetes, particularly with current recommendations for lower intake of fat and higher intake of complex carbohydrates, we determined the relative influence of diet, metabolic control, and family history on lipids in children with type 1 diabetes and control subjects.

RESEARCH DESIGN AND METHODS

Subjects

The study involved 79 children and adolescents with type 1 diabetes aged 8 years

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Abbreviations: ADA, American Diabetes Association; apo, apolipoprotein; BP, blood pressure; CV, coefficient of variation; DCCT, Diabetes Control and Complications Trial; FFQ, food frequency questionnaire; ISPAD, International Society for Pediatric and Adolescent Diabetes; Lp(a), lipoprotein(a).

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Lipid values in diabetes group and control subjects*

	Diabetes	Control	*P* value
n	79	61	
Age (years)	13.6 ± 2.6	13.3 ± 2.5	0.54
Sex (M/F)*	42/37	31/29	0.86
Insulin dose (units · kg^{-1} · day^{-1})	1.12 ± 0.4	—	—
HbA_{1c} (%) (4–6%)	8.8 (6.7–14)	—	—
Duration (years)	4.4 (0.6–16)	—	—
Triglycerides (mmol/l)	0.62 (0.11–3.68)	0.55 (0.10–1.76)	0.39
Total cholesterol (mmol/l)	4.9 ± 1.0	4.3 ± 0.8	<0.001
HDL cholesterol (mmol/l)	1.5 ± 0.3	1.4 ± 0.3	0.029
LDL cholesterol (mmol/l)	3.1 ± 0.8	2.6 ± 0.7	0.001
Lp(a) (mg/l)	128 (<20 to >1280)	85 (<20 to >1280)	0.29
ApoA1	1.4 ± 0.18	1.3 ± 0.19	0.009
ApoB	0.73 ± 0.21	0.63 ± 0.17	0.003
LDL to ApoB ratio	4.1 ± 0.41	4.0 ± 0.54	0.28

Data are means ± SD (Students *t* test) or median (range) (Mann-Whitney *U* test), unless otherwise noted. *χ^2 test.

or more, recruited consecutively from the diabetes clinic at the Women's and Children's Hospital, Adelaide, Australia, which manages 84% of the children with diabetes in South Australia. Subjects had had diabetes for at least 6 months and were well at the time of sample collection, without ketosis or hypoglycemia. No subject had background retinopathy on direct fundoscopy through dilated pupils. Two patients developed microalbuminuria (mean albumin excretion rate on three occasions: 22.9 and 66 μg/min, respectively) after entry into the study. Participants did not differ from the clinic population over 8 years of age in terms of HbA_{1c}, insulin dose, blood pressure (BP), or duration. There were 61 healthy age- and sex-matched control subjects recruited from two sources: friends of the participating patients (n = 43) and subjects attending the Women's and Children's Hospital for minor elective day surgery (n = 18). In the latter group, fasting blood was collected before induction of anesthesia. Medication and smoking history were obtained from the subjects. Baseline characteristics are shown in Table 1. No subject had previously been identified to have hyperlipidemia or had specific dietary intervention for a lipid disorder.

Data were collected on family history of hyperlipidemia (defined as a parent, grandparent, aunt, or uncle with hyperlipidemia requiring dietary or drug treatment) and family history of early atherosclerosis (defined as angina, myocardial infarction, coronary artery graft surgery, transient ischemic attacks, stroke, or peripheral vascular disease with onset before age 55 in a parent, grandparent, aunt, or uncle).

The study was approved by the Human Research Ethics Committee, Women's and Children's Hospital. Written informed consent was obtained from parents/guardians for subjects <16 years and also from all subjects >12 years.

Laboratory

Venous blood samples were collected after an overnight fast of at least 10 h in all subjects and before insulin administration in subjects with diabetes.

