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Statin Therapy and Changes in Hip Circumference among HIV-Infected Subjects in the ALLRT Cohort

Todd T. Brown, MD, PhD¹, Marlene Smurzynski, PhD MSPH², Kunling Wu, M.S.², Ronald J. Bosch, PhD², and Grace A. McComsey, MD³

¹Division of Endocrinology and Metabolism, Johns Hopkins University, Baltimore, MD

²Center for Biostatistics in AIDS Research, Harvard School of Public Health, Boston, MA

³Division of Pediatric Infectious Diseases and Rheumatology, Case School of Medicine, Cleveland, OH

Abstract

Objective—To determine if statin exposure in antiretroviral-treated subjects is associated with increases in hip circumference compared to HIV-treatment without concomitant statin use.

Design/Setting—Prospective, multicenter cohort study.

Participants—2223 subjects in the statin-unexposed group and 371 in the statin-exposed group, who have received antiretroviral therapy for at least 40 weeks, enrolled in the AIDS Clinical Trials Group (ACTG) Longitudinal Linked Randomized Trials (ALLRT) cohort.

Main outcome measure—32-week change in hip circumference.

Results—The 32-week change in hip circumference in the statin-exposed group was 0.60 cm greater (95% Confidence Interval (CI): 0.11, 1.10 cm; $p=0.02$) than that in the statin-unexposed group, after adjustment for age, gender, race, baseline body mass index, and thymidine analogue exposure.

Conclusions—Our findings support the hypothesis that statins may be beneficial in lipoatrophy. Given the limited treatment options for this important problem, further studies are needed to confirm this effect and determine its clinical significance.

Keywords

anthropometry; lipoatrophy; HMG Co-A reductase inhibitors; lipodystrophy; HIV; statin

Introduction

Treatment options for subcutaneous lipoatrophy in HIV-infected patients are limited¹. In a small, 12-week, randomized trial, pravastatin was unexpectedly associated with a significant increase in limb fat compared to placebo². Recently, another small, randomized trial of HIV-infected patients with lipodystrophy failed to reproduce this finding and, in fact, showed a tendency toward decreased limb fat attributable to pravastatin³. We used the AIDS Clinical Trials Group (ACTG) Longitudinal Linked Randomized Trials (ALLRT) cohort to estimate whether HMG-CoA reductase inhibitor (statin) use is associated with changes in hip circumference, an anthropometric measurement which is well-correlated with changes in limb fat⁴.

Methods

Study Population

The ALLRT study is a longitudinal cohort of HIV-infected subjects (age ≥ 13) prospectively randomized to antiretroviral therapy (ART) or treatment strategies within clinical trials of the ACTG. Subjects are seen at 16-week intervals to obtain medication histories, clinical assessments and laboratory measurements⁵. Institutional review boards approve the protocol at participating institutions. Subjects sign written informed consent.

Hip circumference measurements were collected every 16 weeks through April 2006, and thereafter every 48 weeks, using a standardized protocol. Examiners record the circumference to the nearest 0.1-centimeter (cm) at the widest width of the hip. An average is calculated from triplicate measurements. Mid-thigh circumference measurements (mid-way point between the inguinal crease and the top of the patella) were collected in a subset of participants and are used as a secondary outcome measure.

Of the 3050 subjects enrolled in ALLRT with randomized ART treatments, subjects were eligible for inclusion in this analysis if two hip measurements were taken 32 weeks apart and the first hip measurement occurred at least 40 weeks after ART initiation. Hip measurements outside of a pre-determined range were not included (<71 or >169.8 cm). Of the 2670 subjects satisfying these criteria, 2044 never received statins (statin-unexposed) and 626 reported receiving statins during follow-up. Of the latter group, 371 were statin-exposed, 179 were considered statin-unexposed since the first 2 hip measurements 32 weeks apart occurred before initiation of statins, and 76 were excluded from analysis because they were not exposed to statins during an entire 32-week interval between two hip measurements and they could not be counted as unexposed (no hip measurements at a 32-week interval prior to first statin use). The study cohort comprised 2594 HIV-infected subjects (2223 subjects:statin-unexposed group; 371: statin-exposed group) with hip measurements obtained between August 1999 and May 2007.

