—Regular Articles—

Examination of Questionnaire Items regarding Diabetic Peripheral Neuropathy in Epalrestat-treated Patients and Their Usefulness in the Treatment of This Disorder — Influence on Treatment Course

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Epalrestat (Kinedak®) is an aldose reductase inhibitor (ARI) for diabetic peripheral neuropathy. In 41 diabetics, we conducted a questionnaire survey to evaluate symptoms of peripheral neuropathy and select appropriate drug therapy. We investigated 27 patients who participated in the first and second questionnaire surveys. We reviewed questionnaire items, and examined the correlation between the therapeutic effects and responses to the questionnaire. Concerning the usefulness of the questionnaire items, some questions were correlated with the effects. Treatment was effective for somatic neuropathy, but not for autonomic neuropathy. The questionnaire regarding diabetic peripheral neuropathy was useful for somatic neuropathy screening, but it was difficult to detect autonomic neuropathy.

Key words——diabetes mellitus; somatic neuropathy; autonomic neuropathy; epalrestat; aldose reductase inhibitor; questionnaire

INTRODUCTION

The pathogenesis of diabetic peripheral neuropathy may involve the neurocytic accumulation of sorbitol, in which the activity of a rate-limiting enzyme involved in polyol metabolism, aldose reductase (AR), is enhanced in the presence of hyperglycemia.[1] Such accumulation results in an increase in the intracellular osmotic pressure, the intracellular depletion of myo-inositol, a reduction in Na^+–K^+–ATPase activity, and the enhancement of protein saccharification,[2] causing numbness and pain *via* neurocyte hypofunction.[3),4] Epalrestat is a rhodanine derivative, which specifically and potently inhibits AR.

Various clinical studies are being conducted to evaluate the curative effects of epalrestat. In most cases, physicians start therapy with this agent based on patients' reports at the outpatient clinic. Furthermore, its effects on neuropathy-related symptoms are also evaluated based on their reports on symptoms. A diagnosis of diabetic peripheral neuropathy is made using a questionnaire in many diabetes-specialized hospitals, as this method is simple and noninvasive, facilitating the accurate assessment of complaints. However, few studies have investigated question items included in a routinely employed questionnaire. The responses to questions accurately matched to symptoms of peripheral neuropathy may be objective parameters.

In this study, to accurately evaluate symptoms of neuropathy in diabetics and select appropriate drug therapy, we reviewed questionnaire items regarding diabetic peripheral neuropathy (somatic and autonomic neuropathy), and examined their usefulness. In addition, we investigated the correlation between the curative effects of epalrestat and responses to the questionnaire.

METHODS

Subjects and Survey Methods Of 183 diabetics who were treated at the outpatient clinic of the Department of Internal Medicine, Nippon Medical University Tama Nagayama Hospital between August 1999 and October 2001, 128 patients who had not

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received epalrestat were selected, and a request form regarding enrollment in this study was delivered to attending physicians.

Selection criteria included the absence of previous epalrestat therapy and an age of 69 years or younger. We excluded patients with cardiovascular lesions and those with severe hepatopathy/nephropathy. Patients were selected regardless of the presence or absence of peripheral neuropathy, drug therapy for diabetes, combined agents, and diet/exercise therapies. The subjects were 41 patients from whom informed consent regarding participation in this study was obtained. Initially, a questionnaire survey regarding peripheral neuropathy (Table 1) was conducted using an interview system while seated at the counter of the Department of Pharmacy.

This questionnaire was prepared based on the Tohoku 30 000 Patients Questionnaire employed in a survey regarding diabetics, which was conducted between November 1997 and February 1998 in a total of 32 995 diabetics treated in 387 hospitals in the Tohoku district.

