

## Dyslipidemia in Youth with Diabetes: To Treat or Not to Treat?

DAVID M. MAAHS, MD, R. PAUL WADWA, MD, FRANZISKA BISHOP, MS, STEPHEN R. DANIELS, MD, PhD, MARIAN REWERS, MD, PhD,  
AND GEORGEANNA J. KLINGENSMITH, MD

There are an estimated 1.5 million people with type 1 diabetes (T1D) and 20 million with type 2 diabetes (T2D) in the US today, including at least 150 000 under age 20 years.<sup>1</sup> Of growing concern, both T1D and T2D are increasing in youth and manifesting at younger ages,<sup>2-4</sup> implying a longer burden of disease and earlier onset of vascular complications.<sup>5</sup> Cardiovascular disease (CVD) is the leading cause of death in persons with T1D<sup>6</sup> and T2D,<sup>7</sup> and the antecedents of adult CVD are present in children.<sup>8-10</sup> Several studies have demonstrated the tracking of childhood CVD risk factors into adulthood.<sup>9-15</sup> Furthermore, CVD risk factors in childhood correlate with abnormalities in surrogate markers of atherosclerosis (eg, carotid intima-media thickness [IMT] and arterial elasticity)<sup>14,15</sup> and atherosclerotic lesions in pathology evaluations.<sup>9,13</sup> Although recent data indicate that some progress has been made in reducing microvascular complications in T1D<sup>16,17</sup> and that intensive management with lower hemoglobin A1c (HbA1c) levels can reduce CVD events,<sup>18</sup> evidence from the Pittsburgh Epidemiology of Diabetes Complications Study suggests a lack of similar progress in reducing macrovascular complications.<sup>16</sup> Persons with T1D and T2D suffer macrovascular complications and death at earlier ages than nondiabetics.<sup>7,19</sup> Importantly, dyslipidemia is a significant CVD risk factor in persons with diabetes,<sup>7,20-22</sup> and target low-density lipoprotein cholesterol (LDL-c) levels continue to decrease in adults with diabetes mellitus (DM).<sup>7</sup>

Despite recent observational data on the prevalence of dyslipidemia in youth with DM,<sup>23-26</sup> and the publication of American Diabetes Association (ADA) and American Heart Association (AHA) clinical recommendations on treating dyslipidemia in youth with DM,<sup>27-30</sup> there remains a lack of data regarding treatment of dyslipidemic youth with DM on which to base clinical care. Instead, current pediatric recommendations are generated by consensus expert opinion or are extrapolated either from adult data or from treatment data in youth with familial hypercholesterolemia.<sup>27-31</sup>

Given that dyslipidemia is an important and potentially modifiable CVD risk factor, data to inform clinical decision making regarding screening criteria and treatment of dyslipidemia in this high-risk population are of significant public health importance.<sup>32</sup> Data from clinical trials in youth with DM are needed to determine the appropriate management strategy.

In this article, we review recent data and current recommendations on dyslipidemia in youth with DM. We discuss evidence supporting the treatment of dyslipidemia in youth with DM, as well as current treatment options and recommended monitoring. Finally, we address the question of whether or not lipid abnormalities should be treated in youth with DM.

### DATA ON ATHEROSCLEROSIS IN YOUTH

Landmark studies, such as the Bogalusa Heart Study,<sup>33</sup> the Muscatine Study,<sup>34</sup> the Young Finns Study,<sup>14</sup> and the Pathobiologic Determinants of Atherosclerosis in Youth (PDAY) study,<sup>35</sup> have demonstrated that the atherosclerotic process begins in childhood and that the extent of atherosclerosis (based on postmortem examination or use of surrogate markers of atherosclerosis) is related to the presence and degree of CVD risk

From the Barbara Davis Center for Childhood Diabetes, University of Colorado Health Sciences Center, Aurora, CO (D.M., R.W., F.B., M.R., G.K.); Department of Pediatrics, The Children's Hospital, Denver, CO (S.D.); and Department of Preventive Medicine and Biometrics, University of Colorado Health Sciences Center, Denver, CO (M.R.).

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Reprint requests: David Maahs, MD, Barbara Davis Center for Childhood Diabetes, University of Colorado Health Sciences Center, PO Box 6511, Mail Stop A140, Aurora, CO 80045. E-mail: David.Maahs@uchsc.edu.

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|-------|--|--------|--|
| ADA   | American Diabetes Association          | MNT    | Medical nutritional therapy                            |
| AHA   | American Heart Association             | NCEP   | National Cholesterol Education Program                 |
| BMI   | Body mass index                        | NHANES | National Health and Nutrition Examination Survey       |
| CVD   | Cardiovascular disease                 | PDAY   | Pathobiologic Determinants of Atherosclerosis in Youth |
| DISC  | Dietary Intervention Study in Children | T1D    | Type 1 diabetes  |
| DM    | Diabetes mellitus                      | T2D    | Type 2 diabetes  |
| HbA1c | Hemoglobin A1c                         | TC     | Total cholesterol                                      |
| HDL-c | High-density lipoprotein cholesterol   |        |  |
| IMT   | Intima-media thickness                 |        |  |
| LDL-c | Low-density lipoprotein cholesterol    |        |  |

factors. Although hyperglycemia was considered an important CVD risk factor in these studies, no explicit differentiation of T1D versus T2D was made, nor was there specific analysis of subjects with DM. The PDAY study developed a risk score based on CVD risk factors to predict atherosclerosis in persons age 15 to 34 years<sup>35</sup> that has been validated in various subsequent studies,<sup>36-38</sup> and National Health and Nutrition Examination Survey (NHANES) data have been used to establish sex- and age-specific cutpoints standardized to National Cholesterol Education Program (NCEP) thresholds.<sup>39</sup> These studies demonstrate tracking of CVD risk factors, especially for those in extreme categories of abnormal lipid levels, and strongly suggest that efforts to reduce CVD risk factors in youth can reduce the development of atherosclerosis and delay clinical CVD later in life.<sup>40</sup>

