

Regression of Carotid Intima Media Thickness after One Year of Atorvastatin Intervention in Dyslipidemic Obese Teenagers, a Randomized Controlled Pilot Study

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Abstract

Objective: Metabolic syndrome in obese teenagers may contribute to future cardiovascular disease (CVD). We designed a pilot study to evaluate the effect on carotid intima media thickness (cIMT) of Atorvastatin treatment over one year in dyslipidemic obese adolescents (DLP) with metabolic syndrome markers.

Methods: We conducted a randomized double blinded control study. Adolescents 14-18 years old were recruited; 16 DLP were randomized to either 10 mg Atorvastatin or placebo. Both groups had cIMT measurements on the left and right side before and one year after the intervention. These measurements were compared to those of teenagers with familial hypercholesterolemia (FH).

Results: The average left cIMT of the DLP group was 0.582 ± 0.073 mm, and the right, 0.536 ± 0.071 mm, this compared well with measurements from FH individuals, 0.569 ± 0.947 mm and 0.548 ± 0.913 mm (right and left respectively, $p=0.49$). For the DLP group, the average left cIMT decreased only in the statin group to 0.509 ± 0.041 mm ($p=0.04$) but not on the right side 0.555 ± 0.062 ($p=0.5$). On average cIMT decreased by 10% in Atorvastatin treated individuals and increased by 1.6% in placebo treated ones. CIMT correlated best with the diastolic pressure but not with any of the lipid values.

Conclusion: To our knowledge this is the first pilot study that showed cIMT regression in dyslipidemic obese teenagers with features of metabolic syndrome after Atorvastatin therapy over one year. However, future long term studies should look at long term CVD risk reduction.

Keywords: Dyslipidemia; Carotid intima media thickness; Atorvastatin; Atherosclerosis; Children; Metabolic syndrome

Introduction

Childhood obesity is a worldwide health concern. Many obese teenagers show features of metabolic syndrome. There is a growing fear amongst clinicians involved in the care of obese teenagers for an eventual epidemic of early onset cardiovascular disease (CVD). This risk is based on observations from adult cohorts that metabolic syndrome markers increase the risk ratio of CVD events anywhere from 1.5-2 folds [1]. Although long-term observational studies have not been done in teenagers carrying the same risk markers, there is mounting evidence that the same might be expected of them [2]. Atherosclerosis is a continuous process that starts early in childhood, as inferred from post mortem studies clearly establishing that CVD onset starts in the pediatric age range [3]. CVD risk predictions in pediatrics are difficult as the occurrence of cardiac events is quite distant in their future. However, in adults it is clear that other surrogate markers are emerging as targets for intervention [4,5]. One of these tools, a non-invasive one, has been used more consistently to

assess the future risk of events in the CVD prevention field. Intima media thickness (IMT) measurements of the carotid artery (cIMT) have been shown to be good predictors of future cardiovascular events in at-risk individuals [6].

Regression of cIMT over time has been observed in adults, in the context of an aggressive treatment approach of familial hypercholesterolemia (FH) and produced positive cIMT changes over time [7]. Similarly, in FH children CIMT measurements are increased compared to non affected children, and treatment with statins reduces the progression of cIMT thickness over time [8,9]. Obese teenagers with features of metabolic syndrome including dyslipidemia (DLP) have comparable increased cIMT measurements and these track through adulthood [1,10,11].

HMG-CoA reductase inhibitors (Statins) are an FDA approved treatment option for children older than 10 years with familial hypercholesterolemia [12-14]. The treatment algorithm is based on LDL-C level targets [14,15]. However, up to date, no study has evaluated the effect of using statins for the treatment of dyslipidemia in obese teens with metabolic syndrome markers who do not respond to lifestyle modification [16]. In our pilot study we used cIMT

measurements as a surrogate marker of atherosclerosis progression over one year to evaluate the impact of Atorvastatin therapy on obese teenagers with dyslipidemia (DLP) and metabolic syndrome features. At baseline, we also compared the cIMT measurements of a group of DLP teenagers to another with FH as this is a well known high risk group of individuals who have previously shown a potential for regression of their cIMT. Atorvastatin was chosen on the basis of its safety record, the experience gathered so far with the medication and its potential impact on Tg levels and HDL-C, lipid profile markers frequently abnormal in obese teenagers.

