Prevalence Of Abnormal Lipid Profiles And The Relationship With The Development Of Microalbuminuria In Adolescents With Type 1 Diabetes

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Objective. To explore the prevalence of lipid abnormalities and their relationship with albumin excretion and microalbuminuria (MA) in adolescents with type 1 diabetes.

Research Design and Methods. The study population comprised 895 young subjects with type 1 diabetes (490 males): age at the baseline assessment (median[range]): 14.5[10-21.1] years; diabetes duration 4.8[0.2-17] years. 2194 non-fasting blood samples were collected longitudinally for determination of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), and non-HDL-C. Additional annually collected data on anthropometric parameters, HbA1c, albumin-creatinine ratio (ACR) were available.

Results. TC, LDL-C, HDL-C and non-HDL-C were higher in girls than in boys (all p<0.001). A significant proportion of subjects presented sustained lipid abnormalities during follow-up: TC>5.2mmol/l (18.6%), non-HDL-C>3.4mmol/l (25.9%), TG>1.7mmol/l (20.1%), LDL>3.4mmol/l (9.6%). Age and duration were significantly related to all lipid parameters (p<0.001); HbA1c was independently related to all parameters (p<0.001) except HDL-C; whereas BMI SDS was related to all parameters (p<0.05) except TC.

TC and non-HDL-C were independently related to longitudinal changes in ACR (B±SE): 0.03±0.01/1mmol/l; p=0.009 and 0.32±0.14/1mmol/l; p=0.02, respectively. Overall mean TC and non-HDL-C were higher in MA positive (n=115) than in normoalbuminuric subjects (n=780): TC 4.7±1.2 vs 4.5±0.8mmol/l (p=0.04); non-HDL-C 3.2±1.2 vs 2.9±0.8mmol/l (p=0.03).

Conclusions. In this longitudinal study of adolescents with type 1 diabetes, sustained lipid abnormalities were related to age, duration, BMI and HbA1c. Furthermore, ACR was related to both TC and non-HDL-C, indicating a potential role in the pathogenesis of diabetic nephropathy.
Type 1 diabetes is associated with an increased risk for the development of microvascular complications and cardiovascular disease (CVD) (1; 2). Qualitative and quantitative lipid abnormalities are often present in subjects with type 1 diabetes and are related to glycemic control (2). The relationship between dyslipidemia and CVD risk is well documented in adult diabetic populations and treatment with lipid-lowering drugs has been associated with reduced cardiovascular events (2). Clinical and experimental studies have highlighted the potential role of dyslipidemia in the development of microalbuminuria (MA) and diabetic nephropathy (DN) (3). Mesangial, tubulo-interstitial and glomerular changes in the kidney have been associated with lipid levels (3). In animal models of diabetes, treatment of hyperlipidemia with statins has been associated with reduced glomerular injury (3).

Cross-sectional studies in humans have suggested that raised lipid levels are involved in the pathogenesis and progression of renal diseases (3), and treatment of dyslipidemia can reduce albumin excretion (3). In the Steno Study, subjects who developed MA had higher cholesterol levels than subjects who did not progress (4). In addition, in this study, as in others, lower cholesterol levels predicted regression of MA to normoalbuminuria (5). Triglycerides have also emerged as a predictor for the development and progression of renal complications (6). Based on these data it appears that measurement of plasma lipids can add to the prognostic value of albumin excretion in the prediction of subjects at risk of DN.

However, there is a lack of longitudinal studies, particularly in young people with type 1 diabetes, assessing the association between lipid abnormalities and risk for MA. Based mainly on cross-sectional studies, dyslipidemia appears to be more common among youth with diabetes than in the general paediatric population (7; 8) and its relationship with glycemic control has been repeatedly documented (7; 9; 10). In contrast, data on the association between lipid levels and albumin excretion are scant (11; 12).

Therefore, the aim of the present study was to assess the prevalence of lipid abnormalities, their determinants and their relationship with albumin excretion and the development of MA in a large population of young people with type 1 diabetes, followed longitudinally during puberty.

