Cardiovascular Health in Children with Diabetes

a report by
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Significant progress has been made in diabetes care in the past few decades. However, people with diabetes continue to have earlier and increased morbidity and mortality from micro- and macrovascular disease. Extensive data exist to inform clinical guidelines for the care of adults with diabetes. However, limited data exist on cardiovascular disease (CVD) risk factors in youth with diabetes. Specifically, controversy exists on how aggressively CVD risk factors should be treated in youth with diabetes.

In this article we will review data on CVD and its risk factors in people with diabetes, with a specific focus on cardiovascular health in youth with diabetes, and how data on CVD in adults with diabetes applies to youth with diabetes.

Cardiovascular Disease and Its Risk Factors in Adults with Diabetes

Studies such as the Diabetes Control and Complications Trial (DCCT) have demonstrated that in people with type 1 diabetes intensive control of glycemia reduces the risk for the microvascular complications of diabetes such as retinopathy, nephropathy, and neuropathy.[1] The Epidemiology of Diabetes Complications Study (EDIC) showed that the benefit from this intensive control on microvascular complications persists for up to eight years.[2] Similarly, the UK Prevention of Diabetes Study (UKPDS) has shown that lower glycated hemoglobin (HbA_{1c}) is associated with reduced microvascular complications in adults with type 2 diabetes.[3] There are strong data supporting the role of intensive control of glycemia to reduce microvascular complications in both type 1 and 2 diabetes in adults, and data exist to suggest that rates of microvascular complications in people with type 1 diabetes have decreased in the past few decades—a time when overall control of diabetes has improved.[4–6]

Data also exist on the relationship of glycemic control to reduction of macrovascular risk in types 1 and 2 diabetes;[7,8] however, recent studies have raised questions about the optimum glycemic goals in the care of adults with type 2 diabetes.[9,10] The DCCT/EDIC studies have shown that intensive glycemic control over a mean of 6.5 years reduced CVD complications by 57% after a mean of 17 years of follow-up.[7] The Coronary Artery Calcification in Type 1 Diabetes (CACTI) study showed that participants with HbA_{1c} <7.5% had reduced odds of progression of coronary artery calcification (CAC), which is a surrogate marker of coronary artery disease in young adults with type 1 diabetes.[11] Similarly, the UKDPS has shown that myocardial infarctions were reduced by 14% for every 1% reduction in HbA_{1c} in adults with type 2 diabetes.[8] However, these recent studies[9,10] have raised the question of how aggressive glycemic control goals should be in adults with type 2 diabetes, whether the benefits of intensive glycemic control outweigh the risks, and whether the timing of an intensive glycemic control intervention has an effect on CVD outcomes. Furthermore, while there are data to suggest that care for diabetes has improved, as evidenced by reduced rates of microvascular disease in the past few decades,[4–6] data on CVD suggest that substantially less progress has been made in reduction of macrovascular disease rates in people with diabetes.[6,12,13] People with diabetes continue to have increased morbidity and mortality due to CVD, arguing that this should be a focus of research and clinical care to improve the lives of patients with diabetes.

In addition to glycemic control, hypertension and dyslipidemia are also important CVD risk factors, with extensive data to support their role as targets to improve cardiovascular health in people with diabetes.[14] Despite abundant data on the importance of control of blood pressure and dyslipidemia, adequate control of these CVD risk factors is frequently not achieved.[15,16] There are limited data addressing these matters in children and adolescents. Therefore, despite extensive data that support aggressive treatment of CVD risk factors (glycemia, blood pressure, and cholesterol, among others) in adults with diabetes, the question arises as to how these data in adults apply to youth with diabetes and furthermore how these CVD risk factors should be treated in youth with diabetes.

Cardiovascular Disease and Its Risk Factors in Youth with Diabetes

Despite some uncertainty about how aggressive targets should be to optimize cardiovascular health in adults with diabetes, even fewer data

