Spectrum and Prevalence of Atherogenic Risk Factors in 27,358 Children, Adolescents, and Young Adults With Type 1 Diabetes

Cross-sectional data from the German diabetes documentation and quality management system (DPV)

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OBJECTIVE — The aim of this data analysis was to ascertain the type and prevalence rate as well as age and sex distribution of cardiovascular risk factors in type 1 diabetic patients up to 26 years of age.

RESEARCH DESIGN AND METHODS — Cardiovascular risk factors such as obesity, hypertension, dyslipidemia, poor glycemic control, and smoking were analyzed in 27,358 patients who were divided into three groups (prepubertal, pubertal, and adult) using specifically designed diabetes software for prospective disease documentation.

RESULTS — More than half of the patients per age-group had at least one cardiovascular risk factor. Two risk factors were age dependently found in 6.2–21.7% and three or four risk factors in 0.5–4.7%. Elevated values of HbA_{1c}, total cholesterol, and BMI were found most frequently. Hypertension, smoking, and HDL cholesterol were observed more frequently in males, and elevated BMI, total cholesterol, and LDL cholesterol more often in females. Although 28.6% of the patients had dyslipidemia, merely 0.4% of them received medical treatment, and of the 8.1% of the patients with hypertension, only 2.1% of them were given antihypertensive medication.

CONCLUSIONS — With increasing age, a greater number of patients with cardiovascular risk factors were observed. Significant sex differences were seen in the majority of risk factors. Despite the high prevalence of risk factors, only a small minority of patients received antihypertensive or lipid-lowering treatment. Early identification, prevention, and treatment of additional risk factors seem to be necessary, particularly in light of the high incidence of future cardiovascular disease.

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Abbreviations: CVD, cardiovascular disease; DCCT, Diabetes Control and Complications Trial; DPV, diabetes data acquisition system for prospective surveillance; PDAY, Pathobiological Determinants of Atherosclerosis in Youth.

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

Type 1 diabetes is increasingly recognized as an independent risk factor for premature cardiovascular disease (CVD) and elevated cardiovascular death rate in patients aged 20–39 years (1). Postmortem studies in children and youth who had died an unnatural death also showed that the development of atherosclerotic lesions of the vessel wall starts in childhood and that there is a close relationship to cardiovascular risk factors. In the Bogalusa Heart Study (2) and the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study (3), the evaluation of premortal existing risk factors (glycohemoglobin >8%, increased lipids, hypertension, obesity, and smoking) verified their unfavorable influence on the progression of atherosclerosis. Because childhood and adolescence diabetes is commonly associated with additional risk factors (4,5), we conducted this analysis to obtain reliable data about character and prevalence rate as well as age and sex differences of potential atherogenic risk factors in a large population of German children, adolescents, and young adults with type 1 diabetes.

RESEARCH DESIGN AND METHODS

— Based on the continuous diabetes data acquisition system for prospective surveillance (DPV), a cross-sectional analysis was carried out to evaluate associated cardiovascular risk factors in patients with type 1 diabetes. The data documentation DPV started in 1990 and comprises complete demographic characteristics and diabetes-related findings. Anonymous longitudinal data from patients are transmitted for central validation and analyses twice yearly (6,7). Inconsistent data are verified and, if necessary, corrected at the participating centers and reentered in the system. This data analysis considers all type 1 diabetic patients who entered the DPV system by the

end of September 2004 and is primarily focused on cardiovascular risk factors. Pathological changes of the following parameters were defined as potential atherogenic risk factors: lipid risk factors: total cholesterol, LDL cholesterol, and HDL cholesterol; nonlipid risk factors: HbA_{1c} (A1C), BMI, blood pressure, and smoking. We additionally performed both multivariate analyses of each cardiovascular risk factor with regard to age, diabetes duration, sex, and overweight and a trend analysis of risk factors (BMI, dyslipidemia, total cholesterol >200 mg/dl [>5.2 mmol/l], systolic and diastolic hypertension, and A1C >9.0%) covering the period from 1994 to 2004.

