

Association between carotid artery atherosclerosis and coronary artery disease in young females. Reference to sex hormone profile

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Abstract

Background: Atherosclerosis of coronary and peripheral arteries occurs rarely in premenopausal women. It has been postulated that sex hormones protect the vascular wall.

Aim: To evaluate whether ultrasound assessment of the changes in the wall of carotid arteries provides any useful information on the severity of atherosclerosis of the coronary vessels as well as whether the atherosclerotic changes in the wall of carotid arteries are accompanied by oestrogen insufficiency in the premenopausal age.

Methods: The studied group consisted of 65 regularly menstruating women: 21 with coronary artery disease (CAD) revealed by angiography or after myocardial infarction (mean age 44 years) – the CAD group; and 44 healthy woman (mean age 43 years) – the control group. The severity of atherosclerotic changes was determined based on computer-assisted measurement of the intima-media complex thickness (IMC-T) in the common carotid artery. In all women prospective measurement of sex hormone profile was done with enzymatic immunoassay: oestradiol at day 7-9 and day 19-21 of the menstrual cycle and follicle-stimulating hormone (FSH).

Results: The IMC-T value was greater in the CAD group than the control group (0.696±0.124 mm and 0.518±0.064 mm respectively, $p=0.001$). The IMC-T (>0.6 mm) was a good indicator of the occurrence of CAD (OR 15.6, 95% CI 3.65-71.1, $p<0.0001$), with a sensitivity of 73.7% and a specificity of 84.8%. There was a negative correlation between oestradiol level at day 19-21 of the menstrual cycle and IMC-T ($\rho=-0.28$, $p=0.05$).

Conclusions: The IMC-T value >0.6 mm was found to be a sensitive and specific ultrasound parameter that can be useful in detecting the presence of CAD in premenopausal women. The results of the study also suggest a possible association between hormonal profile and early atherosclerotic changes in carotid arteries in premenopausal women.

Key words: atherosclerosis, oestrogens, coronary artery disease, premenopause

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Introduction

Atherosclerosis of the coronary and peripheral arteries rarely occurs in premenopausal women [1-3]. In a number of experimental and clinical studies, a positive influence of oestrogens on the secretory activity of the endothelium, normalisation of serum lipid concentrations as well as their anti-thromboembolic actions was demonstrated. It was hypothesised that sex hormones had a protective effect on the vascular wall [4-6]. However, there are only a few studies investigating the association between the advancement of atherosclerosis and sex hormone profile in regularly

menstruating women. The results of these studies, regarding only coronary artery disease (CAD), are however inconsistent. Hanke et al. [7], Merz et al. [8], Kłóś et al. [9] as well as our group [10] showed that oestradiol concentrations in premenopausal women with CAD are lower, but this was not, however, confirmed by Gorgels et al. [11].

We did not find any studies investigating the association between carotid artery atherosclerosis measured with the validated atherosclerosis marker – thickness of the intima-media complex (IMC-T), and female sex hormones in young women.

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Previous studies have shown an increase of IMC-T in patients with numerous risk factors, such as diabetes mellitus, increased cholesterol concentration and cigarette smoking [12]. The IMC-T has also been shown to be an independent risk factor of cardiovascular events [13, 14].

Numerous authors have demonstrated that the assessment of IMC-T may provide information on the severity of atherosclerosis in coronary vessels. The studies were, however, conducted in groups involving both males and females, and female subjects were usually postmenopausal [15-19]. It is not known whether the same is also true for younger women, who are seemingly 'protected' by oestrogens. The problem may have valuable practical implications. Ultrasound examination of carotid arteries is a simple and non-invasive procedure. If the association between IMC-T values and coronary artery atherosclerosis burden was confirmed, IMC-T would be a useful diagnostic tool in CAD screening in premenopausal women. It would be helpful to make decisions regarding proceeding with coronary angiography or other imaging studies in the differential diagnosis of chest pain in young women, in whom finding the cause of such symptoms is often difficult.

This study was undertaken to answer two questions:

1. Does the ultrasound assessment of carotid arteries bring any useful information regarding the severity of coronary artery atherosclerosis?
2. Are the atherosclerotic changes in carotid arteries (determined based on the measurement of intima-media complex thickness) accompanied by hypoestrogenemia in the premenopausal age?

