Physical activity for the prevention and management of youth-onset type 2 diabetes mellitus: focus on cardiovascular complications

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Abstract

With the growing prevalence of childhood obesity and type 2 diabetes mellitus (T2DM) in youth, the challenge of cardiovascular disease risk management has entered the paediatric realm, affecting specialists, family physicians and allied healthcare professionals alike. Currently, there is little evidence to support optimal strategies for management of T2DM in youth and the associated cardiovascular complications. Physical activity plays a powerful role in the prevention and management of T2DM and cardiovascular disease in adults.

This review will focus on the role of physical activity for the prevention of T2DM in youth and its associated cardiovascular complications. The first part describes the prevalence of cardiovascular risk factors in this cohort. The second part focuses on the role of physical activity in the prevention and management of T2DM in youth. Collectively, the limited intervention and observation studies published to date suggest that daily targets of 60–90 minutes of physical activity and less than 60 minutes of screen time (i.e. time spent in front of a television, computer or video games) are required for the prevention and management of T2DM in youth. Large-scale intervention studies are needed to determine the most effective physical activity strategies for the prevention and management of T2DM in youth.


Key words: cardiovascular disease prevention, childhood obesity, physical activity.

Introduction

The current epidemic of childhood obesity is a major public health concern1–2 and an important determinant of the appearance of type 2 diabetes mellitus (T2DM) before the age of 20 years. The rising prevalence of T2DM in youth poses the unprecedented clinical challenge of prevention and management of cardiovascular disease in a very high-risk paediatric cohort. Since healthcare expenditures associated with obesity and diabetes are significant,4,5 strategies are needed to prevent early-onset T2DM and its complications in children. Although pharmacological strategies are frequently used in adults, lifestyle interventions are preferred for the prevention and management of chronic disease in youth. Here we explore the role of physical activity in the treatment and prevention of T2DM in youth. Where evidence is lacking, we rely on studies performed in adults to inform recommendations for physical activity and T2DM management in youth.

Determinants of T2DM in youth

The epidemiology and classification of T2DM in youth are described elsewhere. Family history, ethnic background, obesity and physical inactivity are well appreciated risk factors for T2DM in youth.6 Recently, longitudinal follow-up of Pima Indian youth demonstrated that clustering of cardiovascular risk factors is also associated with early-onset T2DM. In fact, risk factors associated with the metabolic syndrome were better predictors of the progression to T2DM before the age of 18 years than traditional risk factors such as family history and two-hour glucose levels during an oral glucose tolerance test.7 These data strongly imply that clustering cardiovascular risk factors have a role in the pathogenesis of T2DM in youth. Accordingly, interventions that affect multiple risk factors simultaneously, such as physical activity, would seem ideal for the prevention of T2DM in youth. With that knowledge, it is important to review briefly the CVD-risk factor phenotype associated with T2DM in youth before discussing the role of physical activity in the prevention and management of the disease.

Chronic cardiovascular complications of T2DM in youth

Hypertension

In adults, the coexistence of hypertension and T2DM carries
a greater risk for a cardiovascular event than hypertension alone. Hypertension is by far the most frequent co-morbid cardiovascular disease risk factor associated with T2DM, though exact prevalence rates depend upon the definition of high-normal blood pressure. Early clinic-based studies that used a systolic blood pressure cut-off of the 95th percentile for age, sex and height found that 30–55% of youth with T2DM are hypertensive at presentation. The population-based SEARCH for Diabetes in Youth Study demonstrated that 73% of youth with T2DM have systolic blood pressure values above the 90th percentile for age, height and sex. Importantly, hypertension was roughly twice as prevalent in youth with T2DM compared to youth with type 1 diabetes. Obesity is probably a major determinant of this trend, since population-based studies have documented rates of high-normal blood pressure to be approximately 50% in normoglycaemic overweight adolescents.

**Nephropathy**

Microalbuminuria is another frequently documented risk factor associated with T2DM in youth, which worsens with disease duration. The presence of microalbuminuria at diagnosis ranges from 14–25% and is dependent upon age at presentation and ethnic background. Longitudinal follow-up of individuals diagnosed with T2DM before the age of 25 years demonstrates that the incidence of microalbuminuria is high within the decade following diagnosis and that it may be related to the degree of glycaemic control.