A total of 27,358 patients with type 1 diabetes were consecutively registered at 195 German and Austrian Centers for Pediatrics and Internal Medicine. For reasons of analysis the total number of patients was divided into three age-groups based on the developmental stage: age-group 1 (0.25–11 years) covers childhood or prepuberty, age-group 2 (12–16 years) covers early adolescence or puberty, and age-group 3 (17–26.0 years) covers later adolescence and young adulthood.

Nonlipid risk factors

A1C. For long-term control of the diabetes management, A1C was measured. For risk factor assessment, A1C levels of all patients were divided into two groups: >7.5 and >9.0%. Values of locally measured A1C were standardized according to the Diabetes Control and Complications Trial (DCCT) reference range of 4.05–6.05% (8).

BMI. BMI, derived from weight in kilograms divided by the square of height in meters (2), is an accepted measure of overweight and obesity in children, adolescents, and adults. Reference values in the form of age- and sex-adjusted percentiles allow an individual assessment of BMI data in children and adolescents. Overweight was defined as the 90th–97th BMI percentile and obesity as >97th percentile. BMI values of >25 and >30 kg/m^2 are the corresponding threshold values for adults >18 years of age. Normative data for German children, adolescents, and adults used in the DPV software relate to Kromeyer-Hauschild et al. (9) and Mensink et al. (10).

Hypertension. Systolic and diastolic blood pressure were measured with Riva-Rocci's method, which is based on auscultatory measurements using a standard clinical sphygmomanometer (11). Normative blood pressure data developed by the Task Force on Blood Pressure Control in children served as reference values (12). Hypertension was defined as the median value calculated from at least three measurements taken between September 2003 and September 2004.

Smoking. A patient was documented as a smoker when he or she smoked more than one cigarette per day. Smoking habits were asked for during history taking.

Lipid risk factors

Venous blood samples were taken after a recommended 12-h fasting for plasma concentrations of total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride levels. By the aid of sample tests, we ascertained that in some patients the 12-h fasting period was not sufficiently met. Therefore, we excluded triglycerides from the analysis because triglycerides, unlike cholesterol, show a close relationship to food intake (13).

Total cholesterol. Total cholesterol serves as a screening parameter for hypercholesterolemia and is composed of the cholesterol parts of all plasma lipoproteins that are VLDL, LDL, and HDL. Total cholesterol was measured enzymatically. Values >200 mg/dl (>5.2 mmol/l) were defined as high risk (14).

LDL cholesterol. LDL particles represent the principal atherogenic lipoprotein fraction. LDL cholesterol was calculated from Friedewald's formula if triglyceride levels were <400 mg/dl (<4.7 mmol/l). Plasma elevation of LDL cholesterol >130 mg/dl (>3.4 mmol/l) was classified abnormal and concentrations >160 mg/dl (>4.1 mmol/l) were used as the reference value for patients at high risk who require lipid-lowering pharmacotherapy if diet and lifestyle changes failed (14,15).

HDL cholesterol. HDL particles are responsible for the reverse cholesterol transport from the periphery to the liver and have antiatherogenic activities. HDL concentrations were determined after dextran sulfate–magnesium precipitation of apolipoprotein B–containing lipoproteins. We considered a HDL cholesterol value <35 mg/dl (<0.9 mmol/l) as abnormal according to the National Cholesterol Education Program definition for youth (14).

Statistical methods

All analyses were performed using SAS software (version 9.1; SAS Institute, Cary, NC). Nonparametric statistics (Kruskal-Wallis) were used for comparison among groups. Results were expressed as means ± SD, and $P < 0.05$ was considered statistically significant.

RESULTS

Assessment of cardiovascular risk factors

The prevalence of risk factors showed small changes between 1994 and 2004. There was some increase of BMI but a small decrease in dyslipidemia, total cholesterol >200 mg/dl (>5.2 mmol/l), systolic and diastolic hypertension, and A1C >9.0%. For all patients, the percentages of available data were 71.9–96.2% for nonlipid variables (A1C, BMI, blood pressure, and smoking) and 41.3–70.8% for lipid variables (total cholesterol, LDL cholesterol, and HDL cholesterol) (Table 1).

