RESEARCH ARTICLE / *Araştırma Makalesi*

Is Premature Hair Whitening a Predictor of Hypertension for Healthy Young and Middle-Aged Men?

Erken Saç Beyazlaması Sağlıklı Genç ve Orta Yaşlı Erkekler için Hipertansiyonun Belirleyicisi midir?

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Abstract

Objective Oxidative stress is one of the essential factors in the development of Hypertension (HT). Hair whitening is a visual sign of oxidative stress. We hypothesized that the intensity of premature hair whitening might predict HT development, and we aimed to test it.

Materials and Methods A total of 172 healthy males with different stages of hair whitening were included in the study and evaluated after an average of 86 months. During the follow-up, we compared the data of patients diagnosed with HT to those who remained healthy.

Results Fifty-five (32%) of 172 patients were diagnosed with HT during follow-up period. In terms of demographic characteristics, age (41.48 ± 6.39 vs 44.36 ± 5.25 years; p=0.013), waist circumference (97.52 ± 10.87 vs 104.80 ± 11.94 cm; p=0.004), and body-mass index (27.61 ± 3.56 vs 30.20 ± 3.55 kg/m2; p<0,001) were higher in the HT group, whereas smoking history (p=0.211) was similar between the groups. In univariate analysis carotid intima-media thickness (CIMT)(p=0.013), gamma-glutamyl transferase (GGT)(p=0.021), and uric acid (p<0.001) levels were higher in the HT group; on the contrary, estimated glomerular filtration rate (eGFR)(p=0.039) and high-density lipoprotein (HDL) levels (p=0.026) were lower in this group. There was no difference between groups in terms of hair whitening stage and intensity. In multivariate analysis age (OR=0.143, 95%CI (1.002-1.328), p=0.046), eGFR (OR= -0.058, 95%CI (0.895-0.995), p=0.032), uric acid (OR=0.567, 95%CI (1.032-3.015), p=0.038), GGT (OR=0.030, 95%CI (1.001-1.060), p=0.041), and HDL (OR=-0.129, 95%CI (0.783- 0.986), p=0.028) were independently associated with de nova HT. Body-mass index, CIMT, and the leukocyte count were similar between the groups.

Conclusion Premature hair whitening is not predictive in determining the development of HT in young and middle-aged healthy men.

Keywords Hypertension; young; middle-aged; male; hair; oxidative stress

Öz

Amaç *Oksidatif stres, hipertansiyon (HT) gelişiminde temel faktörlerden biridir. Saç beyazlaması oksidatif stresin görsel bir işaretidir. Erken saç beyazlaması yoğunluğunun HT gelişimini öngörebileceğini varsaydık ve bunu test etmeyi amaçladık.*

Gereç ve Yöntemler *Saç beyazlığı farklı derecelerde 172 sağlıklı erkek çalışmaya dahil edildi ve ortalama 86 ay sonunda değerlendirildi. Takip süresi boyunca HT tanısı alan hastaların verilerini sağlıklı kalanlarla karşılaştırdık.*

Bulgular *Takip süresince 172 hastanın 53'üne (% 32) HT tanısı konuldu. Demografik özellikler açısından yaş (41,48 ± 6,39 vs 44,36 ± 5,25 yıl; p=0,013), bel çevresi (97,52 ± 10,87 vs 104,80 ± 11,94 cm; p=0,004) ve vücut-kitle indeksi (27,61 ± 3,56 vs 30,20 ± 3,55 kg / m2; p<0,001) HT grubunda daha fazla iken, sigara içme öyküsü (p=0,211) gruplar arasında benzerdi. Tek değişkenli analiz sonucunda karotis intima-media kalınlığı (KIMK)(p=0,013), gama-glutamil transferaz (GGT)(p=0,021) ve ürik asit (p<0,001) seviyeleri HT grubunda daha yüksek; tahmini glomerüler filtrasyon hızı (tGFH)(p=0,039) ve yüksek dansiteli lipoprotein (YDL)(p=0,026) düzeyleri ise daha düşüktü. Saç beyazlığı derecesi ve yoğunluğu açısından gruplar arasında fark yoktu. Çoklu değişkenli analiz yapıldığında, yaş (OR=0,143, 95%CI (1,002-1,328), p=0,046), tGFH (OR=-0,058, 95%CI (0,895-0,995), p=0,032), ürik asit (OR=0,567, 95%CI (1,032-3,015), p=0,038), GGT (OR=0,030, 95%CI (1,001-1,060), p=0,041) ve YDL kolesterol (OR=-0,129, 95%CI (0,783- 0,986), p=0,028) de nova HT ile bağımsız ilişkiliydi. Vücut-kitle indeksi, KIMK ve lökosit miktarı iki grup için benzerdi.*

