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Tesamorelin Improves Fat Quality Independent of Changes in Fat Quantity

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Author Contributions

JEL was involved in concept design, data analysis and interpretation, and manuscript development.
KL was involved in manuscript development.
KME was involved in concept design, data analysis and interpretation, and manuscript development.
SA was involved in CT scan interpretation and manuscript development.
GY was the primary statistician and participated in manuscript development.
MPD was involved in data interpretation and manuscript development.
TS was involved in data interpretation and manuscript development.
SG was involved in data interpretation and manuscript development.
JF was involved in data interpretation and manuscript development.
JCM worked for Theratechnologies and facilitated concept development.
CM works for Theratechnologies and reviewed the manuscript.
GAM was involved in concept design, data analysis and interpretation, and manuscript development.
TTB was involved in concept design, data analysis and interpretation, and manuscript development.

Conflicts of Interest

JEL has served as a consultant to Merck and ViiV, and receives research support from Gilead Sciences, OncoImmune and CytoDyn.
KL has no conflicts of interest.
KME has served as a consultant to Gilead Sciences and ViiV.
SA has no conflicts of interest.
GY has no conflicts of interest.
MPD has no conflicts of interest.
TS receives funding to her institution from Novo Nordisk, Inc., for an investigator-initiated grant.
SG has served as a consultant to Theratechnologies, unrelated to the current work.
JF has served on Speakers Bureaus for ViiV, Merck and Gilead, unrelated to the current work.
JCM worked for Theratechnologies.
CM works for Theratechnologies.
GAM serves as scientific consultant for Gilead, Merck, Viiv and has received research support from Gilead, Merck, Roche, Tetraphase, and Astellas.
TTB has served as a consultant to Gilead Sciences, Merck, ViiV Healthcare, and Theratechnologies.

Abstract

Objectives: Fat quality and quantity may affect health similarly or differently. Fat quality can be assessed by measuring fat density on CT scan (greater density=smaller, higher quality adipocytes). We assessed the effects of tesamorelin, a growth hormone-releasing hormone analogue that reduces visceral fat (VAT) quantity in some people living with HIV (PLWH), on fat density.

Design: Participants from two completed, placebo-controlled, randomized trials of tesamorelin for central adiposity treatment in PLWH were included if they had either a clinical response to tesamorelin (VAT decrease ≥8%, ≈70% of participants) or were placebo-treated.

Methods: CT VAT and subcutaneous fat (SAT) density (Hounsfield Units, HU) were measured by a central blinded reader.

Results: Participants (193 responders, 148 placebo) were 87% male and 83% Caucasian. Baseline characteristics were similar across arms, including VAT (−91 HU both arms, p=0.80) and SAT density (−94 HU tesamorelin, −95 HU placebo, p=0.29). Over 26 weeks, mean (SD) VAT and SAT density increased in tesamorelin-treated participants only (VAT: +6.2 (8.7) HU tesamorelin, +0.3 (4.2) HU placebo, p<0.0001; SAT: +4.0 (8.7) HU tesamorelin, +0.3 (4.8) HU placebo, p<0.0001). The tesamorelin effects persisted after controlling for baseline VAT or SAT HU and area, and VAT (+2.3 HU, 95% CI [4.5, 7.3], p=0.001) or SAT (+3.5 HU, 95% CI [2.3, 4.7], p<0.001) area change.

Conclusions: In PLWH with central adiposity who experienced VAT quantity reductions on tesamorelin, VAT and SAT density increased independent of changes in fat quantity, suggesting that tesamorelin also improves VAT and SAT quality in this group.

