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# Can Diabetes Mellitus Lead to Subclinical Vagal Neuropathy? A Prospective Clinical Study

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***Abstract***

**Objective:** Diabetic neuropathy is the most common chronic complication of diabetes mellitus. The vagal nerve and its branches might be affected, and the consequences can be very disastrous. This study aims to show if there is any subclinical vagal nerve involvement in diabetes mellitus.

**Methods:** Fourteen patients with diabetic neuropathy without swallowing difficulty and dysphonia and 15 healthy controls were included in this prospective study. Nerve conduction studies, blink reflex, and swallowing studies were conducted. The results were compared between 2 groups.

**Results:** Blink reflex exhibited abnormalities in patients compared to healthy controls. The recurrent laryngeal nerve motor response latency was significantly longer in patients ($P < .001$), whereas there was no significant difference for the pause period of swallowing.

**Conclusion:** Prolonged distal motor latency of the recurrent laryngeal nerve in spite of normal swallowing pattern at the cricopharyngeal muscle electromyography in patients with diabetic neuropathy suggests subclinical vagal neuropathy and so lower cranial involvement. Patients should be informed about this clinical condition and closely followed up.

**Keywords:** Cranial neuropathy, type 2 diabetes mellitus, diabetic neuropathy, lower cranial neuropathy, vagal neuropathy

## Introduction

Diabetes mellitus (DM) is one of the most common and highly morbid multisystemic disorders affecting both somatic and autonomic components of the nervous system. It is so devastating that if not managed properly and timely, neurological deficits become inevitable at the advanced stage.[1,2] Thus, several subspecialties of medicine, particularly neurology and otorhinolaryngology, have to be getting involved in the management of this devastating disorder. Diabetic neuropathy (DN) is the most common chronic complication of DM and occurs in about 50% of people with considerable morbidity and mortality.[3] Cranial neuropathies, especially the upper cranial nerves (CNs) of the skull base that neurologists face, may become apparent in any stage of the disease, and this involvement may be clinical and/or subclinical.[4-10] Clinical and subclinical involvement of the upper CNs is well known and studied extensively in the current literature[4-10]; however; there is scarce data concerning the involvement of the lower CNs.[6,11,12] Lower cranial neuropathies in DM, especially vagal nerve, have been observed as a cardiovascular and gastrointestinal compromise in previous reports.[6,11,12]

The vagal nerve is a mixed nerve, and it is composed of 80%-90% of sensory afferent fibers and 10%-20% of motor efferent fibers.[13] It is reported that laryngeal sensory neuropathy, which is thought to affect the upper or recurrent laryngeal branches of vagal nerve, is more common in patients with type 2 DM.[13] The recurrent laryngeal branch of the vagal nerve also innervates the cricopharyngeal muscle (CPM) and can be affected by DN.[14] It has been demonstrated that CPM plays a key role in swallowing, and its dysfunction may lead to clinical swallowing difficulties, which are correlated with high morbidity.[14]

There has been no report concerning subclinical vagal nerve involvement in patients with DM; thus, the aim of this prospective clinical study is to seek whether the vagal nerve is involved subclinically in DN and try to give an insight to the readers of this journal about this rare clinical condition.

## Methods

### Study Population

This prospective clinical study was conducted at the electromyography (EMG) laboratory of Istanbul Training and Research Hospital after the local ethics committee (2008-5/8) approved the study. Informed consent was acquired from all participants. Fourteen patients with type 2 DM who were sent to the neurophysiology laboratory for electrophysiological diagnosis of DN and 15 healthy participants were included in this study. Patients with diabetes who had swallowing difficulties, dysphonia, and other focal

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and systemic diseases that can have an effect on the peripheral nerve were excluded.

### Nerve Conduction Studies and Blink Reflex

The Neuro-MEP-Micro EMG system (Neurosoft, Russia) was used to perform electrophysiological studies in the same room at a temperature between 22°C and 24°C. Nerve conduction studies (NCSs) of the peripheral nerves were carried out to confirm diabetic peripheral neuropathy. The patients who were given diagnosis of diabetic peripheral neuropathy clinically and electrophysiologically underwent blink reflex (BR) and swallowing studies. Nerve conduction studies were calculated for median, ulnar, peroneal, posterior tibial, and sural nerves. Also, the posterior tibial nerve F-responses and the soleus muscle H-reflex were evaluated using conventional methods.[15]

Blink reflex has 2 components: an early R1 and a late R2 response. The R1 response is elicited ipsilateral to the side being stimulated, whereas the R2 response is typically present bilaterally. It was recorded for detecting subclinical upper CN involvement by applying the conventional method.[16] Abnormality was accepted for the levels that are beyond 2 SDs based on the normal controls.

