Non-High-Density Lipoprotein Cholesterol in Children with Diabetes: Proposed Treatment Recommendations Based on Glycemic Control, Body Mass Index, Age, Sex, and Generally Accepted Cut Points

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Percentile-based non-high-density lipoprotein cholesterol levels were analyzed by glycemic control, weight, age, and sex of children with type 1 diabetes (n = 26 358). Ten percent of all children and 25% of overweight adolescent girls require both immediate lipid-lowering medication and lifestyle changes to achieve non-high-density lipoprotein cholesterol levels <120 mg/dL and cardiovascular risk reduction. (J Pediatr 2015;167:1436-9).

Non-high-density lipoprotein cholesterol (non-HDL-C) seems to be more predictive of future cardiovascular disease than low-density lipoprotein cholesterol (LDL-C), total cholesterol, or high-density lipoprotein cholesterol (HDL-C) alone for both children and adults.1

In 3 previous articles, we demonstrated that the treatment rate of dyslipidemia in children with type 1 diabetes (T1D) was insufficient.2 Moreover, we showed that cholesterol levels are influenced by age, sex, body mass index (BMI), and diabetes control.3 Then we introduced a diagnostic algorithm for long-term monitoring of non-HDL-C, HDL-C, and LDL-C in children with diabetes and peers without diabetes.4 The main objective of this analysis was to highlight the therapeutic significance of these findings to increase the use of lipid-lowering therapies for dyslipidemias in children with T1D. We analyzed alterations of percentile-based levels of non-HDL-C by influences of worsening glycemic control, overweight, age, and sex.

Methods

The datasets of the German-Austrian Diabetes Documentation and Quality Management System have recently been published elsewhere.5 For the analysis of non-HDL-C, male (53%) and female patients with T1D (n = 26 358, mean non-HDL-C 117 ± 36 mg/dL, mean hemoglobin A1c [HbA1c] 8.3% ± 1.7%) less than 18 years of age were classified into 2 age groups, ≤10 years (childhood/prepuberty) and >10 to <18 years for adolescence/puberty. Patients with LDL-C ≥190 mg/dL, lipid-lowering medication, and other forms of diabetes were excluded. BMI was calculated as body weight/(body height)² (kg/m²). The individual weight status was classified as normal weight (BMI <90th percentile) or overweight (BMI ≥90th percentile) using data from a nationally representative survey of German children.6 HbA1c levels were standardized mathematically to the Diabetes Control and Complications Trial7 reference range (4.05%-6.05%) using the multiple-of-the-mean transformation method.7 Three categories of HbA1c values were established (6% to <7.5%, 7.5% to 9%, and >9%), consistent with the International Society for Pediatric and Adolescent Diabetes Clinical Practice Consensus Guidelines.8,9 Analyses of lipoproteins were performed using standard procedures in accredited laboratories subject to regular quality control according to the guidelines of the German Medical Association.10 Non-HDL-C was calculated by subtracting HDL-C from total cholesterol. Influences of glycemic control, weight-status, age, and sex on non-HDL-C concentrations were assessed for the 25th, 50th, 75th, 90th, and 97th percentiles.

Statistical analysis was performed using SAS ver. 9.3 (SAS Institute, Cary, North Carolina). Descriptive statistics included means for continuous variables. In addition, non-parametric estimation of the 25th, 50th, 75th, 90th, and 97th percentiles for non-HDL-C was implemented using SAS proc univariate. These percentile cut-offs were also calculated for subgroups by age, BMI, sex, and HbA1c.

