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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Young adults with type 1 diabetes are at increased risk of early asymptomatic atherosclerosis, and cardiovascular morbidity and mortality are substantially increased in this group of patients (1–4).

Carotid artery intima-media thickness (cIMT) is a reliable surrogate marker of generalized atherosclerosis because it correlates to coronary artery disease and predicts future cardiovascular events (5,6). Furthermore, it is recommended by the American Heart Association as a noninvasive imaging method for detecting atherosclerosis (6).

Improved blood-glucose control obtained by intensive insulin treatment is associated with delayed atherosclerosis development and fewer cardiovascular events (2,7,8). The Oslo study, a long-term study of intensive insulin treatment in childhood-onset type 1 diabetic patients without symptomatic cardiovascular disease (CVD), demonstrated that long-term glycemic control predicted coronary atherosclerosis, as detected by coronary intravascular ultrasound (IVUS), and was correlated to cIMT (2). Likewise, the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study found that intensive insulin therapy reduces the progression of atherosclerosis, measured by IMT and most important the risk of cardiovascular events compared with conventional therapy (8,9).

The atherosclerotic process starts in childhood and proceeds silently over a long period of time before clinical events occur (1). How early it starts and how aggressively it proceeds is, however, not quite known. Studies on cIMT in children and adolescents with type 1 diabetes have yielded conflicting results (10–13), and so far only small clinic-based studies have been performed. The present study is a population-based study in children and adolescents who use modern intensive insulin treatment, the aim of which is to evaluate early stages of atherosclerosis, its progression and predisposing factors, through follow up every 5th year. In this article, the baseline characteristics of the patients are presented, as well as the results from the first analysis.

RESEARCH DESIGN AND METHODS

— All children and adolescents with type 1 diabetes in Norway are treated at the public hospitals and invited to participate in the Norwegian Childhood Diabetes Registry (NCDR). The NCDR includes data on new-onset diabetes since 1973 and annual benchmarking data since 2001 (14). All but one pediatric department in Norway ($n = 26$) participated in this registration in 2007, with an adherence rate of about 85% of all eligible patients.

A letter of invitation was sent to all type 1 diabetic patients aged 8–18 years registered in the NCDR from the defined south-east health region in Norway ($n = 800$), which is highly representative for the whole country, covering one large city (Oslo), smaller

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cities, towns, and countryside areas. The healthy control subjects were friends (and relatives in a few cases) of the participating diabetic children. The examinations were performed in 2006–2008. Written informed consent was obtained from the parents and from participants older than 12 years of age. The study protocols were approved by the Regional Committee for Research Ethics and the Norwegian Social Science Data Services.

The clinical data were registered on a case record form, which in addition to anthropometric data contained information about diabetes duration, smoking status, blood pressure, current health, additional diseases, and medication, together with family history (first- and second-degree relatives) of diabetes and early CVD (heart attack and/or stroke before age 60 years). The family history was recorded by interview of the participant and the parents.

The following information about the diabetic patients was obtained from the NCDR: insulin regimen (insulin type and dose), acute and chronic complications, urinary microalbumin excretion rate, A1C values, and pubertal stage. Height, weight, and waist circumference 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 NCDR 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-assay 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 ($\Delta V/V$) and absolute (ΔV) change in carotid arterial volume (V) for a change in pulse pressure (Δp), respectively. Distensibilty 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: $DC = (\Delta A/A)/\Delta p = \{[(d + \Delta d)^2 - d^2]/d^2\}/\Delta p$. Similarly, the compliance coefficient (CC) can be rewritten as: $CC = \Delta A/\Delta p = \{\pi[(d + \Delta d)^2 - d^2]\}/4\Delta p$. In addition, wall stress can be calculated by the Yong 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 intersonographer 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 χ^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 A1 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 suitable 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

Table 1—*Clinical characteristics and metabolic and anthropometric data of the participants*

