The degree of premature hair graying as an independent risk marker for coronary artery disease: a predictor of biological age rather than chronological age

Koroner arter hastalığı için bağımsız bir risk öngörücüsü olarak saçın erken beyazlama düzeyi: Zamansal yaştan çok biyolojik yaşın öngörücüsü

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ABSTRACT

Objective: Age is the most important and uncorrectable coronary risk factor at the moment. The concept of measuring aging biologically rather than only chronologically may be of importance in clinical practice. Hair graying is the most apparent sign of biological aging in humans, yet its mechanism is largely unknown. Today, it is known that cardiovascular risk factors (CVRFs), especially in combination, cause premature atherosclerosis. In our opinion, premature hair graying or whitening may represent early atherosclerotic changes as a surrogate of host response to the CVRFs. In this study, we planned to investigate the relationship of hair graying with CVRFs and coronary atherosclerotic burden in order to determine whether it is an independent marker for coronary artery disease (CAD).

Methods: The current study has a cross-sectional observational design. Two hundred and thirteen men who underwent coronary angiography with a suspicion of CAD were enrolled in the study. The patients were evaluated in terms of age, demographical properties and the CVRFs. Hair whitening score (HWS) was defined according to extent of gray/white hairs (1: pure black; 2: black>white; 3: black=white; 4: white>black; 5: pure white). Coronary atherosclerotic burden was assessed by the Gensini score. Analyses were performed in age-matched normal coronary arteries (NCA) and CAD groups. Linear and logistic regression analyses were used for the multivariate analyses of independent variables associated with hair greying.

Results: The CVRFs were higher in CAD group. Hair whitening score (2.7±1.3 vs. 3.3±1.2, p=0.002), hair losing score (1.2±0.9 vs. 1.5±1.0, p=0.038) and xanthelasma rate (24% vs. 45%, p=0.013) were also significantly different between NCA and CAD groups. Age (p<0001), Gensini score (p<0.001) and coronary severity score (p=0.001) were higher in the categories of increased HWS. In multiple logistic regression analysis, only diabetes mellitus (OR: 3.240, 95% CI: [1.017-10.319], p=0.047), low-density lipoprotein cholesterol, (OR: 1.014, 95%CI: [1.001-1.027], p=0.029) and HWS (OR: 1.513, 95% CI: [1.054-2.173], p=0.025) were independently related to presence of CAD. Age (p<0.001), family history of CAD (p=0.004), hyperlipidemia (p=0.02) and serum creatinine levels (p=0.019) were found as independent predictors of hair graying.

Conclusion: In our study, we found that the degree of gray/white hairs is related to extent of CAD. Our findings also suggested that hair graying is a risk marker for CAD independent of age and other traditional risk factors. Biological age may be important in determining total risk of patients. During assessment of cumulative CVRF effects on human body, presence of biological aging signs may be useful in identifying individuals with increased risk of cardiovascular disease. *(Anadolu Kardiyol Derg 2012; 12: 457-63)*

Key words: Hair graying, cardiovascular risk factors, coronary atherosclerotic burden, biological age, chronological age, vascular aging, regression analysis

ÖZET

Amaç: Yaş şu anda en önemli ve değiştirilemez bir koroner risk faktörüdür. Yaşın sadece zamansal olarak değil de, biyolojik olarak da ölçülmesi kavramı klinik pratikte önemli olabilir. Saç beyazlaması, mekanizmaları henüz geniş bir şekilde bilinilmese de, insanlarda biyolojik yaşlanmanın en açık işaretidir. Bugün kardiyovasküler risk faktörlerinin (KVRF) özellikle birlikte bulunduklarında erken ateroskleroza neden oldukları bilinilmektedir. Bizim görüşümüzce, erken başlayan gri veya beyaz saç oluşumu KVRF'lere vücudun yanıtının bir göstergesi olarak erken aterosklerotik değişiklikleri