### Swallowing Studies and Electrophysiological Evaluation of Cricopharyngeal Muscle

Electromyography for CPM was recorded using a bipolar concentric needle electrode that is 5 cm in length and 0.46 mm in size by the same researcher (ZA) using the methodology implemented previously.[17] Electromyographic activity of the CPM, swallowing patterns including duration of pause, and the presence of piecemeal deglutition were evaluated by consecutive 5 mL and 10 mL water swallows after dry swallowing as the needle is in the CPM. Electromyography setup was arranged as follows: analysis time 1 s/div, sensitivity 100 μV, low filter 100 Hz, and high filter 10 kHz during this process.

### The RLN Stimulation

Motor responses of CPM to the electrical stimulation of the recurrent laryngeal nerve (RLN) from the superior-medial part of the sternocleidomastoid muscle were elicited following the swallowing studies. The response with the highest amplitude was accepted for analysis. Also, any motor response elicited by stimulating the opposite side was evaluated. Analysis time 5 ms/div, sensitivity 500 μV/div, low filter 200Hz, and high filter 10 kHz were utilized for EMG setup during this process.

### Statistical Analysis

Data analysis was conducted using IBM Statistical Package for Social Sciences Statistics 17.0 (SPSS Inc.; Chicago, IL, USA). Patients were compared with the control group. Data are presented as mean ± SDs. Comparisons between groups were made using Fischer's exact test for categorical data and Mann–Whitney *U*-test for ordinal and numerical data. $P < .05$ was statistically significant.

## Results

### Patients

The patient group consisted of 7 males with a mean age of 61.8 ± 8.33 years (range 45-76 years), and the controls had 8 males with a mean age of 52.0 ± 8.9 years (range 41-71 years). The mean duration of type 2 DM was 19.4 years (range 10-35 years), and the value of HbA1c was 9%-12% and under poor control.

### Nerve Conduction Studies of Peripheral Nerves and Blink Reflex

Table 1 summarizes the results of NCSs. Nerve conduction studies of the peripheral nerves in patients with diabetes indicated a statistically significant prolonged mean latency and a lower mean amplitude than in the control group ($P < .001$). There was also statistically significant slowing in conduction velocity of the peroneal nerve in DM patients ($P < .001$). Sural nerve action potential was not present in 4 of 14 patients, and its amplitude was low in the remaining 10. All DM patients had distal symmetrical sensorimotor diabetic polyneuropathy according to this electrophysiological evaluation. Regarding BR study, early R1, late R2, and contralateral R2 responses in the patient group were found to be significantly longer than the control group ($P = .0006$, $P < .001$, and $P < .001$, respectively) (Table 2).