Triglycerides and total cholesterol were measured using commercial enzymatic assays on a Beckman Synchron CX5 analyzer (14,15). The interassay coefficient of variation (CV) in our laboratory is 2.1% for triglycerides and 1.5% for total cholesterol. HDL cholesterol was measured using a commercial enzyme-based assay on a Beckman Synchron CX5 analyzer, after precipitation of LDL and VLDL by polyethylene glycol and removal of these by centrifugation (14,15). The interassay CV in our laboratory is 3.2%. LDL cholesterol was calculated using the Friedewald equation [LDL cholesterol = total cholesterol − (HDL cholesterol + triglycerides/2.2)] (14,15). Apolipoprotein (apo)-A1, apoB-100, and lipoprotein(a) [Lp(a)] were measured using endpoint nephelometry (Hyland laser nephelometry PDQ) and the addition of specific monoclonal antibodies, as previously described (16). The ratio of LDL cholesterol to apoB was used as a marker of LDL subclasses (more atherogenic small dense LDL particles have a low LDL-to-apoB ratio) (17,18). HbA_{1c} was measured using high-performance liquid chromatography with a Biorad variant 2 cation exchange column; the instrument was calibrated against DCCT-approved standards. The range is 4–6% in a nondiabetic population.

Food frequency questionnaires

A validated food frequency questionnaire (FFQ) (19) was used to determine dietary intake of energy; total fat; cholesterol; poly-, mono-, and unsaturated fat; carbohydrates; protein; percentage of energy from each of these sources; fiber; and micronutrients during the previous 12 months. We used a quantitative FFQ because we were interested in the intake of multiple nutrients over a long time period in order to determine usual intake and a format that could be used for 140 subjects. The questionnaires were developed by the Human Nutrition Division, Commonwealth Industrial and Scientific Research Organization, South Australia, and modified for use in adolescents and children. Computerized analysis of the questionnaires was undertaken (19). Information on both dietary supplementation with vitamins and the fortification of foods with vitamins was included in the analysis of the FFQ.

Statistics

The data were analyzed on an IBM-compatible computer, using SPSS version

Table 2—*Clinical data and dietary intake in subjects with diabetes and control subjects*

	Diabetes	Control subjects	Recommendation (ISPAD)	*P* value
n	58	43		
Age	13.5 ± 2.4	13 ± 2.7	—	0.356
Sex (M/F)*	32/26	23/20	—	0.867
Duration (years)	3.8 (0.6–13)	—	—	—
Insulin dose (units/kg)	1.1 ± 0.36	—	—	—
HbA_{1c}	8.75 (6.7–14.0)	—	—	—
Energy (kJ)	10,709 ± 3,339	10,129 ± 3,646	Sufficient for normal growth	0.419
Protein (g)	103.5 ± 38.4	93.3 ± 33.8	—	0.178
Total carbohydrate (g)	314.5 ± 95.1	295.3 ± 108.6	—	0.358
Total fat (g)	98.1 ± 36.9	97.3 ± 39.7	—	0.921
Cholesterol (mg)	248.4 ± 122.8	275.0 ± 131.9	<300	0.311
Saturated fat (g)	39.3 ± 16.3	41.4 ± 19.8	—	0.572
Monounsaturated fat (g)	35.5 ± 14.6	33.3 ± 13.7	—	0.445
Polyunsaturated fat (g)	17.5 ± 7.8	16.0 ± 7.6	—	0.345
Complex carbohydrate, (g)	172.9 ± 51.6	138.4 ± 50.7	—	0.001
Fibre intake (g)	33.5 ± 12.2	27.7 ± 11.6	—	0.020
Refined sugar (g)	41.3 ± 25.5	77.9 ± 48.7	—	<0.001
% kJ from protein	16.3 ± 2.1	15.7 ± 2.1	10–15%	0.171
% kJ from carbohydrates	47.5 ± 5.6	46.6 ± 5.1	>50%	0.417
% kJ from complex carbohydrates	26.3 ± 3.8	22.1 ± 4.7	—	<0.001
% kJ from fat	33.6 ± 5.8	35.4 ± 4.7	30–35%	0.093
% kJ from saturated fat	13.4 ± 3.4	14.9 ± 3.8	<10%	0.045
% kJ from polyunsaturated fat	6.0 ± 1.9	5.9 ± 2.1	Up to 10%	0.798
% kJ from monounsaturated fat	12.1 ± 2.4	12.1 ± 1.7	>10%	0.912

Data are means ± SD (Students *t* test) or median (range) (Mann-Whitney *U* test), unless otherwise noted. *χ^2 test.

