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Investigating the Effects of Metabolic Dysregulation on Hair Follicles: A Comparison of HIV-Infected Women With and Without Central Lipohypertrophy

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Abstract

Background—Normal lipid metabolism and functioning of the peroxisome proliferator activated receptor gamma (PPAR-gamma) in the sebaceous gland is critical to maintaining a normal hair follicle. Human immunodeficiency virus (HIV) infection affects lipid metabolism; some have hypothesized a link between PPAR-gamma function and lipodystrophy in HIV infection. Our objective was to determine whether lipodystrophy is associated with altered hair characteristics in HIV-infected women from the Women's Interagency HIV Study (WIHS).

Methods—Hair characteristics and scalp inflammation were assessed by an interviewer-administered questionnaire. Central lipohypertrophy and peripheral lipoatrophy was defined by self report of moderate to severe fat gain in central body sites and fat loss in peripheral body sites, respectively confirmed by clinical examination. Additional covariates considered in the analyses included demographics, behavioral characteristics, medical history, and HIV-related factors.

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Conflict of interest statement: None reported

Results—There were 1037 women with data on all study variables. 76 women reported central lipohypertrophy; only 4 women reported lipoatrophy. Women with central lipohypertrophy were more likely to be older, have a self-reported history of injection drug use, statin medication use, diabetes, elevated cholesterol, and have self-reported less hair and shorter eyelashes. After adjustment for age, central lipohypertrophy was associated with shorter eyelashes (OR 2.3; 95% CI 1.4-3.8).

Conclusions—Central lipohypertrophy was not associated with change in scalp hair texture or scalp inflammation in this cohort. Rather, we found an association between central lipohypertrophy and shorter eyelash length. This finding may be explained by an influence of prostaglandin E2 mediators on eyelash follicles.

Keywords

eyelash; hair; HIV

Introduction

Hair loss in women is a cause of significant psychological distress and concern, and when it occurs in the context of an acute or chronic illness, including human immune virus (HIV) infection, the detrimental impact may be even greater.(1) Since the rapidly dividing cells of hair follicles are influenced by a number of local and systemic factors, hair changes can be a herald of underlying illness or dysregulated immune, hormonal, or metabolic functions.(2) In a large United States cohort of HIV-infected and uninfected women we previously found that hair changes, such as diffuse hair loss and increased shedding, were associated with older age but not HIV status.(3) In this current study, we conducted a follow-up questionnaire asking about hair and scalp changes only in the HIV-infected cohort.

Recent research suggests that various lipid metabolic and inflammatory pathways are involved in regulating hair growth. Specifically, the prostaglandin F2 alpha (PGF-2alpha) analog latanoprost has been FDA approved for enhanced growth of eyelashes.(4-6) Further elucidation of the prostaglandin pathway in balding men has shown that prostaglandin D2 (PGD-2) acts as an inhibitory or counterbalancing effect to PGF-2alpha on the hair follicle.(7) Intermediates of cholesterol biosynthesis can also affect the hair follicle in both animal models and in human hair follicles by inhibiting growth.(8, 9) Both the prostaglandin and cholesterol pathways are likely modulated by the peroxisome proliferator activated receptor gamma (PPAR-gamma) which may act as a master regulator in the sebaceous gland to maintain a homeostatic environment and promote normal hair growth.(10, 11) PPAR-gammas are ligand-activated transcription factors that regulate the expression of target genes involved in many cellular functions including cell proliferation, differentiation and immune/inflammation response.(12) Dysregulation of PPAR-gamma in adipocytes has been linked to the pathogenesis of HIV-associated lipodystrophy.(13, 14) Agonists of PPAR-gamma have been used to treat HIV lipodystrophy.(15)

The aim of our study was to determine whether HIV-infected women who had moderate to severe lipodystrophy reported altered hair growth characteristics compared to HIV-infected women without lipodystrophy.

