Prospective study on clinical characteristics of Japanese diabetic patients with chronic limb-threatening ischemia presenting Fontaine stage IV

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Abstract

The aim of this prospective cross-sectional study was to reveal clinical characteristics of Japanese diabetic patients with chronic limb-threatening ischemia (CLTI) presenting ischemic unhealed ulcer/gangrene (Fontaine stage IV) in the real-world settings. The present study included 132 Japanese diabetic patients who underwent endovascular therapy for CLTI presenting Fontaine stage IV. The prevalence of diabetes-related complications, as well as prior history of ankle-brachial index (ABI) measurement before CLTI onset, was evaluated adopting multiple imputation (50 times). Duration of diabetes was referred to as time from diagnosis. The patients were aged 70 ± 10 years, with duration of diabetes 23 ± 12 years. The diabetes-related complications were so common that only 17% (95% confidence interval: 11–24%) and 25% (17–33%) of the population were free from advanced micro- and macroangiopathies, respectively. The clustering of advanced macroangiopathies was not significantly associated with duration of diabetes ($P=0.62$). On the other hand, that of advanced microangiopathies was significantly positively associated with duration of diabetes ($P=0.004$). However, even in patients with duration of diabetes < 10 years, as many as 63% (38–87%) of patients had at least one advanced microangiopathy. Only 31% (22–39%) of the patients had prior history of ABI measurement before CLTI onset. The history was inversely associated with age ($P=0.005$). In conclusion, the advanced diabetes-related complications were highly prevalent, even in those whose diabetes was diagnosed less than a decade before. In addition, only a few patients had ever undergone ABI measurement before CLTI onset.

Keywords Critical limb-threatening ischemia · Fontaine stage IV · Diabetes-related complication · Prior history of ankle-brachial index measurement

Introduction

Chronic limb-threatening ischemia (CLTI) presenting unhealed ulcers or gangrenes (Fontaine stage IV) is the most advanced form of lower-extremity atherosclerosis. Its prognosis is extremely poor, and most patients ultimately need

revascularization [1]. Diabetes mellitus is a key risk factor for CLTI [1], and a majority of CLTI patients have diabetes mellitus [2].

Given that diabetes mellitus is associated with a variety of complications [3], it would be no surprise if diabetic CLTI patients present various kinds of diabetes-related comorbidities. Such comorbidities would influence the treatment strategies for CLTI. However, data are so far limited on the prevalence of these diabetes-related complications in the real-world settings. We previously explored the prevalence of diabetes-related complications [4], but the study was a retrospective one, and the data on some complications such as neuropathy and carotid atherosclerosis were unavailable.

Another clinical question as to this population was how common the experience of lower limb hemodynamic assessment was before CLTI onset. Routine foot examinations including hemodynamic assessment are recommended as

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an effective strategy for the prevention of foot ulceration in a diabetic population [3]. Ankle–brachial index (ABI) is established as a first-line screening tool for lower limb ischemia, and the importance of its assessment in diabetic patients in clinical practice has been long emphasized [5]. It remained unknown, however, how many diabetic CLTI patients presenting Fontaine stage IV had ever undergone ABI measurement before they developed CLTI.

The aim of the current prospective study was to reveal these clinical characteristics of Japanese diabetic patients with CLTI presenting Fontaine stage IV warranting revascularization in the real-world settings.

Materials and methods

The current prospective cross-sectional study registered consecutive 132 Japanese diabetic patients who underwent endovascular therapy for CLTI presenting unhealed ulcers or gangrenes (Fontaine stage IV) in Kansai Rosai Hospital, Amagasaki City, Japan, between October 2016 and December 2018. Data on their clinical characteristics at revascularization were prospectively and cross-sectionally collected. The current study was performed in accordance with the Declaration of Helsinki, and was approved by the ethics committee of Asahikawa Medical University Hospital (date of approval: July 22, 2016, approval number: 16053), Kansai Rosai Hospital (date of approval: August 5, 2016, approval number: 16D029 g), and Osaka University Hospital (date of approval: August 30, 2016, approval number: 16171). On the grounds that the current study was an observational research without intervention or invasiveness and did not use human biological specimen, the study was considered exempted from written informed consent of patients, in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan. Instead, relevant information regarding the study was open to the public and opportunities for refusal were ensured.