Sonuç *Erken saç beyazlaması, genç ve orta yaşlı sağlıklı erkeklerde HT gelişimini belirlemede öngörücü değildir.*

Anahtar Kelimeler *Hipertansiyon; genç; orta yaş; erkek; saç; oksidatif stres*

INTRODUCTION

Hypertension (HT) is a major treatable cardiovascular risk factor with a high prevalence, and its frequency is increasing due to lifestyle and obesity. Hypertension, together with its complications, causes a considerable burden on national economies.[1,2] It is crucial to prevent the development of HT, thus understanding the factors and mechanisms that cause it.

Despite many experimental and clinical trials, the mechanism of HT is poorly understood. However, recent researches suggest strong evidence that oxidative stress plays a role in HT.[3] The effects of reactive oxygen radicals on the vascular wall and central nervous system are thought to be involved in this process.[4-6] Although researches into the protection of antioxidant therapy in cardiovascular diseases are inconsistent, there is evidence to the contrary. 3 Several clinical studies determined the relationship between oxidative stress-related factors such as uric acid and gamma-glutamyl transferase (GGT) with essential HT.[7-8]

Hair whitening is a simple indicator of oxidative stress that can be detected by inspection.[9] Premature hair whitening is interpreted as an indicator that the biological age is more than the chronological age. Additionally, premature hair whitening is associated with atherosclerotic cardiovascular diseases.[10,11]

We assumed that there might be a relationship between hair whitening and hypertension, and based on this hypothesis (Table 1), we aimed to find the interaction of hair whitening with hypertension in long-term follow-up in healthy young or middle-aged men.

MATERIALS and METHODS

The research was an observational, single-center, cohort study, and included 172 healthy men between the ages of 18-50. The study was performed under the principles stated in the Declaration of Helsinki and approved by Recep Tayyip Erdoğan University Faculty of Medicine, Non-Interventional Clinical Research Ethics Committee (09.09.2019, 219/123)

Table 1: Common pathogenesis of hair whitening and hypertension

Hair Whitening	Hypertension
Melanocyte dysfunction	Protective role of a-MSH
Family history	Family history
Oxidative stress (increased free radicals)	Oxidative stress (increased free radicals)
Inflamatory process	Inflamatory process
Impaired DNA repair	Impaired DNA repair
Correlation with age	Correlation with age
Significant relationship of white hair and hypertension subgroup of CAD patients	One of the main causes of atherosclerosis (CAD)

CAD: Coronary artery disease, MSH: Melanocyte stimulating hormone.

Patients diagnosed with HT under current guidelines were excluded from the study. Subjects with suspected white coat hypertension were evaluated with 24-hour blood pressure Holter and patients diagnosed with HT were excluded from the study. Over 50 years of age, female gender, chronic alcohol use, malignancy, gout, chronic renal failure (eGFR <30 ml/min/1.73m2), atherosclerotic cardiovascular disease, structural heart disease, diabetes mellitus, chronic liver disease, and chronic inflammatory disease were the exclusion criteria. During follow-up, we used face-to-face examination to determine HT. Patients diagnosed with secondary HT were excluded from the study.

Blood samples were drawn by a venous puncture to measure routine blood chemistry parameters after fasting for at least eight hours. Fasting blood glucose, serum creatinine, uric acid, gamma-glutamyl transferase (GGT), bilirubin, high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol, and triglyceride levels were recorded and determined by standard methods. Serum C-reactive protein (CRP) was analyzed using a nephelometric technique (Beckman Coulter Immage 800, Fullerton, CA, USA; normal range, 0–0.8 mg/dl). Body mass index (BMI)

was determined by the following formula: BMI = weight (kg) / height2 (m).

Carotid ultrasonography was performed on subjects using a high-resolution ultrasonography scanner (VingMed Vivid 3, GE Medical System, Horten, Norway) with a 7.0-MHz linear array transducer. An experienced cardiologist, blinded to patient data, performed carotid intima-media thickness (CIMT) measurements from both carotid arteries. Region 1 cm proximal to the carotid bifurcation was identified, and the CIMT of the far wall was evaluated as the distance between the lumen–intima interface and the media–adventitia interface. The CIMT was measured on the frozen frame of a suitable longitudinal image, and the image was magnified to achieve a higher resolution of detail. Measurement was obtained from four contiguous sites at 1-mm intervals, and the average of all eight measurements was recorded for analyses. Intra-observer mean absolute difference in measuring the CIMT was 0.026±0.043 mm (coefficient of variation: 1.6%, intra-class correlation: 0.95). Thickness >1.3 mm was defined as plaque.[12]

Since there is no standardized method of white hair classification, grading was done based on our clinical previous research (Figure 1).[10] Two cardiologists performed visual evaluations. Hair whitening score (HWS) was determined by the percentage of white hair and, the data were categorized: HWS 1 (Trace): <25%; HWS 2 (Mild): 25-50%; HWS 3 (Moderate): 50-75%: HWS 4 (Manifest): 75-100%: HWS 5 (Complete): 100%. The onset age of hair whitening, family history of premature hair whitening, and the percentage of hair loss were determined.