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yansıtabilir. Bu çalışmada KVRF'ler ve koroner aterosklerotik yükün saç beyazlaması ile ilişkisi ve bunun koroner arter hastalığının (KAH) bağımsız bir belirteci olup olmadığının araştırılması amaçlandı.
Yöntemler: Çalışma gözlemsel ve enine-kesitli olarak planlandı. Kliniğimizde KAH şüphesi ile koroner anjiyografi yapılan 213 erkek çalışmaya dahil edildi. Hastalar yaş, demografik özellikler ve KVRF'leri açısından değerlendirildi. Saçın beyazlama derecesi (SBD) gri/beyaz saçların miktarına göre tanımlandı (1: yalnız siyah; 2: siyah>beyaz; 3: siyah=beyaz; 4: beyaz>siyah; 5: yalnız beyaz). Koroner ateroskleroz yükü Gensini skoruna göre belirlendi. Analizler yaş açısından eşitlenmiş normal koroner arterler (NKA) ve KAH gruplarında gerçekleştirildi. Saç beyazlaşma ile ilişkili bağımsız değişkenlerin belirlemesinde çok değişkenli lineer ve lojistik regresyon analizleri kullanıldı.
Bulgular: KVRF'ler KAH grubunda daha yüksekti. SBD (2.7±1.3 vs. 3.3±1.2, p=0.002), saç kaybı düzeyi (1.2±0.9 vs. 1.5±1.0, p=0.038) ve xanthalesma sıklığı (%24 vs. %45, p=0.013) NKA ve KAH grupları arasında ayrıca anlamlı düzeyde farklıydı. Yaş (p<0001), Gensini skoru (p<0.001) ve koroner lezyon ciddiyeti skoru (p=0.001) artan SBD kategorilerinde daha yüksekti. Çok değişkenli lojistik regresyon analizinde, sadece diyabetes mellitus (OR: 3.240, %95 CI: [1.017-10.319], p=0.047), düşük-dansiteli lipoprotein kolesterol [OR: 1.014, %95 CI: (1.001-1.027), p=0.029] ve SBD [OR: 1.513, %95 CI: (1.054-2.173), p=0.025] KAH varlığı ile bağımsız bir şekilde ilişkiliydi. KVRF'lerinin saç beyazlaması üzerine etkileri için yapılan analizde, yaş (p<0.001), KAH için aile öyküsü (p=0.004), hiperlipidemi (p=0.02) ve serum kreatinin düzeyleri (p=0.019) bağımsız öngörücü olarak bulunuldu.
Sonuç: Çalışmamızda gri/beyaz saçların düzeyi KAH'ın yaygınlığı ile ilişkili bulundu. Çalışma sonuçlarımız saç beyazlamasının yaş ve diğer KVRF'lerden bağımsız olarak KAH için bir belirteç olduğunu gösterdi. Biyolojik yaş ve onun kullanımı hastanın toplam riskini belirlemede klinisyenler için önemli olabilir. KVRF'lerinin insan vücudu üzerine birikimsel etkisinin değerlendirilmesinde, biyolojik yaşlanma işaretlerinin varlığı artmış kardiyovasküler riske sahip bireylerin tanımlanmasında kullanışlı olabilir. *(Anadolu Kardiyol Derg 2012; 12: 457-63)*
Anahtar kelimeler: Saç beyazlaması, kardiyovasküler risk faktörleri, koroner aterosklerotik yük, biyolojik yaş, kronolojik yaş, vasküler yaşlanma, regresyon analizi

Introduction

The incidence of atherosclerotic vessel involvement and the hair graying increase with advancing age. Age is the most important and uncorrectable coronary risk factor at the moment. The concept of measuring aging biologically rather than only chronologically may be important in clinical practice. Hair graying is the most apparent sign of biological aging in humans, yet its mechanism is largely unknown.

Atherosclerosis is a chronic inflammatory disease, which develops as a process occurring in the vessel wall, beginning with response to endothelial injury. Endothelial dysfunction is characterized with dysfunction of monolayer endothelial cells covering inside of the vessels. The regenerative capacity of endothelium provides protection against atherosclerosis. Failure of the endothelial repair initiates atherosclerotic inflammation and lesion formation in vascular bed. For a long time, in vascular system, it was believed that the damaged endothelial cells could only be repaired or replaced by proliferation and migration of neighboring endothelial cells (1). However, this concept has changed with the demonstration of variable stem cells in blood, especially endothelial progenitor cells.

