Vertex balding, plasma insulin-like growth factor 1, and insulin-like growth factor binding protein 3

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Background: A recent report suggested that men with vertex balding have higher levels of plasma insulin-like growth factor 1 (IGF-1). The association of its major carrier protein, insulin-like growth factor binding protein 3 (IGFBP-3), with male pattern hair loss has not been examined.

Objective: We evaluated the relations of plasma concentrations of IGF-1 and IGFBP-3 with vertex balding in middle-aged and elderly men.

Methods: Participants were 431 male members of the Health Professionals Follow-up Study who responded to a question in 1992 on their hair pattern at 45 years of age and who were 47 to 81 years old when they provided a blood specimen in 1993-1994. Odds ratios (ORs) of vertex balding associated with IGF-1 and IGFBP-3 were estimated from logistic regression models mutually adjusting for each other and controlling for age at blood draw.

Results: Of the 431 men, 128 had vertex balding at age 45. Compared with men who were not balding, for a 1 standard deviation increase in plasma IGF-1 level (72.4 ng/mL), the OR for vertex balding was 1.31 (95% CI, 0.95-1.81). For a 1 standard deviation increase in plasma IGFBP-3 (957 ng/mL), the OR for vertex balding was 0.62 (95% CI, 0.44-0.88).

Conclusion: Older men with vertex balding have lower circulating levels of IGFBP-3 and higher levels of IGF-1 when controlling for IGFBP-3 level.

Male scalp hair pattern in adulthood has long been known to be influenced by androgens.[1] However, other factors have been explored recently for a role in mediating the transition of the hair follicle through its cycle of growth, senescence, and regeneration. Signorello et al[2] evaluated the relation of serum insulin-like growth factor 1 (IGF-1) and male pattern balding in a case-control study among 51 Greek men older than 65 years and found that men with vertex balding had higher circulating levels of IGF-1 than men without vertex balding. Per 59 ng/mL increase in IGF-1, the relative risk of vertex balding was 1.6 (95% confidence interval [CI], 0.9-3.2) after adjusting for age and 2.0 (95% CI, 1.0-4.6) after also adjusting for steroid hormone concentrations. Serum insulin-like growth factor binding protein 3 (IGFBP-3), the major carrier protein for IGF-1, was not measured in the Greek study. Thus we sought to confirm their finding of higher circulating IGF-1 levels in men with vertex balding and to evaluate whether higher IGFBP-3 level, which reduces IGF-1 bioavailability, is associated with a reduced risk of vertex balding among middle-aged and elderly men.

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MATERIAL AND METHODS

Participants for this analysis were selected from among members of the Health Professionals Follow-up Study, an ongoing prospective cohort study of 51,529 male dentists, veterinarians, pharmacists, optometrists, osteopathic physicians, and podia-

trists, 40 to 75 years old at enrollment in 1986. At baseline the men completed a dietary questionnaire and provided information on demographics, lifestyle factors, and medical history. The men receive questionnaires every 2 years. On the 1992 self-administered questionnaire, the men reported their hair pattern at age 45 using 5 crown-view pictograms based on Norwood's classification of male-pattern baldness[3] and as shown in Olsen et al.[4] Depicted were no to minimal hair loss (Norwood's I), receding hairline only (III), modest vertex balding (IV), moderate vertex balding (V), and substantial vertex balding (VII).

In the period 1993-1995 approximately 18,000 of the men provided a blood specimen. After receipt by overnight courier, the blood, which was collected in tubes containing sodium EDTA and chilled during transport, was centrifuged, aliquoted into plasma, erythrocytes, and buffy coat, and stored in liquid nitrogen freezers. We included men who answered the question on hair pattern and who served as controls in analyses of plasma growth factors in relation to prostate cancer and benign prostatic hyperplasia or who were participants in a study of the change in plasma growth factor levels over a period of a few years. Men who reported a diagnosis of cancer (except nonmelanoma skin cancer) at or before the time of blood draw were excluded.

IGF-1 and IGFBP-3 concentrations were determined by enzyme-linked immunosorbent assay (ELISA) (Diagnostic Systems Laboratory Inc, Webster, Tex) in the laboratory of Dr Pollak. IGF-1 and IGFBP-3 were measured twice, the mean of which was used in the analysis. For the 3 separate analytical runs, mean intrapair coefficients of variation for quality control samples were 2.6%, 6.7%, and 13.2% for IGF-1 and 3.5%, 6.7%, and 11.6% for IGFBP-3.