Statistical Analysis

Continuous variables were presented as the mean ± SD, and categorical variables were defined as percentages. The data were tested for normal distribution using the Kolmogorov-Smirnov test. Student's t-test was used for the univariate analysis of continuous variables for normally distributed numerical variables, the Mann-Whitney U-test was used for non-normally distributed numerical variables, and the $\chi 2$-test was used for categorical variables. Mean values among different groups were compared using analysis of variance (ANOVA). Regression analyses were performed to evaluate the relationships between CIMT and HWS and other CVRFs. All tests of significance were two-tailed. Statistical significance was defined as $p < 0.05$. The Statistical Program for Social Sciences (SPSS for windows 20, Inc., Chicago, IL, USA) was used for all statistical calculations.

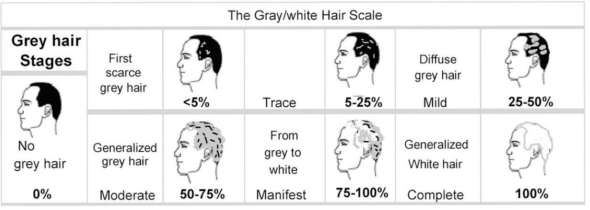

Figure 1: A gray/white-hair scale was used to determine the percentage of hair whitening. Two experienced cardiologists, blinded to the study details, defined the percentage of white hairs in every subject using this scale.

RESULTS

Subjects were followed for an average of 86 months in terms of HT development, and fifty-five (32%) of 172 patients were diagnosed with HT during follow-up period. Age (41.48 ± 6.39 year vs 44.36 ± 5.25; p=0.013), weight (84.16 ± 12.27 vs 90.92 ± 11.39 kg; p=0.003), waist circumference (97.52 ± 10.87 vs 104.80 ± 11.94 cm; p=0.004), and BMI (27.61 ± 3.56 vs 30.20 ± 3.55 kg/m2; p<0,001) were significantly higher, and dyslipidemia was tended to be more common (44 (% 41.9) vs 23 (% 59); p=0.068) in HT group. Smoking, hair whitening percentage and hair whitening score were similar between groups (Table 2).

The right (p=0.015), left (p=0.014), and average (p=0.013) CIMT thicknesses were significantly higher, and the plaque was tended to be more common (p=0.075) in the HT group. In laboratory data, the serum creatinine level (0.89 ± 0.11 vs 0.93 ± 0.14 mg/dL; p=0.05) was higher, and the estimated glomerular filtration rate (eGFR) was lower

