CLINICAL REPORT

Association Between Premature Hair Greying and Metabolic Risk Factors: A Cross-sectional Study

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The association of hair greying with metabolic syndrome is not well known, while association with obesity and coronary artery disease has been suggested. A cross-sectional study was conducted to identify an association between premature hair greying and metabolic risk factors. Of the 1,929 young healthy subjects (1,067 men and 862 women), 704 (36.4%) were categorized in the premature hair greying group. Waist circumference (means of non-premature hair greying vs. premature hair greying, 74.3 vs. 76.3 cm; $p<0.001$), systolic (109.2 vs. 111.7 mmHg; $p<0.001$) and diastolic (65.0 vs. 66.2 mmHg; $p=0.003$) blood pressures, and fasting blood sugar (90.8 vs. 91.6 mg/dl; $p=0.013$) were higher and serum high-density lipoprotein cholesterol (68.1 vs 65.4 mg/dl; $p<0.001$) was lower in premature hair greying group. Multivariate logistic regression analysis showed that metabolic risk factors ≥2 was independently associated with premature hair greying after controlling for confounding factors (odds ratio 1.725; $p=0.036$). The present study revealed an association between premature hair greying and metabolic risk factors.

Key words: hair greying; premature hair greying; metabolic syndrome; metabolic risk factors.

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SIGNIFICANCE

This study presented an association between premature hair graying and metabolic risk factors in young Koreans. Waist circumference, blood pressure, and fasting blood sugar were higher and serum high-density lipoprotein cholesterol was lower in subjects with premature hair graying. The prevalence of subjects who had two or more metabolic risk factors was higher in subjects with premature hair graying than those without. It postulates that premature hair graying can be considered as a clinical marker for evaluating patients at risk for metabolic syndrome.

Hair greying (canities) is a natural age-related occurrence (1). Since everyone develops grey hair with age, it is not considered a disease. Even when a person develops grey hair at a young age, it is thought of as a cosmetic, not a medical, condition. However, as the chances of developing a disease increase with age, many studies have postulated that hair greying could be a predictor of some geriatric diseases. For example, some studies have revealed an association between hair greying and coronary artery disease (CAD) (2–4).

In our previous study, we found that premature hair greying (PHG) is associated with family history of PHG, smoking and obesity (5). Among these factors, smoking and obesity are risk factors for CAD. The National Cholesterol Education Program's Adult Treatment Panel III report (ATP III) viewed CAD as the primary outcome of metabolic syndrome (6), which is a constellation of interrelated risk factors of metabolic origin (metabolic risk factors), such as obesity, dyslipidaemia and hypertension (7). Metabolic syndrome could induce precocious ageing (8). However, an association between hair greying and metabolic syndrome has seldom been studied.

The aim of the present study was to determine if there is an association between PHG and metabolic risk factors, after adjustment for potential confounders. PHG was considered as the presence of grey hair under the age of 30 years in this study, since hair greying usually begins in the fourth decade of life (1). Data about already known associated risk factors, such as family history of PHG and smoking history, were collected using questionnaires. Biochemical and anthropometric parameters related to the metabolic profile were measured, and their association with PHG was analysed.

METHODS

Study design

Healthy participants undergoing regular medical check-ups were recruited at the Center for Health Promotion and Optimal Aging of Seoul National University Hospital, between March 2015 and February 2016. To be included in the study, participants had to be healthy with no acute or chronic disease, aged between 20 and 29 years, and consent to participate in the study. Subjects were excluded if they had an existing hypopigmentary disorder, or had

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taken medication that might induce a hypopigmentary disorder and alopecia (except androgenetic alopecia). The study was approved by the institutional review board of Seoul National University Hospital (IRB number 1409-126-611).

Questionnaire content

The questionnaire covered the presence and severity of grey hair (grade 0, 0; grade 1, less than 10; grade 2, 10–100; and grade 3, more than 100). It has been validated that the subjects' self-reporting of grey hair grade in this questionnaire closely matched the investigator's examination (5). Data on age, sex, the presence of a medical problem, alopecic disease, medication history, family history of PHG, and smoking history were also collected.