Primary Exposure

Statin-exposed subjects began any statin medication prior to the first hip measurement and reported continuous use during the 32-week interval. Statin discontinuations of <21 days were ignored. The statin-unexposed group either never received statins during follow-up or initiated statins only after the second hip measurement.

Statistical Analyses

Average change in hip circumference over the 32-week interval was compared between statin-exposed and statin-unexposed groups. We conducted multivariable linear regression to examine the 32-week change in hip circumference, controlling for age (≥ 50 vs. <50 years), sex (male vs. female), race (Hispanic, white or other vs. black), body mass index (BMI) (25-30, >30 vs. <25 kg/m²) at the first hip measurement, and thymidine analogue exposure prior to the second hip measurement. Years receiving thymidine analogues, protease inhibitor (PI) exposure, non-nucleoside reverse transcriptase inhibitor (NNRTI) exposure, and calendar year of the first measurement were also tested for their effect on the 32-week change. In exploratory analyses, the statin-exposed group was further dichotomized into pravastatin-exposed or non-pravastatin-exposed to determine whether differences exist between different statins. Wilcoxon and chi-square tests were also used to compare groups.

Results

Demographic and Anthropometric Characteristics at First Hip Measurement

Compared to the statin-unexposed group, subjects exposed to statins were more likely to be older, male, white, and overweight/obese (Table 1). Total and non-HDL cholesterol and prevalence of diabetes mellitus were also higher among statin-exposed subjects. Statin-exposed subjects were less likely to have received thymidine analogues compared to the statin-unexposed group (80 vs. 89%, $p<0.0001$), but if exposed to these medications, had received them for a longer period (median 3.4 years (interquartile range (IQR) 2.0, 6.5) vs 1.6 years (IQR 1.5, 3.1), $p<0.001$). In the statin-exposed group, 34% were exposed to pravastatin, whereas 56% received atorvastatin.

32-Week Change in Hip Circumference in Statin-unexposed and Statin-exposed Subjects

The median 32-week change in hip circumference in the statin-exposed and -unexposed groups were 0.0 cm (IQR: -1.7, 2.1) and -0.4 cm (IQR: -2.5, 1.8) ($p=0.005$). In a multivariable regression model (Table 2), the 32-week change in hip circumference in the statin-exposed group was 0.60 cm greater than in the statin-unexposed group (95% Confidence Interval (CI): 0.11, 1.10 cm), after adjustment for age, gender, race, BMI category, and thymidine analog exposure.

We conducted several additional analyses to assess the effect of other covariates on the magnitude of the point estimate derived from the multivariable regression model. First, because of the known effect of thymidine analogue discontinuation on limb fat⁶, we adjusted the regression model for thymidine analogue discontinuation in the 2 years prior to the second hip measurement and found a similar effect of statin exposure (0.61cm [95% CI: 0.11, 1.10 cm]; $p=0.02$). Second, when duration of thymidine analogue use was included in the model, the difference between statin-exposed and statin-unexposed groups was attenuated slightly (0.50 cm [95% CI: -0.01, 1.01 cm]; $p=0.05$). Next, when we included NNRTI exposure prior to the second hip measurement, PI exposure prior to the second hip measurement, or calendar year of the first hip measurement (1999-2000 vs. 2005-2006 and 2001-2004 vs. 2005-2006) similar differences between statin-exposed and statin-unexposed groups were obtained (data not shown).

