Early Signs of Atherosclerosis in Diabetic Children on Intensive Insulin Treatment

A population-based study

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OBJECTIVE — To evaluate early stages of atherosclerosis and predisposing factors in type 1 diabetic children and adolescents compared with age- and sex-matched healthy control subjects.

RESEARCH DESIGN AND METHODS — All children and adolescents with type 1 diabetes, aged 8–18 years in Health Region South-East in Norway were invited to participate in the study (n = 800). A total of 40% (n = 314) agreed to participate and were compared with 118 age-matched healthy control subjects. Carotid artery intima-media thickness (cIMT) and elasticity were measured using standardized methods.

RESULTS — Mean age of the diabetic patients was 13.7 years, mean diabetes duration was 5.5 years, and mean A1C was 8.4%. 97% were using intensive insulin treatment, and 60% were using insulin pumps. Diabetic patients had more frequently elevated cIMT than healthy control subjects: 19.5% were above the 90th centile of healthy control subjects, and 13.1% were above the 95th centile (P < 0.001). Mean cIMT was higher in diabetic boys than in healthy control subjects (0.46 ± 0.06 vs. 0.44 ± 0.05 mm, P = 0.04) but not significantly so in girls. There was no significant difference between the groups regarding carotid distensibility, compliance, or wall stress. None of the subjects had atherosclerotic plaque formation. Although within the normal range, the mean values of systolic blood pressure, total cholesterol, LDL cholesterol, and apolipoprotein B were significantly higher in the diabetic patients than in the healthy control subjects.

CONCLUSIONS — Despite short disease duration, intensive insulin treatment, fair glycemic control, and no signs of microvascular complications, children and adolescents with type 1 diabetes had slightly increased cIMT compared with healthy control subjects, and the differences were more prominent in boys.

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The NCDR since 2001 or from the time of Glycemic burden

4.1–6.4

of Oslo University Hospital, Aker, Oslo, the same central DCCT-standardized laboratory at the clinical chemistry department determined for all participants by high-performance liquid chromatography. A1C, in the morning. Serum glucose, creatinine, and lipid concentrations were measured using standard techniques. Arterial blood pressure was measured according to the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents (15). For the diabetic patients, the pubertal Tanner stage was obtained from the NCDR, together with self-rating. For the control subjects, only the self-rating was performed.

Blood tests

Fasting venous blood samples were taken in the morning. Serum glucose, creatinine, and lipid concentrations were measured using standard methods. A1C, in the NCDS and the present study, was determined for all participants by high-performance liquid chromatography (Variant; Bio-Rad, Richmond, CA) at the same central DCCT-standardized laboratory at the clinical chemistry department of Oslo University Hospital, Aker, Oslo, Norway. The normal reference range was 4.1–6.4 ± 2%, and the intra-assy coefficient of variation was <3%.

Glycemic burden

Annual A1C values were available from the NCDR since 2001 or from the time of diagnosis for the majority of the patients. Mean A1C was calculated from all the A1C values available for each patient from the first NCDR registration until the time of cIMT analysis.

A1 months was calculated using a modified version of the formula developed by Orchard et al. (16). It was calculated as the sum of months from the diagnosis of diabetes until the first A1C value registered in the NCDR multiplied by A1C units above the upper normal reference value (6.4%) of the first registered value, plus the number of months from the first to second registration multiplied by A1C units above the upper normal reference value of the second registered value, and so on until the time of cIMT analysis.

Common carotid artery ultrasonography

A standardized protocol and strict quality control procedures were implemented to achieve reliable ultrasonic measurements of cIMT. Two experienced sonographers, blinded to the participants’ diabetes status and risk factor levels, did all the examinations.

The subjects were studied in the morning under standardized conditions (quiet room, comfortable temperature) with the participant in the fasting state. Blood pressure was measured under resting conditions. High-resolution ultrasonography was performed with a Siemens Acuson Sequoia 512 (Siemens Acuson; Mountain View, CA) ultrasound scanner equipped with a linear array 14-MHz transducer.