**RESEARCH DESIGN AND METHODS**

**Study population: Nephropathy Family Study (NFS) cohort:** The NFS was established between 2000-2005 as part of the Juvenile Diabetes Research Foundation/Wellcome Trust Diabetes Inflammation Laboratory: Genetic Resource Investigating Diabetes (GRID) study (http://www.childhood-diabetes.org.uk/grid.shtml). 1,066 subjects, aged 10-16 years, who had developed type 1 diabetes before the age of 16 years, were recruited throughout four English regions (East Anglia, Birmingham, Bristol and Oxford). Subjects with insulin treated diabetes secondary to other pathologies were excluded. Similarly, children with chronic renal disease or other chronic diseases likely to affect renal function were excluded. The median duration of follow-up is currently 2.3 [interquartile range 1.0-3.4] years.

The longitudinal study schedule comprised annual collection of three consecutive early morning urine (EMU) specimens for centralised measurement of albumin-creatinine ratio (ACR) and blood samples for measurements of HbA1c and lipids.
Ethical approval was obtained from the regional ethics committee, and written informed consent was obtained from the parents together with assent from the children.

**Methods:** Non-fasting blood samples, collected longitudinally between February 2001 and January 2006, were analysed for determination of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), triglycerides (TG), and non-HDL-C. In order to exclude lipid abnormalities related to untreated diabetes, samples collected within the first month of diagnosis were excluded. In addition, patients on treatment with statins were also excluded from the analysis.

A total of 2194 lipid measurements were available from 895 subjects; mean (±SD) 2.5±1.0; median [range]: 3[1-5] measurement/patient. 183 subjects had only one measurement, 254 had 2 measurements, 333 had three measurements, 121 had 4 measurements and only 4 subjects had 5 measurements.

**HbA1c.** Samples were analysed centrally on a TOSOH G7 analyser, using HPLC and absorbance change detection, and DCCT aligned methods. The normal range for HbA1c 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 TC, HDL-C and TG were performed enzymatically on a Dimension RXL system (Dade Behring) using reagents and calibrants supplied by the manufacturer. Between run CV were for TC 1.3% at 3.2mmol/l and 1.2% at 7.5mmol/l; for TG 3.2% at 1.0mmol/l and 1.1% at 2.2mmol/l and for HDL-C 3.3% at 0.6mmol/l and 2.1% at 1.5mmol/l.

LDL-C was calculated with Friedwald’s formula: LDL=TC−HDL-C−TG/2.2.

As our samples were collected in non-fasting conditions non-HDL-C (TC minus HDL-C) was also assessed.

**Urinary albumin and creatinine.** All urine samples were stored at −70°C prior to the centralised analysis in a single reference laboratory. Albumin was measured by a double antibody ELISA method. The within and in-between assay CV were 6 and 12% respectively. Creatinine was measured using a modified Jaffe method (Unimate 7, Roche Diagnostic Systems, Switzerland) on a Cobas Mira (Roche Diagnostic Systems, Switzerland) automated spectrophotometer. The CV was 2% at 2.2 mmol/l.

**Calculations:** Body mass index (BMI) was calculated as weight/height². Standard deviation scores (SDS) for BMI were calculated using the British 1990 Growth Reference and Cole’s LMS method.

ACR was summarized as the geometric mean of three consecutive EMU during each annual assessment. The most recent ACR measurements in relation to the time when each lipid assessment was done (within ±3 months) was used for the analyses of the relationship with lipid levels. A total of 1991 ACR measurements were available from 870 subjects.

MA was defined as an ACR between 3.5-35 mg/mmol in males and between 4.0-40 mg/mmol in females in two out of three consecutive EMU collections during an annual assessment (13). Persistent MA was defined as an ACR within the microalbuminuric range based on 2 out 3 urines or 2 out of 2 urines each year for at least 2 consecutive years. Transient MA was defined as the presence of MA for one year with subsequent regression to normal.