**Table 1.** Results (Mean ± SD) of the Nerve Conduction Tests in Both Patients and Controls

| Nerves | Patients (n = 14) | Controls (n = 15) | *P* |
|---|---|---|---|
| *Median nerve (motor)* | | | |
| Distant latency (ms) | 4.96 ± 1.47 | 3.18 ± 0.2 | .056 |
| Amplitude (mV) | 6.51 ± 2.81 | 11.97 ± 3.54 | **<.001** |
| Conduction velocity (m/s) | 42.27 ± 6.08 | 57.0 ± 2.7 | **<.001** |
| *Ulnar nerve (motor)* | | | |
| Distant latency (ms) | 3.15 ± 0.77 | 2.29 ± 0.25 | .7947 |
| Amplitude (mV) | 5.55 ± 2.06 | 8.54 ± 2.02 | .0955 |
| Conduction velocity (m/s) | 42.69 ± 7.04 | 63.58 ± 2.61 | **<.001** |
| *Peroneal nerve (motor)* | | | |
| Distant latency (ms) | 5.82 ± 1.75 | 3.63 ± 0.61 | **<.001** |
| Amplitude (mV) | 0.78 ± 0.72 | 8.54 ± 2.02 | **<.001** |
| Conduction velocity (m/s) | 30.7 ± 4.02 | 47.66 ± 3.35 | **<.001** |
| *Tibial nerve (motor)* | | | |
| Distant latency (ms) | 6.04 ± 0.93 | 4.59 ± 0.59 | .38049 |
| Amplitude (mV) | 2.02 ± 1.56 | 5.95 ± 2.12 | .00003 |
| Conduction velocity (m/s) | 30.7 ± 4.02 | 47.66 ± 3.35 | **<.001** |
| *Median nerve (sensory)* | | | |
| Distant latency (ms) | 4.22 ± 1.12 | 2.59 ± 0.21 | .07799 |
| Amplitude (μV) | 6.86 ± 3.91 | 42.16 ± 8.92 | **<.001** |
| *Ulnar nerve (sensory)* | | | |
| Distant latency (ms) | 3.17 ± 0.9 | 2.1 ± 0.18 | .39879 |
| Amplitude (μV) | 9.60 ± 6.43 | 43.77 ± 12.44 | **<.001** |
| *Sural nerve (sensory)* | | | |
| Distant latency (ms) | 4.22 ± 0.59 | 2.35 ± 0.285 | **<.001** |
| Amplitude (μV) | 0.6 ± 1.14 | 13.51 ± 3.79 | **<.001** |

n: number, SD: standard deviation, ms: milisecond, mV: milivolt, m:meter, s:second.

**Table 2.** Results (Mean ± SD) of the Blink Reflex Tests in Both Patients and Controls

| Parameters | Patients (n = 14) | Controls (n = 15) | *P* |
|---|---|---|---|
| $R_1$ latency (ms) | 15.52 ± 0.92 | 10.48 ± 0.44 | .0006 |
| $R_2$ latency (ms) | 51.87 ± 5.87 | 32.83 ± 0.69 | **<.001** |
| $R_2C$ latency (ms) | 51.77 ± 5.72 | 32.6 ± 0.75 | **<.001** |

n: number, ms: milisecond, SD: standard deviation.

**Electrophysiological Evaluation of Cricopharyngeal Muscle, Swallowing Studies, and RLN Responses**

High-frequency tonic activity just after entering the CPM muscle was noted in all patients. There was no complication following the examination. Both groups showed normal swallowing pattern that is composed of tonic activity, pre-swallowing burst, rebound burst, and tonic activity at dry, 5 mL, and 10 mL liquid swallows. Piecemeal deglutition was not detected via swallowing. The mean pause duration, recorded from CPM during swallowing, was similar between groups (0.51 s in patients and 0.57 s in controls). The distal motor latency of the RLN responses was significantly prolonged in DM patients ($P < .001$) (Figure 1). The mean distal motor latency of RLN was 5.37 ms (range 3.4-9.6 ms; SD 1.63) in DM patients, whereas it was 3.04 ms (range 2.3-3.6 ms; SD 0.36) in the control group. The mean amplitude of the RLN response in the diabetic group was smaller than the control group (Figure 1). It was 1.80 mV (range 0.5-2.9 mV) in DM patients and 3.04 mV (range 1.8-5.1 mV) in the control group. This was not included in the analysis because the measurement was made with a needle electrode. Contralateral stimulation of the RLN showed no response from CPM in both groups.

## Discussion

Clinical and subclinical involvement of the CNs in DM has been reported to be common in the upper CNs and reported as 1 and 10-55%, respectively.[4-10] Subclinical involvement of the upper CNs was shown in the studies in which BR was employed.[9,10] On the other hand, involvement of the lower CN in DM was reported rarely in some case reports as diabetic vagal mononeuropathy.[6,11,12] Indeed, there is no well-designed study for subclinical lower CN involvement in patients with DN. In the previously published studies, DM patients with clinical symptoms such as dysphagia and esophageal dysmotility in the late stage of the disease were evaluated by using esophageal manometry and NCS of peripheral nerves, and they did not perform needle EMG of CPM and RLN conduction studies.[17,18-20] Kim et al[12] described a case presenting dysphagia with no abnormal finding in vocal cord EMG as diabetic vagal mononeuropathy. Berry and Blair[11] evaluated a series of 25 patients who had vagal mononeuritis by applying needle EMG at the cricothyroid and thyroarytenoid muscles. Diabetes mellitus, being a reason of vagal nerve palsy in this series, was detected in only 2 of their 25 patients.

