Microalbuminuria and Heart Rate Variability in Adolescents With Diabetes

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ABSTRACT

Introduction: Limited clinical and research data are available on early renal and cardiovascular complications in youth with diabetes. The possible associations of elevated microalbuminuria to creatinine (MC) ratios with heart rate variability (HRV) were explored in adolescents with type 1 (T1DM) or type 2 (T2DM) diabetes.

Methods: A descriptive study was conducted with 41 adolescents with diabetes (n = 31 T1DM vs. n = 10 T2DM). Twenty-four hour Holter recordings for determining HRV, urine spot checks for MC ratio, and the most recent measures of glycosylated hemoglobin (A1c) were obtained.

Results: HRV was significantly lower in the T2DM group, while body mass index percentile, triglycerides, and diastolic blood pressure were significantly higher. For the T1DM group, clinical case examples provided evidence of elevated MC ratios (>30μg/mg) occurring in two female subjects who also had decreased HRV measures.

Discussion: Although HRV was not significantly associated with MC ratios for the sample, individual clinical findings can be a warning sign for some adolescents with diabetes. Current recommendations for screening of early renal complications and associated treatment are provided. J Pediatr Health Care. (2010) *24*, 34-41.

KEY WORDS

Diabetes-type 1, diabetes-type 2, adolescents, complications

Diabetes mellitus is one of the leading chronic diseases occurring in youth, affecting approximately 1 out of 500 youth in the United States (Liese et al., 2006). The incidence of type 1 diabetes (T1DM) increases with age, peaking at puberty. Recent prospective national and international registries (DIAMOND and EURODIAB) report a steep rise in T1DM in youth younger than 5 years (Soltesz, Patterson, & Dahlquist, 2007). This increase, along with growing numbers of youth being diagnosed with type 2 diabetes (T2DM) because of the pediatric obesity epidemic, is a warning sign for clinicians to be vigilant not only for adequate diabetes management but also for early indicators of microvascular and macrovascular complications. Although T1DM remains the more common diagnosis in youth, the recent SEARCH for Diabetes in Youth study group found that 15% of 10- to 19-year-olds with diabetes (n = 5030) had T2DM, primarily in minority groups (Liese et al.).

The majority of research exploring the onset and progression of microvascular complications in adolescents has included those with T1DM, with relatively little focus on those with T2DM (Donaghue, Chiarelli, Trotta, Allgrove, & Dahl-Jorgensen, 2007; Mayer-Davis, 2008; Soltesz et al., 2007). The landmark Diabetes Control and Complications Trial (DCCT) (DCCT Research Group, 1993) and subsequent Epidemiology of Diabetes Interventions and Complications (EDIC) Study (Writing Group, 2003) provided longitudinal evidence that intensive glucose control minimized microvascular

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complications of nephropathy, retinopathy, and neuropathy in persons with T1DM, including a cohort of pubertal adolescents. The EDIC study showed that although the improved glucose control in the intensive treatment group was no longer superior to that of the conventional treatment group 4 years after the completion of the DCCT, a positive memory effect of better glucose control continued with 48% less microalbuminuria and 85% less albuminuria (Writing Group). In both the DCCT and EDIC studies, lower resting heart rate, an indicator of better heart rate variability (HRV), was associated with the intensive treatment group (Paterson, Rutledge, Cleary, Lachin, & Crow, 2007).

The most recent economic statistics on the costs of diabetes in the United States estimate the national burden of direct medical expenditures to be $116 billion in 2007, an upward trend comprised mostly of treatment expenses for diabetes-related complications (American Diabetes Association [ADA], 2008a). Hence, strong evidence exists of the need for prevention and early screening for complications in our youth with diabetes.

The purpose of this article is to present the findings of a study that examined the presence of microalbuminuria and possible relationship to lower HRV as a marker of early cardiovascular autonomic neuropathy in adolescents with T1DM or T2DM. Clinical implications for identifying adolescents with diabetes who may be at risk for the development of early microvascular complications are discussed and practice guidelines are presented.

