Original article

Factors affecting the progression of atherosclerosis in the coronary arteries

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Abstract

Background: The induction and progression of atherosclerotic changes is complex and influenced by many factors. The most important are enhanced concentration of LDL cholesterol, enlarged production of free radicals, the inflammatory reaction, endothelial damage, decreased concentration of HDL and increased prothrombotic activity.

Aim: To define the factors influencing the atherosclerotic process in the coronary arteries of patients with coronary disease in serial coronary examinations.

Methods: In the 2nd Department of Cardiology in the Medical University of Lodz, 8989 coronary angiography studies were performed between January 1999 and May 2004. The second intervention in the earlier studied patients was made because of clinical indications. The investigation included 177 consecutive patients (128 men and 49 women) in whom the coronary angiography was executed at least twice.

Results: A significantly larger degree of atherosclerotic process occurred in the group of patients younger than the average age of the studied group (p=0.004), in those with a family history of circulatory diseases (p=0.02), as well as in patients with numerous risk factors of coronary disease (p=0.01). In the well-fitted model of the prediction of progression of vascular changes, according to the Gensini Score in individual time (p <0.02), two independent parameters were identified – gender (p=0.04) and statin therapy (p=0.03). The odds ratio with 95% confidence interval in males was 2.1 (1.1-5.2), and for the use of statin – 0.48 (0.21-0.91).

Conclusions: Significant progression of atherosclerotic changes in the coronary vessels was confirmed in the studied population. In the group of men faster progression of atherosclerotic changes, in particular of lesions in the proximal parts of the coronary arteries, was confirmed, whereas therapy with statins significantly slowed down this process in all studied sections of the coronary arteries, especially in their distal parts.

Key words: arteriosclerosis, progression of atherosclerotic process, coronary arteries

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Introduction

Atherosclerosis involves formation of multiple focal lesions in the internal and medial layers of the coronary artery walls resulting in decreased elasticity and narrowed lumen. The atherosclerotic process is the effect of long--lasting defensive response to factors having a harmful influence on the vascular wall. This response is a chronic, fibroproliferative inflammatory process [1]. The natural history of atherosclerosis has progressive character in subsequent years. It is determined by typical cardiovascular risk factors [2] and individual profile.

The aim of this study was to define factors affecting coronary artery disease (CAD) progression.

Methods

The material for the study was collected in 1999–2004, making use of 8989 coronary angiographies performed. Patients who underwent coronary angiography at least twice were selected for further assessment. Patients underwent repeated coronary angiography if clinically indicated. The causes of subsequent examinations were as follows: recurring pain, progression of heart failure symptoms, new (segmental) impairment of contractility or lowering of left ventricular ejection fraction, positive result of electrocardiographic or echocardiographic stress tests or radionuclide tests. The study involved 177 consecutive patients (including 128 males and 49 females), who

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Table I. Age and cause of first hospitalisation of the studied patients

Parameter	Study group (n=177)	Females (n=49)	Males (n=128)
Mean age	55±10	59±9	53±0*
Number of patients with stable coronary artery disease	21	9	12
Number of patients with ACS NSTEMI	89	25	64
Number of patients with ACS STEMI	67	15	52

** p <0.05 males compared to females.*
Abbreviations: ACS – acute coronary syndrome, NSTEMI – non-ST--elevation myocardial infarction

underwent coronary angiography at least twice. Table I shows the causes of the first hospitalisation. Mean age of the study group was 55±10 years, in the female group 59±9 years, and in male group 53±10 years.

Atherosclerotic changes in coronary arteries in the studied patients were analysed and described using serial coronary angiographies. The changes were defined by percentage of lumen narrowing, using a semi-quantitative method – the Gensini Score System [3]. Vessels in which revascularisation had ever been carried out were excluded from being analysed. Changes in Gensini Score reflecting progression or regression of atherosclerotic changes within coronary arteries were analysed. Assessment was made to find out what factors have an impact on progression and regression of these changes within coronary arteries and in their proximal and distal segments. Proximal part of the coronary arteries was defined as the initial 1/3 of the vessel including side branches, and the distal part as the end 2/3 of the vessel including mid and distal segments of the right and left coronary arteries with their branches. The following factors were analysed: age, gender, obesity, family history, smoking, arterial hypertension, diabetes, peripheral artery disease, past stroke, paroxysmal atrial fibrillation, known CAD with CCS class, known heart failure with NYHA class assessment, past hepatitis, basic laboratory test results, additional tests (resting ECG, echocardiography, Holter ECG monitoring, exercise test), and medical therapy (acetylsalicylic acid, thienopyridine derivatives, ACE-I, statins, beta-blockers). Sixty-seven data together were analysed. Results of basic laboratory tests in the studied group are presented in Table II. Table III shows the profile of coronary disease risk factors among patients. Table IV shows the pharmacotherapy used.

