

## Evaluation of the intima-media complex in patients with systemic lupus erythematosus

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### Abstract

**The aim of the study** was to determine whether there are any differences in the intima-media thickness (IMT) of carotid arteries between the group of patients with systemic lupus erythematosus (SLE) and the control group, and whether these differences are a consequence of SLE or independent factors of atherosclerosis development.

**Material and methods:** The patients were divided into three groups: the study group ( $n = 25$ , mean age: 39.8 years) consisting of patients suffering from SLE; the subgroup ( $n = 13$ , mean age: 39.2 years) consisting of patients suffering only from SLE without any accompanying diseases; and the control group ( $n = 25$ , mean age: 37.1 years) consisting of healthy patients (not suffering from SLE or any other disease of the connective tissue). The IMT of the left and right common carotid arteries (LCCA, RCCA) was measured by means of ultrasound.

**Results:** The analysis performed with the Mann-Whitney  $U$  test showed that a statistically significant difference of IMT occurs between the control group and the study groups ( $p = 0.006$  for LCCA and  $p < 0.001$  for RCCA), while there is no such relation ( $p = 0.86$  for RCCA and  $p = 0.095$  for LCCA) between the control group and the subgroup.

**Conclusions:** The group of patients with SLE was found to have an increased IMT in comparison with the reference group. The unfavorable influence of independent factors of atherosclerosis development on the increase of the IMT value in patients with lupus was thus indicated. This observation suggests a faster atherosclerotic process in this group of patients.

**Key words:** carotid intima-media thickness, lupus erythematosus systemic.

### Streszczenie

**Celem badań** było określenie, czy występują różnice w grubości kompleksu intima-media (IMT) tętnic szyjnych pomiędzy grupą pacjentów z toczeniem trzewnym układowym (SLE) i grupą kontrolną, a jeśli tak, to czy różnice te są następstwem tocznia czy niezależnych czynników rozwoju miażdżycy.

**Materiał i metody:** Pacjentów podzielono na trzy grupy. Grupa badana ( $n = 25$ , średni wiek: 39,8 roku) obejmowała chorych na toczeń trzewny układowy. Do podgrupy badanej ( $n = 13$ , średni wiek: 39,2 roku) włączono pacjentów chorujących jedynie na SLE, bez żadnych chorób towarzyszących. Do grupy kontrolnej włączono 25 zdrowych pacjentów (średni wiek: 37,1 roku), bez cech SLE lub innych schorzeń tkanki łącznej. Metodą ultrasonograficzną mierzono IMT obu tętnic szyjnych wspólnych.

**Wyniki:** W analizie przeprowadzonej z użyciem testu  $U$  Manna-Whitneya wykazano, że dla obu tętnic szyjnych zachodzi znamienna statystycznie różnica wartości IMT pomiędzy grupą kontrolną a badaną ( $p = 0,006$  dla LCCA i  $p < 0,001$  dla RCCA), lecz brakuje takiej zależności pomiędzy grupą kontrolną a podgrupą badaną ( $p = 0,86$  dla RCCA i  $p = 0,095$  dla LCCA).

**Wnioski:** W grupie chorych na SLE stwierdzono większą grubość kompleksu intima-media w porównaniu z populacją ludzi zdrowych. Wykazano ponadto istotny wpływ niezależnych czynników rozwoju miażdżycy na zwiększenie grubości kompleksu intima-media u pacjentów z toczeniem trzewnym układowym. Obserwacja ta pozwala wnioskować o szybszym procesie miażdżycowym w tej grupie chorych.

**Słowa kluczowe:** grubość kompleksu intima-media, toczeń trzewny układowy.

### Introduction

Over 90% of cases of stricture or obstruction of internal carotid arteries are caused by atherosclerosis. Atherosclerotic plaques are usually localized in the area of artery

bifurcation – most often within the common carotid artery bulb and in the ostia of internal and external carotid arteries, more rarely in the proximal part of the common carotid artery. The development of ultrasound diagnostics has

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enabled non-invasive evaluation of atherosclerotic changes through the examination of echogenicity, the structure and some dimensions of vessels. The measurement of the intima-media thickness is of special importance in diagnosing atherosclerotic changes [1, 2].

