Algorithm-Based Cholesterol Monitoring in Children with Type 1 Diabetes

K. Otfried Schwab, MD[1], Jürgen Doerfer, MD[1], Christa Scheidt-Nave, MD[2], Bärbel-Maria Kurth, PhD[2], Andreas Hungele[3], Nicole Scheuing[3], Andreas Krebs, MD[1], Axel Dost, MD[4], Tilman R. Rohrer, MD[5], Edith Schober, MD, PhD[6], and Reinhard W. Holl, MD[3], on behalf of the German/Austrian Diabetes Documentation and Quality Management System (DPV) and the German Health Interview and Examination Survey for Children and Adolescents (KiGGS)*

Objective To facilitate child-specific and diabetes-related cholesterol control, we developed a monitoring algorithm derived from population-based reference values.

Study design Low-density lipoprotein (LDL)-, non-high-density lipoprotein (HDL)-, and HDL cholesterol percentile values were calculated for children with type 1 diabetes (T1D) and their peers without T1D within algorithm-based categories of sex, age: 1-10 vs >10-<18 years, body mass index: <90th vs ≥90th percentile, and hemoglobin A1c <6%, 6%-<7.5%, 7.5%-9%, >9%. Analyses included 26 147 patients sampled from a German/Austrian population-based registry for T1D (Diabetes Documentation and Quality Management System) and 14 057 peers without diabetes participating in the national Health Interview and Examination Survey for Children and Adolescents in Germany.

Results Reference percentile values for cholesterol were derived as a diagnostic algorithm aimed at supporting long-term cholesterol control. Taking account of a patient's sex, age-group, weight-, and hemoglobin A1c-category, the flowcharts of the algorithm developed separately for LDL-, non-HDL-, and HDL cholesterol allow comparing his/her cholesterol levels with population-based reference percentile values of peers without T1D.

Conclusions The population-based algorithmic approach applied to LDL-, non-HDL-, and HDL cholesterol allows referencing children with T1D with regard to their peers without T1D and, if necessary, suggests corrections of glycemic control to optimize long-term cholesterol levels. *(J Pediatr 2014;164:1079-84)*.

Type 1 diabetes (T1D) is associated with an increased long-term risk of cardiovascular disease (CVD) originating in childhood.[1,2] Major contributory factors are hyperglycemia, hypertension, dyslipidemia, overweight, and tobacco use which are amenable to prevention and treatment.[3-5] We analyzed two comprehensive databases, the German/Austrian Diabetes Documentation and Quality Management System (DPV)[6] and the German Health Interview and Examination Survey for Children and Adolescents (KiGGS)[7]. An earlier manuscript of our group showed that lipid profiles are influenced by 4 factors, age and sex as non-modifiable and body mass index (BMI)-SD score and hemoglobin A1c (HbA1c)-levels as principally modifiable factors.[8] Considering these results, we developed a percentile-based diagnostic algorithm for cholesterol. Our principal objective of this population-based cross-sectional analysis is not to establish new, generally accepted cholesterol targets. In addition, we sought to support the pediatric diabetologist in decision-making regarding dyslipidemia.

Methods

All analyzed data of patients with T1D were extracted from the multicenter German/Austrian DPV database which was approved by the local Ethics Committee of the University of Ulm, Germany.[3,6] DPV centers continuously collect demographic characteristics and diabetes-related findings. After local anonymization, data are transmitted for central validation and analysis twice a year. Inconsistent data are reviewed, corrected at the respective center if necessary,

BMI	Body mass index
CVD	cardiovascular disease
DPV	Diabetes Documentation and Quality Management System
HbA1c	Hemoglobin A1c
HDL	High-density lipoprotein
KiGGS	Health Interview and Examination Survey for Children and Adolescents
LDL	Low-density lipoprotein
T1D	Type 1 diabetes

From the [1]Department of Pediatrics and Adolescent Medicine, University Medical Center, Freiburg, Germany; [2]Department of Epidemiology and Health Reporting, Robert Koch Institute, Berlin, Germany; [3]Institute of Epidemiology and Medical Biometry, University of Ulm, Ulm, Germany; [4]Department of Pediatrics and Adolescent Medicine, University of Jena, Jena, Germany; [5]Division of Pediatric Endocrinology, Department of General Pediatrics and Neonatology, Saarland University Medical Center, Homburg, Germany; and [6]University Children's Hospital, Vienna, Austria

*A list of DPV and KiGGS participating centers is available at www.jpeds.com (**Appendix**).

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Table I. Characteristics of patients with T1D and non-diabetic peers

Characteristics	Patients with diabetes (n = 26 147)	Non-diabetic peers (n = 14 057)	P
Age, years	13.6 ± 3.9	10.1 ± 4.6	<.0001‡
Age range, years	1.0-17.9	1.0-17.9	NS
Male sex, %	53	51	.0049§
BMI, kg/m^2	21.2 ± 4.0	18.5 ± 3.8	<.0001‡
BMI SDS	0.301 ± 0.861	-0.002 ± 1.000	<.0001‡
HbA1c, %*	8.3 ± 1.7	4.8 ± 0.4	<.0001‡
LDL cholesterol, mg/dL†	94 ± 29	93 ± 24	.0346‡
Non-HDL cholesterol, mg/dL†	117 ± 36	107 ± 27	0001‡
HDL cholesterol, mg/dL†	60 ± 16	56 ± 13	.0001‡

NS, not significant.
Data are means ± SD unless otherwise indicated.
*Standardized according to the Diabetes Control and Complications Trial.[12]
†To convert mg/dL to mmol/L, multiply by a factor of 0.0259.
‡Kruskal-Wallis test.
§χ^2 test.

and reentered into the system. In this cross-sectional analysis of April 2012, patient data from 298 German and Austrian DPV centers were analyzed at the Department of Epidemiology, University of Ulm, Germany. Data for the years 2000-2011, considering the latest observation year per patient, were included in the analysis.

