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Link to publisher's version: *http://dx.doi.org/10.1111/bjd.14529*

Citation: Noordam R, Gunn DA, van Drielen K et al (2016) Both low circulating insulin-like growth factor-1 and high-density lipoprotein cholesterol are associated with hair loss in middle-aged women. British Journal of Dermatology. 175(4): 728-734.

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Low circulating insulin-like growth factor-1 and high density lipoprotein associate with hair loss in middle-aged women

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Key words: alopecia, biological markers, epidemiology, women

Number of words abstract: 200

Number of words manuscript: 2,899

Number of references: 40

Number of tables: 2

Number of figures: 2

Capsule summary:

- Multiple biomarkers have been associated with female hair loss, but studies showed inconsistent results.
- We identified low HDL cholesterol and low Insulin-like growth factor-1 as independent risk factors for female hair loss.
- When replicated, pathways leading to female hair loss can be identified as potential treatment targets.

Abstract

Background: Multiple biomarkers have been associated with hair loss in women, but studies showed inconsistent results.

Objective: We investigated the association between markers of cardiovascular disease risk (e.g., serum lipid levels and hypertension) and aging (e.g., 25-hydroxyvitamin D and insulin-like growth factor) with hair loss in a population of middle-aged women.

Methods: In a random subgroup of 323 middle-aged women (mean age: 61.5 years) from the Leiden Longevity Study, hair loss was graded by three assessors using the Sinclair scale; women with a mean score higher than 1.5 were classified as cases with hair loss.

Results: Every standard deviation increase in HDL cholesterol was associated with a 0.65 times lower risk (95% confidence interval [CI]: 0.46–0.91) of hair loss; for IGF-1 the risk was 0.68 times lower (95% CI: 0.48–0.97) per standard deviation increase, independent of the other studied variables. Women with both IGF-1 and HDL cholesterol levels below the median of the study population had a 3.47 times higher risk (95% CI: 1.30–9.25) of having hair loss.

Limitations: The observational setting limits causal inference of the findings.

Conclusion: Low HDL cholesterol and IGF-1 were associated with a higher risk of hair loss in women.

Introduction

Hair loss has a prevalence of approximately 70 percent in men and 30 percent in women under the age of 70 years[1, 2] with androgenic alopecia as the most common form. The pathogenesis of hair loss, in both men and women, involves increasing numbers of miniaturized hair follicles together with a shorter anagen (growth) phase and longer telogen (rest) phase. These changes result in shorter and thin vellus-like hairs[1, 3], and ultimately in a loss of hair.

Several studies support the overall assumption that hair loss in men and hair loss in women are two different entities, being predominantly genetically determined in men[4, 5] and mainly environmentally determined in women[6]. For example, hair loss in men starts with bitemporal recession, which is followed by mid-frontal hair loss and vertex baldness[2], while hair loss in women (e.g., female pattern hair loss or FPHL) is predominantly characterized by diffuse reduction in scalp hair density on the crown and frontal scalp without recession of the hair-line from the forehead[1]. Furthermore, androgens clearly play a role in hair loss in men, but not in women[4, 7, 8]. Accordingly, randomized clinical trials on the use of finastride, a type II 5-alpha-reductase inhibitor which inhibits the conversion of testosterone into dihydrotestosterone, only improved hair growth in men and not in women[9, 10].

The risk of FPHL has been found to increase in those that smoke[11], have high cholesterol and high triglyceride levels[12], coronary heart disease (CHD)[13, 14], insulin resistance[14-16], metabolic syndrome[12, 14, 17], and blood pressure and hypertension[11]. However, most of these factors have been inconsistently associated with FPHL. For example, the association between smoking and FPHL was not observed in four other cohorts[12, 13, 17, 18], and the association with insulin resistance was dependent on the presence of the metabolic syndrome[19]. Also, findings were often observed in univariate models, which makes it difficult

to determine the independence of the findings. Furthermore, studies often selected participants prior to inclusion[12, 14].

