

Arteriosclerosis Obliterans Complicating Chronic Renal Failure in Patients on Hemodialysis

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Abstract: This study was undertaken 1) to characterize arteriosclerosis obliterans (ASO) in patients receiving hemodialysis for chronic renal failure and 2) to identify determinants of these patient's characteristics. All 91 patients receiving hemodialysis for chronic renal failure in October 2000 at a single clinic were followed for 5 years. ASO was present in 20 (22.0%) of the 91 patients on hemodialysis. The characteristics of ASO in our series were as follows: Fontaine classification I was in 5 limbs (5/34; 14.7%), II in 15 limbs (15/34; 44.1%), III in 7 limbs (7/34; 20.6%) and IV in 7 limbs (7/34; 20.6%). Forty-one point two percent (41.2%; 14/34) were classified as having critical limb ischemia. During the follow-up period, necrosis in extremities due to ASO per year accounted for 11.1% among all diabetic patients receiving hemodialysis. Independent factors found to affect the survival rate included the presence/absence of ASO and ischemic heart disease (IHD). Patients with a history of both ASO and IHD has about 10.9 times the annual death rate of hemodialysis patients without a history of either of these complications. The occurrence of ASO during the follow-up period, among ASO-free patients at the start of the study, marked 10.7% in 5 years. (J Jpn Coll Angiol, 2007, 47: 163-170)

Key words: arteriosclerosis obliterans (ASO), hemodialysis, chronic renal failure (CRF), ischemic heart disease (IHD), critical limb ischemia

Introduction

Following recent advances in technology for hemodialysis, the number of patients with chronic renal failure receiving long-term hemodialysis remains to be increasing. Arteriosclerosis obliterans (ASO) has attracted attention as a significant clinical problem in hemodialysis patients. Although several epidemiological studies on the development of ASO in hemodialysis patients are reported, there are few reports of follow-up studies on the progression of symptoms of ASO among them. The present study aimed at investigating the characteristics of ASO in hemodialysis patients with chronic

renal failure and at identifying determinants of patients' characteristics who are on hemodialysis for chronic renal failure. These hemodialysis patients were followed up for a period of 5 years.

Subjects and Methods

In October 2000, 91 patients received maintenance hemodialysis for chronic renal failure at the Seishokai Kikukawabashi Clinic. All of these patients were enrolled in this study after giving informed consent. They were divided into the ASO group and the ASO-free group. A questionnaire and analysis of medical records were performed on all 91 patients in October 2000. After 5 years of follow-up, the same questionnaire and analysis of medical

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Table 1 Background variables (sex, age, duration of hemodialysis, smoking history, complications, disease responsible for chronic renal failure)

	ASO	ASO-free	p value
No.	20	71	
Sex (male: female)	14:6	46:25	0.6640
Age	74.10 ± 10.03	59.09 ± 14.17	< 0.0001
Average period of HD (months)	56.10 ± 38.05	83.83 ± 67.07	0.0808
Smoking			
Present smoker	6 (30%)	21 (30%)	
Precious smoker	4 (20%)	18 (25%)	
Non smoker	6 (30%)	32 (45%)	
Unknown	4 (20%)	0	
Complications			
Diabetes mellitus	13 (65%)	14 (14%)	< 0.0001
Hypertension	17 (85%)	55 (77%)	0.5502
Ischemic heart disease	5 (25%)	6 (8%)	0.0593
Cerebrovascular disease	4 (20%)	4 (6%)	0.0670
Malignancy	1 (5%)	6 (8%)	> 0.9999
Etiology of CRF			
Chronic glomerulonephritis	3 (15%)	36 (51%)	0.0048
Diabetic nephropathy	12 (60%)	11 (15%)	< 0.0001
Nephrosclerosis	3 (15%)	10 (14%)	> 0.9999
Polycystic kidney	0	3 (4%)	> 0.9999
Gouty nephropathy	0	2 (3%)	> 0.9999
IgA nephropathy	0	3 (4%)	> 0.9999
Other	2 (10%)	4 (6%)	
Unknown	0	2 (3%)	

records were conducted in October 2005 on those patients who had not dropped out of the follow-up. **Table 1** shows the composition of the questionnaire. The presence/absence of ASO was determined on the basis of clinical symptoms, physical findings, ankle-brachial pressure index (API). In addition, near-infrared spectroscopy (NIRS), angiography, magnetic resonance angiography (MRA) or ultrasonography were carried out only for those who underwent the examinations. Patients with at least one of the following factors applying were diagnosed with ASO:

- 1) API < 0.9.
- 2) Rated by NIRS as type 1 or 2 after 5 minutes of treadmill exercise (2.4 km/hr) at an inclination of 12 degrees.¹⁻³
- 3) Detection of arterial obstructive lesions by angiography, MRA or ultrasonography.
- 4) Having undergone lower limb amputation on the basis

of a diagnosis of ASO.

