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Hair whitening and obesity are independently related to ascending aorta dilatation in young-middle aged men

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ABSTRACT

OBJECTIVE: Hair whitening (HW) is strongly linked with aging. Ascending aortic dilation and HW share common etiologic factors. We investigated the association of HW with ascending aortic diameters.

METHODS: Our study included 93 male subjects aged below fifty years. All patients underwent echocardiography to measure ascending aortic diameter, in addition to routine biochemistry tests, and physical examination, and thorough medical history. Hair whitening score (HWS) was defined according to the percentage of white hair (HWS 1 <25%; HWS 2: 25–50%; HWS 3: 50–75%; HWS 4: 75–100).

RESULTS: Patients with highest HWS were older, and had higher percentage of hypertension and family history of HW. Moreover, this subgroup had increased ascending aortic diameter, higher serum uric acid, and lower total bilirubin concentrations. Multivariate analyses including age, hypertension, height, waist circumference, CRP, and family history of HW identified body weight and HW score as the independent predictors of ascending aortic diameter.

CONCLUSION: An independent association between the degree of hair whitening and ascending aortic dilation exists in middle-aged men, which may depend on co-existing factors that enhance both pathologies rather than causality. We think that oxidative stress may be one of these stressors.

Keywords: Ascending aorta dilatation; hair greying; hair whitening; men; obesity; oxidative stress.

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Hair whitening (HW), a frequently encountered situation related in elderly, is strongly linked with aging. Higher oxidative stress and lower anti-oxidant capacity in addition to aging may be the most important factor for HW [1]. Other factors that may cause HW besides oxidative stress are family history of hair whitening, smoking, obesity, inflammatory conditions, androgen use, and social stress [2–8].

Interestingly, risk factors for premature hair whitening (PHW) including obesity, smoking, aging, inflammatory conditions, and oxidative stress also have major roles in cardiovascular diseases mainly atherosclerotic process [9–11]. Intrigued by these results, several investigators and we have demonstrated the association of especially premature HW with endothelial dysfunction, the extent of coronary artery disease, and myocardial in-

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farction [12–16]. Christoffersen et al. demonstrated that although affected by atherosclerotic risk factors, hair whitening was not an independent predictor of coronary artery disease (CAD) in an epidemiologic study. However, hair whitening remained significantly associated with myocardial infarction after adjusting for age and gender [16]. This study revealed that even if individuals were within similar age groups, the intensity of hair whitening was related to atherosclerosis.

Although these studies have mainly focused on the relation of hair whitening with atherosclerotic diseases, there is a reasonable possibility that hair whitening may be associated with different cardiovascular pathologies, which in fact may be affected by oxidative stress, the most important mediator of hair whitening. Ascending aortic dilation (AAD) is such a disorder [17, 18]. AAD is a clinical entity based on cystic medial degeneration/necrosis, which culminates in acute and deadly complications like aortic dissection, and rupture. Besides congenital reasons, age, smoking and atherosclerosis are associated with AAD [19, 20]. We have previously demonstrated that epicardial adipose tissue, and endothelial dysfunction is independently related with AAD [21, 22]. Since AAD and hair whitening share common etiologic factors, we thought that these pathologies might be related as well. We planned to investigate this association in our study.

MATERIALS AND METHODS

Patient selection and Study Protocol

Our study, having cross-sectional and observational design, included 93 male subjects aged below fifty years. The study was conducted in accordance with the principles stated in the Declaration of Helsinki and was approved by the local Ethics Committee. All patients underwent echocardiography to measure ascending aortic diameter, routine biochemistry tests, and physical examination in addition to thorough medical history.

We excluded patients with concomitant cardiovascular disease, familial aortic dilation, Marfan syndrome, bicuspid aortic valve, Ehlers Danlos syndrome and similar connective disease disorders, malignancy, chronic renal and hepatic failure, obstructive biliary disorders, hair whitening due to autoimmune diseases, and patients who dye hair or who has excessive balding that preclude correct identification of hair whitening.

