

Association of Trigeminal Neuralgia and Diabetes Mellitus: A Retrospective Study

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Abstract

Background and Aim: This study aimed to evaluate the relationship of diabetes mellitus (DM) and trigeminal neuralgia (TN) in order to provide new insight for TN pathogenesis.

Materials and Methods: This retrospective cross-sectional study compared the prevalence of DM in patients with TN and healthy controls without TN during 2007-2018. Totally, 193 participants were enrolled in the patient and control groups. These participants were selected among patients referred to the Oral and Maxillofacial Medicine Department of Dental School of Shiraz University of Medical Sciences. The age and gender of patients were matched in the two groups. DM (types 1 and 2) was diagnosed based on patient reports and routinely requested lab tests (fasting blood sugar, 2-hour post-prandial). The odds ratio (OR) and Chi-square test were used to compare the mean values.

Results: The prevalence of DM in TN patients and control group was 11.4% and 9.8%, respectively. The mean age of the participants was 56.96±13.66 and 56.46±13.47 years in the TN and control groups, respectively. The difference in TN prevalence between the two groups was not significant (P=0.62).

Conclusion: Although the prevalence of DM in patients with TN was higher than the control group, this difference was not significant (P>0.05). Women with TN showed DM 25% more than men with TN.

Key Words: Trigeminal Neuralgia; Diabetes Mellitus; Pain

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Introduction

Diabetes mellitus (DM) is one of the most common metabolic diseases.[1,2] The prevalence of DM has been on increase; this rate was 8.5% with 4.6 million cases of DM in Iran in 2015.[3] According to the World Health Organization, DM complications are divided into 2 categories. Microvascular complications include blindness due to retinopathy, renal failure because of nephropathy, and impotence

and diabetic foot ulcers due to neuropathy. Macrovascular complications include cardiovascular diseases and insufficient end organ blood flow. Proper metabolic control in DM postpones the complications. The oral manifestations of DM are periodontal disease, dental caries, fungal infections, impaired wound healing, xerostomia, and burning mouth sensations.[4]

Trigeminal neuralgia (TN) is a neuropathic pain

which causes sudden, brief stabbing and recurrent pain.[5,6] TN is more common in middle aged or old adults. TN can occur repeatedly and lasts for a few seconds. The attacks may begin with stimulation of the trigger zone, which may be located within the trigeminal nerve pathway.[7] TN is a neuropathic pain with different etiologies, causing demyelization in the trigeminal zone. Neurovascular compression, multiple sclerosis, tumors and cysts, and DM are the most popular causes.[8,9] Facial diabetic neuropathy commonly affects the cranial nerves 3, 4 and 6. The ophthalmic and maxillary branches of the trigeminal nerve are less commonly involved.[10]

There are several reports about painful facial neuropathy. Based on neuropathic nature of TN and several types of painful diabetic neuropathies, there are a few reports about the possible correlation of these two conditions.[11-13]

With respect to what has been mentioned, it seems plausible to determine the possible relationship of TN with DM. To the best of our knowledge, there are few studies about the relationship of TN and DM. The involvement of the oculomotor, trochlear, and abducent cranial nerves in diabetic neuropathy has been commonly reported.[14] In the same way, more involvement of the ophthalmic and mandibular branches of the trigeminal nerve in TN has been reported in DM patients.[14]

In an epidemiological study, 21.9% of patients with TN had DM; while, this rate was 12.9% in the control group. This difference in prevalence was significant ($P=0.01$). Also, the mandibular branch involvement was reported more frequently. Xu et al.[12] concluded that DM can be assumed as a risk factor for TN development. Therefore, in this study, we aimed to assess the correlation of DM and TN, to gain new insight regarding TN pathogenesis.

Materials and Methods

This cross-sectional study compared the prevalence of DM in patients with primary TN and healthy controls without TN during 2007-2018. In the control group, 193 healthy participants were enrolled. The protocol of this study which was conducted according to the ethical principles of Helsinki[15] was approved by the ethics committee of Shiraz University of Medical Sciences (IR.SUMS.REC.1397.455)