Metabolic profile measurement

Height, weight, waist circumference, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured. Biochemical data associated with metabolic risk factors were collected including total cholesterol, high-density lipoprotein cholesterol (HDL-cholesterol), low-density lipoprotein cholesterol (LDL-cholesterol), triglyceride, and fasting blood sugar (FBS).

Body mass index (BMI) was calculated and participants were categorized as underweight (BMI <18.5 kg/m^2), normal weight ($18.5 \leq$BMI<25 kg/m^2), overweight ($25 \leq$BMI<30 kg/m^2), and obese (BMI≥ 30 kg/m^2) according to the WHO classification (9).

The diagnosis of metabolic syndrome can be made if a patient has 3 of 5 metabolic risk factors according to ATP III criteria. The risk factors are central obesity (waist circumference: men >90 cm, women >80 cm in Asians), elevated triglycerides (≥ 150 mg/dl), reduced HDL-cholesterol (men <40 mg/dl, women <50 mg/dl), elevated blood pressure (SBP ≥ 130 mmHg or DBP ≥ 85 mmHg), and elevated FBS (≥ 100 mg/dl) (6). Based on these ATP III criteria, central obesity group, high blood pressure group, high triglycerides group, low HDL group, and high FBS group were defined in this study.

Statistical analysis

Items unanswered in the questionnaire were regarded as missing data. The difference between continuous variables associated with metabolic risk factors were analysed using Student's *t*-test.

To identify the risk factors for metabolic syndrome components in patients with PHG, we first performed a univariate logistic regression analysis. Factors with $p<0.10$ were identified and a multivariate logistic regression analysis was performed including those factors.

Factors associated with the severity of PHG were identified using ordinal logistic regression analysis. Similarly, factors with $p<0.10$ in the univariate ordinal logistic regression analysis and putative candidate factors with moderate association were analysed using multivariate ordinal logistic regression analysis.

Statistical analyses were performed using IBM SPSS Statistics 22 (IBM Corp., Armonk, NY, USA) and *p*-values <0.05 were considered significant.

RESULTS

Demographic and clinical characteristics of the study population

A total of 2,025 participants were recruited. After exclusion of participants who answered incomplete questionnaires (6) or met the predefined exclusion criteria (90), 1,929 participants (1,067 men and 862 women) were eligible for final inclusion (**Fig. 1**). The mean ± standard deviation (SD) age of the participants was 23.7 ± 2.3 years. Of the 1,929 participants, 704 (36.4%) with grey hair were categorized as the PHG group, whereas 1,225 (63.6 %), without grey hair, were categorized as the non-PHG group (**Table I**).

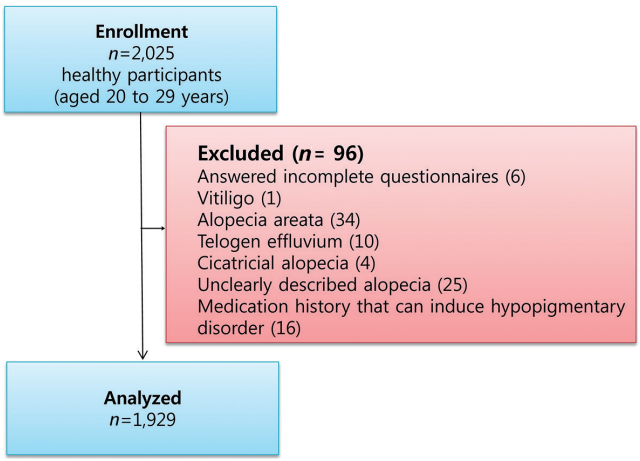

Fig. 1. Flow diagram of study population in this study.

The comparison of demographic factors and previously reported risk factors for PHG between the 2 groups is described in Table I. Male sex (odds ratio (OR), 1.830, $p<0.001$), age (OR 1.130, $p<0.001$), family history of PHG (OR 4.930, $p<0.001$), and being overweight (OR 1.389, $p=0.026$) were significantly associated with PHG; whereas smoking (OR 1.304, $p=0.064$) showed mild association with PHG in our study population.