The questionnaire items consisted of 6 questions regarding somatic neuropathy and 6 questions regarding autonomic neuropathy. In responding to questions from the patients, answers were limited to the meanings of question items so that there was no influence on the questionnaire results. Subsequently, we randomly divided 41 patients into epalrestat-treated and untreated groups using the envelope method. In the former, 1 tablet (50 mg) of epalrestat (Kinedak®) was orally administered before meals 3 times a day. After 24 weeks (6 months), a second questionnaire survey was similarly conducted.

Table 1. Questionnaire regarding Diabetic Peripheral Neuropathy

【Questions regarding somatic neuropathy】
Q. 1: Do you sometimes experience numbness of the hands and feet?
Q. 2: Do you sometimes experience coldness or flush of the hands and feet?
Q. 3: Do you feel like there is paper sticking to the soles of your feet while walking?
Q. 4: Do you often stumble while walking?
Q. 5: Do you often get a cramp in your calf?
Q. 6: Have you ever been unaware of pain or burns?
【Questions regarding autonomic neuropathy】
Q. 7: Do you sometimes experience upset stomach?
Q. 8: Do you sometimes experience repeated constipation and diarrhea?
Q. 9: Is a long time required for urination?
Q. 10: Is sweating abnormally marked?
Q. 11: Do you sometimes experience palpitation at rest?
Q. 12: Do you sometimes experience vertigo?

Statistical Analysis The patients' responses to the questionnaire were expressed as numerical data: ''absent'': 1 point, ''it was previously present, but is currently absent'': 2 points, ''sometimes present'': 3 points, and ''always present'': 4 points. The following statistical methods were employed.

Initially, to examine whether the contents of questions regarding peripheral neuropathy are appropriate, we analyzed the correlation between question items using the regression analysis method. Subsequently, we analyzed differences in the first and second questionnaire results between the epalrestat-treated and untreated groups using the Mann-Whitney test. In the former, we compared the results between the first and second questionnaire surveys using Wilcoxon's test. A similar test was also conducted in the latter. In addition, to evaluate the therapeutic effects of epalrestat, we compared the sum of the scores for 6 questions regarding somatic neuropathy and that regarding autonomic neuropathy on the first questionnaire survey in the epalrestat-treated group, with the sum of the scores for these questions on the second survey after 24 weeks using Wilcoxon's test. A similar test was also conducted in the untreated group.

RESULTS

Patient Background The subjects consisted of 28 males and 13 females, with a mean age of 60.3±7.6 years (mean±SD). The mean duration of disease was 10.9±7.8 years. The mean body mass index (BMI) was 24.7±5.3, and the mean HbA1c level was 6.6±1.2%. No patient had any cardiovascular lesion or severe liver/kidney dysfunction. Complications other than diabetes included hypertension in 3 patients, hyperlipidemia in 8, and the two disorders concomitant in 7.

In the subjects, blood sugar control was relatively favorable. There were no symptoms of neuropathy, nephropathy, or retinopathy as diabetic complications, suggesting mild diabetes in all patients. The first questionnaire survey was conducted in 41 patients, and, after 24 weeks, the second survey could be

performed in 27 patients, excluding 14 who dropped out of this study due to self-discontinuation, the administration of agents other than the test agent, a change of his/her address, or withdrawal from this study.

Finally, we investigated 27 patients who participated in the first and second questionnaire surveys. They consisted of 19 males and 8 females, with a mean age of 60.0±9.6 years. The mean duration of disease was 9.8±7.0 years. The mean BMI was 25.1±4.8, and the mean HbA1c level was 6.6±1.1%. Of the 27 patients, 12 were treated with epalrestat. They consisted of 8 males and 4 females, with a mean age of 60.6±7.5 years. The mean duration of disease was 8.5±4.9 years. The mean BMI was 24.5±5.0. The mean HbA1c level was 6.8±1.3%. The other 15 patients belonged to the untreated group. There were 11 males and 4 females, with a mean age of 59.6±11.2 years. The mean duration of disease was 10.9±8.3 years. The mean BMI was 25.6±4.6, and the mean HbA1c level was 6.4±1.0%.