Methodology

Study design

We conducted a randomized double blind control trial to evaluate the effect of Atorvastatin therapy on cIMT measurements in obese post pubertal teenagers between the age of 14 and 18 years old with dyslipidemia (DLP). These teenagers were recruited from the weight management clinic in accordance with the criteria for metabolic syndrome diagnosis based on the Cardiovascular Health and Risk Reduction in Children and Adolescents Guidelines by the presence of combination of 3 or more of the following risk factors: obesity, high blood pressure, Dyslipidemia (low HDL-C<1.0 mmol/L, elevated Non-HDL-C> 3.7 mmol/L, elevated triglyceride levels of >1.7 mmol/L), impaired fasting glucose, elevated fasting insulin level [12]. Written informed consent was obtained from their parents as well as from the patients themselves. This study received Research Ethics Board approval at Hôpital Maisonneuve-Rosemont.

For the purpose of comparing cIMT measurements, a group of teenagers between the age of 14 and 18 years old diagnosed with familial hypercholesterolemia (FH) was recruited. They were selected on the basis of a Total-C>7.0 mmol/L or a LDL-C before treatment of >4.1 mmol/L, generally well accepted surrogate markers of FH in the absence of mutation analysis confirmation [17]. Those teenagers were recruited before any treatment initiation.

Clinical and biochemical assessments

Baseline assessment included; systolic and diastolic blood pressures, waist circumference measurements (WC), body mass index (BMI) and biochemical profiles. The teenagers with DLP had measurements before and after the intervention. Blood pressure was measured on the right arm with the help of an automated device (Dynamap). WC was measured by the same person at the midpoint between lower rib and iliac crest directly on the skin using a flexible tape measure. Total cholesterol (Tot-C), HDL-C and Triglyceride (Tg) levels were measured using a standard kit. The LDL-C level was calculated using the Friedewald equation. Exclusion criteria included any cause of secondary dyslipidemia including renal failure and hypothyroidism which were ruled out at the enrolment visit by measurement of creatinine and TSH levels.

All teenagers underwent an oral glucose tolerance test (OGTT) to rule out the presence of asymptomatic type 2 diabetes with insulin levels being measured at the fasting and 2 h post glucose ingestion time points. HOMA-IR scores were calculated using the formula: $\text{insulin (mcU/ml)} \times \text{fasting glucose (mmol/L)} / 22.5$. C-reactive protein (CRP) levels were also measured before and after intervention.

Carotid Intima Media Thickness (cIMT) Measurement

cIMT was measured on the right and left carotid arteries. The same ultrasonographer did all cIMT measurements. The ultrasonographer was blinded to the patient assignment group. cIMT was measured in b-mode at the level of the common carotid artery, proximal to the bulb on the far wall. The images were recorded on a Video Home System (VHS) tape and sent to an outside lab for standardized measurements (Prevention concepts, Santa Monica, California); the outside lab technicians were also blinded to the patient's group assignment. The continuous video recording used by this lab allows for multiple images to be collected both sagittally and transversally, is fully computerized and automated and only showed a variability of $\pm 3\%$. The measurement technique is shown in Figure 1.

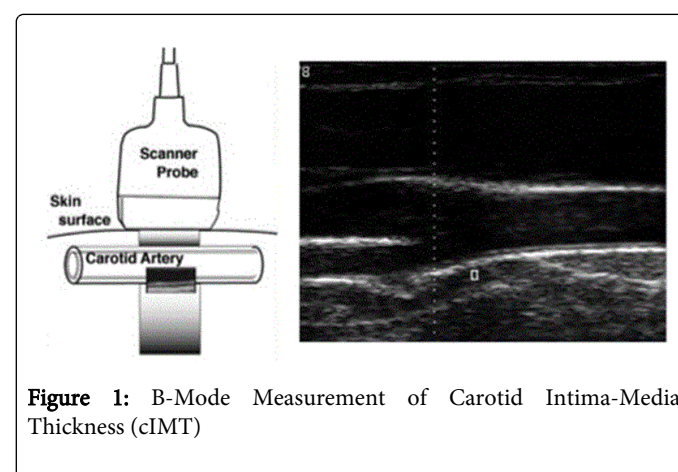


Figure 1: B-Mode Measurement of Carotid Intima-Media Thickness (cIMT)

