Carotid ultrasonographic parameters as markers of atherogenesis and mortality rate in patients on hemodialysis

Ultrazvučni parametri karotidnih arterija kao markeri ateroskleroze i mortaliteta kod bolesnika na hemodializiri

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Abstract

Background/Aim. Vascular endothelium plays an important role in atherogenesis. The aim of this study was to estimate the correlation of endothelium malfunction and atherosclerosis in patients on hemodialysis. Methods. The investigation was designed as a clinical, non-randomized, five-year study in the “Kragujevac” Clinical Center and included 146 patients. We evaluated demographic characteristics, smoking, duration of dialysis, existence of tissue calcification and duplex ultrasound parameters of the carotid artery. All lethal outcomes, including the cause and time of death were recorded. Results. The cumulative survival rate was 57.5%. Survival was short in patients with wider lumen diameter of the carotid arteries. Carotid artery lumen diameter in men was wider than in women. The area cross section was closely related to the cross section of intima media (r = -0.261; p = 0.028). Positive correlations were found between the serum total protein level and carotid artery lumen diameter (r = 0.235; p = 0.047), cross section intima media (r = 0.269; p = 0.022) and cholesterol (r = 0.248; p = 0.037). Time on dialysis showed a negative correlation with carotid artery cross section (r = -0.241; p = 0.04), while age was positively correlated with intima media (r = 0.295; p = 0.013), lumen diameter (r = 0.296; p = 0.012) and intima media cross section (r = 0.347; p = 0.003). Regression analysis pointed to predictive importance of carotid artery lumen diameter for survival (Beta = 0.437; p = 0.011) of the examined patients. The cumulative rate of survival was 57%. Conclusion. In our study patient age correlated positively with all parameters of arteriosclerosis. The average duration of dialysis was negatively associated with carotid artery diameter, which was significantly higher in males. Regression correlation analyses indicated that the survival rate of the patients on hemodialysis was lower if the carotid artery diameter was larger.

Key words: arteriosclerosis; hemodialysis; endothelium, vascular; ultrasonography; mortality; carotid artery, common.

Apstrakt

Uvod/Cilj. Endotel krvnih sudova ima veliki značaj u procesu aterogeneze. Cilj ovog rada bio je da se utvrdi ko-relacija endotelne disfunkcije i ateroskleroze kod bolesnika na hemodializiri. Metode. Studija je organizovana kao klinička i nerandomizirana, u periodu 2004–2008. godine u Centru za hemodializu Kliničkog centra „Kragujevac“. Analizirane su demografske karakteristike, pušenje, dužina trajanja hemodializije, mekotkivne kalcifikacije i dopler ultrazvučni parametri karotidnih arterija. Evidentirani su svi letalni ishodi, uzrok i vreme smrti. Rezultati. Kod muškaraca zabeležen je statistički značajni širi prečnik karotidnih arterija u odnosu na žene. Pozitivna korelacija postignuta je između površine poprečnog preseka i debline intime medije (r = 0,913; p < 0,0001), kao i prečnika karotidnih arterija (r = 0,527; p < 0,0001). Holesterol negativno utiče na prečnik karotidnih arterija (r = -0,278; p = 0,019). I trigliceridi negativno koreliraju sa površinom poprečnog preseka intime medije (r = -0,261; p = 0,028). Pozitivna korelacija utvrđena je između nivoa ukupnih proteina u serumu i prečnika lumena karotidnih arterija.

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Patients treated by dialysis have 10–20 times higher risk of suffering from cardiovascular diseases and 5–10 times greater incidence of stroke than the population in general. Such a high frequency is a consequence of an atherogenesis process caused by numerous metabolic abnormalities but this can be explained only partially by already known mechanisms. The present theory on arteriosclerosis emphasizes that it is initiated by endothelium malfunction primarily caused by increased levels of free radicals, homocysteine and LDL, while among infectious agents cytomegalovirus and Chlamydia pneumoniae are important. If an anti-inflammatory response is not sufficiently effective to prevent or amortize these risk factors, then the arteriosclerosis process develops by stimulation, migration and proliferation of smooth muscle cells, which leads to thickening of the artery wall. This is followed by narrowing of the lumen due to gathering of connective tissue in the intima with consequent endothelium malfunction. Evaluation of intima and media thickening of the carotid arteries is a good indicator of coronary arteriosclerosis and an independent predictor of cardiovascular mortality not only in dialysed population but also in population before dialysis.

The aim of this study was to determine the extent of endothelium malfunction and arteriosclerosis and its correlation with clinical and biochemical parameters in patients on chronic hemodialysis.