To confirm the absence of deviation between the epalrestat-treated and untreated groups among 41 patients who participated in the first questionnaire survey, we compared background factors using the *t*-test. Similarly, we analyzed these factors in 27 patients who participated in the second survey. In addition, we similarly compared them between the 27 patients and 14 who dropped out of this study. The results are shown in Table 2.

There were no significant differences in background factors between the epalrestat-treated and untreated groups on either questionnaire survey, indicating that there was no deviation in patient assignment on either survey. Furthermore, there were also no significant differences between the 27 patients and 14 who dropped out of this study, suggesting that there was no systematic deviation in these 14 patients.

Usefulness of Question Contents in the Questionnaire regarding Peripheral Neuropathy As shown in Fig. 1, we performed regression analysis to examine the correlation among the question items. We calculated the correlation coefficient (R). The results showing significant differences are summarized in Table 3.

In 27 patients who participated in the first and second surveys, the first survey showed that there was a correlation between Questions 10 (''Is sweating abnormally marked?'') and 12 (''Do you sometimes experience vertigo?'') (R=0.49615).

Table 2. Background Factors of the Subjects

First questionnaire survey	Epalrestat-treated group (n=21) (Male: 13, Female: 8)	Untreated group (n=20) (Male: 15, Female: 5)	p-value
Age	59.4±6.8	60.8±10.5	NS (p=0.621)
Duration of disease (years)	9.6±6.2	11.1±7.6	NS (p=0.256)
BMI	25.1±4.6	23.2±5.2	NS (p=0.244)
HbA1c (%)	6.4±0.9	6.7±1.1	NS (p=0.280)

Second questionnaire survey	Epalrestat-treated group (n=12) (Male: 8, Female: 4)			Untreated group (n=15) (Male: 11, Female: 4)		
Age	60.6±7.5			59.6±11.2		NS (p=0.610)
Duration of disease (years)	8.5±4.9			10.9±8.3		NS (p=0.201)
BMI	24.5±5.0			25.6±4.6		NS (p=0.497)
HbA1c (%)	6.5±0.8			6.8±0.9		NS (p=0.256)
	12 patients who participated in the second survey	9 patients who dropped out of this study	p-value	15 patients who participated in the second survey	9 patients who dropped out of this study	p-value
Age	60.6±7.5	59.1±10.9	NS (p=0.858)	59.6±11.2	61.4±9.9	NS (p=0.263)
Duration of disease (years)	8.5±4.9	9.8±4.8	NS (p=0.432)	10.9±8.3	11.8±6.8	NS (p=0.514)
BMI	24.5±5.0	25.3±4.7	NS (p=0.623)	25.6±4.6	22.9±7.5	NS (p=0.252)
HbA1c (%)	6.5±0.8	6.3±1.1	NS (p=0.420)	6.8±0.9	6.6±1.2	NS (p=0.536)

mean±S.D.