Lipid levels were categorised, based on the National Cholesterol Education Programme (14) and American Heart Association (15) guidelines, as follow: high TC: >5.2mmol/l, borderline TC: 4.4-5.2mmol/l; high LDL-C: >3.4mmol/l, borderline LDL-C: 2.9-
Lipids in youth with diabetes

3.4mmol/l; low HDL-C: <0.9mmol/l; high TG: >1.7mmol/l; high non-HDL-C: >3.4mmol/l.

Statistical analyses: Data are summarised as mean±SD or median [range] for continuous variables and as cell frequencies and percentages for categorical variables. Non-normally distributed variables (ACR, 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±standard error (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 genders, whereas BMI SDS was significantly higher in girls than in boys. Levels of TC, LDL-C, HDL-C and non-HDL-C were higher in girls than in boys (all p<0.001), whereas TG levels were comparable. These gender differences in lipid levels persisted after adjustment for BMI (Table 1). Similar gender differences in lipid parameters persisted during the subsequent follow-up visits (data not shown).

Categories of lipid levels at baseline and during follow up: A high prevalence of high and borderline lipid levels was found at the baseline visit and these abnormalities persisted during follow-up (see Figure A1 in the online appendix available at http://care.diabetesjournals.org). Mean frequency of lipid abnormalities during follow-up was: TC: 18.6%; TG: 20.1%; non-HDL-C 25.9%, LDL-C: 9.6%, low HDL-C: 2.5%; borderline TC: 34.8%, borderline LDL-C: 12.7%.

Lipids and HbA1c: There was a significant association between mean lipid levels, except HDL-C, and mean HbA1c (TC: r=0.35; LDL-C: r=0.21; TG: r=0.40; non-HDL-C: r=0.36; all p<0.001). These associations were significantly stronger in girls than in boys (TC: r=0.45 vs 0.25, p<0.01; LDL-C: r=0.31 vs 0.10, p<0.01; TG: r=0.41 vs 0.26, p<0.05).

Longitudinal predictors of lipids levels: A longitudinal evaluation of factors associated with lipid levels was performed in the 711 subjects with more than one lipid assessment, with age, gender, duration of diabetes, HbA1c and BMI-SDS as the independent variables. In a covariate model, age was significantly related to all lipid parameters; HbA1c was independently related to all parameters except HDL-C; whereas BMI SDS was related to all parameters except TC (Table 2). Similar results were obtained when duration was included as a covariate instead of age (data not shown).

The analysis was then repeated separately for males and female, with similar findings, except for the relationship between lipid levels and age, which persisted in boys but was no longer significant in girls (data not shown).

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, gender, duration, BMI SDS and HbA1c. TC and non-HDL-C were independently related to changes in log ACR during follow-up.

During follow up, 115 (13%) subjects developed MA (28 persistent and 87 transient MA). Age-related changes in TC and non-HDL-C and specifically the rise in their levels after the age of 15-16 years, were particularly marked in subjects with persistent MA when
compared with those with transient MA and normoalbuminuria (Figure 1).

Mean concentrations of TC (4.7±1.2 vs 4.5±0.8mmol/l, p=0.04) and non-HDL-C (3.2±1.2 vs 2.9±0.8mmol/l, p=0.03) were higher in subjects developing MA when compared to those with normoalbuminuria (see Table A1 in the online appendix available at http://care.diabetesjournals.org). However, these differences disappeared after adjusting for HbA1c. MA positive subjects also presented a high percentage of abnormal lipid levels, specifically TC and LDL-C when compared to 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 glycemic control. In addition, we found that TC and non-HDL-C were significantly related to albumin excretion during the study period.