Intervention

The DLP group was randomized through a computer generated system on a one to one basis. Accordingly, the DLP patient's either received placebo (which was manufactured by the sponsor) or Atorvastatin 10 mg according to the computer code. Patients, physicians, pharmacists and the study team were all blinded to the patient assignment group. Children of the FH group were not followed up for treatment in this trial. They were treated by their clinicians and followed up accordingly.

Lifestyle modification

All DLP groups received nutritional and exercise counselling. The diet consisted of "low-fat, low-cholesterol diet, such as the American Heart Association (AHA) Step I diet, for children with dyslipidemia that was modified to the patient's preferences and baseline diet [12]. The lifestyle protocol consisted of 4 visits with the same dietician following the initial assessment based on a food record. The initial target was 500 Kcal less than the reported intake and this was adjusted at each visit. Counselling on opportunities for increased activity, decreases in sedentary behaviour were also discussed at each session. All these teenagers were actively followed in a weight management clinic and had thus been instructed on lifestyle changes prior to the start of the study.

Study follow up

Patients in the DLP groups were followed up every 3 months. The follow up included lab evaluation for liver transaminases (ALT and

AST) as well as creatine kinase. In addition to, monitoring of side effects, compliance with medication was assessed through retrieving the pill bottles and proceeding to a pill count.

Statistical Analysis

We estimated the sample size needed to show significant difference in the thickness of the intima over one year by the reference data from the central lab to be 20 individuals (i.e. 10 in each group). IBM SPSS for Mac version 22 was used for all the statistics. Normally distributed data is presented as mean with standard deviation (SD) and non-parametric data as median with interquartile range. Within group comparisons were assessed using paired t-tests or non-parametric equivalent (Wilcoxon signed rank test). CIMT measurements of individuals were compared with normative data published by different groups. Results for boys and girls were pooled as previous studies have shown repeatedly that there are no striking sex differences before adulthood [18,19]. Comparisons were also made with FH teens at

baseline. Comparisons were then made between values pre and one year post intervention for maximal, minimal and average thickness of left and right carotid arteries. Linear regression correlations were established between cIMT and blood pressure, BMI, lipid values, HOMA-IR score and fasting insulin.

Two sets of analyses were done in this study, a per protocol analysis between groups using t-tests, and for the intent to treat analysis, a paired t-tests with the last available observation carried forward used when data was missing.

Results

Baseline characteristics

Twenty six teenagers were recruited for this study, sixteen in the DLP group and ten in FH group. The baseline characteristics of both groups are shown in Table 1.