We conducted several sensitivity analyses to assess the robustness of the observed statin effect. We refit the multivariable regression model excluding those receiving thiazolidinediones ($n=19$) or metformin ($n=34$) at the first hip measurement and obtained similar differences between statin-exposed and statin-unexposed groups (data not shown). We also refit the regression model including only those who received thymidine analogues through the second hip measurement ($n=1719$) and found a slightly increased effect of statin exposure (0.68 cm [95% CI: 0.11, 1.1 cm]; $p=0.02$).

In a supplementary analysis to assess the effect of statin exposure at other sites, we investigated 32-week change in thigh circumference in statin-exposed and statin-unexposed groups in the subset with available data ($n=2449$). We found no difference between the groups in the same adjusted model used for hip circumference (-0.04 cm [95% CI: -0.49, 0.43 cm]; $p=0.88$). However, when we included in the adjusted model only those who had received thymidine analogues through the second measurement ($n=1657$), we found that the effect of statin use on 32-week thigh circumference change (0.52 cm [95% CI: -0.07, 1.11 cm]; $p=0.08$) was similar to the effect observed for hip circumference.

Differences between Statins in the 32-week Change in Hip Circumference

Of the 371 statin-exposed subjects, 126 received pravastatin and 245 received other statin medications, primarily atorvastatin. The median 32-week change in hip circumference in the pravastatin group was -0.5 cm (IQR: -2.0, 1.7 cm) and 0.3 cm (IQR: -1.5, 2.3 cm) in the non-pravastatin group. In the multivariable model, the difference between the two statin groups in the 32-week change in hip circumference was of borderline significance (-0.71 cm [95% CI: -1.65, 0.23 cm]; $p=0.13$), suggesting that atorvastatin may have a greater effect in attenuating the decrease in hip circumference.

Discussion

In this large, well-characterized cohort of HIV-infected subjects, we found that 32-week change in hip circumference was greater in individuals receiving statin medications compared to those not exposed to statins. These findings are consistent with the results of a small, randomized trial of pravastatin conducted by Mallon et al., in which pravastatin use was associated with a 0.53 kg increase in limb fat, compared to placebo over 12 weeks of treatment ².

The magnitude of the observed effect in our study appears to be considerably less than the point estimate derived from the Mallon study, although it is difficult to compare the results because different measurement techniques were used. If we extrapolate from ACTG 384 in which dual-energy x-ray absorptiometry (DXA) and hip circumference measurements were performed in a subset of HIV-infected subjects randomized to ddI/d4T or AZT/3TC plus efavirenz, nelfinavir, or both, our observed 0.6 cm difference would correspond to approximately 0.22 kg of limb fat ⁴. Similarly, using a cross-sectional dataset of 374 HIV-infected subjects who had both anthropometric and DXA data ⁷, each cm in hip circumference was associated with a 0.367 ± 0.012 kg difference in DXA-measured limb fat mass ($r^2=0.79$, $p < 0.00001$) (Steven Grinspoon, personal communication). With these data, our observed difference between statin-exposed and -unexposed groups would be a 0.22 kg difference in limb fat. Although there are limitations to this type of extrapolation, it is likely that the effect of statin exposure on limb fat is small. However, it is similar in magnitude to the effect of switching off of d4T for 24 weeks as observed in the TARHEEL study ⁸.

The underlying pathophysiologic mechanisms of statins on adipose tissue deserve further attention. Statin therapy reduces inflammation, which may in turn reduce adipocyte apoptosis ⁹, a key mechanism in the pathogenesis of lipoatrophy ^{10;11}. Circulating levels of inflammatory cytokines have recently been shown to be predictive of lower amounts of subcutaneous fat in HIV-infected subjects in the MACS cohort ¹². Another potential mechanism is that statins may increase the uptake of triglycerides and cholesterol into adipocytes. In hypercholesterolemic rabbits, atorvastatin has been shown to increase the uptake of oxidized LDL-cholesterol into adipocytes ¹³. In humans, pravastatin and atorvastatin have both been shown to increase chylomicron clearance in men with atherogenic dyslipidemia ^{14;15}. It is not clear whether triglycerides from these particles are stored in adipocytes. However, the recent observation that simvastatin use over a 6-month period was associated with 4.2% increase in body fat measured by bioelectrical impedance analysis in HIV-uninfected men with high cardiometabolic risk would support this hypothesis ¹⁶.