In our study the mean frequency of high and borderline TC during follow-up was 18.6% and 34.8%, respectively. A large proportion of subjects had a high non-HDL-C (25.9%), whereas the frequency of low HDL-C 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-C, even though these parameters are less reliable, given that blood samples were collected in non-fasting 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 out of five children with type 1 diabetes presented a TC above 5.2 mmol/l, similar to our results. Data from the Oxford Regional Prospective Study (ORPS) showed that 15.3% subjects had a TC above 5.2 mmol/l and 17.9% TG above 1.7 mmol/l (12). Similar data have been reported in a study from the US where 15.2% children had a high TC (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 about 10-20%, in cholesterol levels during puberty (21). This has been constantly reported in boys, whereas in girls the picture has been more controversial, as some studies have not shown any pubertal decline in TC (22). However, an influence of age and puberty on lipid levels has not been always 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 diabetes 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 HbA1c was HDL-C, similarly to previous findings in adults (24). The lack of a relationship between HbA1c and HDL-C
could be due to opposite effects of glycemia on different HDL subclasses, which cannot be detected by simply assessing total HDL-C (24). A strong relationship between other lipid parameters and HbA1c 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 cholesteryl esters from HDL to ApoB containing lipoproteins (2). The strong relationship between lipid levels and HbA1c underlines the role of a 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 HbA1c were associated with improvements in lipid levels only in subjects with the least weight gain during the interventional period (25). These observations have been related to a state of insulin resistance/hyperinsulinemia associated with increased body weight (23).

The relationship between MA and dyslipidemia has not been extensively investigated in young people with type 1 diabetes. In adult populations, increased TC and/or TG have been associated with MA (6), although associations with lipid abnormalities were found to be more marked in patients with macroalbuminuria (6; 23). With respect of paediatric populations with diabetes, data from the ORPS showed that the prevalence of MA increased across tertiles of TC (12) and a recent German study have shown a predictive value of both LDL-C and TG on the development of persistent MA (11). In the present study, we examined lipid levels in relation to changes in albumin excretion, as a continuous variable, and the development of MA. Increased TC and non-HDL-C levels were independently related to ACR during follow-up, even after adjusting for glycemic control and other confounding factors. In addition, the changes in lipid levels with age in subjects with persistent MA were remarkable when compared with those with transient MA or normoalbuminuria. Both TC and non-HDL-C showed a marked increase from the age of about 15 years in individuals developing persistent MA. It is interesting that in our study population the mean age at MA onset was 15 years, therefore providing further support for a potential relationship between lipid levels and MA. Overall lipid levels were higher in subjects developing MA when compared with normoalbuminuric subjects. However, these differences were probably related to the worse glycemic control in subjects with MA as they disappeared when adjusting for HbA1c.

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-C, were also influenced by glycemic control. A significant number of subjects presented high and borderline lipid levels that persisted over time. TC and non-HDL-C were closely related to albumin excretion during follow-up, suggesting a potential role in the pathogenesis of DN. These results highlight the need of screening for dyslipidemia in adolescents with
type 1 diabetes in order to early identify subjects at risk for complications, who need more intensive follow-up and perhaps other therapeutic interventions.

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Disclosure: the authors do not have any conflict of interest to declare
REFERENCES
Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Male</th>
<th>Female</th>
</tr>
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<tbody>
<tr>
<td>N</td>
<td>895</td>
<td>490</td>
<td>405</td>
</tr>
<tr>
<td>Age at diagnosis (yrs)</td>
<td>9.6 [0.2-17.2]</td>
<td>9.8 [0.2-16.5]</td>
<td>9.5 [0.2-17.2]</td>
</tr>
<tr>
<td>Duration at 1st assessment (yrs)</td>
<td>4.8 [0.2-17]</td>
<td>4.8 [0.2-16.9]</td>
<td>5.0 [0.2-17]</td>
</tr>
<tr>
<td>BMI SDS</td>
<td>0.8 ± 0.97</td>
<td>0.70 ± 0.97</td>
<td>0.87 ± 0.97</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>9.3 ± 1.9</td>
<td>9.2 ± 1.8</td>
<td>9.4 ± 1.9</td>
</tr>
<tr>
<td>Total Cholesterol (mmol/l)</td>
<td>4.5 ± 0.9</td>
<td>4.3 ± 0.8</td>
<td>4.7 ± 1.0*</td>
</tr>
<tr>
<td>HDL-Cholesterol (mmol/l)</td>
<td>1.6 ± 0.4</td>
<td>1.6 ± 0.4</td>
<td>1.7 ± 0.4*</td>
</tr>
<tr>
<td>LDL-Cholesterol (mmol/l)</td>
<td>2.3 ± 0.7</td>
<td>2.2 ± 0.7</td>
<td>2.5 ± 0.8*</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.0 [0.2- 8.5]</td>
<td>1.0 [0.2-7.3]</td>
<td>1.0 [0.3-8.5]</td>
</tr>
<tr>
<td>Non-HDL-Cholesterol (mmol/l)</td>
<td>2.9 ± 0.9</td>
<td>2.7 ± 0.8</td>
<td>3.1± 1.0*</td>
</tr>
</tbody>
</table>

