Original Article

Absence of Preceding Intermittent Claudication and its Associated Clinical Features in Patients with Critical Limb Ischemia

Mitsuyoshi Takahara¹, Osamu Iida², Yoshimitsu Soga³, Akio Kodama⁴ and Nobuyoshi Azuma⁵;
on behalf of the SPINACH study investigators

¹Department of Metabolic Medicine, Osaka University Graduate School of Medicine, Suita, Japan

²Department of Cardiology, Kansai Rosai Hospital, Amagasaki, Japan

³Department of Cardiology, Kokura Memorial Hospital, Kitakyushu, Japan

⁴Division of Vascular Surgery, Department of Surgery, Nagoya University Graduate School of Medicine, Nagoya, Japan

⁵Department of Vascular Surgery, Asahikawa Medical University, Asahikawa, Japan

Aim: The current study investigated how prevalent the absence of a prior history of intermittent claudication would be in patients with critical limb ischemia (CLI) and examined the associated clinical features.

Methods: We used a database of 559 Japanese CLI patients participating in a multicenter prospective study. A history of intermittent claudication prior to CLI onset was surveyed at registration. The 95% confidence interval (CI) of its prevalence was calculated using the Clopper-Pearson method. Logistic regression analysis was performed to assess the association between the clinical features and the absence of preceding intermittent claudication.

Results: The study subjects were 73 ± 10 years old and 67% were male. Tissue loss occurred in 82% of this population. The prevalence of the absence of prior intermittent claudication was 50% [95% CI: 46-55%]. In multivariate logistic regression analysis, a non-ambulatory status, diabetes mellitus, and regular dialysis were significantly and independently associated with the lack of a prior history of intermittent claudication (all $p < 0.05$). Indeed, the presence of these features was associated with a higher prevalence of the lack of the history. Regular dialysis, but not non-ambulatory status or diabetes mellitus, lost its statistical significance after further adjustment for the presence of isolated infrapopliteal lesions, whereas the presence of isolated infrapopliteal lesions itself was significantly associated with a lack of prior intermittent claudication.

Conclusions: The absence of a prior history of intermittent claudication was prevalent in CLI patients. Patients with a non-ambulatory status, diabetes mellitus, and regular dialysis were more likely to lack a prior history of intermittent claudication.

J Atheroscler Thromb, 2015; 22: 718-725.

Key words: Critical limb ischemia, Intermittent claudication, Non-ambulatory status, Diabetes mellitus, Regular dialysis

Introduction

Critical limb ischemia (CLI) is a manifestation of peripheral arterial disease (PAD) characterized by

Address for correspondence: Mitsuyoshi Takahara, Department of Metabolic Medicine, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan
E-mail: takahara@endmet.med.osaka-u.ac.jp

Received: October 5, 2014

Accepted for publication: December 9, 2014

chronic ischemic rest pain or tissue loss. CLI patients have an extremely poor prognosis for both survival and limb salvage, such that they ultimately require revascularization, and they are clinically distinct from PAD patients presenting with intermittent claudication¹⁾.

The severity of PAD has been classically described to follow the order of intermittent claudication, rest pain, and tissue loss, in accordance with conventional clinical classifications such as those of Fon-

taine and Rutherford^{2,3}). However, in clinical practice, some patients develop CLI without experiencing any intermittent claudication; CLI patients sometimes lack a preceding history of intermittent claudication and are asymptomatic prior to CLI development¹). To date, few detailed clinical data are available regarding the prevalence of such CLI patients lacking a prior history of intermittent claudication and their clinical characteristics^{1,4,5}).

Aim

The aim of the current study was to investigate the absence of a history of intermittent claudication and to examine its associated clinical features in a Japanese CLI population.