Baseline characteristics of the patient were recorded. Hypertension (HT) was defined as the active use of antihypertensive drugs or documentation of blood pressure more than 140/90 mmHg. Diabetes mellitus was defined as fasting plasma glucose levels over 126 mg/dl or glucose level over 200 mg/dl at any measurement or active use of antidiabetic treatment. Patients who were using tobacco products on admission and those quitted smoking within the last year were considered as smokers. The family history for CAD was defined as a history of CAD or sudden death in a first-degree relative before the age of 55 years in men and 65 years in women.

Routine measurements

Blood samples were drawn by venipuncture to measure routine blood chemistry parameters after fasting for at least 8 hours. Fasting blood glucose, serum creatinine, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglyceride levels were recorded. Glucose, creatinine, and lipid profile were determined by standard methods. Serum CRP was analyzed using a nephelometric technique (Beckman Coulter Immage 800; Fullerton, CA, USA; normal range 0–0.8 mg/dL). Serum uric acid levels were evaluated using enzymatic colorimetric method (the uricase-peroxidase method) by clinical chemistry auto-analyzer (Aeroset, Abbott Laboratory, Abbott Park, IL, USA). Body mass index (BMI) was determined by the following formula: BMI = weight (kg)/height^2 (m).

Measurement of ascending aortic diameter

Transthoracic echocardiography was performed using GE-Vingmed Vivid S5 (GE-Vingmed Ultrasound AS, Horten, Norway) using a 2.5–3.5 MHz transducer. Parasternal long-axis view was used to visualize the aortic root and proximal ascending aorta. The aortic diameter was measured between the inner edges of the aortic lumen perpendicular to the long axis 2 cm above the sinotubular junction at end-diastole in views showing the largest aortic diameters.

The evaluation of hair whitening intensity

We used a gray/white-hair scale to determine the percentage of hair whitening (Fig. 1). Due to the lack of a standardized scale to determine premature hair whitening in the current literature, we assessed this scale for reproducibility in the first 25 subjects. Two experienced cardiologists who were totally blinded to the study details defined the percentage of white hair in every subject using this scale (between 0% and 100%) in our outpatient

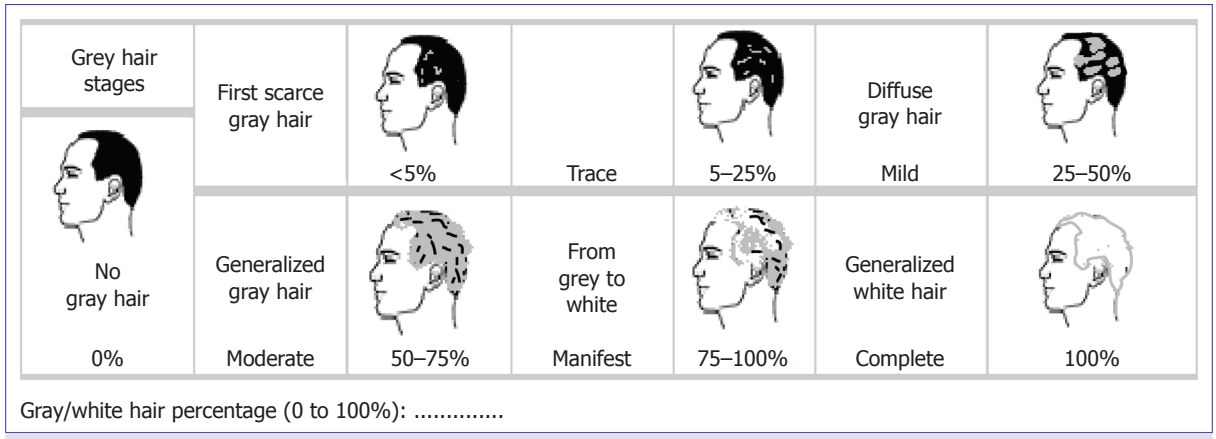

FIGURE 1. The gray/white hair scale

clinic. The intra-observer and inter-observer variabilities for this method were 1.3% and 1.9%, respectively. On presentation, to categorize the data, the hair whitening score (HWS) was defined according to the percentage of white hair (HWS 1 (Trace): <25%; HWS 2 (Mild): 25–50%; HWS 3 (Moderate): 50-75%: HWS 4 (Manifest): 75–100%: HWS 5 (Complete): 100%). Onset age of HW, and family history of early hair whitening were also determined.