The details of diagnostic method of ASO are showed on the **Table 2**.

To identify determinants of the patients' survival, cumulative survival rates were compared among the groups of patients divided by the presence/absence of ASO, ischemic heart disease (IHD), cerebrovascular disease (CVD), diabetes mellitus (DM), hypertension (HT) and malignant tumors. Furthermore, factors whose p value was less than 0.1 in univariate analysis were subjected to multivariate analysis to identify factors affecting the survival rate independent of other factors.

Statistical analysis

Chi-squared test and Fisher's exact test served as statistical analysis of 2 × 2 contingency tables, and Kaplan-Meier

Table 2 The details of diagnostic method of ASO are showed on the Table 2 (Repetition cases are included)

Diagnostic method	Number
Past history of limb amputation	3
API	14
NIRS	1
Ultrasonography	2
MRA	0
Angiography	9

API: ankle-brachial pressure index, NIRS: near-infrared spectroscopy, MRA: magnetic resonance angiography

method and log-rank test as survival analysis. Proportional hazard model was used for multivariate analysis of survival rates.

Results

Survey in October 2000

ASO was present in 20 (22.0%) of the 91 hemodialysis patients. Table 1 shows the results of the first questionnaire survey of the 91 patients in October 2000. Age, diabetes mellitus (DM) and the disease responsible for chronic renal failure are the background variables found to differ significantly between the ASO group and the ASO-free group. The ASO group is characterized by more advanced age and a higher prevalence of diabetes mellitus than the ASO-free group. There was no significant inter-group difference in sex, mean duration of hemodialysis and smoking.

Clinical symptoms were classified according to the Fontaine classification in the ASO group. Fontaine classification I was in 5 limbs (5/34; 14.7%), II in 15 limbs (15/34; 44.1%), III in 7 limbs (7/34; 20.6%) and IV in 7 limbs (7/34; 20.6%). Thus, severe ischemia (Fontaine classification III or IV) was seen in 41.2% (14/34) of all limbs in this group.

In the ASO group, 6 of the 12 cases (11 of 20 limbs) with Fontaine classification I or II were treated with medication. None of the Fontaine classification I or II cases underwent vascular reconstruction. Of the 8 cases (14 limbs) with severe limb ischemia (Fontaine III and IV), 2 cases (2 limbs) had undergone vascular reconstruction previously and 4 cases (5 limbs) amputation. Major amputation had been performed

in 2 cases (3 limbs, including 1 case of bilateral major amputation), Syme amputation in 1 case (1 limb) and minor amputation in 1 case (1 limb). The remaining 2 cases (4 limbs) had received drug therapy previously.

Long-term outcome of limbs

Two cases in the ASO group and 4 cases in the ASO-free group were transferred to other hospitals during follow-up. Twelve cases in the ASO group and 12 cases in the ASO-free group died during the follow-up. Follow-up was possible in the other cases. The number of cases followed up for 5 years was 6 in the ASO group and 55 in the ASO-free group. The follow-up period was 50.8 ± 18.3 months (37.4 ± 23.0 months in the ASO group and 54.6 ± 14.8 months in the ASO-free group), which was significantly shorter in the ASO group ($p < 0.0001$). Figures 1 and 2 graphically represent the changes in Fontaine classification for each case from October 2000 to the last survey, in both the ASO and ASO-free group.

ASO group

One case (1 limb) with Fontaine classification II (8.3%) showed an improvement in API of 0.2 or more during the follow-up. This case had received oral anti-platelet drug therapy. API in this case improved, but the symptom of intermittent claudication persisted.

Worsening was seen in 2 cases (2 limbs). In these 2 cases (2 limbs) with Fontaine classification II, ischemia had worsened to Fontaine classification IV 5 years later. One of these 2 cases had received drug therapy, and the other case had not received drug treatment or exercise training. The case was classified in Fontaine II in 2000, progressed to Fontaine IV throughout the course, resulting in revascularization. Of the 2 cases (4 affected limbs) with severe ischemia treated by drug therapy alone, 1 case (1 limb) underwent major amputation 3 months later, the other was followed for 5 years while receiving conservative therapy.