Methods

Study Population and Definitions

We used a clinical database obtained from the Surgical reconstruction versus Peripheral INtervention in pAtients with critical limb isCHemia (SPINACH) study (UMIN000007050), an ongoing multicenter, prospective, observational study designed to investigate the efficacy of bypass surgery and endovascular therapy in Japanese patients with CLI due to arteriosclerosis obliterans. The details have been described elsewhere⁶). CLI was diagnosed by vascular surgeons and interventional cardiologists when at least one of the following criteria was fulfilled: (1) chronic ischemic foot rest pain with either ankle pressure <50 mmHg, toe blood pressure <30 mmHg, or skin perfusion pressure <30 mmHg, (2) chronic ischemic foot ulcer or gangrene with either ankle pressure <70 mmHg, toe blood pressure <50 mmHg, or skin perfusion pressure <40 mmHg, and (3) evident critical chronic ischemia indicated by other modalities including transcutaneous oxygen tension. The study was performed in accordance with the Declaration of Helsinki and it was approved by the Ethics Committee at Asahikawa Medical University and all other participating institutions. Written informed consent was obtained from every participant. A total of 563 Japanese CLI patients were registered in the SPINACH study between January 2012 and March 2013, and a prior history of intermittent claudication was surveyed at registration. The presence of prior intermittent claudication and its duration as well as the ambulatory status before CLI onset were determined by self-report and medical records. The patients were determined to be ambulatory if they were able to walk with no aid or with sticks, whereas a non-ambulatory status was

determined if the patient required a wheelchair or was bedridden. Diabetes mellitus was defined as a fasting glucose level ≥ 126 mg/dl, casual fasting glucose level ≥ 200 mg/dl, hemoglobin A1c level $\geq 6.5\%$, past diagnosis, and/or treatment with anti-diabetic medications. Hypertension was defined as a systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, past diagnosis, and/or treatment for hypertension. Dyslipidemia was defined as a low-density lipoprotein cholesterol level ≥ 140 mg/dl, high-density lipoprotein cholesterol level <40 mg/dl, triglyceride level ≥ 150 mg/dl, past diagnosis, and/or treatment for dyslipidemia. These cutoff levels were determined by the current domestic diagnostic criteria for individual diseases⁷⁻⁹). A history of cardiovascular disease was defined as ischemic heart disease with or without revascularization and stroke (including transient ischemic attack) with or without after effects.

Of the 563 total registered patients, the prior history status of intermittent claudication was unable to be obtained in two patients (0.35%), who were therefore excluded from the current study. Furthermore, another two patients were also excluded because of missing data regarding the ambulatory status before CLI onset and the smoking status. Consequently, 559 patients (99.3%) were included in the current study. In patients with bilateral CLI, the unilateral limb with the more severe Rutherford classification was selected to represent the values of both limbs. When bilateral limbs had the same severity, one limb was selected randomly. The random selection was based on the random number generation using IBM SPSS Statistics Version 22 (SPSS Inc.). The selection probability was set to be 1/2, meaning that either limb was selected with equal probability.

Statistical Analysis

Data are given as the means and standard deviations (SD) for continuous variables or as percentages for discrete variables, unless otherwise mentioned. A *p* value <0.05 was considered statistically significant. Statistical differences between two groups were evaluated by the unpaired *t* test for continuous variables and by the chi square test for discrete variables. The 95% confidence interval (CI) of the prevalence of the absence of preceding intermittent claudication was assessed by the Clopper-Pearson method. Logistic regression analysis was performed to assess the association between the absence of preceding intermittent claudication and the following clinical features: sex, age, ambulatory status before CLI onset, smoking, diabetes mellitus, hypertension, dyslipidemia, history of cardiovascular disease, regular dialysis, bilateral

CLI, and Rutherford classification. We additionally investigated these associations after further adjustment for anatomical distribution of arterial lesions. In this additional analysis, 112 patients (20%) were excluded due to missing data regarding complete angiographical assessments throughout the aortoiliac, femoropopliteal, and infrapopliteal arteries; the remaining 447 patients (80%) were included in the analysis. Isolated infrapopliteal lesions were determined when the arterial lesions were localized in infrapopliteal vessels and aortoiliac and femoropopliteal vessels were free from the arterial lesions. In addition, we also examined the association between pressure sensation and a prior history of claudication. Pressure sensation 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 heads¹⁰. Impaired pressure sensation was defined as when a patient was unable to correctly feel the pressure applied by the monofilament at any of the sites. In this supplementary analysis, 94 patients (17%) were excluded due to missing data regarding pressure sensation, leaving 465 patients (83%) included in the analysis. All statistical analyses were performed using IBM SPSS Statistics Version 22 (SPSS Inc.).