Statistical analyses

Continuous variables were given as mean ± SD; categorical variables were defined as percentages. Data were tested for normal distribution using the Kolmogorov-Smirnov test. Spearman's rank correlation coefficient was used to analyze the relationship between the variables. Mean values were compared by ANOVA test among different groups. Multiple linear regression analyses were used to assess multivariate relations among ascending aortic diameter and hair whitening degree and study parameters. In these analyses, a stepwise method for all independent variables was used. After first pre-elimination, linear regression analysis with enter method was repeated.

Statistical significance was defined as $p<0.05$. All tests of significance were two-tailed. The SPSS statistical software (SPSS for windows, version 15.0, Inc., Chicago, IL, USA) was used for all statistical calculations.

RESULTS

Patient characteristics

Baseline characteristics of the group are presented in Table 1. Our study included 93 male subjects with the

TABLE 1. Baseline demographics and clinical characteristics of study population

Variables	Patients (n=93)
Age, years	44±6
Height, m	1.7±0.1
Weight, kg	88.5±12.9
Waist circumference, cm	102±12
Hypertension, %	23.7
Diabetes Mellitus, %	5.4
Smoking status, %	41.9
Ex-smoker, %	37.7
Dyslipidemia, %	43
Family history of CAD, %	29
HW age, years	29±10
Family history of HW	17.6%
Glucose, mg/dL	98±26
Creatinine, mg/dL	0.89±0.12
Uric acid, mg/dL	5.6±1.2
T. Bilirubin, mg/dL	0.92±0.51
Total cholesterol, mg/dL	205±42
LDL-Cholesterol, mg/dL	128±34
HDL-Cholesterol, mg/dL	41±9
Triglycerides, mg/dL	176±102
CRP,mg/dL,	0.42±0.50
Leukocytes, 103/mm³	7.7±1.6
Ascending aortic diameter, mm	34±4
Percentage of HW	47±39
HW score (1–5)	2.4±1.3

CAD: Coronary artery disease; CRP: C-reactive protein; HDL: High density lipoprotein; HW: hair whitening; LDL: Low density lipoprotein; Continuous variables were given as mean±SD; categorical variables were defined as percentages.

Table 2. The relation between hair whitening degree and study parameters

Variables n (93)	0–25% (36)	25–50% (16)	50–75% (12)	75–100% (29)	p
Age, years	42±5	43±5	46±5	48±5	<0.001
Diabetes Mellitus, %	5.5	6.2	8.3	3%	NS
Hypertension, %	8.3	18.6	33.3	41.4	0.014
Dyslipidemia, %	44.4	37.5	50	41.4	NS
Smoking, %	38.8	50	50	37.9	NS
Ex-smoker, %	29.2	30	50	47.6	NS
Family history of premature CAD	22.2	50	33.3	24.1	NS
Height, m	1.75±0.06	1.72±0.075	1.76±0.076	1.75±0.068	NS
Weight, kg	86±11	85±15	88±12	94±14	0.09
Waist circumference, cm	99±15	99±15	104±11	105±13	NS
HW age, years	23±20	34±3	32±4	27±7	0.01
Family history of HW	0%	0%	0%	55%	<0.001
Glucose, mg/dL	101±36	97±11	86±7	100±18	NS
Creatinine mg/dL	0.89±0.14	0.91±0.13	0.86±0.10	0.89±0.11	NS
Uric acid, mg/dL	5.3±1.2	5.2±1.2	5.3±0.9	6.1±1.4	0.043
Total bilirubin, mg/dL	1.01±0.57	1.19±0.65	0.71±0.24	0.75±0.35	0.027
Total cholesterol, mg/dL	202±46	207±32	203±42	209±43	NS
HDL-C, mg/dL	42±11	40±6	42±5	39±7	NS
LDL-C, mg/dL	124±37	128±23	128±35	133±36	NS
Triglycerides, mg/dL	168±86	199±103	169±89	178±123	NS
CRP, mg/dL	0.25±0.15	0.30±0.15	0.89±1.20	0.49±0.24	0.001
Leukocytes, $10^3/mm^3$	7.60±1.36	7.67±1.37	8.13±2.25	7.74±1.63	NS
Ascending aortic diameter, mm	32.8±3.34	32.4±2.96	34.5±3.68	36.8±3.2	<0.001