	Total			Male			Female		
	Diabetes	Control	*P*	Diabetes	Control	*P*	Diabetes	Control	*P*
n	314	118		155	53		159	65	
Age (years)	13.8 ± 2.8	13.2 ± 2.6	0.73	13.4 ± 2.80	13.3 ± 2.44	0.7	14.1 ± 2.85	13.2 ± 2.7	0.03
Duration of diabetes (years)	5.5 ± 3.4			5.6 ± 3.4	0		5.4 ± 3.4		0
Pubertal stage (Tanner)	3.2 ± 1.5	2.9 ± 1.4	0.36	2.9 ± 1.6	2.8 ± 1.4	0.52	3.5 ± 1.4	3.0 ± 1.4	0.15
Height (cm)	160.4 ± 14.4	156.8 ± 13.6	0.02	160.6 ± 14.7	157.6 ± 16.2	0.24	160.3 ± 12.3	156.2 ± 12.6	0.02
Weight (kg)	54.9 ± 16.7	47.9 ± 13.4	<0.001	53.3 ± 17.4	46.9 ± 12.1	0.004	56.5 ± 14.4	48.7 ± 14.4	0.001
BMI (kg/m^2)	20.9 ± 3.939	19.1 ± 0.3	<0.001	20.1 ± 3.6	18.6 ± 2.3	0.001	21.6 ± 4.1	19.5 ± 3.6	0.001
Waist circumference (cm)	71.2 ± 10.0	66.7 ± 6.7	<0.001	70.3 ± 10.0	65.9 ± 6.5	0.001	72.1 ± 9.9	67.4 ± 6.8	<0.001
SBP (mmHg)	101.0 ± 10.1	98.0 ± 10.2	0.006	101.0 ± 9.8	96.8 ± 10.7	0.01	101.0 ± 10.3	99.0 ± 9.6	0.18
DBP (mmHg)	60.5 ± 8.3	58.5 ± 7.8	0.22	59.6 ± 8.4	58.1 ± 9.2	0.29	61.5 ± 8.2	58.8 ± 6.2	0.009
Smoking	11 (3.5)	2 (2)	0.53	2 (1.3)	0 (0)	1	9 (5.7)	2 (3.1)	0.52
Urinary albumin-to-creatinine ratio	1.4 ± 3.7	1.3 ± 1.9	0.72	1.8 ± 4.9	1.1 ± 1.7	0.32	1.0 ± 1.1	1.5 ± 2.0	0.11
S-creatinine (μmol/l)	53.1 ± 10.3	54.5 ± 10.1	0.23	53.7 ± 10.8	55.5 ± 10.2	0.3	52.5 ± 9.7	53.6 ± 9.9	0.43
Fasting blood glucose (mmol/l)	10.9 ± 4.8	4.9 ± 0.4	<0.001	10.1 ± 5.1	4.9 ± 0.4	<0.001	10.8 ± 4.5	4.8 ± 0.5	<0.001
A1C (%)	8.4 ± 1.3	5.3 ± 0.5	<0.001	8.3 ± 1.2	5.3 ± 0.6	<0.001	8.4 ± 1.3	5.3 ± 0.4	<0.001
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 ± 101.5		
Total cholesterol (mmol/l)	4.6 ± 0.9	4.3 ± 0.8	0.002	4.6 ± 0.8	4.3 ± 0.8	0.11	4.7 ± 0.8	4.4 ± 0.7	0.004
HDL cholesterol (mmol/l)	1.8 ± 0.4	1.70 ± 0.4	0.07	1.8 ± 0.4	1.7 ± 0.5	0.8	1.8 ± 0.4	1.7 ± 0.3	0.20
LDL cholesterol (mmol/l)	2.5 ± 0.7	2.3 ± 0.7	0.028	2.5 ± 0.7	2.2 ± 0.7	0.13	2.5 ± 0.7	2.4 ± 0.7	0.09
LDL-to-HDL cholesterol ratio	1.5 ± 0.6	1.5 ± 0.7	0.7	1.5 ± 0.7	1.4 ± 0.7	0.48	1.5 ±0.6	1.5 ± 0.6	0.99
Total-to-LDL cholesterol ratio	2.7 ± 0.8	2.7 ± 0.8	0.7	2.7 ± 0.8	2.6 ± 0.8	0.48	2.7 ± 0.7	2.7 ± 0.7	0.89
Triglycerides (mmol/l)	0.8 ± 0.4	0.7 ± 0.4	0.32	0.8 ± 0.4	0.7 ± 04	0.35	0.8 ± 0.4	0.8 ± 0.4	0.51
ApoB (g/l)	0.7 ± 0.2	0.7 ± 0.2	<0.001	0.7 ± 0.2	0.7 ± 0.2	0.02	0.8 ± 0.2	0.7 ± 0.2	0.006
ApoA1 (g/l)	1.6 ± 0.3	1.5 ± 0.3	0.003	1.6 ± 0.3	1.5 ± 0.3	0.48	1.6 ± 0.3	1.4 ± 0.3	<0.001
ApoB-to-ApoA1 ratio	0.5 ± 0.2	0.5 ± 0.3	0.75	0.5 ± 1.6	0.5 ± 0.2	0.37	0.5 ± 0.1	0.5 ± 0.3	0.44
Insulin dose (U/kg/day)	0.9 ± 0.4			0.9 ± 0.3			0.9 ± 0.4		
Injections per day									
1–2	1 (0.4)			0			1 (0.6)		
3	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 95th percentile	Above 90th 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 Järvisalo 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 regime. 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-Patridiou 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

