Original Article

Androphenotypic Features in Patients with Coronary Artery Disease

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Abstract

Objective: It has been a debate whether phenotypic features are associated with increased risk of coronary heart disease. Proposed explanations for this relation include biological aging, individual susceptibilities, and androgens which contribute to both the atherosclerotic process and dermatological signs. The results of the studies are inconsistent and most are not based on cardiovascular imaging techniques. Here, association between androphenotypic features and the risk and severity of coronary artery disease (CAD) in men is evaluated. **Methods:** This case–control study consists of 166 male patients with angiography-proven CAD and 160 age-gender-matched controls. Gensini score of angiograms (for severity of CAD) and phenotypic characteristics including androgenetic alopecia (AGA), thoracic hairiness (TH), hair graying a diagonal earlobe crease (DEC), and hairy ear (HE) were recorded. Men with well-established cardiovascular risk factors were excluded. **Results:** AGA, DEC, and HE were significantly more frequent in patients with CAD than controls (98.2% and 83.1% [$P < 0.001$], 61.4% and 23.8% [$P < 0.001$], 69.3% and 50.6% [$P = 0.001$], respectively). As the severity of AGA increased, the incidence of heart disease was increasing in patients. The presence of TH and AGA was found to be related to higher Gensini scores. **Conclusion:** The exact mechanism between these phenotypic features and CAD still remains to be elucidated. However, observation of visible aging signs is easy and inexpensive. AGA, HE, and DEC may be used as early screening tools for CAD.

Keywords: Androgenetic alopecia, coronary artery disease, ear lobe crease, hair greying, risk factors, thoracic hairiness

Introduction

Androgenetic alopecia (AGA), thoracic hairiness (TH), hair greying (HG), and diagonal earlobe crease (DEC) have been proposed as risk factors for coronary artery disease (CAD).[1-3] Biological aging, individual susceptibilities, and androgens are suggested explanations for both atherosclerotic process and dermatological features.[4-6] Results of the studies on the relationship between androphenotypic features and cardiovascular risk factors are inconsistent.[3,6-9] In most of them, diagnosis of atherosclerosis was not based on certain cardiovascular imaging techniques but only the patient's history. The purpose of this study is to investigate the association of cutaneous phenotypic features with angiographically proven coronary atherosclerosis. The effects of the severity of cutaneous features and coronary atherosclerotic burden were also evaluated.

Methods

This is a case–control study performed in 1-year period. One hundred and sixty-six men with CAD proven by angiography performed in Celal Bayar University Hospital Cardiology Clinic were included in the study. Control group consisted of 160 age-matched healthy males who admitted to the dermatology outpatient clinic of the same hospital with the dermatologic diagnoses without any systemic involvement (such as tinea pedis and irritant eczema). None of them had any sign or history of a cardiac disease. Males with well-established cardiovascular risk factors including hypertension, diabetes, dyslipidemia, abdominal obesity, family history of myocardial infarction, alcohol consumption, and smoking (with the

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cutoff values according to the WHO criteria) were excluded to assess the relation of the phenotypic features with CAD independently.[10] The tenets of the Declaration of Helsinki were observed. Ethical approval was received from the Local Ethics Committee of Celal Bayar University. Informed consent was obtained from all patients.

Assessment of andro-phenotypic dermatological signs

The presence of AGA, TH, HG, a DEC, and hairy ear (HE) was recorded in both patients and controls. DEC was defined as a crease stretching obliquely from the outer ear canal toward the border of the earlobe at least in one earlobe. HE was assigned when there were hairs on the auricula independent from its intensity.

Assessment of the severity of androphenotypic dermatological signs

The Norwood-Hamilton (N-H) classification[11] was used to grade AGA. "N-H scale I, II, and III alopecias" were described as "mild or absent," "N-H scale lll vertex, IV and V" as "moderate AGA," and N-H scale VI and VII as "severe AGA."

TH was categorized as "mild or absent" when there were none or few sparse hairs on the chest; "moderate" when a larger area of the chest was hairy; and "intensive" when the hairiness of the chest spread to the back and/or shoulders.

HG was defined as "mild or absent" when there were no gray hair or individual gray hairs scattered over the scalp; "moderate" when there were gray sideburns; and "intensive" when the hair was completely gray/white.

Gensini scores of angiograms for grading the severity of the coronary disease

Gensini score taking into account both the extent and the severity of the lesions in coronary angiography was calculated for each patient to evaluate the severity of CAD. This scoring system grades the stenosis in the epicardial coronary arteries (1 for 1%–25% stenosis, 2 for 26%–50% stenosis, 4 for 51%–75% stenosis, 8 for 76%–90% stenosis, 16 for 91%–99% stenosis, and 32 for total occlusion) and multiplies this number by a constant number determined according to the anatomical position of the lesion.[12] Gensini scores were calculated and evaluated by the cardiologist in the study team.