RISKS FOR MICROALBUMINURIA AND DECREASED HEART RATE VARIABILITY

Nephropathy and cardiovascular dysautonomia are devastating microvascular complications of diabetes that tend to occur concurrently in adults who experience the ravages of diabetes (Faulkner, Hathaway, Milstead, & Burghen, 2001). Microalbuminuria, a precursor of nephropathy, is associated with cardiovascular complications and mortality in adults with diabetes (Zandbergen et al., 2007). Microalbuminuria is recognized as the earliest marker of renal disease and is an independent predictor of cardiovascular morbidity and mortality in persons with diabetes (Garg & Bakris, 2002; Lambers Heerspink, Brinkman, Bakker, Gansevoort, & de Zeeuw, 2006). The ADA's Standards of Medical Care (2008b) define microalbuminuria via random urine spot check as an albumin-to-creatinine (ACR) ratio of >30 μg/mg and <300 μg/mg, with higher values indicative of proteinuria and worsening renal decline.

Recent longitudinal data reveal that progressive renal function deterioration is an early event in a significant proportion of the young adults with T1DM and microalbuminuria (Perkins et al., 2007). In large clinical studies of youth with T1DM, poor glycemic control, elevated blood pressure, and dyslipidemia are associated with microalbuminuria (Dost et al., 2008; Raile et al., 2007). However, in a study of a clinical sample of 394 pediatric patients with T1DM, McVean, Eickhoff, and McDonald (2008) did not find an association between poor glycemic control and microalbuminuria but did reveal that 14% of their patients had microalbuminuria. Based on the finding that microalbuminuria may not be tied to poor glycemic control but may be part of the natural history of T1DM, McVean and colleagues suggested that early baseline screening for microalbuminuria approximately 6 months after diagnosis of T1DM is warranted. Despite the even more limited research with youth who have T2DM, a particular concern is the significantly higher prevalence rate of elevated ACR ratio reported by the multi-site SEARCH for Diabetes in Youth Study for those with T1DM versus T1DM (9.2% vs. 22.2%, respectively) (Maahs et al., 2007).

Cardiovascular dysautonomia resulting from microvascular damage to parasympathetic and sympathetic fibers predicts increased risks for cardiovascular arrhythmias, sudden death, and myocardial infarction in adults with diabetes. Since the 1970s, the seminal work by Ewing and colleagues unveiled the predictive relationship between cardiovascular autonomic neuropathy and mortality in adults with T1DM (Ewing, Campbell, & Clarke, 1980). More recently, the Hoorn Study also found increased mortality in adults with T2DM who had decreased cardiovascular autonomic function (Gerritsen et al., 2000). Within the pediatric literature, HRV (a measure of cardiovascular autonomic function) was lower in adolescents with T1DM compared with healthy control subjects (Boysen, Lewin, Hecker, Leichter, & Uhlemann, 2007; Faulkner et al., 2001) and lower in youth with T2DM versus T1DM (Faulkner, Quinn, Rimmer, & Rich, 2005). No studies have addressed the concurrent association of lower cardiovascular autonomic function and microalbuminuria.

STUDY DESIGN AND METHODS

The heart rate variability data for this investigation were obtained from a larger, cross-sectional descriptive study entitled "Cardiovascular Risks in Adolescents with Diabetes" (NIH R01 NR07719). The current study presented here incorporated a secondary analysis of demographic and clinical data collected from participants enrolled in the larger study. Institutional review board approval was obtained and remains current. Current microalbumin to creatinine (MC) ratio and A1c data obtained from clinical records that had not been analyzed previously were merged with HRV data. Secondary analysis of data is a research methodology in which data in a previous study are used to answer additional research questions concerning the specific sample. Such further analysis can aid in greater understanding of interrelationships of key variables that need future study (Coyer & Gallo, 2005).

Power Analysis

Although a secondary analysis of an existing dataset was used for this study, we computed a power analysis a priori to determine the adequacy level for obtaining significant moderate correlations between measures of HRV and microalbuminuria. Using Power Analysis & Sample Size (PASS) (Number Cruncher Statistical System [NCSS] Statistical & Power Analysis Software, Dr. Jerry L. Hintze, Kaysville, Utah), a sample size of 50 was estimated in order to obtain a two-tailed test of significant difference between a null hypothesis correlation of 0.00 and an alternative hypothesis correlation of 0.40, with a power of 0.84 and α of 0.05. We recognize that having data on 41 subjects is a limitation and contributed to the study being under-powered for determining statistical significance. However, because of the dearth of clinical research focusing on early microvascular changes in this population, we report data here that have relevant clinical significance.