In the SEARCH for Diabetes in Youth study, the presence of albumin-to-creatinine ratio > 30 µg/m (> 3 mg/mmol) was evident in 22% of adolescents with T2DM and 9% of adolescents with type 1 diabetes. Interestingly, the differences in microalbuminuria were observed independent of age, disease duration, level of glycaemic control and insulin resistance.

Persistent microalbuminuria throughout adolescence places patients with T2DM at significant risk for premature end-stage renal disease. Follow-up of Pima Indian young adults who developed T2DM before the age of 20 years demonstrated a five-fold (confidence intervals [CI] 2.2–9.8) higher incidence of end-stage renal disease, compared with those who developed T2DM after the age of 20 years. Similar findings were observed in a Japanese cohort diagnosed with T2DM before the age of 30 years. Collectively, the frequent presence of hypertension and susceptibility for nephropathy place adolescents with T2DM at significant risk for premature end-stage renal disease.

**Dyslipidaemia**

In general, dyslipidaemia is frequent in youth with T2DM. Specifically, elevated levels of serum triglycerides (45–60%), total cholesterol (33–60%), low-density lipoprotein cholesterol (LDL-C) (24–41%) and low high-density lipoprotein cholesterol (HDL-C) (15–45%) are frequent at presentation. As for hypertension, determination of rates of dyslipidaemia is complicated by a lack of consensus over thresholds for elevated values in adolescents. Importantly, however, the presence of dyslipidaemia exceeds rates seen in population-based studies of obese youth, suggesting an independent additive effect of T2DM. The Search for Diabetes in Youth Study supports this concept by demonstrating that glycosylated haemoglobin (HbA1C) is positively associated with total cholesterol, LDL-C and triglyceride levels and negatively associated with HDL-C in youth with T2DM. Interestingly, the prevalence of high-normal total cholesterol (65%), LDL-C (43%) and triglycerides (40%) was more than two-fold higher in those with poor glycaemic control (HbA1C > 9.5%) than in those with adequate control (HbA1C < 6.7%) or peers with type 1 diabetes. Within our own experience, elevated total cholesterol (< 4.68 mmol/L), triglyceride (> 1.5 mmol/L), LDL-C (> 2.82 mmol/L) and apolipoprotein B levels (< 0.9 mmol/L) are evident in 65–75% of Canadian First Nation’s youth with T2DM at initial presentation (Sellers et al., unpublished data). The long-term consequences of premature dyslipidaemia combined with poor glycaemic control in this cohort are unknown: however, they are likely to be associated with significant risk for the early development of cardiovascular disease.

**Hepatic steatosis**

Hepatic steatosis is the most common form of liver disease in obese individuals and is associated with an increased risk of cirrhosis and portal hypertension. The prevalence of elevated liver enzymes in youth with T2DM is generally higher than population-based estimates in obese youth. As with most other risk factors, the definition of ‘high-normal’ determines the prevalence rates. We have observed alanine transaminase values greater than twice the upper limit of normal (60 mmol/L) in 22% of our clinical cohort, while 16% displayed values three times the upper limit of normal (Dean et al., unpublished observations). Recent population-based studies demonstrate that liver enzymes are less sensitive than direct estimates of hepatic lipid content, like magnetic resonance spectroscopy. It is likely therefore that the rates of hepatic steatosis are higher than those previously reported in the literature.

**Subclinical risk factors**

Clinic-based studies of small cohorts reveal that adolescents with T2DM are characterised by elevated levels of high-sensitivity C-reactive protein and reduced serum adiponectin. Although studies of youth with T2DM are lacking, endothelial dysfunction and arterial stiffness are documented features of obesity, type 1 diabetes and the metabolic syndrome in adolescents. Finally, central adiposity is a characteristic feature of impaired glucose tolerance and T2DM in adolescents and may be involved in risk factor clustering in youth. Future studies are needed to determine the earliest manifestations of cardiovascular disease in this high-risk cohort.