Statistical analysis

All statistical analyses were performed using SPSS V.21.0 for Windows (SPSS, Chicago, Illinois, USA). Continuous variables were defined by the mean ± standard deviation and median, minimum-maximum values. Categorical variables were defined as percentages. Kolmogorov–Smirnov test was used for the determination of normal distribution. Mann–Whitney U-test was used for independent group comparisons, and the Chi-square test was used for the categorical variables between two groups. The relative risks were estimated as odds ratios. Logistic regression analysis was utilized for determining the risk factors. $P < 0.05$ was considered statistically significant.

Results

One hundred and sixty-six patients and 160 controls were evaluated. The mean ages of the coronary cases (59.8 ± 11.09) and noncoronary controls (60.2 ± 9.71) did not show a statistically significant difference ($P = 0.698$). AGA, DEC, and HE were significantly more frequent in patients with CAD than controls. AGA was present in 98.2% of patients and 83.1% in controls ($P < 0.001$). The presence of earlobe crease was 61.4% in patients and 23.8% in controls ($P < 0.001$), and 69.3% of patients had HE while 50.6% of controls had ($P = 0.001$). The presence of TH (68.1% of controls and 59% in patients, $P = 0.107$) and HG (96.3% of controls and 85.5% in patients, $P = 0.001$) was not significantly associated with the risk of CAD.

We investigated the relationship between the grades of the phenotypic signs and the severity of CAD to see if more severe forms of dermatological findings were associated with a higher risk of coronary disease. The incidence of CAD was observed to increase as the severity of AGA increased ($P = 0.01$) [Graph 1]. The presence of TH, HE, and AGA was related to higher Gensini scores [Graph 2].

The relative risk ratio of coronary disease for a particular dermatological sign was detected as odds ratios [Table 1]. Multivariate logistic regression analysis was used to control the effects of the dermatological signs other than the analyzed one and age; the strongest predictors of coronary disease were DEC, AGA, and HE with odds ratios of 5.19, 3.69, and 1.99, respectively.

Discussion

This study showed that the phenotypic characteristics AGA, DEC, and HE were associated with the presence of angiography-proven CAD in males. This association was further supported by the observation that CAD was also more frequent in more severe forms of AGA when compared with less severe forms. In addition, the presence of AGA and HE was associated not only with the frequency of CAD but also with its severity.

AGA is the most investigated factor for cardiovascular risk.[13,14] A meta-analysis evaluating six studies revealed that the severity of AGA is related with the greater risk of heart disease.[15] In addition to CAD, hyperlipidemia, hyperinsulinemia, insulin resistance, metabolic syndrome, and hypertension were also reported to be more common in patients with AGA.[16] These metabolic conditions are similar to the complications expected in women with polycystic ovarian syndrome (PCOS), and it is well known that hypertrichosis and female type AGA are the phenotypic features of PCOS.[17-19] It has been suggested that men with early AGA can be considered the male phenotypic equivalents of women with PCOS.[17]

Androgens may be responsible for the severity of dermatological signs such as alopecia and TH as well as the atherosclerotic process.[1] Androgen receptors are both present on the scalp and

in blood vessels where they are involved in smooth muscle cell proliferation, an important component of the atherosclerotic process.[20] The pathogenesis of DEC is explained by the thinning of epidermis, dermis, and by degeneration of elastin in aging skin.[21] Previous studies have emphasized that both the earlobe and myocardium are supplied by end arteries containing few collaterals.[21,22] Therefore, atherosclerosis leading to local vascular insufficiency may cause consequent skin atrophy and DEC.

The presence of TH, despite being associated with higher Gensini scores within the coronary patient group, was not significantly different between patients and controls in this study. Body hairiness is basically associated with ethnicity. TH is more common in Mediterranean men when compared with Asian ones. Although some studies define TH as an independent predictor for CAD,[1] perhaps due to the ethnic factors mentioned, it may not be distinguishable for our population.

The human HEs phenotype is considered a Y-linked heritable trait.[23] HE was related with CAD and higher Gensini scores in our study population. Similar results have been reported in populations of different genetic origin.[24] Studies which previously showed an association between Y-chromosome haplogroup I and CAD presents a strong link for a Y-linked heritable component of CAD.[23] It has also been suggested that long-term androgenicity is a possible cause of accelerated atherosclerosis in a patient as well as eventual virilization and hair growth on the skin of the ears.[24]

HG, which is often associated with chronological aging, has not been identified as an additional risk factor for CAD in our study. It is unclear why melanocytes cease melanin synthesis in the hair follicle.[2] A case–control study reported that only an early HG which appears before the age of 35 is related to CAD,[25] and in another one, HG was associated with myocardial infarction only in their participants under 45 years of age.[1] The mean age of our study group was 60 years. In this study, as in some studies in the literature,[1] we evaluated the HG status of both patients and controls at the time of their hospital admission. Our results suggest that studies questioning the age of onset of HG can yield more efficient results while evaluating the risk of hair graying and CAD with further studies in our population.

