Diabetology International (2019) 10:231–235
https://doi.org/10.1007/s13340-018-0387-6

SHORT COMMUNICATION

Clinical characteristics of Japanese diabetic patients with critical limb ischemia presenting Fontaine stage IV

Mitsuyoshi Takahara[1] · Osamu Iida[2] · Yukihiro Fujita[3] · Masakazu Haneda[3]

Received: 26 September 2018 / Accepted: 27 November 2018 / Published online: 8 December 2018

Abstract

The aim of the current study was to reveal the clinical characteristics of Japanese diabetic patients with critical limb ischemia (CLI) presenting ischemic unhealed ulcer/gangrene (Fontaine stage IV) in the real-world settings. The current retrospective cross-sectional study included consecutive 282 Japanese diabetic patients who underwent endovascular therapy for CLI presenting Fontaine stage IV. The prevalence of diabetes-related complications was estimated adopting multiple imputation (50 times). The patients were aged 70 ± 10 years. Median duration of diabetes was 21 (interquartile range 12–31) years. The prevalence of proliferative diabetic retinopathy, end-stage renal disease on regular dialysis, stroke, coronary artery disease, and chronic heart failure was estimated at 48% (95% confidence interval 39–56%), 52% (46–58%), 34% (28–39%), 48% (42–54%), and 35% (29–41%), respectively. The prevalence of stroke, coronary artery disease, and chronic heart failure was not significantly associated with the duration of diabetes (all $p > 0.05$). On the other hand, the prevalence of proliferative diabetic retinopathy and end-stage renal disease on regular dialysis was significantly positively associated with the duration of diabetes (both $p < 0.05$). However, these prevalences reached as high as ~ 30% even in patients with duration of diabetes < 10 years. In conclusion, the advanced stage of diabetes-related complications was prevalent in patients with CLI presenting Fontaine stage IV.

Keywords Critical limb ischemia · Fontaine stage IV · Diabetes-related complication · Prevalence

Introduction

Critical limb ischemia (CLI) is the most advanced form of peripheral arterial disease (PAD), presenting ischemic rest pain (Fontaine stage III) or unhealed ulcer/gangrene (Fontaine stage IV) due to chronic severe ischemia. Patients with CLI, especially presenting Fontaine stage IV, have an extremely poor prognosis for both survival and limb salvage, and most of them ultimately need revascularization [1]. Diabetes mellitus is a well-known risk factor for CLI [1], and a majority of patients who develop CLI have diabetes mellitus [2].

Diabetes mellitus is associated not only with the risk of CLI, but also with the risk of other diabetic complications [3]. It would be no surprise if diabetic patients developing CLI present a various kind of other diabetic complications. Comorbidities often influence the treatment strategies for CLI in clinical practice, and it would be of healthcare importance to reveal these prevalences in the real-world settings. However, no detailed data are so far available regarding the prevalence.

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

Materials and methods

The current retrospective cross-sectional study included consecutive 282 Japanese diabetic patients who underwent endovascular therapy for CLI presenting unhealed ischemic

✉ Mitsuyoshi Takahara
takahara@endmet.med.osaka-u.ac.jp

[1] Department of Diabetes Care Medicine, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan

[2] Cardiovascular Center, Kansai Rosai Hospital, 3-1-69 Inabaso, Amagasaki, Hyogo 660-8511, Japan

[3] Division of Metabolism and Biosystemic Science, Department of Internal Medicine, Asahikawa Medical University, Asahikawa, Hokkaido 078-8510, Japan

ulcers or gangrenes (Fontaine stage IV) in Kansai Rosai Hospital, Amagasaki City, Japan, between 2003 and 2010. Data on their clinical characteristics at revascularization for CLI were retrospectively collected from the medical records. Duration of diabetes was referred to as the time from diagnosis of diabetes, rather than from the onset of diabetes. 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 no.: 16053), Kansai Rosai Hospital (date of approval: August 5, 2016, approval no.: 16D029g), and Osaka University Hospital (date of approval: August 30, 2016, approval no.: 16171). On the grounds that the current study was an observational research study using only existing materials, the study was considered exempt from 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.