Definitions

Duration of diabetes was referred to as time from diagnosis of diabetes, rather than that from onset of diabetes. Duration of diabetes, as well as past history of smoking and ABI measurement before CLTI onset, was determined by self-report and medical records. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, past diagnosis, and/or treatment for hypertension [6]. Dyslipidemia was defined as low-density lipoprotein cholesterol levels ≥ 140 mg/dl, high-density lipoprotein cholesterol levels < 40 mg/dl, triglycerides levels ≥ 150 mg/dl, past diagnosis, and/or treatment for dyslipidemia [7]. Diabetic retinopathy was classified into no

diabetic retinopathy, non-proliferative diabetic retinopathy, and proliferative retinopathy, which were diagnosed by ophthalmologists. History of vitreous surgery for vitreous hemorrhage and photocoagulation for retinopathy included proliferative retinopathy. Diabetic nephropathy was classified into stage 1 (pre-nephropathy with urinary albumin < 30 mg/g creatinine and estimated glomerular filtration rate ≥ 30 ml/min/1.73 m²), stage 2 (incipient nephropathy presenting microalbuminuria [urinary albumin 30–299 mg/g creatinine] and estimated glomerular filtration rate ≥ 30 ml/min/1.73 m²), stage 3 (overt nephropathy presenting macroalbuminuria [urinary albumin ≥ 300 mg/g creatinine] or persistent proteinuria [urinary protein ≥ 0.5 g/g creatinine] and estimated glomerular filtration rate ≥ 30 ml/min/1.73 m²), stage 4 (kidney failure presenting estimated glomerular filtration rate < 30 ml/min/1.73 m²), and stage 5 (dialysis therapy) [8]. Neuropathy was assessed by the Semmes–Weinstein 5.07 monofilament at the following four podalic sites: the distal great toe and the first, third, and fifth metatarsal heads [9]. The number of insensate sites out of the four examining sites was counted. Stroke included symptomatic cerebral infarction persisting neurological aftereffects and cerebral hemorrhage requiring hospitalization. Carotid atherosclerosis was evaluated by ultrasound. Carotid stenosis was defined as $\geq 50\%$ stenosis in vessel diameter or $\geq 75\%$ stenosis in vessel lumen area. History of carotid endarterectomy or carotid artery stenting was included in carotid stenosis. In cases free from carotid stenosis, the maximum intima-media thickness (IMT) of the whole carotid artery was measured. The maximum IMT ≥ 1.1 mm was regarded as significant carotid atherosclerosis. Ischemic heart disease was defined as angina pectoris and myocardial infarction. Heart failure was determined when patient had history of hospitalization for heart failure. The clustering of advanced microangiopathies was referred to as the accumulation of proliferative diabetic retinopathy, diabetic nephropathy stage 5 (dialysis therapy), and insensateness at all the four examined podalic sites, whereas the clustering of advanced macroangiopathies was as that of stroke, carotid stenosis, and ischemic heart disease. We also retrospectively searched medical records for the medical institutions and clinical departments where the study subjects were regularly treated for their diabetes. The information was available in 100 patients (76%), who were treated at 73 medical institutions in 17 cities.

Statistical analysis

Data are given as mean $\pm$ SD for continuous variables and as percentages for discrete variables, unless otherwise mentioned. The estimated prevalence of diabetes-related comorbidities and prior history of ABI measurement before CLTI onset are presented with the 95% confidence intervals (CI).

The association of duration of diabetes with the clustering of advanced micro- and macroangiopathies was investigated using cumulative logistic regression models. The estimated mean or prevalence of baseline characteristics of patients with and without prior history of ABI measurement before CLTI onset is presented with the 95% CIs. *P* values for the intergroup difference were derived from linear regression models for continuous variables, binomial logistic regression models for dichotomous variables, and cumulative logistic regression models for ordinal discrete variables, respectively. Since the current dataset contained missing data, multiple imputation (50 times) was adopted. All statistical analyses were performed using R software Program version 3.1.0 (R Development Core Team, Vienna, Austria).