In the present study, swallowing was evaluated by CPM-EMG. Motor unit potentials (MUPs) were normal in appearance; MUPs were usually biphasic or triphasic in shape. Abnormal spontaneous activity or pathological spontaneous activity was not observed in resting EMG. Normal swallowing pattern was recorded in both groups. In addition, piecemeal deglutition was not determined. The duration of swallowing as well as pause duration of patients with DN was also similar in the control group. Essentially, swallowing studies with CPM-EMG were studied earlier in various disease groups.[17,21,22] Ertekin et al[19,20] reported abnormal MUPs and pathological pause duration in patients with neurological disorders. In another study, piecemeal deglutition was reported in patients suffering from gastroesophageal reflux.[17] As far as we know, a swallowing study by CPM-EMG has not been conducted yet in patients with diabetes. The swallowing pattern of CPM-EMG was found normal in our patients. However, a normal swallowing pattern may not prove that structures involving swallowing are clearly intact in our DM patients because, in spite of prominent dysphagia, significant disturbance in needle EMG and abnormal swallowing pattern were not seen in patients with neuromuscular disease.[22,23]

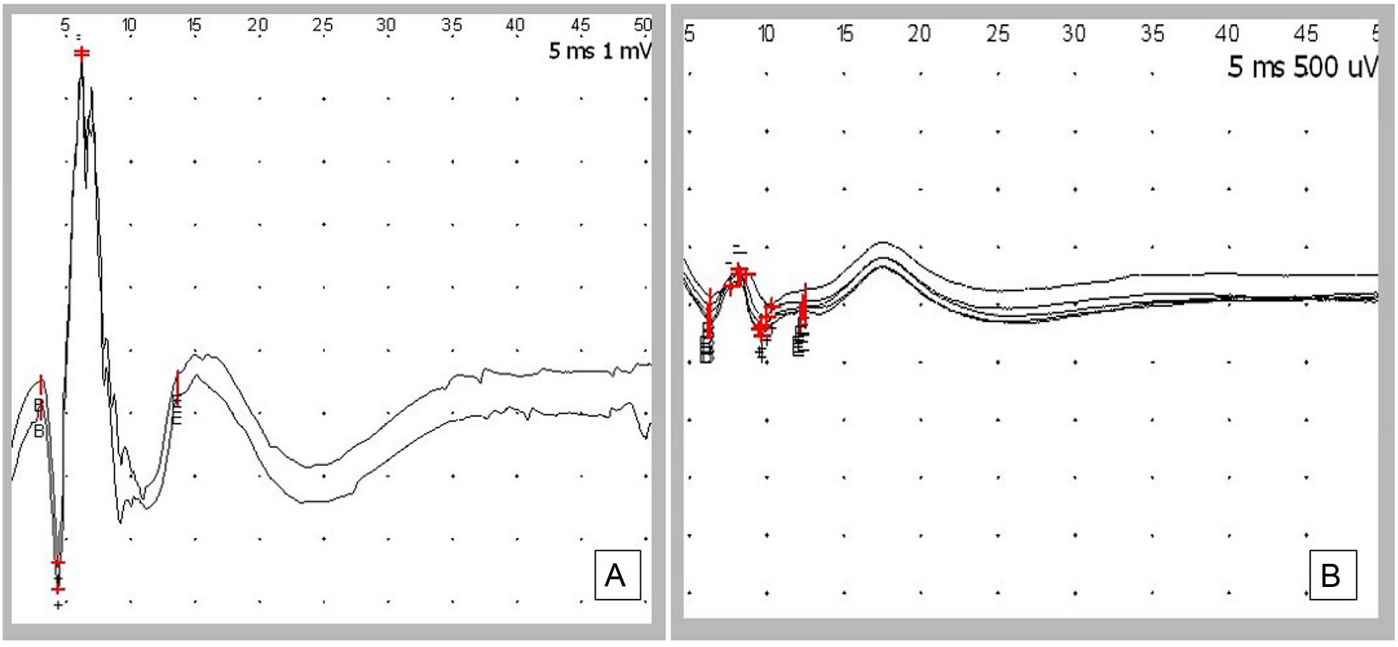


**Figure 1.** The recurrent laryngeal nerve motor responses recorded from cricopharyngeal muscle in the control group (A) and patients (B).