Table 2: Demographic characteristics of groups with and without hypertension.			
	Healthy (n=117)	**Hypertension (n=55)**	**p value**
	Demographic data		
Age (years) (Mean ±SD)	41,48 ± 6,39	44,36 ± 5,25	**0,013**
Height (cm) (Mean ±SD)	174,50 ± 6,02	173,56 ± 6,34	0,416
Family history of CAD N (%)	18 (%17,1)	12 (%30,8)	0,074
Dyslipidemia N (%)	44 (%41,9)	23 (%59)	0,068
Cigaret N (%)			
Never smoked	48 (%45,7)	12 (%30,8)	
Quit smoking	13 (%12,4)	8 (%20,5)	0,211
Smoking	44 (%41,9)	19 (%48,7)	
Weight (kg) (Mean ±SD)	84,16 ± 12,27	90,92 ± 11,39	**0,003**
WC (cm) (Mean ±SD)	97,52 ± 10,87	104,80 ± 11,94	**0,004**
BMI (kg/m2) (Mean ±SD)	27,61 ± 3,56	30,20 ±3,55	**<0,001**
	Carotis Doppler ultrasonography data		
Right CIMT (cm) (Mean ±SD)	0,76 ± 0,14	0,83 ± 0,14	**0,015**
Left CIMT (cm) (Mean ±SD)	0,77 ± 0,14	0,84 ± 0,14	**0,014**
Mean CIMT (cm) (Mean ±SD)	0,77 ± 0,14	0,83 ± 0,14	**0,013**
Presence of CP N (%)	8 (%7,7)	7 (%17,9)	0,075
	Labaratory data		
Fasting Glucose (mg/dL) (Mean±SD)	95,05 ± 8,70	94,49 ± 11,28	0,802
Creatinine (mg/dL) (Mean ±SD)	0,89 ± 0,11	0,93 ± 0,14	**0,050**
eGFR (ml/min/1.73m2) (Mean ±SD)	102,41 ± 15,07	95,97 ± 15,62	**0,039**
Uric acid (Mean ±SD)	5,20 ± 1,09	6,17 ± 1,39	**<0,001**
Total bilirubin (mg/dL) (Mean ±SD)	0,81 ± 0,40	0,84 ± 0,46	0,738
Direct bilirubin (mg/dL) (Mean ±SD)	0,30 ± 0,13	0,28 ± 0,11	0,380
Indirect bilirubin (mg/dL) (Mean±SD)	0,52 ± 0,30	0,57 ± 0,37	0,459
Tot cholesterol (mg/dL) (Mean ±SD)	202,50 ± 40,92	206,39 ± 45,58	0,635
Triglyceride (mg/dL) (Mean ±SD)	166,58 ± 126,49	206,68 ± 114,58	0,090
HDL (mg/dL) (Mean ±SD)	43,48 ± 10,50	39,36 ± 5,14	0,026
LDL (mg/dL) (Mean ±SD)	124,86 ± 36,41	131,56 ± 35,54	0,360
GGT (U/L) (Mean ±SD)	29,67 ± 20,44	41,37 ± 29,23	0,021
CRP (mg/dL) (Mean ±SD)	0,36 ± 0,37	0,40 ± 0,25	0,568
Leukocyte (103/mm3) (Mean ±SD)	7,42 ± 1,64	8,26 ± 1,61	0,031
Lymphocyte (103/mm3) (Mean ±SD)	2,44 ± 0,76	2,79 ± 0,78	0,028
Monocyte (103/mm3) (Mean ±SD)	0,62 ± 0,18	0,69 ± 0,14	0,053
Neutrophil (103/mm3) (Mean ±SD)	4,06 ± 1,25	4,48 ± 1,23	0,102
Hgb (mg/dL) (Mean ±SD)	14,98 ± 1,11	15,02 ± 0,99	0,836

BMI: Body mass index, CIMT: Carotid intima-media thickness, CP: Carotid plaque, CRP: C-reactive protein, eGFR: Estimated glomerular filtration rate, GGT: Gamma-Glutamyl Transferase, HDL: Highdensity lipoprotein, Hgb: Hemoglobin, LDL: Low-density lipoprotein. WC: Waist circumference

(p=0.039) in the HT group. High-density lipoprotein cholesterol levels were lower (p=0.026) in this group, and no difference was found between the other lipid parameters. Uric acid (p<0.001) and GGT (p=0.021) were higher in the HT group. There was no difference between fasting glucose, total, direct, indirect bilirubin, and CRP levels (Table 2). The leukocyte (p=0.031), lymphocyte (p=0.028), and monocytes (p=0.053) count were higher in patients with HT, but there was no difference between groups in terms of neutrophil count.

In multivariate analysis age (OR=0.143, 95% CI (1.002-1.328), p=0.046), eGFR (OR=-0.058, 95% CI (0.895-0.995), p=0.032), uric acid (OR=0.567, 95% CI (1.032-3.015); p=0.038), GGT (OR=0.030, 95% CI (1.001-1.060); p=0.041) and HDL (OR=-0.129, 95% CI (0.783-0.986); p=0.028) had correlation with HT. Although there was no statistical significance (p=0.078), BMI tended to be associated with HT development. There was no relation between mean CIMT thickness and HT (Table 3).

Table 3: Multivariate analysis of newly developed hypertension related factors.

	B	S.E.	95 % C.I. for EXP (B)		P
			Lower	Upper	
Age (yrs)	0,143	0,072	1,002	1,328	**0,046**
BMI (kg/m2)	0,170	0,097	0,981	1,433	0,078
Mean CIMT (cm)	-4,321	2,841	0,070	3,478	0,128
eGFR (ml/min/1.73m2)	-0,058	0,027	0,895	0,995	**0,032**
Uric acid (mg/dL)	0,567	0,274	1,032	3,015	**0,038**
GGT (U/L)	0,030	0,014	1,001	1,060	**0,041**
WBC (103/mm3)	-0,063	0,226	0,603	1,461	0,779
HDL (mg/dL)	-0,129	0,059	0,783	0,986	**0,028**
Constant	-1,536	5,343			0,774

BMI: Body mass index, CIMT: Carotid intima-media thickness, eGFR: Estimated glomerular filtration rate, GGT: Gamma-Glutamyl Transferase, HDL: highdensity lipoprotein, WBC: White blood cell

DISCUSSION

The present study showed in young and middle-aged men, age, HDL, eGFR, uric acid, and GGT had an independent relationship with HT in the long term. Although no statistical significance, BMI seemed to play a role in the development of HT. Hair whitening intensity and premature hair whitening did not predict HT. The study is the first to investigate the relationship between hair whitening and development of HT.