Methods

Our research included 146 patients, 84 (57.5%) men and 62 (42.5%) women, of average age 58 ± 12.2 years, treated by chronic hemodialysis in the Center for Dialysis of the “Kragujevac” Clinical Center. The patients were monitored from 2004 to 2008 in a clinical and non-randomized study design. Demographic and clinical characteristics of the patients (time of dialysis, soft tissue calcifications identified by X-ray diagnosis of the pelvis, extremities and skull, smoking habits) were analysed. All lethal cases were recorded with the time and cause of death. The study was approved by the Ethics Board of the Clinical Center “Kragujevac”, in accordance with the Declaration of Helsinki for Medical Research.

Routine biochemical analyses were carried out by flow cytometry using a Coulter device and spectrophotometrically with an Ilab-600 instrument. The blood for biochemical tests was taken in the mid of the week, before the hemodialysis.

Arteriosclerosis was defined by ultrasonography performed with an SDU-220 Shimadzu instrument (Tokio, Japan) using a 7.5-MHz high-resolution probe. The atherogenesis markers were thickness of intima media and lumen diameter of the carotid arteries. Intima media thickness was defined as a low-level echo grey band that did not project into the arterial lumen and was measured during the diastolic phase as a distance between the leading edge of the first and second echogenic line. The average measurement of the obtained values was taken as intima media thickness and was considered abnormal when it exceeded 0.82 mm. Computa tion of cross section intima media (CSIM) was calculated as follows: \( CSIM = 3.14 \times \frac{\text{lumen diameter}^2 - \text{intima media thickness}^2}{2} \times \text{lumen diameter} \). Measurements were made 2 cm below and above the carotid bifurcation, three measurements on each side. The carotid arteries are favourable for exploration because their middle layer is distinctly weak, so thickening of intima media is more important in such elastic arteries than in the so-called muscle arteries. Ultrasonic examinations were made once a year, all of them by the first author.

Statistical analysis was made with the Instat program (GraphPad Software Inc, San Diego, USA). The \( \chi^2 \) test was employed for testing hypotheses. The associations between two variables was analysed by the Pearson’s correlation. Kaplan-Meier analysis was used for determination of the cumulative rate of survival. A \( p \) value < 0.05 was considered statistically significant.

Results

The average duration of dialysis in our 146 patients was 83 ± 53.25 months. Their mean carotid artery intima media thickness was 0.91 ± 0.198 mm and lumen diameter was 6.96 ± 0.99 mm, while cross section of intima media was 26.81 ± 8.18 mm. Soft tissue calcifications were noticed in 22% of our patients. Almost three quarters of them were either active or passive smokers. A total number of patients with a lethal outcome was 62 (42.5%), out of which 32 (52%) suffered from cardiovascular disease. Infections, diabetes mellitus complications and other causes participated equally at 16% (Table 1).

The cumulative survival rate was 57.5% (Figure 1).
The cumulative rate of patient survival at the end of the study was 57.5%.

The mean lumen diameter of the carotid arteries in men was 7.45 ± 1.03 mm, while in women it was 6.87 ± 0.80 mm. The difference was statistically significant \((p = 0.013)\) (Figure 2).

There were positive correlations between the cross section of intima media of the carotid arteries and the thickness of intima media \((r = 0.913; p < 0.001)\) and the lumen diameter \((r = 0.527; p < 0.001)\). On the other hand, dialysis length was negatively associated with carotid artery lumen diameter \((r = -0.241; p = 0.04)\). Negative correlations were also found between serum cholesterol concentration and carotid artery lumen diameter \((r = -0.278; p = 0.019)\) and between triglyceride level and the cross section intima media \((r = -0.261; p = 0.028)\), while a positive correlation was identified between triglyceride and cholesterol concentrations \((r = 0.617; p < 0.001)\). Serum total protein concentration was positively associated with intima media thickness \((r = 0.235; p = 0.047)\), cross section of intima media surface \((r = 0.269; p = 0.022)\) and total cholesterol \((r = 0.248; p = 0.037)\). Serum albumin also showed a similar relation with cholesterol \((r = 0.436; p < 0.001)\) and the total protein concentration \((r = 0.634; p < 0.001)\). A total calcium concentration was correlated with serum protein level \((r = 0.295; p = 0.012)\). Inorganic phosphorus negatively correlated with cholesterol \((r = -0.239; p = 0.048)\) and calcium concentrations \((r = -0.280; p < 0.0001)\) (Table 2). Age correlated positively with intima media thickness \((r = 0.295; p = 0.013)\), lumen diameter \((r = 0.296; p = 0.012)\) and the intima media cross section \((r = 0.347; p = 0.003)\) (Table 3).

Cox regression analysis showed a statistical significance for the relation between carotid artery lumen diameter and patient survival \((\Beta = 0.437; p = 0.011)\) (Table 4). Survival was shorter in patients with wider lumen diameter of carotid arteries.