Number of cardiovascular risk factors

Apart from the ratio of males to females, all patient characteristics and risk factors mentioned in Table 1 showed statistically significant differences between the age-groups. Overall, 69% of 27,358 subjects investigated had one or more of the risk factors analyzed. The vast majority of patients showed one risk factor (53%), followed with decreasing frequency by patients without any risk factor (31%), two risk factors (14%), and three to four risk factors (2%). Two or more risk factors per patient were found most frequently in patients of age-group 3. All differences among age-groups were statistically significant ($P < 0.001$). Multivariate analyses showed that overweight (BMI) was most closely related (β value/estimate = 0.184, $P < 0.001$) to the number of cardiovascular risk factors, followed by age (β value/estimate = 0.033, $P < 0.001$) and diabetes duration (β value/estimate = 0.012, $P < 0.001$).

Distribution of cardiovascular risk factors per age-group

Both nonlipid and lipid risk factors showed the same age-dependent distribution (Fig. 1). The lowest number of affected patients belonged to age-group 1 and the highest to age-group 3. Elevated values of A1C, total cholesterol, and BMI were found most frequently. All calculated group differences reached statistical significance ($P < 0.0001$).

Table 1—*Clinical and laboratory characteristics per age-group in patients with type 1 diabetes*

Characteristic	Total number of patients	Frequency of complete records (%)	Age-group 1	Age-group 2	Age-group 3	*P* value*
Age (years)	27,358	100.0	7.5 ± 2.5	13.7 ± 1.4	18.5 ± 2.3	<0.0001
Age range (years)	27,358	100.0	0.25–11	12–16	17–26	
Male sex (%)	27,358	100.0	51.7	51.7	52.5	NS
Age at diagnosis (years)	27,358	100.0	5.0 ± 2.5	8.8 ± 3.6	10.4 ± 4.4	<0.0001
Diabetes duration (years)	27,358	100.0	2.5 ± 2.3	4.9 ± 3.6	8.2 ± 4.8	<0.0001
A1C (%)†	26,308	96.2	7.8 ± 1.5	8.5 ± 1.8	8.6 ± 2.0	<0.0001
Any dyslipidemia (%)	19,359	70.8	22.3	29.4	34.2	<0.0001
Lipid-lowering therapy (%)	27,358	100.0	0.08	0.3	0.8	<0.0001
Total cholesterol (mg/dl)‡	18,917	69.1	174 ± 40	182 ± 48	184 ± 47	<0.0001
LDL cholesterol (mg/dl)‡	11,286	41.3	95 ± 35	101 ± 40	105 ± 40	<0.0001
HDL cholesterol (mg/dl)‡	12,811	46.8	62 ± 19	62 ± 17	59 ± 18	<0.0001
Raised systolic BP (%)	25,184	92.1	5.8	7.4	11.0	<0.0001
Raised diastolic BP (%)	25,178	92.0	3.9	3.2	2.6	<0.0001
BP-lowering therapy (%)	27,358	100.0	0.2	1.4	4.8	<0.0001
BMI SDS	25,145	91.9	0.42 ± 0.9	0.45 ± 0.9	0.42 ± 0.9	<0.0075
BMI >90th percentile (%)	25,145	91.9	16.4	20.0	25.0	<0.0001
Smoking (%)	19,683	71.9	0.24	10.53	34.75	<0.0001

Data are means ±SD unless otherwise indicated. *Kruskal-Wallis test. †DCCT standardized. ‡To convert values to mmol/l, multiply by 0.02586. BP, blood pressure; SDS, standard deviation score.

Sex distribution of cardiovascular risk factors

Nonlipid risk factors. The percentage of elevated A1C values (>7.5%, $P < 0.001$; >9.0%, $P < 0.05$) and BMI (90th–97th or >97th percentile, $P < 0.001$, respectively) were higher in female than in male subjects (Fig. 2). Frequency of hypertension and current smoking were significantly higher in males than in females ($P < 0.001$, respectively).