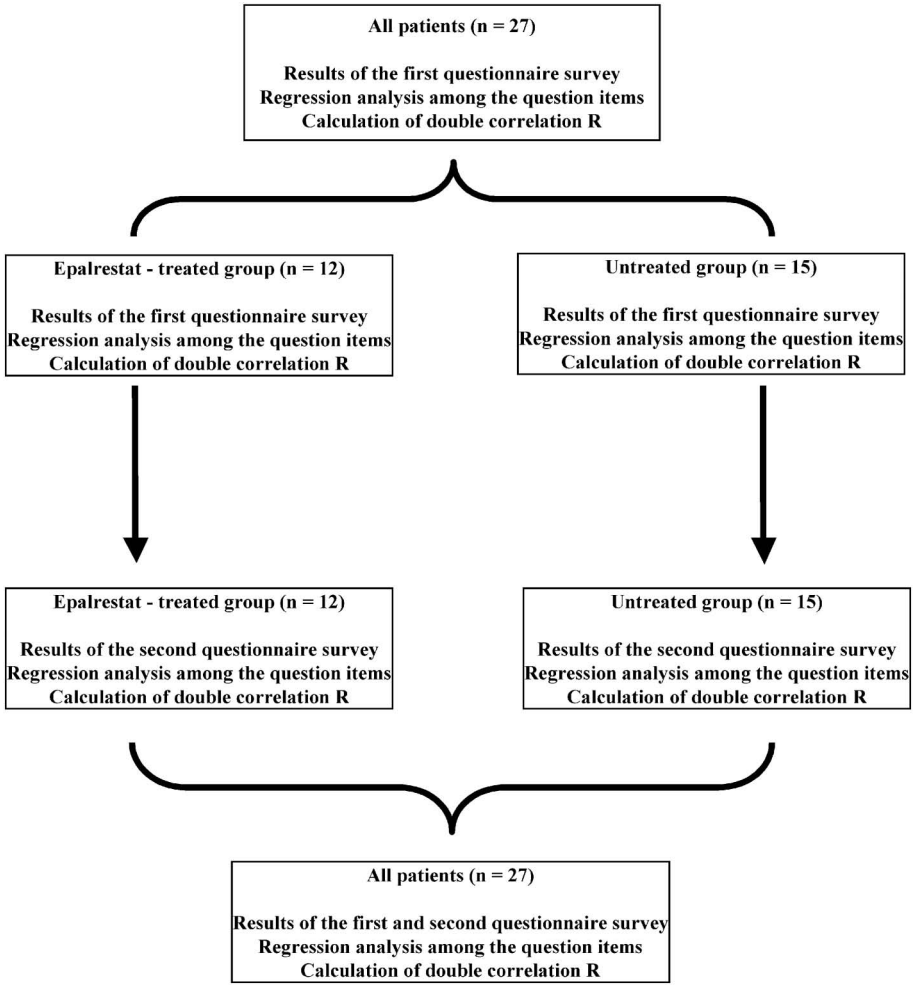

Fig. 1. Analytical Chart of Regression Analysis (double correlation R)

Table 3. Results of Regression Analysis regarding the Questionnaire Items

Patient conditions	*n*	Question number	*vs*	Question number	Double correlation R
All patients (first survey)	27	Q. 10	*vs*	Q. 12	0.496**
Epalrestat-treated patients (first survey)	12	Q. 1	*vs*	Q. 10	0.603*
		Q. 4		Q. 7	0.795**
		Q. 10		Q. 12	0.817**
Epalrestat-treated patients (second survey)	12	Q. 4	*vs*	Q. 7	0.757**
		Q. 9		Q. 10	0.592*
		Q. 9		Q. 11	0.629*
Untreated patients (first survey)	15	/	*vs*	/	/
Untreated patients (second survey)	15	Q. 4	*vs*	Q. 5	0.537*
All patients (first and second surveys)	54	Q. 1	*vs*	Q. 3	0.347**
		Q. 4		Q. 7	0.269*
		Q. 5		Q. 9	0.304*
		Q. 7		Q. 10	0.271*
		Q. 7		Q. 12	0.291*
		Q. 10		Q. 12	0.318*

*: $p<0.05$. **: $p<0.01$.

In 12 patients treated with epalrestat, the first survey showed that there was a correlation between Questions 4 (''Do you often stumble while walking?'') and 7 (''Do you sometimes experience upset stomach?'') (R=0.79515). There was also a correlation between Questions 1 (''Do you sometimes experience numbness of the hands and feet?'') and 10 (R=0.60286). In this group, there was also a correlation between Questions 10 and 12 (R=0.8165), as demonstrated in the above 27 patients.

In these 12 patients, the second survey showed a correlation between Questions 9 (''Is a long time required for urination?'') and 10 (R=0.59216). There was also a correlation between Questions 9 and 11 (''Do you sometimes experience palpitation at rest?'') (R=0.62881). As shown by their first survey results, there was a correlation between Questions 4 and 7 (R=0.75665).