With aging, there is a decrease in several age-related domains, including physiological function, endocrine function, musculoskeletal function, immune function and cognitive function, for which different biomarkers are available[20]. The aims of this study were twofold. First, we investigated the association between female pattern hair loss with age, smoking, history of diabetes, hypertension and stroke, and available markers of specific subdomains of physiological function that are related to increased CVD risk, notably cardiovascular function, glucose metabolism, body composition and inflammation as well as with available endocrine markers of aging (related to the growth hormone /insulin-like growth factor-1 axis, hypothalamic pituitary (HPA axis), hypothalamic pituitary thyroid (HPT) axis and 25-hydroxyvitamin D)[21]. Second, we aimed to investigate whether identified factors were specifically risk factors for women or also associated with hair loss in middle-aged men.

Methods

Ethics statement

This study has been approved by the Medical Ethical Committee of the Leiden University Medical Center. Written informed consent was obtained from all study participants.

Study setting

The Leiden Longevity Study was originally designed to identify genetic and phenotypic markers related to familial longevity. A detailed description about the design and recruitment strategy has been described elsewhere[22, 23]. In short, between 2002 and 2006 a total of 421 Caucasian families were recruited. Families were eligible for inclusion when at least two long-lived siblings were still alive, had the same parents and fulfilled the age criterion of being at least 89 years for men and 91 years for women, which represents less than 0.1% of the overall Dutch population in 2001. There were no selection criteria on health or demographic characteristics. Additionally, offspring of these nonagenarians were included, because proper controls at high age are lacking. The partners thereof were included as controls with a similar age, lifestyle and environment.

Study design and population

The study was conducted using a cross-sectional study design comprising all eligible female offspring and partners of the Leiden Longevity Study. Participants were included in this study when they had donated a non-fasted blood sample (collected between 2002 and 2006) and when a facial photograph was taken for the assessment of the degree of hair loss (collected between 2006 and 2008). From a random subpopulation of 323 female participants also facial photographs were taken for the assessment of the degree of hair loss. These data

were also available for 322 male participants, which were used to study whether observed markers related to FPHL are sex-specific or general markers of hair loss in both sexes.

Hair loss assessment

Participants came to the research center without any makeup or having used any hairstyling products for the photographs. Photographs used for the assessment of hair loss were taken of the vertex of the head with the scalp hair parted along the midline. We used the average score from three assessors who gave independent assessments using the 5-point Sinclair scale for determining the degree of hair thinning in females[24]. We considered participants with a Savin score higher than 1.5 as cases with FPHL. Participants with a Savin score equal or below 1.5 were considered as controls. Hair loss in men was determined using the Hamilton score[4], and used continuously.

Assessment of determinants

The following potential markers were studied: age, body mass index (BMI), percentage of body fat, systolic and diastolic blood pressure, smoking status, 25-hydroxyvitamin D, HDL cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, adiponectin, leptin, glucose, insulin, insulin-like growth factor-1 (IGF-1), thyroid-stimulating hormone (TSH), free triiodothyronine (fT3), high sensitivity C-reactive protein (hsCRP), aspartate aminotransferase (ASAT), dehydroepiandrosterone sulfate (DHEAS), and history of diabetes, hypertension and stroke.

Biochemical measures. Non-fasting blood samples were drawn and processed within 2 hours. The Cobas e411 (Roche Diagnostics, Almere, the Netherlands) was used for measuring 25-hydroxyvitamin D level. The levels of HDL cholesterol, triglycerides, leptin, adiponectin, hsCRP and glucose were measured using the Hitachi Modular P800 or the Cobas

Integra 800 (Roche Diagnostics, Almere, the Netherlands). LDL cholesterol was calculated using the Friedewald formula[25]. The Immulite 2500 from Siemens DPC (Los Angeles, CA, USA) was used for measuring IGF-1 and insulin. TSH and fT3 were measured on the Modular E170, DHEAS was measured using the Chemiluminescent Microparticle Immunoassay technology on a Abbott ci8200 (Abbott, Abbott Park, USA).