Lipid risk factors. Total cholesterol and LDL cholesterol levels were higher in female than in male subjects ($P < 0.0001$, respectively). However, no significant difference of HDL cholesterol was found between female and male subjects.

Frequency of pharmacotherapy

A high percentage of patients had dyslipidemia (28.6%); 8.1% of the patients had systolic hypertension and 2.5% diastolic hypertension. However, the percentage of patients who received lipid-lowering (0.4%) or blood pressure–lowering (2.1%) treatment was extremely low (Table 1).

CONCLUSIONS

— There has been growing awareness during the past few years that type 1 diabetes is an independent risk factor for premature atherosclerotic CVD, which can be accelerated by potentially atherogenic risk factors such as hypertension, dyslipidemia, hyperglycemia, obesity, smoking, albuminuria, or physical inactivity (1,5,16). Our results showed that 69% of the 27,358 subjects investigated had one or more of the cardiovascular risk factors analyzed in this study. Multiple risk factors and their interrelationships but also a family history of premature cardiovascular disease, increasing age, or longer duration of diabetes are discussed in the literature as main determinants of enhanced risk for future CVD (17,18).

A detailed profile analysis of our diabetes registry showed that the number of patients at risk, divided into three distinct age-groups, is significantly increasing with age with respect to all risk factors. The most frequently diagnosed risk factor was a raised A1C value. Poor glycemic control is particularly associated with the development of long-term microvascular complications (19), which could be proven impressively by the DCCT (20). In a more recent DCCT publication, an association between glycemia and intima-media thickness, an accepted marker for early atherosclerosis, in patients with type 1 diabetes was demonstrated (21). Further investigations could show that there is a direct relationship between A1C levels and the extent of atherosclerosis. Gerstein et al. (22) found that the intima-media thickness increased 0.026 mm for every 0.9% increase in A1C ($P < 0.0001$). In another study, A1C levels >7.5% were identified as a strong risk factor for progression of coronary artery calcification in type 1 diabetic patients aged 22–50 years (23). The British Diabetic Association Cohort Study investigated 23,752 patients with type 1 diabetes. Compared with the general population, type 1 diabetic patients aged 20–39 years had a fivefold higher risk of dying from cardiovascular events (1).

Overweight and obesity are thought to be cardiovascular risk factors per se with regard to the development of dyslipidemia, hypertension, type 2 diabetes, and the metabolic syndrome (24,25). If obese children become obese adults, one of the long-term consequences may be early atherosclerosis and increased cardiovascular morbidity (26,27). According to our results, overweight, obesity, and hypertension were found in 3.8–15.5% of the patients observed. Prevention and treatment of these modifiable risk factors should begin as early as possible because counseling of the patient, lifestyle modification, and pharmacologic therapy are quite promising interventions to retard damage or avoid further harm.

The high percentage of smokers in many countries is alarming. The Global Youth Tobacco Survey reported data for 16,416 U.S. students aged 13–15 years, of whom 23.1% are currently using any tobacco product (28). In the PDAY study (4), a 44.0% prevalence of smoking in