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**Table 1**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Volumes</th>
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<tbody>
<tr>
<td>Age (years), (mean ± SD)</td>
<td>58 ± 12.2</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>84/62</td>
</tr>
<tr>
<td>Duration of hemodialysis (months), (mean ± SD)</td>
<td>83 ± 53.25</td>
</tr>
<tr>
<td>Doppler parameters (mean ± SD)</td>
<td></td>
</tr>
<tr>
<td>intima media (mm)</td>
<td>0.91 ± 0.198</td>
</tr>
<tr>
<td>LD (mm)</td>
<td>6.96 ± 0.99</td>
</tr>
<tr>
<td>CSIM (mm)</td>
<td>26.81 ± 8.18</td>
</tr>
<tr>
<td>Calcifications (yes/no)</td>
<td>32/114</td>
</tr>
<tr>
<td>Smoking history (yes/no)</td>
<td>104/42</td>
</tr>
<tr>
<td>Exitus lethalis (n/%)</td>
<td>62/42.5</td>
</tr>
<tr>
<td>Cause of death (n/%)</td>
<td></td>
</tr>
<tr>
<td>cardiovascular diseases</td>
<td>32/52</td>
</tr>
<tr>
<td>infectious disease</td>
<td>10/16</td>
</tr>
<tr>
<td>D. mellitus complication</td>
<td>10/16</td>
</tr>
<tr>
<td>other</td>
<td>10/16</td>
</tr>
</tbody>
</table>

LD – lumen diameter; CSIM – cross section intima media

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**Fig. 2 – Carotid artery diameter in men and women**

The mean lumen diameter of the carotid arteries in men was 7.45 ± 1.03 mm and in women 6.87 ± 0.80 mm. The difference was statistically significant \((p = 0.013)\).

Table 2.

Cox regression model of the effect of Doppler parameters of the carotid arteries on the survival of patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Beta</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>IM</td>
<td>0.799</td>
<td>0.30</td>
</tr>
<tr>
<td>LD</td>
<td>0.437</td>
<td>0.011*</td>
</tr>
<tr>
<td>CSIM</td>
<td>-0.037</td>
<td>0.12</td>
</tr>
</tbody>
</table>

*Statistically significant result; IM – intima media; LD – lumen diameter; CSIM – cross section intima media

Discussion

Epidemiological data show that more than 400,000 Americans suffer from kidney insufficiency, while 300,000 are treated by chronic dialysis, incurring an annual expenditure of around 23 billion dollars

During the last 20 years, the annual death rate of about 20% is still alarmingly high. Although patients with terminal kidney insufficiency may suffer from a number of traditional risk factors which can increase mortality rate, such as hypertension, insulin resistance, dyslipidemia, these cannot fully explain a high mortality rate, which is five times higher than in patients without such risk factors

More than a half of those dying suffer from a cardiovascular disease

It is known that patients with chronic kidney insufficiency are predisposed for cardiovascular diseases, due to risk factors additional to other causes, such as old age, hypertension, diabetes mellitus, smoking or dyslipidemia

It is thought that an intima media thickness of 0.8 mm creates conditions for atherogenesis but there is no single opinion about a media thickness value that is a risk for cardiovascular mortality in patients on dialysis. The most
frequent assertion is that the measurement must be > 1 mm. Some studies for estimating these factors do not only measure intima media thickness but also whether it is homogenous. Namely, non-homogenous intima media in dialysis patients may predict early changes in artery wall structure leading to arteriosclerotic plaque. Intima media thickness is not just an indicator of atherogenesis, but also a reaction to hemodynamic changes, which are very striking in dialysis patients.\(^3\),\(^13\),\(^14\). The mean value of intima media thickness in our patients was 0.91 mm, lumen diameter 6.96 mm and the cross section of intima media 26.8 mm. Our results are not in accordance with data in the available literature pointing to the predictive importance of intima media thickness for cardiovascular mortality. However, techniques for measuring intima media vary and mean values obtained from particular section points can be interpreted in different ways. This is a limiting factor in all studies on intima media, which can be moderated partially by calculating the cross section of intima media thickness. There is a need for identification of all the risk factors that can lead to the development of cardiovascular disease before clinical appearance of the disease. That is why estimation of atherogenesis B-mode ultrasonography is an important step in evaluation of cardiovascular diseases. However, it is not quite clear whether enlargement of the intima media represents a physiological response to a hemodynamic occurrence\(^3\),\(^14\) or whether it is the environment in which the process of atherogenesis is initiated. On the other hand, it is very difficult to separate intima and media. Other factors also contributed to enlargement of the artery diameter, such as old age, primary vascular diseases and hypertension. Although intima media represents an important marker of arteriosclerosis in epidemiological and clinical studies, other alternative procedures should be considered for predictive importance, because traditional risk factors are only partially confirmed. Namely, some epidemiological studies indicate that B-mode ultrasonic examination is not sufficiently accurate and that the difference ranges from 0.00067, which is confirmed by a mathematical method. Endothelium malfunction should be estimated in asymptomatic people as well, as it is clear that the strategy of optimal risk reduction for its appearance is an important procedure in disease prevention\(^15\).