The participants were examined in the supine position with the head turned slightly to both sides. After identifying the bulb, longitudinal images of the common carotid artery (CCA) were obtained by combined B-mode and color Doppler. The scan was focused on the far wall, and the resolution box was used to magnify the far wall segment 10–20 mm proximal of the carotid bulb, where all measurements were done. Several images were acquired by using an anterior oblique angle (30° from midline) and lateral (100° from midline) (17). The IMT of the far wall was measured during end diastole (R-wave of the electrocardiogram). Three scans on both sides were selected, and nine (3 × 3) measurements of maximum far wall IMT on both sides were averaged; thus, the conclusive mean IMT of each patient was calculated from a total of 18 measurements. The CCA and the carotid bulb region were also scanned for the presence of atherosclerotic plaques, defined as a distinct area of the vessel protruding from >50% of the adjacent parts of the intima-media layer (18). All scans were digitally stored on the internal hard disk for subsequent offline analysis. One experienced reader (K.H.S.), blinded to the subjects’ clinical details, performed all measurements. Carotid elastic behavior was measured from the maximal end-diastolic interadventitial lumen diameter at end-diastole (R-wave of the electrocardiogram) and end-systole. Two measurements each of diastolic and systolic diameters on both sides were averaged. The diameter change was calculated as the difference between the systolic and diastolic averages.

Characterization of the carotid arteries’ elastic behavior was performed through distensibility and compliance, defined as the relative (ΔV/V) and absolute (ΔV) change in carotid arterial volume (V) for a change in pulse pressure (ΔP), respectively. Distensibility reflects the mechanical load of the artery wall, and compliance reflects the ability to store volume (19). Both are generally expressed as changes in lumen cross-sectional area (A) during the cardiac cycle. The expression for distensibility coefficient (DC) in terms of end-diastolic diameter (d) and the change in diameter (Δd) from diastole to systole, assuming a circular lumen cross-section, is: DC = ∆A/∆d = π[(d + ∆d)² - d²]/Δd/ΔP. Similarly, the compliance coefficient (CC) can be rewritten as: CC = ∆V/ΔP = πd²/Δd². In addition, wall stress can be calculated by the Young modulus, E, which is the ratio of stress and circumferential strain in the vessel wall (19). E is related to DC as (assuming h = IMT): E = (d/h)/DC.

A total of 12 subjects presented twice within 8 weeks for the determination of intra- and interobserver variability, and the IMT was measured without knowledge of the previous values. For IMT measurements the between-sonographer intraclass correlation coefficient (ICC) for mean IMT was 1.0 (95% CI 0.997–1.000). The within-subject ICC was 0.99 (0.977–0.999) for the first sonographer and 0.96 (0.790–0.994) for the second sonographer.

Statistical analysis

Demographic and clinical data are presented as means ± SD or proportions.
Differences in continuous variables between males and females were tested with the Student t test for normally distributed data and the Mann-Whitney U test for non-normally distributed data. The \( \chi^2 \) test for contingency tables with different degrees of freedom was obtained to detect associations between categorical independent variables. Adjustment for multiple confounding was done using linear regression analysis with a manual backward procedure.

Multivariate analyses were preceded by estimation of the correlation between potential confounders. A significance level of 5% was used. All statistical analysis was done using the SPSS software package for Windows, version 15.0 (SPSS, Chicago, IL).

Elevated values of the IMT measurements were defined as above the 90th and 95th centile of the healthy control subjects.