Methods

Study group

Examination of carotid arteries was conducted in 65 regularly menstruating women, divided into groups of healthy subjects and those with CAD. The CAD group included women (n=21) with CAD documented by means of coronary angiography (changes narrowing the lumen

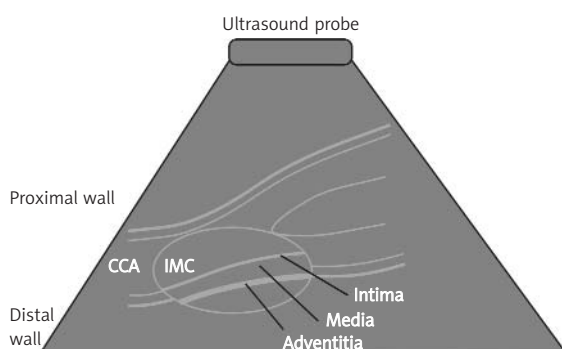


Figure 1. Ultrasound of the carotid arteries

Abbreviations: CCA – common carotid artery, IMC – intima-media complex

of the artery >50%) or presenting with previous myocardial infarction documented in the medical history, 3 months prior to the study. Mean age was 43.8 ± 3.9 years (mean \pm SD), and the body mass index (BMI) 27.4 ± 4.6 . Hypertension was demonstrated in 11 (58%) patients, and diabetes mellitus in 1 patient; 13 (68%) patients smoked cigarettes.

The healthy group (n=44) consisted of subjects who were believed to be absolutely healthy, aged 43 ± 4.1 , with BMI 26 ± 7.3 . Hypertension was observed in 4 (9%) patients, and 18 (39%) patients were cigarette smokers.

Exclusion criteria included pregnancy, natural and iatrogenic menopause, irregular menstrual cycles irrespective of cause, follicle-stimulating hormone (FSH) concentration >15 mIU/ml (as a biochemical criterion of menopause), use of hormonal replacement therapy or hormonal contraception in medical history (within 3 months prior to study initiation), polycystic ovary syndrome, the presence of symptoms of any organic and/or systemic disease (other than hypertension and diabetes), alcohol abuse, and medication or drug abuse in past medical history.

Ultrasound examination of the carotid arteries

The examination was performed using a SONOS 5500 device with linear vascular probe 3-11 MHz (Hewlett-Packard, Andover, Massachusetts, USA). A detailed assessment of the bifurcation of the common carotid artery, 1 cm proximally to the bulb of the common carotid artery, was performed. The intima-media complex thickness was measured. It was defined as the distance between the surface of the intima and blood and the surface of the media and adventitia (Figure 1). The measurements were performed on the posterior wall of the common carotid artery (so-called 'far wall'), 1 cm proximally to the bulb of the common carotid artery. The records of the carotid artery examinations were archived on magneto-optical discs, and subsequently analysed using computer-assisted automatic contour outlining using Q LAB software – Quantification software (Philips Ultrasound, Botell, WA, USA).

Measurement of blood concentrations of sex hormones

Oestradiol concentration was measured during days 7-9, 13-15 and 19-21 of the menstrual cycle using the ultrasensitive enzyme immunoassay AxSYM Oestradiol (Abbott). Follicle-stimulating hormone (FSH) concentration was measured at day 7-9 of the menstrual cycle, using a macroparticle enzyme immunoassay (MEIA) designed for quantitative detection of the FSH hormone concentration in human serum or plasma – AxSYM FSH test (Abbott).

These two tests have international quality certification – ISO.

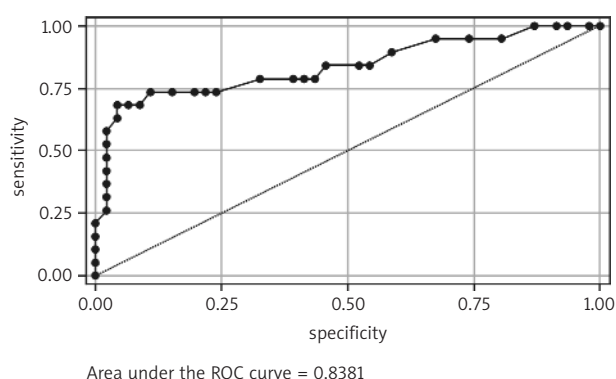


Figure 2. Sensitivity and specificity of IMC-T >0.6 mm as a predictor of CAD

Statistical methods

All examined parameters were described using standard statistical methods, and included: mean and standard deviation, medians and quartiles for continuous variables and tables of frequency for discrete variables.

For variables that followed a distribution close to normal, Student’s t-test was used to compare continuous variables between independent groups. When the distribution was not normal, Kruskal-Wallis’ test was performed. The χ^2 test or Fisher’s exact test were performed for comparison of percentages.

Our models included CAD risk factors [concentration of triglycerides (TGL) and high density lipoproteins (HDL), cigarette smoking, hypertension and body mass index (BMI) >25]. All continuous variables were replaced by binary variables, with median values used as the cut-off points. Using the stepwise elimination method, with the level of 0.1 deemed necessary to remain within the model, statistically significant variables were identified at the level of $p < 0.05$.

Linear correlations between IMC-T and the concentrations of FSH, oestrogens and progesterone were assessed using Spearman’s correlation coefficient. All tests were two-sided and the significance level was established at 5%. The calculations were carried out using Stata v. 8.2 software.