Heart Rate Variability

Twenty-four hour HRV was measured by use of the 3-channel SpaceLabs Burdick Model 92510 digital Holter Recorder (Deerfield, WI). The methods of HRV analysis used in this study have been reported previously but are included here for clarification because these techniques are not common in pediatric practice (Faulkner et al., 2005). HRV measures are classified into *frequency* and *time* domain analyses. Power spectral analysis of HRV quantifies and discriminates between sympathetic and parasympathetic autonomic function over a 24–hour period by recording the frequency (Hz) of R–R variation. Abnormalities detected by this test are more sensitive indicators of autonomic dysfunction than are conventional tests, particularly in patients with diabetes who have diminished 24–hour R–R interval variability (Ewing, Neilson, & Travis, 1984).

The SpaceLabs Vision Premier ECG Analysis and Editing software system utilizes the Fast Fourier Method of Spectral Analysis to calculate the frequency domain. Use of Fast Fourier Transformations provides a mathematical representation of the spectrum of frequency, also called Hertz (Hz), variations of R–R intervals from a 24–hour Holter monitor recording. Frequency domain measures of total Hz (0.01–1.00), low Hz (0.05-0.15), and high Hz (0.15-0.40) are converted to log transformation by the computer software to correct for skewness. Normally, low-frequency Hz activity (primarily adrenergic) predominates during waking hours and high frequency Hz activity (cholinergic) predominates during sleep.

Time domain analysis is computed on differing computations of the measurement of the standard deviation of heart period, based on sinus R-R intervals over time (Cowan, 1995). The time domain analysis of heart rate variability can be further divided into two categories. One category is derived from the R-R intervals, using means and standard deviations of the intervals measured in milliseconds. Measures in this category include the SDNN and SDANN. The SDNN is the standard deviation of all R-R intervals during a 24-hour period. Values for SDNN that are less than 50 milliseconds have been associated with sudden cardiac death (Kleiger, Miller, Bigger, & Moss, 1987). The SDANN is the standard deviation of the means of R-R intervals found in successive 5-minute time periods over 24 hours. The calculation for SDANN makes it the most resistant HRV measure for QRS labeling errors and the best measure for circadian fluctuation in heart rate (Cowan). The second category of time domain variables is derived from differences between adjacent R-R intervals and includes indices that are independent of circadian rhythms. The pNN50 is the proportion of the total R-R intervals that have differences of successive R-R intervals greater than 50 milliseconds. The rMSSD is the square root of the mean squared differences of successive R-R intervals. Reflecting alterations in autonomic function that are primarily vagally mediated, the pNN50 and rMSSD correlate highly with high-frequency power, reflecting parasympathetic modulation (Cowan).

Each QRS complex was identified and labeled. The analyzed data file was scanned and manually edited to locate and correct possible errors in QRS labeling that would negatively affect measurement of heart rate variability. The software program allowed for re-labeling of QRS complexes that occasionally may be incorrectly identified as ectopy or artifact. For each data file, only R-R intervals derived from normal sinus rhythm were used to calculate heart rate variability with power spectral analysis. Average 24-hour heart rate also was reported.

Clinical Data

Fasting lipids, glycosylated hemoglobin (HbA_{1c}), resting heart rate, and blood pressure data were collected at the same time that the Holter monitor was applied for HRV recordings. Blood pressure was measured twice in the sitting position using a standard sphygmomanometer with the subject's upper arm resting at heart level and then averaged. Urine spot checks for MC ratio were collected during routine clinic visits and evaluated using particle-enhanced turbidometric inhibition immunoassay with the Dade *aca* analyzer (Dade International, Wilmington, DE). The Beckman Synchron CX-7 Analyzer (Beckman-Coulter, Inc., Brea, CA) was used to determine total cholesterol (cholesterol oxidase), triglycerides (glycerophosphate oxidase), and high-density lipoprotein cholesterol (direct, immunoinhibition), and low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald equation (Friedewald, Levy, & Fredrickson, 1972). Glycosylated hemoglobin (HbA_{1c}) was measured using ethylenediamine tetraacetic acid whole blood analysis with High Performance Liquid Chromatography (HPLC) (BioRad Laboratories, Hercules, CA). Laboratory procedures

TABLE 1. Demographics

	Male	Female
T1DM (n = 31)		
White	10	11
Black	4	4
Hispanic	1	1
T2DM (n = 10)		
White	0	0
Black	2	6
Hispanic	1	1

T1DM, Type 1 diabetes; T2DM, type 2 diabetes.