The intima-media complex is a structure of the arterial wall from the tunica adventitia-tunica media borderline to the tunica media-vessel lumen borderline. Ultrasound examinations of the intima-media thickness (IMT) were introduced into clinical diagnostics in the 1980s. Insufficient resolution of the early ultrasound devices entailed lower precision of the measurements, and this in turn contributed to considerable divergences in the results obtained by different centers conducting the studies. As a consequence of the technical advancement of ultrasound devices, the IMT measurement was made automated and the examination itself became more significant in the diagnostic process.

According to the concept of parallel and simultaneous development of atherosclerosis [3-5] in many arterial areas, atherosclerotic processes occurring in carotid arteries are representative of analogous processes occurring in other vessels. Common carotid arteries are easy to be imaged by ultrasonography, and so the IMT measurement in those arteries provides a precious source of information about atherosclerotic processes progressing in arteries in the areas difficult to access for diagnosis. The increased IMT was shown to correlate with the presence of atherosclerotic changes in the coronary [6], renal [7] and lower limb [8] arteries. The IMT measurement in the carotid artery in its extracranial part can serve as an early marker of atherosclerotic changes and a risk factor for atherosclerotic organic complications [1, 2]. This very thickening of the complex triggers a long process of building the atherosclerotic plaque, whose fracturing in the future activates a cardiovascular incident. Independent studies show that there is a relation between the increased thickness of the IMT complex in the common carotid artery and the risk of both cerebral stroke and myocardial infarction [9]. These studies have also found that the increased IMT measurement in the carotid artery is accompanied by a raised susceptibility to myocardial infarction and ischemic cerebral stroke [10, 11]. The IM complex thickness is an independent risk factor for those diseases.

According to the standards established by the Polish Ultrasound Society in 2008 [12], the normal IMT value is less than 1 mm. In patients with IMT values of 1.00-1.29 mm, the thickening of the IMT complex is diagnosed, while a value of IMT higher than 1.3 mm should be treated as an indicator of diffuse atherosclerotic changes. The European Society of Arterial Hypertension (2003) recognized IMT exceeding 0.9 mm as a sign of organ damage. Moreover, there are suggestions in the literature [13] to treat IMT values higher than 1 mm as the equivalent of a coronary disease.

It is not only the absolute IMT value, but also the annual growth of this parameter, which is of great significance. A further increase of IMT by 0.1 mm increases the risk of

myocardial infarction by 10-15% and that of a cerebral stroke by 13-18% [14].

Systemic lupus erythematosus (SLE) is one of the diseases a common manifestation of which is a morbid process that occupies the heart or vessels. The two-degree mortality model for patients with SLE [15] assumes that infection and nephropathy are an early cause of death, while cardiovascular incidents are late causes. It should be noted that symptomatic atherosclerosis occurs only in 6-10% of SLE patients, but the presence of subclinical atherosclerosis can be confirmed in as many as 30-40% [16, 17]. Arterial hypertension, hyperlipidemia and diabetes are additional, independent factors of atherosclerosis development in patients with SLE [17], which is why identifying patients from the cardiovascular incident risk group becomes a substantial matter.

One of the diagnostic tests of atherosclerosis development in SLE patients can be the IMT measurement in the ultrasound examination [18, 19]. This examination is non-invasive, does not require contrast media, is cheap and widely accessible, and, therefore, it allows one to identify patients from the cardiovascular risk group.

The aim of the study was to determine:

- whether there are differences in the thickness of the carotid arteries intima-media complex between the group of patients with systemic lupus erythematosus and the control group, and
- whether these differences are a consequence of lupus or independent factors of atherosclerosis development.

## Material and methods

The IMT of common carotid arteries was compared in two patient groups:

- The study group consisted of 25 patients, including 21 women and 4 men at the age of 29-52 years (mean age 39.8 years), suffering from systemic lupus erythematosus. The lupus diagnosis was proposed on the basis of the criteria developed by the American College of Rheumatology (updated in 1997 [20]). The mean duration of the disease at the time of taking the IMT measurement was 4 years. The accompanying diseases in this group included arterial hypertension (7 cases – grade 1 or higher according to the ESH/ESC classification), hyperlipidemia (12 cases – diagnosis: TC  $\geq$  5 mmol/l and/or LDL-C  $\geq$  3.0 mmol or TG  $\geq$  1.7 mmol/l), diabetes type 2 (2 cases, diagnosed according to the WHO criteria). At the time of the examination the patients did not report any diseases other than those mentioned above. The IMT measurement was performed as part of the diagnostics of the cardiovascular condition.
- The control group consisted of 25 healthy patients, including 20 women and 5 men at the age of 20-51 years (mean age 37.1 years), who underwent routine check-up examinations and in whom neither any criteria of lupus or any other disease of the connective tissue, nor any features of the metabolic syndrome, arterial hypertension, hyperlipidemia or pathologic glucose tolerance were found.