Study limitations

The limitation of this study is the relatively small number of patients. In addition, it was not possible to perform angiography in the healthy control group for ethical reasons. As a case–control study, it was not also possible to fully control all factors that can increase cardiovascular risk in both groups. Yet, we think that excluding patients with known cardiovascular risk factors may minimize those potential limitations.

Conclusion

This study revealed a significant association between the visible phenotypic findings AGA, HE, and DEC and the risk of CAD in the Turkish population. The exact mechanism between these phenotypic features and CAD remains to be elucidated. However, the observation of visible aging signs is easy and inexpensive. They may be used as early screening tools for CAD. In future, some findings may be added to the cardiovascular risk score models such as Framingham risk Score, or a useful scale can be created to reflect biological age into clinical practice. Modifications in lifestyle, early screening, and follow-up for cardiovascular disease may be useful in males with the mentioned cutaneous features. Further studies with broad study groups, preferably prospective cohort ones, are required to better evaluation of this relationship.

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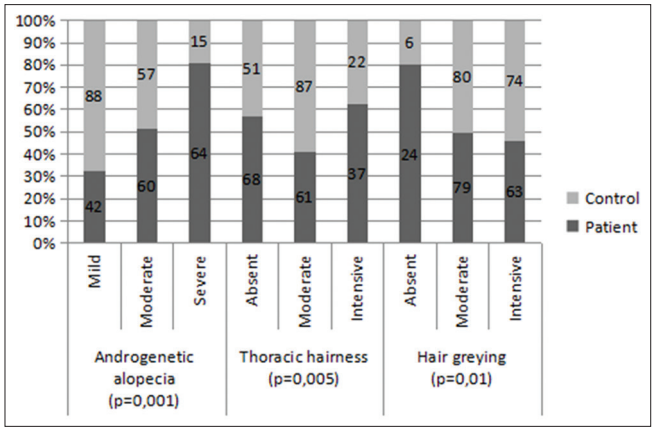
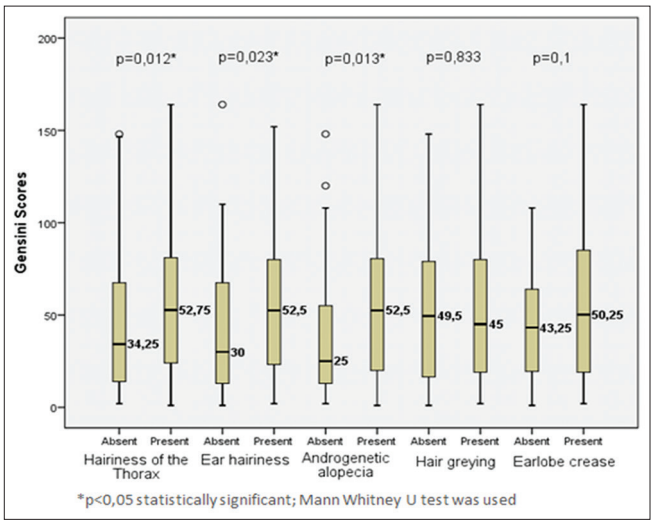
Nil.

Conflicts of interest

There are no conflicts of interest.



Graph 1: Grades of dermatophenotypic signs in coronary artery disease patients and noncardiac controls



Graph 2: Associations of dermatophenotypic signs with Gensini scores (severity) in coronary patients

Table 1: The relative risk ratio (95% confidence interval) of coronary disease for men with a particular dermatological sign

	Univariate OR (95% CI)	*P*	Multivariate OR (95% CI)	*P*
Earlobe crease	5.11 (3.16-8.26)	0.000	5.19 (3.02-8.92)	0.000
Androgenetic alopecia	3.608 (2.25-5.76)	0.000	3.69 (2.12-6.43)	0.000
Ear hairiness	2.19 (1.39-3.45)	0.001	1.99 (1.16-3.42)	0.012
Thoracic hairiness	0.67 (0.42-1.062)	0.089	0.43 (0.24-0.76)	0.004
Hair graying	0.23 (0.09-0.58)	0.002	0.16 (0.05-0.49)	0.001
Age	0.99 (0.97-1.01)	0.717	0.97 (0.94-1.00)	0.119

CI: Confidence interval, OR: Odds ratio

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