In summary, there is a high prevalence of cardiovascular disease risk factors associated with T2DM in youth. Longitudinal follow-up studies are needed to assess the long-term cardiovascular morbidity and mortality associated with prolonged exposure to risk factor clustering in this high-risk cohort. Management of the major cardiovascular disease burden is a significant clinical challenge in this paediatric cohort, as the long-term complications of drug therapy have
yet to be described. Physical activity is a proven lifestyle strategy for the prevention and management of T2DM in adults. A growing body of evidence suggests that physical activity should be considered a first-line therapy for the prevention and management of T2DM in youth.

**Physical activity and the prevention of T2DM in youth**

**Physical activity and adiposity in youth**

Adiposity is a major determinant of T2DM in youth and is the most relevant modifiable clinical index of diabetes risk in youth. Until recently, the targets for physical activity required for optimal weight management in youth were developed from studies of self-reported activity patterns. The development of accurate and reliable tools to quantify movement objectively has enabled the study of physical activity and diabetes risk in youth at the population level. Accordingly, several large population-based surveys of youth aged 9–18 years have demonstrated that the risk of childhood overweight decreases in a dose-response manner for each increment in physical activity. Longitudinal cohort studies support cross-sectional observations by demonstrating that declines in physical activity throughout adolescence are associated with an increased trajectory of weight gain. In fact, weight gain in adolescent girls is about three times higher in those achieving < 30 minutes of activity daily relative to active peers performing > 60 minutes of activity daily. Randomised controlled trials of physical activity and weight maintenance have elicited mixed results, but for the most part they demonstrate reductions in adiposity and moderate changes in body weight with increasing physical activity. In contrast, community-based interventions that typically include large numbers of healthy weight children rarely elicit changes in body mass or adiposity despite successfully increasing self-reported physical activity patterns. In summary, although observational data suggest that 60–90 minutes of physical activity daily are needed to maintain a healthy body weight in youth, randomised controlled studies are needed in healthy and overweight youth to confirm these observations.

**The role of intensity when prescribing a ‘dose’ of physical activity**

In addition to duration, the intensity of activity should be considered in the prescription of a ‘dose’ (i.e. duration, intensity and frequency) of activity for the management and prevention of overweight and T2DM in youth. One of the benefits of objective measures of physical activity is that they provide an index of the intensity of physical activity in addition to total physical activity time. Using this technology, dose-response relationships between moderate–vigorous physical activity and adiposity have recently been demonstrated in children and adolescents. In some cases the time spent engaged in moderate–vigorous activity was more closely associated with adiposity than total daily activity. One intervention study was originally designed to delineate the differences in high- and low-intensity physical activity on adiposity and metabolic risk factors in overweight youth, but proved inconclusive. In the absence of intervention studies, observational studies provide convincing evidence that greater amounts of moderate–vigorous physical activity are associated with a reduced risk of overweight. Taken together, these data suggest that the inclusion of moderate–vigorous intensity is preferred for the prevention of weight gain and subsequent risk for T2DM in youth.

**Physical activity and insulin sensitivity in youth**

A resistance to insulin-mediated glucose disposal is one of the earliest manifestations of T2DM in youth. Physical activity is considered a cornerstone in the prevention of T2DM by improving insulin sensitivity and through direct effects on glucose uptake in skeletal muscle. Large cross-sectional studies demonstrate that physical activity is positively associated with insulin sensitivity in children and adolescents. For example, the European Youth Heart Study found that clustered metabolic risk (including insulin sensitivity) increased in a dose-response manner with declining physical activity patterns in children who were nine and 15 years old. Longitudinal studies support these findings, for increased habitual physical activity in childhood or adolescence significantly attenuates the risk for T2DM in young adulthood. Specifically, higher levels of habitual physical activity patterns in adolescence were associated with lower fasting insulin levels in young adulthood. Unfortunately, there are few longitudinal studies of objectively measured physical activity and insulin sensitivity throughout childhood. Therefore, the dose-response relationship between changes in physical activity patterns and the trajectory of diabetes risk remains unclear.