Comparison of metabolic profiles between premature hair greying and non-premature hair greying groups

The metabolic profiles and the differences between the 2 groups are summarized in **Table II**. Waist circumfe-

Table I. Comparison of demographic and clinical characteristics between premature hair greying (PHG) and non-PHG group

	Non-PHG	PHG	OR (95% CI)	*p*-value
Subjects, *n* (%)	1,225 (63.6)	704 (36.4)		
Age, years, mean±SD	23.4±2.3	24.1±2.3	1.130 (1.086–1.177)[a]	<0.001
Sex, *n* (%)	1,225 (100)	704 (100)		
Female	613 (50.0)	249 (35.4)	1.000 (Ref.)	_
Male	612 (50.0)	455 (64.6)	1.830 (1.512–2.215)	<0.001
Family history of PHG, *n* (%)	1,225 (100)	704 (100)		
No	888 (72.5)	243 (34.5)	1.000 (Ref.)	_
Yes	169 (13.8)	228 (32.4)	4.930 (3.861–6.295)	<0.001
Unaware	168 (13.7)	233 (33.1)	_	
Obesity categories[b], *n* (%)	1,210 (100)	698 (100)		
Underweight	151 (12.5)	61 (8.7)	0.701 (0.511–0.961)	0.027
Normal	939 (77.6)	541 (77.5)	1.000 (Ref.)	_
Overweight – obese	120 (9.9)	96 (13.8)	1.389 (1.041–1.853)	0.026
Smoking, *n* (%)	1,220 (100)	703 (100)		
No	1,088 (89.2)	607 (86.3)	1.000 (Ref.)	_
Yes	132 (10.8)	96 (13.7)	1.304 (0.984–1.727)	0.064

[a]Odds ratio (OR) of age row is for each additional year. Odds of having PHG increase with OR as age increases by 1 year. [b]WHO criteria.
SD: standard deviation; CI: confidence interval.

Table II. Comparison of metabolic profiles between non-premature hair greying (PHG) group and PHG group

Metabolic profiles	Non-PHG Mean±SD, *n*	PHG Mean±SD, n	*p*-value
Obesity			
Waist circumference	74.3±8.0, 1,210	76.3±8.2, 698	<0.001
Body mass index	21.2±3.5, 1,225	21.9±3.5, 704	<0.001
Triglyceride	79.3±44.4, 1,218	81.9±39.1, 700	0.207
Cholesterol			
Total cholesterol	177.0±27.7, 1,218	177.1±29.3, 700	0.911
HDL-cholesterol	68.1±14.9, 1,218	65.4±15, 700	<0.001
LDL-cholesterol	93.1±24.9, 1,218	95.4±25.7, 700	0.054
Blood pressure			
Systolic blood pressure	109.2±11.9, 1,223	111.7±11.4, 704	<0.001
Diastolic blood pressure	65.0±8.4, 1,223	66.2±8.1, 704	0.003
Fasting blood sugar	90.8±6.6, 1,218	91.6±6.7, 700	0.013

SD: standard deviation; HDL: high-density lipoprotein; LDL: low-density lipoprotein.

rence ($p<0.001$), BMI ($p<0.001$), SBP ($p<0.001$), DBP ($p=0.003$) and FBS ($p=0.013$) were significantly higher and serum HDL-cholesterol ($p<0.001$) was significantly lower in the PHG group than in the non-PHG group.

According to ATP III criteria, we investigated the prevalence of each metabolic risk factor in PHG and non-PHG groups (**Table III**). Prevalence of all metabolic risk factors tended to be higher in PHG group (central obesity (OR 1.249), high triglyceride (OR 1.262), low HDL-cholesterol (OR 1.419), high blood pressure (OR 1.332) and high FBS (OR 1.092)), but they were not statistically significant.

Considering that the risk of CAD becomes greater when there is a combination of metabolic risk factors (10), we counted the number of metabolic risk factors in each subject and compared it between the PHG group and the non-PHG group. The prevalence of subjects who had metabolic risk factors ≥2 were higher in the PHG group than in the non-PHG group (OR 1.659, $p=0.011$).