The current study has once again demonstrated that HT was prepared over the years before its clinical manifestations and that clinical HT is only the visible part of the iceberg. The increase in CIMT and plaque in the carotid before HT emerged is one of the most concrete evidence of this argument. Although it does not reach a significant level in multivariate analysis, the result that chronic inflammatory cells such as monocytes and lymphocytes were higher in the HT group also supports the issue. Studies have shown that chronic inflammation is involved in the development of HT.[13] C-reactive protein levels were similar between the groups. That hs-CRP had not been used, or lack of inflammation due to low-risk patients in the study may explain this finding.

Higher waist circumference and BMI indicate a poor lifestyle and eating habits in patients with HT. The low HDL level was an independent predictor of HT development. The fact that HDL is a sedentary marker of lifestyle seems to be compatible with this finding.[14] Lower eGFR in patients with HT might be indicative of a subclinical renal dysfunction. The uric acid and GGT levels were correlated with the development of HT in many clinical trials.[7-8] Our research confirmed this data once more.

Hair follicles are complex structures, and the underlying mechanisms of pigment loss, causing hair whitening, are unclear. Disruption of DNA repair, loss of telomerase, androgen, inflammation, and decreased antioxidant capacity

are thought to lead the deterioration in melanin synthesis.[15-16] Arck PC et al. showed the role of oxidative stress in the aging of human hair follicles.[17] Inflammation and oxidation affecting melanocytes appear to be the main mechanisms of the relationship between hair whitening and atherosclerotic heart disease. Premature hair whitening is a risk factor for coronary artery disease and myocardial infarction.[18,19] Our theory was that chronic inflammation and oxidative stress affecting hair pigments could predict HT development. However, there was no relationship between premature hair whitening and hair whitening intensity with HT development. This result may be due to other factors that play a more active role in hair whitening than inflammation and oxidative stress.

Bilirubin is a potent natural antioxidant and has been shown to have a protective effect from HT. However, the design of these studies differed from the present research. Female subjects, participants already diagnosed with HT, and factors difficult to follow, such as alcohol dependence, were not excluded in these studies.[20-22] Another possibility may be that the effect of bilirubin on HT is weak, and the power of our research could not reveal this effect.

It is noteworthy that cigarette smoking had no role in the development of HT even though it causes an immediate increase in blood pressure by triggering spontaneous sympathetic activity. Smoking is known to increase oxidative stress, but in the present study, there was no difference in the development of HT among smokers compared to non-smokers.[23,24] Few epidemiological studies have confirmed this result.[25] Nevertheless, the consequence is paradoxical, considering the role of oxidative stress in the development of HT.

Obesity is one of the public health problems and a crucial risk for the development of cardiovascular diseases. In the HT group, BMI was on the border of obesity. Although there was no statistical significance, BMI was higher in the HT group, and there was a tendency to be significant in multivariate analysis. Similarly, waist circumference was higher in the HT group. The relationship between BMI and waist circumference with HT coincides with the results from similar studies.[26,27]

We found that, at 86 months of follow-up, the development of HT was at a rate of 32% in healthy male subjects. This rate would be higher if male subjects with diabetes or comorbid diseases were included in the study. The results show that proper ground is formed before HT occurs. Detection and prevention of this ground may cause delay and inhibition of HT development.

Limitations

This study was performed on a limited number of healthy males under the age of 50. It was conducted on a single ethnic population and a single geographical location. Due to the seasonal conditions of the region and the similarities of people's lifestyles, some results did not correspond to epidemiological data, including large populations. The fact that the intensity of hair whitening cannot be determined by a standardized method is a disadvantage for such studies. We believe that on premature hair whitening to predict the development of HT, researches with standardized tools in larger populations can give more accurate results.

CONCLUSION

Age, serum GGT, uric acid, HDL level, and eGFR have an independent relationship with HT development in healthy men under the age of 50. However, premature hair whitening has no role on predicting HT development.

Conflict of Interest

Authors have no conflict of interest to declare.

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