TABLE 2. Clinical characteristics of the sample*

	T1DM	T2DM
BMI (kg/m^2)‡	23.0 ± 3.12	37.1 ± 7.1
BMI percentile‡	76.2 ± 16.9	98.0 ± 1.4
Tanner stage	4.10 ± 0.91	4.70 ± 0.68
Duration of diabetes (y)‡	6.43 ± 3.36	2.88 ± 1.94
HbA1c (%)‡	8.82 ± 1.66	7.05 ± 1.76
MC ratio μg/mg	11.09 ± 13.48	5.41 ± 4.88
Systolic BP mmHg	112 ± 12	118 ± 13
Diastolic BP‡	63 ± 9	74 ± 10
TChol mg/dL	172 ± 27	168 ± 41
HDL mg/dL	53 ±12	44 ± 14
LDL mg/dL	108 ± 26	97 ± 30
Tgl mg/dL†	59 ± 28	141 ± 96

BMI, Body mass index; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MC, microalbuminuria to creatinine; T1DM, type 1 diabetes; T2DM, type 2 diabetes; TChol, total cholesterol; Tgl, triglycerides.
**Reported as mean and standard deviation.*
†P < .05.
‡P < .01.

included quality control measurements by routine calibration of all assay equipment.

Data Analysis

All data were analyzed using SPSS 14.0 (SPSS, Inc., Chicago, IL). Descriptive data are reported as means and standard deviations. Comparisons of clinical data between youth with T1DM versus T2DM were conducted using Mann Whitney U tests because of the small and unequal sample sizes. Correlations among measures of HRV and MC ratio were computed using Spearman Rank Coefficients.

RESULTS

The final sample used for the secondary analysis consisted of those adolescents who had completed the larger parent study and who also had microalbuminuria screening documented within the same month the other data were collected. Table 1 provides the gender and racial/ethnic description for the sample. Of the 31 adolescents with T1DM, 61% were receiving two or more insulin injections per day versus 39% who were receiving pump therapy. Of the 10 adolescents with T2DM, 60% were receiving at least one insulin injection per day along with additional oral medications: four were taking insulin and metformin; two were taking insulin and a thiazolidinedione. The remaining four adolescents with T2DM were on the following medication regimes: one received metformin and a sulfonylurea; two received metformin only; and one received a thiazolidinedione only. Clearly, these findings suggest considerable variation in the medications that are being prescribed for the goal of achieving optimal glucose control.

TABLE 3. Differences in heart rate variability*

	T1DM	T2DM
Average heart rate	83 ± 10	89 ± 11
Resting heart rate	71 ± 10	73 ± 9
TotHz (ln ms^2)‡	8.45 ± .65	7.70 ± .68
HiHz (ln ms^2)‡	6.86 ± .84	5.87 ± .98
LoHz (ln ms^2)‡	7.18 ± .65	6.32 ± .71
SDNN (ms)‡	156 ± 34	115 ± 34
SDANN (ms)‡	128 ± 30	98 ± 27
pNN50†	22 ± 13	13 ± 13
rMSSD (ms)†	65 ± 30	41 ± 25

Hz, Hertz; pNN50, % of adjacent R-R intervals with ≥50 ms difference; rMSSD, square root of the mean of the sum of squares of differences between adjacent R-R intervals; SDANN, standard deviation of all the means of R-R intervals of each 5-minute block; SDNN, standard deviation of all R-R intervals; T1DM, type 1 diabetes; T2DM, type 2 diabetes.
**Reported as means and standard deviations.*
†P < .05.
‡P < .01.

Adolescents with T1DM had a significantly higher prescribed insulin dose than did those with T2DM who were receiving insulin therapy along with other diabetes medications (1.04 ± 0.29 vs. 0.45 ± 0.29 U/Kg, $P < .01$). Significant differences in both clinical characteristics and HRV values for subjects with T1DM versus T2DM are presented in Tables 2 and 3. Duration of diabetes, HbA1c, and both frequency and time domain measures of HRV were higher in those with T1DM. Age and gender-adjusted body mass index percentile, triglyceride level, and diastolic blood pressure were higher in youth with T2DM. No significant associations between measures of HRV and microalbuminuria were found in either those with T1DM or T2DM. However, a major clinical finding was that two female adolescents with T1DM who were similar in age (13.7 years) exhibited microalbuminuria. Details of their clinical characteristics and HRV measures are listed in Table 4. Although statistically significantly associations between measures of HRV and MC ratio were not found for the adolescents in either group, these two female adolescents with T1DM and microalbuminuria had lower HRV measures than did the subgroup with T1DM from this analysis (see Table 3). These differences also

TABLE 4. Clinical characteristics and heart rate variability of female adolescents with microalbuminuria