The mammalian hair follicle represents a unique, highly regenerative system that contains numerous stem cells. The stem cells at the base of hair follicles produce melanocytes, the cells that produce and store pigment in hair. The death or dysfunction of the melanocyte stem cells causes the onset of graying (2). Similar to the vascular system, these stem cells have CD34 expression as well, and they may be related to functional maintenance of human hair follicle (3).

Today, it is known that cardiovascular risk factors (CVRFs), especially in combination, cause premature atherosclerosis and we think that they may lead to premature and intense hair graying by possible interactions on follicular epithelium and resident stem cells similar to their effects on endothelium and circulating progenitor stem cells (3, 4).

Previous studies with various sample sizes and different patient populations including coronary artery disease (CAD), myocardial infarction (5-11) noticed the association between premature graying and CAD (12). Several of these reports also showed association between premature hair whitening and myocardial infarction, although many are relatively outdated and have some methodological limitations, especially in determining the extent of CAD and intensity of hair whitening. In addition, there are also conflicting results for this issue in the literature. Therefore, we tested and detailed this antecedent finding in this study.

In this study, we investigated the relationship of hair graying with CVRFs and coronary atherosclerotic burden and to determine whether it is an independent marker for CAD.

Methods

Study design and patients

The current study, having a cross-sectional observational design, was conducted in the cardiology clinic at the Rize Education and Research Hospital in Rize, Turkey.

Two hundred and thirteen men who underwent coronary angiography with the suspicion of CAD between April 2010 and December 2010 were enrolled. All patients had chest pain or angina equivalent symptoms with either positive treadmill test or myocardial perfusion study. Study population was divided into different subgroups according to absence or presence of CAD and percentage of gray/white hairs. Patients with recent acute coronary syndrome either with or without ST-segment elevation (within one month before enrollment), non-ischemic dilated cardiomyopathy, evidence of ongoing infection or inflammation, hepatic or cholestatic disease, hematological disorders and known malignancy were excluded from the study. Women were also excluded from study; because of exact determination of HWS in women is not possible due to hair coloring.

The study was performed in accordance with the principles stated in the Declaration of Helsinki and approved by the local

Ethics Committee of Rize University, Faculty of Medicine. Informed consent was obtained from all patients prior to the study.

Cardiovascular risk factors

Clinical characteristics, which consisted of multiple descriptors from each patient's history and physical examination, were collected by physicians from cardiology laboratory of each patient and were stored in the database of coronary angiography laboratory at our institutions. The patients were evaluated in terms of age, demographical properties and the CVRFs. Hypertension (HT) was defined as the active use of antihypertensive drugs or documentation of blood pressure more than 140/90 mmHg. Diabetes mellitus (DM) 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 to our hospital 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 for men and 65 years for women.

C-reactive protein (CRP), routine biochemistry including glucose and lipids were measured. Serum CRP was analyzed using a nephelometric technique (Beckman Coulter Immage 800; Fullerton, CA, USA; normal range 0-0.8 mg/dL).

Hair graying assessment

We used a gray/white-hair scale to determine the percentage of hair graying (Fig. 1). Due to lack of a standardized scale in the current literature for the determination of premature hair graying, we formed and checked this scale for reproducibility in the first 25 subjects. Two experienced cardiologists who were totally blinded to the study details defined a percentage of white hairs for every subject by this scale (between 0 and 100%) in outpatient clinic. The intra-observer and inter-observer variability for this method were 1.5% and 5%, respectively.

In presentation, for categorization of data, hair whitening score (HWS) was defined according to percentage of gray/white hairs (1: pure black; 2: black>white; 3: black=white; 4: white>black; 5: pure white). Family history of early hair graying, hair loss score were also determined. Hair losing was scored as 0: none, 1: mild, 2: moderate, 3: severe.

Xanthelasma was described as plaque-like yellow lesions near the inner canthus of the eyelids (13). Arcus senilis, or corneal arcus, was described as a yellowish-white ring around the cornea (13). Earlobe crease was described as a line running diagonally from the bottom of the ear opening to the ear's lower tip (14). We excluded autoimmune related hair losing or graying disorders from the study.