Results

The clinical characteristics of the study population are summarized in Table 1. They were aged 72 ± 10 years, and 72% were male. Type 1 diabetes accounted for 3%. Duration of diabetes was 23 ± 12 years, whereas hemoglobin A1c levels were $7.0 \pm 1.6\%$. Multiple imputation estimated that patients with duration of diabetes ≥ 20 years accounted for 64% (95% CI 55–72%), whereas 18% (11–24%) of patients had hemoglobin A1c levels $\geq 8\%$. Mean body mass index was 23.2 ± 4.3 kg/m². The prevalence of obesity (defined as body mass index ≥ 25 kg/m²) was estimated at 28% (21–36%), whereas leanness (body mass index < 18.5 kg/m²) was estimated at 9% (4–13%).

Diabetes-related complications

The estimated prevalence of diabetes-related complications is shown in Table 2. The prevalence of proliferative diabetic retinopathy and dialysis therapy was 46% (37–55%) and 66% (58–74%), respectively, whereas 82% (75–89%) of patients had one or more insensate podalic sites out of the four examined sites. Patients with stroke, carotid stenosis, ischemic heart disease, and heart failure accounted for 21% (14–28%), 21% (16–32%), 61% (52–69%), and 24% (17–31%), respectively. Only 17% (11–24%) and 25% (17–33%) of the population were free from advanced micro- and macroangiopathies.

As demonstrated in Table 3, the clustering of advanced macroangiopathies was not significantly associated with duration of diabetes ($P=0.62$). On the other hand, that of advanced microangiopathies was significantly positively associated with duration of diabetes ($P=0.004$). The association was still significant after adjustment with sex, age, hypertension, dyslipidemia, and smoking (adjusted odds ratio 1.55 [1.14–2.11] per 10-year increment, $P=0.006$). However, even in patients with duration of diabetes

Table 1 Patient characteristics

<i>n</i>	132
Male sex	95 (72%)
Age (years)	72 ± 10
Type 1 diabetes	4 (3%)
Duration of diabetes (years)	23 ± 12
(missing data)	11 (8%)
Body mass index (kg/m ²)	23.2 ± 4.3
(missing data)	2 (2%)
Ambulation	
Self-ambulatory	86 (65%)
In a wheelchair	40 (30%)
Bed-ridden	6 (5%)
Current smoking	23 (17%)
History of smoking	74 (62%)
(missing data)	12 (9%)
Hypertension	126 (95%)
Dyslipidemia	99 (75%)
Rutherford category 6	36 (27%)
(Missing data)	1 (1%)
Anti-diabetic medication	
No medication	20 (15%)
Non-insulin medications	47 (36%)
Insulin use	65 (49%)
Hemoglobin A1c (%)	7.0 ± 1.6
(Missing data)	5 (4%)
Aspirin use	108 (82%)
Thienopyridine use	80 (61%)
Cilostazol use	16 (12%)
Medical institution where diabetes was treated	
Hospital	35 (35%)
Clinic	65 (65%)
(Missing data)	32 (24%)
Clinical department where diabetes was treated	
Diabetology	15 (15%)
Dialysis	56 (56%)
Others	29 (29%)
(Missing data)	32 (24%)

Data are presented as mean $\pm$ SD or frequency (percentage)

< 10 years, as many as 63% (38–87%) of patients had at least one advanced microangiopathy.

Prior history of ABI measurement before CLTI onset

Patients who had prior history of ABI measurement before they developed CLTI accounted for only 31% (22–39%) of the study population. Table 4 summarizes clinical characteristics of patients with and without prior history of ABI measurement before CLTI onset. The clinical characteristics were not significantly different between the groups,