A total of 193 patients with TN who had been referred and admitted to the Oral and Maxillofacial Medicine Department participated in this study. The data of the patients with TN were evaluated by the researchers. All patients with other systemic diseases which can cause neuropathy such as renal failure, gastrointestinal disease, thyroid dysfunction, and connective tissue disease were excluded from the study.[16] The demographic data of patients and their systemic disease i.e. DM (type 1 or 2) were registered. The prevalence of DM in the control group and patients with TN, based on their age and gender, was studied. The age and gender of both groups were matched. Their DM (type 1 or 2) was diagnosed based on the routinely requested lab tests (fasting blood sugar, 2-hour post-prandial). The patients, who were under treatment in this center had periodic lab tests including fasting blood sugar and 2-hour post-prandial. All patients with TN who were under treatment in Shiraz Oral and Maxillofacial Medicine Department, had complete lab tests including DM screening test (fasting blood glucose and 2-hour post prandial) were enrolled. If their lab tests were suspicious, referral and consultation were routinely performed.

Fasting blood glucose more than 126 mg/dL (7 mmol/L) or higher on two separate tests and 2-hour post prandial more than 200 mg/dl confirmed the diagnosis of DM.[17] The data were evaluated using SPSS version 18. $P<0.05$ was considered significant. The odds ratio (OR) with 95% confidence interval (CI) and Chi

square test were used to evaluate the association of DM and TN.

Results

The prevalence of DM in 193 TN patients and 193 age- and gender-matched controls including 110 women (57%) and 83 men (43%) with a mean age of 56.96 ± 13.66 and 56.46 ± 13.47 years, respectively, was evaluated. Twenty-two patients (11.4%) with TN had DM [20 patients had type 2 (10.34%) and 2 patients had type 1 DM (1.03%)]. In the control group, 19 patients (9.8%) had DM [18 patients had type 2 (9.3%) and 1 patient had type 1 DM (0.5%)]. The prevalence of DM in TN patients and controls is presented in Table 1. The difference in prevalence of DM in TN patients in comparison with controls was not significant as shown by the Chi-square test ($P=0.62$). The odds ratio (OR) for DM in patients with TN was 1.18 (95% CI: 0.62-2.26) which did not show a significant risk for diabetic patients to be affected by TN. The prevalence of type 2 DM in patients with TN was significantly higher than type 1 ($P=0.01$). However, there was no difference between the prevalence of type 1 ($P=0.71$) or type 2 ($P=0.69$) DM between TN patients and healthy controls.

The pattern of DM prevalence in patients with TN and the control group based on age is described in Table 1. The prevalence of DM in the control group based on gender was not significantly different ($P=0.93$), while this difference was significant in TN patients ($P=0.01$). In the TN group, the number of women with DM was more than men.

No considerable association was noted between DM and TN in males or females. The OR was 1.76 (95% CI: 0.79- 3.92).

The prevalence of DM in TN patients and the control group based on age is presented in Table 2.

The prevalence of DM in patients with TN and the control group did not have a significant

difference based on age ($P=0.08$ and $P=0.14$, respectively).

Discussion

In our study, the prevalence of DM in TN patients was 11.4%, which was not significantly higher ($P=0.62$) than the DM prevalence in the healthy control group (9.8%). TN or tic douloureux is a paroxysmal, electric shock-like, perforating and sharp neuropathic pain. TN occurs unilaterally and often affects the mandibular and maxillary trigeminal branches.[9] A significant percentage of DM patients experience painful neuropathic pain, described as 'hot', 'burning', 'pins and needles', and 'electric'-like sensation.[18,19] Facial neuropathy by involvement of the third, fourth and sixth cranial nerves is more common than by the involvement of the fifth cranial nerve.[10] In a recent study on 256 patients with TN, Xu et al.(12) reported a prevalence of 21.9% for DM in TN patients in comparison with the prevalence of 12.9% for DM in the control group. The two groups were matched in terms of age and gender. The DM prevalence in the control group and patients with TN was significantly different ($P=0.01$) in their study. Based on their results, they introduced DM as a risk factor for TN with an OR of 1.89.