Coronary angiography

Standard selective coronary angiography with at least four views of the left coronary system and two views of the right coronary artery was performed to all patients using the Judkins technique. Coronary angiograms were recorded on compact discs in DICOM format. Atherosclerotic coronary involvement was assessed by the number of vessels involved (vessel score) and by a severity score. Significant stenosis was determined visually and defined as ≥50% reduction in lumen diameter in any view compared with the nearest normal segment. Vessel score ranged from 0 to 4, depending on the vessels involved (0: normal, 1: <50% luminal narrowing, 2, 3 and 4: ≥50% luminal narrowing for 1, 2 and 3 vessels respectively). Coronary atherosclerotic burden was assessed using the Gensini score (15).

Statistical analysis

The SPSS statistical software (SPSS 15.0 for windows, Inc., Chicago, IL, USA) was used for all statistical calculations.

Continuous variables are given as mean±standard deviation and median (25^{th}-75^{th} percentile); categorical variables are defined as percentages. Data were tested for normal distribution

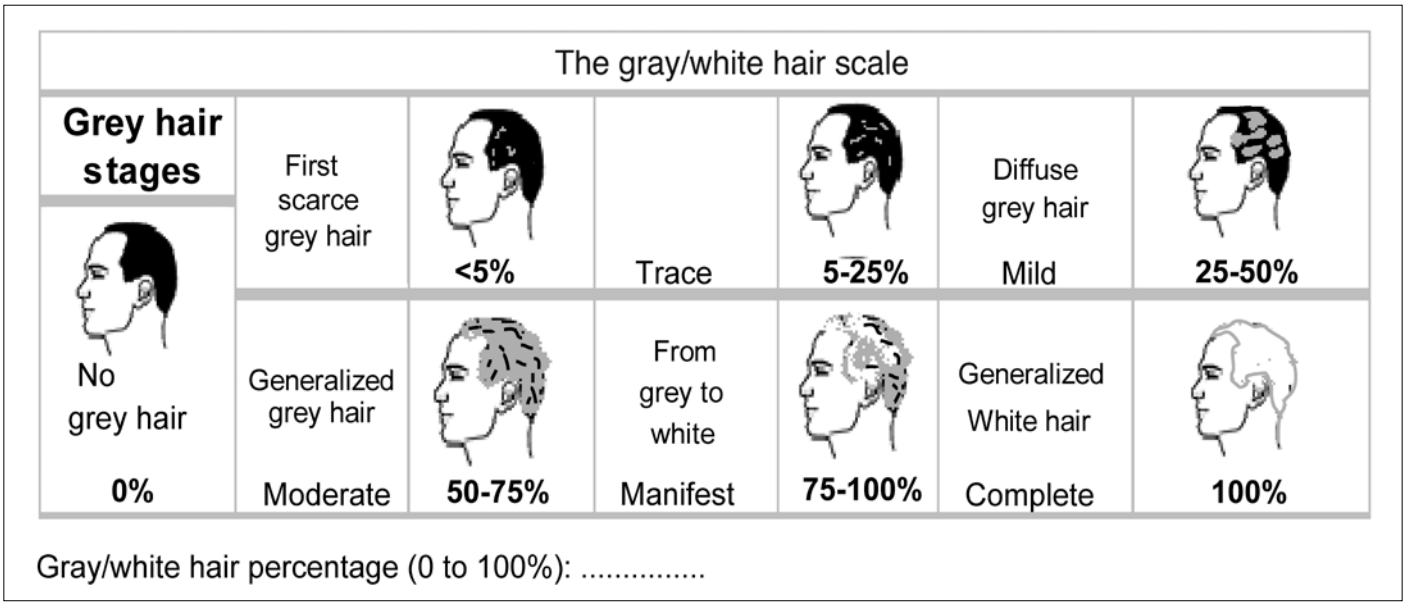

Figure 1. A gray/white-hair scale was used to determine the percentage of hair whitening. Two experienced cardiologists who were totally blind to the study details defined a percentage of white hairs for every subject by this scale (between 0 and 100%)