Materials and Methods

Study population

The Women's Interagency HIV Study WIHS includes 2,791 HIV-infected women and 975 HIV-uninfected women. Detailed descriptions of recruitment, retention, and data and collection methods have been reported previously.(16-19) In brief, twice yearly evaluations include demographic information, medical and behavioral histories, physical examinations, and laboratory evaluations. Study protocols were reviewed and approved by the institutional review boards, and written informed consent was obtained from the participants.

Hair questionnaire

During the WIHS visit 29 (October 1 2008 through March 31 2009) questions assessing current hair density, change in hair characteristics, eyebrow and eyelash length, hair grooming practices, and signs and symptoms of scalp inflammation were interviewer-administered to all HIV-infected women. For example, women were asked: "How much hair do you have now as compared to when you were 15 years old: more, same, or less?"

Study variables

The dependent variables in these analyses were hair changes as reported on the hair questionnaire. The primary independent variable was moderate or severe body fat changes, determined by a combination of participant self-report and visual assessment by a clinician as compared to the prior assessment. Women with peripheral fat loss (decreases in arm, leg, buttocks, or cheeks) were defined as having peripheral lipoatrophy and those with central fat accumulation (increases in neck, upper back, abdomen, breasts, or waist) were defined as having central lipohypertrophy.

Other independent variables included in the analyses were age, race, education, cigarette smoking, history of injection drug use and diabetes, high cholesterol, use of PPAR-gamma agonists and statins, and HIV-related factors (HAART use, current CD4 cell count, and HIV RNA). We categorized reported HIV medications according to the guidelines published by the DHHS at the time of the study visit.(20)

Analytic methods

Contingency table analyses were performed to compare the distribution of participant characteristics by central lipohypertrophy and *P* values were based on Chi-square or Fisher exact tests. The hair change variables that were significant in bivariate analyses were then used as the dependent variables in backward stepwise logistic regression models. The independent variables that were retained at the $P \leq 0.1$ level in these models were then analyzed in a non-step model, until all predictors has a p-value of <0.1, and the results reported. Statistical analyses were performed using SAS® software version 9.2.(21)

Results

A total of 1232 HIV-infected women completed the questionnaire assessing hair and scalp characteristics. After excluding women with a recent history (<6 months) of chemotherapy,

pregnancy, childbirth, and current breast feeding, there were 1055 women with self-report and examination data on fat change and 1037 women with data on all study variables. Four women had moderate or severe peripheral lipoatrophy, 72 women had moderate or severe central lipohypertrophy, and four had both. Because of the small number of participants with only peripheral lipoatrophy (N=4), we did not analyze peripheral lipoatrophy as a separate covariate. Participant characteristics by presence of central lipohypertrophy are shown in Table 1. Women with central lipohypertrophy were more likely to be older, have a self-reported history of injection drug use, statin medication use, diabetes, elevated cholesterol, and have self-reported less hair and shorter eyelashes.

In multivariable logistic regression analysis, increasing age was associated with significantly increased odds of less hair (OR=1.22 per 10 year increase; 95%CI 1.06-1.41) and central lipohypertrophy was associated with marginally increased odds of less hair (OR=1.61; 95% CI 0.98-2.65) (Table 2, column 2). In multivariable logistic regression analysis for self-report of shorter eyelashes, both older age (OR 1.36; 95%CI 1.15-1.61) and central lipohypertrophy (OR 2.27; 95% CI 1.38-3.75) were significant (Table 2, column 3).

Discussion

In our cohort of HIV-infected women, we did not find an association of central lipohypertrophy with either change in scalp hair texture or increased inflammatory scalp symptoms. Interestingly, we found a greater than 2-fold higher association of reported shorter eyelash length (as opposed to no change or longer eyelash length) with central lipohypertrophy.