In the statistical analysis, men with any vertex balding were compared with men with no to minimal hair loss or receding hairline only. To evaluate differences in plasma IGF-1 and IGFBP-3 concentrations between men with and without vertex balding, the t test was used.[5] Because plasma IGF-1 and IGFBP-3 are strongly correlated, we adjusted IGF-1 and IGFBP-3 levels for each other using residuals analysis.[6] The residuals method consisted of regressing IGF-1 on IGFBP-3 concentrations using linear regression, obtaining the residuals, and recentering the residuals at the value for IGF-1 for the mean IGFBP-3 concentration among the men. We used logistic regression to estimate odds ratios (ORs) and 95% CIs for the association of IGF-1 and IGFBP-3 with vertex balding, adjusting for age at blood draw (continuous).[7] IGF-1 and IGFBP-3 levels were entered into the model as continuous terms or in tertiles. We assessed the presence of confounding by cigarette smoking (cumulative in 10 pack-year increments), race (African American [9.5% of men], Asian [12.3%], other heritage [3.5%], white), and ever having a diagnosis of diabetes mellitus (yes, 4.4% of men) by the time of blood draw by entering terms for each of these into the logistic regression model along with the terms for IGF-1 and IGFBP-3.

To evaluate whether the associations between plasma IGF-1 and IGFBP-3 levels and balding vary by age or cumulative smoking, we ran separate logistic regression models among men who were younger than the median age (<64.75 years) or who were the median age or older, and separately for those who ever smoked or who never smoked. We assessed whether any differences in these associations were present by entering the cross-product terms for age at blood draw (continuous) or cumulative smoking (continuous) and IGF-1 and IGFBP-3 levels (continuous) along with the main effects terms into a logistic regression model. We evaluated the statistical significance of the estimates for the cross-product terms using the Wald test.[7] To assess whether the associations for IGF-1 and IGFBP-3 and balding varied by racial group, we fit 3 models, one with the two main effect terms for IGF-1 (continuous) and IGFBP-3 (continuous), one with the cross-product terms for each race and IGF (continuous) along with the main effect term for IGFBP-3 (continuous), and the remaining one with the cross-product terms for each race and IGFBP-3 (continuous) along with the main effect term for IGF-1 (continuous). We tested the difference in fit between the main effect model and the two models with the cross-product terms using the likelihood ratio test.[7] All analyses were conducted using SAS software version 6.12 (SAS Institute, Cary, NC).

RESULTS

Among the 431 men who were 47 to 81 years old when they provided blood, 128 reported that at age 45 they had modest to substantial vertex balding. Between the similarly aged men with and without vertex balding, there was no statistically significant difference in plasma IGF-1 concentration (Table I). However, men with vertex balding had lower circulating levels of IGFBP-3 ($P = .02$). Because IGF-1 and IGFBP-3 are strongly correlated (Pearson correlation coefficient: $r = 0.72$, $P < .0001$), we determined whether there is a difference in IGF-1 levels adjusting for IGFBP-3 levels using the residuals method and vice versa. Men with vertex balding were more likely to have higher circulating IGF-1 for a given IGFBP-3 level ($P = .11$) and lower circulating IGFBP-3 for a given IGF-1 level ($P = .002$) than men without vertex balding (Table I).

Table I. Plasma concentrations of IGF-1 and IGFBP-3 according to vertex balding* at age 45: Health Professionals Follow-up Study 1994

Plasma constituent	Vertex balding	Not vertex balding	*P* value†
No. of men	128	303	
Age at blood draw in 1994 (y)	64.7 ± 8.3	63.8 ± 8.2	.3
Unadjusted			
IGF-1 (ng/mL)	185.0 ± 71.4	190.2 ± 72.4	.5
IGFBP-3 (ng/mL)	3049 ± 871	3285 ± 957	.02
Mutually adjusted‡			
IGF-1 (ng/mL)	194.4 ± 44.4	186.2 ± 50.3	.11
IGFBP-3 (ng/mL)	3084 ± 536	3270 ± 664	.002

Data are presented as mean ± standard deviation.
*Modest, moderate, or substantial vertex balding as self-reported using pictograms in 1992.
†For comparison using the *t* test.
‡By residuals analysis.