Our study has several limitations. First, we used hip circumference as a surrogate for limb fat. Although hip circumference measurements are well-correlated with limb fat ⁴, are easily utilized in a clinic setting, and are sensitive to changes with ART-initiation ⁴ and d4T discontinuation ¹⁷, a more precise measure of limb fat should be used in future studies. Second, our population included all eligible ALLRT subjects, not just those who had evidence of lipoatrophy. Further studies, however, should be conducted in this population, since this group has the highest likelihood of benefit. Third, allocation of statins was not randomized, and like

any observational study, the effect of statin exposure could be attributable to other unmeasured factors not included in our multivariable analysis. In particular, as would be expected, the statin-exposed group was more likely to be older, white, male, and have a larger BMI, compared to the statin-unexposed group. Although we adjusted for these variables, confounding by indication, such as differences in exercise and diet, which are not measured in the ALLRT study, may have influenced the results. Finally, multiple different statins were used in the cohort. Although not statistically significant, exposure to statins other than pravastatin (primarily atorvastatin) tended to have a greater effect in attenuating the decrease in hip circumference over 32 weeks compared to pravastatin exposure. Further studies should consider using atorvastatin to evaluate the effect of statins on limb fat.

In conclusion, in a large cohort of HIV-infected patients, statin exposure was associated with an attenuation in the decrease in hip circumference over 32-weeks, consistent with an effect on peripheral fat seen in a small clinical trial². Given limited treatment options for lipoatrophy, additional studies are needed to confirm this effect and determine its clinical significance.

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Table 1

Subject demographic and clinical characteristics at the first hip measurement by statin exposure (N=2,594).

		Total (N=2,594)	Exposure Status		p-value
			Statins (N=371)	No Statins (N=2,223)	
Sex	Male	2158 (83%)	322 (87%)	1836 (83%)	0.05*
	Female	436 (17%)	49 (13%)	387 (17%)	
Race	Black	708 (27%)	76 (20%)	632 (28%)	<.001*
	Hispanic	503 (19%)	61 (16%)	442 (20%)	
	White + other	1383 (53%)	234 (63%)	1149 (52%)	
Age	Median	41	46	40	<.001*
	<30	234 (9%)	8 (2%)	226 (10%)	
	30-39	918 (35%)	63 (17%)	855 (38%)	
	40-49	961 (37%)	166 (45%)	795 (36%)	
	50-59	376 (14%)	99 (27%)	277 (12%)	
	60-69	93 (4%)	30 (8%)	63 (3%)	
	≥70	12 (0%)	5 (1%)	7 (0%)	
	<50	596 (23%)	87 (23%)	509 (23%)	0.88*
Nadir CD4	50 - 200	904 (35%)	125 (34%)	779 (35%)	
	>200	1094 (42%)	159 (43%)	935 (42%)	
	<25	1254 (48%)	159 (43%)	1095 (49%)	0.04*
BMI	25-30	935 (36%)	141 (38%)	794 (36%)	
	<30	405 (16%)	71 (19%)	334 (15%)	
	Mean (s.d.)	97.8 (10.2)	98.4 (11.2)	97.7 (10.0)	0.51†
Hip Circumference (cm)	Median	96.5	96.5	96.5	
	Q1, Q3	91.4, 102.2	91.5, 102.4	91.4, 102.1	
Type of statin taken	Atorvastatin		209 (56%)		
	Pravastatin		126 (34%)		
	Lovastatin		7 (2%)		
	Simvastatin		16 (4%)		

