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Prevalence and significance of cardiometabolic risk factors in children with type 1 diabetes

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Abstract

Type 1 diabetes (T1D) is a common disease of childhood with a current prevalence of almost 2 cases per 1000 adolescents according to the third National Health and Nutrition Examination Survey (NHANES). Modern insulin treatment has resulted in improved quality of life for children diagnosed with this chronic disorder. However, T1D continues to carry a long term burden of increased microvascular and macrovascular complications and mortality risk. Compared to the non-diabetic population patients with T1D are more likely to have one or more cardiovascular risk factors and often at an earlier age. Since the prevalence of cardiovascular risk factors increases with age in young people with T1D there is a clear need for early screening and counseling to prevent their occurrence and manage long term health ramifications. The purpose of this review is to describe how traditional risk factors for cardiovascular disease like lipid profile, hypertension, obesity, and insulin resistance contribute to the accelerated atherosclerosis seen in young people with T1D. A summary is given of the guidelines and recommendations published for clinical care for these subjects.

Background and Significance

Type 1 diabetes (T1D) is a common disease of childhood with a current prevalence of 1.7/1000 among adolescents according to the third National Health and Nutrition Examination Survey (NHANES). Since the discovery of insulin enormous strides in T1D treatment has resulted in improved quality of life for patients diagnosed with this chronic disorder. However, T1D continues to carry a long term burden of increased microvascular and macrovascular complications and mortality risk. The British Diabetic Association Cohort Study showed that all cause mortality was higher in patients with T1D than in the general population at all ages 1. Type 1 diabetes narrows the gender gap for cardiovascular risk; whereas in the general population women have lower risk for cardiovascular disease, in patients with T1D, cardiovascular risk is similar for men and women. 1·2. Men and women with T1D had a cumulative mortality rate of 35% from coronary artery disease by the age of 55 years, compared to only 4–8% in non-diabetic people 2. Collectively, these and other findings underscore the fact that medical management of T1D should extend beyond blood glucose control, to include reducing the cardiovascular risk that accompanies T1D. Since T1D appears predominantly during childhood, people with T1D are at greater risk for developing coronary events early in life and face a lifetime requiring medical attention3.

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Thus, it is important that patients, family members and care providers understand the interaction of T1D and CV risk. The purpose of this review is to describe how traditional risk factors for cardiovascular disease like abnormal lipid profile (i.e., hypercholesterolemia, hypertriglyceridemia), hypertension, obesity, and insulin resistance accelerate atherosclerosis in young people with T1D. A brief discussion is also included on cardiac dysfunction in these patients.

Vascular Function in type 1 diabetes

The prevalence of cardiovascular risk factors in patients with T1D has been shown to be equal to or greater than in people without diabetes, and yet those with diabetes are less likely to be receiving appropriate treatment. In a study of ~27,000 German children and young adults (up to 26 y old) with T1D, more than half had at least one arteriogenic risk factor and 21% had two risk factors ⁴. Despite the presence of hypertension (8%) and dyslipidemia (29%) few of these patients were receiving antihypertensive or lipid-lowering medications. This study also demonstrated that the presence of cardiovascular risk factors increased with age, suggesting the need for early screening and counseling to prevent their occurrence and early treatment if present.

The implications of cardiovascular risk factors appearing among young T1D is becoming increasingly clear and should be of concern to patients and their healthcare providers. Presence of childhood cardiovascular risk factors has been unequivocally shown to be associated with accelerated atherosclerosis in the Bogalusa Heart study and the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study^{5,6}. Several studies have reported that atherosclerosis is accelerated among T1D patients using carotid intima medial thickness (CMT) as their primary outcome measure ^{7,8}, while others have shown similar findings using radial artery tonometry ⁹ or measuring coronary artery calcifications ¹⁰.