Table II. Results of biochemical tests in the studied group

Parameter	Mean	Range
Total cholesterol [mg/dl]	196.6±45.5	95-427
HDL cholesterol [mg/dl]	42±11	19.8-86
LDL cholesterol [mg/dl]	120.6±90.4	68-251
Triglycerides [mg/dl]	172±93.5	32-607
CK [U/dl]	491±1203.3	17-8471
CK-MB [U/dl]	54.7±127	4-1151
TnI [ng/dl]	1.29±3.6	0.012-18
Urea [mg/dl]	35±12.8	15.5-104.7
Creatinine [mg/dl]	1.05±0.3	0.53-3.47
AST [U/dl]	77±136	14-846
ALT [U/dl]	45.9±40.9	8-250

Abbreviations: CK – creatine phosphokinase, CK-MB – creatine MB isoenzyme, TnI – troponin I, AST – aspartate transaminase, ALT – alanine transaminase

Table III. Prevalence of coronary risk factors in the studied patients

Parameter	Number (%)
Arterial hypertension	110 (62%)
Diabetes mellitus	27 (15%)
Overweight	24 (13.5%)
Smoking	65 (37%)
Positive family history	14 (8%)
Atrial fibrillation	13 (7%)
Peripheral artery disease	7 (4%)
Stroke	5 (3%)

Statistical methods

The results are presented as mean values ± SD or numbers and percentages. All quantitative variables were initially analysed for normal distribution using the W Shapiro-Wilk test. If the value of W statistics was significant ($p < 0.05$) then the hypothesis of a normal distribution was rejected. The significance of differences of quantitative variables between groups was analysed using the T-test for independent samples, or U Mann-Whitney test depending on normality of variable distribution. The assessment of correlation of two quantitative variables was made using Spearman nonparametric correlation test after verifying for normal distribution. Statistical analysis of differences in group sizes was carried out using χ^2 test with Yates' correction or Fisher's exact test depending on the group size. Multivariable analysis was made using logistic regression, in which Gensini Score index change over time was treated as a binominal feature (lesion progression compared to no progression). Estimation of logistic regression equation was made using the quasi

Table IV. Medical therapy in the studied patients

Drug	% of patients
Angiotensin-converting enzyme inhibitors	53%
Thienopyridine derivatives	67%
Statin	75%
Beta-blocker	79%
Aspirin	88%

Table V. Clinical parameters affecting the progression of coronary atherosclerosis

Clinical parameters	Patients with disease progression in the coronary arteries (n=122)	Patients with no disease progression in the coronary arteries (n=55)	p
Mean age	54±10.3	58±9.7	0.004
Positive family history	11%±31%	2%±13%	0.02
Number of risk factors	2.3±1.0	1.9±0.9	0.01

Newton method. In order to estimate loss function, maximum likelihood method was used. Adjusting binomial variable prediction model was carried out using step regression analysis. Values of $p < 0.05$ were found significant. Statistica PL 6.0 software (StatSoft Polska) was used for statistical analyses.

Results

Mean time between subsequent examinations was 15 months, with a maximum of 63 months and a minimum of 3 months. A tendency towards growing atherosclerotic lesions was noticed during examination. During follow-up, the mean Gensini Score increased. Mean initial Gensini Score was 21.9±29.7 points, mean final Gensini Score was 35.7±38.4 points. Regression of atherosclerotic process was confirmed in 2 patients. Mean Gensini Score increase over a year was 15.4 points on a point scale according to Gensini for all arteries, 8.6 points for proximal arteries and 10.3 for distal arteries. Among the examined clinical parameters some had a significant effect on progression of atherosclerosis ($p < 0.05$) (Table V). Atherosclerotic process was more severe in patients younger than the mean age of the study population, in patients with family history of cardiovascular disease and in patients with multiple risk factors of CAD.

On the basis of logistic analysis performed, progression or lack of progression of atherosclerotic lesions according to Gensini Score helped to establish the binominal variable prediction model [4]. In the adjusted prediction model of progression of arterial lesions according to Gensini Score in time unit ($p < 0.02$) there are two variables left: gender ($p=0.04$) and statin therapy ($p=0.03$). Odds ratio with 95% CI calculated for changes in variable range was 2.1 (1.1-5.2) in females and 0.48 (0.21-0.91) for statin use.