Table 2 Estimated prevalence of diabetes-related complications

Retinopathy	No diabetic retinopathy	38% [29–46%]
	Non-proliferative diabetic retinopathy	16% [10–23%]
	Proliferative diabetic retinopathy	46% [37–55%]
Nephropathy	Stage 1 (pre-nephropathy)	6% [2–10%]
	Stage 2 (incipient nephropathy)	12% [6–17%]
	Stage 3 (overt nephropathy)	8% [3–13%]
	Stage 4 (kidney failure)	8% [4–13%]
	Stage 5 (dialysis therapy)	66% [58–74%]
Neuropathy	No insensate site	18% [11–25%]
	1 insensate site	18% [10–25%]
	2 insensate sites	22% [13–30%]
	3 insensate sites	18% [11–26%]
	4 insensate sites	24% [17–32%]
Stroke		21% [14–28%]
Carotid atherosclerosis	Carotid IMT ≤ 1.0 mm	7% [2–12%]
	Carotid IMT ≥ 1.1 mm	70% [61–78%]
	Carotid stenosis	24% [16–32%]
Ischemic heart disease	No ischemic heart disease	39% [31–48%]
	Angina pectoris	56% [48–65%]
	Myocardial infarction	5% [1–8%]
Heart failure		24% [17–31%]
Microangiopathy clustering	No advanced microangiopathy	17% [11–24%]
	1 advanced microangiopathy	38% [30–47%]
	2 advanced microangiopathies	35% [27–44%]
	3 advanced microangiopathies	9% [4–14%]
Macroangiopathy clustering	No advanced macroangiopathy	25% [17–33%]
	1 advanced macroangiopathy	47% [38–57%]
	2 advanced macroangiopathies	24% [17–32%]
	3 advanced macroangiopathies	3% [0–6%]

Data are estimated prevalence [95% confidence interval], using multiple imputation

Table 3 Micro- and macroangiopathy clustering by duration of diabetes

		Duration of diabetes				Odds ratio of duration of diabetes (per 10-year increase)
		< 10 years	10–20 years	20–30 years	≥ 30 years	
Microangiopathy clustering	No advanced one	37% [13–62%]	23% [7–39%]	14% [3–26%]	8% [0–17%]	1.52 [1.15–2.01] ($P=0.004$)
	1 advanced one	41% [15–68%]	33% [14–52%]	43% [25–60%]	37% [23–52%]	
	2 advanced ones	21% [0–43%]	41% [22–59%]	33% [16–49%]	39% [24–54%]	
	3 advanced ones	0% [0–2%]	3% [0–10%]	10% [0–20%]	16% [5–27%]	
Macroangiopathy clustering	No advanced one	48% [22–74%]	21% [6–36%]	17% [5–29%]	26% [13–39%]	1.08 [0.80–1.44] ($P=0.62$)
	1 advanced one	18% [0–38%]	49% [30–69%]	65% [49–81%]	43% [28–58%]	
	2 advanced ones	33% [9–58%]	30% [12–48%]	18% [5–31%]	22% [10–35%]	
	3 advanced ones	1% [0–6%]	0% [0–0%]	0% [0–0%]	9% [1–17%]	

Data are estimated prevalence [95% confidence interval], with the use of multiple imputation. Odds ratios of duration of diabetes for diabetes-related complications [95% confidence intervals] were derived from the cumulative logistic regression model

except for age; patients without prior history of ABI measurement was significantly older ($P=0.005$). Indeed, when the population was stratified according to age, a low

prevalence of prior history of ABI measurement was more marked in older patients (Table 5).

Table 4 Comparison between patients with and without prior history of ABI measurement before CLTI onset