RESULTS — The present study involved 314 diabetic patients (participation rate about 40%) and 118 healthy control subjects from a geographically defined region. The diabetic patients in this study were compared with the diabetic patients in the rest of the country as registered in the NCDR. Data from the NCDR in 2007 was used for comparison (data not shown). The diabetic patients in this study were found to be representative of diabetic patients in the whole country, and the recruitment procedure makes this study a population-based study. A1C in the diabetic patients in this study was similar to that in the rest of the country (8.43 vs. 8.49%). The diabetic patients in this study were older than the rest of the diabetic children in the country (13.3 ± 2.7 vs. 12.5 ± 3.8 years; \( P < 0.001 \)), had slightly longer diabetes duration (5.1 ± 3.3 vs. 5.0 ± 3.9 years; \( P = 0.04 \)), and had higher BMI (20.6 ± 3.5 vs. 20.0 ± 3.8 kg/m\(^2\); \( P = 0.04 \)). However, only children older than 8 years of age were included in the present study, and all other patients registered in the NCDR were used for comparison. Significantly more participants in the present study were using intensive insulin treatment (97 vs. 95%; \( P < 0.01 \)), and more were using insulin pumps (60 vs. 48%; \( P < 0.001 \)), than in the rest of the diabetic patients in the country. Otherwise the groups were similar (\( P > 0.05 \)), for instance regarding blood pressure, lipid status, pubertal stage, and family history of early CVD and type 2 diabetes.

The characteristics of the participants in the present study are shown in Table 1. The groups (diabetic patients and healthy control subjects) were similar regarding sex, age, and pubertal stage. However, a significant difference was observed between the groups regarding height, weight, BMI, and waist circumference, with higher values among the diabetic subjects for all parameters. In the diabetic group as a whole, the mean values of systolic blood pressure, total cholesterol, LDL cholesterol, and apolipoprotein B (ApoB) were significantly higher than in the control subjects, although within the normal range. However, the apolipoprotein A1 (ApoA1) values and HDL levels were also higher in the diabetic group than in control subjects, making the groups similar regarding total-to-HDL cholesterol ration and ApoB-to-ApoA1 ratio (Table 1). There was no difference between the groups regarding family history of early CVD and/or type 2 diabetes (data not shown).

All but 33 subjects (11%) with diabetes had urinary albumin excretion rates in the normoalbuminuric range. The 33 subjects had only modest microalbuminuria, and none had persistent microalbuminuria. None of the patients with diabetes had evidence of microvascular complications, such as retinopathy, clinical neuropathy, or overt nephropathy. There was no difference between diabetic patients and control subjects regarding mean values of urinary albumin-to-creatinine ratio (Table 1).

More diabetic patients had elevated cIMT values; 19.5% were above the 90th centile and 13.1% above the 95th centile of the healthy control subjects for IMT values (\( P < 0.001 \)). Although these findings were more pronounced among the males, the same tendency was observed among the females as well (data not shown). Regarding the parameters of carotid artery elasticity (DC, CC, and DS), the proportion of diabetic patients above the 90th or 95th centile was not significantly elevated compared with the healthy control subjects (Table 2).

The boys had higher mean cIMT than the girls (0.46 ± 0.06 vs. 0.44 ± 0.05 mm; \( P = 0.008 \)). The diabetic patients had a slightly higher mean cIMT than the control subjects (0.45 vs. 0.44 mm) (Table 3), but the difference was not statistically significant, even after adjusting for multiple confounders. The mean cIMT was, however, significantly higher among diabetic boys than age-matched healthy control subjects (0.46 ± 0.06 vs. 0.44 ± 0.05 mm; \( P = 0.04 \)) but not among diabetic girls. A significant difference between patients and control subjects was not found for mean values of CC (9.95 vs. 9.90), DC (0.35 vs. 0.36), or carotid wall stress (0.13 in both groups). No plaque formation was observed in any of the children studied.

A direct association between IMT and age was not found. However, an increase in IMT with age was shown through the first three age quartiles, but no further increase was found in the fourth age quartile.

An association between IMT and A1C or lipid levels was not found in the group as a whole, or in the diabetic patient group only, or in either sex. The same is true regarding family history of early CVD and/or type 2 diabetes in the family.