Results

The characteristics of the study population are shown in **Table 1**. The 559 analyzed CLI patients

Table 1. Characteristics of the study population

<i>n</i>	559
Male sex	375 (67%)
Age (years)	73 ± 10
Non-ambulatory status before CLI onset	145 (26%)
Smoking	89 (16%)
Diabetes mellitus	403 (72%)
Hypertension	489 (87%)
Dyslipidemia	394 (70%)
History of ischemic heart disease	228 (41%)
History of stroke	122 (22%)
Regular dialysis	295 (53%)
Bilateral CLI	104 (19%)
Rutherford classification	
Category 4	88 (16%)
Category 5	366 (65%)
Category 6	105 (19%)

Data are the means ± SD or numbers (percentages).

were 73 ± 10 years of age and included 375 males (67%). The Rutherford classification categories 4, 5, and 6 accounted for 16%, 65%, and 19% of the population, respectively. Of the 295 total patients who received regular dialysis, the duration of dialysis was unknown in 21 patients (7%); in the remaining 274 patients (93%), the median duration of dialysis (interquartile range) was 7 (4–11) years.

As shown in **Fig. 1**, a total of 281 patients (50%)

Fig. 1. Prevalence of a prior history of intermittent claudication in CLI patients
IC, intermittent claudication.

Table 2. Characteristics of the patients with and without prior intermittent claudication

	Patients with claudication history (<i>n</i> = 278)	Patients without claudication history (<i>n</i> = 281)	<i>P</i> value
Male sex	187 (67%)	188 (67%)	0.927
Age (years)	73 ± 10	73 ± 10	0.648
Non-ambulatory status before CLI onset	46 (17%)	99 (35%)	< 0.001
Smoking	51 (18%)	38 (14%)	0.119
Diabetes mellitus	184 (66%)	219 (78%)	0.002
Hypertension	242 (87%)	247 (88%)	0.761
Dyslipidemia	204 (73%)	190 (68%)	0.135
History of ischemic heart disease	120 (43%)	108 (38%)	0.255
History of stroke	58 (21%)	64 (23%)	0.584
Regular dialysis	128 (46%)	167 (59%)	0.002
Bilateral CLI	58 (21%)	46 (16%)	0.172
Rutherford classification			< 0.001
Category 4	61 (22%)	27 (10%)	
Category 5	164 (59%)	202 (72%)	
Category 6	53 (19%)	52 (18%)	

Data are the means ± SD or numbers (percentages).

Table 3. Associations between the clinical features and a lack of prior intermittent claudication

	Unadjusted odds ratio	Adjusted odds ratio
Male sex	0.98 [0.69, 1.40] (<i>p</i> = 0.927)	1.03 [0.70, 1.52] (<i>p</i> = 0.883)
Age (years)	1.00 [0.99, 1.02] (<i>p</i> = 0.745)	1.01 [0.99, 1.03] (<i>p</i> = 0.568)
Non-ambulatory status before CLI onset	2.74 [1.84, 4.09] (<i>p</i> < 0.001)	2.78 [1.81, 4.26] (<i>p</i> < 0.001)
Smoking	0.70 [0.44, 1.10] (<i>p</i> = 0.120)	0.76 [0.46, 1.26] (<i>p</i> = 0.293)
Diabetes mellitus	1.80 [1.24, 2.63] (<i>p</i> = 0.002)	2.03 [1.34, 3.09] (<i>p</i> = 0.001)
Hypertension	1.08 [0.65, 1.78] (<i>p</i> = 0.761)	0.95 [0.56, 1.63] (<i>p</i> = 0.864)
Dyslipidemia	0.76 [0.53, 1.09] (<i>p</i> = 0.136)	0.74 [0.50, 1.10] (<i>p</i> = 0.137)
History of ischemic heart disease	0.82 [0.59, 1.15] (<i>p</i> = 0.255)	0.73 [0.50, 1.07] (<i>p</i> = 0.105)
History of stroke	1.12 [0.75, 1.67] (<i>p</i> = 0.584)	0.93 [0.60, 1.44] (<i>p</i> = 0.748)
Regular dialysis	1.72 [1.23, 2.40] (<i>p</i> = 0.002)	1.71 [1.17, 2.48] (<i>p</i> = 0.005)
Bilateral CLI	0.74 [0.48, 1.14] (<i>p</i> = 0.173)	0.71 [0.45, 1.12] (<i>p</i> = 0.140)
Rutherford classification	1.41 [1.06, 1.88] (<i>p</i> = 0.018)	1.28 [0.94, 1.74] (<i>p</i> = 0.119)