	DLP		P value	DLP N=16	FH N= 10	P value
	Placebo N= 8	Atorvastatin N=8				
Male sex, n (%)	7 (87%)	5 (62.5%)	0.2	12 (81%)	5 (50%)	0.04
Age, years	15.5 ± 1.1	15.5 ± 1.5	1	15.4 ± 1.3	15.2 ± 1.8	0.8
Weight, Kg	103.8 ± 37.3	107.2 ± 23.7	0.8	105.3 ± 29.3	77.1 ± 15.4	0.01
BMI\$, kg/m ²	33.6 (29.1,43.3)	35.6 (31,4)	0.8*	38.6 ± 9.1	26.3 ± 3.7	0.001
BMI z score ^s	2.8 (2.3,3.7)	3.2 (2.3,3.7)	0.7*	3.1 ± 0.7	1.4 ± 1.2	<0.01*
WC, cm	113.18 ± 25.2	114.43 ± 16.1	0.9	--	--	--
Blood pressure, mm HG						
Systolic	126.2 ± 15.3	122.8 ± 12.6	0.6	124.5 ± 13.8	116.5 ± 14.1	0.1
Diastolic	70.8 ± 7.9	74.3 ± 6.5	0.3	72.6 ± 7.2	68.5 ± 7.8	0.21
Lipids, mmol/L						
TC	4.1 ± 0.4	4.7 ± 0.6	0.1	4.7 ± 0.7	6.4 ± 1.6	0.001
Triglyceride	1.7 ± 0.1	2.3 ± 0.7	0.06	2.0 ± 0.5	1.5 ± 0.6	0.04
HDL-C	0.8 ± 0.1	0.8 ± 0.1	0.5	0.9 ± 0.1	1.2 ± 0.2	0.001
LDL-C	2.6 ± 0.5	2.8 ± 0.6	0.5	2.8 ± 0.6	4.5 ± 1.5	<0.001
Tot C/ HDL-C	5.0 ± 0.7	5.3 ± 0.7	0.6	5.2 ± 0.7	5.5 ± 0.7	0.37
Non -HDL	3.4 ± 0.5	3.9 ± 0.6	0.1	3.8 ± 0.6	5.2 ± 1.3	0.001
HOMA-IR	5.8 ± 2.9	10.2 ± 3.3	0.03	--	--	--
FBG, mmol/L	4.8 ± 0.3	4.8 ± 0.3	0.8	--	--	--
Carotid intima media measurement, mm						
Mean Right	0.522 ± 0.086	0.550 ± 0.057	0.4	0.536 ± 0.071	0.548 ± 0.913	1
Mean Left	0.602 ± 0.085	0.560 ± 0.054	0.2	0.582 ± 0.073	0.552 ± 0.155	0.49

Values are given as mean \pm SD or indicated otherwise. BMI, body mass index; WC, Waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; CRP, C-reactive protein; HOMA-IR, homeostatic model assessment for insulin resistance; FBS, fasting blood sugar. FBS, fasting blood sugar. *Mann-Whitney U test, [§]Median and interquartile range 25-75

Table 1: Baseline characteristics of Dyslipidemia group (DLP) and Familial hypercholesterolemia group (FH)

Both groups were comparable at baseline except for LDL-C values, weight and BMI, as expected. Thirty percent of the DLP teenagers had high systolic blood pressure; 2 pre-hypertension and 4 hypertension. All but 1 of the DLP teens had a high HOMA score (i.e. >3.99). Only 3 were found to have a high CRP. One patient admitted to smoking.

At baseline the average cIMT measurements for the DLP and FH groups were 0.536 ± 0.071 mm and 0.548 ± 0.913 mm respectively for the right side; 0.582 ± 0.073 mm and 0.552 ± 0.155 mm for the left

side. These were not significantly different as shown in Table 1. Overall, the left carotid typically showed an increased thickness as compared to the right side. The mean difference was $0.051 \text{ mm} \pm 0.099$ mm ($p=0.01$). The cIMT measurements post intervention for the Atorvastatin group are presented in Table 2. The changes post intervention was significant in the maximum and average left cIMT measurements for both groups.

cIMT, mm	Pre	Post	P value [§]	P value*	Pre	Post	P value [§]	P value*
Min left	0.508 ± 0.205	0.555 ± 0.075	0.78	0.25	0.522 ± 0.071	0.467 ± 0.049	0.07	0.86
Min right	0.500 ± 0.084	0.520 ± 0.044	0.78	0.55	0.524 ± 0.63	0.469 ± 0.015	0.27	0.09
Max left	0.645 ± 0.091	0.609 ± 0.084	0.78	0.04	0.588 ± 0.054	0.546 ± 0.034	0.06	0.42
Max right	0.553 ± 0.086	0.585 ± 0.073	0.61	0.08	0.582 ± 0.058	0.542 ± 0.041	0.46	0.76
Average left	0.602 ± 0.086	0.579 ± 0.077	0.92	0.03	0.561 ± 0.054	0.509 ± 0.041	0.049	0.56
Average right	0.522 ± 0.086	0.555 ± 0.063	0.56	0.1	0.550 ± 0.057	0.504 ± 0.012	0.35	0.27

Values are given as mean \pm SD, [§]Group analysis, *Paired t-tests intent to treat analysis, Bold values statistically significant

Table 2: cIMT changes pre and post intervention in dyslipidemic teenagers

CIMT showed a combined (average left and right) 1.8% progression over the study year in the placebo group, whereas the Atorvastatin treated group showed a 9% reduction. That amounts to a combined decrease of 10.8% of cIMT progression over 1 year. Again, the impact was much more pronounced on the left side (12% reduction).