Table 3—*CIMT and vessel elasticity*

	Total			Male			Female		
	Diabetes	Control	*P*	Diabetes	Control	*P*	Diabetes	Control	*P*
cIMT (mm)	0.45 ± 0.054	0.44 ± 0.045	0.11	0.46 ± 0.057	0.44 ± 0.057	0.04	0.44 ± 0.050	0.44 ± 0.044	0.94
DC (kPa^{-1})	0.35 ± 0.026	0.36 ± 0.023	0.48	0.35 ± 0.025	0.35 ± 0.020	0.93	0.36 ± 0.027	0.36 ± 0.024	0.42
CC (m^2/kPa^{-1})	9.95 ± 0.657	9.90 ± 0.564	0.48	10.08 ± 0.680	10.06 ± 0.534	0.83	9.82 ± 0.610	9.78 ± 0.560	0.58
Yongs modulus (kPa)	4.17 ± 1.438	4.30 ± 0.951	0.38	4.29 ± 1.075	4.37 ± 1.013	0.62	4.06 ± 1.718	4.24 ± 0.901	0.42

Data are means ± SD.

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 overinsulinization 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 diabetes 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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References

1. Dahl-Jørgensen K, Larsen JR, Hanssen KF. Atherosclerosis in childhood and adolescent type 1 diabetes: early disease, early treatment? Diabetologia 2005;48:1445–1453
2. Larsen J, Brekke M, Sandvik L, Arnesen H, Hanssen KF, Dahl-Jorgensen K. Silent coronary atheromatosis in type 1 diabetic patients and its relation to long-term glycemic control. Diabetes 2002;51:2637–2641
3. Margeirsdottir HD, Larsen JR, Brunborg C, Overby NC, Dahl-Jørgensen K, Norwegian Study Group for Childhood Diabetes. High prevalence of cardiovascular risk factors in children and adolescents with type 1 diabetes: a population-based study. Diabetologia 2008;51:554–561
4. Skrivarhaug T, Bangstad HJ, Stene LC, Sandvik L, Hanssen KF, Joner G. Long-term mortality in a nationwide cohort of childhood-onset type 1 diabetic patients in Norway. Diabetologia 2006;49:298–305
5. Lorenz MW, von Kegler S, Steinmetz H, Markus HS, Sitzer M. Carotid intima-media thickening indicates a higher vascular risk across a wide age range: prospective