In 15 patients who were not treated with epalrestat, the first survey showed that there was no correlation among the question items. In these 15 patients, the second survey showed a correlation between Questions 4 and 5 (''Do you often get a cramp in your calf?'') (R=0.53651).

We analyzed the correlation based on the results of the first and second questionnaire surveys in 27 patients (n=54). There were correlations between Questions 1 and 3 (''Do you feel like there is paper sticking to the soles of your feet while walking?'') (R=0.34696), between Questions 4 and 7 (R=0.26905), between Questions 5 and 9 (R=0.30428), between Questions 7 and 10 (R=0.27073), and between Questions 7 and 12 (R=0.29057). In addition, there was also a correlation between Questions 10 and 12 (R=0.31814).

Significance Test between the Epalrestat-treated and Untreated Groups As shown in Fig. 2, to compare the results between the two groups on the first and second surveys, the significance of differences between 2 independent groups was tested using the Mann-Whitney test. To examine differences between the first and second survey results in the two groups, significance between 2 associated groups was tested using Wilcoxon's test. The results are shown in Table 4.

When testing significance between 2 independent groups, there were no significant differences in any question item between the epalrestat-treated and un-

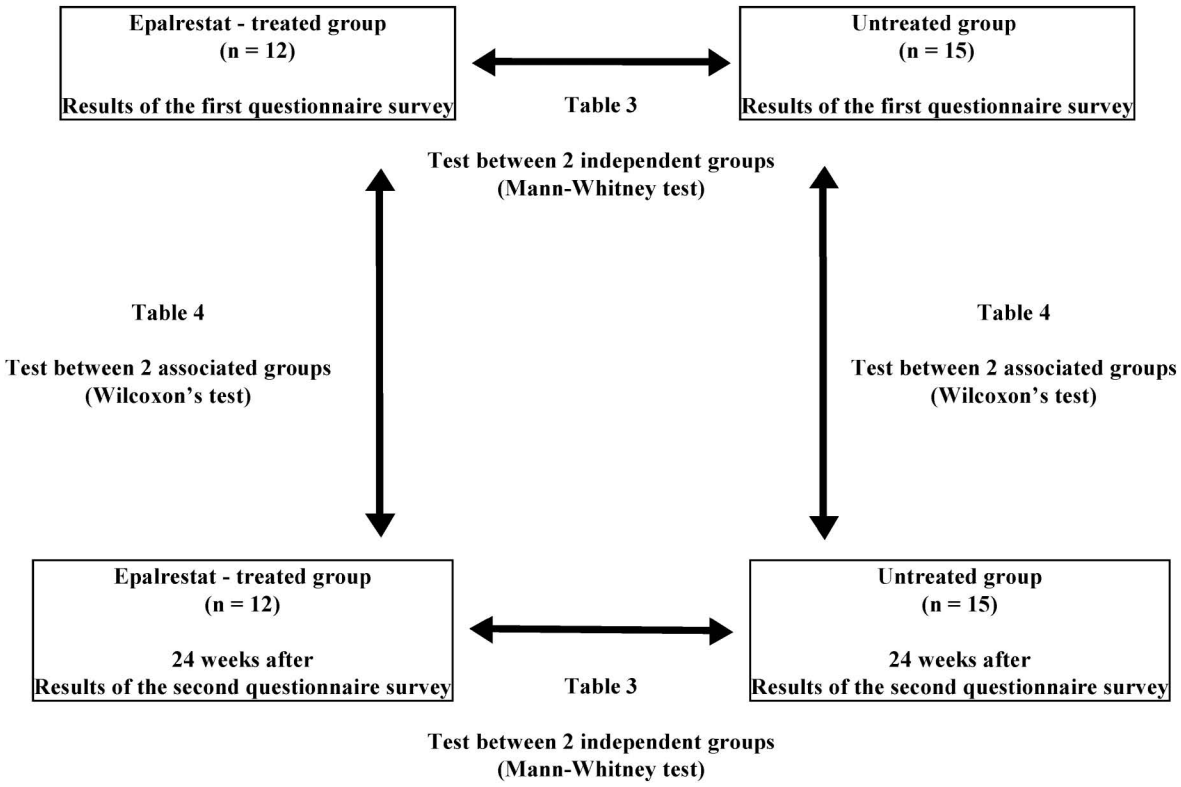

Fig. 2. Analytical Chart of a Test between 2 Groups

Table 4. Results of Tests regarding Each Question between 2 Groups

	Epalrestat-treated group (n=12) Results of the first questionnaire survey	Epalrestat-treated group (n=12) Results of the second questionnaire survey	Untreated group (n=15) Results of the first questionnaire survey
Epalrestat-treated group (n=12) Results of the second questionnaire survey	Wilcoxon signed-ranks test Q. 1: $p<0.05$ Q. 3: $p<0.05$	—	—
Untreated group (n=15) Results of the first questionnaire survey	Mann-Whitney's U test All questions NS	—	—
Untreated group (n=15) Results of the second questionnaire survey	—	Mann-Whitney's U test All questions NS	Wilcoxon signed-ranks test All questions NS

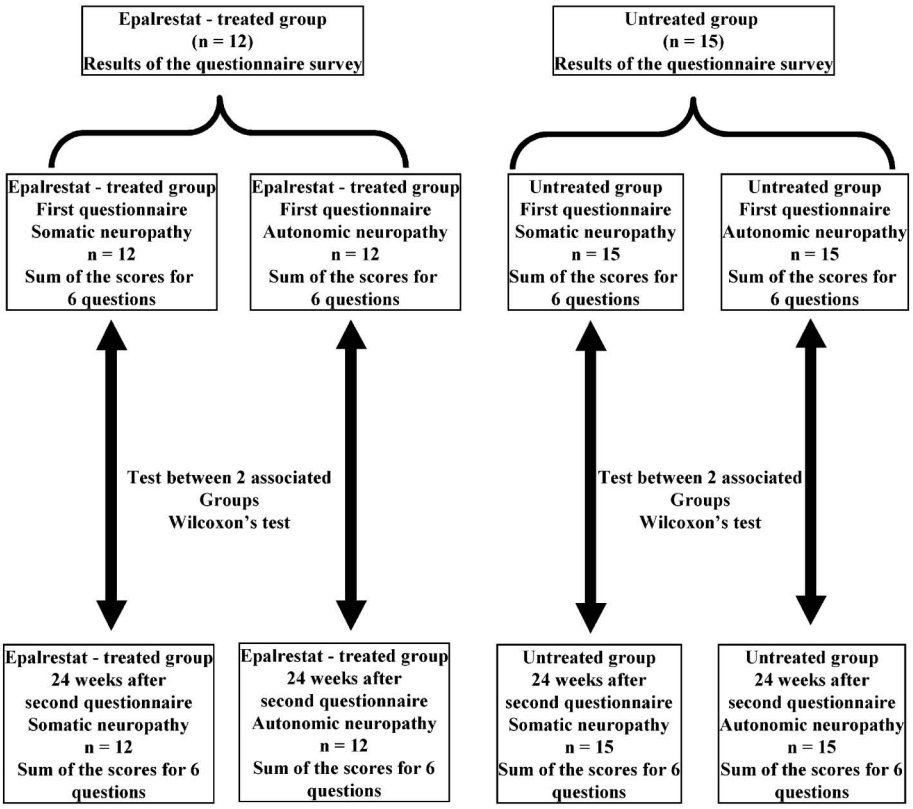

Fig. 3. Analytical Chart of Diabetic Peripheral Neuropathy
Test between 2 groups regarding somatic/autonomic neuropathy

treated groups. Another significance test between 2 associated groups showed that there were no significant differences in any question item in the untreated group. However, in the epalrestat-treated group, there was a significant difference between the pre- and posttreatment responses to Question 1 (p= 0.0191). Furthermore, there was also a significant difference in the response to Question 3 (p=0.0425).