Other measures. The age at the moment of the facial photographs was used in the analyses. Weight (in kilograms), height (in meters), systolic and diastolic blood pressure were measured by research nurses at the study center. BMI was calculated by dividing weight with height squared. Four blood-pressure measurements (systolic and diastolic) were taken at two different time points maximally 2 hours apart. The mean thereof was used for analyses. The percentage of body fat was determined using the In-Body (720) body composition analyzer. A detailed description of the In-Body (720) body composition analyzer has been published elsewhere[26]. A lifestyle questionnaire was used to determine smoking status (current or non-smoker). Disease history (diabetes mellitus, hypertension, and stroke) was defined on the basis of records of the general practitioner.

Statistical analyses

The initial analyses were only conducted in females. As the outcome FPHL was dichotomized, analyses were conducted with logistic regression. For the analyses, we considered offspring and controls as one study population. All continuous markers were transformed into Z-scores. Therefore, all results of these markers should be interpreted as the effect per standard deviation increase. We conducted the analyses using a two-step approach. First, we conducted analyses in which we studied all markers separately, and adjusted for age. Second, we conducted one multivariable analysis including the determinants that had a p-value below 0.1 in the univariate analysis, adjusted for age. A composite score was

calculated for the markers that reached statistical significance (p-value<0.05) in the multivariate analysis. In this score, numerical data was dichotomized based on the median of the study population (low/high). Participants were allowed to have missing data. Missing markers of cardiovascular disease or aging were estimated using multiple imputations (5 times).

A number of sensitivity analyses were conducted. In case of glucose and insulin, the univariate analyses were repeated for participants without diabetes. Furthermore, in case of systolic and diastolic blood pressure, the univariate analyses were repeated in participants without hypertension. As multiple determinants in the present study were previously described to be different between offspring and partners (e.g., glucose, 25-hydroxyvitamin D[27, 28]), analyses were additionally stratified for these groups to study potential effect modification by study group.

The determinants that reached statistical significance in the multivariable analysis on FPHL were also studied with respect to baldness in men. For these variables, a similar composite score was calculated per participant. As the Hamilton score was normally distributed, these analyses were conducted using linear regression models.

All statistical analyses were conducted using SPSS v.20 for Windows (SPPS Inc., Chicago, IL, U.S.A.). P-values below 0.05 were considered statistically significant.

Results

Study characteristics

The general characteristics of the study population are presented in **Table 1**. In short, the study population comprised women with a mean age of 61.5 years and a BMI of 26.4 kg/m^2; of the studied diseases, hypertension was most common (25.7%).

Markers of health and disease and female hair loss

Of the 323 female participants, 43 (13.3%) participants were defined as cases with FPHL.

The associations between the markers with FPHL are presented in **Table 2**. Per standard deviation higher level of HDL cholesterol and IGF-1, the risk of female hair loss was significantly lower (HDL cholesterol: 0.59 [95% CI: 0.42 – 0.83]; IGF-1: 0.64 [95% CI: 0.45 – 0.90]). Furthermore, we observed a trend toward an association between higher diastolic blood pressure and higher risk of hair loss (95% confidence interval [CI]: 0.95 – 1.86). None of the others studies variables were associated with FPHL (p-value > 0.1). The sensitivity analyses on glucose and insulin (excluding women with diabetes mellitus), and systolic and diastolic blood pressure (excluding women with hypertension) did not materially change the results (results not shown). Furthermore, results were similar for offspring and partners (results not shown).

The observed effect estimates of diastolic blood pressure, HDL cholesterol and IGF-1 did not change when we included these variables together in a multivariate analysis (**Table 2**). One standard deviation higher level of HDL cholesterol and IGF-1 were statistically significantly associated with a lower risk of hair loss (HDL cholesterol: 0.65 [95% CI: 0.46 – 0.91]; IGF-1: 0.68 [95% CI: 0.48 – 0.97]).