data from the Carotid Atherosclerosis Progression Study (CAPS). Stroke 2006; 37:87–92
6. Greenland P, Abrams J, Aurigemma GP, Bond MG, Clark LT, Criqui MH, Crouse JR 3rd, Friedman L, Fuster V, Herrington DM, Kuller LH, Ridker PM, Roberts WC, Stanford W, Stone N, Swan HJ, Taubert KA, Wexler L. Prevention Conference V: Beyond secondary prevention: identifying the high-risk patient for primary prevention: noninvasive tests of atherosclerotic burden: Writing Group III. Circulation 2000;101:E16–E22
7. Larsen JR, Brekke M, Bergengen L, Sandvik L, Arnesen H, Hanssen KF, Dahl-Jorgensen K. Mean HbA1c over 18 years predicts carotid intima-media thickness in women with type 1 diabetes. Diabetologia 2005;48:776–779
8. Nathan DM, Lachin J, Cleary P, Orchard T, Brillon DJ, Backlund JY, O'Leary DH, Genuth S, Diabetes Control and Complications Trial, Epidemiology of Diabetes Interventions and Complications Research Group. Intensive diabetes therapy and carotid intima-media thickness in type 1 diabetes mellitus. N Engl J Med 2003;348:2294–2303
9. Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, Raskin P, Zinman B, Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 2005;353:2643–2653
10. Yavuz T, Akçay A, Omeroğlu RE, Bundak R, Sükür M. Ultrasonic evaluation of early atherosclerosis in children and adolescents with type 1 diabetes mellitus. J Pediatr Endocrinol Metab 2002;15:1131–1136
11. Järvisalo MJ, Putto-Laurila A, Jartti L, Lehtimäki T, Solakivi T, Rönnemaa T, Raitakari OT. Carotid artery intima-media thickness in children with type 1 diabetes. Diabetes 2002;51:493–498
12. Gunczler P, Lanes R, Lopez E, Esaa S, Villarroel O, Revel-Chion R. Cardiac mass and function, carotid artery intima-media thickness and lipoprotein (a) levels in children and adolescents with type 1 diabetes mellitus of short duration. J Pediatr Endocrinol Metab 2002;15:181–186
13. Atabek ME, Kurtoglu S, Pirgon O, Baykara M. Arterial wall thickening and stiffening in children and adolescents with type 1 diabetes. Diabetes Res Clin Pract 2006;74:33–40
14. Margeirsdottir HD, Larsen JR, Kummernes SJ, Brunborg C, Dahl-Jørgensen K. The establishment of a new national network leads to quality improvement in childhood diabetes: implementation of the ISPAD Guidelines. Pediatr Diabetes 2010;11:88–95
15. Libby P, Nathan DM, Abraham K, Brunzell JD, Fradkin JE, Haffner SM, Hsueh W, Rewers M, Roberts BT, Savage PJ, Skarlatos S, Wassef M, Rabadan-Diehl C, National Heart, Lung, and Blood Institute, National Institute of Diabetes and Digestive and Kidney Diseases Working Group on Cardiovascular Complications of Type 1 Diabetes Mellitus. Report of the National Heart, Lung, and Blood Institute-National Institute of Diabetes and Digestive and Kidney Diseases Working Group on Cardiovascular Complications of Type 1 Diabetes Mellitus. Circulation 2005;111:3489–3493
16. Orchard TJ, Forrest KY, Ellis D, Becker DJ. Cumulative glycemic exposure and microvascular complications in insulin-dependent diabetes mellitus: the glycemic threshold revisited. Arch Intern Med 1997;157:1851–1856
17. Touboul PJ, Hennerici MG, Meairs S, Adams H, Amarenco P, Desvarieux M, Ebrahim S, Fatar M, Hernandez Hernandez R, Kownator S, Prati P, Rundek T, Taylor A, Bornstein N, Csiba L, Vicaut E, Woo KS, Zannad F, Advisory Board of the 3rd Watching the Risk Symposium 2004, 13th European Stroke Conference. Mannheim intima-media thickness consensus. Cerebrovasc Dis 2004;18:346–349
18. Tonstad S, Joakimsen O, Stensland-Bugge E, Leren TP, Ose L, Russell D, Bønaa KH. Risk factors related to carotid intima-media thickness and plaque in children with familial hypercholesterolemia and control subjects. Arterioscler Thromb Vasc Biol 1996;16:984–991
19. Reneman RS, Meinders JM, Hoeks AP. Non-invasive ultrasound in arterial wall dynamics in humans: what have we learned and what remains to be solved. Eur Heart J 2005;26:960–966
20. Järvisalo MJ, Jartti L, Näntö-Salonen K, Irjala K, Rönnemaa T, Hartiala JJ, Celermajer DS, Raitakari OT. Increased aortic intima-media thickness: a marker of preclinical atherosclerosis in high-risk children. Circulation 2001;104:2943–2947
21. Peppa-Patrikiou M, Scordili M, Antoniou A, Giannaki M, Dracopoulou M, Dacou-Voutetakis C. Carotid atherosclerosis in adolescents and young adults with IDDM: relation to urinary endothelin, albumin, free cortisol, and other factors. Diabetes Care 1998;21:1004–1007
22. Stein JH, Douglas PS, Srinivasan SR, Bond MG, Tang R, Li S, Chen W, Berenson GS. Distribution and cross-sectional age-related increases of carotid artery intima-media thickness in young adults: the Bogalusa Heart Study. Stroke 2004;35: 2782–2787
23. Holl RW, Grabert M, Sorgo W, Heinze E, Debatin KM. Contributions of age, gender and insulin administration to weight gain in subjects with IDDM. Diabetologia 1998;41:542–547
24. Sass C, Herbeth B, Chapet O, Siest G, Visvikis S, Zannad F. Intima-media thickness and diameter of carotid and femoral arteries in children, adolescents and adults from the Stanislas cohort: effect of age, sex, anthropometry and blood pressure. J Hypertens 1998;16:1593–1602