The combined thickness of the carotid artery intimal and medial wall as measured non-invasively by an ultrasound has been shown to be associated with prevalence of adverse cardiovascular events. Increased CMT has been shown to be associated with increasing prevalence of stroke and myocardial infarction later on in life in both middle aged men and women in the Atherosclerosis Risk in Communities study and elderly population in the Rotterdam study ^{11,12}. Results from the Epidemiology of Diabetes Interventions and Complications study (EDIC), a long term follow up study of the Diabetes Control and Complications Trial (DCCT), showed that adults with T1D had increased CMT compared to healthy non diabetic population 6 years into the study. The population that had received intensive treatment during the DCCT had much less progression in their CMT compared to the cohort who had received conventional treatment. However there was not a significant difference in their percent HbA1C at that time, suggesting the presence of 'metabolic memory' ⁷. Collectively these data suggest glycemic control may have long lasting effects, both beneficial and detrimental on cardiovascular morphology and function.

The studies of CMT in children are much less clear, with some reports demonstrating that T1D is associated with increased CMT compared to children without diabetes ^{13,14} while others report finding no difference ¹⁵. However, one of the limitations of these studies is that most have tested fewer than 55 subjects and therefore it is unclear if the results are representative. What is needed are larger prospective studies of the pediatric T1D population to better delineate if increased CMT is present in this population, the time of appearance relative to diagnosis and its relation to glycemic control and other cardiovascular risk parameters. Other measures of vascular function like carotid artery distensibility, brachial artery diameter, and flow-mediated dilatation has also been shown to be abnormal in

children with T1D 15. Endothelial dysfunction seems to be an integral part of the pathogenesis underlying the increased cardiovascular complications seen in T1D patients but it is still unclear how early it appears and whether it can be ameliorated by good glycemic control.

Hypertension and Nephropathy

Hypertension and the development of nephropathy seem to be inextricably linked. Abnormalities of blood pressure including loss of nocturnal dip (the normal drop in blood pressure at night), increase in 24 hour ambulatory systolic blood pressure and increase in the pulse pressure have each been shown to precede worsening of microalbuminuria (Table 1). It is not yet clear if these abnormalities precede the development of nephropathy or are the result of early and subtle nephropathic changes in genetically susceptible individuals. Hypertension could also be part of accelerated vascular aging seen in people with T1D 16. Patients with diabetic nephropathy have increased prevalence of cardiometabolic risk factors including hypertension as well as increased cardiovascular mortality as shown in multiple studies (Table 2). Abnormal lipid profiles and lipoprotein subclasses have all been variably described once subjects with T1D develop nephropathy leading to increased atherogenesis.

The earliest detectable sign of diabetic nephropathy is microalbuminuria. Microalbuminuria is defined as an increase in the albumin excretion rate of between 20 to 200 micrograms/min or an albumin concentration of 30–300 mg/l in an early morning urine sample. In children with T1D there is a high prevalence of transient microalbuminuria 17 with some longitudinal studies suggesting that approximately 50% might spontaneously revert to normoalbuminuria 18. The exact prevalence and prognostic significance of microalbuminuria in the pediatric population is still uncertain. One challenge for clinicians is that microalbuminuria risk increases during puberty. Microalbuminuria has very rarely been described in prepubertal children with T1D and is usually associated with a diagnosis of diabetes before the age of 5 years and with a long prepubertal duration of disease. Genetic susceptibility may play a large part in why some children develop overt nephropathy after developing microalbuminuria while some revert to a normal state. Further research is still needed to clarify the characteristics of progressors. Once overt nephropathy develops it is usually associated with hypertension and a higher prevalence of cardiovascular risk factors. Hence every effort should be made to prevent its occurrence.

Cardiac Dysfunction

Patients with diabetes are at increased risk to develop heart failure independent of having an underlying ischemic heart disease. It has been postulated that long standing hyperglycemia causes primary changes in the myocardium leading to heart failure though the exact molecular mechanism is still unclear. Several investigative tools, including echocardiogram and Doppler studies, have revealed the presence of diastolic dysfunction in asymptomatic patients with T1D even in the absence of coronary artery disease or systemic hypertension 19,20. Similar to the findings in adults, adolescents with T1D were also found to have cardiac functional abnormalities and females were more likely to be affected than males 21. This is very important clinically, as it is known that women with diabetes have a 5-fold increased risk for developing cardiac failure 22 compared to those without diabetes. Additionally, the presence of cardiomyopathy makes the heart more susceptible to hypertension and ischemia-induced damage 23,24. Further research is needed to elucidate the pathogenesis behind diabetic cardiomyopathy and to prevent its occurrence.