Keywords

HIV; tesamorelin; fat density; VAT; SAT

INTRODUCTION

Compared to the general population, people living with HIV (PLWH) are at increased risk for age-associated, non-communicable comorbidities such as cardiovascular and other metabolic diseases.[1, 2] Adipose tissue (AT) disturbances, including lipodystrophy and generalized obesity, are common, multifactorial in origin and contribute to metabolic disease risk in PLWH.[3] While historical risk factors for AT dysfunction are known, ongoing efforts are needed to fully understand contributing factors and optimal treatments for obesity and lipodystrophy among PLWH in the modern era of antiretroviral therapy (ART).[3, 4]

Adipose tissue is an endocrine and inflammatory organ that contains adipocytes, connective tissue, nerves, vascular tissues and immune cells all functioning as one unit. By secreting leptin, adiponectin and other factors, AT responds to hormonal and neuronal signals and plays an active role in metabolic homeostasis.[5] Significant research has focused on the roles of visceral (VAT) and subcutaneous (SAT) AT quantity in the development of metabolic disease,[6, 7] with the assumption that changes in AT quality (or function) are related to changes in quantity. However, as in the case of metabolically healthy obesity, increases in AT quantity are not always associated with obvious cardiometabolic

consequences.[8] Similarly, AT quality can vary at any given AT quantity, and recent investigations suggest that AT quality may contribute to metabolic health independently of quantity.[9]

AT quality can be measured by AT density on computed tomography (CT) scanning, where, in healthy persons, denser AT represents smaller, better quality adipocytes, and lower density represents larger, more lipid-engorged, poorer quality adipocytes.[10, 11] The clinical implications of differences in AT density have been suggested in general population observational cohorts such as the Framingham Heart Study, where lower VAT and SAT density were associated with lower adiponectin levels and greater cardiovascular disease risk.[9, 12] We have previously demonstrated that expected cross-sectional relationships between circulating immuno-metabolic biomarker profiles and SAT and VAT density are disrupted in men with HIV compared to men without HIV.[13] However, the effects of specific therapeutic interventions on AT density and other surrogate markers of AT function in PLWH are unknown.

Tesamorelin, a growth hormone-releasing hormone analogue, is approved for the treatment of central adiposity/lipohypertrophy in PLWH.[14] Indeed, compared to placebo, tesamorelin significantly decreases VAT and improves lipid profiles in PLWH over 26–52 weeks of treatment.[14–16] However, tesamorelin's effect(s) on AT density are unknown. Using data from two completed, randomized-controlled trials of tesamorelin for central adiposity in PLWH, we aimed to determine: 1) the effects of tesamorelin on VAT and SAT density over 26 weeks, and 2) baseline and 26-week relationships between SAT and VAT density and serum adipokine and inflammatory biomarker concentrations in PLWH. We hypothesized that, compared to placebo, tesamorelin therapy would be associated with increased AT density and improved biomarker profiles.

METHODS

Study population

This analysis used data from two randomized (2:1), Phase 3 trials of tesamorelin vs placebo for the treatment of abdominal fat accumulation in PLWH.[15, 16] Participant criteria were the same for both trials. Patients were adults (18–65 years old) living with HIV who had been on stable ART for at least 8 weeks and had evidence of central adiposity, defined as a waist circumference/waist-to-hip ratio ≥95 cm/0.94 for males and ≥94 cm/0.88 for females.[17] Participants were also required to have $CD4^+$ T lymphocyte count >100 cells/mm^3 and HIV-1 RNA <10,000 copies/mL. Patients were randomized 2:1 to receive a daily subcutaneous injection of tesamorelin 2mg or placebo. Therapeutic response to tesamorelin was defined as a VAT decrease ≥8%, which occurred in approximately 70% of tesamorelin-treated participants.[17] As previously published, responders were not significantly different from non-responders with respect to demographic, clinical, or immunological variables.[18] To better understand tesamorelin's potentially therapeutic effects, for this analysis we restricted inclusion to tesamorelin responders (i.e. those with a continued indication for therapy) and placebo-treated participants. Additionally, only data from the initial 26-week primary endpoint was used.

CT measurements

CT cross-sectional imaging can be used to estimate both AT quantity (area in cm^2) and quality (density in Hounsfield Units, HU).[2, 10, 17, 19] Study participants underwent single-slice, abdominal L4-L5 CT scanning at baseline and week 26 for assessment of VAT and SAT area.[15, 16] For this analysis, CT scans were re-analyzed for AT density by a single, blinded reader using a semi-automatic segmentation image analysis program (Exelis Visual Information Solutions, Boulder, CO). AT density was defined by CT attenuation of −190 to −30 HU, in which a more negative value represents lower density.[10] SAT was distinguished from VAT by tracing along the fascial plane of the internal abdominal wall.