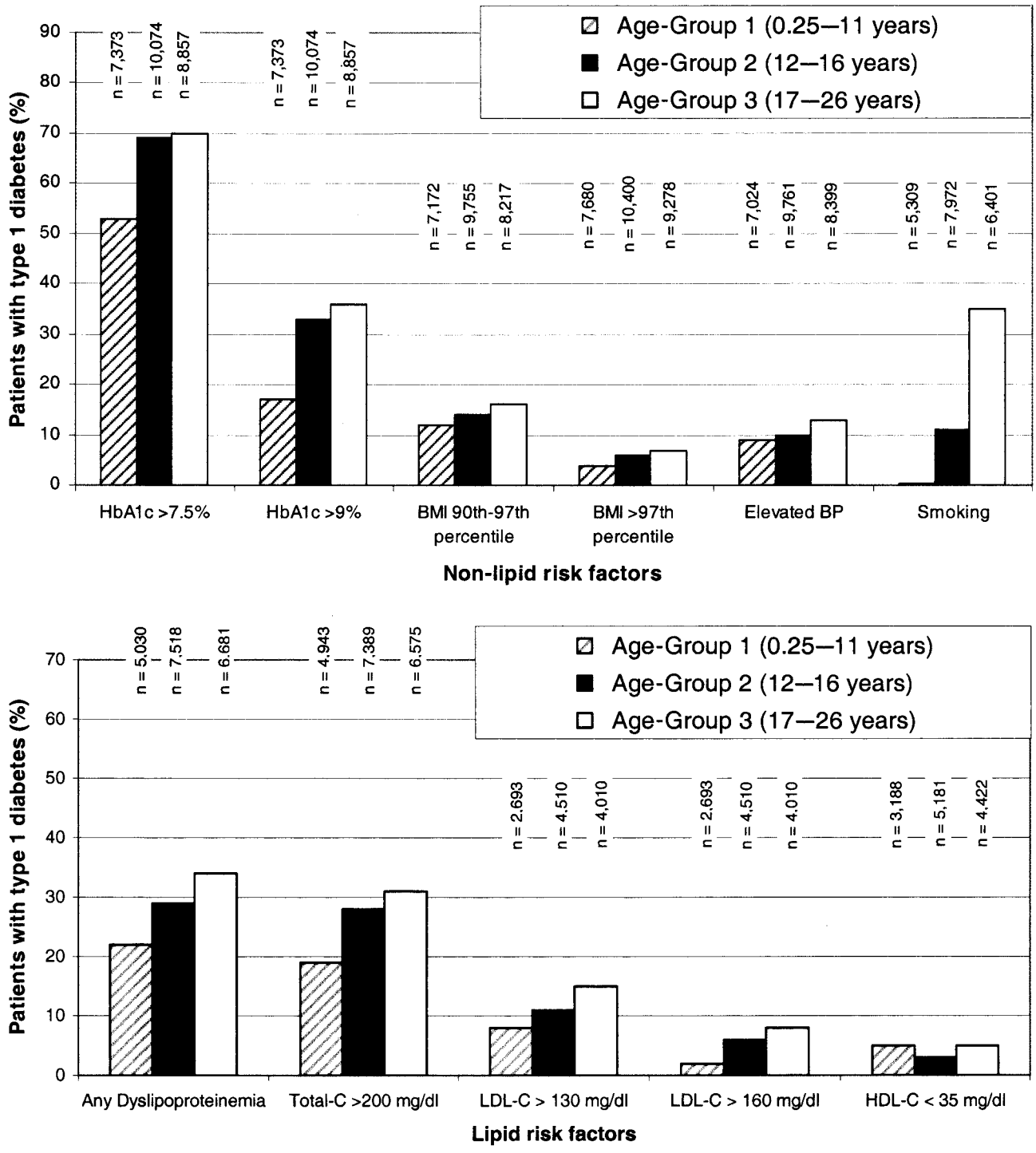

Figure 1—*Age distribution of cardiovascular risk factors, divided into nonlipid and lipid parameters. The total number of patients investigated per age-group is shown above each bar.*

subjects aged 15–34 was calculated. The Behavioral Risk Factor Surveillance System in the U.S. indicated that the prevalence of smoking among adults with diabetes was 23.6% in 1990 and 23.2% in 2001. Among participants without diabetes, the prevalence was similar, showing 24.2% in 1990 and 23.2% in 2001 (29). All these studies show a similar prevalence of smokers compared with our data.