**Tab. I.** Descriptive statistics of the variables

| Variable [mm]  | N  | Mean | Min. | Max. | Lower quartile | Upper quartile | Standard deviation |
|----------------|----|------|------|------|----------------|----------------|--------------------|
| Study group    |    |      |      |      |                |                |                    |
| LCCA           | 25 | 0.88 | 0.40 | 1.10 | 1.00           | 1.00           | 0.25               |
| RCCA           | 25 | 0.90 | 0.40 | 1.30 | 0.90           | 1.00           | 0.22               |
| Study subgroup |    |      |      |      |                |                |                    |
| LCCA           | 13 | 0.75 | 0.40 | 1.10 | 0.40           | 1.00           | 0.29               |
| RCCA           | 13 | 0.78 | 0.40 | 1.10 | 0.50           | 1.00           | 0.24               |
| Control group  |    |      |      |      |                |                |                    |
| LCCA           | 25 | 0.68 | 0.40 | 1.20 | 0.60           | 0.70           | 0.19               |
| RCCA           | 25 | 0.61 | 0.40 | 1.30 | 0.50           | 0.70           | 0.21               |

Lipid disorders, diabetes and arterial hypertension are independent atherosclerosis [21] development factors, which is why a subgroup of patients suffering only from systemic lupus erythematosus and without any accompanying diseases was selected from the study group. The subgroup included 13 patients (11 women, 2 men) at the age of 29-50 years (mean age 39.2 years).

The study was approved by the Ethics Committee of the Silesian Medical University. Written informed consent was obtained from patients of the study and the control group.

A USG Vivid 7 device with a 3.6 MHz probe was used in the study. The thickness of the intima-media complex of both common carotid arteries (LCCA, RCCA) was measured at the distance of about 1 cm from the bulb. The IMT measurement was taken at the cross section of the vessel, the innermost layers, where the focus of the device was set. The distance between the first, clearly separated bright line (vessel lumen – tunica media borderline) and the second bright line (tunica media – tunica adventitia borderline) determined the complex thickness. The measurement was made with 0.1 mm accuracy. Ten measurements were performed for each carotid artery.

For each series of measurements, the observations that did not fit into the range of mean value  $\pm 1 \times$  standard deviation were treated as odd values and were removed from the series. The IMT measurement for each series was the arithmetic mean of the remaining observations. The data received from the examinations were analyzed statistically. The character of random variable distribution was assessed by means of the Kolmogorov-Smirnov test. Variance cohesion in groups was determined on the basis of Levene's test at the significance level of  $p = 0.05$ . The data obtained from the test were analyzed by the ANOVA single-factor variance analysis (with Scheffe's post-hoc test analysis) or its non-parametric equivalent, the ANOVA Kruskal-Wallis test (in this case, the Mann-Whitney  $U$  test with the significance level of  $p = 0.05$  was used in the post-hoc analysis for each pair of groups). Calculations were carried out by means of Statistica ver. 10.

## Results

Basic descriptive statistics of the study groups are shown in Table I. The analysis of the result of the Kolmogorov-Smirnov test indicates that the distribution of the random variable differs from the normal one. In Levene's test, the homogeneity ( $p = 0.3351$ ) for the RCCA variable was proved, while for the LCCA variable there was no variance homogeneity in the groups ( $p = 0.068$ ). A further analysis involved non-parametric tests (Kruskal-Wallis and Mann-Whitney  $U$  tests).

The performed ANOVA Kruskal-Wallis test showed a statistically significant difference of mean IMT values in the analyzed groups (for LCCA  $p = 0.024$ , for RCCA  $p = 0.005$ ). The results are presented in Figure 1.