All the cases that underwent bypass operation developed complications with severe ischemia in the lower limb in 2000, or had worsening of ischemic symptoms in the lower limb to severe ischemia during the follow-up. The former underwent axillo-bifemoral bypass, and the latter minor amputation after left femoral artery-anterior tibial artery bypass

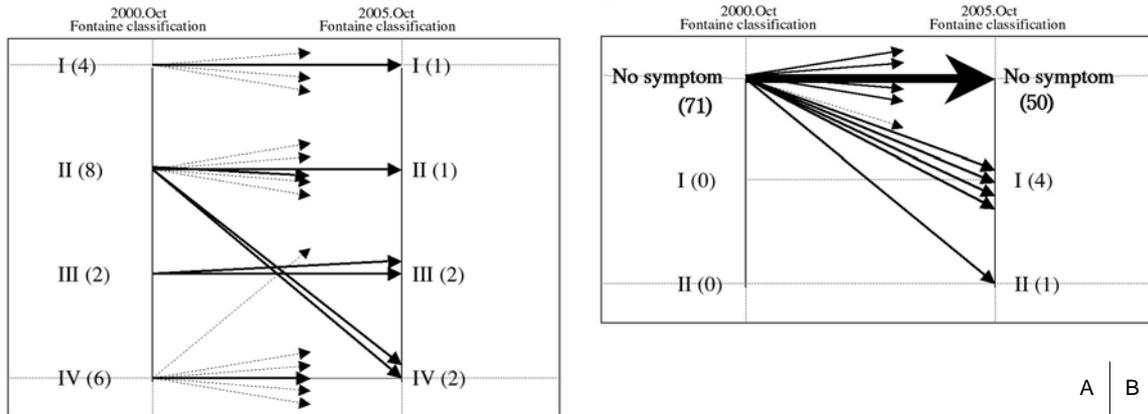


Figure 1 Changes in Fontaine classification of limb ischemia from first survey to survey 5 years later. () shows the number of cases alive in October 2005. The case that died is shown as a dotted line.
A: ASO group
B: ASO-free group

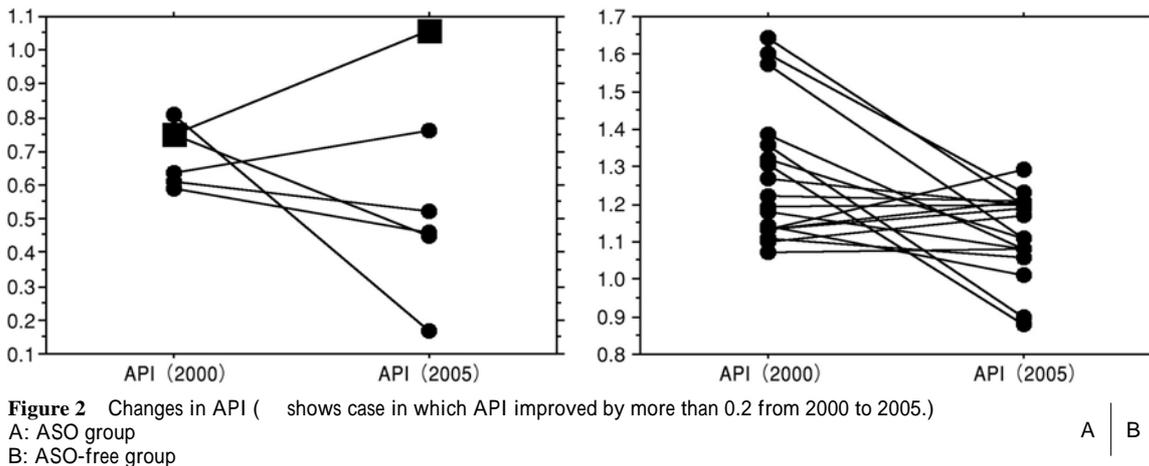


Figure 2 Changes in API (shows case in which API improved by more than 0.2 from 2000 to 2005.)
A: ASO group
B: ASO-free group

operation.

ASO-free group

During the follow-up, a diagnosis of ASO was newly made in 6 cases (8 limbs) of the 71 cases (142 limbs). Limb ischemia was classified as Fontaine classification I in 5 cases (7 limbs) and II in 1 case (1 limb).

Long-term survival rate

The 5-year survival rate for the entire population studied accounted for 72.3%.

Effect of ASO on survival rate

Figure 3 shows the cumulative survival curves for the ASO group and ASO-free group.

The 5-year cumulative survival period was significantly longer in the ASO-free group (82.2%) than in the ASO group (35.7%) ($p < 0.0001$).