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exist on what these targets should be in youth with diabetes and what measures should be taken to obtain these goals beyond intensive glycemic control and healthy diet and lifestyle. In the past few years, several guidelines that address CVD health in youth with diabetes have been published by the American Diabetes Association (ADA),[17,18] the American Heart Association (AHA),[19,20] the American Academy of Pediatrics (AAP),[21] and the International Society of Pediatric and Adolescent Diabetes (ISPAD).[22] These guidelines are based on extrapolation of data from adults and from epidemiological studies in youth (such as the Bogalusa Heart Study[23] and the Pathobiologic Determinants of Atherosclerosis in Youth study,[24] among others). These studies have demonstrated that CVD risk factors in childhood track from youth to adulthood[25] and that these CVD risk factors are associated with atherosclerotic lesions on autopsy in young individuals who have died of accidental causes.[26] Unlike studies in adults with diabetes, in which cohorts can be followed for both micro- and macrovascular disease events, such 'hard' clinical outcomes are not expected to occur in youth with diabetes for decades or longer. This requires studies to rely on surrogate markers of CVD health. The use of such surrogate markers introduces the potential for doubt as to the veracity of outcomes depending on multiple factors, including the pathophysiological relationship of the surrogate marker to the clinical end-point.[27] Therefore, designing a study to demonstrate improvements in CVD health in youth with diabetes presents significant challenges. However, both type 1 and 2 diabetes are increasing in youth and both are presenting at earlier ages.[28–30] There is concern that youth who develop diabetes will have a longer burden of disease and therefore may potentially manifest diabetes complications, including CVD, at earlier ages.[31] Therefore, the question of how aggressive to be with treatment of CVD risk factors becomes an important question for the future health of our pediatric patients with diabetes.

What Is Known About Cardiovascular Disease Risk Factors in Youth with Diabetes?

Although glycemic control is the cornerstone of diabetes care, even in the DCCT the mean HbA_{1c} for adolescents compared with adults in both the intensively and conventionally treated arms was 1–2% higher. Despite this, rates of hypoglycemia were higher in adolescents than in adults.[32] More recently, post-DCCT published studies have shown that mean levels of HbA_{1c} have remained higher than current glycemic goals, with the Hvidore study reporting a mean HbA_{1c} of 8.6% in over 2,000 youths with type 1 diabetes worldwide.[33] Of note, these data from Hvidore are post-DCCT in which it was shown conclusively that intensive glycemic control improves vascular outcomes in type 1 diabetes.

A number of factors have been suggested to play a role in poorer glycemic control in youth than in adults, including insulin resistance of puberty, fear of hypoglycemia (especially in youth with hypoglycemic unawareness and the inability to effectively communicate to care-givers about this), and the psychological challenges of adolescence, etc.

There is great hope that technological advances will lead to improved glycemic outcomes. For example, the recent Juvenile Diabetes Research Foundation (JDRF)-funded trial of continuous glucose monitors (CGMs) demonstrated a significant reduction in the number of subjects with type 1 diabetes to reduce their HbA_{1c} below the goal of 7% in adults, but this outcome was not demonstrated in those 15–24 years of age who wore the CGM for only ~30% of the study period.[34] Further psychosocial research is needed on barriers to improved care in youth with diabetes and how to overcome these challenges. Data on care for youth with type 2 diabetes are more limited. Reviews of type 2 diabetes in youth worldwide and its complications have recently been published.[30,35]

Hypertension is a known CVD risk factor. Blood pressure should be checked at least annually in youth with diabetes and compared with age-specific percentile charts. ISPAD recommends treatment of blood pressure >90th percentile for age, gender, and height if lifestyle intervention is ineffective.[22] The SEARCH for Diabetes in Youth study has reported a prevalence of abnormal blood pressures in 6.8 and 28.2% of youth with types 1 and 2 diabetes, respectively, with few youth receiving pharmacological treatment to lower blood pressure.[36]

We have recently reviewed the data on dyslipidemia in youth with diabetes.[37] Among youth with type 1 and 2 diabetes in the SEARCH study, 14 and 24% of youth with type 1 and 2 diabetes, respectively, had low-density lipoprotein cholesterol (LDL-C) >130mg/dl. Although the guidelines for the pharmacological treatment of dyslipidemia in youth with diabetes are relatively recent, the limited data suggest that few youth with diabetes and dyslipidemia are treated with pharmacological agents (<1%).[37]

In addition to the well-established CVD risk factors of glycemia, hypertension, and dyslipidemia, other factors are known to have an adverse effect on CVD health, such as obesity, insulin resistance, smoking, and kidney disease (generally first manifested as albuminuria). Indeed, it has been proposed that the current prevalence of childhood obesity may result in an increase of 5–16% in coronary heart disease, with more than 100,000 extra cases attributable to this increased childhood obesity in the next 15 years.[38] Obesity has a central role in the development of type 2 diabetes in youth and has also increased in youth with type 1 diabetes.[39] The prevalence of obesity is similar in youth with type 1 diabetes to that in non-diabetic youth.[40] Insulin resistance is increased in youth with type 2 diabetes, but also in youth with type 1 diabetes at levels similar to that of non-diabetic obese youth.[41] In contrast to adults, in whom smoking cessation is a goal, in youth the goal is to prevent the initiation of smoking. Regrettably, an elevated prevalence of smoking has been reported in youth with diabetes,[42,43] adding another avoidable risk factor for CVD. Albuminuria is an early manifestation of kidney disease and is reported in 5–10% of youth with type 1 diabetes.[44] Of concern, the reported rates of microalbuminuria (or an elevated albumin–creatinine ratio) in youth with type 2 diabetes have been reported to be two to three times higher than in youth with type 1 diabetes.[44,45]

How Aggressive Should Endocrinologists Be in the Treatment of Cardiovascular Disease Risk Factors in Youth with Diabetes?