Statistical analysis

Data are given as mean ± SD for continuous variables and as percentages for dichotomous variables, if not otherwise mentioned. The difference of body mass index between patients with and without end-stage renal disease on regular dialysis was assessed by the Welch's *t* test. The prevalence of diabetes-related comorbidities in the population is presented with the 95% confidence interval (CI). The association between the prevalence and patient backgrounds including the duration of diabetes was investigated using logistic regression model, in which respective diabetes-related comorbidities were entered as the dependent variable and patient backgrounds were entered as the explanatory variables. Since the current retrospective 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 are summarized in Table 1. They were aged 70 ± 10 years. Duration of diabetes was recorded in 174 patients (62%), and the median value (interquartile range) was 21 (12–31) years. Hemoglobin A1c levels were measured in 252 patients, and the mean value was 7.2 ± 1.5%. Multiple imputation estimated that patients with duration of diabetes ≥ 20 years accounted for 55% (95% confidence interval 48–62%); whereas 23% (17–28%) of patients had hemoglobin A1c levels ≥ 8%. Mean body mass index was 21.5 ± 3.3 kg/m^2; the value was not significantly different between patients without and with end-stage renal disease on regular dialysis (21.6 ± 3.4 and 21.4 ± 3.3 kg/m^2, $p = 0.78$). The prevalence of obesity (defined as body mass index ≥ 25 kg/m^2) was estimated at 13% (9–17%) based on multiple imputation, whereas leanness (body mass index < 18.5 kg/m^2) was estimated at 18% (13–23%).

The estimated prevalence of diabetes-related complications is shown in Table 2. The prevalence of proliferative

Table 1 Patient characteristics

n	282
Male sex	68% (193/282)
Age (years)	70 ± 10 (*n* = 282)
Duration of diabetes (years)	21 (12–31) (*n* = 174)
Hemoglobin A1c (%)	7.2 ± 1.5 (*n* = 252)
Body mass index (kg/m^2)	21.5 ± 3.3 (*n* = 266)
Smoking	32% (91/282)
Hypertension	81% (229/282)
Dyslipidemia	54% (153/282)
Ankle-brachial index	0.69 ± 0.28 (*n* = 245)
Systolic blood pressure (mmHg)	142 ± 27 (*n* = 209)
Diastolic blood pressure (mmHg)	73 ± 14 (*n* = 208)
Total cholesterol (mg/dl)	166 ± 41 (*n* = 255)
High-density lipoprotein cholesterol (mg/dl)	43 ± 15 (*n* = 246)
Low-density lipoprotein cholesterol (mg/dl)	98 ± 32 (*n* = 265)
Triglycerides (mg/dl)	119 ± 61 (*n* = 252)
Medication	
Insulin	47% (100/212)
Sulfonylurea	14% (30/212)
Glinide	6% (12/212)
Alpha-glucosidase inhibitor	16% (33/212)
Biguanide	2% (4/212)
Thiazolidinedione	3% (7/212)
Dipeptidyl-peptidase 4 inhibitor	0.5% (1/212)
Renin–angiotensin system inhibitor	48% (102/212)
Calcium blocker	39% (83/212)
Beta antagonist	12% (26/212)
Diuretic	27% (58/212)
Statin	20% (42/212)
Fibrate	1% (2/212)
Nicotinic acid	7% (14/212)
Eicosapentaenoic acid	4% (9/212)
Dipyridamole	2% (4/212)
Beraprost	22% (46/212)
Sarpogrelate	19% (41/212)
Cilostazol	28% (60/212)
Thienopyridine	32% (68/212)
Aspirin	73% (155/212)

Data are presented as mean ± SD for continuous variables and percentage (*n*) for discrete variables, with the exception of those on duration of diabetes, which are summarized as median (interquartile range). The number of patients with the data available is also demonstrated

Table 2 Estimated prevalence of diabetes-related complications

	Overall population	Duration of diabetes				Adjusted odds ratio of duration of diabetes (per 10-year increase)
		< 10 years	10–20 years	20–30 years	≥ 30 years	
Proliferative diabetic retinopathy	48% [39–56%]	30% [13–48%]	44% [28–60%]	53% [35–70%]	59% [43–75%]	1.70 [1.15–2.53] ($p = 0.009$)
End-stage renal disease on regular dialysis	52% [46–58%]	35% [20–49%]	48% [35–61%]	59% [46–72%]	61% [49–73%]	1.56 [1.21–2.02] ($p = 0.001$)
Stroke	34% [28–39%]	34% [18–50%]	34% [22–46%]	36% [23–48%]	31% [19–43%]	0.90 [0.69–1.19] ($p = 0.47$)
Coronary artery disease	48% [42–54%]	47% [32–62%]	46% [33–59%]	50% [38–63%]	49% [37–62%]	1.02 [0.80–1.30] ($p = 0.88$)
Chronic heart failure	35% [29–41%]	35% [20–50%]	36% [24–49%]	32% [20–45%]	38% [25–50%]	0.97 [0.75–1.25] ($p = 0.79$)