In the ASO group, the causes of death were ischemic heart disease (4 cases), infection (2 cases), cerebral infarction (1 case), malignancy (1 case), disseminated intravascular coagulation (1 case), liver cirrhosis (1 case) and unknown (2 cases). In the ASO-free group, they were ischemic heart

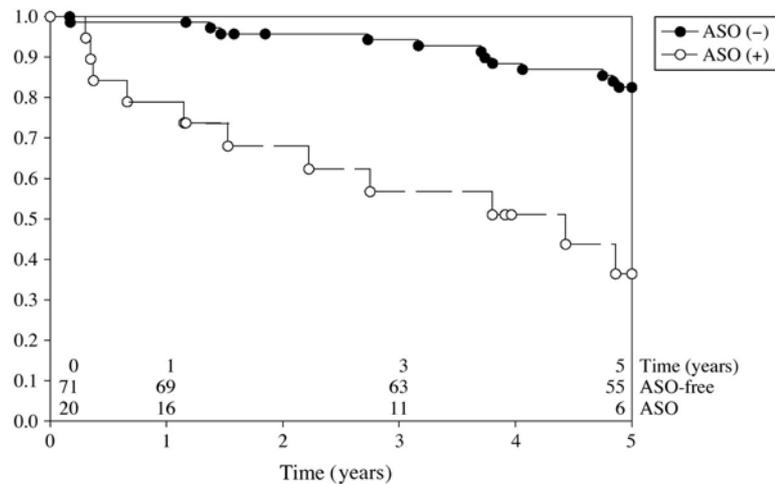


Figure 3 Cumulative survival curves for ASO group and ASO-free group

disease (2 cases), infection (4 cases), cerebral infarction (3 cases), malignancy (1 case) and unknown (2 cases). There was no significant inter-group difference in the cause of death.

Factors determining survival

The survival rate differed depending on age and the presence/absence of ASO, IHD and CVD, but average period of hemodialysis (HD) and the presence/absence of diabetes mellitus, hypertension, malignancy or collagen disease (**Table 3**) did not affect the survival rate.

On the basis of these results, we performed multivariate analyses. Multivariate analysis of factors related to age, period of HD and the presence/absence of ASO, IHD and CVD were performed. ASO and IHD were shown to be independent factors (**Table 4**). The annual death rate for hemodialysis patients with a history of ASO and IHD was about 10.9 times that for hemodialysis patients without a history of these diseases.

Discussion

Epidemiology

The number of patients receiving hemodialysis for chronic renal failure continues to increase. The statistics of the Japanese Society for Dialysis Therapy places an estimated number of such patients at about 248,000.⁴ The disease responsible for chronic renal failure is reported to be chronic glomerulonephritis in about 45.1% of all cases, followed by

diabetic nephropathy (30.2%), nephrosclerosis and polycystic kidney. The male-to-female ratio of patients receiving hemodialysis is 3:2, indicating a male predominance. The most affected age group of hemodialysis patients is 60–69, followed by 70–79 and then 50–59.⁴ In Japan, the cumulative survival rate of patients who were introduced into hemodialysis therapy in 2003 is marked at 87.0% at one year.⁴ The cumulative survival rate of patients who were introduced into hemodialysis therapy in 1999 is 62.0% at 5 years. The major causes of death in hemodialysis patients are heart failure (25.1%), cerebrovascular disease (10.6%), infection (18.8%), malignancy (9.0%) and myocardial infarction (5.4%). Among the patients analyzed in the present study, the mortality from cardiovascular complications was higher than that of the entire population of Japanese patients with chronic hemodialysis, while the mortality from malignant diseases tended to be slightly lower. The mortality from cerebrovascular disease for the ASO-free group did not differ markedly from that for the entire Japanese population data, while that of the ASO group tended to be slightly lower. Nakamura et al. reported that the prevalence of ASO in patients with chronic renal failure on dialysis was 13.5%.⁵ O'Hare reported that the prevalence of ASO in these patients ranged from 5.5% to 29%, and commented that it was not easy to make the diagnosis of ASO in patients on chronic hemodialysis.