	Participant #1	Participant #2
Ethnicity/race	Hispanic White	Non-Hispanic White
BMI (kg/m^2)	23.8	25.2
BMI percentile	89	92
Tanner stage	5	5
Duration of diabetes (y)	7.7	6.5
HbA1c (%)	8.3	8.3
MC ratio μg/mg	47	58
Systolic BP mmHg	122	98
Diastolic BP mmHg	70	50
TChol mg/dL	199	213
HDL mg/dL	83	67
LDL mg/dL	107	137
Tgl mg/dL	43	44
Average heart rate	93	91
Resting heart rate	67	76
TotHz (ln ms^2)	7.93	7.68
HiHz (ln ms^2)	6.08	5.56
LoHz (ln ms^2)	6.85	6.49
SDNN (ms)	118	155
SDANN (ms)	100	139
pNN50	6.8	4.38
rMSSD (ms)	29	27

BMI, Body mass index; BP, blood pressure; HDL, high-density lipoprotein; Hz, Hertz; LDL, low-density lipoprotein; MC, microalbuminuria to creatinine; pNN50, % of adjacent R-R intervals with ≥50 ms difference; rMSSD, square root of the mean of the sum of squares of differences between adjacent R-R intervals; SDANN, standard deviation of all the means of R-R intervals of each 5-minute block; SDNN, standard deviation of all R-R intervals; TChol, total cholesterol; Tgl, triglycerides.

are noted in comparison with average HRV values for the larger sample of youth with T1DM (n = 105) from the previously published parent study (Faulkner et al. 2005). It is noteworthy that McVean et al. (2008) also reported that adolescents with T1DM and microalbuminuria were significantly more likely to be female.

CLINICAL IMPLICATIONS

Given the risks for poor outcomes in adults with diabetes and the greater numbers of youth being diagnosed, there is a tremendous need to focus on prevention of microvascular complications in youth with either T1DM or T2DM. The estimated lifetime risk of developing diabetes for persons born in 2000 is 32.8% for males and 38.5% for females. Females have higher residual lifetime risks at all ages (Narayan, Boyle, Thompson, Sorensen, & Williamson, 2003). The current clinical practice recommendation for managing diabetes and preventing complications in youth are primarily based upon expert evidence (ADA, 2008b). Because of the limited clinical studies, particularly randomized clinical trials with adolescents who have diabetes, practitioners must rely on the expert opinion of leaders in pediatric endocrinology who oversee the care of larger numbers of youth with diabetes. The careful assessment of subtle cardiovascular changes such as an elevated resting heart rate, a marker of a decline in parasympathetic autonomic modulation, along with microalbuminuria, may be preliminary signs of microvascular alterations in need of referral and treatment to avert future complications. Similar to adults with diabetes, youth who may experience these microvascular changes also can have risks for macrovascular disease as well, including hypertension and dyslipidemia. Clinical recommendations from the ADA (2008b) and the International Society of Pediatric and Adolescent Diabetes (Donaghue et al., 2007) are provided in the text box at the end of this article.

Given the risks for poor outcomes in adults with diabetes and the greater numbers of youth being diagnosed, there is a tremendous need to focus on prevention of microvascular complications in youth with either T1DM or T2DM.

Lifestyle modifications, including reduced sodium and saturated fat intake and increased physical activity, are first-line therapies for reducing cardiovascular risks in adolescents with diabetes. However, when blood pressure and blood cholesterol goals are not met, pharmacologic treatment may be indicated. Blood pressure goals in children are based on normal percentiles for age, sex, and height. Angiotensin-converting enzyme (ACE) inhibitors are the choice pharmacological treatment for consistently elevated blood pressure in youth with diabetes. Additionally, ACE inhibitors protect kidney function by reducing albumin excretion rates, preserving glomerular filtration rate, and ultimately delaying progression to overt

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nephropathy (Lewis, Hunsicker, Bain, & Rohde, 1993). ACE inhibitors such as Vasotec (enalapril), Zestril (lisinopril), or Accupril (quinapril) are the primary treatment for microalbuminuria. The most common adverse effects are cough, hyperkalemia, hypotension, dizziness, metallic taste, and rash.