Apart from the so-called classical risk factors for cardiovascular mortality, other contributing factors which lead to vascular calcification are also important. Those are, primarily, an increased level of inorganic phosphate, parathyroid hormones and the calcium phosphate product. However, close attention must be paid to metastatic calcifications in patients with hyperparathyroidism, who often show signs of adynamic bone disease, due to an inability to store calcium surpluses\(^16\),\(^17\). There are some contradictory findings which indicate that increased levels of inorganic phosphate and calcium phosphate product, do not necessarily lead to soft tissue calcification in vivo, even though high phosphate concentration induces calcification in vitro. This suggests that hyper-phosphatemia may cause calcification but the effect is annulled due to the existence of homeostatic mechanisms. One factor protecting against vascular calcification is the smooth muscle cell of blood vessel endothelium. Under experimental conditions, using an animal model, an analogue of vitamin D which indirectly causes hyperphosphatemia, was found to have a negative effect on the endogenous protective mechanism, leading to vascular calcification. This demonstrates a complex mechanism in an in vivo environment, which cannot be easily reproduced under in vitro and ex vivo conditions. However, it is clear that hyperphosphate represents a changed medium creating conditions for vascular calcification\(^20\),\(^22\). All these complex mechanisms are probably reasons why our results do not point to joint activity of Doppler ultrasonic markers of atherogenesis and the imbalance of calcium and phosphate metabolism, together with the level of parathyroid hormone. Thus, only 22% of our patients had calcifications, which is lower than other data stating that 27% of patients on dialysis and 29% on peritoneal dialysis\(^23\),\(^24\) had a clear picture of soft tissue calcifications.

There are findings that relate the increase of intima media thickness to a high risk for vascular calcification in patients with diagnosed vascular calcifications. It is obvious that the thickness of intima media can be seen as a cause-consequence connection between vascular risk factors and the clinical appearance of arterial occlusive disease symptoms\(^25\). An increase of intima media is related to death from myocardial stroke. Hypertrophy of the intima media of 0.1 mm increases the risk of coronary morbidity by 11%. It is estimated that in symptomatic individuals, enlargement of intima media thickness by 0.03 mm per evaluation year represents a valid indicator for cardiovascular morbidity. Periodical evaluation of Doppler parameters of carotid arteries provides important information on possible progression of arteriosclerosis and can be a valid sign of successful therapy in arteriosclerosis\(^26\),\(^27\). Some studies, however, point to a less solid relation between intima media thickness of the carotid artery and coronary arteriosclerosis\(^28\). These doubts reduce the importance of carotid artery intima media, as a predictive factor of cardiovascular morbidity\(^29\). Nevertheless, it has been confirmed that older individuals have hypertrophic intima media\(^30\) and all the ultrasonic arteriosclerosis markers are in interrelated correlation with conventional atherogenic risk factors, the duration of dialysis and age\(^31\) in the first place. The results of our study also show positive correlations of all morphological indices of carotid artery arteriosclerosis with age, while the duration on dialysis correlates negatively with carotid artery lumen diameter. We also showed a statistically significant difference in carotid artery diameter in relation to sex of the examined patients. An increase of lumen diameter of the carotid arteries was significantly more apparent in males of dialysis, which is in accordance with the known conventional atherogenic risk factors. Regression analysis of the effect of Doppler parameters of the carotid arteries on a patient survival indicated lumen diameter as a statistically significant independent variable. Namely, a higher value of this parameter was associated with shorter patient survival, which shows that noninvasive quantification of arteriosclerosis is an important predictor of cardiovascular mortality.
Cardiovascular diseases are the main cause of death of patients on dialysis, as they represent 43–52% of the total mortality index. Out of the general mortality rate in our patients, which was 42.5%, a cardiovascular cause of death was confirmed in 52%. The cumulative survival rate was 57.5% which matches the trend of patient survival in other studies.

**Conclusion**

In our study patient age correlated positively with all parameters of arteriosclerosis. The average duration of dialysis was negatively associated with carotid artery diameter, which was significantly higher in males. Regression correlation analysis indicated that the survival rate of the patients was lower if the carotid artery diameter was larger.

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