In our study, the prevalence of DM in 193 TN patients was 11.4%; this value was 9.8% in the control group. Although the prevalence of DM in patients with TN was higher than the control group, this difference was not significant ($P=0.62$). In contrast to the study by Xu et al, (12) the findings of the present study did not confirm the higher incidence of DM in patients with TN. The difference in sample size might be an important reason for this controversy. Also, the prevalence of DM in the general population can play an important role in this finding. The ethnicity, nutritional status, lifestyle, education, health services, and even the culture of different populations can be effective in this

Table 1- Prevalence of DM in TN patients and controls based on gender

| Group | | | DM status | | Total | |
|---------|--------|--------|--------------|----------|-------|--------|
| | | | Non-diabetic | Diabetic | | |
| Control | Gender | Female | Number | 99 | 11 | 110 |
| | | | Percentage | 90.0% | 10.0% | 100.0% |
| | | Male | Number | 75 | 8 | 83 |
| | | | Percentage | 90.4% | 9.6% | 100.0% |
| | Total | | Number | 174 | 19 | 193 |
| | | | Percentage | 90.2% | 9.8% | 100.0% |
| Case | Gender | Female | Number | 92 | 18 | 110 |
| | | | Percentage | 83.6% | 16.4% | 100.0% |
| | | Male | Number | 79 | 4 | 83 |
| | | | Percentage | 95.2% | 4.8% | 100.0% |
| | Total | | Number | 171 | 22 | 193 |
| | | | Percentage | 88.6% | 11.4% | 100.0% |

Table 1- Prevalence of DM in TN patients and controls based on gender

| Group | | | DM status | | Total | |
|--------------|--------------|-------|-------------|----------|-------|--------|
| | | | Nondiabetic | Diabetic | | |
| Control | | ≤40 | Number | 21 | 1 | 22 |
| | | years | Percentage | 95.5% | 4.5% | 100.0% |
| | Age Category | 41-60 | Number | 92 | 7 | 99 |
| | | | Percentage | 92.9% | 7.1% | 100.0% |
| | | ≥61 | Number | 61 | 11 | 72 |
| | | | Percentage | 84.7% | 15.3% | 100.0% |
| | Total | | Number | 174 | 19 | 193 |
| | | | Percentage | 90.2% | 9.8% | 100.0% |
| | Case | | ≤40 | Number | 22 | 0 |
| | | | Percentage | 100.0% | 0.0% | 100.0% |
| Age Category | | 41-60 | Number | 89 | 10 | 99 |
| | | | Percentage | 89.9% | 10.1% | 100.0% |
| | | ≥61 | Number | 60 | 12 | 72 |
| | | | Percentage | 83.3% | 16.7% | 100.0% |
| Total | | | Number | 171 | 22 | 193 |
| | | | Percentage | 88.6% | 11.4% | 100.0% |

regard.

Both diabetic neuropathy and TN are considered as neuropathic pains. The patients with DM are commonly affected by diabetic neuropathy.[19,20] A meta-analysis concluded that the patients with type 2 DM reported peripheral diabetic neuropathy more frequently than those with type 1 DM.[21] The result of our study was in line with the findings of this meta-analysis.[21]

Oral hypoesthesia and hyperalgesia as sensory symptoms of patients with DM are reported in patients with long-term diabetic neuropathy. (22) Their pathogenesis can be linked in some aspects. A more popular etiopathogenesis for TN is trigeminal sensory fibers' demyelination induced by proximity of the neurons and blood vessels, chronic inflammation, or space-occupying masses.[23]

In DM, oxidative stress caused by polyol pathway activation, autoxidation of glucose and its metabolites, and increased generation of free radicals can lead to nerve damage and diabetic neuropathy.[24-27] Hence, poorly controlled hyperglycemia can accelerate the peripheral nerve damage by increasing pro-inflammatory cytokines such as IL-6 and TNF- α which can alter the sodium channel expression of nociceptive neurons and their ectopic discharge.[28,29]

Change in ion channel expression and consequent hyper-excitability link these changes to neuropathic pain.[30] Up-regulation of sodium channel voltage is reported in this classification of pains.[31,32] Damage of trigeminal sensory fibers due to poor glycemic control and the proceeding pathological events may increase the risk of TN in diabetic patients. Although the present study did not confirm the higher risk of TN in patients with DM, more evaluations are required to assess this hypothesis more accurately. Considering the presence of an age- and sex-matched control group, enrolment of the control and case groups from a specific population with similar

culture and food habits can minimize the confounding factors. These situations can affect the overall prevalence of DM in a population since DM is an insidious disease which can progress slowly in many patients who have been undiagnosed for a long time and can cause several complications. Evaluating the relationship of DM and TN can lead to a better understanding of controlling the sugar serum level which is an important factor in decreasing the probability of TN development.

Conclusion

Although the prevalence of DM in patients with TN was higher than the control group, this difference was not statistically significant.

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Conflict of interests

There are no conflict of interests to declare.

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