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Heritability of the femoral intima media thickness

Bence Fejer [a,1], Adam D Tarnoki [a,b,*,1], David L Tarnoki [a,b,1], Pierleone Lucatelli [c], Levente Littvay [d], Pal Maurovich-Horvat [e], Adam L Jermendy [e], Attila Kovacs [e], Erika Godor [a], Corrado Fagnani [f], Maria A Stazi [f], Andrea A Molnar [e,g,h], Fabrizio Fanelli [c], Carlo Cirelli [c], Filippo Farina [i], Claudio Baracchini [i], Giorgio Meneghetti [i], Giacomo Pucci [j], Gyorgy Jermendy [k], Bela Merkely [e], Giuseppe Schillaci [j], Emanuela Medda [f]

[a] Department of Radiology, Semmelweis University, 78/A Üllői Street, Budapest 1082, Hungary
[b] Hungarian Twin Registry, 29 Erdélyi Street, Budapest 1212, Hungary
[c] Vascular and Interventional Radiology Unit, Department of Radiological, Oncological and Anatomo-Pathological Sciences, Sapienza University of Rome, Viale Regina Elena 324, 00161 Rome, Italy
[d] Central European University, 9 Nador Street, Budapest 1051, Hungary
[e] MTA-SE Cardiovascular Imaging Research Group, Heart and Vascular Center, Semmelweis University, 18 Hataror Street, Budapest 1122, Hungary
[f] Genetic Epidemiology Unit, National Centre of Epidemiology, Surveillance and Health Promotion; Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Rome, Italy
[g] Research Group for Inflammation Biology and Immunogenomics of Hungarian Academy of Sciences, Semmelweis University, 44 Róbert Károly Krt., Budapest 1134, Hungary
[h] Department of Cardiology, Military Hospital, 44 Róbert Károly Krt.., Budapest 1134, Hungary
[i] Department of Neurosciences, University of Padua School of Medicine, via Giustiniani 5, 35128 Padova, Italy
[j] Università di Perugia, Unità di Medicina Interna, Ospedale "S. Maria", Viale Tristano di Joannuccio, 1, 05100 Terni, Italy
[k] 3rd Department of Internal Medicine, Bajcsy Zsilinszky Hospital, 89-91 Maglódi Street, Budapest 1106, Hungary

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ABSTRACT

Background: The measurement of femoral intima-media thickness (IMT) is underutilized in the clinical practice, although it is a surrogate marker of cardiovascular disease.
Materials and methods: 388 Hungarian and Italian twins (121 monozygotic, 73 dizygotic pairs) underwent bilateral B-mode sonography of femoral arteries. IMT was measured by semiautomated software, where available, or by calipers.
Results: Within-pair correlation in monozygotic twins was higher than in dizygotics for each parameter. Age-, sex- and country-adjusted genetic effect accounted for 43.9% (95% confidence interval, CI 21.3%–65.2%) and 47.2% (95% CI, 31.4%–62.6%) of the variance of common and superficial femoral artery IMT, respectively, and unshared environmental effect for 56.1% (95% CI 34.6%–78.5%) and 52.8% (95% CI, 37.2%–68.5%). These results did not change significantly after correcting for body mass index or central systolic blood pressure.
Conclusions: Genetic factors have a moderate role in the determination of common and superficial femoral IMT; however, the influence of environmental (lifestyle) factors remains still relevant. Environmental factors may have a role in influencing the genetic predisposition for femoral vascular hypertrophy.

1. Introduction

Peripheral artery disease has long been underestimated and underdiagnosed in the primary care setting [1,2]. In the European Union, 17 million individuals are estimated to have peripheral artery disease, with a prevalence of 20% in people aged over 65 years [3]. Femoral atherosclerosis has been associated with higher cardiovascular risk in patients with lower extremity peripheral artery disease. Femoral atherosclerosis is a marker disease with high diagnostic and prognostic impact for prediction of coronary and other cardiovascular events.

Abbreviations: BMI, body mass index; MZ, monozygotic; DZ, dizygotic; CCA, common carotid artery; CFA, common femoral artery; SFA, superficial femoral artery; IMT, intima media thickness; SBP, systolic blood pressure; DBP, diastolic blood pressure; A, additive genetics (heritability); C, shared environmental variance component; E, unique environmental variance component; AIC, Akaike information criteria; BIC, Bayesian information criteria; LL, log likelihood.

