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Pediatric Atorvastatin in Diabetes Trial (PADIT): A Pilot Study to Determine the Effect of Atorvastatin on Arterial Stiffness and Endothelial Function in Children with Type 1 Diabetes Mellitus

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ABSTRACT

Fifty-one children with type 1 diabetes mellitus (DM1) participated in a double blinded, randomized, cross-over pilot study to determine whether 12 weeks of daily atorvastatin (20 mg daily) would reduce arterial stiffness and improve endothelial function. Secondary analysis demonstrated potential reduction of arterial stiffness following atorvastatin therapy ($p = 0.06$). Additional long-term prospective studies with larger numbers of patients are needed.

INTRODUCTION

Type 1 diabetes mellitus (DM1) is a potent risk factor for premature cardiovascular disease (CVD)[1]. Children with DM1 as young as 10 years have abnormal vessel stiffness and function demonstrable by non-invasive techniques[2]. Early and aggressive management of CVD risk factors, such as blood pressure and lipidemia, may reduce the long-term risks for CVD in children with DM1[3]. Because long-term data are not yet available, lipid lowering therapy for the prevention of CVD in children with DM1 remains controversial[4]. We explored whether a short course of atorvastatin could reduce arterial stiffness and improve endothelial function in children with DM1. We hypothesized that 12 weeks of atorvastatin administration would improve measures of arterial stiffness and endothelial function, and reduce low-density lipoprotein cholesterol (LDL-C).

METHODS

A randomized, double-blinded, cross-over pilot study of 12 weeks daily atorvastatin (20 mg po vs placebo) was performed. Fifty-one patients (25 male) between 10 and 21 years of age with DM1 for at least one year were enrolled. Patients were recruited regardless of baseline LDL-C, body mass index (BMI), or glycated hemoglobin (HbA_{1c}) measurements. Diagnosis of DM1 was confirmed by both a typical clinical history and positive results for at least one diabetes-related autoantibody. Exclusion criteria included use of antihypertensive or lipid lowering drugs, pregnancy, and renal, cardiovascular, or liver disease. Each patient underwent four study visits: (1) baseline, (2) randomization, (3) cross-over, and (4) study completion.

Radial artery tonometry, which provides a measure of arterial stiffness (augmentation index corrected to heart rate of 75 [AI_{75}]) and reactive hyperemia peripheral artery tonometry (RH-PAT), which provides a measure of endothelial function (RH-PAT score), were assessed at each visit following an 8 hour fast and 24 hour avoidance of caffeine, as previously described[2,3]. Height, weight,

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blood pressure, and Tanner staging were recorded at all visits. Following arterial stiffness and endothelial function testing, blood was obtained for lipid profile, aspartate aminotransaminase (AST), alanine aminotransferase (ALT), creatine kinase (CK), glucose, and HbA_{1c}. A spot urine sample was obtained for evaluation of albuminuria standardized by creatinine (mg/g) in all patients and for human chorionic gonadotropin in females. The study was approved by the University of Florida Institutional Review Board. Each parent or participant over 18 signed and was provided a copy of an informed consent document, and younger children signed an assent form. Oversight was provided by the University of Florida Pediatric Data & Safety Monitoring Committee.

Statistical considerations

The primary dependent variable was AI_{75}, as in our previous case-control study[3]. A study of 23 evaluable subjects per group (~90% of 50 total) would have 80% power at p = 0.05 two-sided to detect a difference of 0.42 standard deviations in AI_{75}. Primary analysis was planned to evaluate the difference in AI_{75} during the first treatment period and that in the second treatment period. Secondary analysis of change during the atorvastatin period alone was performed using one sample, two-sided t-tests.

Study population

Fifty-one patients consented to participation in the study; 49 patients completed randomization, and 45 patients completed all study visits. Two patients voluntarily withdrew from the study before randomization and three patients voluntarily withdrew during study drug therapy because of difficulty coming to the hospital for study visits. Baseline LDL-C was 2.25 mmol/l (87 mg/dl) and HbA_{1c} 8.3%. Sadly, one patient committed suicide while taking placebo.

RESULTS

While no significant differences in either AI_{75} (p = 0.32) or RH-PAT score (p = 0.43) were observed when comparing the groups randomized to atorvastatin then placebo versus placebo then atorvastatin (primary analysis), secondary analysis demonstrated a plausible decrease in AI_{75} during the atorvastatin period alone (p = 0.06). Laboratory, tonometry, RH-PAT values, and p values for the primary and secondary analyses are provided in Table 1.

Pill counts performed at the end of each 12 week intervention indicated patients took an average of 83% of the study medication. Lipid profiles were predictably affected by atorvastatin with no significant changes in high density lipoprotein cholesterol or triglycerides but decreases in both total cholesterol and LDL-C (p <0.001). The point estimate of effect of 20 mg daily atorvastatin on LDL-C over the 12 week study intervention was a reduction of 0.75 ± 0.51 mmol/l (29 ± 20 mg/dl). No change in AST was observed during atorvastatin therapy (p = 0.21). ALT increased 4.3 U/l (p = 0.0021). No study patients developed AST or ALT elevations more than twice the upper limit of normal and no changes in serum CK were observed during atorvastatin therapy. Fasting glucose, HbA_{1c}, blood pressure, and albuminuria did not correlate with AI_{75} or RH-PAT score.