In the current study, our patient group showed significant prolonged RLN motor response latency and smaller mean amplitude compared to the controls. These results suggest that DM has caused demyelinating damage in the nerve components, including the axons. This can be seen in the distal symmetric form of DN as a consequence of nerve fiber degeneration. In the case of distal symmetric neuropathy, demyelination develops as a secondary change to diffuse or multifocal axonal loss.[23] However, the underlying mechanism is unclear for diabetic cranial neuropathies. It is reported as predominantly interested in vascular or immunologic etiology rather than chiefly a metabolic component of diabetic symmetric distal neuropathies.[24,25] There were no clinical findings related to major vascular disorders in our patients. Nevertheless, this does not mean that there are no microvascular changes. Since hyperglycemia starts all pathological cascades of DM, maintaining blood sugar levels as either protective or therapeutic in DM becomes very important.

### Study Limitations

The authors of this study are aware of the limitations in this study. The first and most important limitation is that the number of patients included is very limited. Because CPM-EMG is an invasive examination and negative effects may be observed with the stimulation of RLN, the number of patients who accepted the examination may be low. Second, the control group could not be age matched to the DM group. It cannot be excluded that this may have contributed to the difference in distal motor latency. Third, we only conducted the electrophysiological study for CPM innervated by the RLN. Applying electrophysiological examination to the accessory and hypoglossal nerves could have increased the value of this study. Finally, we included healthy volunteers as the control group of this study. One more control group including the diabetic patients without DN could help us understand the CPM-EMG and swallowing patterns in diabetes, which is strongly suggested for future studies.

## Conclusion

In conclusion, DM is a multisystem disease that has acute and chronic complications. Diabetic peripheral neuropathy and upper CN involvement are well-known complications that may impair quality of life. This study showed that DM can lead to subclinical vagal neuropathy, thereby lowering CN involvement in patients with DN. Diabetic vagal neuropathy can be observed as a life-threatening cardiovascular and/or gastrointestinal compromise. Patients should be informed about the lower CN involvement and should be followed up closely.

**Ethics Committee Approval:** Ethical committee approval was received from the Ethics Committee of University of Health Sciences, Istanbul Training and Reseach Hospital University (Approval no: 5/8, Date: 2/5/2008).

**Informed Consent:** Written informed consent was obtained from the patients who agreed to take part in the study

**Peer-review:** Externally peer-reviewed.

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**Declaration of Interests:** The authors have no conflict of interest to declare.