Table 1. Baseline characteristics of the study population

Variables	NCA (48)	CAD (165)	*p
Age, years	54±12	56±8	NS
Height, cm	171±8 170 (167-175)	171±6 172 (168-175)	NS
Weight, kg	83±14	87±13	NS
BMI, kg/m^2	29±6	29±4	NS
Hypertension, n (%)	16 (33)	91 (55)	0.009
Diabetes mellitus, n (%)	5 (10)	45 (28)	0.012
Smoking, n (%)	33 (68)	111 (67)	NS
Smoking, pack/year	15±18 19 (0-30)	23±26 20 (0-35)	NS
Hyperlipidemia, n (%)	25 (52)	129 (78)	<0.001
Family history of CAD, n (%)	11 (23)	74 (45)	0.013
Systolic blood pressure, mmHg	132±11	130±16	NS
Diastolic blood pressure, mmHg	79±7 80 (70-80)	82±11 90 (70-90)	NS
Glucose, mg/dL	102±20 98 (90-108)	121±55 102 (93-123)	NS
Creatinine, mg/dL	0.9±0.2 0.84 (0.77-0.95)	0.9±0.4 0.87 (0.80-0.97)	NS
Total cholesterol, mg/dL	184±33	199±44	0.018
LDL, mg/dL	115±28	128±37	0.013
HDL, mg/dL	40±8	40±11	NS
Triglyceride, mg/dL	147±109 103 (78-170)	159±86 132 (100-195)	0.045
CRP, mg/dL	0.57±0.75 0.36 (0.22-0.54)	0.58±0.65 0.39 (0.23-0.66)	NS
Gensini score	0±0 0 (0-0)	26±30 11 (3-46)	<0.001
LVEF%	57±14	57±12	NS
Hair whitening score	2.7±1.3 2 (2.0-3.8)	3.3±1.2 3 (2-4)	0.002
Family history of early hair graying, n (%)	23 (48)	68 (41)	NS
Hair losing score	1.2±0.9 1 (0-2)	1.5±1.0 1 (1-2)	0.038
Xanthalesma, n (%)	11 (23)	74 (45)	0.013
Arcus senilis, n (%)	3 (6)	7 (4)	NS
Earlobe crease, n (%)	18 (38)	84 (51)	NS
Hair thinning, n (%)	9 (19)	23 (14)	NS
Medications			
ASA / Clopidogrel, n (%)	17 (35)/0 (0)	76 (46)/10 (6)	NS/NS
Statin, n (%)	5 (10)	48 (29)	0.008
ACEI / ARB, n (%)	8 (17)/9 (19)	50 (30)/30 (18)	NS/NS
BB, n (%)	15 (31)	59 (36)	NS
CCB, n (%)	3 (6)	18 (11)	NS
OAD/Insulin, n (%)	0 (0)	18 (11)	0.015
Nitrate, n (%)	3 (6)	21 (13)	NS

Data are presented as mean±SD, median (25-75th percentile) and number (percentage)
*Student's t-test, Mann-Whitney U Test, and Chi-square test
ACEI - angiotensin converting enzyme inhibitor, ARB - angiotensin II receptor blocker, ASA - acetylsalicylic acid, BB - beta blocker, BMI - body mass index, CAD - coronary artery disease, CCB - calcium channel blocker, CRP - C-reactive protein, HDL - high-density lipoprotein, LDL - low-density lipoprotein, LVEF - left ventricular ejection fraction, NCA - normal coronary arteries, OAD - oral anti-diabetic drugs
Hair losing score (0-3) (0: none, 1: mild, 2: moderate, 3: severe); Hair whitening score (1-5) (1: pure black; 2: black>white; 3: black=white; 4: white>black; 5: pure white)

using the Kolmogorov-Smirnov test. Continuous variables with normal distribution were compared by Student's t-test and non-normal disturbed variables by Mann-Whitney U test, and the Chi-square test was used for the categorical variables between two groups. Mean values were compared by ANOVA for normal distributed variables and Kruskal-Wallis test for non-normal disturbed ones among different groups. Linear and logistic regression analyses were used for the multivariate analysis of independent variables which were included if they were significantly different in the univariate analyses.

Logistic regression for presence of CAD as dependent variable was used for multivariate analysis of relevant independent variables including age, HT, DM, hyperlipidemia, family history of CAD, LDL cholesterol, triglyceride and hair whitening score. Linear regression for hair whitening score as dependent variable was used for multivariate analysis of relevant independent variables including age, HT, DM, hyperlipidemia, family history of CAD, smoking and creatinine.