10.0.7 software (SPSS, Chicago, IL). To assess group differences, Student's *t* tests were used for normally distributed data and the Mann-Whitney *U* test for nonnormally distributed data. Pearson's correlation coefficient was used to assess correlations between variables with normal distribution and Spearman's correlation for nonnormally distributed data. A backwards multiple linear regression analysis was used to identify significant determinants of lipids. Separate analyses were completed on each individual lipid variable as the dependent variable. Only variables with at least a marginally significant ($P < 0.1$) association with the considered dependent variable were included as independent variables in the initial multiple regression model. Data that were not normally distributed were log-transformed for this analysis, e.g., HbA_{1c}, triglycerides, Lp(a), and BMI. The term β indicates the adjusted correlation coefficient in the regression analyses. A *P* value <0.05 was considered statistically significant.

RESULTS — FFQs were completed by 58 (73%) subjects with diabetes and 43 (70%) control subjects. Subjects who completed a FFQ did not differ in any variable (age, duration of diabetes, insulin dose, HbA_{1c}, or BP) from those who did not. Results for lipid values and the FFQ are shown in Tables 1 and 2.

Subjects with diabetes

HbA_{1c} correlated with percentage energy derived from sugar ($r = -0.26$, $P = 0.05$) and with borderline significance with fiber intake ($r = -0.25$, $P = 0.06$), total sugar intake ($r = -0.25$, $P = 0.06$), total carbohydrate intake ($r = -0.24$, $P = 0.07$), and percentage energy from saturated fat ($r = 0.23$, $P = 0.08$).

Independent variables considered in the initial multivariable regression model for total cholesterol were HbA_{1c} and duration of diabetes. Similarly, independent variables for LDL cholesterol were HbA_{1c}, percentage energy from monounsaturated fat, and percentage energy from complex carbohydrates. Independent variables for apoB were HbA_{1c}, age, and diastolic BP. Independent variables for HDL cholesterol were HbA_{1c}, BMI, height, weight, systolic and diastolic BP, and percentage energy from complex carbohydrates. Independent variables for apoA1 were HbA_{1c}, height, weight, BMI, and systolic BP. Independent variables for triglycerides were age, HbA_{1c}, intake of sugar, insulin dose, percentage energy from sugar, and percentage energy from complex carbohydrates. Independent variables for Lp(a) were HbA_{1c}, insulin dose, weight, BMI, total carbohydrate intake, and percentage energy from carbohydrates. Independent variables for the LDL-to-apoB ratio were age, insulin dose, systolic BP, diastolic BP, and percentage energy from complex carbohydrates.

In this analysis, significant associations remained between *1*) total cholesterol and HbA_{1c}(ln) ($\beta = 0.43$, $P < 0.001$); *2*) LDL cholesterol and HbA_{1c}(ln) ($\beta = 0.4$, $P < 0.001$); *3*) apoB and HbA_{1c}(ln) ($\beta = 0.32$, $P = 0.006$) and diastolic BP ($\beta = 0.25$, $P = 0.03$); *4*) HDL cholesterol and diastolic BP ($\beta = -0.35$, $P = 0.006$), percentage energy from complex carbohydrates ($\beta = -0.34$, $P = 0.009$), and HbA_{1c}(ln) ($\beta = 0.24$, $P = 0.05$); *5*) apoA1 and HbA_{1c}(ln) ($\beta = 0.32$, $P = 0.004$) and height ($\beta = -0.3$, $P = 0.008$); *6*) triglycerides(ln) and percentage energy from complex carbohydrates