Laboratory assessments

Biomarkers measured in the parent studies included: total cholesterol, HDL cholesterol, triglycerides, adiponectin, C-reactive protein (CRP), plasminogen activator inhibitor (PAI)-1 activity, tissue plasminogen activator (TPA) activity and insulin-like growth factor (IGF)-1. Insulin resistance was estimated using the homeostatic assessment model (HOMA-IR), defined as fasting plasma glucose (mg/dL) x fasting serum insulin (μlU/mL)/405.[20] Plasma lipid profiles were measured using standard methods at Quintiles Laboratories (Smyrna, GA and W. Lothian, Scotland, UK). Inflammatory markers were measured centrally at Gamma-Dynacare (Brampton, Ontario, Canada). Serum PAI-1 antigen and tPA antigen levels were measured from blood samples drawn in CTAD vacutainers (containing sodium citrate, theophylline, adenosine and dipyridamole) using ELISA kits (Biopool, Umea, Sweden). The intra-assay coefficient of variation (CV) for the PAI-1 antigen assay was 3.6–16.9%, and the inter-assay CV was 4.3–6.8%. The intra-assay CV for the tPA antigen assay was 7.8–9.5%, and the inter-assay CV was 4.6–9.7%. Plasma CRP was measured by nephelometry using a BNII analyzer (Siemens Diagnostics, Tarrytown, NY, USA) with a mean CV of 6.4%. Serum adiponectin levels were determined using an ELISA kit (B-Bridge International, Inc., Sunnyvale, CA, USA); intra-assay CV was 3.0–5.3%, and inter-assay CV was 6.3–7.6%. Serum IGF-1 was measured at Esoterix (Calabasas Hills, CA, USA).

Statistical analysis

Change in AT density from baseline to week 26 were compared between treatment arms using Wilcoxon matched-pairs signed-rank tests. Linear regression models were fit to compare the change in AT density between tesamorelin-responders and placebo-treated participants over the 26-week period. Spearman partial correlation coefficients were used to assess associations between changes in AT density and area, and changes in measured biomarkers. All statistical analyses were performed in Stata statistical software program (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC.).

RESULTS

Study population

Participants included 193 tesamorelin-responders and 148 placebo-treated participants. Participants were similar at baseline in characteristics including age, sex, race/ethnicity, use

of concomitant medications, BMI, $CD4^+$ T lymphocyte counts, time since HIV diagnosis and duration of ART therapy. Most participants had suppressed HIV-1 RNA at the baseline visit. Of the 39 in the responder arm and 35 in the placebo arm with detectable HIV-1 RNA, the median (interquartile range) values were 167 (52 – 1210) and 270 (81 – 591), respectively. The majority of participants were male and Caucasian (Table 1). Between the two treatment groups, mean (standard deviation, SD) waist circumference was similar (p=0.32). No between-group differences were observed between baseline mean SAT density (−94.1 [10.7] HU) in the tesamorelin and placebo arms (−95.3 [10.9] HU) (p=0.29). Baseline mean VAT density was also equivalent in the two arms (−91.2 [8.8] HU in the tesamorelin arm, −91.4 [8.9] HU in the placebo arm, p=0.80).

Changes in SAT and VAT density

Over the course of 26 weeks, mean SAT density increased significantly in the tesamorelin group (+4.0 [8.7] HU, within-group p<0.0001) compared to the placebo group (+0.3 [4.8] HU, within-group p=0.15), with a 3.7 (0.7) HU greater increase in the tesamorelin vs placebo arms (p<0.0001). When controlling for baseline SAT density, baseline SAT area, and change in SAT area, the effect of tesamorelin vs placebo on SAT density persisted (+3.5 HU, 95% CI [2.3, 4.7], p<0.001, Supplemental Figure 1) (Table 2).