* Corresponding author at: Department of Radiology, Semmelweis University, 78/a Ulloi Street, H-1082 Budapest, Hungary.
E-mail addresses: bence.fejer@gmail.com (B. Fejer), tarnoki2@gmail.com (A.D. Tarnoki), tarnoki4@gmail.com (D.L. Tarnoki), pierleone.lucatelli@gmail.com (P. Lucatelli), levi@littvay.hu (L. Littvay), maurovich.horvat@gmail.com (P. Maurovich-Horvat), adam.jermendy@gmail.com (A.L. Jermendy), kovatti@gmail.com (A. Kovacs), godorerika@gmail.com (E. Godor), corrado.fagnani@iss.it (C. Fagnani), stazi@iss.it (M.A. Stazi), molnandi@gmail.com (A.A. Molnar), fabrizio.fanelli@uniroma1.it (F. Fanelli), dottcirelli@gmail.com (C. Cirelli), farippo@gmail.com (F. Farina), claudiobaracchini@gmail.com (C. Baracchini), giorgio.meneghetti@unipd.it (G. Meneghetti), giacomo.pucci@gmail.com (G. Pucci), gyjermendy@mail.datanet.hu (G. Jermendy), merkely.bela@gmail.com (B. Merkely), giuseppe.schillaci@unipg.it (G. Schillaci), emanuela.medda@iss.it (E. Medda).
[1] These authors contributed equally to this work.

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Measurement of femoral intima-media thickness (IMT), a measure of vascular hypertrophy, can be easily performed by B-mode ultrasound scanning to detect early atherosclerosis [4].

Increased femoral IMT is considered a surrogate marker of cardiovascular disease [5–8]. Femoral IMT has been associated with carotid [7] and coronary atherosclerosis [8] as well. It has been shown that femoral IMT increases sharply after 18 years of age, especially in men and the geometry of femoral artery is related to blood pressure and body growth [8]. The risk factors that favor the development of femoral vascular hypertrophy consist of advanced age, male gender, weight, fat mass, hyperlipidemia, smoking, hypertension and diabetes [8,9]. Although femoral IMT has been proposed to be a novel cardiovascular risk factor [8], the relative importance of heritable effects influencing its development is unknown. Currently, there is relatively little information with regard to genetic contributions to the femoral atherosclerosis. Therefore, the purpose of our study was to assess the heritability of the femoral IMT that will not only help to understand the underlying pathomechanism but, in case of the influence of genetic factors, it might also contribute to call the attention to the early diagnosis upon screening of individuals at high risk of developing femoral vascular hypertrophy.

2. Material and methods

2.1. Subjects and study design

388 twins (246 Hungarian from Budapest and its broader area; 142 Italian from Padua, Perugia, Terni and their broader area; 242 monozygotic/MZ/, 146 dizygotic/DZ/; 119 males and 269 females; mean age 53 ± 14 years) considering themselves healthy, recruited from the Hungarian and Italian Twin Registries, underwent B-mode sonography of bilateral common and superficial femoral arteries in a volunteer-based fashion in this cross-sectional multicentre twin study in 2013 and 2014 [10,11]. Hungarian twins were investigated as part of the BUDAPEST-GLOBAL study [12]. Moreover, additional younger twin pairs between 18 and 45 were also studied with femoral ultrasound. Twin pairs of other than Caucasian ethnicities were not involved in the study. Additional exclusion criteria were pregnancy and individuals with a history of femoral surgery.

The twins were contacted by the researchers of the Hungarian and Italian twin registries and the investigations were described in detail. All subjects were asked not to smoke 3 h, not to eat 1 h, not to drink alcohol and coffee 10 h prior to the measurements in order to exclude the effects of these factors on the vascular tone. A multiple self-reported questionnaire based on seven-part, self-reported response, was used to maximize the accuracy of zygosity classification [13]. All study subjects gave informed consent prior to entering the study after explanation of the nature and possible consequences of the study, which was conducted in full compliance with regulations of the Ethical Committee of Semmelweis University. The tenets of the Declaration of Helsinki were followed.

The vascular measurements were obtained in large university hospitals in Budapest as well as in Padua, Perugia and Terni in Italy. Participants were asked to fill in a questionnaire in order to report a complete past medical history, risk factors and diseases. Weight measurements were carried out by a clinically validated OMRON BF500 body consistency monitor (Omron Healthcare Ltd., Kyoto, Japan). Body height was verified simultaneously using a tape in order to calculate the body mass index (BMI). Peripheral and central (aortic) blood pressures were measured with TensioMed Arteriograph device (Medexpert Ltd., Budapest, Hungary). Disease history and risk factors (see Table 1) were assessed by a standardized questionnaire. The Hungarian measurements were performed by two investigators (BF, ADT). The Padua, Perugia and Terni measurements were performed by the same investigators (ADT, DLT) together. Both members of the twin pairs were scanned by the same radiologist at all times.