Data are estimated prevalence [95% confidence interval], based on multiple imputation ($n = 50$). Odds ratios of duration of diabetes for diabetes-related complications [95% confidence intervals] were adjusted for age and sex, which were derived from the logistic regression model

diabetic retinopathy, end-stage renal disease on regular dialysis, and coronary artery disease reached about a half, whereas that of stroke and chronic heart failure was estimated at about one-third. The prevalence of stroke, coronary artery disease, and chronic heart failure was not significantly associated with the duration of diabetes. On the other hand, the prevalence of proliferative diabetic retinopathy and end-stage renal disease on regular dialysis was significantly positively associated with the duration of diabetes. However, these prevalences reached as high as ~ 30% even in patients with duration of diabetes < 10 years. The association of the duration of diabetes with proliferative diabetic retinopathy and end-stage renal disease on regular dialysis remained significant even with adjustment for sex, age, hypertension, and dyslipidemia (Table 3). In the population, age was negatively associated with the prevalence of proliferative diabetic retinopathy and end-stage renal disease on regular dialysis, whereas age as well as hypertension were positively associated with that of stroke. On the other hand, male sex was positively associated with the prevalence of coronary artery disease.

Discussion

The current retrospective study demonstrated the clinical characteristics of Japanese diabetic patients with CLI presenting Fontaine stage IV in the real-world settings.

Previous studies reporting the clinical characteristics of Japanese diabetic patients in clinical practice showed that their age and duration of diabetes were on an average around 60s and 10 years, respectively [4–7], indicating that the current study population were almost a decade older, with about a decade longer duration of diabetes. Furthermore, body mass index was distributed lower in the current study population, even without end-stage renal disease on regular dialysis, meaning that obesity was less prevalent and leanness was more prevalent. In contrast to a general diabetic population, there would be potentially a greater demand for nutritional intervention to ameliorate malnutrition rather than overeating in the population.

Although its association with the duration of diabetes remained to be investigated, the prevalence of diabetes-related complications in diabetic CLI patients with tissue

Table 3 Association of patient backgrounds with the prevalence of diabetes-related complications

	Duration of diabetes (per 10-year increase)	Male (versus female)	Age (per 10-year increase)	Hypertension	Dyslipidemia
Proliferative diabetic retinopathy	1.74 [1.17–2.61]*	0.62 [0.26–1.48]	0.44 [0.28–0.71]*	0.76 [0.26–2.21]	0.96 [0.38–2.47]
End-stage renal disease on regular dialysis	1.61 [1.24–2.10]*	1.12 [0.63–1.96]	0.45 [0.34–0.61]*	0.59 [0.29–1.18]	0.74 [0.44–1.26]
Stroke	0.86 [0.64–1.16]	1.27 [0.71–2.26]	1.93 [1.43–2.61]*	2.22 [1.02–4.83]*	0.97 [0.57–1.65]
Coronary artery disease	1.04 [0.81–1.34]	2.12 [1.24–3.63]*	1.20 [0.94–1.52]	0.79 [0.42–1.50]	1.44 [0.88–2.35]
Chronic heart failure	0.93 [0.72–1.22]	1.01 [0.58–1.76]	1.22 [0.94–1.58]	1.52 [0.76–3.04]	0.70 [0.42–1.18]

Data are adjusted odds ratios [95% confidence interval] of patient backgrounds (duration of diabetes, sex, age, hypertension, and dyslipidemia) for respective diabetes-related complications, which were derived from the logistic regression model with multiple imputation ($n = 50$)

*$p < 0.05$

loss was reported by a few previous studies [8–12]. Those studies demonstrated that the prevalence of coronary artery disease and chronic heart failure was 29–68% and 17–38% [8–12], almost consistent with our findings. On the other hand, stroke seemed more prevalent in the current study population than in their study population [9]. This might reflect the characteristic of a Japanese population, which has a higher incidence of stroke relative to coronary artery disease than a Caucasian population [13]. One research group reported that the prevalence of retinopathy was around 40% in a diabetic CLI population in whom a majority (~ 90%), but not all, suffered from tissue loss [14]. Although the data with the population limited to Fontaine stage IV were not presented, the prevalence seemed broadly similar to that in our study population. The prevalence of end-stage renal disease on regular dialysis varied considerably with the report, ranging from ~ 5 to ~ 50% [8, 12, 14], which might be affected by the health insurance system in each country.