Data represent odds ratios with 95% CI and *p* values. The adjusted odds ratios were obtained from multivariate logistic regression model in which all of the variables listed above were entered.

lacked a prior history of intermittent claudication. The 95% CI of this prevalence was calculated to be 46-55%. In patients with a prior history of intermittent claudication, the majority had a duration of less than 5 years (**Fig. 1**). **Table 2** demonstrates the differences in the clinical features between patients with and without a prior history of intermittent claudication. There was a significant difference in the non-ambulatory status, diabetes mellitus, regular dialysis, and Rutherford classification. The duration of dialysis

was not significantly associated with a lack of prior intermittent claudication (*p* = 0.199 by the Mann-Whitney *U* test).

We subsequently performed logistic regression analysis to investigate the association between the clinical features and a lack of a prior history of intermittent claudication (**Table 3**). According to a multivariate logistic regression analysis, non-ambulatory status, diabetes mellitus, and regular dialysis were significantly and independently associated with a lack of a

Fig. 2. Prevalence of the absence of a prior history of intermittent claudication in CLI patients classified according to clinical features

The risk factors were defined as (1) a non-ambulatory status, (2) diabetes mellitus, and (3) regular dialysis, as shown in Table 2. Error bars represent 95% CI.

Table 4. Association between the clinical features and a lack of prior intermittent claudication after further adjustment for isolated infrapopliteal lesions

	Adjusted odds ratio
Male sex	1.18 [0.75, 1.85] ($p=0.470$)
Age (years)	1.01 [0.99, 1.03] ($p=0.437$)
Non-ambulatory status before CLI onset	2.97 [1.85, 4.77] ($p<0.001$)
Smoking	0.79 [0.45, 1.39] ($p=0.420$)
Diabetes mellitus	2.28 [1.40, 3.72] ($p=0.001$)
Hypertension	1.03 [0.55, 1.92] ($p=0.935$)
Dyslipidemia	0.91 [0.58, 1.42] ($p=0.678$)
History of ischemic heart disease	0.79 [0.52, 1.21] ($p=0.272$)
History of stroke	0.95 [0.58, 1.56] ($p=0.846$)
Regular dialysis	1.43 [0.94, 2.19] ($p=0.099$)
Bilateral CLI	0.62 [0.36, 1.05] ($p=0.073$)
Rutherford classification	1.16 [0.81, 1.65] ($p=0.416$)
Isolated infrapopliteal lesion	1.85 [1.16, 2.96] ($p=0.010$)

Data represent odds ratios with 95% CI and p values. The adjusted odds ratios were obtained from multivariate logistic regression model in which all of the variables listed above were entered. Note that 112 patients (20%) in whom the complete angiographical assessments throughout the aortoiliac, femoropopliteal, and infrapopliteal arteries were not obtained were excluded from this analysis.

prior intermittent claudication history. These findings indicate that patients with these clinical features are more likely to lack a prior history of intermittent claudication. Indeed, as shown in **Fig. 2**, the presence of these features was associated with a higher prevalence

of the absence of prior intermittent claudication.

