ABSTRACT

Aim: to evaluate correlation between blood glucose control, corneal sensitivity and lacrimal secretion in type 2 DM with peripheral neuropathy

Methods: a cross sectional study has been conducted in 20 type DM with peripheral neuropathy and 20 without peripheral neuropathy at the Department of Internal Medicine and Ophthalmology, Ciptomangunkusumo Hospital, Faculty of Medicine University of Indonesia, from August through November 2002. All subject underwent a comprehensive medical examination, including esthesiometer Semmes-Weinstein 10 g, HbA1c, Schirmer test, and corneal sensitivity measurements.

Results: the mean corneal sensitivity was significantly lower in diabetic patients with neuropathy (p= 0.000). HbA1c was related to corneal sensitivity (p=0.016)

Conclusion: in type 2 DM with peripheral neuropathy, corneal sensitivity was demonstrated to be significantly decrease, all of which seems to be due to the status of blood glucose control.

Key words: peripheral neuropathy, lacrimal secretion, corneal sensitivity.

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease, which is characterized by hyperglycemia due to defect on insulin secretion, insulin function, or both. In 1995, DM prevalence at adolescence group was about 7.4%, and it is estimated to increase up to 9% in 2025. In Indonesia the prevalence of DM in 1980 was 1.5% - 2.3% in population over 15 years old. And, in Manado the prevalence was 6.1%. The survey of Department of Health 1980 reveals that DM occupied the 18th rank disease. And it is estimated that there will be 7 million of diabetics patient in 2020. Waspadji found that DM cases was increasing from 1.7% to 5.6% between 1982 and 1993 in Jakarta. In 1985, Bahar reported was that the prevalence of peripheral neuropathy was 58% while autonomic parasympathetic neuropathy was 11.9%. By using 10 g monofilament Suryotono found 53.1% neuropathy in DM patient with diabetic foot ulcer while it was only 9.7% in those without diabetic ulcer. By using electromyography, Yuson found 82.3% neuropathy cases in diabetic patient, without neuropatic symptom. On 2000, Atlas of Diabetes, it is estimated about 125 million Indonesian people aged over 20 years old. With assumption of DM prevalence of about 4.6%, there will be 5.6 million people of diabetic patient, and this number will increase in 2020 up to 8.2 million patients. It will lead to a big problem, particularly in the management of DM complications.

Hyperglycemia may cause chronic microvascular complication such as on kidney and eyes, and macrovascular complication on coronary, foot and brain blood vessel, as well as neurological defect. The most founded neurological defect is symmetric distal sensory polyneuropathy. The symptoms of neuropathy usually appear after 9-10 years of DM. Indeed, Pirart found about 12% neuropathy cases in recent diabetic patient. The most founded symptoms are numbness,
weakness and losing of pain sensation.\textsuperscript{16,17} Chronic hyperglycemia also cause neurological defect in the eyes. The cornea is innervated by sensory nerves, i.e. first branch of the fifth cranial (Trigeminus) nerve.\textsuperscript{18} Defect on this nerve causes lower corneal sensitivity and impaired secretion of lacrimal gland resulting in lowering of blinking reflex. That will increase the risk of corneal ulcer.\textsuperscript{19} In 1995-1998, Rahmadhani\textsuperscript{20} reported that 6.5\% of corneal ulcer cases were accompanied by DM. Regarding the ophthalmologic complication of diabetic patient, we should are interested in evaluating the cornea and secretion of lacrimal glands in diabetic patient, especially on those who have developed peripheral neuropathy.

\textbf{METHODS}

The data was collected at the Department of Internal Medicine, Division of Endocrinology and Metabolism and at the Department of Ophthalmology Division of Infection and Immunology Faculty of Medicine University of Indonesia / Cipto Mangunkusumo Hospital Jakarta from August through November 2002. The data was collected by consecutive random sampling method, then inclusion and exclusion criteria and complete explanation about the study were implemented. Comprehensive history, physical examination, and also HbA1c examination by ELISA method were conducted. The peripheral neuropathy examination was done by monofilament 10 g \textit{Semmes-Weinstein} on the first digit of left and right foot. The examination of vibration sensation was done by 128 Hz tuning fork. The examination of autonomic heart function was done by SRR5 GSM AHM utility. Corneal neuropathy was examined by \textit{Cochet-Bonnet} esthesiometer. Lacrimal gland secretion was examined by \textit{Schirmer Test}.