Other factors for which the results were statistically borderline turned out to be:

(1) male gender – association with atherosclerosis progression within proximal arteries, $p=0.053$,
(2) higher heart rate showed a relation with atherosclerosis progression in coronary arteries, $p=0.059$,
(3) statin therapy – association with reduced atherosclerosis progression in distal arteries, $p=0.071$, and
(4) the use of angiotensin-converting enzyme inhibitors – relation with reducing atherosclerosis progression in distal arteries, $p=0.081$.

Discussion

Our study confirmed age-related differences in the atherosclerotic process course. The difference between men and women in the incidence of atherosclerosis result from biological and psychological distinctions. The incidence of CAD in males is on the rise after 45 years old, and in the over-60 age group it remains stable. In females the process escalates due to the beginning of menopause, especially after 55 years of age [5]. Endocrine activity of the ovaries is the most essential defensive mechanism in women. Higher oestrogen concentration in women results in higher HDL cholesterol levels. During menopause, the HDL level is decreased to the one observed in men, whereas LDL level increases [4]. These are males who more often smoke, abuse alcohol, do not obey indications regarding prevention of CAD, show lower compliance in case of treatment necessity (arterial hypertension, diabetes mellitus, stable CAD), and show worse adjustment to stressful situations.

The study also confirmed that pharmacotherapy plays a vital role in impeding atherosclerosis progression. The first statin was discovered by A. Endo over 30 years ago [6]. From that time, numerous studies were conducted proving the influence of statins on modulation of atherosclerotic process, resulting in lengthening of patients' survival and guidelines on statin use. Statins act by inhibiting cholesterol biosynthesis, contributing in this way to reducing LDL concentration and secondly to increasing number of LDL receptors [7]. Lowered cholesterol concentration handicaps production of dolichols, ubiquinone, prenylated proteins and isoprenoids. Besides, statins play an important role in t-RNA and glycoprotein synthesis, cell membrane activity, interactions between cells, cell differentiation and electron transport. Multi-directional effects of statins are known as pleiotropy [8].

Research on statin therapy showed that: (1) simvastatin limits adhesion and rate of migration of leukocytes at the vascular wall, and reduces MCP-1 synthesis, (2) cerivastatin decreases monocytes adhesion potential, (3) fluvastatin decreases sICAM-1 and sP-selectin levels, (4) atorvastatin decreases expression of MCP-1 and activity of NF-κB, and also (5) statins increase synthesis of nitrous oxide, weaken pressor activity of angiotensin II through reduction of AT II type 1 receptors, decrease concentration of soluble adhesion molecules, inhibit interaction of leukocytes

with endothelium, decrease synthesis of IL-6, TNF-α, hs-CRP (CARE, PRINCE, AFCAPS/TexCAPS trials), decrease synthesis of PAI-1, inhibit synthesis of thromboxane and modulate platelet function, and decrease proliferation of myocytes [9-12].

The use of statins results in stabilisation of atherosclerotic plaque by reducing the number of macrophages, collagen production and smooth myocytes.

Many clinical trials have confirmed the role of statins and their multiple potential effects. Treatment with simvastatin for 4 weeks caused a greater arterial flow in the forearm after acetylcholine administration [10]. It has also been revealed that using pravastatin for 6 weeks in patients after acute coronary syndromes led to an increase in the endothelium-dependent dilation of the brachial artery by 42% caused by flow increase [9]. However, the ASCAP trial showed that using lovastatin for 34 months led to a decrease in mean maximum thickness of the internal-medium layer of the internal artery at a rate of 0.009 mm/year on average. In the placebo group this index was increasing at a rate of 0.006 mm/year [10].

The first large study which proved that the atherosclerotic process is likely to regress was the ASTEROID trial (*A Study to Evaluate the Effect of Rosuvastatin on Intravascular Derived Coronary Atheroma Burden*). The aim of this study was to assess the regression of atherosclerotic lesions in coronary arteries by very intensive lowering of cholesterol LDL levels using the strongest currently available statin – rosuvastatin. Patients over 18 years old with at least one 20-50% atherosclerotic lesion confirmed on coronary angiography were enrolled. The enrolled subjects received rosuvastatin at a dose of 40 mg/daily. Follow-up period was 24 months. Progress of the atherosclerotic process was verified by intracoronary ultrasonography at the beginning and at the end of follow-up period. The evaluation of all endpoints indicated an inhibitory effect on, and in some cases regress of, the atherosclerotic process. Mean change of the percent atheroma volume (PAV) was –0.98%, and median –0.79% (97.5% CI –1.21% to –0.53%). Mean change of atheroma volume in the artery segment with baseline largest plaque volume was –6.1 mm^3, and median –5.6 mm^3 (97.5% CI –6.8 to –4.0 mm^3) ($p < 0.001$ in comparison to the baseline examination). For normalised plaque volume mean change was –14.7 mm^3 [11].