A further analysis performed with the Mann-Whitney  $U$  test indicated (Table II, Table III) that a statistically significant difference of IMT values for both carotid arteries occurs between the control and the study groups ( $p = 0.006$  for LCCA and  $p < 0.001$  for RCCA), while there is no such relation ( $p = 0.86$  for RCCA and  $p = 0.095$  for LCCA) between the control group and the study group of patients suffering only from lupus (without coexisting diseases as independent factors of atherosclerosis development).

## Discussion

Numerous studies show that there is a relation between an increased IMT in the common carotid artery and the risk of both cerebral stroke and myocardial infarction [1, 2, 7-11, 13, 19, 22]. It was found that the increased thickness of the intima-media complex of internal and external carotid arteries is accompanied by increased susceptibility to myocardial infarction and ischemic cerebral stroke [10, 11]. The thickness of the IMT complex is an independent risk factor of those diseases. According to the concept of parallel atherosclerosis development [3-5], early atherosclerotic changes observed in the lumen of peripheral arteries are a reflection of a generalized atherosclerotic process in other vessels. For that reason, measurement of the in-

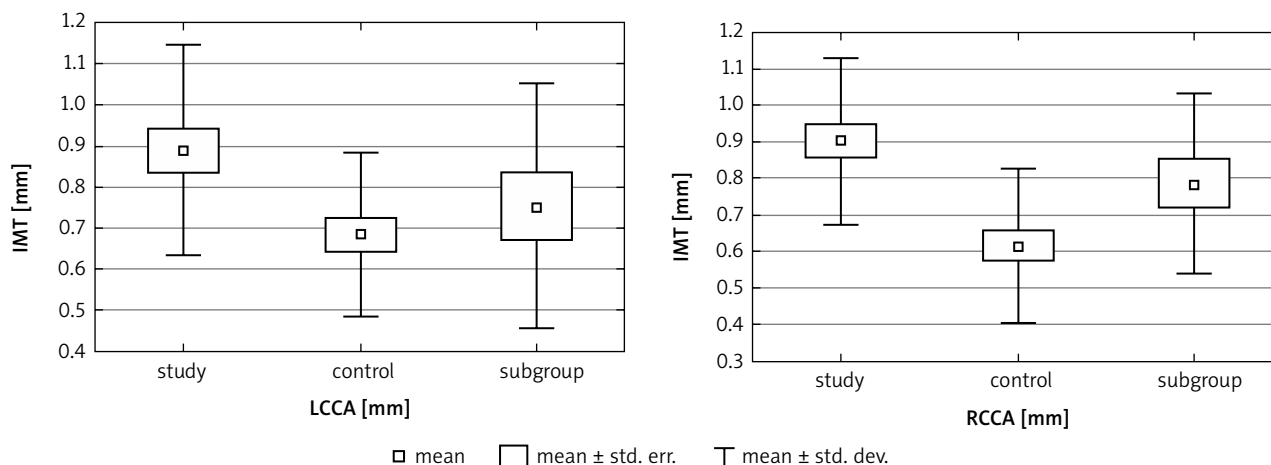


Fig. 1. Mean IMT values of the left and right carotid artery in the analyzed groups

Tab. II. Results of the Mann-Whitney *U* test for the study group versus the control group

| IMT [mm] | Study group |      |                    | Control group |      |                    | <i>P</i> |
|----------|-------------|------|--------------------|---------------|------|--------------------|----------|
|          | <i>N</i>    | Mean | Standard deviation | <i>N</i>      | Mean | Standard deviation |          |
| LCCA     | 25          | 0.88 | 0.25               | 25            | 0.68 | 0.19               | 0.006    |
| RCCA     | 25          | 0.90 | 0.22               | 25            | 0.61 | 0.21               | < 0.001  |