The sample needed was 40 DM patients, 20 patients with peripheral neuropathy and 20 patients without peripheral neuropathy respectively, by power of 80\%, 0.05 significance, and correlation coefficient of 0.45.

Data was expressed in text, table and graphic form. The obtained data was processed with computerization. The univariate analysis was applied: to calculate mean and standard deviation (SD), bivariate analysis: to observe correlation within 2 variable by Chi square test. And multivariate analysis was used to calculate correlation of some variables with peripheral neuropathy incident by using logistic regression. P value of 0.05 was taken as limit of significance.

\textbf{RESULTS}

Subjects of this study were divided into 2 groups, i.e. the group with peripheral neuropathy, and the group without peripheral neuropathy. Each group consists of 20 subjects. In neuropathy group, the duration of disease ranged from 1 – 27 years with the mean of 10.6 years. In the group without neuropathy, the duration of DM ranged from 1 – 21 years with mean value of 8.1 years. The age of subjects in neuropathy group ranged from 45 – 69 years with mean value of 59.0 years while in the group without neuropathy ranged from 44 – 67 years, with mean value of 57.1 years. Both group were socio-demographically equal and statistically has no significant difference.

\textbf{Socio Demographic Characteristic}

Table 1 sohows that most of the patients aged between 50-69 years. There was more female in the group without neuropathy.

\textbf{Clinical Characteristic}

Table 2 we could observe the mean value of HbA1c level in neuropathy group was significantly higher than the group without neuropathy. Corneal sensitivity of both group have been decreased, but it was significantly lower in the group with peripheral neuropathy. Most of DM tipe 2 patients have
decreasing vibration sensation and abnormal autonomic reflex. Generally, the Schirmer of both group decreased.

Table 1. Group Demographic Characteristic

<table>
<thead>
<tr>
<th>Variable</th>
<th>Type 2 DM</th>
<th></th>
<th></th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Neuropathy (n = 20)</td>
<td>Without Neuropathy (n = 20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>2</td>
<td>2</td>
<td>0,335</td>
<td></td>
</tr>
<tr>
<td>40 – 49 years</td>
<td>8</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 – 59 years</td>
<td>10</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>8</td>
<td>5</td>
<td>0,500</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>12</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td>8</td>
<td>6</td>
<td>0,629</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>10</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>7</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occupation</td>
<td>9</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>11</td>
<td>9</td>
<td>0,100</td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
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</tr>
</tbody>
</table>

Table 2. Group Clinical Characteristic

<table>
<thead>
<tr>
<th>Variable</th>
<th>Type 2 DM</th>
<th></th>
<th></th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Neuropathy (n = 20)</td>
<td>Without Neuropathy (n = 20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean value of DM period (years)</td>
<td>10,6</td>
<td>8,1</td>
<td>0,296</td>
<td></td>
</tr>
<tr>
<td>Mean value of HbA1c Level (%)</td>
<td>7,4</td>
<td>6,5</td>
<td>0,037</td>
<td></td>
</tr>
<tr>
<td>Vibration Sensation</td>
<td>17 (85%)</td>
<td>16 (80%)</td>
<td>1,000</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>3 (15%)</td>
<td>4 (20%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autonomic Reflex</td>
<td>13 (65%)</td>
<td>12 (60%)</td>
<td>1,000</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>7 (35%)</td>
<td>8 (40%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cornea Sensitivity</td>
<td>20 (100%)</td>
<td>15 (75%)</td>
<td>0,047</td>
<td></td>
</tr>
<tr>
<td>Decrease</td>
<td>0</td>
<td>5 (25%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schirmer Test</td>
<td>20 (100%)</td>
<td>20 (100%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decrease</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

n = subject amount  p = significance

Correlation Between Corneal Sensitivity and Peripheral Neuropathy

On table 3 we could observe that generally the eyes’ corneal sensitivity of both group has been decreased. The group with peripheral neuropathy has lower corneal sensitivity than the group without neuropathy and statistically there was significant difference (p<0.05).