Taking into account the occurrence of at least one abnormality among the lipid variables we analyzed, the number of patients with any dyslipidemia increased significantly from 22.3% in age-group 1 to 34.3% in age-group 3. Total cholesterol values >200 mg/dl (>5.2 mmol/l) emerged in about 26% of all patients, LDL cholesterol >130 mg/dl (>3.4 mmol/l) in about 11%, and LDL cholesterol >160 mg/dl (>4.1 mmol/l) in about 5.3%. In-

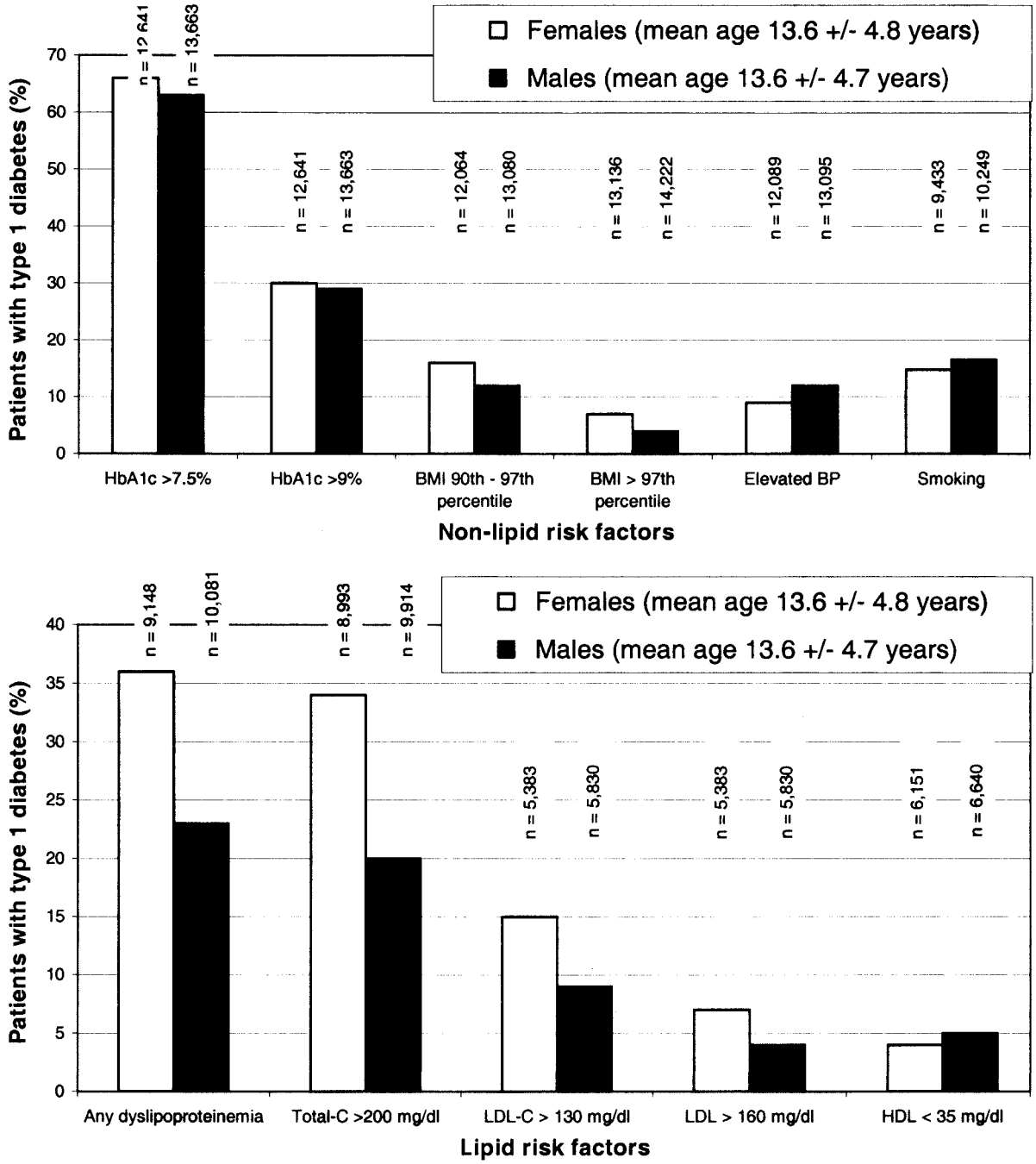

Figure 2—*Sex distribution of cardiovascular risk factors, divided into nonlipid and lipid parameters. The total number of patients investigated is shown above each bar.*

sulin deficiency is associated with reduced activity of LDL receptors, and glycation of LDL particles reduces their receptor affinity, thereby impairing the clearance of LDL cholesterol and increasing their susceptibility to oxidation. Longer diabetes duration, hyperglycemia, albuminuria, hypertriglyceridemia, and lower HDL cholesterol are associated with elevated levels of small dense LDL particles that are extremely atherogenic (30, 31).