As previously stated, no clinical trials exist on which to base treatment decisions of CVD risk factors in youth with diabetes. However, there are currently two clinical trials in progress in which the treatment of CVD risk factors in youth with diabetes will be addressed. The Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study is a multicenter clinical trial in which more than 700 youth with type 2 diabetes have been randomized to receive metformin, metformin plus a thiazolidinedione, or metformin plus intensive therapeutic lifestyle

intervention. In addition to glycemia, subjects will also have other CVD risk factors such as hypertension and dyslipidemia intensively treated using algorithms based on ADA guidelines.[46] Another multicenter study in the UK proposes to study the effect of statin and angiotensin-converting enzyme inhibitors (ACE-I) therapy on the development of micro-albuminuria and surrogate markers of CVD in youth with type 1 diabetes (www.controlled-trials.com/ISRCTN91419926/).

In the absence of data from clinical trials demonstrating that treatment of CVD risk factors improves health outcomes in youth with diabetes, endocrinologists caring for youth with diabetes are left with practice guidelines and some uncertainty about how best to implement these recommendations in their individual patients. There is broad consensus among pediatric endocrinologists that lowering HbA_{1c} is important for the prevention of future micro- and macrovascular disease. However, given the increased rates of hypoglycemia in youth, there is debate about how low the goal should be for HbA_{1c}, as this must be balanced with the increased risk for hypoglycemia as mean glycemia is reduced.

Interestingly, data exist to suggest that both hypo- and hyperglycemia may have adverse effects on neurocognitive function.[47] While physicians are cognizant of the future risks of vascular disease from hyperglycemia, many parents of children with type 1 diabetes have a heightened fear of hypoglycemic events, which unfortunately are too frequent and generally are a more immediate concern. Similarly, the future effects of hypertension and dyslipidemia—both of which are typically asymptomatic—on vascular health can seem far off and hypothetical to both a teenager and his/her parents. A number of arguments can be made both for and against pharmacological treatment of CVD risk factors in youth with diabetes. We have recently reviewed these arguments for dyslipidemia in youth with diabetes.[37] Arguments for treatment include: tracking of CVD risk factors into adulthood, childhood CVD risk factors predict abnormalities of surrogate markers in childhood and adulthood, earlier diabetes results in a longer diabetes disease burden, and a potentially adverse vasculometabolic memory. Conversely, arguments against pharmacological treatment are: caution should be exercised in children (*primum non nocere*), the 10-year risk for a CVD event is minimal and the number needed to treat to prevent an event is not calculable but is likely to be large, the complications of life-long pharmacological treatment of a CVD risk factor are unknown, the cost would be high, and there are no safety or outcome data.

One barrier to treatment of CVD risk in youth with diabetes is that pediatric endocrinologists are less accustomed to treating hypertension and dyslipidemia than endocrinologists who care for adult patients, for whom the pharmacological treatment of these problems in their patients with diabetes is commonplace. One may speculate that endocrinologists who primarily care for adults but also have adolescent patients with diabetes may be more likely to initiate pharmacological therapy of CVD risk factors than pediatric endocrinologists, although no data exist on this.

In conclusion, while there are ample data in adults with both type 1 and 2 diabetes to support aggressive treatment of CVD risk factors including glycemia, blood pressure, and dyslipidemia, the data in youth with diabetes to support treatment of these CVD risk factors are limited. While guidelines exist from a number of organizations, these are based on expert opinion, extrapolation from studies in adults or youth with conditions other than diabetes, and epidemiological data. Although it has been established that youth with diabetes have CVD risk factors, debate on how aggressive treatment of these risk factors should be will continue. Clinical trials and additional data from epidemiological studies are needed to demonstrate safe and cost-effective health benefits of treatment of CVD risk factors in youth with diabetes. In the next decade we should see the completion of various clinical trials and other epidemiological data on CVD complications of youth with diabetes who have been followed over time. Until such data are available, the debate will continue to be more reliant on opinion than actual evidence. ■