Table II. Relation of vertex balding* with plasma IGF-1 and IGFBP-3: Health Professionals Follow-up Study 1994

	Tertile†					
	1	2	3	Unit‡	OR§	*P* value§
IGF-1‖						
Cases/controls	47/102	35/102	46/99			
Median (ng/mL)	123.1	181.9	251.2	72.4		
OR	1.00	1.00	1.86		1.31	.09
95% CI	Referent	0.56-1.78	0.93-3.70		0.95-1.81	
IGFBP-3‖						
Cases/controls	53/101	43/101	32/101			
Median (ng/mL)	2429	3195	4149	957		
OR	1.00	0.69	0.42		0.62	.008
95% CI	Referent	0.39-1.22	0.21-0.86		0.44-0.88	

*Modest, moderate, or substantial vertex balding as self-reported using pictograms in 1992 versus no or little hair loss or receding hairline only.
†ORs from a logistic regression model with plasma level entered as two indicator variables and adjusted for age at blood draw (continuous). Tertile cut points for plasma levels of each factor were determined from the distribution of levels among the controls.
‡One standard deviation.
§From a logistic regression model with plasma level entered as a continuous term and adjusted for age at blood draw (continuous).
‖Mutually adjusted.

Because IGFBP-3 influences the bioavailability of IGF-1, we mutually adjusted for these two plasma levels and controlled for age at blood draw. Compared with men in the bottom tertile of IGF-1, the OR for vertex balding in the top tertile of IGF-1 was 1.86 (95% CI, 0.93-3.70) (Table II). Men in the top tertile of IGFBP-3 had a statistically significantly 58% lower risk of vertex balding than men in the bottom tertile. For a 1 standard deviation increase in IGF-1 of 72.4 ng/mL, the OR for vertex balding was 1.31 (95% CI, 0.95-1.81; $P = .09$). For a 957 ng/mL increase in IGFBP-3, the OR for vertex balding was 0.62 (95% CI, 0.44-0.88; $P = .008$) (Table II). These results were essentially unchanged when we excluded from the referent group 97 men who reported receding hairline only (IGF-1: OR = 1.26, 95% CI [0.90-1.77]; IGFBP-3: OR = 0.61, 95% CI [0.42-0.89]). There was no evidence that the risk of balding associated with IGF-1 or IGFBP-3 was stronger with increasing extent of vertex balding at age 45 in an analysis limited only to men with vertex balding.

Because smoking may influence the IGF axis, we controlled for cumulative smoking (in 10 pack-year increments). The OR for vertex balding modestly increased to 1.02 (95% CI, 0.57-1.84) and 2.00 (95% CI, 0.99-4.04) for the middle and top tertiles of IGF-1 and decreased to 0.66 (95% CI, 0.37-1.18) and 0.40 (95% CI, 0.19-0.84) for the middle and top tertiles of

IGFBP-3. Although there appears to be racial variation in the IGF axis in this cohort, race did not confound the relation between vertex balding and IGF-1 (OR for tertile 2: 0.98, tertile 3: 1.82) and IGFBP-3 (OR for tertile 2: 0.69, tertile 3: 0.45). Ever having a diagnosis of diabetes mellitus by the time of blood draw, which was reported by 4.4% of the men, also did not confound this relation (IGF-1, OR for tertile 2: 1.00, tertile 3: 1.86; IGFBP-3, tertile 2: 0.69, tertile 3: 0.42). The relation of vertex balding with IGF-1 and IGFBP-3 did not statistically significantly vary by level of cumulative smoking (*P* interaction: IGF-1 0.9, IGFBP-3 0.8) or racial group (*P* interaction: IGF-1 0.5, IGFBP-3 0.2).

Among younger men (<64.75 years), for whom plasma levels were assessed closer in time to the reference age for report on balding, the ORs for vertex balding in the top tertiles of IGF-1 and IGFBP-3 were 2.72 (95% CI, 0.89-8.31) and 0.64 (95% CI, 0.22-1.86), respectively. For men who were older at the time of blood draw, the ORs for vertex balding in the top tertiles of IGF-1 and IGFBP-3 were 1.52 (95% CI, 0.56-4.14) and 0.23 (95% CI, 0.07-0.79), respectively. The differences in these associations for balding and IGF-1 (*P* interaction = .8) and IGFBP-2 (*P* interaction = .3) by age were not statistically significant.