A supplementary analysis demonstrated that regular dialysis, but not non-ambulatory status or diabetes mellitus, lost its statistical significance after further adjustment for isolated infrapopliteal lesions, whereas

the presence of isolated infrapopliteal lesions itself was significantly associated with a lack of a prior intermittent claudication history (**Table 4**). Indeed, there was a significant relationship between regular dialysis and isolated infrapopliteal lesions ($p=0.025$); the odds ratio was calculated to be 1.64 (95% CI: 1.06-2.54).

Analysis of Ambulatory Patients

We also performed these analyses after excluding patients with a non-ambulatory status prior to CLI onset. Consequently, both diabetes mellitus and regular dialysis again had a significant and independent association with the lack of a claudication history, with adjusted odds ratios of 2.42 (95% CI: 1.46-4.02) ($p=0.001$) and 1.53 (95% CI: 1.00-2.35) ($p=0.0499$), respectively. In the multivariate model in which the presence of isolated infrapopliteal lesions were additionally included, diabetes mellitus and isolated infrapopliteal lesions, but not regular dialysis, showed a significant association. The adjusted odds ratios of diabetes mellitus, regular dialysis, and isolated ifrapopliteal lesions in this model were 2.54 (95% CI: 1.41-4.58) ($p=0.002$), 1.20 (95% CI: 0.74-1.95) ($p=0.463$), and 1.72 (95% CI: 1.00-2.94) ($p=0.048$), respectively.

Association of Pressure Sensation

There was a significant association between impaired pressure sensation and a lack of prior intermittent claudication; the unadjusted odds ratio was 1.47 (95% CI: 1.01-2.15) ($p=0.045$). However, the significance was lost after adjusting for non-ambulatory status, diabetes mellitus, and regular dialysis ($p=0.346$), whereas non-ambulatory status, diabetes mellitus, and regular dialysis had an independent association with a lack of prior intermittent claudication (all $p<0.05$).

Discussion

The current study revealed that the absence of a prior history of intermittent claudication was prevalent in CLI patients, and that non-ambulatory status, diabetes mellitus, and regular dialysis were associated with the absence of such a history. Patients with these clinical features were more likely to lack a prior history of intermittent claudication.

The association between non-ambulatory status and the absence of claudication history has been empirically well recognized and is pathophysiologically reasonable. The association could be explained by the dependence of claudication on physical activity. Sedentary patients who do not walk long distances

rarely experience symptoms of intermittent claudication, even if the blood flow in the lower extremities is sufficiently reduced¹¹. These patients can develop CLI without a history of preceding intermittent claudication when their reduced blood flow interferes with the healing of trauma-induced wounds or when a further reduction in blood flow leads to ischemic rest pain. Despite these feasible explanations, few clinical data regarding this association have been available so far. The current clinical findings confirmed that the association was significant and independent of other clinical backgrounds. At the same time, it was demonstrated that a non-ambulatory status was not the sole determinant of the absence of preceding intermittent claudication.

The current study showed that diabetes mellitus and regular dialysis were also associated with the absence of intermittent claudication prior to CLI development, independently of a non-ambulatory status. Patients with diabetes mellitus and on regular dialysis were more likely to develop CLI without any experience of intermittent claudication. These findings suggest the clinical necessity to establish practical systems for the screening of patients at high risk of CLI and for the early detection of CLI in asymptomatic patients with diabetes mellitus and those on regular dialysis. Although the true mechanisms behind these findings remain unclear, one possible explanation for the association with diabetes mellitus might be impaired pain perception¹¹. Diabetic patients are more likely to experience an impaired pain perception due to peripheral neuropathy. A decrease in pain perception might mask the symptoms of intermittent claudication. Although data from the monofilament test were available in the current study, this test assesses the pressure sensation and does not directly assess pain perception. Previous studies suggest that neurological assessments which are not specific for pain perception might fail to detect an inverse association with claudication history¹². Future studies directly assessing pain perception are needed to verify this hypothesis. On the other hand, the association with regular dialysis may be explained by the distal region of vessel involvement, which is a major atherosclerotic manifestation of renal failure on dialysis¹³. In the current study, regular dialysis was significantly and independently associated with the absence of a prior history of intermittent claudication, but not after adjustment for isolated infrapopliteal lesions. These findings indicate that the absence of prior intermittent claudication in patients under regular dialysis is explained by the localization of arterial lesions in infrapopliteal vessels, i.e., a lack of arterial lesions above