		Total (N=2,594)	Exposure Status		p-value
			Statins (N=371)	No Statins (N=2,223)	
	Fluvastatin		4 (1%)		
	Cervistatin		4 (1%)		
	Rosuvastatin		5 (1%)		
AZT/D4T exposure @	Yes	2274 (88%)	298 (80%)	1976 (89%)	< .001 *
	No	320 (12%)	73 (20%)	247 (11%)	
AZT/D4T exposure ©	Yes	2024 (78%)	265 (71%)	1759 (79%)	< .001 *
	No	570 (22%)	106 (29%)	464 (21%)	
Diabetes history	Yes	124 (5%)	41 (11%)	83 (4%)	< .001 *
	No	2470 (95%)	330 (89%)	2140 (96%)	
Metformin in use	Yes	34 (1%)	11 (3%)	23 (1%)	< .001 *
	No	2560 (99%)	360 (97%)	2200 (99%)	
Glitazones use	Yes	19 (1%)	11 (3%)	8 (0%)	< .001 *
	No	2575 (99%)	360 (97%)	2215 (100%)	
Total cholesterol (mg/dl)	Mean (s.d.)	201 (49)	224 (59)	197 (46)	< .001 †
	Median	195	220	191	
	Q1, Q3	168, 228	188, 252	166, 224	
Non-HDL (m g/dl)	Mean (s.d.)	155 (49)	181 (57)	150 (45)	< .001 †
	Median	150	176	146	
	Q1, Q3	123, 182	142, 207	120, 176	
Years on AZT/D4T #	Mean (s.d.)	3.0 (2.8)	4.4 (3.4)	2.7 (2.7)	< .001 †
	Median	1.8	3.4	1.6	
	Q1, Q3	1.5, 3.6	2.0, 6.5	1.5, 3.1	
Years on HAART ‡	Mean (s.d.)	2.3 (1.8)	3.7 (2.3)	2.1 (1.5)	< .001 †
	Median	1.8	3.5	1.6	
	Q1, Q3	1.5, 3.3	2.1, 5.2	1.5, 2.8	

* Pearson's Chi-Square Test.

[†] Wilcoxon Test.

@ AZT/D4T exposure prior to 2nd hip=yes, if subjects had at least 21 days of D4T or AZT exposure starting from 24 months preceding the first hip measurement through the second hip measurement; otherwise, =no.

© AZT/D4T exposure prior to 2nd hip=yes, if subjects had at least 1 year of total time on AZT/D4T prior to the second hip measurement, AND had at least 21 days of D4T or AZT exposure starting from the 12 months preceding the first hip measurement through the second hip measurement; otherwise, =no.

Cumulative total years on AZT/D4T from initiation of AZT/D4T through the second hip measurement.

[‡] Cumulative total years on HAART from initiation of HAART through the second hip measurement. HAART definition: (i) two or more NRTIs in combination with at least one PI or one NNRTI; (ii) one NRTI in combination with at least one PI and at least one NNRTI; (iii) a regimen containing ritonavir and saquinavir in combination with one NRTI and no NNRTIs; and (iv) an abacavir- or tenofovir-containing regimen of three or more NRTIs in the absence of both PIs and NNRTIs.

Table 2

Multivariable linear regression model of the 32-week change in hip circumference in statin-exposed vs – unexposed ALLRT participants

Covariate	32-week change in hip circumference (cm)	95% CI	p-value
Exposed group (vs unexposed group)	0.60	(0.11 , 1.10)	0.02
Age at 1st hip: ≥50 vs <50	−0.16	(−0.61 , 0.28)	0.5
Male (vs Female)	−0.29	(−0.76 , 0.18)	0.2
Hispanic (vs Black)	−0.15	(−0.65 , 0.35)	0.6
(White + Other) (vs Black)	−0.06	(−0.47 , 0.35)	0.8
BMI: 25-30 (vs <25)	−0.38	(−0.76 , −0.01)	0.04
BMI: >30 (vs <25)	−0.50	(−1.00 , 0.00)	0.05
AZT/D4T exposure prior to 2nd hip	−0.82	(−1.34 , −0.31)	0.002