CAD: Coronary artery disease; CRP: C-reactive protein; HDL: High density lipoprotein; HW: hair whitening; LDL: Low density lipoprotein; Continuous variables were given as mean±SD; categorical variables were defined as percentages. *Mean values were compared by ANOVA test among different groups.

mean age of 44±6. Starting age of HW was 29±10, and approximately 18% of patients confirmed a family history of HW. Percentage of HW was variable (47±39) with a mean HW score of 2.4±1.3.

Hair whitening and study parameters

As we stratified the group according to quartiles of HW, patients with the highest degree of HW were older, and had higher percentage of hypertension and family history of HW (Table 2). Moreover, this subgroup had increased ascending aortic diameter, higher serum uric acid, and lower total bilirubin concentrations.

Correlations of ascending aortic diameter with study parameters

The strongest association existed between ascending aortic diameter and percentage of HW (r=0.513, p<0.001) (Table 3). Age, body weight, waist circumference, serum uric acid and CRP concentrations were positively correlated, whereas HW age and total bilirubin concentrations were negatively correlated with ascending aortic diameter. The correlations between ascending aortic diameter and HW percentage was moderate, however the remaining correlations were weak.

Multivariate analyses

Multivariate analyses including age, hypertension, height, waist circumference, CRP, and family history of HW identified body weight (β±SE=0.09±0.03, p=0.001), and HW score (β±SE=1.35±0.27, p<0.001) as the independent predictors of ascending aortic diameter.

Table 3. The correlations between ascending aortic diameter and study parameters

Variables, n (93)	Ascending aortic diameter
Hair whitening score	r=0.504, p<0.001
Percentage of HW	r=0.513, p<0.001
HW age, years	r=-0.275, p=0.025
Age, years	r=0.371, p=0.001
Height, m	r=0.261, p=0.012
Weight, kg	r=0.386, p<0.001
Waist circumference, cm	r=0.275, p=0.022
Uric acid, mg/dL	r=0.278, p=0.008
CRP, mg/dL	r=0.325, p=0.002
Total bilirubin, mg/dL	r=-0.097, p=0.388

CRP: C-reactive protein; HW: hair whitening; Spearman's rank correlation coefficient was used to analyze the relationship between the variables.

DISCUSSION

We revealed that ascending aortic dilation was significantly associated with hair whitening and obesity. The relation between AAD and HW is novel. We hypothesize that this association is not causal, which might exist mainly due to co-existing etiologic factors and parallel pathogenic processes.

Oxidative stress might be major etiologic agent in this parallel process. Even though, neither of our laboratory values did not correlate with oxidative stress directly, bilirubin known with antioxidant properties had an inverse relationship with hair whitening [23]. Moreover, an oxidative stress product in ischemic conditions, serum uric acid concentration was related to ascending aortic diameter [24]. We observed a similar association between hair whitening and serum uric acid. Additionally, C reactive protein (CRP), an inflammatory marker was correlated to both hair whitening and aortic dilation. This result was concurrent with previous studies that support the inflammatory hypothesis regarding hair whitening [16]. Even though our results may not directly link hair whitening and aortic dilation to oxidative stress, data support our hypothesis.

Aging is a natural course indubitably related to higher oxidative stress [16, 25]. The imbalance between increased oxidant molecules and decreased antioxidant factors cause accumulation of free radicals. These radicals affect cellular membrane, lipids, DNA, proteins and crucial enzymes. Melanocytes might be influenced by oxidative stress, which in turn disturb melanocyte function and melanin synthesis. This is the currently accepted mechanism of hair whitening.