Plasma Lipids, Lipoproteins, and Glycemic Control

Dyslipidemia has been better characterized and more significantly associated with cardiovascular morbidity in subjects with type 2 diabetes (T2D) compared to T1D. The increased cardiovascular mortality seen in subjects with T1D is only partly explained by abnormal lipid and lipoprotein profiles. Dyslipidemia is very strongly linked to glycemic status with poorly controlled subjects showing a worse lipid profile. Interestingly there appears to be a sex difference in lipid profiles with T1D women having higher total cholesterol levels even after glycemic control is optimized. This may explain why women with T1D have similar cardiovascular mortality as men, rather than their normal mortality advantage before menopause.²⁵

Children with T1D have also been shown to exhibit abnormal lipid profiles. The SEARCH for diabetes study examined the differing lipid abnormalities among children with type 1 and type 2 diabetes ²⁶. Dyslipidemia was more frequent in youth with either T1D or T2D, compared to their non diabetic counterparts. T2D subjects had higher triglyceride levels while T1D youth had higher LDL cholesterol levels. Only a small proportion of the subjects with dyslipidemia (1%) received pharmacological therapy suggesting a discrepancy in identifying and appropriately addressing this important cardiovascular risk variable. In a recent consensus statement the American Diabetes Association (ADA) defined optimal levels of each lipid class in children and adolescents with T1D (Table 3) ²⁷. However, the exact threshold at which pharmacological treatment should be initiated is still unclear especially since the safety of many lipid lowering agents has not yet been established in children. Long term randomized trials are therefore needed to examine the safety and efficacy of these agents in decreasing cardiovascular mortality in children with T1D.

Multiple apolipoprotein abnormalities have been described to account for the increased cardiovascular mortality seen in patients with T1D. These include elevated apolipoprotein (a) ²⁸, and apolipoprotein C III levels ²⁹. T1D subjects frequently have normal to high HDL cholesterol levels but suffer from inappropriately high cardiovascular events. An abnormality in distribution of lipoprotein subclasses has been postulated to explain this seemingly paradoxical finding. Some studies have shown an association between elevated lipoprotein (a) levels and cardiovascular mortality in T1D ³⁰ while others have not found any such association ³¹. Also, elevated apolipoprotein (a) levels have been suggested as the plausible mechanism behind the increased occurrence of macrovascular disease in T1D patients with proteinuria ³². A 15-year follow up study in Switzerland showed apolipoprotein B to be a strong predictor of cardiovascular mortality in T1D ³³ suggesting that measuring apolipoproteins may develop into a more useful clinical tool than a fasting lipid profile that is the current standard.

It is not yet resolved whether poor glycemic control or abnormal lipids and lipoproteins are more accountable for the accelerated atherogenesis seen in patients with T1D. A recent review by Kanter et al ³⁴ examined the evidence supporting the contribution of each of these factors toward the increased atherogenesis seen in diabetes. Studies on LDL receptor-deficient mice that have hyperglycemia but show no dyslipidemia demonstrate an independent role of hyperglycemia on accelerating the formation of atherosclerotic lesions. The Diabetes Complications and Control Trial (DCCT) included people ages 13–63 years with T1D, who were randomly assigned to intensive insulin therapy requiring multiple daily injections and frequent finger stick blood glucose monitoring or the conventional regimen of fixed twice a day insulin regimen. At the end of the study it was unequivocally proven that patients on intensive insulin regimen had less microvascular complications than patients on conventional regimen³⁵.

Obesity and Insulin Resistance in Type 1 Diabetes

With the obesity epidemic there has been a growing interest in the presence of insulin resistance in T1D patients or what is sometimes referred to as 'double diabetes'. Insulin resistance has been postulated not only to accelerate the cardiovascular risk in T1D but is also theorized to cause earlier beta cell dysfunction in individuals predisposed to autoimmunity, according to the accelerator hypothesis 36.