Our finding that inflammatory alopecias and inflammatory symptoms were not increased in the HIV-infected women with central lipohypertrophy, as compared to HIV-infected patients without central lipohypertrophy, was somewhat unexpected. The sebaceous gland, an appendage which is associated with every hair follicle, has been noted to play an integral role in maintaining the normal physiology of the hair follicle, and folliculo-sebaceous unit has emerged as a more appropriate term when referring to this functional unit.(10) PPAR-gamma is a key regulator of a number of cellular functions that occur in this appendage, with the most dominant feature being lipid production. Maternal PPAR-gamma-deficient milk in mice has been shown to cause hair loss in nursing neonates.(22) Loss of PPAR-gamma function in the human sebaceous gland is known to initiate pro-inflammatory pathways and lead to inflammatory alopecias.(11, 22) Microarray analysis of patients with one type of inflammatory scarring alopecia, lichen planopilaris, show down regulation of PPAR-gamma related pathways.(11) A patient with lichen planopilaris who was treated with pioglitazone showed improvement in clinical and histologic abnormalities.(23) Patients with peripheral insulin resistance syndromes (including polycystic ovary syndrome) who have central lipohypertrophy have been reported to have decreased scalp hair and increased facial hair.(24) In women with polycystic ovary syndrome and hirsutism, PPAR-gamma agonists have been used as treatment.(12)

Although we did not measure PPAR gamma directly, the patients with lipohypertrophy had an increased frequency of metabolic dysfunction evidenced by a higher frequency of self-

reported diabetes, and elevated cholesterol. Use of PPAR-gamma agonist medications were not prevalent in this cohort and did not differ between the women with and without lipohypertrophy. Despite metabolic dysfunction in the peripheral adipocytes, it is conceivable that HIV-infected women with lipohypertrophy had levels of PPAR-gamma that were functionally adequate in the folliculo-sebaceous unit. Another consideration is that a significant number of the HIV-infected with lipohypertrophy were taking a statin medication. Alteration of the cholesterol pathway could also have influenced the functionality of PPAR-gamma, leading to a metabolic environment conducive to hair growth. Lastly, it is known that polymorphisms in PPAR-gamma may account for a subset of HIV-infected patients developing lipodystrophy.(25) It is possible that these polymorphisms may somehow protect from hair loss when expressed in the sebaceous glands.

HIV infection has been associated with trichomegaly (unusually long eyelashes) in several published studies.(3, 26-29) However, it is unclear as to whether the presence of the virus itself, chronic illness, or other inflammatory or local mediators lead to lengthening of eyelashes. The prostaglandin pathway has recently been shown to influence hair growth both positively and negatively.(7) Bimatoprost, an analog of PGF2a, is a known mediator of eyelash growth.(4-6, 30) Stimulation of PGE2 in the hair follicle has been proposed as the mechanism by which minoxidil leads to scalp hair growth. Furthermore, PCR analysis of plucked follicles show that most hair cell types produce PGE2 and/or PGF2a.(31) Interestingly, PGE2 levels have been found to be higher in the setting of HIV infection/ AIDS due to excess production by macrophages.(32, 33) Thus elevated PGE2 levels in HIV infection may be an important factor in HIV-induced trichomegaly. Our findings of an association between central lipohypertrophy and shorter eyelashes may be due to a shortening or normalization in eyelash length after treatment associated normalization of health.

Of interest is the possibility that systemic metabolic dysfunction could result in shorter hair in a very focal region, the eyelashes. The reasons for this include the possibility that hair follicles have differential expression and response patterns depending on anatomic location. It is known that follicles of the scalp and body (beard, chest) respond differently to androgens and to other hormones.(34) Even different regions of the scalp behave variably; in hereditary thinning, hair on the top of the scalp is affected, but hair along the temporal and occipital fringe is spared.(35) This illustrates the tissue-specific and location-specific variability that hormonal signals can have on the hair follicle. In addition to hormonal signals, the hair follicle is regulated by a number of other highly orchestrated local and systemic factors.(36) Although the signals influencing eyelash growth have not been extensively studied, it is likely that eyelash follicles have unique characteristics compared to follicles elsewhere.

A potential limitation of our study is that we relied on self-reported hair and scalp changes and not all potential causes leading to hair loss were evaluated. Some of these reported changes may have been due to aging rather than HIV infection or ART. We also used a self-reported measure to determine fat changes; however these were corroborated by a clinical visual inspection. Prior studies of HIV-infected women using objective measures of regional

fat have shown that lipoatrophy is the predominant pattern of fat change in women.(37-40) In this study, the majority of women with fat changes had central fat gain, which may have been a result of normal aging and not an alteration in fatty metabolism with underlying PPAR dysfunction. Nonetheless, our findings are important as they may inform future studies in both HIV-infected and HIV-uninfected women regarding a possible link between central obesity and hair disorders. Assessing how prostaglandins might mediate HIV-related changes is also a topic to be investigated.