Participants with both IGF-1 and HDL cholesterol level below the median of the study population had a 3.47 times higher risk to have hair loss (**Figure 1**), which was statistically significant (95% CI: 1.30 – 9.25). Participants with either a level of IGF-1 or HDL cholesterol level below the median of the study population also had a higher risk of hair loss, but this was not statistically significant. Furthermore, there was a significant trend across the study groups ($\text{p-value}_{trend} = 0.011$).

Association IGF-1 and HDL and hair loss in men

In a second analysis, a total of 322 men with a mean age of 61.1 years (SD = 6.5) were included. Neither IGF-1 nor HDL cholesterol level were, after adjustment for age, associated with a higher mean Hamilton score. Furthermore, men with a level of IGF-1 and HDL cholesterol lower than the median of the study population had no higher mean Hamilton score than males with serum levels above the median (**Figure 2**).

Discussion

In the present study, we aimed to assess the association between markers cardiovascular disease risk and aging with FPHL at middle-age. Of the studied markers, higher levels of HDL cholesterol and IGF-1 were associated with a lower risk of FPHL in univariate models. These associations remained similar in the multivariate analysis, which suggests that HDL cholesterol and IGF-1 were independently associated with FPHL. Furthermore, neither HDL cholesterol nor IGF-1 were associated with baldness in men.

The association between high HDL cholesterol level and less hair loss in women suggests a role for cardiovascular risk factors in the process of hair loss. However, the association between HDL cholesterol and FPHL has not been found in female European or Korean populations[17, 18]. Furthermore, HDL cholesterol was not associated with male baldness in our study population, which is similar to findings of other studies[12, 17]. A meta-analysis on determinants of hair loss, in which hair loss in men and women was treated as the same phenotype, also found no association between HDL cholesterol and hair loss[14]. However, the heterogeneity in their results was large, which speculatively could be in part driven by sex differences. Hence, further studies are required to confirm the link between HDL cholesterol and hair loss in women.

Although associations between cardiovascular disease or its risk factors and FPHL have been observed previously in a number of studies[12, 13, 15, 16], including the present study, a pathogenic link has yet to be fully elucidated. Interestingly, patients with primary cicatricial alopecia, a class of rare inflammatory disorders characterized by the destruction of hair follicles and permanent hair loss, were shown to have an impaired cholesterol biosynthetic pathway in the skin and hair follicles[29]. Cholesterol precursors stimulated pro-inflammatory processes and recruitment of macrophages, which ultimately resulted in the destruction of the hair follicle[29]. Indeed, an accumulation of cholesterol precursors in murine skin was shown to

cause defects in hair growth, but was also shown to be reversible with simvastatin treatment[30]. Furthermore, deficits in cholesterol biosynthesis, as seen, for example, in congenital hemodysplasia with ichthyosiform erythroderma and limb defects and desmosterolosis, are also accompanied by hair loss[31]. Conversely, an inherited form of hypertrichoses is caused by genetic mutations in the *ABCA5* leading to increased cholesterol levels in the lysosome[32]. Based on these studies, cholesterol metabolism might have an essential role in hair growth, and thus could be a potential target for treatment.

The association between cardiovascular risk and FPHL is also supported by the trend between high diastolic blood pressure and increased risk of FPHL in our study population, although not statistically significant in the multivariable model. An association between high blood pressure (both systolic and diastolic) and hair loss has been observed previously in women[11, 12]. Again though, two other studies observed no significant link between blood pressure and FPHL, which highlights the contradictory results in literature[17, 18]. Indeed, as the association between FPHL and diastolic blood pressure was only borderline significant in this study, further research is required to determine whether blood pressure or correlates thereof are truly associated with FPHL.