Table 3—*Diabetic subjects with and without hyperlipidemia*

	LDL ≥3.35 mmol/l	LDL <3.35 mmol/l	*P* value
n	28	51	
Age (years)	14.1 ± 2.4	13.3 ± 2.7	0.19
Sex (M/F)*	16/12	26/25	0.6
Duration (years)	5.3 (0.8–14.6)	4.0 (0.6–15.8)	0.19
Insulin dose ($mg \cdot kg^{-1} \cdot day^{-1}$)	1.1 ± 0.37	1.1 ± 0.37	0.72
HbA_{1c} (%)	9.3 (8–14)	8.4 (6.7–14)	0.007
Energy intake (kJ)	10,262 ± 3,838	10,859 ± 2,958	0.52
Protein intake (g)	97.6 ± 44.6	105.7 ± 34.3	0.45
Total carbohydrate intake (g)	309.0 ± 122.4	315.1 ± 75.9	0.82
Total fat intake (g)	91.9 ± 31.8	100.8 ± 38.2	0.38
Cholesterol intake (mg)	212.4 ± 84.8	258.9 ± 135.0	0.18
Saturated fat intake (g)	33.9 ± 11.6	41.2 ± 17.1	0.09
Monounsaturated fat intake (g)	34.8 ± 14.6	36.0 ± 14.5	0.77
Polyunsaturated fat intake (g)	16.8 ± 7.4	18.2 ± 8.5	0.54
Complex carbohydrate intake (g)	177.7 ± 62.0	169.6 ± 44.2	0.57
Fibre intake (g)	34.5 ± 16.2	33.6 ± 9.4	0.79
Refined sugar intake (g)	35.6 ± 23.1	44.7 ± 26.8	0.21
% kJ from protein	16.0 ± 2.0	16.5 ± 2.4	0.39
% kJ from carbohydrates	48.1 ± 4.6	47.2 ± 6.1	0.59
% kJ from complex carbohydrates	28.0 ± 2.8	25.4 ± 4.0	0.012
% kJ from fat	33.4 ± 4.8	33.7 ± 6.2	0.89
% kJ from saturated fat	12.4 ± 2.9	13.8 ± 3.5	0.16
% kJ from polyunsaturated fat	6.2 ± 2.0	6.01 ± 2.0	0.9
% kJ from monounsaturated fat	12.5 ± 2.2	12.0 ± 2.6	0.43

Data are means ± SD (Students *t* test) or median (range) (Mann-Whitney *U* test), unless otherwise noted. *χ^2 test.

($\beta = 0.33$, $P = 0.01$) and insulin dose ($\beta = 0.26$, $P = 0.036$); 7) Lp(a)(ln) and sugar intake ($\beta = 0.28$, $P = 0.036$) and BMI(ln) ($\beta = 0.38$, $P = 0.005$); and 8) the LDL-to-apoB ratio and systolic BP ($\beta = -0.27$, $P = 0.024$).

There was no difference in total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, Lp(a), apoA1, apoB, or the apoB-to-LDL ratio between subjects with or without a family history of early-onset cardiovascular disease or a family history of lipid disorders.

The National Cholesterol Education Program (20) has recommended dietary intervention for children with LDL cholesterol >3.35 mmol/l (>130 mg/dl). We analyzed the data to determine what factors were different in children with LDL cholesterol >3.35 mmol/l. A total of 28 children with diabetes had LDL cholesterol >3.35 mmol/l (of whom 20 completed a FFQ), compared with 9 control children ($\chi^2 = 7.5$, $P = 0.006$). Subjects with diabetes and LDL cholesterol >3.35 mmol/l had significantly higher HbA_{1c} and higher percentage energy derived from complex carbohydrates than those with LDL cholesterol <3.35 mmol/l (Table 3). Results in control children are not shown.

CONCLUSIONS — We confirm that hyperlipidemia remains common in children and adolescents with type 1 diabetes and that metabolic control is the major determinant of elevated LDL and total cholesterol. Dietary factors contribute minimally to hyperlipidemia in children and adolescents with type 1 diabetes, except as they impact on metabolic control. This study was limited by its cross-sectional nature, and the results may be less applicable to populations with higher intakes of fats than those observed here.