There was significant correlation between Left mean cIMT measurements and diastolic blood pressure $r=0.6$, $P<0.01$. No significant correlations could be established between left cIMT and lipid values, HOMA score, waist circumference, systolic blood pressure measurements and CRP levels.

Mean lipid and lipoprotein levels at baseline and 1 year post intervention are shown in Table 3. Both Atorvastatin and placebo group had similar lipid profiles at baseline. The total cholesterol to HDL-C ratio showed significant improvement in the treatment arm, from 5.4 ± 0.8 mmol/L to 4.37 ± 0.7 mmol/L ($P=0.04$). None of the other biochemical marker changes over time were found to be significant.

	Placebo			Atorvastatin		
	Pre	Post	P	Pre	Post	P
Weight, kg	104.5 ± 36.3	107.5 ± 39.5	NS	107.2 ± 23.6	100.3 ± 23.15	NS
BMI, kg/m ^{2§}	33.6 (29.1, 43.3)	33.8 (28.4, 47.6)	0.72*	35.6 (31,44)	34.7 (31, 44)	0.8*
BMI z score [§]	2.8 (2.3, 3.7)	2.8 (2.2,4.0)	0.77*	3.16 (2.3, 3.7)	3.01 (2.46, 3.8)	0.7*
WC, cm	113.2 ± 25.2	113.5 ± 24.9	NS	116.9 ± 15.6	113.6 ± 14.4	NS
Lipid profile, mmol/L						
TC	4.3 ± 0.4	4.5 ± 1.1	NS	4.7 ± 0.6	4.1 ± 0.6	NS
Tg	1.7 ± 0.1	2.1 ± 0.9	NS	1.7 ± 0.1	2.1 ± 1.6	NS

HDL-C	0.8 ± 0.1	0.9 ± 0.1	NS	0.8 ± 0.1	0.9 ± 0.7	NS
LDL-C	2.6 ± 0.5	2.7 ± 0.8	NS	2.8 ± 0.6	2.4 ± 0.5	NS
Tot C/ HDL-C	5.1 ± 0.7	5.2 ± 1.7	NS	5.4 ± 0.8	4.3 ± 0.7*	0.04
Non-HDL	3.4 ± 0.5	3.6 ± 1.1	0.44	3.9 ± 0.6	3.4 ± 0.7	0.07
HOMA-IR	5.8 ± 2.9	3.3 ± 0.9	0.31	10.2 ± 3.3	7.6 ± 2.7	0.18
FBS, mmol/L	4.6 ± 0.3	4.8 ± 0.3	0.1	5.0 ± 0.2	4.8 ± 0.3	0.2

BMI, body mass index; WC, Waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; CRP, C-reactive protein; HOMA-IR, homeostatic model assessment for insulin resistance; FBS, fasting blood sugar. Values are given as mean ± SD or indicated otherwise. *Wilcoxon Signed Rank test. †Median and interquartile range 25-75.

Table 3: Pre and post intervention clinical features and laboratory values in placebo treated (P) and statin treated (Rx) dyslipidemic teenagers

Overall the lifestyle intervention worked relatively well. Five teenagers (31%) had their BMI decrease and one saw the BMI remain the same following the counselling at one year follow up. Half recorded better waist circumference measurements and 31% an actual decrease in weight, 15% achieving more than a 5 Kg weight loss.

Safety and compliance

The overall adherence for medication uptake in the group was 86%. No significant medication associated side effects were found.