In this study, a high level of IGF-1 was associated with a lower risk of hair loss in women (but not in men) independently of HDL cholesterol levels. IGF-1 has an essential role in hair cycle control, hair follicle development, and hair shaft differentiation[33-35]. Although the IGF-1 levels measured in this study were in serum, secreted levels of IGF-1 in sebum from the skin are strongly correlated to serum levels[36]. Hence, this data suggests that lower circulating IGF-1 reflects lower IGF-1 levels in the hair bulb which could reduce hair growth and differentiation. In men, there is conflicting data on IGF-1 links to hair loss. Whereas we found no significant association between baldness in men and serum IGF-1, Platz *et al*[37] found a higher level of IGF-1 associated with a higher risk of male baldness, and

Panchaprateep and Asawanonda[38] found significantly lower levels of IGF-1 secreted from dermal papilla cells from balding sites. Within the present study population we previously observed significant associations between high levels of IGF-1 and lower degree of skin wrinkling[39] and a lower degree of skin pigmentation[40], indicating a more general role of IGF-1 in skin aging features which potentially also effects hair loss. How reduced levels of IGF-1 could ultimately induce hair loss in women but not men is unclear and, as this is the first study to find a link between serum IGF-1 and FPHL, replication of these results is therefore warranted.

This study has a few limitations. First, the observational setting of the study limits the possibility to infer causality of IGF-1 and HDL cholesterol levels with hair loss. Second, the serum measures were measured in serum collected approximately 4 years before photographs for hair loss assessment were collected. However, this could actually be a strength of the study as, although the stability of IGF-1 and HDL cholesterol over the years is uncertain, the process of hair loss takes a number of years and could be captured more precisely in studies with determinants assessed a number of years earlier. Third, the assessment by photographs gives only an approximation of the degree of hair loss, and hair color can influence the assessment of FPHL, as the scalp can be identified more easily with dark hair than with grey hair[6]; both factors could have resulted in reduced accuracy of the FPHL data. Finally, as the insulin and glucose levels were measured in non-fasted samples, which could be a reason for why we did not observe an association with insulin resistance as previously reported[15, 16]. Further studies using oral glucose tolerance tests (OGTT) or intravenous glucose tolerance tests (IGTT) are required to better investigate glycaemic control and FPHL.

In conclusion, a higher level of IGF-1 and HDL cholesterol were found to be independently associated with a higher degree in hair loss in middle-aged women. Given the limitations of the present study and the contradictory results present in the literature, larger

studies are required to confirm the association between IGF-1, HDL cholesterol and FPHL. Furthermore, additional studies are required to elucidate whether circulating HDL cholesterol and IGF-1 levels reflect levels in the hair bulb, and how reduced levels could induce hair loss.

Acknowledgements

We would like to thank all participants, the secretary staff, Meriam H.G.F. van der Star and Ellen H.M. Bemer-Oorschot for their contribution to this study. We would also like to thank Sarah Paterson for the FPHL grading.

Funding

This study was funded by the Innovation Oriented research Program on Genomics (SenterNovem; IGE01014 and IGE5007), the Centre for Medical Systems Biology (CMSB), the Netherlands Genomics Initiative/Netherlands Organization for scientific research (NGI/NOW; 05040202 and 050-060-810, NCHA), Unilever PLC and the EU funded Network of Excellence Lifespan (FP6 036894).

Conflict of interest

Although no products were tested, it is possible this manuscript could promote anti-aging products which could lead to financial gain for Unilever.

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Table 1: Characteristics of the study population