The Pittsburgh Epidemiology of Diabetes Complications Study looked at the three separate definitions of the metabolic syndrome and their components to compare the ability to predict the major outcomes of T1D: coronary heart disease, renal failure and diabetes-related death. The three definitions of metabolic syndrome used were those from the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), the International Diabetes Federation (IDF), and the World Health Organization (WHO). The NCEP ATP III considers a patient to have metabolic syndrome if they have abnormalities in three out of the five components: waist circumference, triglycerides, HDL cholesterol, systolic blood pressure and fasting glucose. The IDF considers abdominal obesity a mandatory component of the metabolic syndrome. Patients must therefore have an enlarged waist circumference plus two of the other abnormalities which includes 1) elevated triglycerides, 2) decreased HDL cholesterol, 3) elevated systolic or diastolic blood pressure, 4) elevated fasting glucose. WHO requires the presence of impaired glucose tolerance, diabetes and/or insulin resistance for the diagnosis of metabolic syndrome and two other abnormalities. Those could be 1) elevated systolic or diastolic blood pressure, 2) elevated triglycerides and/or reduced HDL cholesterol levels, 3) elevated waist-to-hip ratio, and 4) microalbuminuria. The analysis by the Pittsburgh group revealed that the individual components of the metabolic syndrome predicted the major outcomes better than the separate definitions, with HbA1C and microalbuminuria the strongest predictors of major outcomes³⁷. Thus in the clinical setting, it may be more prudent to pay attention to these individual factors than the presence or absence of metabolic syndrome based on the current definitions.

In the DCCT, insulin resistance, as measured by estimated glucose disposal rate, was associated with an increased risk for both microvascular and macrovascular complications. Estimated glucose disposal rate was based on clinical factors of the patient that show a close relationship to insulin resistance when measured using the euglycemic hyperinsulinemic clamp method. Those clinical factors included waist-to-hip ratio, hypertension and HbA1c. Although patients on an intensive regimen tended to gain weight and develop metabolic syndrome compared to their counterparts on a conventional regimen, the improved glycemia tended to provide protection against the cardiovascular complications of diabetes 38.

Insulin resistance and obesity have also received attention in children with T1D. Insulin dose per body surface area and insulin dose per ideal body weight seem to reflect the influence of overweight and hence insulin resistance in children with T1D³⁹. However it has not yet been shown whether the being overweight is associated with adverse cardiovascular risk profile in children with T1D. Further research is still needed in this area. If being overweight is associated with an adverse cardiovascular risk profile in children, then the use of insulin sensitizers may be useful option, though there is still no evidence that it would change the cardiovascular risk.

Recommendations: Guidelines for Treatment

The American Diabetes Association has published a consensus statement on care of children and adolescents with T1D⁴⁰. The glycemic target for children varies with age due to the devastating effect that hypoglycemia can have on young children (Table 4). Recommendations on monitoring for hypertension, microalbuminuria and dyslipidemia are

also available. Hypertension in children is defined as a blood pressure above the 95th percentile for age, sex and height or if above 130/80. High normal hypertension has been defined as a blood pressure between 90th–95th percentile for age, sex and height. Dietary intervention consisting of eliminating added salt in the diet and an increase in physical activity is recommended as the first line of treatment. If blood pressure continues to be high normal or elevated, addition of a pharmacological agent is advised, using, as a first choice, an angiotensin converting enzyme inhibitor as this drug also protects against microalbuminuria. An annual screen for microalbuminuria should be performed starting at 10 years of age or sooner if the child has had diabetes for ≥ 5 years. Suggested screening tests include spot urine microalbumin-to-creatinine ratio, timed overnight sample or a 24 hour urine analysis. Diagnosis of microalbuminuria is based on two abnormal results out of three measurements on separate dates. As with treatment of hypertension the recommended first line of therapy for microalbuminuria is an angiotensin converting enzyme inhibitor. The patient is to be carefully educated on the importance of good glycemic control and cessation of smoking if appropriate.