	Patients without history of ABI measurement	Patients with history of ABI measurement	<i>P</i> value
Male sex	70% [60–79%]	77% [64–91%]	0.38
Age (years)	74 [72–76]	69 [65–72]	0.005
Type 1 diabetes			
Duration of diabetes (years)	22 [19–25]	24 [20–28]	0.33
Body mass index (kg/m ²)	23.1 [22.1–24.1]	23.1 [22.1–25.1]	0.60
Ambulation			0.56
Self-ambulatory	64% [54–74%]	68% [53–84%]	
In a wheelchair	31% [21–41%]	29% [14–44%]	
Bed-ridden	5% [1–10%]	2% [–2–7%]	
Current smoking	16% [9–24%]	20% [7–33%]	0.66
History of smoking	57% [46–67%]	66% [49–82%]	0.39
Hypertension	95% [90–99%]	97% [92–102%]	0.52
Dyslipidemia	77% [68–86%]	71% [56–86%]	0.55
Rutherford category 6	28% [19–38%]	26% [12–41%]	0.81
Anti-diabetic medication			0.44
No medication	20% [11–28%]	5% [–3–13%]	
Oral medication	32% [22–41%]	45% [29–61%]	
Insulin	49% [38–59%]	50% [34–66%]	
Hemoglobin A1c (%)	7.1 [7.1–7.1]	7.1 [6.1–7.1]	0.30
Aspirin use	84% [76–92%]	77% [64–91%]	0.39
Thienopyridine use	65% [55–75%]	51% [34–68%]	0.18
Cilostazol use	11% [4–18%]	14% [3–26%]	0.61
Medical institution where diabetes was treated: hospital	38% [27–49%]	45% [27–62%]	0.53
Clinical department where diabetes was treated			
Diabetology	15% [7–24%]	26% [10–41%]	0.25
Dialysis	49% [38–60%]	55% [38–71%]	0.60
Others	36% [25–46%]	20% [5–34%]	0.13
Microangiopathy clustering			0.081
No advanced microangiopathy	20% [11–29%]	11% [0–21%]	
1 advanced microangiopathy	41% [30–52%]	33% [17–48%]	
2 advanced microangiopathies	31% [21–41%]	44% [28–60%]	
3 advanced microangiopathies	8% [2–14%]	13% [1–24%]	
Macroangiopathy clustering			0.71
No advanced macroangiopathy	26% [16–35%]	23% [9–37%]	
1 advanced macroangiopathy	47% [37–58%]	48% [31–64%]	
2 advanced macroangiopathies	25% [16–34%]	23% [8–38%]	
3 advanced macroangiopathies	2% [–1–5%]	6% [–2–14%]	

Data are estimates of mean values or prevalence [95% confidence interval], with the use of multiple imputation. *P* values between groups were derived from the linear regression model for continuous variables, the binomial logistic regression model for dichotomous variables, and the cumulative logistic regression model for ordinal discrete variables

Table 5 Proportion of prior history of ABI measurement before CLTI onset in age groups

Age	< 60 years	60–69 years	70–79 years	≥ 80 years	Overall
Proportion	54% [27–81%]	41% [23–58%]	23% [9–36%]	22% [6–37%]	31% [22–39%]

Data are estimated proportion [95% confidence interval], with the use of multiple imputation

Discussion

The current prospective cross-sectional study demonstrated clinical characteristics of Japanese diabetic patients with CLTI presenting Fontaine stage IV in the real-world settings. Diabetes-related complications were highly prevalent; only 17% (11–24%) and 25% (17–33%) of the population were free from advanced micro- and macroangiopathies. Only 31% (22–39%) of the population had prior history of ABI measurement before CLTI onset.

Average age and duration of diabetes in a general diabetic population in Japan have been reported to be around 60 s and 10 years, respectively [10, 11], indicating that the current study population was almost a decade older, with about a decade longer duration of diabetes. These findings were consistent with our previous retrospective research [4]. On the other hand, mean body mass index in the current study population seemed slightly higher than that in our previous report (23.2 vs. 21.5 kg/m²), although it was still lower than in a concurrent general diabetic population (~25 kg/m²) [11–13]. Literature indicates that body mass index of a Japanese diabetic population has increased as compared with decades ago [10]. Our previous study [4] surveyed a diabetic CLTI population between 2003 and 2010, about a decade earlier. During the past decade, mean body mass index of a diabetic population with CLTI presenting Fontaine stage IV might similarly have increased.

Diabetes-related complications were much more prevalent in a diabetic CLTI population presenting Fontaine stage IV than were reported in a general diabetic population [10–13]. Along with lower limb ischemia, neuropathy is well known as a major contributor to foot ulceration [3, 9]. The current study confirmed that loss of pedal protective sensation was very common in diabetic patients with CLTI presenting Fontaine stage IV warranting revascularization, suggesting that neuropathy would have cooperatively affected the development and progress of the current foot ulcers and gangrenes in the majority of the population. In addition, these patients might have a high risk of recurrent ulceration in future, even if the current wounds were completely healed after successful lower limb revascularization.