All tests of significance were two-tailed. Statistical significance was defined as $p<0.05$.

Results

Clinical characteristics

Baseline characteristics of study population are presented in Table 1. The CVRFs were higher in CAD group. Hair whitening score (HWS, 2.7±1.3 vs 3.3±1.2, p=0.002), hair losing score (1.2±0.9 vs 1.5±1.0, p=0.038) and xanthelasma rate (24% vs 45%, p=0.013) were also significantly different between normal coronary arteries (NCA) and CAD groups (Table 1).

Value of hair greying in prediction of CAD

Age (p<0001), Gensini score (p<0.001) and coronary severity score (p=0.001) were high in the categories of increased HWS (Table 2). In multiple logistic regression analysis, only diabetes mellitus (OR: 3.240, 95% CI: [1.017-10.319], p=0.047), low-density lipoprotein (LDL) cholesterol (OR: 1.014, 95% CI: [1.001-1.027], p=0.029) and HWS (OR: 1.513, 95% CI: [1.054-2.173], p=0.025) were independently related to presence of CAD (Table 3).

Relationship of hair greying with risk factors of CAD

Multiple linear regression analysis, evaluating the effects of CVRFs on hair graying, revealed age (p<0.001), family history of CAD (p=0.004), hyperlipidemia (p=0.02) and creatinine (p=0.019) as independent factors associated with HWS (Table 4).

Discussion

In this study, we investigated the relationship of hair graying intensity, which is a sign of biological aging in humans, with CVRFs and coronary atherosclerotic burden to determine whether it is related to CAD independent of chronological age and other CVRFs. We found that hair-graying score independently related to coronary atherosclerotic burden. In addition, hair-graying intensity associated with age, hyperlipidemia and family history of CAD and creatinine levels.

Table 2. The distribution of study parameters in categories of the hair whitening in men

Variables	Categories of the hair whitening (n=213)						
	Pure Black Hair	Black>White	Black=White	White>Black	Pure White Hair	*F/ Chi-square	*p
Age, years	47±7	52±9	55±8	59±8	63±8	19	<0.001
Height, m	1.71±0.07	1.72±0.06	1.71±0.06	1.72±0.06	1.70±0.08	0.7	NS
Weight, kg	86±12	86±13	86±16	87±13	84±17	0.9	NS
BMI, kg/m^2	29±3	29±5	29±6	30±4	29±6	0.1	NS
Hypertension, %	30	45	57	59	48	7	NS
Diabetes mellitus, %	22	21	13	28	41	9	NS
Smoking, %	65	73	60	69	72	6	NS
Family history of CAD, %	18	39	49	48	26	9	NS
Hyperlipidemia, %	74	66	75	77	69	2	NS
Total cholesterol, mg/dL	201±44	194±42	193±36	202±47	186±42	0.5	NS
LDL, mg/dL	132±36	123±36	126±33	126±38	122±37	0.9	NS
HDL, mg/dL	41±8	40±9	38±11	41±10	43±13	0.9	NS
Triglycerides, mg/dL	144±112 107 (89-168)	158±92 122 (93-200)	164±79 136 (109-203)	174±102 146 (98-217)	113±49 100 (84-128)	10	NS
Glucose, mg/dL	113±44	121±58	104±27	115±37	134±78	0.1	NS
Creatinine, mg/dL	0.92±0.16 0.88 (0.80-1.00)	0.85±0.13 0.82 (0.76-0.90)	0.93±0.24 0.88 (0.80-1.00)	1.03±0.57 0.90 (0.80-0.99)	0.87±0.15 0.84 (0.77-0.92)	8	NS
CRP, mg/dL	0.44±0.34 0.31 (0.22-0.55)	0.57±0.64 0.35 (0.22-0.60)	0.56±0.51 0.42 (0.24-0.70)	0.50±0.55 0.34 (0.19-0.58)	0.93±1.14 0.40 (0.24-1.10)	3	NS
Ejection fraction, %	57±14	56±14	59±9	55±14	56±14	0.9	NS
Gensini score	2.7±4.6 1 (0-3)	18.4±24.4 5.3 (0-37)	20.3±31.0 6 (1-27)	25.9±29.4 8.5 (2-51)	23.6±37.9 5 (1-45)	18	<0.001
Coronary severity score	0.7±0.8 1 (0-1)	1.6±1.4 1 (1-3)	1.6±1.4 1 (1-2)	2.0±1.2 2 (1-3)	1.6±1.3 1 (1-3)	16	0.001
Presence of CAD, %	55	71	77	91	79	14	0.006