Table 4. The independent association of ascending aortic diameter with study parameters

Linear regression analysis	Dependent variable: Ascending aortic diameter					
Independent variables	p	Beta (Standardized)	Beta±SE (Unstandardized Coefficients)	p	Beta (Standardized)	Beta±SE (Unstandardized Coefficients)
Age, years	0.337	0.111	0.07±0.07			
Hypertension	0.420	0.089	0.72±0.88			
Height, m	0.758	-0.040	-2.50±8.08			
Weight, kg	0.048	0.608	0.16±0.08	0.001	0.339	0.09±0.03
Waist circumference, cm	0.223	-0.333	-0.10±0.08			
Uric acid, mg/dL	0.313	0.110	0.30±0.29			
CRP, mg/dL	0.991	0.001	0.01±0.72			
Family history of HW	0.166	0.167	1.6±1.1			
HW score	0.001	0.413	1.12±0.32	<0.001	0.501	1.35±0.27
Constant	0.061		27±14	<0.001		23±2.2
Adjusted R^2	0.426	0.442				

SE: standard error; CRP: C-reactive protein; HW: hair whitening; Multiple linear regression analyses were used to assess multivariate relations among ascending aortic diameter and hair whitening degree and study parameters.

Aortic aneurysm is an inflammatory disorder characterized by weakening of aortic wall and ensuing aortic dilation due to increased turnover of connective tissue. Although the mechanism is not completely understood, hemodynamic stress on aortic wall, transmural inflammation, and destructive remodeling of the extracellular matrix have been plausibly blamed [26–29]. Inflammatory mediators augment matrix metalloproteinase (MMP) activity, which causes disruption of extracellular matrix, and subsequent remodeling of the aortic wall [30–33]. Since reactive oxygen species enhance MMPs, oxidative stress, in addition to inflammation, has a possible role in pathogenesis of aortic aneurysms [34]. Ejiri and coworkers demonstrated higher oxidative stress in patients with thoracic aortic aneurysm compared to controls, which was associated with p22phox-based NADH/NADPH oxidase expression [17]. Another study demonstrated decreased basal and oxidative stress induced metallothionein expression in ascending aortic aneurysms of bicuspid aortic valve patients [35]. Since metallothionein is a stress-induced metal binding protein that regulates MMP activity, and is up-regulated under oxidative stress, this study demonstrated the importance of imbalance between oxidant and anti-oxidant molecules in the pathogenesis of aortic aneurysm.

Another independent predictor of our study is body weight. Body weight determines obesity, and obesity is associated with increased visceral, perivascular, and epicardial adipose tissue. We previously demonstrated the relationship of epicardial adipose tissue with ascending aortic dilation [22].

Aortic dilation and aneurysm is an important disorder that might cause death due to aortic dissection and rupture. Since clinical symptoms and signs are scarce, diagnosis is usually incidental. Therefore, clues that suggest aortic dilation may be helpful for diagnosis in the early phase of this condition. Even though early diagnosis is important, there are not viable options to delay or stop further aortic dilation, possibly due to the fact that the mechanisms of aortic dilation is not fully elucidated. The demonstrated association between HW and aortic dilation may add valuable data and help to understand the mechanisms' of both HW and aortic dilation.

Study limitations

Our study has several limitations, the most important of which is the small number of subjects. Our study is observational in design; therefore our results do not implicate causality. Not utilizing better predictors of total oxidative stress is also a major limitation, making the proposed co-existing factors more speculative. There is not a standardized method for grading of HW. A more standardized method rather than visual grading could have strengthened our results.

Conclusion

There is an independent association between the degree of hair whitening and ascending aortic dilation in young-middle aged men, which may depend on co-existing factors that enhance both pathologies rather than causality. We think that oxidative stress may be one of these stressors.

Conflict of Interest: The authors declare no conflict of interest.

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