Stroke and coronary artery disease were much more prevalent in the current study population compared to a general diabetic population in Japan [4–7]. Since CLI, stroke, and coronary artery disease are all manifestations of atherosclerosis, it would be no surprise that the three conditions commonly overlap with one another. Indeed, it is well recognized that patients with CLI have a high prevalence of stroke and coronary artery disease [1]. The current study did not detect any significant association between the prevalence of these cardiovascular diseases and duration of diabetes. The finding might be explained by the fact that the impact of hyperglycemia on the increased risk of cardiovascular diseases can be observed even in the early stage of diabetes [15, 16]. The prevalence of cardiovascular diseases was rather related to sex, age, and hypertension, indicating that the likelihood that diabetic CLI patients are exposed to other cardiovascular diseases would vary with these concurrent cardiovascular risk factors.

The prevalence of proliferative diabetic retinopathy and end-stage renal disease on regular dialysis in the study population exceeded that of the overall retinopathy and nephropathy in a general diabetic population [13], indicating that the advanced stage of microangiopathy would be much more prevalent in a diabetic CLI population than in a general diabetic population. One possible explanation of this would be a longer duration of diabetes in CLI patients. Indeed, the prevalence of the advanced stage of microangiopathy was positively associated with the duration of diabetes in the current study population. However, it should be noted that the prevalence was as high as ~ 30% even in patients with duration of diabetes < 10 years. Given that the duration of diabetes was referred to as the time from diagnosis, the exposure time to diabetes would be much longer than the recorded duration of diabetes in patients whose diabetes was left undiagnosed for long years. Such patients might be prevalent in a diabetic CLI population. In addition, diabetes might be poorly controlled even after its diagnosis in the population. The prevalence of the advanced stage of microangiopathy seemed higher, even compared to patients with other cardiovascular diseases [17–19]. The natural history of progression of diabetes-related complications might be different between CLI patients and those with other cardiovascular diseases.

Several study limitations should be mentioned. First, the current study was a retrospective single-center research. Future multicenter prospective studies with a larger sample size will be needed to validate the current findings. Second, we surveyed the clinical data till 2010 and did not include more recent data, simply because most reports on the clinical characteristics of other diabetic populations in Japan were often based on the data up to ~ 2010. Consequently, this strategy enabled us to compare our data to those of the contemporary populations. On the other hand, our study left the most recent trends unevaluated. Third, the type of diabetes was seldom clarified in the medical records, and the data were unavailable in this retrospective study. Future studies prospectively collecting these data are needed. Fourth, the current study analyzed a database of 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, the clinical characteristics might not be substantially different.

In conclusion, the current retrospective study demonstrated the clinical characteristics of Japanese diabetic patients with CLI presenting Fontaine stage IV in the real-world settings. The advanced stage of diabetes-related complications was prevalent, even in those in whom diabetes was diagnosed less than a decade before.

Acknowledgements This study was supported by a Grant-in-Aid (No. 201709007A and No. 201608012A) for Scientific Research from the Ministry of Health, Labour and Welfare of Japan.

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.

References

1. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, et al. Inter-society consensus for the management of