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## References

1. Singh R, Kishore L, Kaur N. Diabetic peripheral neuropathy: current perspective and future directions. *Pharmacol Res*. 2014;80:21-35. [CrossRef]
2. Tesfaye S, Selvarajah D. Advances in the epidemiology, pathogenesis and management of diabetic peripheral neuropathy. *Diabetes Metab Res Rev*. 2012;28(suppl 1):8-14. [CrossRef]
3. Feldman EL, Callaghan BC, Pop-Busui R, et al. Diabetic neuropathy. *Nat Rev Dis Primers*. 2019;5(1):41. [CrossRef]
4. Tracy JA, Dyck PJ. The spectrum of diabetic neuropathies. *Phys Med Rehabil Clin N Am*. 2008;19(1):1-26. [CrossRef]
5. Eshbaugh CG, Siatkowski RM, Smith JL, Kline LB. Simultaneous, multiple cranial neuropathies in diabetes mellitus. *J Neuroophthalmol*. 1995;15(4):219-224. [CrossRef]
6. Mathew J, Mohan M, Menon A. Multiple cranial neuropathies in a patient with diabetes mellitus. *Ann Indian Acad Neurol*. 2019;22(3):353-355. [CrossRef]
7. Watanabe K, Hagura R, Akanuma Y, et al. Characteristics of cranial nerve palsies in diabetic patients. *Diabetes Res Clin Pract*. 1990;10(1):19-27. [CrossRef]
8. Nazliel B, Yetkin I, Irkeç C, Koçer B. Blink reflex abnormalities in diabetes mellitus. *Diabetes Metab Res Rev*. 2001;17(5):396-400. [CrossRef]
9. Mazzotta G, Del Gatto F, Firenze C, Gallai V. The blink reflex in diabetic patients. *Electromyogr Clin Neurophysiol*. 1988;28(6):291-294.
10. Urban PP, Forst T, Lenfers M, Koehler J, Connemann BJ, Beyer J. Incidence of subclinical trigeminal and facial nerve involvement in diabetes mellitus. *Electromyogr Clin Neurophysiol*. 1999;39(5):267-272.
11. Berry H, Blair RL. Isolated vagus nerve palsy and vagal mononeuritis. *Arch Otolaryngol*. 1980;106(6):333-338. [CrossRef]
12. Kim YJ, Paeing SH, Bae JS. Diabetic vagal mononeuropathy manifesting with isolated dysphagia. *Neurol Asia*. 2015;20:187-189.
13. Tubbs RS, Rizk E, Shoja MM, Loukas M, Barbaro N, Spinner RJ, eds. *Nerves and Nerve Injuries: History, Embryology, Anatomy, Imaging, and Diagnostics*. MA: Academic Press; 2015.
14. Hammond CS, Davenport PW, Hutchison A, Otto RA. Motor innervation of the cricopharyngeus muscle by the recurrent laryngeal nerve. *J Appl Physiol (1985)*. 1997;83(1):89-94. [CrossRef]
15. Fisher MA. H-reflex and F-response studies. In: Fisher MA, ed. *Aminoff's Electrodiagnosis in Clinical Neurology*. 6th ed. China: Saunders; 2012:407-420.
16. Kimura J. Studies of the facial nerve and the blink reflex. In: Kimura J, ed. *Electrodiagnosis in Diseases of Nerve and Muscle Principles and Practice*. 4th ed. NY: Oxford University Press; 2013:180-201.
17. Alkan Z, Demir A, Yigit O, et al. Cricopharyngeal muscle electromyography findings in patients with gastroesophageal reflux disease. *Otolaryngol Head Neck Surg*. 2012;147(2):295-301. [CrossRef]
18. Wang X, Pitchumoni CS, Chandrarana K, Shah N. Increased prevalence of symptoms of gastroesophageal reflux diseases in type 2 diabetics with neuropathy. *World J Gastroenterol*. 2008;14(5):709-712. [CrossRef]
19. Zhao J, Frøkjaer JB, Drewes AM, Ejskjaer N. Upper gastrointestinal sensory-motor dysfunction in diabetes mellitus. *World J Gastroenterol*. 2006;12(18):2846-2857. [CrossRef]
20. Hüppe D, Tegenthoff M, Faig J, et al. Esophageal dysfunction in diabetes mellitus: is there a relation to clinical manifestation of neuropathy? *Clin Investig*. 1992;70(9):740-747. [CrossRef]
21. Ertekin C, Seçil Y, Yüceyar N, Aydoğdu I. Oropharyngeal dysphagia in polymyositis/dermatomyositis. *Clin Neurol Neurosurg*. 2004;107(1):32-37. [CrossRef]
22. Ertekin C, Yüceyar N, Aydoğdu I, Karasoy H. Electrophysiological evaluation of oropharyngeal swallowing in myotonic dystrophy. *J Neurol Neurosurg Psychiatry*. 2001;70(3):363-371. [CrossRef]
23. Kimura J. Polyneuropathies and mononeuropathies multiplex. In: Kimura J, ed. *Electrodiagnosis in Diseases of Nerve and Muscle*. 4th ed. New York: Oxford University Press; 2013:658-755.
24. Raff MC, Sangalang V, Asbury AK. Ischemic mononeuropathy multiplex associated with diabetes mellitus. *Arch Neurol*. 1968;18(5):487-499. [CrossRef]
25. Said G, Goulon-Goeau C, Lacroix C, Moulonguet A. Nerve biopsy findings in different patterns of proximal diabetic neuropathy. *Ann Neurol*. 1994;35(5):559-569. [CrossRef]