In the diabetic patients, there was no association between IMT and diabetes duration or glycemic burden (mean A1C or calculated A1c months). However, there was an association between IMT and age of diabetes onset (\( P = 0.045 \)).

CONCLUSIONS — The diabetic subjects in this study showed signs of early atherosclerosis by having elevated cIMT two to three times more frequently than healthy control subjects, the difference being most prominent in the boys. cIMT is found to be well suited as a surrogate end point in clinical studies (1,5,6). It correlates well with cardiovascular risk factors and coronary atherosclerosis (1) and is an independent predictor of future cardiovascular events (5). It also shows a good correlation with invasive examinations such as coronary angiography and IVUS (1,7). cIMT is a well-validated and safe examination with high reproducibility that can be repeatedly performed with no adverse effect on the patient. However, this method relies on the technician, and procedures must be standardized to avoid inaccurate estimation of cIMT measurements. If such issues are resolved, this method can be appropriate for identifying and possibly monitoring subjects at an increased risk of future vascular events (1,5,6).

Studies on cIMT in children and adolescents have yielded conflicting results; some studies show increased cIMT in diabetic patients, whereas others do not (10–13,20,21). The different results may...
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Table 1—Clinical characteristics and metabolic and anthropometric data of the participants

|                        | Total                  | Male                  | Female                 |
|------------------------|------------------------|-----------------------|------------------------|
| n                      | 314                    | 155                   | 159                    |
| Age (years)            | 13.8 ± 2.8             | 13.4 ± 2.80           | 14.1 ± 2.85            |
| Duration of diabetes (years) | 5.5 ± 3.4             | 5.6 ± 3.4             | 5.4 ± 3.4             |
| Pubertal stage (Tanner) | 3.2 ± 1.5              | 2.9 ± 1.6             | 3.5 ± 1.4              |
| Height (cm)            | 160 ± 4.14             | 160.6 ± 14.7          | 160.3 ± 12.3           |
| Weight (kg)            | 54.9 ± 16.7            | 53.3 ± 17.4           | 56.5 ± 14.4            |
| BMI (kg/m²)            | 20.9 ± 3.939           | 20.1 ± 3.6            | 21.6 ± 4.1             |
| Waist circumference (cm)| 71.2 ± 10.0            | 70.3 ± 10.0           | 72.1 ± 9.9             |
| SBP (mmHg)             | 101.0 ± 10.1           | 101.0 ± 9.8           | 101.0 ± 10.3           |
| DBP (mmHg)             | 60.5 ± 8.3             | 59.6 ± 8.4            | 61.5 ± 8.2             |
| Smoking                | 11 (3.5)               | 2 (2)                 | 9 (5.7)                |
| Urinary albumin-to-   | 1.4 ± 3.7              | 1.8 ± 4.9             | 1.0 ± 1.1              |
| creatinine ratio       | 53.1 ± 10.3            | 53.7 ± 10.8           | 52.5 ± 9.7             |
| S-creatinine (μmol/l)  | 10.9 ± 4.8             | 10.1 ± 5.1            | 10.8 ± 4.5             |
| A1C (%)                | 8.4 ± 3.3              | 8.3 ± 12.2            | 8.4 ± 1.3              |
| Mean A1C (%)           | 8.2 ± 1.0              | 8.1 ± 1.0             | 8.2 ± 1.0              |
| A1 months*             | 119 ± 104.1            | 120.8 ± 107.1         | 117.9 ± 105.1          |
| Total cholesterol (mmol/l) | 4.6 ± 0.9             | 4.6 ± 0.8             | 4.7 ± 0.8              |
| HDL cholesterol (mmol/l) | 1.8 ± 0.4             | 1.8 ± 0.4             | 1.8 ± 0.4              |
| LDL cholesterol (mmol/l) | 2.5 ± 0.7             | 2.5 ± 0.7             | 2.5 ± 0.7              |
| LDL-to-HDL cholesterol ratio | 1.5 ± 0.6             | 1.5 ± 0.7             | 1.5 ± 0.6              |
| Total-to-LDL cholesterol ratio | 2.7 ± 0.8             | 2.7 ± 0.8             | 2.7 ± 0.7              |
| Triglycerides (mmol/l) | 0.8 ± 0.4              | 0.8 ± 0.4             | 0.8 ± 0.4              |
| ApoB (g/l)             | 0.7 ± 0.2              | 0.7 ± 0.2             | 0.8 ± 0.2              |
| ApoA1 (g/l)            | 1.6 ± 0.3              | 1.6 ± 0.3             | 1.6 ± 0.3              |
| ApoB-to-ApoA1 ratio    | 0.5 ± 0.2              | 0.5 ± 0.2             | 0.5 ± 0.2              |
| Insulin dose (U/kg/day)| 0.9 ± 0.4              | 0.9 ± 0.3             | 0.9 ± 0.4              |
| Injections per day     | 1 (0.4)                | 0                     | 1 (0.6)                |
| 1–2                    | 6 (2.4)                | 3 (2.5)               | 3 (2.3)                |
| ≥4                     | 95 (37.5)              | 45 (37.5)             | 50 (37.6)              |
| Insulin pumps          | 151 (59.7)             | 72 (60)               | 79 (59.3)              |