Table III. Metabolic risk factor and their association with premature hair greying (PHG)

	Non-PHG *n* (%)	PHG *n* (%)	OR (95% CI)	*p*-value
1. Central obesity				
Normal	1,131 (93.5)	642 (92)	1.000 (Ref.)	–
Central obesity[a]	79 (6.5)	56 (8)	1.249 (0.875–1.782)	0.221
2. Triglyceride				
Normal	1,165 (95.6)	662 (94.6)	1.000 (Ref.)	–
High[a]	53 (4.4)	38 (5.4)	1.262 (0.823–1.935)	0.286
3. High-density lipoprotein-cholesterol				
Normal	1,182 (97)	671 (95.9)	1.000 (Ref.)	–
Low[a]	36 (3)	29 (4.1)	1.419 (0.862–2.335)	0.169
4. Blood pressure				
Normal	1,162 (95)	658 (93.5)	1.000 (Ref.)	–
High[a]	61 (5)	46 (6.5)	1.332 (0.898–1.976)	0.155
5. Fasting blood sugar				
Normal	1,099 (90.2)	626 (89.4)	1.000 (Ref.)	–
High[a]	119 (9.8)	74 (10.6)	1.092 (0.804–1.483)	0.574
Metabolic risk factor clustering, *n* (%)				
≤1	1,154 (95.4)	646 (92.6)	1.000 (Ref.)	–
≥2	56 (4.6)	52 (7.4)	1.659 (1.124–2.449)	0.011

[a]ATP III criteria. OR: odds ratio; CI: confidence interval.

Table IV. Independent factors associated with premature hair greying (PHG) using multivariate logistic regression analysis

	OR (95% CI)	*p*-value
Age	1.125 (1.069–1.184)	<0.001
Male sex	1.801 (1.407–2.304)	<0.001
Family history of PHG	5.243 (4.065–6.763)	<0.001
Metabolic risk factor ≥2[a]	1.725 (1.035–2.874)	0.036

[a]ATP III criteria.
OR: odds ratio; CI: confidence interval.

Independent factors associated with the presence and the severity of premature hair greying

In univariate logistic regression analysis, the potential factors for metabolic syndrome components in patients with PHG were age, sex, family history of PHG, smoking and metabolic risk factors ≥2 ($p<0.10$). To identify independent factors associated with PHG, these factors were further analysed by multivariate logistic regression analysis. We found that a family history of PHG (OR 5.243, $p<0.001$), male sex (OR 1.801, $p<0.001$), metabolic risk factor ≥2 (OR 1.725, $p=0.036$) and age (OR 1.125, $p<0.001$) were significantly associated with PHG (**Table IV**).

Regarding the association between the severity of PHG and clinical factors, we further analysed 704 participants with PHG. In the univariate ordinal logistic regression analysis, age, sex, family history of PHG, and presence of metabolic risk factor ≥2 were identified as candidate factors ($p<0.10$). In addition, smoking history was analysed, as it was a putative candidate factor. In multivariate ordinal logistic regression analysis, family history of PHG (OR 5.968, $p<0.001$), male sex (OR 1.981, $p<0.001$), metabolic risk factor ≥2 (OR 1.605, $p=0.049$) and age (OR 1.137, $p<0.001$) were significantly associated with the severity of PHG (**Table V**).

DISCUSSION

The present study found that presence of metabolic risk factors ≥2, as well as higher age, male sex, and family history of PHG were significantly associated with the presence and severity of PHG. These results provide, to the best of our knowledge, the first evidence that metabolic syndrome is independently associated with PHG after controlling the confounding factors. In addition, the numbers of participants in this study was close to 2,000, which lends credibility to the results. Interestingly, obesity, previously identified as a risk factor of PHG, is a major causative factor for developing metabolic syndrome (11).