Results were similar for VAT, with only tesamorelin-treated participants experiencing a significant increase in mean VAT density (tesamorelin: +6.2 [8.7] HU, p<0.0001; placebo: +0.3 [4.2] HU, p=0.18), with a 5.9 (0.7) HU greater increase in the tesamorelin vs placebo arm (p<0.0001). The effect in the tesamorelin arm was attenuated but remained significant after adjusting for baseline VAT density, baseline VAT area, and change in VAT area, (+2.3 HU, 95% CI [0.9, 3.7], p=0.001, Supplemental Figure 1) (Table 2).

Partial correlations between AT density and biomarker concentrations

At baseline, AT area and density significantly correlated with each other (VAT: −0.47, p<0.0001; SAT: −0.53 (p<0.001). After controlling for baseline VAT or SAT area, respectively, baseline VAT density correlated positively with tPA activity and HOMA-IR, whereas baseline SAT density correlated negatively with adiponectin concentrations and HOMA-IR (Table 3). Baseline VAT density also correlated negatively with total cholesterol after adjusting for baseline VAT area (Table 4). SAT density correlated negatively with HDL cholesterol after adjusting for baseline SAT area, with a trend observed for baseline SAT density and triglyceride concentrations.

Over 26 weeks, significant negative correlations were observed between changes AT density and area, suggesting higher density at lower quantities of AT (VAT: r=−0.44, p<0.001; SAT: r=−0.24, p<0.001). Changes in adiponectin and IGF-1 concentrations positively correlated with changes in both VAT and SAT densities (adjusted for changes in VAT and SAT area, respectively) (Table 3). Changes in VAT and SAT density correlated negatively with changes in total cholesterol and triglyceride concentrations after adjusting for changes in VAT and SAT area, respectively (Table 4).

DISCUSSION

Our chief aim was to determine the effect of tesamorelin on CT-quantified VAT and SAT density, a validated measure of AT quality. Our results indicate that tesamorelin significantly increases AT density in PLWH on ART who experienced clinically significant VAT reductions on tesamorelin (responders) compared to placebo. The effects of tesamorelin on VAT and SAT density were maintained after adjusting for baseline AT density, baseline AT area, and changes in AT area. As such, tesamorelin may independently improve VAT and SAT function in tesamorelin responders, a hypothesis supported by our observations that increases in VAT and SAT density are associated with: 1) decreases in VAT and SAT area; 2) increases in circulating adiponectin concentrations, and 3) improved total cholesterol and triglyceride concentrations. Thus, in addition to reducing VAT area, tesamorelin may be a novel therapeutic intervention to improve VAT and SAT function in PLWH.

To this end, we observed that greater increases in fat density were associated with greater increases in adiponectin over 26 weeks. Adiponectin is secreted by AT and plays a significant role in modulation of insulin sensitivity.[27] Adiponectin levels are traditionally suppressed with VAT accumulation, leading to insulin resistance, systemic inflammation and vascular dysfunction;[21, 27–30] indeed, high levels have been found to be independently associated with a lower risk of acute coronary syndrome.[21, 27–30] In the Multicenter AIDS Cohort Study, men living with HIV had lower levels of adiponectin independent of AT area, [31] corroborating prior data suggesting an HIV-specific effect on suppression of adiponectin secretion/AT function.[32]

We postulate that tesamorelin may have a unique role in improving AT function and modulating cardiometabolic risk in PLWH, independent of traditional obesity paradigms. Indeed, the combined benefit of reduced VAT quantity and improved VAT and SAT quality could have significant ramifications for PLWH, in whom AT dysfunction, AT redistribution and obesity are prevalent.[3, 4] The potentially deleterious metabolic effects of excess VAT and SAT quantity are well-defined,[6] yet relationships between AT quality and metabolic disease are either just beginning to be understood[21, 22] or are currently extrapolated from the obesity literature, where adipocyte lipid engorgement leads to a pro-inflammatory state with tissue hypoxia, mitochondrial exhaustion, immune cell activation and infiltration, and disruption of lipid and glucose metabolism.[23] Additionally, while baseline relationships between AT density and immuno-metabolic parameters can be confounded by heterogeneity of participant characteristics, including body mass index and history of exposure HIV medications with known lipotoxicity, this study aimed to assess the effects of tesamorelin therapy on AT density, in which a clear treatment effect was observed.