Tab. III. Results of the Mann-Whitney *U* test for the study subgroup versus the control group

| IMT [mm] | Study subgroup |      |                    | Control group |      |                    | <i>P</i> |
|----------|----------------|------|--------------------|---------------|------|--------------------|----------|
|          | <i>N</i>       | Mean | Standard deviation | <i>N</i>      | Mean | Standard deviation |          |
| LCCA     | 13             | 0.75 | 0.29               | 25            | 0.68 | 0.19               | 0.860    |
| RCCA     | 13             | 0.78 | 0.24               | 25            | 0.61 | 0.21               | 0.095    |

tima-media complex is presently a recognized evaluation method both of the initial and advanced atherosclerotic changes and also a control method of the applied pharmacotherapy efficiency. The method of IMT measurement is also used in determining the probability of the occurrence of coronary disease and evaluation of the risk of cardiovascular incidents in the general population [23]. Studies performed in numerous research centers [16, 17, 24, 25] indicate faster progression of the atherosclerotic process in people suffering from diseases of the connective tissue, including systemic lupus erythematosus. However, the results presented in this study show that such progression occurs mainly in patients with additional factors of atherosclerosis development, such as lipid disorders, diabetes or arterial hypertension.

The statistical analysis of results, due to the lack of normal distribution of the random variable in the study groups, used non-parametric tests, i.e. the ANOVA Kruskal-Wallis and Mann-Whitney *U* tests [26, 27]. These tests can be used for measurable and ordinal data, the distribution of which does not comply with Student *t*-test assumptions. In the case of measurable data, the null hypothesis is based on the lack of significant differences between arithmetic

means. It is assessed [28] that the strength of the Mann-Whitney *U* test is about 95% of that of the Student *t*-test. In the present study, the test strength in the pair of study-control groups was 0.89, while in the control-subgroup pair it was 0.53. It is assumed [26] that a satisfactory test strength is over 0.75, and so the results of the comparison between the control group and the subgroup should be treated cautiously.

The results of the studies show that the intima-media complex thickness among the patients with systemic lupus erythematosus is statistically bigger than among the healthy subjects of the same age. The mean IMT value for the study group was from 0.2 mm (LCCA) to 0.3 mm (RCCA) higher than for the control group. There were some people in both groups who had minimal values (0.4 mm) and maximal values (1.3 mm), yet the number of people with a thickened intima-media complex (IMT equal to or higher than 1.0 mm) was considerably higher in the study group. These explicit tendencies did not occur between the control group and the subgroup suffering only from lupus. In this case, the difference was only 0.15 mm. Following the criteria of the Polish Ultrasound Society [12], only 4% of cases of the IMT value in the whole study group were understood as in-

dicating the presence of diffused atherosclerotic changes, while as many as 72% of cases had a justified diagnosis of thickened intima-media complex. The important fact is that not a single case was diagnosed in the group suffering only from lupus, where the IMT > 1.3 mm, while the number of cases with a thickened complex was almost two times smaller and amounted to 41%. These observations confirm the results obtained by other research centers, which proved fast progression of the atherosclerotic process among people suffering from systemic diseases of the connective tissue, including lupus [16, 17, 24]. However, they also indicate that the dynamics of this process depend on additional, coexisting factors, such as hyperlipidemia, arterial hypertension or diabetes.

Systemic lupus erythematosus is a chronic autoimmune disease occupying numerous tissues and organs. This disease can develop at any age, but the incidence peak falls at the age of 20 to 40 years. Clinical experience suggests that the inflammatory process develops in the cardiovascular system in a high percentage of patients suffering from SLE (up to 60%). It was proved [25] that it can involve the pericardium, myocardium, endocardium, valves and coronary and peripheral vessels. Early vessel atherosclerosis, occurring even in pediatric patients, is a complication common for systemic diseases of the connective tissue. The IMT examination should become a fundamental one for all patients with diagnosed diseases of the connective tissue and should be performed regularly in order to prevent the unfavorable consequence of developing atherosclerosis [29]. The doctor also should recommend to this group a lifestyle that will prevent the occurrence of other factors of atherosclerotic changes.

## Conclusions

The group of patients with SLE was found to have increased thickness of the intima-media complex in comparison with the population of healthy subjects. Moreover, the unfavorable influence of independent factors of atherosclerosis development on the increase of the IMT value in patients with lupus was observed. This observation suggests faster progression of the atherosclerotic process in this group of patients.

The measurement of IMT enables observation of progression of atherosclerosis in asymptomatic patients. It provides priceless time, during which a proper treatment can be administered and a long-term observation can be carried out. The fact that IMT measurement is cheap, repeatable and easy to perform is of great importance, which is why we believe that it should be used more widely as a non-invasive screening test in atherosclerosis diagnostics and monitoring.

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## Disclosure

The authors report no conflicts of interest.

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