### DATA ON LIPIDS IN YOUTH WITH DIABETES

Recent data indicate the existence of dyslipidemia in youth with DM. In an earlier retrospective cross-sectional analysis, we found that 18.6% of children with T1D had an abnormal total cholesterol (TC) (>200 mg/dL) or high-density lipoprotein cholesterol (HDL-c) (<35 mg/dL) level.<sup>23</sup> Longitudinal analysis of data from the same clinic population revealed sustained abnormalities in a similar range.<sup>26</sup> HbA1c was significantly related to TC and non-HDL-c (calculated as TC minus HDL-c), and body mass index (BMI) z-score was inversely related to HDL-c.

Evidence of abnormal fasting lipid levels in youth with DM has come from the SEARCH for Diabetes in Youth study, in which 3% of subjects with T1D had an LDL-c level >160 mg/dL, 14% had an LDL-c level >130 mg/dL, and almost half (48%) had an LDL-c level over the recommended threshold of 100 mg/dL.<sup>24</sup> Reported prevalences were higher in youth with T2D, at 9%, 24%, and 57% for these same cutpoints, suggesting that obesity has a negative impact on LDL-c (although much more research is needed on the mechanism of the increase in LDL-c sometimes seen in obesity). A recent review of complications in youth with T2D reported a wide ranging incidence of dyslipidemia (15% to 62.5%).<sup>41</sup> The SEARCH for Diabetes in Youth study found that only 1% of youth with T1D and 5% of those with T2D were receiving therapy with lipid-lowering medications. Our data and the SEARCH data<sup>42</sup> support the importance of optimizing glycemic control and lifestyle interventions aimed at obesity as essential components of managing lipid abnormalities in this population.

In a large (n = 27 358) cross-sectional T1D cohort from Germany and Austria, Schwab et al<sup>25</sup> documented the presence of dyslipidemia (defined as TC >200 mg/dL, LDL-c > 130 mg/dL, or HDL-c < 35 mg/dL) in 29% of the subjects under age 26 years, with a higher percentage (34%) in the 17- to 26-year age group. Only 0.4% of this cohort was receiving lipid-lowering medications, including 0.8% of the 17- to 26-year-olds.<sup>25</sup>

Data from the aforementioned studies suggest that initiation of lipid-lowering medications in children with DM is lacking in light of newer, more aggressive recommendations for lowering lipid levels from the ADA and AHA. Applying the 2003/2005 ADA or 2006/2007 AHA guidelines to these data may not reflect current practice, however. With the rise in obesity in all youth,<sup>43</sup> including youth with DM,<sup>44</sup> increasing numbers of children likely will meet the criteria for treatment; however, to date no outcome data exist to support the pharmacologic treatment of CVD risk factors in youth with T1D or T2D.<sup>32</sup> Retrospective data on the pharmacologic treatment of dyslipidemia<sup>26</sup> suggest that more rigorous therapy, as well as patient education on the importance of continued therapy, may be needed to meet current ADA and AHA goals for lipid levels.

### DATA ON LIPIDS IN ADULTS WITH DM

Although lipid levels in patients with T1D have been found to be comparable to or better than those in nondiabetic adults (lower TC, LDL-c, and triglyceride and higher HDL-c levels),<sup>45</sup> adults with T1D still commonly have dyslipidemia and are known to be at greater risk for atherosclerotic disease compared with the general population. Dyslipidemia clearly is a major risk factor for atherosclerosis and CVD in adults with both T1D and T2D.<sup>7</sup> The NCEP considers the presence of DM to be the risk equivalent of a history of coronary disease, with similar goals for lipid-lowering.<sup>46</sup> There is a concern that the lipids in persons with DM may be more atherogenic than usual; possible mechanisms for this include differences in lipoprotein particle size, LDL-c oxidation, and increased transvascular LDL-c transport in patients with T1D.<sup>46-48</sup>

In contrast, dyslipidemia in T2D is characterized by decreased HDL-c and elevated triglyceride levels with variable TC and LDL-c levels, although LDL-c particles are smaller, denser, and more atherogenic.<sup>7</sup> Studies using statins to reduce LDL-c levels by 30% to 40% in adults with T2D have shown a 30% to 40% relative reduction in the risk of coronary heart disease.<sup>21,22</sup>

In summary, adults with T1D have been reported to have a better lipoprotein profile than nondiabetic adults,<sup>45</sup> but abnormal lipid levels in T1D subjects predict worse CVD outcomes.<sup>20</sup> Although the effectiveness of statin therapy to lower elevated LDL-c levels in adults with T2D is well established,<sup>7</sup> to date no clinical trials have demonstrated that LDL-c reduction results in improved CVD outcomes in those with T1D. Most of the pediatric lipid data are for youth with T1D, whereas in adults, more data are available for T2D. Along with CVD, dyslipidemia also may be an important risk factor for microvascular complications in persons with DM.<sup>49</sup> The relationship of dyslipidemia to microvascular and macrovascular complications, and whether or not this differs by DM type, merit further study.

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