Curative Effects of Epalrestat As shown in Fig. 3, Wilcoxon's test was employed in all 4 tests to examine differences between 2 associated groups. The results are shown in Table 5. In the untreated group, the p-values between the first and second survey results regarding somatic/autonomic neuropathy were 0.5076 and 0.0831, respectively. In the epalrestat-treated group, the p-values were 0.0058 and

Table 5. Effects of Epalrestat on Peripheral Neuropathy

	Epalrestat-treated group ($n=12$)		Untreated group ($n=15$)	
	Somatic neuropathy (Sum of the scores for Questions 1 to 6)	Autonomic neuropathy (Sum of the scores for Questions 7 to 12)	Somatic neuropathy (Sum of the scores for Questions 1 to 6)	Autonomic neuropathy (Sum of the scores for Questions 7 to 12)
Wilcoxon's signed-ranks test (between the first and second questionnaire survey results)	$p<0.01$	NS	NS	NS

0.7263, respectively. Thus, the latter showed a significant difference between the first and second survey results regarding somatic neuropathy.

DISCUSSION

In Japan, only epalrestat, as an aldose reductase inhibitor (ARI), has been approved for diabetic peripheral neuropathy including somatic (numbness and pain) and autonomic (abnormal heart beat changes, vertigo, gastrointestinal disorders, and erectile dysfunction (ED)) neuropathy.

In 1981, a preclinical study of epalrestat was conducted. In November 1981, a phase I clinical trial was initiated. Single-dose and 5-day administration studies confirmed its safety. Subsequently, a phase II dosimetry study was performed. The optimal dose was evaluated as 150 mg/day. A phase III, double-blind, comparative, clinical study using a placebo as a control agent was conducted from 1987 until 1989. The results were published in 1990,[4] demonstrating the efficacy of this agent.

Several multi-center, long-term, open studies investigated the usefulness of epalrestat in the treatment of diabetic neuropathy.[5] However, in most studies, symptoms were assessed based on patients' reports using a questionnaire.[6–8]

No method to objectively evaluate diabetic peripheral neuropathy has been established. Its assessment depends on patients' reports *via* a questionnaire. Therefore, it must be reviewed whether questionnaire items facilitate the accurate evaluation of peripheral neuropathy. In addition, factors including the duplication of question contents, accurate understanding by patients, and the appropriate number of questions may be important, influencing the results of a questionnaire survey. We examined the correlation among the question contents. Among the items regarding autonomic neuropathy, there was a correlation between 2, showing the highest correlation coefficient: ''Is sweating abnormally marked?'' and ''Do you sometimes experience vertigo?''. In addition, there was a correlation between 2 questions: ''Do you often stumble while walking?'' and ''Do you sometimes experience upset stomach?''. However, the former reflects somatic neuropathy, and the latter reflects autonomic neuropathy; as the intentions of these questions differ, it may be impossible to delete one of these. As described above, 2 question items regarding autonomic neuropathy showed the most marked correlation. In this case, it may be possible to delete either from question items in preparing a future questionnaire for diabetics, or when one question shows the symptom's presence, the other may be excluded.

Pfeifer *et al*. summarized the clinical results of previous studies regarding the effects of various ARIs, including alrestatin, sorbinil, ponalrestat, tolrestat, and epalrestat, on diabetic neuropathy.[9] According to their study, the response rates to ARIs in patients with distal symmetric neuropathy and those with autonomic neuropathy with respect to the number of clinical trials were 70 and 61%, respectively. The response rates with respect to the number of patients were 89 and 61%, respectively. Thus, many studies indicated the relationship between AR and diabetic neuropathy, as well as the efficacy of ARIs. However, some studies refuted the curative effects of ARIs. Inoue *et al*. administered epalrestat to 9 patients with diabetic neuropathy for about 12 months. They conducted a questionnaire survey to evaluate symptoms, and investigated the nerve conduction velocity.[10] They indicated that both the neurological test results and symptoms were ameliorated in 4 patients. However, in some patients, the amelioration rate for the former was not completely consistent with that for the latter.