The International Society for Pediatric and Adolescent Diabetes (ISPAD) recommendations for dietary fat intake in young people with type 1 diabetes include sufficient energy for normal growth without obesity, with <30% of total energy as fats as follows: >10% of total energy as monounsaturated fat, <10% of total energy as saturated fats, up to 10% of total energy as polyunsaturated fats, and <300 mg/day cholesterol (10). The American Diabetes Association (ADA) recommends an individualized healthy diet with intake similar to other children, comparable to the ISPAD recommendations (11). The National Cholesterol Education Program suggests dietary intervention in children with LDL cholesterol >3.35 mmol/l (130 mg/dl) (20). Our results suggest that treatment of lipid disorders in young people with diabetes should be directed primarily at improving metabolic control rather than focusing on dietary lipid intake. Although diet is an important part of achieving good metabolic control, restriction of cholesterol and saturated fat without attention to overall metabolic control is unlikely to be successful. In the current study, subjects with diabetes and elevated LDL cholesterol had a higher intake of complex carbohydrates and a lower intake of saturated fat than those without elevated LDL cholesterol. Changing the percentage of energy from carbohydrates and fat is also difficult in young people (21,22), and it is possible that attempting to control lipid abnormalities in children with type 1 diabetes using dietary approaches alone will be counterproductive.

Most previous studies investigating the dietary intake of both children

(21,23,24) and adults (22,25) with type 1 diabetes have found the majority of subjects to have diets with higher fat content and lower complex carbohydrate content than those recommended, although Randecker et al. (26) found average intakes close to recommendations. In our study, average dietary intakes were close to the ADA and ISPAD recommendations, with mean saturated fat intake being slightly above and carbohydrate intake slightly below the recommendations. Children with diabetes had healthier diets than control subjects. These results indicate that when the recommendations are achieved, dietary fats contribute minimally to hyperlipidemia in children with type 1 diabetes. We also found correlations between HbA_{1c} and the intake of fiber, total sugar, and total carbohydrates, suggesting that these may be useful dietary targets in improving metabolic control. A recent short-term intervention study in children suggested potential beneficial effects from the increased intake of monounsaturated fat in adolescents with diabetes (21).

Although most studies of lipids in children with type 1 diabetes have shown increased cholesterol and triglycerides, particularly with poor metabolic control (2–5), results for HDL cholesterol have been conflicting. Some investigators have found normal or lower HDL cholesterol in type 1 diabetes (3,5,6,17,27,28), whereas others have found higher HDL cholesterol in children (2,29,30) and adults (31). In this study, higher levels of HDL and its major apo, apoA1, were found in children and adolescents with diabetes than in control subjects. We found that in children with diabetes, HDL cholesterol was independently associated with diastolic BP, HbA_{1c}, and percentage energy intake of complex carbohydrates, whereas apoA1 was independently associated with HbA_{1c} and height. One explanation for increased HDL cholesterol in type 1 diabetes is peripheral hyperinsulinism caused by insulin-mediated lipoprotein lipase activity (31,32). Treatment-related variations in the degree of hyperinsulinism may explain the differences in results observed in these studies.

The ratio of LDL cholesterol to apoB is a marker of LDL subclasses, with small dense LDL particles, which are more atherogenic, having a lower ratio (18,33). Azad et al. (17) found this ratio to be lower in children with type 1 diabetes than in control subjects, and they found small dense LDL to be associated with poorer metabolic control. The current study has not confirmed these results, with no difference in the LDL-to-apoB ratio between children with diabetes and control subjects and no association with HbA_{1c}. Our data, therefore, do not suggest a preferential accumulation of small dense LDL particles in children and adolescents with type 1 diabetes. This difference may reflect better metabolic control in the current study, or the different population studied.

In summary, hyperlipidemia is common in children and adolescents with type 1 diabetes who adhere to current dietary recommendations. It relates primarily to metabolic control, with limited impact from dietary factors. Treatment of hyperlipidemia should primarily be directed at improving metabolic control.

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