Data are median [range] and mean ± SD; *p<0.01 for girls vs boys
BMI SDS: body mass index standard deviation score; HDL: high-density lipoprotein; LDL: low-density lipoprotein; ns: not significant; MA: microalbuminuria

Table 2. Independent predictors of lipids levels during follow-up

<table>
<thead>
<tr>
<th></th>
<th>B ± SE</th>
<th>p</th>
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<tbody>
<tr>
<td><strong>Total Cholesterol</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.042 ± 0.014</td>
<td>0.004</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>0.161 ± 0.016</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI SDS</td>
<td>0.077 ± 0.043</td>
<td>ns</td>
</tr>
<tr>
<td>Log Triglycerides</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.018 ± 0.005</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>0.045 ± 0.005</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI SDS</td>
<td>0.062 ± 0.014</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>HDL-Cholesterol</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>-0.038 ± 0.006</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>0.001 ± 0.007</td>
<td>ns</td>
</tr>
<tr>
<td>BMI SDS</td>
<td>-0.06 ± 0.019</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>LDL-Cholesterol</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.050 ± 0.011</td>
<td>0.013</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>0.072 ± 0.013</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI SDS</td>
<td>0.079 ± 0.03</td>
<td>0.025</td>
</tr>
<tr>
<td><strong>Non-HDL-Cholesterol</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.080 ± 0.013</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>0.160 ± 0.015</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI SDS</td>
<td>0.138 ± 0.040</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Data are from 712 subjects with more than 1 lipid measurement and are adjusted for repeated measurements and for gender. BMI SDS: body mass index standard deviation score; HDL: high-density lipoprotein; LDL: low-density lipoprotein; ns: not significant.
Table 3. Relationship between lipid parameters and albumin-creatinine ratio (ACR)

<table>
<thead>
<tr>
<th></th>
<th>B±SE*</th>
<th>P*</th>
<th>B±SE**</th>
<th>P**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>0.041 ± 0.011</td>
<td>&lt;0.001</td>
<td>0.033 ± 0.013</td>
<td>0.009</td>
</tr>
<tr>
<td>Log Triglycerides</td>
<td>0.12 ± 0.033</td>
<td>&lt;0.001</td>
<td>0.72 ± 0.037</td>
<td>ns</td>
</tr>
<tr>
<td>HDL-Cholesterol</td>
<td>-0.006 ± 0.026</td>
<td>ns</td>
<td>0.03 ± 0.007</td>
<td>ns</td>
</tr>
<tr>
<td>LDL-Cholesterol</td>
<td>0.007 ± 0.015</td>
<td>ns</td>
<td>-0.002 ± 0.016</td>
<td>ns</td>
</tr>
<tr>
<td>Non-HDL-Cholesterol</td>
<td>0.47 ± 0.012</td>
<td>&lt;0.001</td>
<td>0.32 ± 0.14</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Dependent variable is Log ACR. Regression coefficients B are for each 1 mmol/l increase in lipid levels.

*unadjusted values; **adjusted values for age, gender, duration, BMI SDS and HbA1c
ACR: albumin-creatinine ratio; HDL: high density lipoprotein; LDL: low density lipoprotein; ns: not significant
Figure 1. Longitudinal changes in total cholesterol and non-HDL-Cholesterol with age in subjects with normoalbuminuric subjects (MA-) and in those with transient and persistent microalbuminuria (MA).