Peripheral nerves consist of somatic and autonomic nerves. Diabetic peripheral neuropathy affects the two types of nerve. The results of the first and second

questionnaire surveys with respect to the epalrestat-treated and untreated groups (Table 4) showed significant differences in the responses to questions ''Do you sometimes experience numbness of the hands and feet?'' and ''Do you feel like there is paper sticking to the soles of your feet while walking?'' in the epalrestat-treated group (24-week treatment), reflecting the clinical effects of epalrestat. The two symptoms represent somatic neuropathy among symptoms of peripheral neuropathy in diabetics. The relief of these symptoms was demonstrated by the questionnaire survey results, which may be very significant. As shown in Table 5, there was a significant difference in the sum of the scores for the questions regarding somatic neuropathy between the first and second survey results in the epalrestat-treated group. Based on these results, epalrestat significantly relieved symptoms of somatic neuropathy alone. This was possibly because symptoms of somatic neuropathy could be more sensitively recognized compared to those of autonomic neuropathy. However, from a different viewpoint, epalrestat administration did not relieve any symptom of autonomic neuropathy based on the analysis results. These findings suggest that symptoms of somatic neuropathy, such as numbness/pain as well as sensory paralysis (hypoesthesia) of the hands/feet, can be evaluated using questionnaire items. However, it may be difficult to accurately evaluate autonomic neuropathy, which is involved in the onset of gastrointestinal/cardiovascular disorders and sudden death, based on the results of a questionnaire survey alone.

Some studies reviewed the assessment of neuropathy without administering epalrestat. Takahashi conducted a questionnaire survey in 137 patients with diabetic neuropathy, and reported that numbness was the most frequent, followed by pain, coldness, and imperception. He emphasized the importance of objective sensory and neurological tests in the diagnosis and treatment of numbness.[11] In addition, Miyamoto *et al*. measured the F-wave conduction velocity of the median and tibial nerves in 35 patients with type II diabetes, and indicated that there was no correlation between the duration of diabetes and F-wave conduction velocity of the tibial nerve. In addition, they reported that the F-wave conduction velocity was reduced early after the onset in some patients.[12] They concluded that the measurement of the F-wave conduction velocity might be an objective evaluation criterion for diabetic neuropathy, although no objective index of diabetic neuropathy has been established. In addition, studies using various objective indices of diabetic neuropathy were conducted in a large number of hospitals.[13–17]

CONCLUSION

The 3 major diabetes-related complications consist of retinopathy, nephropathy, and neuropathy. Concerning retinopathy and nephropathy, diagnostic criteria, methods for evaluating the condition, and treatment procedures have been established. However, with respect to somatic neuropathy, which is reported to cause symptoms in the early stage, diagnostic criteria using a tuning fork and keyboard instrument were recently published. It is difficult to accurately evaluate the condition regarding peripheral neuropathy, which consists of somatic and autonomic neuropathy, and changes in the severity. A misdiagnosis may markedly reduce diabetics' quality of life in the future, or induce severe neuropathy. Based on the results of this study, epalrestat may be effective for somatic neuropathy. On the other hand, it is difficult for patients to recognize symptoms of autonomic neuropathy. The accuracy of condition assessment using a questionnaire was limited. Furthermore, it was impossible to evaluate the effects of epalrestat on autonomic neuropathy based on the questionnaire survey results, and this method was not favorable with respect to drug therapy. In the future, a method for objectively evaluating autonomic neuropathy should be established, and the method to screen the autonomic neuropathy level should be reviewed.

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