Our results demonstrated benefits on both VAT and SAT quality (density) independent of changes in AT quantity, with associated improvements in circulating adiponectin, total cholesterol and triglyceride concentrations, supporting the hypothesis that tesamorelin therapy could improve AT function. Although we did not demonstrate a significant correlation between improvements in VAT or SAT density and HOMA-IR in this analysis, insulin resistance in PWLH is multi-factorial,[24] and in studies of both PLWH and persons with diabetes, tesamorelin therapy has had a neutral effect on parameters of insulin glucose

homeostasis.[25, 26] As such, the lack of such a correlation in this analysis does not dampen our enthusiasm for our primary findings.

This analysis has several limitations. First, it is limited by the predominately Caucasian and male patient demographic enrolled into the parent clinical trials; consequently, our results may not be generalizable to women or persons of color. Second, for this post-hoc analysis, we limited our analysis to participants who were either placebo-treated or tesamorelin-responders (70%). As we did not evaluate those persons who received tesamorelin but failed to exhibit an adequate VAT response, we were not able to assess whether tesamorelin also has effects on AT density in persons without VAT reductions on tesamorelin. However, future analyses of completed or ongoing trials of tesamorelin may be able to fill these gaps. Additionally, we were able to demonstrate additional potential benefits of tesamorelin for those who experience reductions in VAT quantity/who would continue to receive tesamorelin in clinical practice, providing more practical and clinically relevant results. Despite these limitations, the randomized nature of the initial registrational trials and the large sample size strengthen our results. Finally, our analysis employed CT scanning, a readily available, non-invasive, accurate and precise tool for assessment of AT quantity and quality.

Conclusions

Tesamorelin increases VAT and SAT density in adult PLWH with central adiposity independent of changes in fat quantity. These increases in AT density correlated with increases in circulating adiponectin concentrations and improved lipid profiles. Tesamorelin may be an effective intervention for improving VAT and SAT function in PLWH.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1:

Baseline Demographic and Clinical Characteristics.

Characteristics	Tesamorelin (N = 193)	Placebo (N = 148)	P Value
Age (years)	47.8 (7.3)	48 (7.6)	0.79
Male (%)	89.1	83.8	0.15
Race (%)			0.10
White	86.0	78.4	
Black or African American	9.3	11.5	
Others	4.7	10.1	
Use of lipid lowering treatment (%)	52.8	43.9	0.10
Use of testosterone (%)	24.9	17.6	0.10
Body mass index (kg/m^2)	28.9 (4.2)	28.6 (4.3)	0.60
Waist circumference (cm)	105.1 (9.6)	104.1 (8.2)	0.32
CD4$^+$ T cell count (cells/μL)	563.0 (400.0–774.0)	560.0 (416.0–785.0)	0.72
Time since HIV diagnosis (months)	178.4 (122.6–217.9)	155.9 (115.7–205.3)	0.06
ART duration (months)	49.5 (29.2–82.2)	48.2 (28.3–73.4)	0.28
ART type			0.65
NNRTI + NRTI	32%	35%	
NNRTI + PI _ NRTI	7%	9%	
PI + NRTI	48%	48%	
NRTI only	6%	4%	
Other	7%	4%	
VAT area (cm^2)	197.0 (86.2)	188.7 (84.8)	0.38
VAT density (HU)	−91.2 (8.8)	−91.4 (8.9)	0.80
SAT area (cm^2)	217.6 (119.3)	228.6 (122.3)	0.41
SAT density (HU)	−94.1 (10.7)	−95.3 (10.9)	0.29

Data are presented as mean (SD) or median (IQR) for continuous measures, and % for categorical measures. ART=antiretroviral therapy, NNRTI=non-nucleoside reverse transcriptase inhibitor, NRTI=nucleoside reverse transcriptase inhibitor, PI=protease inhibitor, VAT=visceral adipose tissue, SAT=subcutaneous adipose tissue, HU=Hounsfield Units

Table 2:

AT Density (HU) by Randomization Arm.