	Total (N = 323)
General characteristics	
Age (years)	61.5 ± 6.0
Body mass index (kg/m^2)	26.4 ± 4.7
Body fat percentage	35.1 ± 7.4
Systolic blood pressure (mmHg)	140 ± 21
Diastolic blood pressure (mmHg)	82 ± 11
Current smoking, n (%)	35 (10.8)
Non-fasted serum markers	
25-hydroxyvitamin D (ng/mL), median (IQR)	42.7 (38.0 – 48.7)
High density lipoprotein (mmol/L)	1.6 ± 0.5
Low density lipoprotein (mmol/L)	3.4 ± 1.0
Triglycerides (mmol/L), median (IQR)	1.40 (1.0 – 2.1)
Adiponectin (mg/L), median (IQR)	6.1 (4.6 – 8.6)
Leptin (ng/mL), median (IQR)	22.4 (11.7 – 39.8)
Glucose (mmol/L)	5.9 ± 1.2
Insulin (mU/L), median (IQR)	16.0 (10.0 – 29.0)
Insulin-like growth factor-1 (nmol/L)	17.2 ± 5.1
Thyroid-stimulating hormone (mU/L), median (IQR)	1.7 (1.1 – 2.5)
Free Triiodothyronine (pmol/L)	3.9 ± 0.7
C-reactive protein (mg/L)	1.3 (0.7 – 3.1)
Aspartate aminotransferase (U/L)	19.0 (15.0 – 25.0)
Dehydroepiandrosterone sulfate (μmol/L)	3.1 (1.9 – 4.7)
Disease history	
Diabetes, n (%)	14 (4.3)
Hypertension, n (%)	83 (25.7)
Stroke, n (%)	5 (1.5)

All data is presented with mean ± SD unless otherwise stated.

Abbreviations: IQR, interquartile range

Table 2: Association between markers of health and aging and FPHL

	Univariate model		Multivariate model	
	OR	95% CI	OR	95% CI
General characteristics				
Age	1.23	0.89 – 1.71	1.15	0.82 – 1.61
Body mass index	1.14	0.82 – 1.58		
Body fat percentage	1.22	0.87 – 1.70		
Systolic blood pressure	1.29	0.91 – 1.84		
Diastolic blood pressure	1.33	0.95 – 1.86*	1.28	0.91 – 1.82
Smoking, yes	1.00	0.34 – 2.95		
Non-fasted serum markers				
25-hydroxyvitamin D	0.72	0.68 – 1.30		
High density lipoprotein	0.59	0.42 – 0.83†	0.65	0.46 – 0.91
Low density lipoprotein	1.03	0.74 – 1.43		
Triglycerides	1.13	0.81 – 1.57		
Adiponectin	0.92	0.67 – 1.28		
Leptin	1.15	0.83 – 1.60		
Glucose	1.19	0.85 – 1.67		
Insulin	1.23	0.88 – 1.72		
Insulin-like growth factor 1	0.64	0.45 – 0.90†	0.68	0.48 – 0.97
Thyroid-stimulating hormone	0.86	0.62 – 1.19		
Free Triiodothyronine	0.96	0.70 – 1.33		
High-sensitivity C-reactive protein	1.31	0.94 – 1.82		
Aspartate aminotransferase	1.14	0.81 – 1.60		
Dehydroepiandrosterone sulfate	0.99	0.69 – 1.43		
Disease history				
Diabetes, yes	1.05	0.23 – 4.89		
Hypertension, yes	1.05	0.51 – 2.19		
Stroke, yes	1.59	0.17 – 14.6		

Results depicted at the relative risk of a standard deviation increase of a determinant or as indicated otherwise. All analyses were adjusted for chronological age. Abbreviations: CI, confidence interval; OR, odds ratio. * p-value < 0.1. † p-value < 0.05.