Data are means ± SD and n (%). *The number of months from the diagnosis until the first registered A1C value multiplied by A1C units above the upper normal reference value (6.4%) of the first registered value, plus the number of months from the first to second registration multiplied by A1C units above the upper normal reference value of the second registered value, and so on until the time of cIMT analysis.

Table 2—Diabetic patients above 90th and 95th percentile values of healthy control subjects for cIMT, carotid artery elasticity, and various CVD risk factors

|                              | Above 90th percentile | Above 95th percentile |
|------------------------------|-----------------------|-----------------------|
| cIMT                         | 41 (14.0)             | 61 (19.4)             |
| DC                           | 21 (6.7)              | 30 (9.6)              |
| CC                           | 22 (7.0)              | 43 (13.7)             |
| Yong modulus                 | 30 (9.6)              | 347 (15.0)            |
| SBP                          | 18 (5.8)              | 37 (12.0)             |
| DBP                          | 23 (7.5)              | 45 (14.6)             |
| Total cholesterol            | 33 (10.7)             | 50 (16.3)             |
| LDL cholesterol              | 30 (9.8)              | 63 (20.5)             |
| HDL cholesterol              | 22 (7.0)              | 45 (14.7)             |

Data are n (%).

depend on different ultrasound techniques used, as well as different populations. The most referred study on the subject, conducted by Jarvsiilo and colleagues (11, 20), found significantly elevated IMT in both the aorta and carotid artery of diabetic patients compared with control subjects. The difference was, however, greater in the aorta (20), which was not examined in this study. In contrast to our study, which is a population-based study with a large number of patients, most other studies were clinic-based studies with a small number of participants and generally did not include information about insulin regimen. Though the children and adolescents in this study had only slightly elevated mean cIMT, with significant changes in the boys only, a significantly higher number of the diabetic patients had cIMT above the normal level, indicating more atherosclerosis development in the diabetic group compared with the control group.

The sex difference in cIMT observed in our study is in concordance with the general population of children and adolescents whereby atherosclerosis and CVD are more common among males than females (22). Similarly, Peppa-Patridou et al. (21) found greater IMT values in male type 1 diabetic adolescents than in male control subjects (0.52 ± 0.09 and 0.45 ± 0.06, respectively; P = 0.015). Some study results indicate that the sex benefit on atherosclerosis and
CVD might be lost in adult women with type 1 diabetes (7). However, this tendency was not observed among the young patients in this study.