Table 3 Comparison of survival rate of patients by clinical variables (Kaplan-Meier's method and log rank test)

Group	No. of patients	Survival rate (%)		Log-rank test p value
		3-year	5-year	
Total	91			
Sex				0.2554
Male	60	84.4	68.0	
Female	31	90.2	80.2	
Age				0.0099
60 years old	58	80.9	63.0	
< 60 years old	33	96.8	89.9	
Average period of HD				0.8811
6 years	48	85.1	72.0	
< 6 years	43	87.9	72.5	
Major complications				
ASO				< 0.0001
Present	20	58.9	35.7	
Absent	71	94.2	82.2	
Diabetes mellitus				0.8442
Present	27	77.1	73.0	
Absent	64	90.4	72.1	
Hypertension				0.9817
Present	72	84.3	72.6	
Absent	19	94.4	70.8	
Ischemic heart disease				0.0037
Present	11	54.5	45.5	
Absent	80	90.9	76.0	
Cerebrovascular disease				0.0014
Present	8	57.1	28.6	
Absent	83	88.9	76.1	
Malignancy				0.4197
Present	7	85.7	51.4	
Absent	84	86.5	73.8	
Collagen disease				0.8908
Present	3	100	66.7	
Absent	88	85.9	72.5	

Table 4 Results of multivariate analysis using proportional hazard model

Factor	Hazard ratio	95% confidence interval
ASO	3.868	1.685–8.879
Ischemic heart disease	2.817	1.111–7.141
Cerebrovascular disease	2.190	0.784–6.084
Age	2.687	0.776–9.305

Progression of ASO

Of the 91 hemodialysis patients studied, 22.0% (20/91) had ASO and 8.8% (8/91) had severe limb ischemia. el-Reshaid et al. reported that the annual incidence of ischemia of the extremities due to ASO was 0.086 per 1000 general population (0.0086%), while it was 7.1 per 1000 non-diabetic hemodialysis patients (0.71%) and 41.4 per 1000 diabetic hemodialysis patients (4.14%).⁶ In the present study, 2 patients developed lower limb necrosis due to ASO during the 5-year follow-up, and both of these cases were diabetic patients. Thus, the annual incidence of lower limb necrosis due to ASO in the diabetic hemodialysis patients in the present study was 11.1%. According to Dormandy et al., in approximately three quarters of the patients, the disease will symptomatically stabilize soon after its onset and only about a quarter will significantly deteriorate. And the patient who develops intermittent claudication has only 1.5–5.0% chance of ever requiring a major amputation.⁷ Their study, which included hemodialysis patients with chronic renal failure, revealed a high percentage of lower limb amputation among ASO-complicated cases (10.0%, 2/20).

There is no previous report on the incidence of ASO among initially ASO-free cases of chronic renal failure during the course of hemodialysis. In the present study, 8.4% (6/71) of the 71 patients in the ASO-free group were diagnosed as having developed ASO during the 5-year follow-up. The incidence of ASO during hemodialysis in initially ASO-free patients on hemodialysis was about 10.7% per 5 years by Kaplan-Meier's method.

ASO in patients receiving maintenance hemodialysis is characterized by (1) a high percentage of diabetic patients, (2) multiple stenoses of the superficial femoral artery and diffuse stenosis of crural arteries, and (3) arterial calcification in the periphery.⁸ Peripheral lesions associated with ASO are often extensive.^{9,10} Severe limb ischemia is also seen frequently.^{11,12} In the present study, the percentage of ASO-complicated cases with severe limb ischemia was as high as 40.0%.

Factors determining survival

Of the 8 patients with severe limb ischemia, 3 (37.5%) died within one year. The survival rate for patients with

severe limb ischemia was marked at 62.5% at one year and fell to 33.3% at 5 years. According to a report of the TransAtlantic Inter-Society Consensus (TASC), the one-year survival rate for patients with severe limb ischemia ranged from 20% to 50%.¹³ In the present study, analysis of survival curves by log-rank test suggested that four variables—age, ASO, IHD and CVD—served as significant determinants of survival curves. When we performed multivariate analysis on the basis of this finding, ASO and IHD were found to be independent factors, and the prognosis was significantly poorer for cases complicated by either of these two diseases. The presence of hypertension or diabetes mellitus and average period of HD did not affect the prognosis. The annual mortality rate for hemodialysis patients with a history of ASO and IHD was about 10.9 times that for hemodialysis patients without these complications.

Ono reported that a low value of API indicated poor life expectancy in patients on dialysis in Japan.¹⁴ Whether intervention to improve the survival rate is possible for patients with these poor survival factors is an important future issue.

Conclusion

(1) Of patients receiving maintenance hemodialysis for chronic renal failure, 22.0% had ASO. Severe limb ischemia was seen in 41.2% of all limbs of these ASO-complicated cases.

(2) The 5-year cumulative survival period was significantly longer in the ASO-free group (82.2%) than in the ASO group (35.7%) ($p < 0.0001$).

(3) ASO and IHD were identified as the factors reducing the survival rate of hemodialysis patients with chronic renal failure were ASO and IHD.

(4) The incidence of ASO during hemodialysis in initially ASO-free patients on hemodialysis was about 10.7% per 5 years.

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