peripheral arterial disease (TASC II). Eur J Vasc Endovasc Surg. 2007;33(Suppl 1):S1–75.
2. Iida O, Takahara M, Soga Y, Kodama A, Terashi H, Azuma N. Three-year outcomes of surgical versus endovascular revascularization for critical limb ischemia: the SPINACH study (Surgical Reconstruction Versus Peripheral Intervention in Patients With Critical Limb Ischemia). Circ Cardiovasc Interv. 2017;10:e005531.
3. Haneda M, Noda M, Origasa H, Noto H, Yabe D, Fujita Y, et al. Japanese clinical practice guideline for diabetes 2016. Diabetol Int. 2018;9:1–45.
4. Yokoyama H, Kawai K, Kobayashi M. Microalbuminuria is common in Japanese type 2 diabetic patients: a nationwide survey from the Japan Diabetes Clinical Data Management Study Group (JDDM 10). Diabetes Care. 2007;30:989–92.
5. Hayashino Y, Izumi K, Okamura S, Nishimura R, Origasa H, Tajima N. Duration of diabetes and types of diabetes therapy in Japanese patients with type 2 diabetes: the Japan Diabetes Complication and its Prevention prospective study 3 (JDCP study 3). J Diabetes Investig. 2017;8:243–9.
6. Sone H, Katagiri A, Ishibashi S, Abe R, Saito Y, Murase T, et al. Effects of lifestyle modifications on patients with type 2 diabetes: the Japan Diabetes Complications Study (JDCS) study design, baseline analysis and 3 year-interim report. Horm Metab Res. 2002;34:509–15.
7. Ueki K, Sasako T, Kato M, Okazaki Y, Okahata S, Katsuyama H, et al. Design of and rationale for the Japan Diabetes Optimal Integrated Treatment study for three major risk factors of cardiovascular diseases (J-DOIT3): a multicenter, open-label, randomized, parallel-group trial. BMJ Open Diabetes Res Care. 2016;4:e000123.
8. Uccioli L, Gandini R, Giurato L, Fabiano S, Pampana E, Spallone V, et al. Long-term outcomes of diabetic patients with critical limb ischemia followed in a tertiary referral diabetic foot clinic. Diabetes Care. 2010;33:977–82.
9. Lejay A, Georg Y, Tartaglia E, Gaertner S, Geny B, Thaveau F, et al. Long-term outcomes of direct and indirect below-the-knee open revascularization based on the angiosome concept in diabetic patients with critical limb ischemia. Ann Vasc Surg. 2014;28:983–9.
10. Freisinger E, Malyar NM, Reinecke H, Lawall H. Impact of diabetes on outcome in critical limb ischemia with tissue loss: a large-scaled routine data analysis. Cardiovasc Diabetol. 2017;16:41.
11. Noronen K, Saarinen E, Alback A, Venermo M. Analysis of the elective treatment process for critical limb ischaemia with tissue loss: diabetic patients require rapid revascularisation. Eur J Vasc Endovasc Surg. 2017;53:206–13.
12. Meloni M, Izzo V, Giurato L, Del Giudice C, Da Ros V, Cervelli V, et al. Recurrence of critical limb ischemia after endovascular intervention in patients with diabetic foot ulcers. Adv Wound Care (New Rochelle). 2018;7:171–6.
13. Yokoyama H, Matsushima M, Kawai K, Hirao K, Oishi M, Sugimoto H, et al. Low incidence of cardiovascular events in Japanese patients with type 2 diabetes in primary care settings: a prospective cohort study (JDDM 20). Diabet Med. 2011;28:1221–8.
14. Faglia E, Dalla Paola L, Clerici G, Clerissi J, Graziani L, Fusaro M, et al. Peripheral angioplasty as the first-choice revascularization procedure in diabetic patients with critical limb ischemia: prospective study of 993 consecutive patients hospitalized and followed between 1999 and 2003. Eur J Vasc Endovasc Surg. 2005;29:620–7.
15. Fujishima M, Kiyohara Y, Kato I, Ohmura T, Iwamoto H, Nakayama K, et al. Diabetes and cardiovascular disease in a prospective population survey in Japan: the Hisayama study. Diabetes. 1996;45(Suppl 3):S14–6.
16. Nakagami T. Hyperglycaemia and mortality from all causes and from cardiovascular disease in five populations of Asian origin. Diabetologia. 2004;47:385–94.
17. Kuwashiro T, Sugimori H, Ago T, Kuroda J, Kamouchi M, Kitazono T. The impact of predisposing factors on long-term outcome after stroke in diabetic patients: the Fukuoka Stroke Registry. Eur J Neurol. 2013;20:921–7.
18. Kawasaki S, Misawa H, Tamura Y, Kondo Y, Satoh S, Hasegawa O, et al. Relationship between coronary artery disease and retinopathy in patients with type 2 diabetes mellitus. Intern Med. 2013;52:2483–7.
19. Tsuboi S, Miyauchi K, Kasai T, Ogita M, Dohi T, Miyazaki T, et al. Impact of red blood cell distribution width on long-term mortality in diabetic patients after percutaneous coronary intervention. Circ J. 2013;77:456–61.