We also demonstrated that almost all, but not all of the diabetic CLTI population had carotid atherosclerosis. It would be of clinical interest that some cases presenting CLTI were free from carotid atherosclerosis, whereas CLTI, the most advanced form of lower extremity atherosclerosis, is often referred as to a marker for generalized, severe atherosclerosis [14].

The prevalence of other diabetes-related complications was almost consistent with that in our previous retrospective research [4], as well as other previous reports [15–20]. An apparently lower prevalence of stroke and heart failure

than in our previous retrospective research might come from stricter definitions of the complications in the current study; asymptomatic cerebral infarction and heart failure not requiring hospitalization were not included in the current study.

The current study did not detect any significant association between the clustering of advanced macroangiopathies and duration of diabetes, whereas the clustering of advanced microangiopathies was positively correlated with duration of diabetes. These findings, consistent with our previous retrospective research [4], might be explained by the fact that the risk of cardiovascular diseases can be elevated not only by long-standing diabetes but also by the early stage of diabetes and other metabolic risk factors, whereas the progression of microangiopathy is strongly and mainly affected by a long exposure of hyperglycemia [3, 21, 22]. Clinically more important would be, however, the fact that advanced microangiopathies were highly prevalent even in patients with duration of diabetes < 10 years. It is known that advanced diabetes-related complications are observed even in subjects whose diabetes was diagnosed less than a decade before [23]. However, the prevalence was much higher in the current study population with CLTI than in a general diabetic population. Given that the duration of diabetes was defined as time from diagnosis and not from onset, the current finding suggests that diabetes might be left undiagnosed (and therefore untreated) for long years in a majority of the population. Furthermore, their diabetes might be poorly controlled even after its diagnosis. Advanced microangiopathies seemed more prevalent in the current population than in patients with other cardiovascular diseases [24–26]. The natural history of progression of diabetes-related complications might differ between patients with CLTI and those with other cardiovascular diseases.

The present study also revealed that only a few diabetic CLTI patients presenting ulcers and gangrenes had ever undergone ABI measurement before CLTI onset. Clinical guidelines have often emphasized the importance of a routine foot examination as an effective strategy for the prevention of diabetic foot [3]. If lower limb ischemia had been routinely evaluated in these patients, the risk of CLTI development might have been minimized. The subsequent analysis showed that the prevalence of history of ABI measurement was negatively associated with age. Although the true reasons for this association remain unknown, older patients, presumably more likely living a sedentary life and therefore less likely complaining of claudication, might have fewer chances to undergo ABI measurement. Furthermore, clinical inertia might have been more common in older patients. Further detailed survey on foot examination in a diabetic population will be needed.

There were several limitations in the present study. First, the current study did not collect the data regarding

symptoms of hind-limb ischemia or neuropathy, the presence of which might be important prior to diagnosis of CLTI and dispose physicians to perform ABI measurement. Second, the current study was a single-center research. The data might be affected by the characteristics of the hospital. Future multicenter studies will be needed to validate the current findings. Third, data on duration of diabetes and past history of ABI measurement before CLTI onset were based on self-report as well as medical records. Recall of the history might be at risk of inaccuracy. Fourth, the current study analyzed patients undergoing endovascular therapy, and did not include those undergoing surgical reconstruction. However, our previous observational study indicated that the clinical backgrounds were broadly similar between the two treatment groups [2]. Although a similar survey on patients undergoing surgical reconstruction will be needed, clinical characteristics might not be substantially different.

In conclusion, the current prospective cross-sectional study demonstrated the clinical characteristics of Japanese diabetic patients with CLTI presenting Fontaine stage IV in the real-world settings. The advanced diabetes-related complications were highly prevalent, even in those whose diabetes was diagnosed less than a decade before. In addition, only a few patients had ever undergone ABI measurement before CLTI onset.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interests associated with this manuscript.

Human rights statement All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later revision.

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