The goal for LDL cholesterol for youth with diabetes is less than 100 mg/dL. Statins are now approved for youth older than 10 years who have elevated LDL cholesterol (ADA, 2008b). Clinical trials of statin usage in children and adolescents with familial or severe hypercholesterolemia have not found adverse effects to be greater than those in adults. However, the American Heart Association's statement on drug therapy of high-risk lipid abnormalities in children and adolescents emphasizes that long-term safety and compliance are a concern (McCrindle et al., 2007). Although clinical studies have not found adverse effects on sexual or physiological development in youth, the possible impact on psychological and intellectual development have not been evaluated. Examples of statins that have U.S. Food and Drug Administration pediatric labeling include Lipitor (atorvastatin), Zocor (simvastatin), Pravachol (pravastatin), and Mevacor (lovastatin). Common adverse effects of statin therapy include muscle pain or weakness, stomach pain, nausea, vomiting, constipation, and diarrhea. In rare cases, statin therapy can cause liver failure or rhabdomyolysis, that is, muscle deterioration that can lead to kidney failure. A major caveat in prescribing either ACE inhibitors or statins to female adolescents is the contraindication in pregnancy because of risks for birth defects. Therefore, comprehensive counseling and effective contraception as needed should be included in any treatment plan.

Awareness of the potential complications and strategies for comprehensive baseline assessments and routine evaluation is the first line of defense for optimal treatment.

Consulting with practitioners who have experience managing early diabetes complications in youth is essential for any practitioner in primary care who might assess early warning signs in adolescents with diabetes. Awareness of the potential complications and strategies for comprehensive baseline assessments and routine evaluation is the first line of defense for

BOX. Suggested clinical implications

- Optimize glycemic control
  - — HbA_{1c} <7.5% for adolescents, general recommendation
  - — HbA_{1c} <7.0% for adolescents if excessive hypoglycemia does not occur
- Individualized medical nutrition therapy (MNT) for each adolescent based on current need for any weight loss, physical activity level, and balanced with pharmacologic treatment with insulin and/or other oral agents
- Individualized exercise plan to achieve at least 60 minutes of moderate activity/day for at least 5 days per week
- Annual screening for microalbuminuria with random spot urine for MC ratio initiated at age 10 years and after having T1DM for 5 years (ADA, 2008b); microalbuminuria screen after 2 years if diagnosed with T1DM during adolescence (Donaghue et al., 2007) and at time of diagnosis for those with T2DM
  - — Urine spot screen should be first voided morning urine
  - — Confirmed elevation of MC ratio >30 μg/mg on two additional urine specimens—referral for treatment with ACE inhibitor titrated to normalization of microalbuminuria excretion
  - — Evaluate elevated MC ratio following intense exercise or menstrual bleeding (risk for false reading); exercise may provide false increases in albumin excretion because of elevated intravascular pressure in arterioles and increases in albumin filtration across the glomerular basement membrane (Lane, Ford, Larson, Chambers, & Lane, 2004)
- Annual screen for elevated systolic and/or diastolic blood pressure that is above the 90th percentile for age, sex, and height; if blood pressure is elevated, obtain repeat measures on three separate days; implement lifestyle modification with diet, exercise, and weight loss to decrease blood pressure; if unsuccessful after 3 to 6 months, begin pharmacologic treatment with ACE inhibitor*; if diastolic and/or systolic blood pressure is above the 95th percentile, begin pharmacologic treatment immediately
- Lipid screen should occur at puberty for youth with T1DM and at the time of diagnosis for those with T2DM (because of increased risk for dyslipidemia with T2DM); referral or begin treatment with statin therapy* if LDL-C is above 130 mg/dL and one or more cardiovascular risk factor is present or if LDL-C is above 160 mg/dL
- Emphasize no smoking or a plan to stop smoking because of increased cardiovascular risks with diabetes

*__Important note:__ *Statins and ACE inhibitors should not be used during pregnancy; pregnancy prevention is necessary if adolescents are being treated with either of these medications.*

Data from American Diabetes Association, 2008b; Donaghue et al., 2007.

optimal treatment. Decisions to implement drug therapies to treat microalbuminuria or elevated LDL cholesterol levels must review the risk to benefit ratio in youth and incorporate ongoing evaluation of clinical outcomes. With so few clinical studies on the best evidence for managing early complications in youth with diabetes currently available, a growing number of practitioners in the immediate future will be faced with the dilemma of choosing a treatment plan based on expert opinion. While there is a tremendous need for randomized clinical trials to determine the best strategies to combat early complications in these youth, the challenges of conducting these studies in this population are acknowledged. Therefore, greater efforts are needed to disseminate key information to practitioners regarding clinically significant findings that may occur in select adolescents and require appropriate referrals. The keen assessment of preliminary complications by one practitioner who may not have otherwise considered their occurrence just might make a huge difference in the life of an adolescent learning to live with diabetes.

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