the knee, in these patients. Atherosclerotic lesions responsible for symptoms of intermittent claudication are usually found in the artery proximal to the affected muscle group; calf and thigh muscle pains, the most common symptoms, are often caused by affected above-the-knee arteries¹⁴⁻¹⁶. The lack of a prior history of intermittent claudication might reflect the lack of affected above-the-knee arteries in CLI patients. The current study did not assess the type of claudication (e.g., calf or thigh claudication). Future studies are needed to validate this hypothesis.

In the current study, the lack of a claudication history was not significantly associated with sex, age, smoking, hypertension, dyslipidemia, or a history of cardiovascular disease. Although these clinical features are well-known risk factors of atherosclerotic diseases, including PAD, as are diabetes mellitus and renal failure on dialysis¹, the current findings suggest they might not be closely involved in the specific pattern of CLI development (i.e., either via claudication or not) in patients with PAD.

Neither bilateral CLI nor the Rutherford classification had an independent association with a lack of claudication history in the current study. The lack of prior intermittent claudication might be observed at a similar frequency regardless of the CLI severity.

The current study had some limitations. First, the history of intermittent claudication was based on self-report as well as medical records at registration. Patients' recall of the history might be at risk of inaccuracy. Second, the complete angiographical assessment throughout aortoiliac, femoropopliteal, and infrapopliteal arteries were not obtained in all of the participants. Third, although the current study included more than 500 CLI patients, it was insufficient to detect a weaker association, e.g., an association with an odds ratio less than 1.5. Future studies with a larger sample size are needed to conclude that clinical features which was not significantly associated with the lack of claudication history in the current study was really not associated at all.

Conclusion

The absence of a prior history of intermittent claudication was prevalent in CLI patients. Patients with a non-ambulatory status, diabetes mellitus, and regular dialysis were more likely to lack a prior history of intermittent claudication.

Acknowledgments

The SPINACH Study is sponsored by Abbott

Vascular Japan Co., Ltd, Boston Scientific Japan K.K., Cook Japan Incorporated, Goodman Co., Ltd, Johnson & Johnson K.K., Kaken Pharmaceutical Co., Ltd, Kaneka Medix Corporation, Medicon Inc., Medikit Co., Ltd, Medtronic Japan Co., Ltd, Mitsubishi Tanabe Pharma Corporation, MSD K.K., St. Jude Medical Japan Co., Ltd, Taisho Toyama Pharmaceutical Co., Ltd, Terumo Corp., W.L. Gore & Associates, Co., Ltd (in alphabetical order). The funding companies played no role in the design of the study, selection of the enrolled patients, revascularization procedures or equipment, or interpretation of the data. The authors declare no conflicts of interest related to the current report.

Conflicts of Interest

There are no conflicts of interests associated with this manuscript.