The IMC recurrence analysis was carried out using Pearson’s correlation test and the calculation of the relative error was performed according to the formula $(A - B)/[(A + B)/2]$, where A is the first measurement and B the second measurement of the respective variable.

Results

Changes in the carotid arteries vs. CAD

Detailed results of the IMC-T measurements are shown in Table I.

It was demonstrated that changes in the carotid arteries were significantly greater in women with CAD compared with the group of healthy women, and also that

Table I. Intima-media complex thickness (IMC-T) in healthy subjects and in women with coronary artery disease (CAD)

Parameter	Healthy women n=44	CAD group n=21	p
IMC-T [mm] (min, max)	0.53±0.08 (0.42, 0.81)	0.68±0.15 (0.46, 0.94)	0.0013 ^a
Women with IMC-T >0.6 mm	6/38 (16%)	8/13 (62%)	0.002 ^b

^a Kruskal-Wallis test
^b Fisher exact test

Table II. Significance of the intima-media complex thickness (IMC-T) in predicting coronary artery disease (CAD)

Parameter	Healthy women	CAD group
IMC-T ≤0.6 mm	39 (89%)	7 (33%)
IMC-T >0.6 mm	5 (11%)	14 (67%)
Total	44 (100%)	21 (100%)

OR 15.6, 95% CI 3.65-71.1, $p < 0.0001$

Table III. Association between intima-media complex thickness (IMC-T) and concentrations of sex hormones in selected days of menstrual cycle

Hormone	Day of menstrual cycle	n	Correlation with IMC-T
Oestradiol	7-9	51	$\rho = -0.009, p = 0.95$
	13-15	26	$\rho = -0.05, p = 0.79$
	19-21	49	$\rho = -0.28, p = 0.05$
Follicle-stimulating hormone	7-9	51	$\rho = 0.07, p = 0.60$

Spearman’s correlation

the prevalence of IMC-T >0.6 mm was four times higher in the CAD group. A value of IMC-T >0.6 mm predictive for CAD was established based on the assessment of the area under the ROC curve (Figure 2). The results are shown in Table II and Figure 2. The risk of CAD in women with IMC-T >0.6 mm was almost 15 times higher than in women with IMC-T ≤0.6 mm. It was established that IMC-T >0.6 mm is a factor predictive of CAD in the examined patients with sensitivity of 73.7% and specificity of 84.8%.

In our study the relative error of the IMC-T measurement for the same observer was 2.5%, and the correlation index 96%. The relative error between independent observers was 2.6% and the correlation index 91%.

Carotid (IMC-T) vs. sex hormone levels

The results illustrating correlations between IMC-T and concentrations of sex hormones are displayed in Table III. A weak, negative, linear correlation was found

between oestradiol concentration measured at day 19-21 of the menstrual cycle and IMC-T. No such correlations were found at days 7-9 and 13-15 or between IMC-T and FSH concentration.

Discussion

The aim of this study, among others, was to assess whether the ultrasound examination of the walls of carotid arteries brings any useful information on the severity of coronary artery atherosclerosis in young females. The results of our study demonstrate that the status of the coronary vessels can be indirectly evaluated based on the measurement of carotid IMC-T. It can be a useful parameter in establishing indications for coronary angiography or other imaging studies in young female patients with chest pain.

The IMC-T value in women with CAD was on average 0.15 mm higher than in healthy individuals. In the examined group of patients a significantly lower IMC-T was demonstrated, which results from the young age of examined patients and is consistent with observations made in previous studies [13, 14], indicating a need to modify the reference values. In our study the cut-off point for the ROC curve was set at 0.6 mm. We showed that in a menstruating woman presenting with IMC-T >0.6 mm, the risk of CAD might be even eight times higher than in the general population. We also demonstrated that IMC-T >0.6 mm was a good predictor of CAD, with test sensitivity of 73.7% and specificity of 84.8%.

The results of this study cannot be directly compared with other available reports because the previous ones were carried out in a general population of women and men, and not in a homogeneous group of premenopausal women. What is important, the correlation between the changes in the walls of the carotid and coronary arteries was shown only for much higher IMC-T values. In the ARIC studies [20] it was demonstrated that IMC-T of more than 0.8 mm indicates an increased risk of cardiovascular events. Also the Rotterdam Study [21] documented higher prevalence of atherosclerotic changes in the coronary arteries in patients with IMC-T >0.84 mm, whereas the risk of cardiovascular events increased in patients with IMC-T ranging from 0.75 to 0.9 mm. In patients with asymptomatic CAD, the mean IMC thickness was >0.75 mm [22]. Similar observations were reported by Hodis et al. and O'Leary et al.'s studies [23, 24]. It seems important to emphasise that the marginal IMC-T value, that is indicative of the risk of CAD, is relatively low in premenopausal women and is >0.6 mm, which is considered as being within the normal range. As was shown, it is not sufficient to predict CAD (with high sensitivity and specificity) in this population.