In summary, our study did not find an association of central lipohypertrophy with change in scalp hair texture or scalp inflammation in HIV-infected women. We did, however, observe a significant association of central lipohypertrophy with shorter eyelash length which suggests a different mechanism of action than PPAR-gamma and may point to a specific influence of prostaglandin E2 mediators on eyelash follicles.

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Table 1

Participant characteristics by central lipohypertrophy among 1055 HIV-infected women in the WIHS.

	Central lipohypertrophy		
	No	**Yes**	**P-value**
Age, years			
<=35	110 (11%)	3 (4%)	
35-44	375 (38%)	22 (29%)	0.02 *
45-54	372 (38%)	36 (47%)	
>=55	122 (12%)	15 (20%)	
Race			
Non-Hispanic White	117 (12%)	13 (17%)	0.27 **
Hispanic White	128 (13%)	9 (12%)	
African American	557 (57%)	36 (47%)	
Other	177 (18%)	18 (24%)	
Educational Attainment			
<7 years	72 (7%)	5 (7%)	0.78 *
7-11 years	296 (30%)	23 (30%)	
High School	269 (28%)	21 (28%)	
Some College	265 (27%)	24 (32%)	
≥ 4 years college	76 (8%)	3 (4%)	
Smoking Status			
No	634 (65%)	49 (64%)	0.96 **
Yes	345 (35%)	27 (36%)	
Injection Drug Use			
No	766 (78%)	43 (57%)	<0.001 **
Yes	213 (22%)	33 (43%)	
Elevated cholesterol			
No	847(81%)	122(12%)	0.0052**
Yes	57(5%)	18(2%)	
Diabetes			
No	893(85%)	81(8%)	<0.001**
Yes	58(6%)	16(2%)	
Use of PPAR-gamma agonist			
No	965(91%)	14(1%)	0.22*
Yes	74(7%)	2(.2%)	
Statin Use			

	Central lipohypertrophy		
	No	**Yes**	**P-value**
No	891(84%)	88(8%)	0.0024**
Yes	61(6%)	15(1%)	
CD4 cell count			
<200	102 (11%)	8 (11%)	
200-499	374 (39%)	27 (36%)	0.88 **
>500	487 (51%)	40 (53%)	
HIV RNA copies			
<81	551 (58%)	51 (69%)	
81-999	150 (16%)	12 (16%)	0.11 *
1000-9999	104 (11%)	7 (9%)	
>9999	139 (15%)	4 (5%)	
Antiretroviral Therapy			
None	241 (25%)	17 (22%)	0.31 *
Mono/ Combination	10 (1%)	2 (3%)	
HAART	728 (74%)	57 (75%)	
Less Hair			
No	440 (46%)	25 (33%)	0.03 **
Yes	521 (54%)	51 (67%)	
Shorter Eyelashes			
No	744 (79%)	43 (60%)	0.0002 **
Yes	201 (21%)	29 (40%)	
Change in Hair Texture			
No	603 (63%)	43 (57%)	0.28 **
Yes	357 (37%)	33 (43%)	
Scalp Inflammation			
No	625 (66%)	48 (63%)	0.65 **
Yes	326 (34%)	28 (37%)	

* Fisher's exact test of significance.

** Chi-square test of significance.

Table 2

Adjusted logistic regression for self-report of less hair and shorter eyelashes among 1037 HIV-infected women in the WIHS.

Variable	Adjusted Odds Ratio for Less Hair (95% CI)	Adjusted Odds Ratio for Shorter Eyelashes(95% CI)
Age (per 10 years)	1.22 (1.06-1.41)	1.36 (1.15-1.61)
Central lipohypertrophy	1.61 (0.98-2.65)	2.27 (1.38-3.75)