Correlation Between Schirmer Test and Peripheral Neuropathy

On table 4, the mean value of Schirmer test in peripheral neuropathy group was lower than the group without neuropathy, but statistically there was no significant difference in both groups.

Correlation HbA1c Level and Corneal Sensitivity

On table 5, we could observe the correlation (R=0.38) between HbA1c and corneal sensitivity, which was statistically significant (p = 0.016). The correlation pattern was negative.

Correlation Between Schirmer Test and Autonomic Reflex

Table 6, showed that the Schirmer test result has been decreased in all the patients and there was significant correlation between Schirmer test and autonomic neuropathy.
DISCUSSION

This study is a comparative cross sectional study. Independent variable was only valued once, hence we may not observe the effect of that independent variable to peripheral neuropathy incident. Limitation of this study was that it did not use examination of nerve conduction velocity to evaluate peripheral neuropathy, which may detect neuropathy up to 100%. Monofilament may be used to evaluate peripheral neuropathy because it has sensitivity and specificity value of 95 and 82% respectively.22 The Schirmer test was not an exact examination to evaluate lacrimal gland secretion, but this examination was clinically simple and inexpensive so that grossly we may use it to evaluate lacrimal gland secretion.

Prevalence of DM neuropathy of children is about 2% which will be increase in keeping with the DM period. Pirart reported that neuropathy cases has been increased from 12% to 50%. Palumbo et al reported 4% to 15%, after 20 and 25 years.21 In Cipto Mangunkusumo Hospital, Jakarta, Asril Bahar in 1985 reported that diabetic neuropathy incidence was about 7.02 SD 5.5 years. Partanen et al20 found the mean of neuropathy complication was 10 years. In this study, we found mean DM period of neuropathy group was 10.6 years and in the group without neuropathy tehre was 8.1 years. The correlation between DM period and neuropathy was statistically not significant. This was due to the subject of study hard to precisely predict when he has DM, hence it was hard to predict how long was the DM period. These fact was supported by Pirart who found neuropathy complication in 12% of recent DM patients.

This study found that mean value of HbA1c level in peripheral neuropathy group was significantly higher than the group without neuropathy. The effect of blood glucose control on the development of DM complication has been studied by The United Kingdom Prospective Diabetes Study (UKPDS).23 It supported the hyperglycemia theory which causes microvascular complication, and they found that by controlling the blood glucose (HbA1c level less than 7%) the development of complication such as nephropathy, retinopathy and neuropathy will decrease. Other study that has been conducted by The Diabetes Control and Complications Trial (DCCT)24 in DM type 1 patients, found that by controlling the blood glucose, it will decrease the risk of DM complication. This study was not aimed to find the effect of HbA1c to neuropathy complication because this study was cross sectional. But this study revealed that HbA1c level in peripheral neuropathy group was higher than the group without peripheral neuropathy.

Generally we found that the correlation between peripheral neuropathy and corneal sensitivity of this study has been decreased in both groups. In peripheral neuropathy group, all of its subjects (100%) have low corneal sensitivity, while in the group without peripheral neuropathy 75% of patients have low corneal sensitivity. The mean value of corneal sensitivity in peripheral neuropathy group was significantly lower than the group without peripheral neuropathy. Dogru et al25 found the mean value of corneal sensitivity in DM patient with peripheral neuropathy and without peripheral neuropathy. The decreased corneal sensitivity in DM patient was part of peripheral poly-neuropathy. Study of diabetics rats found morphological changes in their corneal nerve cells. Rosenberg et al26 found decreased corneal nerve fibres in diabetics patient, while their corneal sensitivity decreased only in the group of severe neuropathy. This result was different from Dogru et al particularly in the group without neuropathy. This difference may be due to different examination method of peripheral neuropathy. Dogru et al used the examination of nerve conduction velocity, hence it may detect nerve disorder at early stage. As known, the corneal nerve fibres is 400 times more momerous than the feet nerves. Although the decrease on nerve conduction in feet, the corneal nerve disorder has not observed yet.