1. No authors listed, *N Engl J Med*, 1993;329: 977–86.
2. No authors listed, *JAMA*, 2003;290:2159–67.
3. No authors listed, *Lancet*, 1998; 352:837–53.
4. Maahs DM, Rewers M, *J Clin Endocrinol Metab*, 2006;91:3757–9.
5. Hovind P, Tarnow L, Rossing K, et al., *Diab Care*, 2003;26:1258–64.
6. Pambianco G, Costacou T, Ellis D, et al., *Diabetes*, 2006;55:1463–9.
7. Nathan DM, Cleary PA, Backlund JY, et al., *N Engl J Med*, 2005;353:2643–53.
8. Stratton IM, Adler AI, Neil HA, et al., *BMJ*, 2000;321: 405–12.
9. Gerstein HC, Miller ME, Byington RP, et al., *N Engl J Med*, 2008;358: 2545–59.
10. Patel A, MacMahon S, Chalmers J, et al., *N Engl J Med*, 2008;358:2560–72.
11. Snell-Bergeon JK, Hokanson JE, Jensen L, et al., *Diab Care*, 2003;26:2923–8.
12. Libby P, Nathan DM, Abraham K, et al., *Circulation*, 2005;111: 3489–93.
13. Rewers M, *Diab Care*, 2008;31:830–32.
14. *Diab Care*, 2008;31 (Suppl. 1):S12–S54.
15. Maahs DM, Kinney GL, Wadwa P, et al., *Diab Care*, 2005;28:301–6.
16. Wadwa RP, Kinney GL, Maahs DM, et al., *Diab Care*, 2005;28:1051–6.
17. Silverstein J, Klingensmith G, Copeland K, et al., *Diab Care*, 2005;28:186–212.
18. *Diab Care*, 2003;26:2194–7.
19. Kavey RE, Allada V, Daniels SR, et al., *Circulation*, 2006;114:2710–38.
20. McCrindle BW, Urbina EM, Dennison BA, et al., *Circulation*, 2007;115:1948–67.
21. Daniels SR, Greer FR, *Pediatrics*, 2008;122:198–208.
22. Donaghue KC, Chiarelli F, Trotta D, et al., *Pediatr Diabetes*, 2007;8:163–70.
23. Berenson GS, Srinivasan SR, Bao W, et al., *N Engl J Med*, 1998;338:1650–56.
24. McGill HC Jr, McMahan CA, Malcom GT, et al., *Arterioscler Thromb Vasc Biol*, 1995;15:431–40.
25. Bao W, Srinivasan SR, Valdez R, et al., *JAMA*, 1997;278:1749–54.
26. McGill HC Jr, McMahan CA, Malcom GT, et al., *Arterioscler Thromb Vasc Biol*, 1997; 17:95–106.
27. Vasan RS, *Circulation*, 2006;113:2335–62.
28. Liese AD, D'Agostino RB Jr, Hamman RF, et al., *Pediatrics*, 2006;118: 1510–18.
29. EURODIAB ACE Study Group, *Lancet*, 2000;355:873–6.
30. Pinhas-Hamiel O, Zeitler P, *J Pediatr*, 2005;146: 693–700.
31. Pavkov ME, Bennett PH, Knowler WC, et al., *JAMA*, 2006;296:421–6.
32. Diabetes Control and Complications Trial Research Group, *J Pediatr*, 1994;125:177–88.
33. Danne T, Mortensen HB, Hougaard P, et al., Hvidore Study Group, *Diab Care*, 2001;24:1342–7.
34. Tamborlane WV, Beck RW, Bode BW, et al., *N Engl J Med*, 2008;359:1464–76.
35. Pinhas-Hamiel O, Zeitler P, *Lancet*, 2007;369:1823–31.
36. Gunther AL, Liese AD, Bell RA, et al., *Hypertension*, 2009;53(1):6–12.
37. Maahs DM, Wadwa RP, Bishop F, et al., *J Pediatr*, 2008;153: 458–65.
38. Bibbins-Domingo K, Coxson P, Pletcher MJ, et al., *N Engl J Med*, 2007;357:2371–9.
39. Libman IM, Pietropaolo M, Arslanian SA, et al., *Diab Care*, 2003;26:2871–5.
40. Lawrence JM, Liese AD, Liu L, et al., *Diab Care*, 2008;31:2251–7.
41. Nadeau K, West N, Sorenson E, et al., *Diabetes*, 2008;57: A500–A501.
42. Schwab KO, Doerfer J, Hecker W, et al., *Diab Care*, 2006;29:218–25.
43. Sellers EA, Yung G, Dean HJ, *Pediatr Diabetes*, 2007; 8:384–90.
44. Maahs DM, Snively BM, Bell RA, et al., *Diab Care*, 2007;30:2593–8.
45. Eppens MC, Craig ME, Cusumano J, et al., *Diab Care*, 2006;29:1300–1306.
46. Zeitler P, Epstein L, Grey M, et al., *Pediatr Diabetes*, 2007;8:74–87.
47. Ryan CM, *Pediatr Diabetes*, 2008;9: 527–30.