Data are presented as mean±SD, median (25-75th percentile) and number (percentage)

*ANOVA, Kruskal-Wallis and Chi-square tests

BMI - body mass index, CAD - coronary artery disease, CRP - C-reactive protein, HDL - high-density lipoprotein, LDL - low-density lipoprotein

The hair follicle is one of the most complex units of the human body. Although graying and whitening of hair is understood as a loss of pigment in the shaft, its molecular and cellular bases are partially understood. Theses for gradual loss of pigmentation include attenuation of enzymes involved in melanogenesis, impaired DNA repair, loss of telomerase, and antioxidant mechanisms (14, 16-20). These proposed mechanisms are also valid in atherosclerosis. Oxidant stress, androgens, inflammatory process, senescence of functioning cells were all proposed for atherosclerosis as well. In our opinion, CVRFs may have some negative effects on follicular cells including resident epithelial, neural, and mesenchymal stem cells similar to their effects on endothelium and progenitor stem cells in vasculature. Thus, while follicular cell dysfunction and cell apoptosis cause hair whitening and loss, these findings can simultaneously represent atherosclerotic influence due to the common mechanisms and individual host responses to CVRFs.

Although hair graying in different ages is a very common phenomenon, the events that cause and control natural and pathological hair graying and whitening in humans are not yet clear. We know that CVRFs have negative effects on endothelium and circulating stem cell function and may cause progressive cell senescence.

The mammalian hair follicle represents an unequaled, highly regenerative system that contains many different stem cells. Hair follicle undergoes life-long cycles of rapid growth. These transformations are controlled by changes in the local milieu, based on changes in activity of a number of cytokines, hormones and neurotransmitters (4). The stem cells at the base of hair follicles produce melanocytes, the cells that produce and store pigment in hair. The death or dysfunction of the melanocyte stem cells causes the onset of graying (2). Similar to the vascular system, these stem cells have CD34 expression as well, and

Table 3. Prediction of presence of CAD in study population: multiple logistic regression analysis

Independent variables	Odds Ratio (95% CI)	†p
Age, years	1.00 (0.95-1.05)	0.880
HT	2.06 (0.93-4.52)	0.071
DM	3.24 (1.01-10.31)	0.047
Family history of CAD	2.04 (0.75-5.49)	0.157
Hyperlipidemia	1.75 (0.75-4.06)	0.190
LDL, mg/dL	1.01 (1.00-1.02)	0.029
HDL, mg/dL	0.99 (0.96-1.03)	0.936
Triglyceride, mg/dL	1.00 (0.99-1.00)	0.645
Hair whitening score	1.51 (1.05-2.17)	0.025

†Logistic regression with Enter method
Dependent variable - presence of CAD, independent variables: age, HT, DM, hyperlipidemia, family history of CAD, LDL cholesterol, triglyceride, hair whitening score
CAD - coronary artery disease, CI - confidence interval, DM - diabetes mellitus, HDL - high-density lipoprotein, HT - hypertension, LDL - low-density lipoprotein

Table 4. Relationship of cardiovascular risk factors with hair whitening score

Variables	β±SE	Standardized Coefficients	*p
Age, years	0.060±0.006	0.528	<0.001
HT	-0.036±0.132	-0.015	0.758
DM	0.192±0.139	0.073	0.168
Hyperlipidemia	0.332±141	0.122	0.020
Family history of CAD	0.382±131	0.151	0.004
Smoking	0.189±131	0.079	0.149
Creatinine, mg/dL	0.294±0.124	0.124	0.019
Constant	-1.082±0.421	-	0.011
R^2		0.319	

*Linear regression with Enter method
Dependent variable - hair greying score
β±SE - beta and standard error, CAD - coronary artery disease, CVRFs - cardiovascular risk factors, DM - diabetes mellitus, HT - hypertension

they may be related to functional maintenance of human hair follicle (3). We speculate that CVRFs have some effects on local milieu in the hair follicle, thus depress follicle function because of local reactions.