The effect of DM on lacrimal gland secretion was studied by Moss et al27 who found correlation between DM and dry eye syndrome. Dry eye is disorder that occured on eye ball’s surface because of decrease lacrimal gland secretion or increase evaporation of tear film. In this study there was decreased lacrimal gland secretion in both groups. The mean value of Schirmer test in peripheral neuropathy group was lower than the group without neuropathy. The result of statistic test revealed no significant difference. Dogru et al found Schirmer test result in the group with and without peripheral neuropathy. Martin Gobbels28 found lower lacrimal gland secretion in diabetics patient than normal control, the same results has also been reported by Saito et al.29 There are multifactorial causes of decreased lacrimal gland secretion such as autoimmune disease, inflammation, trauma and diabetes mellitus. The results of this study differ from that of Dogru’s et al. It may be due to other factors such as smoking, coffee, and multivitamin usage which did not excluded from this study.
In addition, hormonal factor such as decreased estrogen hormone in menopause female can also affect the lacrimal gland secretion. Most of subjects in this study were female above 50 years-old, so there was possibility of menopause. This was supported by Susiyanti\textsuperscript{30} in the Department of Ophthalmology Faculty of Medicine, Cipto Mangunkusumo Hospital who found that the severity of dry eye will increase along with the period of amenorrhea post menopause.

There was negative correlation between HbA1c level and corneal sensitivity of blood glucose effect to corneal sensitivity in this study, which revealed every 1 percent raise in HbA1c level will decrease 1.9 mm corneal sensitivity, and it was statistically significant. The result of animal experiment found that high blood glucose decreased mioinositol concentration and increased sorbitol level on Schwan cell and axon that resulting damage corneal nerve cells. Dogru et al who found lower corneal sensitivity in DM patient with bad metabolic control compared to good metabolic control. Seifart\textsuperscript{31} in his study found that higher level of HbA1c will increase the risk of dry eye development, the same thing was found by Palmoski\textsuperscript{32}.

Examination of vibration sensation is usually used to evaluate neuropathy in nerve fibres with large diameter. In diabetics patient, neuropathy may occurred in small or large nerve but usually found in both combination. Neuropathy of small nerve usually precede the large. In this study we found 17 subjects (85%) of peripheral neuropathy group with decrease vibration sensation while in the group without peripheral neuropathy there was 16 subjects (80%), but statistically there was no significant difference. Sorman\textsuperscript{33} found that vibration sensation has better sensitivity to detect peripheral neuropathy than monofilament. This difference because neuropathy may occur in large or small nerves. We need further study to determine the type of nerve involved in neuropathy.

Autonomic neuropathy is part of diabetic neuropathy. Prevalence of autonomic neuropathy range from 17 – 40%. In diabetic patient with peripheral neuropathy there was 50% cases accompanied by asymptomatic autonomic neuropathy. Mortality rate of autonomic neuropathy ranged from 15 - 40%. Cardiovascular reflex was used to detect autonomic neuropathy. This study found 13 subjects (65%) in peripheral neuropathy group with abnormal autonomic reflex while in the group without neuropathy there was 12 subjects (60%). These revealed that autonomic neuropathy has been occurred in peripheral neuropathy group and the group without neuropathy, but it was statistically has no significant difference. Sundvissk\textsuperscript{34} found that autonomic neuropathy has strong correlation with peripheral neuropathy in diabetic patients.

In the group of type 2 DM patients with or without autonomic neuropathy, mean value of their Schirmer test was decreased. There was significant difference of that decrease in both groups. Andersen\textsuperscript{35} found that there is no significant difference of lacrimal gland secretion in diabetic patient with and without autonomic neuropathy. Different result of these studies possibly because of abnormal autonomic neuropathy classification in this study was combining intermediate and abnormal group, so that the abnormal amount is greater than normal and it affected the statistical count.

CONCLUSION

Corneal sensitivity in type 2 DM patient with peripheral neuropathy was lower and has significant difference compared to diabetic patient without peripheral neuropathy. Lacrimal gland secretion in type 2 DM patient with peripheral neuropathy has no significant difference compared to diabetic patient without peripheral neuropathy.

There was significant correlation between blood glucose control (HbA1c) and corneal neuropathy incidence.

We need to evaluate the corneal sensitivity of type 2 DM patient with peripheral neuropathy.

There should be well blood glucose control (HbA1c) in type 2 DM patient to reduce the incidence of corneal neuropathy.

REFERENCES

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