DISCUSSION

We observed that middle-aged and elderly men who reported modest to substantial vertex balding at age 45 have lower circulating levels of IGFBP-3 and higher levels of IGF-1 when controlling for IGFBP-3 level. Growth factors are beginning to emerge as contributors to hair growth and loss. IGF-1 is an abundant endocrine, paracrine, and autocrine growth control factor that promotes proliferative activity in epithelial and mesenchymal cells in numerous organ systems,[8] including the hair organ. In vitro, human hair elongation is stimulated in a dose-dependent manner over normal range concentrations by IGF-1, and IGF-1 appears to inhibit the hair follicle from entering the catagen phase of the growth cycle.[9] Higher serum levels of IGF-1 were associated with vertex balding in a study of elderly Greek men.[2]

In the hair organ, IGF-1 is produced by connective tissue constituents,[10] and IGF-1 gene expression is enhanced by androgens.[11] In androgen-responsive tissue, IGF-1 may act locally to positively mediate the induction of 5α-reductase by dihydrotestosterone.[12] This action of IGF-1 may be consequential for the development of balding because conversion of testosterone to dihydrotestosterone in the scalp by 5α-reductase type 2 is essential for androgenetic alopecia.[13] Indeed, oral 5α-reductase type 2 inhibitors are now used to prevent further hair loss and to induce hair regrowth in men with male pattern balding.[13] Experimental administration of the 5α-reductase type 2 inhibitor finasteride results in diminished expression of IGF-1 and its receptor and enhanced expression of IGFBP-3 in the rat prostate, an androgen-dependent tissue.[14] IGFBP-3 is the major carrier protein that modulates the bioavailability of IGF-1[15] and thus may also be a regulator of mediators of hair growth and cycle control. Our findings are compatible with both the direct association of IGF-1 and the modulating effect of IGFBP-3 on male pattern balding.

Local concentrations of IGF-1 and IGFBP-3 in the hair follicle or surrounding connective tissue are likely the levels most relevant for assessment in relation to balding. Although it is unknown how well blood and other tissue levels correlate, circulating IGF-1 levels have been shown to be associated with prostate,[16-18] breast,[19-22] and colon[23,24] cancer in several epidemiologic studies. Imperfect correlation of plasma and target hair follicle levels likely results in our having underestimated the strength of the associations between IGF-1 and IGFBP-3 with vertex balding.

The relevant time period for assessment of IGF-1 and IGFBP-3 exposure in relation to the onset of vertex balding is not clear. We measured plasma levels in men well after the start of vertex hair loss; for some men this span may have been up to 6 decades. IGF-1 levels are known to decline with age.[25] Whether men with the highest bioavailable circulating levels of IGF-1 currently would also be the men with the highest levels at the time preceding the development of hair loss has not been examined. At least over a short period of 3 years in older adulthood, we previously showed that IGF-1 and IGFBP-3 levels are well correlated (r = 0.70 and 0.68, respectively).[26] Nevertheless, there was no clear evidence that the associations between balding and IGF-1 and IGFBP-3 varied among men who were younger, and for whom plasma levels were assessed closer in time to the reference age for report on balding, or older at the time of blood draw.

Misclassification of hair loss is possible because of self-assessment of hair pattern up to 36 years in the past. However, there was little correlation (r = 0.04) between age at blood draw (approximately 2 years after self-report on hair pattern) and balding at age 45, suggesting that systematic underestimation or overestimation of the extent of vertex balding by elderly compared with middle-aged participants was not extensive.

The association between IGF-1 and vertex balding was only evident in our study after adjusting for IGFBP-3, and the magnitude of the association for

IGF-1 adjusted for IGFBP-3 was not as great as shown for IGF-1 by Signorello et al.[2] Differences in the two studies that might contribute to the disparity in the strength of the association between IGF-1 and vertex balding include different IGF-1 assays, older average age in the Greek study, interviewer-assessed balding in the Greek study versus self-report in our study, and IGF-1 and balding assessed concurrently in the Greek study versus 2 to 36 years apart in our study. In the Greek study, adjustment for sex hormones and sex hormone–binding globulin enhanced the risk of vertex balding associated with IGF-1. Although not presented here because of possible noncomparability of hormone data among the 3 samples that we included in this analysis, adjustment for sex steroids and sex hormone–binding globulin did not appear to alter our estimates for the relation of vertex balding with IGF-1 or IGFBP-3. Despite these methodologic and population differences between the two studies, both the study in elderly Greek men[2] and our study indicate that the IGF-1 axis may be important in male pattern hair loss.

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