In the past, several studies have reported the possibility of grey hair being a risk factor for CAD. Therefore, metabolic syndrome may be associated with hair greying because CAD is a major clinical outcome of metabolic syndrome. Analysing the cohort from The Copenhagen City Heart Study, the relative risk of myocardial infarc-

Table V. Factors associated with the severity of premature hair greying (PHG) using multivariate ordinal logistic regression analysis

	Number of white hairs				
	<10	10–100	>100	OR (95% CI)	*p*-value
Age, mean±SD	23.9±2.3	24.4±2.5	24.7±2.3	1.137 (1.082–1.194)	<0.001
Sex, *n* (%)					
Female	185 (74.3)	55 (22.1)	9 (3.6)	1.000 (Ref.)	–
Male	274 (60.2)	145 (31.9)	36 (7.9)	1.981 (1.547–2.537)	<0.001
Family history of PHG, *n* (%)					
No	187 (77.0)	48 (19.8)	8 (3.3)	1.000 (Ref.)	–
Yes	112 (49.1)	87 (38.2)	29 (12.7)	5.968 (4.683–7.606)	<0.001
Metabolic risk factor[a], *n* (%)					
≤1	424 (65.6)	181 (28.0)	41 (6.3)	1.000 (Ref.)	–
≥2	29 (55.8)	19 (36.5)	4 (7.7)	1.605 (1.002–2.569)	0.049

[a]ATP III criteria.
SD: standard deviation; CI: confidence interval.

tion was 1.9 (95% confidence interval 1.2–2.8) for men with completely grey hair compared with men with no grey hair (2). In addition, a recent study measured carotid artery intima thickness, a surrogate marker of CAD, in young and middle-aged men and found it to be related to grey hair (3). There was also an observational study reporting that the incidence of CAD was higher in men with more severe grey hair (12).

Of late, the relationship between hair greying and metabolic syndrome has become a subject of interest. Al-Hamamy et al. (13) reported that the peak onset of hair greyness was the fourth decade in people with metabolic syndrome, while it was the fifth decade in those without, which suggests that people with metabolic syndrome tend to develop grey hair earlier. Chakrabarty et al. (14) compared various biochemical parameters between 37 cases of PHG (aged 15–25 years) and 37 age- and gender-matched controls, and found that HDL-cholesterol was lower in the PHG group than in the control group. These studies also support the association between metabolic syndrome and hair greying, although Al-Hamamy's study had limitations, such as the lack of age-control in the study population and the possibility of recall bias about the onset of hair greying. In addition, Chakrabarty's study had the limitation of a very small sample size.

Family history of PHG showed the most prominent association with PHG in this study. These results imply that genetic factors are strongly associated with PHG. In the genome-wide association scan in over 6,000 Latin Americans, the first genetic locus (rs12203592 in interferon regulatory factor 4 gene (*IRF4*)) associated with hair greying was revealed (15). *IRF4* was reported to interact with microphthalmia-associated transcription factor (MITF) (16). However, this study focused not on the PHG, but on general hair greying. A further study is necessary to elucidate this strong genetic background of PHG.

Currently, the accumulation of intracellular oxidative stress is considered to be a mechanism of hair greying (17). The production of endogenous oxidative stress during melanogenesis can disturb the maintenance of melanocyte stem cells in hair follicles and eventually turn hair grey (18). Additional oxidative stress can also accelerate the hair greying process. Association of PHG with metabolic risk factors supports this hypothesis, since they can be induced by, or lead to, oxidative stress (19, 20).

The present study has some limitations. First, the study cannot assess the causal relationship because of its cross-sectional design. Secondly, the participants were all Korean with black hair. It has been reported that the mean onset of hair greying is earlier in white people than in Asians (17). Therefore, our study may be biased towards more severe, relatively early onset PHG. Studies of other ethnicities are necessary for generalization.

In conclusion, this study revealed an association between PHG and the number of metabolic risk factors. This study postulates that PHG can be considered as a clinical marker for evaluating patients at risk of metabolic syndrome. Furthermore, a prospective study can be planned to elucidate whether subjects with PHG eventually develop a higher incidence of metabolic syndrome than the general population.

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The authors have no conflicts of interest to declare.

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