DISCUSSION

Determining when to initiate lipid lowering therapy in children with DM1 remains a difficult task. Given that DM1 is conservatively associated with a 2-3 fold increase in CVD risk and is a risk factor for future cardiovascular events equal to that of having had a previous myocardial infarction, further efforts are needed to accurately identify and aggressively treat those children with DM1 at the highest risk for CVD[1]. While our pilot study confirmed atorvastatin's LDL-C lowering capabilities and documented an excellent short-term safety profile, the primary analysis failed to demonstrate an associated improvement in arterial stiffness or endothelial function. Secondary analysis did, however, provide proof of principle that 12 weeks of atorvastatin therapy may be associated with reduced arterial stiffness in children with DM1. Current ADA recommendations for children with DM1 suggest initiation of pharmaco-

TABLE 1

Changes during Period 1 versus Period 2 (two sample statistics) and changes during atorvastatin period alone (one sample statistics)

	Mean ± SD at study entry	Primary analysis Two sample statistics		Secondary analysis One sample statistics	
		Point estimate of atorvastatin effect (SE) (n = 44)	**Two sample p value**	**Point estimate of atorvastatin effect ± SD** (n = 45)	**One sample p value**
	(n = 49 baseline)				
AI_{75} (%)	4.37 ± 13	-2.18 (2.14)	0.32	-2.0 ± 7.0	0.06
RH-PAT	1.77 ± 0.5	-0.11 (0.14)	0.43	-0.03 ± 0.5	0.75
HbA_{1c} (%)	8.3 ± 1.2	0.30 (0.27)	0.27	0.18 ± 1.0	0.23
Total cholesterol (mmol/l)	4.27 ± 1.0	-1.06 (0.17)	<0.001	-0.77 ± 0.63	<0.001
LDL-cholesterol (mmol/l)	2.25 ± 0.7	-1.14 (0.15)	<0.001	-0.74 ± 0.52	<0.001
LDL-cholesterol change (%)				-31 ± 18.7	<0.001
HDL-cholesterol (mmol/l)	1.6 ± 0.35	0.076 (0.057)	0.19	0.0026 ± 0.2	0.92
Triglycerides (mmol/l)	0.94 ± 0.59	0.018 (0.1)	0.86	0.07 ± 0.4	0.27
Glucose (mmol/l)	10.82 ± 4.7	1.95 (1.65)[#]	0.24	1.22 ± 6.2	0.20
AST (U/l)	20 ± 8.4	2.4 (1.9)[†]	0.21	1.1 ± 4.6[‡]	0.12
ALT (U/l)	15 ± 5.5	4.3 (1.3)[†]	0.002	2.8 ± 5.7[‡]	0.002
Urine microalbumin/creatinine (mg/g)	4 ± 5.9	19.3 (27.2)*	0.48	25.1 ± 173*	0.34
BMI	22.6 ± 4.3	-0.29 (0.21)	0.15	-0.1 ± 0.8	0.39
BMI percentile	67.9 ± 25.8	-2.52 (2.55)	0.33	-2.0 ± 9.9	0.17
Average systolic BP (mm Hg)	105 ± 9.9	3.50 (2.50)	0.17	3.1 ± 10.0	0.04
Average diastolic BP (mm Hg)	67 ± 9.7	-1.41 (2.48)	0.57	-0.8 ± 10.0	0.62
Heart rate (beats/min)	75 ± 15.2	1.23 (2.72)	0.65		

Mean value at study entry, point estimate of atorvastatin effect, and p value for major study endpoints using the primary analysis (two sample statistics of the change during period 1 versus change during period 2). Also shown are point estimates of atorvastatin effect ± SD and p value using one sample statistics (secondary analysis). Negative point estimates suggest lower values following the atorvastatin treatment period.

* Outlier prone variable; [#] n = 42; [†] n = 43; [‡] n = 44.

To convert cholesterol values from mmol/l to mg/dl multiply by 38.67. To convert triglycerides from mmol/l to mg/dl multiply by 88.6.

AI_{75} = augmentation index corrected to heart rate of 75; RH-PAT = reactive hyperemia peripheral artery tonometry; SD = standard deviation; SE = standard error.

logical therapy when LDL-C is >4.14 mmol/l (160 mg/dl), or when LDL-C is >3.36 mmol/l (130 mg/dl) in a child with additional CVD risk factors[5]. Because few of our study patients had baseline LDL-C levels above 4.14 mmol/l (130 mg/dl), our study was not adequately powered to determine whether these higher risk patients might have improved endothelial function or arterial stiffness measures while taking atorvastatin. In adults with DM1, both the ADA and AHA recommend initiation of pharmacological therapy if LDL-C is >2.59 mmol/l (100 mg/dl). These recommendations are largely based on the growing evidence that adults benefit from statin therapy regardless of initial LDL-C values. As pediatric data continue to document the accumulation of CVD risk in early childhood and the relative safety of statins in children, the threshold for pharmacological therapy in high risk children, including those with DM1, will likely continue to be lowered[6].

Additional efforts, including those aiming to examine the potential relationship between altered inflammatory cytokines and statin therapy, are urgently needed to better understand the pathophysiology of vascular dysfunction in children with DM1. Large, prospective, multi-center studies targeting children with LDL-C >2.59 mmol/l (100 mg/dl), employing long-term statin therapy (>1 year) and using sensitive anatomical and functional surrogate markers for CVD are needed to provide evidence-based recommendations for the prevention of premature CVD in children with DM1.

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