Lebon et al. (12) who noticed the association between premature graying and coronary artery disease reported the first study on this issue. They concluded that premature graying of the hair is an independent risk factor. Our findings also supported these observations and detailed them. Afterwards, subsequent studies with various sample sizes were performed in different patient populations including CAD, myocardial infarction in black or white men or women (5-11). Several of these reports also showed association between premature hair whitening and myocardial infarction, although many are relatively outdated and have some methodological limitations, especially in determining the extent of CAD and intensity of hair whitening. Therefore, there are conflicting results in the literature. Schnohr et al. (8) published a report with data derived from the Copenhagen City Heart Study. The authors identified male pattern baldness as a risk factor for myocardial infarction as well as hair graying and facial wrinkling. The authors, however, revoked their conclusions afterwards (9). In a relatively new study by Miric et al. (10) moderately grey hair yielded a significant relative risk of MI, but only in men under the age of 45 years. Mansouri et al. (11) investigated the relation between premature hair graying as well as androgenic alopecia and CAD in women, and demonstrated a significant association. In our study, we also tested this antecedent finding and discovered supportive results.

As a risk marker, increased HWS may be important for atherosclerotic vessel involvement, but at any given age, it is clear that the absence of gray hair does not prevent the appearance of CAD. On the other hand, in cumulative assessment of CVRFs on human body, presence of biological aging signs may be useful in identifying individuals with increased risk of cardiovascular disease.

Because premature hair graying was found to be a cardiovascular risk factor independent of chronological age and other traditional CVRFs, it may be a marker of atherosclerosis that cannot be explained by the traditional CVRFs and predicted by risk scores. Previous studies has shown a relationship between hair whitening and incidence of MI or presence of CAD, however the relationship between premature hair graying and coronary atherosclerotic burden has not been searched therefore premature hair graying was not determined as an independent risk marker for extent of atherosclerosis until now.

Atherosclerosis is a consequence of chronic inflammatory reactions in the vessel wall. These inflammatory reactions begin with the increase in endothelial permeability caused by endothelial dysfunction, which represents the impaired balance between vascular damage and repair. Recently, it was proved that endothelium is not alone to balance against damaging effect of CVRFs in vasculature. In this reparative process, a more important role seemed to belong to EPC in circulation. After firstly defined by Asaraha et al. (21), we have gained more knowledge about their source, roles, levels and functionality. CVRFs, like aging, DM, hyperlipidemia and smoking, affect the EPC count and act destructively (22-29). Recently, these effects are emphasized for the development of atherosclerosis.

Biological age may be important in determining patient's total cardiovascular risk. Various skin conditions are considered to be characteristic markers for increased coronary disease risk. People exposed to different risk factors and environmental effects have individual responses, which can be determined by the genetics and life habits. Classical risk scores like Framingham risk score use the same parameters and chronological age for everybody but the usage of biological age may be important in these calculations. Greying or whitening of hair and baldness are common signs of aging, which may play a role as indicators of the biological age of an individual. In the future, a useful scale may be introduced to predict biological age into clinical practice. Currently physicians use individual sense to do this but in our opinion a generally accepted scale is needed for this purpose. In addition, it

is possible that we could learn more about pathophysiology of atherosclerosis by investigating causative genetic and environmental factors that determine premature hair whitening.

Study limitations

In our study, study population consisted of patients with known CVRFs, which may produce relatively higher risk population than age- and gender-matched individuals and this selection bias is likely to affect the predictive power of HWS for CAD. In addition, relatively racially homogenous population due to a restrictive geographic area and no possibility to establish causality as an epidemiological study was the other limitations of our study.

Conclusion

Our findings suggested that the degree of hair graying is related to presence of CAD independent of chronological age and other CVRFs. Further studies are needed to clarify how hair graying or whitening represent host response to the CVRFs by possible functioning cell interrelations in vasculature. In cumulative assessment of CVRFs on human body, presence of premature hair graying may be useful in identifying individuals with increased risk of cardiovascular disease.

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