Randomised controlled trials in overweight youth affirm that physical activity (primarily aerobic activity) enhances insulin sensitivity in childhood. Significant reductions in fasting insulin (18–20%) and the insulin response to an oral glucose challenge (23%) were seen following 16–20 week aerobic-based interventions consisting of 40–60 minutes at moderate–vigorous intensities, three times each week. A third study demonstrated that resistance training three days per week for 16 weeks improved insulin sensitivity by ~20% in overweight Hispanic adolescents. Therefore, resistance training should be considered an important adjunct to aerobic-based physical activity for diabetes prevention programs in high-risk youth, independent of changes in body composition.

In summary, aerobic-based physical activity lasting 40–60 minutes daily for a minimum of four months is likely to enhance insulin sensitivity, and may reduce the risk for T2DM in overweight youth. The addition of resistance exercise may also be beneficial. From a clinical and public health perspective, physical activity should be sustained throughout adolescence as the improvements in insulin sensitivity are reversed following cessation of exercise. Finally, long-term intervention studies similar to the Diabetes Prevention Project are needed in youth to understand better the role of physical activity in lowering diabetes risk in overweight youth.

**Sedentary (screen) time**

Increased screen time (defined as time spent watching television, working on a computer or playing video games) is frequently cited as a key determinant of the rising prevalence
of obesity in youth. Population-based studies recently confirmed this assumption, demonstrating an independent and causal association between screen time and metabolic risk in youth.60,62,69 In general, these studies demonstrate a significant association between daily television viewing time and adiposity in youth aged nine to 15 years. In fact, adiposity and risk factor clustering increase incrementally with increasing screen time, independent of physical activity patterns.31,32 Impressively, interventions that target screen time reduction effectively attenuate weight gain in young children.60,62,69 These data highlight the fact that sedentary time is an independent risk factor for unhealthy weight gain in youth and possibly for diabetes risk. Current recommendations suggest that screen time be considered an independent risk factor for obesity and therefore should be targeted as an independent lifestyle factor in the management of diabetes risk in youth.60,67

**Physical activity and cardiovascular disease risk management**

The American Diabetes Association and American Heart Association recommend that lifestyle strategies are critical to attain targets for glycaemic control and a reduced cardiovascular disease risk profile.66,67 For physical activity, the guidelines recommend achieving more than one hour of daily moderate–vigorous physical activity and reduction of screen time below two hours daily. For dietary goals, adolescents are asked to achieve: total and saturated fat intake < 30% and 10%, respectively; fibre intake 25–35 g daily; and increased consumption of fruit and vegetables. These guidelines are based almost entirely on observational studies and/or intervention studies in adults with T2DM. Currently, randomised controlled trials of physical activity and cardiovascular risk reduction have yet to be performed in youth with T2DM. However, insight into the potential benefit of physical activity on cardiovascular risk can be gained from randomised controlled trials of overweight normoglycaemic adolescents.

Exercise alone or in combination with diet has been shown to enhance insulin sensitivity, reduce systolic blood pressure, lower total cholesterol, raise HDL-C and improve endothelial function in overweight adolescents.25,26,28,47 Based on this evidence, clinical targets should include: (1) a minimum of 60 minutes of physical activity daily; (2) reduction of screen time below two hours daily; and (3) achievement of a weight loss of 7–10% of body weight for the prevention and management of T2DM in youth.74

**Concluding remarks**

In conclusion, T2DM in youth is associated with a cluster of cardiovascular disease risk factors. The premature onset of hyperglycaemia and risk factor clustering predicts an increased risk of hard clinical end points. The observation that T2DM in youth is associated with a significant increase in end-stage renal disease should be considered a harbinger for other major cardiovascular-related morbidity in this cohort. Accordingly, aggressive strategies are needed to achieve adequate cardioprotection for youth diagnosed with T2DM. The successful risk reduction achieved with intensive lifestyle therapy in overweight youth and in adults with glucose intolerance should serve as the platform for the management of cardiovascular disease risk in youth with T2DM. Based on this evidence, clinical targets should include: (1) a minimum of 60–90 minutes of physical activity of moderate–vigorous intensity, daily; (2) screen time should be limited to < 60 minutes daily; and (3) achievement of a weight loss of 7–10% of body weight for the prevention and management of T2DM in youth.

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**Conflicts of interest statement**

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