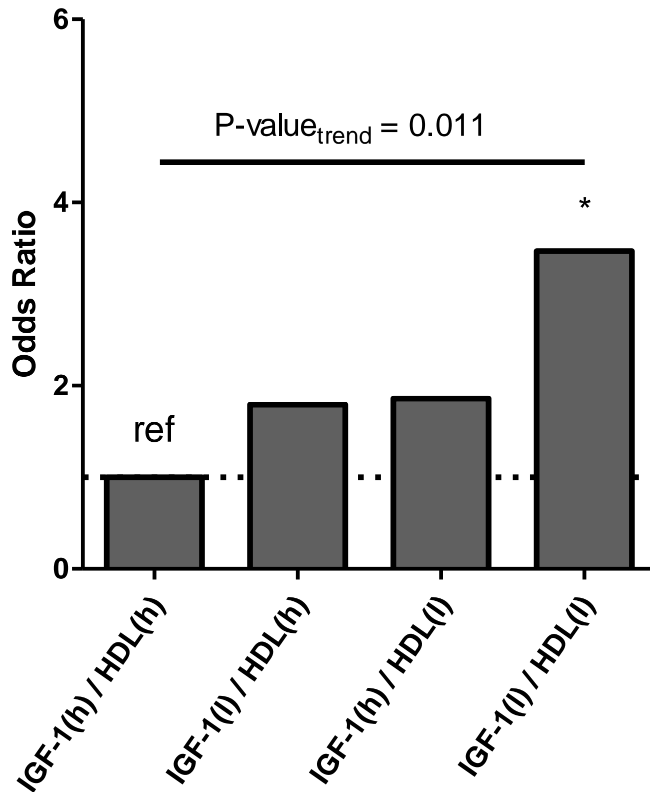

Figure 1: IGF-1 and HDL status (low and high) and risk of female pattern hair loss

Abbreviations: h, high; HDL, high-density lipoprotein; IGF-1, insulin-like growth factor-1; l, low. *) p-value < 0.05 with respect to the reference group. Analysis was adjusted for age. Low IGF-1, range between 6.49 and 16.6 nmol/L; high IGF-1, range between 16.8 and 37.4 nmol/L; low HDL cholesterol, range between 0.42 and 1.57 mmol/L; high HDL cholesterol, range between 1.58 and 3.24 mmol/L. In the high IGF-1 and high HDL group, there were 6 cases of female pattern hair loss. On both the high IGF-1 and low HDL as well as the low IGF-1 and high HDL, there were 9 cases. In the low IGF-1 and low HDL, there were 19 cases.

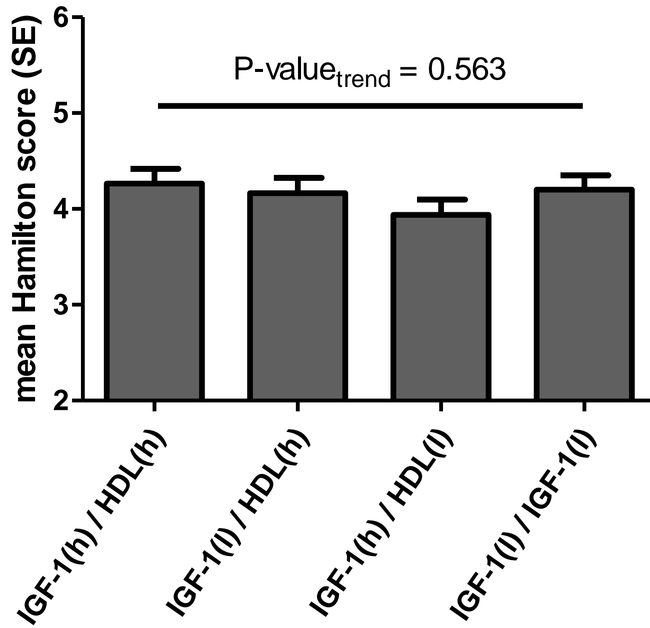

Figure 2: IGF-1 and HDL status (low and high) and the mean degree of hair loss in men

Abbreviations: h, high; HDL, high-density lipoprotein; IGF-1, insulin-like growth factor-1; l, low; SE, standard error of the mean. Results depicted as the mean Hamilton score and the standard error of the mean. Analysis adjusted for age. Low IGF-1, range between 3.90 and 16.9 nmol/L; high IGF-1, range between 17.0 and 35.5 nmol/L; low HDL cholesterol, range between 0.18 and 1.20 mmol/L; high HDL cholesterol, range between 1.21 and 2.51 mmol/L. A total of 86 participants were in the high IGF-1 and high HDL group. There were 75 participants in the group with low IGF-1 and high HDL, and 74 participants in the group with high IGF-1 and low HDL. 87 participants had a low IGF-1 and a low HDL.