Discussion

This study, for the first time, signals potential benefit of using Atorvastatin for children with dyslipidemia and metabolic syndrome features to alter the Atherosclerosis process. The main finding of this pilot study is that the left cIMT thickness was significantly reduced over one year after Atorvastatin intervention. Hence, decrease atherosclerosis progression as we hypothesized. Interestingly, the only site where cIMT measurement is significantly changed was the left carotid artery, where the thickness is maximal. CIMT being thicker on the left side has been described in other studies; it is otherwise not well understood [1]. The fact that both the per protocol and the intent to treat analyses revealed significant changes at the left carotid artery site points towards it being a potential useful marker for monitoring impact of interventions in future studies. We may speculate this means that an aggressive treatment approach using Statins could benefit those with the highest cIMT readings.

CIMT measurements are not part of the routine follow up of teenagers at risk for future CVD and as such, there are no threshold values above which treatment is mandated. We found that the values found in our DLP group represented values more than the 95th percentile for cIMT measured in children of similar age and sex; and were comparable to values found in FH in the same age group [18-21]. This in itself could constitute a stronger argument to treat these patients since they could carry the same atherosclerotic risk based on their baseline cIMT measurements and potential for tracking. Very few studies have looked prospectively at cIMT changes in teenagers following an intervention. Positive changes were reported in FH affected individuals after a Statin intervention [7,8]. We are thus not surprised to see similar results in teenagers with DLP consequently this could translate into reduction of future CVD risk.

Only DBP correlated with cIMT in our cohort. It has been reported in adults that cIMT values correlate with age, sex and blood pressure values. There are also reports showing multiple correlations with different lipid values or markers of insulin resistance but this is not as well established in the pediatric age group [11].

In our study, the exact mechanism for the regression of cIMT measurements remains undetermined. LDL-C levels did not change significantly despite Atorvastatin therapy. In this group though, they were not considered high. However, the only biochemically significant change seen was a decrease in the total-C to HDL-C ratio. Interestingly, while the lipid profiles of the 2 groups (FH and DLP) were quite different, their total-C to HDL-C ratios was remarkably similar. This ratio has not been extensively studied in pediatrics as a marker of future CVD but may; based on adult data, also represent an important marker for future studies. Furthermore, fasting non-HDL-C levels are strongly associated with metabolic syndrome features as inferred from recent study in US youth [16,22].

Our study had many strong points that overcame many of the limitations reported in studies evaluating Statins use in FH. Our study design was a randomized controlled double-blinded study with a placebo arm; this allowed an unbiased analysis. We have shown that monitoring cIMT changes over one year is possible and may be clinically relevant. The predictive role of cIMT in pediatrics is yet to be established on a wide scale but it may play a more prominent role in the future to assess more specific individual risk and then tailor the treatment accordingly [18]. Both intensive lifestyle and Statin interventions could be monitored through cIMT, and perhaps more specifically left cIMT measurements, in at-risk individuals to determine the impact of specific interventions. Our work opens a relatively new pediatric paradigm in targeting higher risk individuals for prevention of future CVD.

We had few limitations in the pilot study, mainly, the small sample size. Unfortunately we could not recruit as many patients as needed per the sample size calculation. Nevertheless, we were able to show significant differences between groups. This will need to be replicated in a larger prospective cohort. A second limitation is that some individuals failed to complete all the analyses. This was addressed by an intention to treat analysis. While the intent to treat analysis revealed significant positive changes as well in the untreated group, the treatment group's comparisons were likely affected by using the last observation carried forward approach, which amounts to no change

being seen in the group where most values are missing, in this case, the treatment group.

Conclusion

This is, to our knowledge, the first pilot study looking at treating and prospectively monitoring at risk DLP teenagers with the help of serial cIMT measurements. In this small study, we were able to show regression of cIMT over a one year period. What might be inferred from our pilot study is that dyslipidemic obese teenagers with the thickest cIMTs, expected to be at higher future risk, could see their cIMTs regress with Statin therapy over one year. The exact mechanism or biochemical marker is yet to be unravelled with larger prospective trials, although we found the ratio of total cholesterol to HDL-C correlated with these changes. We believe this study has potentially great clinical significance as it opens the door for early consideration of Statin therapy in higher risk dyslipidemic individuals when lifestyle modification fails to improve the biochemical profile and cIMT thickness over time. However, future studies should look at longer-term effects of Statins therapy on cIMT measurements and possible reduction of long term CVD risk as seen in the adult population.

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