	Tesamorelin Responders (N=193)	Placebo (N=148)	P value
Baseline *			
VAT density	−91.2 (8.8)	−91.4 (8.9)	0.80
SAT density	−94.1 (10.7)	−95.3 (10.9)	0.29
26-week change *			
VAT density	6.2 (8.7)	0.3 (4.2)	<0.001
SAT density	4.0 (8.7)	0.3 (4.8)	<0.001
	Difference in 26-week change between Tesamorelin vs Placebo		
Unadjusted 26-week change ⌘	Estimated Slope	95%CI	p-value
VAT density (95% CI)	5.9	(4.5, 7.3)	<0.001
SAT density (95% CI)	3.7	(2.3, 5.2)	<0.001
Adjusted 26-week change **⌘			
VAT density (95% CI)	2.3	(0.9, 3.7)	0.001
SAT density (95% CI)	3.5	(2.3, 4.7)	<0.001

* mean (standard deviation)

** adjusted for baseline AT density, baseline AT area and change in AT area

⌘ HU effect size estimate and 95% confidence interval

AT=adipose tissue, VAT=visceral adipose tissue, SAT=subcutaneous adipose tissue, HU=Hounsfield Units

Table 3:

Partial* Correlations Between AT Density and Biomarker Concentrations.

	VAT HU	P value	SAT HU	P value
Baseline*				
Adiponectin (μg/mL)	0.11	0.14	−0.21	0.007
CRP (mg/L)	−0.10	0.22	0.03	0.72
PAI-1 Activity (IU/mL)	−0.02	0.81	0.10	0.23
TPA Activity (IU/mL)	0.17	0.03	−0.10	0.20
HOMA-IR	0.12	0.02	0.21	<0.001
IGF-1 (ng/mL)	−0.05	0.31	−0.04	0.41
	Change in VAT HU	**P value**	**Change in SAT HU**	**P value**
26-week change**				
Adiponectin (μg/mL)	0.19	0.02	0.18	0.02
CRP (mg/L)	0.04	0.57	0.11	0.15
PAI-1 Activity (IU/mL)	−0.05	0.50	−0.02	0.83
TPA Activity (IU/mL)	0.06	0.42	0.03	0.69
HOMA-IR	−0.02	0.73	0.02	0.69
IGF-1 (ng/mL)	0.09	0.08	0.14	0.01

*Adjusted for baseline AT area

**Adjusted for change in AT area

CRP=C-reactive protein, PAI-1=plasminogen activator inhibitor, IU=international units, TPA=tissue plasminogen activator, HOMA-IR=homeostatic assessment model assessment of insulin resistance, IGF-1=insulin-like growth factor-1, VAT=visceral adipose tissue, SAT=subcutaneous adipose tissue, HU=Hounsfield Units

Table 4:

Partial Correlations Between AT Density and Lipid Concentrations (mmol/L).

	VAT HU	P value	SAT HU	P value
Baseline*				
Total cholesterol	−0.15	0.005	−0.06	0.28
HDL	−0.06	0.25	−0.23	<0.001
Triglycerides	−0.03	0.56	0.10	0.06
TC:HDL	0.01	0.84	0.18	0.001
26-week change**	**Change in VAT HU**	**P value**	**Change in SAT HU**	**P value**
Total cholesterol	−0.06	0.22	−0.14	0.009
HDL	0.03	0.54	0.02	0.73
Triglycerides	−0.04	0.44	−0.09	0.09
TC:HDL	−0.04	0.43	−0.09	0.09

*Adjusted for baseline AT area

**Adjusted for change in AT area

AT=adipose tissue, VAT=visceral adipose tissue, SAT=subcutaneous adipose tissue, HU=Hounsfield Units, HDL=high-density lipoprotein, TC:HDL=total cholesterol to high-density lipoprotein ratio