2.2. Femoral ultrasonography

Bilateral femoral arteries were measured by duplex (B-mode and color Doppler) ultrasonography with 5–10 MHz linear array high-frequency probes (in Padua: Toshiba Aplio XG, in Perugia: Sonoscape S8, in Terni: Esaote MyLab 60, in Hungary: Philips HD-15) by trained radiologists. Following the proper identification of the two parallel echogenic lines of lumen-intima and media-adventitia interfaces, IMT was measured in the far wall after appropriate adjustment of the focus. First, the common femoral artery was assessed and IMT was obtained 1–2 cm proximal from the bifurcation. Afterwards, segment of the proximal superficial femoral artery was insonated 1–2 cm distal from the bifurcation. In case of plaques, IMT was measured in the plaque-free segments. No ECG gating was applied.

The IMT was analyzed in the saved offline DICOM images by QLAB (Philips Healthcare, Best, The Netherlands) software in Hungary in at least 0.5 cm long segment where IMT was best identifiable (Fig. 1). The program averages all IMT values of this segment and the average value has been used in further analysis. Electronic calipers were used at the time of scanning in the Italian centers since automated IMT measurement was not available. At least two readings were obtained for each of the arterial segments and the average values of the two recordings were used in the analysis to increase the accuracy. In order to eliminate the effect of different techniques in Italy and Hungary, country was controlled for in all of the analyses by regressing country out of the phenotypes.

Table 1
Baseline characteristics of study subjects included in the statistical analysis (121 MZ, 73 DZ twin pairs).

	Total (n = 388)	Monozygotic (n = 242)	Dizygotic (n = 146)	P	Hungarian (n = 246)	Italian (n = 142)	P value
Zygosity (nMZ:nDZ)	242:146	–	–	–	160:86	82:60	<0.001
Male:female, n:n	119:269	82:160	38:108	0.48	82:164	37:105	0.10
Age, years	49.7 ± 13.4	48.8 ± 13.3	50.9 ± 13.5	0.12	53.0 ± 12.3	45.0 ± 13.6	<0.001
Right CFA IMT, mm	0.58 ± 0.16	0.58 ± 0.15	0.60 ± 0.18	0.28	0.59 ± 0.15	0.57 ± 0.18	0.24
Right SFA IMT, mm	0.44 ± 0.10	0.43 ± 0.09	0.45 ± 0.11	0.15	0.46 ± 0.09	0.40 ± 0.10	<0.001
Left CFA IMT, mm	0.59 ± 0.17	0.57 ± 0.16	0.61 ± 0.18	0.003	0.60 ± 0.17	0.57 ± 0.17	0.04
Left SFA IMT, mm	0.44 ± 0.10	0.43 ± 0.09	0.45 ± 0.10	0.08	0.46 ± 0.08	0.42 ± 0.11	<0.001
Brachial SBP, mm Hg	121.3 ± 14.6	121.4 ± 14.4	121.1 ± 14.9	0.83	123.2 ± 14.4	118.6 ± 14.5	<0.001
Brachial DBP, mm Hg	74.0 ± 10.3	74.1 ± 9.9	73.9 ± 10.7	0.92	76.2 ± 10.1	70.9 ± 9.8	<0.001
Central SBP, mm Hg	119.0 ± 18.3	119.1 ± 18.2	118.8 ± 18.5	0.85	122.6 ± 17.5	114.0 ± 18.3	<0.001
BMI, kg/m^2	26.2 ± 4.9	26.1 ± 0.9	26.2 ± 4.9	0.92	27.2 ± 5.1	24.7 ± 4.2	<0.001
Hypertension, n (%)	114 (29.3)	65 (26.9)	49 (33.6)	0.61	90 (36.6)	24 (16.9)	<0.001
Diabetes, n (%)	19 (4.9)	12 (5.0)	7 (4.8)	0.74	17 (6.9)	2 (1.4)	0.01
Hypercholesterolemia, n (%)	116 (29.9)	66 (27.2)	50 (34.2)	0.60	93 (37.8)	23 (16.2)	<0.001
Smoking, n (%)	155 (39.9)	82 (33.9)	73 (50.0)	0.04	84 (34.1)	71 (50.0)	0.17

BMI, body mass index; MZ, monozygotic; DZ, dizygotic; CFA, common femoral artery; SFA, superficial femoral artery; IMT, intima media thickness; SBP, systolic blood pressure; DBP, diastolic blood pressure. Data are shown as mean ± standard deviation where appropriate.

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