Data of peers without T1D were based on KiGGS, which was conducted by the Robert Koch Institute, Berlin, Germany, from May 2003-May 2006.[7] KiGGS was approved by the Charité/Universitätsmedizin Berlin ethics committee and the Federal Office for the Protection of Data. Participants were randomly selected from the official registers of local residents in 167 nationwide sampling units. This comprehensive survey employed questionnaires, computer-assisted medical interviews, physical examinations, as well as blood and urine testing by central laboratories.

The analysis included 26 147 registered female and male DPV patients with T1D under the age of 18. For stratification purposes, patients with T1D and HbA1c values from <6% to >9% were analyzed. Patients with low-density lipoprotein (LDL) cholesterol >190 mg/dL (>4.91 mmol/L), lipid lowering treatment, and other forms of diabetes were excluded from the analysis. A total of 14 057 participants of the KiGGS survey aged 1 to <18 years were eligible for analysis unless they had diabetes mellitus, HbA1c ≥6.0%, LDL cholesterol ≥190 mg/dL (≥4.91 mmol/L), or with lipid lowering medication. The distribution of characteristics among DPV patients and KiGGS participants is summarized in **Table I**.

For algorithmic approach, both DPV patients and KiGGS participants were divided into 2 age-groups based on the developmental stage: age-group 1 (≤10 years) for childhood or prepuberty, and age-group 2 (>10 to <18 years) for adolescence or puberty.[9,10] BMI was calculated as body weight/(body height)^2 (kg/m^2). The individual weight status of DPV-patients and KiGGS-participants was classified as normal weight (BMI <90th percentile) or overweight (BMI ≥90th percentile) using German national reference data,[11] which are also valid for Austrian children. Evaluation of the glycemic status was achieved by the determination of HbA1c. To adjust for differences between laboratories, HbA1c levels were standardized according to the Diabetes Control and Complications Trial.[12] Analyses of lipoproteins were performed using automated instrumentation according to standard procedures in accredited laboratories that are subject to regular internal and external quality control according to guidelines of the German Medical Association.[13] Non-high-density lipoprotein (HDL) cholesterol was calculated by subtracting HDL cholesterol from total cholesterol.

An algorithm was created for an individualized monitoring of percentile-based concentrations of LDL cholesterol and non-HDL cholesterol (50th, 75th, 90th, 97th percentile) and HDL cholesterol (3rd, 10th, 25th, 50th percentile) in children with T1D and their peers without T1D to reveal influences of glycemic control, age, sex, and BMI on these lipoproteins. The first step of the algorithm considers increasing age and sex differences as nonmodifiable factors. The second step includes the BMI-for-age-and-sex of children with T1D and their peers without T1D as a modifiable factor, categorized into normal weight and overweight. The third step considers glycemic control as the most important modifiable factor that is associated with lipid levels. Four categories of clinically relevant HbA1c values were established largely in line with the International Society for Pediatric and Adolescent Diabetes Clinical Practice Consensus Guidelines 2009.[14] The level of glycemic control is therefore ideal (no diabetes) if the HbA1c value (Diabetes Control and Complications Trial derived, 12) is <6.05%. HbA1c values of 6.05%-<7.5% indicate optimal glycemic control, values between 7.5% and 9% suboptimal control, and values >9% are classified as high risk levels.

The diagnostic flowcharts (**Tables II-IV**) describe the basic algorithmic approach used when analyzing changed levels of LDL-, non-HDL-, and HDL cholesterol in children with T1D. In order to promote the implementation of the algorithm, we developed a tabular presentation, which describes the procedure for the use of the 3 cholesterol flowcharts on a step-by-step basis (**Table V**; available at www.jpeds.com).

Statistical Analyses

Statistical evaluation was performed by SAS v. 9.3 (SAS Institute, Cary, North Carolina). Descriptive statistics include means and SD or percentage for dichotomous variables. Unadjusted group comparisons were performed by Kruskal–Wallis or χ^2 tests. In addition, nonparametric estimation of percentiles using SAS proc univariate (50th, 75th, 90th, and 97th for LDL cholesterol and non-HDL cholesterol, and 50th, 25th, 10th, and 3rd for HDL cholesterol) was calculated. These percentile cut-offs were also calculated for subgroups according to age, BMI, sex, and a general linear model was used to compare lipid values among groups of patients, adjusting for age (categorized), sex, BMI (categorized), and HbA1c categories. Adjusted means were calculated to compare children with T1D and their peers without T1D with adjustment for multiple comparisons