Results

Based on percentiles of non-HDL-C, the synoptic Figure illustrates the effect of rising HbA1c values from 6% to

<table>
<thead>
<tr>
<th>BMI</th>
<th>Body mass index</th>
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<tbody>
<tr>
<td>HbA1c</td>
<td>Hemoglobin A1c</td>
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<tr>
<td>HDL-C</td>
<td>High-density lipoprotein cholesterol</td>
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<tr>
<td>LDL-C</td>
<td>Low-density lipoprotein cholesterol</td>
</tr>
<tr>
<td>non-HDL-C</td>
<td>Non-high-density lipoprotein cholesterol</td>
</tr>
<tr>
<td>T1D</td>
<td>Type 1 diabetes</td>
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</tbody>
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Figure. Percentile-based distribution of non-HDL-C levels related to HbA1c elevations from 6% (open triangle) to >9% (black triangle) in children with T1D; A, aged ≤10 years and B, aged >10 years. The vertical lines indicate the recommended acceptable (<120 mg/dL) and high (≥140 mg/dL) limit values for non-HDL-C. To convert values from mg/dL to mmol/L, multiply by 0.02586.
Non-HDL-C levels increased with increasing HbA1c. The proportion of non-HDL-C levels ≥120 mg/dL was 25% and 10% for levels ≥140 mg/dL, irrespective of glycemic control, weight, age, or sex. In overweight girls aged >10 years, the rate of non-HDL-C levels ≥140 mg/dL was even as high as 25%. The distribution ranges of non-HDL-C levels were based on the effect of increasing HbA1c values from 6% to >9% and were generally smaller in patients aged <10 years than in patients ≥10 years. They were smallest in patients with the lowest non-HDL-C levels and broadest in patients with the highest non-HDL-C levels, indicating that the influence of worsening glycemic control increases with increasing non-HDL-C.

**Discussion**

It has been demonstrated that childhood non-HDL-C is as important as LDL-C in predicting subclinical atherosclerosis in adulthood. Therefore, non-HDL-C levels might be a suitable variable to differentiate between children with diabetes at low or high risk of developing early cardiovascular disease. Non-HDL-C level <120 mg/dL is the recommended treatment goal for children with diabetes, whereas levels ≥140 mg/dL are classified as high. Among 6- to 19-year-old children and adolescents in the US, the mean non-HDL-C level was 108 ± 0.5 mg/dL (n = 7058), comparable with the mean level of 107 ± 27 mg/dL (n = 14 057) observed in German and Austrian children and adolescents (mean age 10.1 ± 4.6 years). The SEARCH study found that children and adolescents with T1D with HbA1c ≥7.5% had a mean non-HDL-C level of 116.5 mg/dL. This is similar to our patients with a mean non-HDL-C level of 117 ± 36 mg/dL at a mean HbA1c value of 8.3% ± 1.7%, indicating that non-HDL-C levels of children in Germany and Austria are comparable with those observed in the US. Thus, these results may be valid for German and Austrian as well as American children.

Non-HDL-C levels ≥120 mg/dL were detected in 25% of our patients indicating a need for intensified lifestyle changes. High non-HDL-C levels ≥140 mg/dL were found in 10% of all cases and in as many as 25% of overweight adolescent girls, indicating a need for immediate lipid-lowering medication together with lifestyle changes. This recommendation of more frequent use of lipid-lowering medication at non-HDL-C levels ≥140 mg/dL is based on several factors. We believe there is no reasonable prospect of achieving non-HDL-C levels <120 mg/dL by improved glycemic control and/or weight loss alone, and because almost all patients with optimal glycemic control and normal weight belong to this group. Patients with non-HDL-C ≥140 mg/dL because of poor diabetes control and/or overweight might be able to reduce non-HDL-C to a certain extent by lifestyle changes and improved diabetes control but would not achieve the non-HDL-C treatment goal. Current guidelines might incorporate this new information regarding immediate lipid lowering treatment, especially because non-HDL-C gains increasing importance as a cardiovascular risk factor in children.

In summary, we provide information about the scope of increased non-HDL-C levels attributable to worsening HbA1c, increasing age, sex differences, and overweight. To achieve the non-HDL-C goal of <120 mg/dL, simultaneous implementation of lipid-lowering medication and lifestyle changes are recommended for 10% of all patients and 25% of overweight adolescent girls with T1D, whose non-HDL-C levels remain ≥140 mg/dL despite optimal glycemic control and normal weight.

**References**

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