The second aim of this study was to answer the question whether atherosclerotic changes in the walls of carotid arteries are accompanied by oestrogen

insufficiency in the premenopausal age. It has been suggested for many years that oestrogens inhibit the development of atherosclerotic changes in the arteries, and it is an epidemiological phenomenon, widely described, that in premenopausal women the clinical signs of atherosclerosis occur much less frequently. Such a hypothesis has a broad theoretical background because a number of experimental studies have demonstrated that oestrogens both enhance the secretory function of the endothelium and decrease the activity of the coagulation system [4-6]. However, the hypothesis discussed here has not been confirmed in clinical studies. There are very few published reports available, presented in the first part of this report, regarding the association between oestrogens and CAD in premenopausal women. The results of these studies suggest that a causative association actually exists. These studies however are relatively small and do not provide comprehensive explanations but rather encourage further investigations.

In major medical databases we did not find any studies reporting an association between atherosclerotic changes in the carotid arteries and sex hormones in premenopausal women. The lack of published data on this subject might be explained by the limited number of subjects affected and difficulties with obtaining the statistical material. This is one of the limitations to this study too. However, the results of our study do not exclude completely that in young females with atherosclerotic changes in carotid arteries, subclinical oestrogen insufficiency may occur. Our study may stimulate further research to confirm or exclude the hypothesis that oestrogen insufficiency is one of the causes of atherosclerosis in young females.

Conclusions

1. Measurement of the intima-media complex can be a useful screening and diagnostic tool in detection of CAD in premenopausal women. In case of clinical suspicion of CAD, measured IMC-T of more than 0.6 mm could help to make the decision to proceed with more invasive diagnostic procedures.
2. Our results suggest a possible association between the level of oestrogen hormones and early carotid atherosclerotic lesions in premenopausal woman. They do not falsify the hypothesis of the influence of female sex hormones on the development of atherosclerosis; however, they implicate the need to conduct further prospective studies to clarify this issue.

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Miażdżyca tętnic szyjnych a choroba wieńcowa u młodych kobiet. Odniesienie do profilu hormonów płciowych

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Streszczenie

Wstęp: Miażdżyca tętnic wieńcowych i obwodowych występuje rzadko u kobiet przed menopauzą. Postulowano, że to hormony płciowe działają ochronnie na ścianę naczyniową.

Cel: Ocena, czy pomiar ultrasonograficzny zmian w ścianie tętnic szyjnych przynosi użyteczne informacje na temat zaawansowania miażdżycy w naczyniach wieńcowych oraz czy w wieku przedmenopauzalnym zmianom miażdżycowym w ścianie tętnic szyjnych towarzyszy niedobór estrogenów.

Metody: Grupę badaną stanowiło 65 regularnie miesiączkujących kobiet: 21 z udokumentowaną angiograficznie chorobą wieńcową (CAD) lub po przebytym zawale serca, średni wiek 44 lata (grupa CAD), i 44 kobiety w poczuciu zdrowia, średni wiek 43 lata (grupa kontrolna). Zaawansowanie zmian miażdżycowych oceniano za pomocą komputerowego pomiaru grubości kompleksu *intima-media* (IMC-T) w tętnicy szyjnej wspólnej. U wszystkich kobiet wcześniej wykonano prospektywne oznaczenie profilu hormonów płciowych metodą immunoenzymatyczną: estradiolu w 7.–9. i 19.–21. dobie cyklu oraz hormonu folikulotropowego (FSH).

Wyniki: Grubość kompleksu *intima-media* była większa w grupie CAD w porównaniu z grupą kontrolną (odpowiednio 0,696±0,124 mm i 0,518±0,064 mm, p=0,001). Wartość IMC-T >0,6 mm była dobrym wskaźnikiem występowania CAD (OR 15,6, 95% CI 3,65–71,1, p <0,0001), o czułości 73,7% i specyficzności 84,8%. Stwierdzono istnienie negatywnej korelacji pomiędzy poziomem estradiolu w 19.–21. dobie cyklu płciowego a IMC-T ($\rho=-0,28$, p=0,05).

Wnioski: Stwierdzono, że wartość IMC-T >0,6 mm jest czułym i swoistym parametrem ultrasonograficznym, który może być użytecznym narzędziem do oceny występowania CAD u kobiet przed menopauzą. Wyniki badania sugerują ponadto możliwość istnienia związku pomiędzy profilem hormonalnym kobiet przed menopauzą a wczesnymi zmianami miażdżycowymi w tętnicach szyjnych.

Słowa kluczowe: miażdżyca, estrogeny, choroba wieńcowa, wiek przedmenopauzalny

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