The risk factor profiles of our patients vary according to sex. Raised blood pressure and current smoking were lower in female than in male subjects, whereas increased A1C, total cholesterol, LDL cholesterol, and BMI values emerged in female subjects. It is known that women with type 1 diabetes have an increased risk of developing CVD and, therefore, equalizing the sex difference seen in the general population (32). In addition to the risk factors discussed here, several variables are related to CVD in women such as age, fasting triglyceride levels, albumin excretion rate, retinopathy, fat distribution, and depressive symptomatology (15,33).

With regard to the management of additional atherogenic risk factors, there is a considerable discrepancy in juvenile type 1 diabetic patients between the high risk for future cardiovascular morbidity and the low treatment rate of modifiable risk factors such as hypertension and dys-

lipidemia. The main reason may be the lack of drugs that are generally recognized as safe and effective for long-term use in diabetic children and adolescents.

Besides regular risk factor testing, it is also necessary to draw therapeutic conclusions from abnormal findings to continuously improve quality of diabetes care long term. In a recently published retrospective cohort study, 1,765 adult patients with type 1 or type 2 diabetes were included if they had at least two visits within 24 months. The authors found that despite a high rate of annual A1C, blood pressure, and cholesterol measurements, rates of required medication initiation and dose adjustment were comparatively low (34).

Although vascular complications are normally subclinical during childhood and adolescence, cardiovascular risk factors should be given our full attention to reduce risk by optimal metabolic control and lifestyle modification (35,36). Only if these efforts are insufficient is pharmacotherapy a reasonable form of treatment, but it must be individualized based on the number of atherogenic risk factors, family history, and existing complications.

Hypertension in children and adolescents with type 1 diabetes may primarily be treated early with ACE inhibitors, as was the case in 83% of our patients. These agents have antihypertensive effects and reduce the incidence of microalbuminuria and nephropathy (37).

Besides hypertension, dyslipidemia is a common concomitant disease in patients with diabetes. Moderate hypertriglyceridemia, lower HDL cholesterol levels, and hypercholesterolemia with elevated levels of LDL cholesterol and small, dense LDL particles can be seen in type 1 diabetes (5,38). The American Diabetes Association strongly recommends lipid-lowering pharmacotherapy for patients with LDL >160 mg/dl (>4.1 mmol/l) but for LDL cholesterol values between 130 and 159 mg/dl (3.4 and 4.1 mmol/l, respectively) only if nutrition therapy and lifestyle changes fail. In any case, the treatment target is LDL cholesterol <100 mg/dl (<2.6 mmol/l) (15). In adults with diabetes, fibrates are recommended for hypertriglyceridemia with lower HDL cholesterol (11% in our study) and statins for reducing total and LDL cholesterol (54% in our study) (39). So far, in a limited number of children with familial and severe hypercholesterolemia, statins showed good LDL cholesterol–lowering efficacy and a low rate of side effects (40). Beyond these effects, statins improve endothelial dysfunction and have antioxidant, antithrombotic, and anti-inflammatory properties that may contribute to their antiatherogenic efficacy (41,42).

In conclusion, this representative analysis demonstrates the high age-dependent frequency of atherogenic risk factors in children and adolescents with type 1 diabetes and underlines the importance of an early search for these risk factors. Significant sex differences were computed for most of the risk factors. The discrepancy between a high prevalence of cardiovascular risk factors and the low rate of antihypertensive and lipid-lowering treatment deserves special consideration.

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