References

- 1) Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG: Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *Eur J Vasc Endovasc Surg*, 2007; 33 Suppl 1: S1-S75
- 2) TASC: Management of peripheral arterial disease: Trans Atlantic Inter-Society Consensus (TASC). *Eur J Vasc Endovasc Surg*, 2000; 19 (Suppl A): S1-S250
- 3) Novo S: Classification, epidemiology, risk factors, and natural history of peripheral arterial disease. *Diabetes Obes Metab*, 2002; 4 Suppl 2: S1-S6
- 4) Varu VN, Hogg ME, Kibbe MR: Critical limb ischemia. *J Vasc Surg*, 2010; 51: 230-241
- 5) Becker F, Robert-Ebadi H, Ricco JB, Setacci C, Cao P, de Donato G, Eckstein HH, De Rango P, Diehm N, Schmidli J, Teraa M, Moll FL, Dick F, Davies AH, Lepantalo M, Apelqvist J: Chapter I: Definitions, epidemiology, clinical presentation and prognosis. *Eur J Vasc Endovasc Surg*, 2011; 42 Suppl 2: S4-S12
- 6) Azuma N, Iida O, Takahara M, Soga Y, Kodama A: Surgical reconstruction versus peripheral intervention in patients with critical limb ischemia - a prospective multicenter registry in Japan: The SPINACH study design and rationale. *Vascular*, 2014; 22: 411-420
- 7) Seino Y, Nanjo K, Tajima N, Kadowaki T, Kashiwagi A, Araki E, Ito C, Inagaki N, Iwamoto Y, Kasuga M, Hanafusa T, Haneda M, Ueki K: Report of the committee on the classification and diagnostic criteria of diabetes mellitus. *J Diabetes Investig*, 2010; 1: 212-228
- 8) Shimamoto K, Ando K, Fujita T, Hasebe N, Higaki J, Horiuchi M, Imai Y, Imaizumi T, Ishimitsu T, Ito M, Ito S, Itoh H, Iwao H, Kai H, Kario K, Kashiwara N, Kawano Y, Kim-Mitsuyama S, Kimura G, Kohara K, Komuro I, Kumagai H, Matsuura H, Miura K, Morishita R, Naruse M, Node K, Ohya Y, Rakugi H, Saito I, Saitoh S, Shimada K, Shimosawa T, Suzuki H, Tamura K, Tana-

- hashi N, Tsuchihashi T, Uchiyama M, Ueda S, Umemura S: The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2014). *Hypertension Res*, 2014; 37: 253-387
- 9) Teramoto T, Sasaki J, Ishibashi S, Birou S, Daida H, Dohi S, Egusa G, Hiro T, Hirobe K, Iida M, Kihara S, Kinoshita M, Maruyama C, Ohta T, Okamura T, Yamashita S, Yokode M and Yokote K: Executive summary of the Japan Atherosclerosis Society (JAS) guidelines for the diagnosis and prevention of atherosclerotic cardiovascular diseases in Japan -2012 version. *J Atheroscler Thromb*, 2013; 20: 517-523
 - 10) Boulton AJ, Armstrong DG, Albert SE, Frykberg RG, Hellman R, Kirkman MS, Lavery LA, Lemaster JW, Mills JL, Sr., Mueller MJ, Sheehan P, Wukich DK: Comprehensive foot examination and risk assessment: a report of the task force of the foot care interest group of the American Diabetes Association, with endorsement by the American Association of Clinical Endocrinologists. *Diabetes Care*, 2008; 31: 1679-1685
 - 11) American Diabetes Association: Peripheral arterial disease in people with diabetes. *Diabetes Care*, 2003; 26: 3333-3341
 - 12) Tres GS, Lisboa HRK, Syllos R, Canani LH, Gross JL: Prevalence and Characteristics of Diabetic Polyneuropathy in Passo Fundo, South of Brazil. *Araq Bras Endocrinol Metab*, 2007; 51: 987-992
 - 13) Wasmuth S, Baumgartner I, Do DD, Willenberg T, Saguner A, Zwahlen M, Diehm N: Renal insufficiency is independently associated with a distal distribution pattern of symptomatic lower-limb atherosclerosis. *Eur J Vasc Endovasc Surg*, 2010; 39: 591-596
 - 14) Schmieder FA, Comerota AJ: Intermittent claudication: magnitude of the problem, patient evaluation, and therapeutic strategies. *Am J Cardiol*, 2001; 87: 3D-13D
 - 15) Meru AV, Mittra S, Thyagarajan B, Chugh A: Intermittent claudication: an overview. *Atherosclerosis*, 2006; 187: 221-237
 - 16) Mohler ER, 3rd: Peripheral arterial disease: identification and implications. *Arch Intern Med*, 2003; 163: 2306-2314