The diabetic patients in this study had higher BMI than the control subjects. Children and adolescents with type 1 diabetes have been found to be more prone to a high BMI than their nondiabetic peers, especially adolescent girls and those using intensive insulin treatments. This is often explained by overinsulization during intensive insulin treatment, frequent hypoglycemic episodes treated by additional food intake, and nutritional liberation leading to increased energy intake (23).

No association between conventional CVD risk factors, such as blood pressure and LDL cholesterol, and vascular structure and function, such as cIMT and/or distensibility, compliance, and wall stress, could be detected in this study. However, the blood pressure and cholesterol values were within the normal range, the patients were young with short disease duration, and the changes in cIMT were small, which might explain why no associations between conventional CVD risk factors and vascular structure and function could be found.

A direct association between cIMT and age was not found in this study. Although cIMT increases with age in adults, this relationship has not been as clearly demonstrated in children and adolescents. Our results are in concordance with results from Sass et al. (24) who found no correlation between age and cIMT in a group of 160 normal control subjects 10–18 years old.

Chronic glycemic exposure (the degree and duration of hyperglycemia) has been associated with macrovascular complications and increased cardiovascular risk in adult diabetic patients (2,8,9). In the present study no association between cIMT and glycemic control (A1C at the time of study) or glycemic burden was observed. However, the changes in IMT were small, the observational period was short and the cumulative glycemic exposure was low. Orchard et al. (16) found that it took ~1,000 A1 months exposure of on average for a micro vascular complication to develop compared with an average of 119 A1 months of exposure in this study. Furthermore, the studies showing association between glycemic control and degree of atherosclerosis, using image techniques, have done so after a long observational period (2,7–9).

An association between cIMT and age of diabetes onset was observed in this study. The mechanism behind this is not clear. It is possible that age might somehow influence the metabolic effects of diabetes on the vasculature and that an early manifestation of the disease may result in early onset and accelerated progression of atherosclerosis. In any case, these results do not support the general impression that the early prepubertal years of diabetic patients do not affect the development of vascular complications.

The results from this study indicate that children and adolescents with type 1 diabetes have more atherosclerotic changes than healthy control subjects, even with short disease duration and despite intensive insulin treatment and fair metabolic control, and these changes are most prominent among boys. This is a baseline examination in a longitudinal prospective study, and though the results indicate more advanced atherosclerotic development in the diabetic group, it is reassuring that the changes are small in this group of young patients at this early stage of the disease.

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H.D.M. organized the study, analyzed the data, and wrote the manuscript. K.H.S. researched data, contributed to the discussion, and reviewed/edited the manuscript. J.R.L. reviewed/edited the manuscript. C.B. researched data and reviewed/edited the manuscript. K.D.-J. initiated and supervised the study, contributed to the discussion, and reviewed/edited the manuscript.

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**Table 3—cIMT and vessel elasticity**

|                | Total                  |           | Male                  |           | Female                 |           |
|----------------|------------------------|-----------|-----------------------|-----------|------------------------|-----------|
| cIMT (mm)      | 0.45 ± 0.054           | 0.44 ± 0.045 | 0.46 ± 0.057          | 0.44 ± 0.057 | 0.44 ± 0.050           | 0.44 ± 0.044 |
| DC (kPa⁻¹)     | 0.35 ± 0.026           | 0.36 ± 0.023 | 0.35 ± 0.025          | 0.35 ± 0.020 | 0.36 ± 0.027           | 0.36 ± 0.024 |
| CC (m²/kPa⁻¹)  | 9.95 ± 0.657           | 9.90 ± 0.564 | 10.08 ± 0.680         | 10.06 ± 0.534 | 9.82 ± 0.610           | 9.78 ± 0.560 |
| Yongs modulus  | 1.17 ± 1.438           | 1.30 ± 0.951 | 1.29 ± 1.075          | 1.37 ± 1.013 | 4.06 ± 1.718           | 4.24 ± 0.901 |

Data are means ± SD.

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