Currently, the effect of statins on the atherosclerotic process is well proven. Another question with no straightforward answer is: which dose and which statin to use. Bearing in mind the current knowledge from conducted studies, a dose increase seems to influence only some of the assumed endpoints in the studies performed [12].

Study limitations

The study was conducted in patients most of whom were males. Women constituted the minority in this study (28%), which could have entailed a failure to disclose risk factors typical for female gender. Due to the impact of intervention procedures on atherogenesis, arteries treated with angioplasty were not taken into account. Patients received drugs of proven anti-atherosclerotic action, which undeniably influenced progression of atherosclerotic lesions.

Conclusions

1. Males demonstrate significantly faster rate of progression of atherosclerotic lesions, regarding especially lesions in the proximal segments.
2. Statin therapy is associated with significant decrease of atherosclerosis progression in all analysed parts of the coronary arteries, in particular the distal segments.
3. It is vital to administer more intensive pharmacotherapy compatible with published study results and cardiology standards in the observed patients with increased risk of cardiovascular disease. Using statins and angiotensin-converting enzyme inhibitors should be considered. Optimisation of heart rate is also crucial.

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Czynniki wpływające na dynamikę zmian miażdżycowych w naczyniach wieńcowych

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Streszczenie

Wstęp: Indukcja i progresja zmian miażdżycowych są procesami złożonymi i wieloczynnikowymi. Do najważniejszych czynników należą: podwyższone stężenie frakcji LDL cholesterolu, zwiększone wytwarzanie wolnych rodników, reakcja zapalna, uszkodzenie śródbłonka, obniżenie stężenia frakcji HDL cholesterolu, zwiększona aktywność prozakrzepowa.

Cel: Określenie czynników wpływających na proces miażdżycowy w tętnicach wieńcowych u osób z chorobą wieńcową w seryjnych badaniach koronarograficznych.

Metodyka: Do badania włączono kolejnych 177 chorych, u których wykonano koronarografię co najmniej 2-krotnie, spośród 8989 badań koronarograficznych wykonanych w latach 1999–2004 w II Klinice Kardiologii UM w Łodzi. Badana grupa chorych obejmowała 128 mężczyzn i 49 kobiet. Koronarografię przeprowadzano zgodnie z decyzją lekarza prowadzącego, po wcześniejszej ocenie stanu chorego na podstawie badania podmiotowego, przedmiotowego oraz badań dodatkowych. Średni wiek w grupie badanej to 55±10 lat, w grupie kobiet 59±9 lat, a w grupie mężczyzn 53±10 lat. Analizie poddano zmiany miażdżycowe w tętnicach wieńcowych, opisywane w seryjnych badaniach koronarograficznych. Zmiany zostały określone na podstawie procentowego zwężenia światła naczyń za pomocą metody oceny półilościowej – *Gensini Score System*.

Wyniki: Stopień zaawansowania procesu miażdżycowego był istotnie większy w grupie młodszych chorych w stosunku do średniej wieku w grupie badanej (p=0,004), z obciążonym wywiadem rodzinnym w kierunku chorób układu krążenia (p=0,02), oraz u chorych z większą liczbą czynników ryzyka choroby wieńcowej (p=0,01). W dopasowanym modelu predykcji progresji zmian naczyniowych wg *Gensini Score* w jednostce czasu (p <0,02) ustalono obecność dwóch parametrów istotnych statystycznie, które mają wpływ na postęp procesu miażdżycowego – płeć (p=0,04) oraz leczenie statynami (p=0,03). Dla płci męskiej iloraz szans (OR) wynosił 2,1, 95% CI 1,1–5,2, a dla zastosowania statyn OR=0,48, 95% CI 0,21–0,91.

Wnioski: W badaniu stwierdzono dynamicznie przebiegający proces miażdżycowy w naczyniach wieńcowych. W grupie mężczyzn tempo narastania zmian miażdżycowych było większe, zwłaszcza w proksymalnych odcinkach tętnic wieńcowych. Statynoterapia wiąże się ze zwolnieniem progresji miażdżycy w odniesieniu do wszystkich badanych odcinków tętnic wieńcowych, zwłaszcza ich części dystalnej.

Słowa kluczowe: miażdżyca, progresja procesu miażdżycowego, odcinek proksymalny, dystalny tętnic wieńcowych

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