Screening for dyslipidemia in children with T1D has been recommended either at diagnosis if there is a positive family history or at age 12 years if the family history is unremarkable. Positive family history includes a history of hypercholesterolemia, a cardiovascular event in anyone below the age of 55 years, or an unknown family history. If lipid levels are normal, it is recommended to repeat screening at five year intervals. Treatment of dyslipidemia is based on target LDL cholesterol of <100 mg/dl. Pharmacological therapy is recommended if LDL cholesterol is >160 mg/dl, or if LDL cholesterol is persistently between 130–159 mg/dl even after the institution of Medical Nutrition Therapy. The preferred choice of pharmacological agent is not stated and has been left to the discretion of the individual practitioner.

Conclusion and Summary

Cardiovascular mortality and morbidity continues to be high in patients with type 1 diabetes in spite of the great advances made in the field of insulin delivery and blood sugar management. A holistic approach is needed to address all the cardiovascular risk factors that are commonly seen in these patients instead of just focusing on the glycemic control. Since T1D is a disease of childhood, pediatric endocrinologists and pediatricians need to be aware of the high burden of cardiovascular disease in this population. The old adage “Prevention is better than Cure” rings true, especially so in this population.

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Table I

Blood pressure (BP) abnormalities in T1D and its relation to nephropathy.

Study (ref#)	Subjects	Length of follow-up	Outcome
41	148 non-microalbuminuric, non-hypertensive insulin dependent patients	4 years	BP and HbA1C higher in persistent microalbuminuric patients
42	44 normoalbuminuric T1D patients and 21 healthy individuals	3.1 years	Increase in 24 hour ambulatory systolic BP was associated with development of microalbuminuria
43	53 normotensive normoalbuminuric T1D patients	5 years	Night time diastolic BP increased in patients who progressed to over nephropathy
44	3250 T1D patients of the EURODIAB prospective complications study	7.4 years	Association of age with pulse pressure (an estimate of arterial stiffness) stronger in presence of microvascular complications especially nephropathy
16	2988 T1D patients and 5486 non diabetic controls	Cross-sectional study	Change in pulse pressure more pronounced in patients with nephropathy
45	604 T1D patients	16 years	Lower BP associated with lower risk for developing proteinuria

Table II

Nephropathy and cardiovascular (CV) disease in patients with T1D

Study (ref#)	No of T1D subjects	Country of Origin	Outcomes
46	3250	16 European countries	Co-linearity between microalbuminuria, diabetes duration and hypertension and CV disease
47	939	Denmark	Nephropathy associated with small increase in CV mortality
48	462	Sweden	Risk for CV death 18.3 times higher in patients with microalbuminuria
49	404	United Kingdom	Hypertension and nephropathy strongly predict CV mortality

Table III**Management of dyslipidemia in children/adolescents with diabetes**

Screening
After glycemic control is achieved:
Type 1
Obtain lipid profile at diagnosis (if >12 years of age) and then, if normal, every 5 years
Begin screening prior to age 12 years (if prepubertal) only if family history is positive
Type 2
Obtain lipid profile at diagnosis and then every 2 years
Goals
LDL <100 mg/dl
HDL >35 mg/dl
Triglycerides <150 mg/dl
Treatment strategies
Dietary modification
Maximize glycemic control
Weight reduction, if indicated
Medications
Age >10 years
LDL $\geq$ 160 mg/dl: begin medication
LDL 130–159 mg/dl: consider based on CVD risk profile
Statins $\pm$ resins, as first-choice
Fibric acid derivatives if triglycerides > 1,000 mg/dl
Manage other CVD risk Factors
Blood Pressure
Tobacco
Obesity
Inactivity

Reproduced from ADA guidelines 27

Table IVAge-specific glycemic goals as recommended by American Diabetic Association.⁴⁰

Age range	Target HbA1c
<6 years	7.5–8.5%
6–12 years	≤8%
13–19 years	<7.5%