RESEARCH ARTICLE

# Significance of Blink Reflex as a Neurophysiological Marker of Diabetic Peripheral Neuropathy

Sulaf E. Izzat[1*], Ghassan T. Saeed[2]

[1]Department of Physiology, College of Medicine, Baghdad University, Baghdad, Iraq
[2]Department of Medicine, College of Medicine, Baghdad University, Baghdad, Iraq

*Received: 07th June, 2023; Revised: 10th June, 2023; Accepted: 19th June, 2023; Available Online: 25th June, 2023*

## ABSTRACT

**Background:** The cranial neuropathies incidence is higher in diabetic patients in comparison to healthy people. The III and VII cranial nerves are commonly affected, but trigeminal, glossopharyngeal, and vagus nerves are also affected. The blink reflex is a measure of the cranial and CNS conduction pathways.

**Method:** The study included a group of 60 diabetic patients compared with 60 healthy individuals (non-diabetic) without any pain, paresthesia, or weakness in either limb.

**Objective:** This research aims to assess the significance of the blink reflex in the early detection of cranial neuropathy in diabetic patients, as well as to compare the blink reflex abnormalities in diabetic patients with HbA1c, length of DM, and sural nerve amplitude.

**Results:** A significant statistical difference between the cases and control was for (R.1) latency, (I.R.2) latency, (C.R.2) latency, (I.R.2) duration, and (C.R.2) duration with a *p-value* <0.001. No statically significant correlation was found between the duration of diabetes mellitus and the blink reflex parameters. Regarding HbA1c, a significant positive association with (I.R.2) latency and (C.R.2) latency was noted (r = 0.3, *p-value* <0.001), and also a strong negative correlation association was found with (I.R.2) duration and (C.R.2) duration (*p-value* <0.001). Sural nerve amplitude correlated negatively with blink reflex latencies and positively with blink reflex duration

**Conclusion**: The blink reflex test is an effective tool for diagnosing cranial neuropathy in individuals with diabetes without clinical symptoms or proof of CNS damage.

**Keywords:** Blink reflex, Diabetes mellitus, Diabetic neuropathy.

International Journal of Drug Delivery Technology (2023); DOI: 10.25258/ijddt.13.2.13

**How to cite this article:** Izzat SE, Saeed GT. Significance of Blink Reflex as a Neurophysiological Marker of Diabetic Peripheral Neuropathy. International Journal of Drug Delivery Technology. 2023;13(2):538-541.

**Source of support:** Nil.

**Conflict of interest:** None

## INTRODUCTION

Diabetes mellitus is a group of metabolic, polygenic syndromes characterized by hyperglycemia caused by insulin deficiency or resistance.[1] Diabetic peripheral neuropathy (DPN) is a major outcome of T2DM.[2] Neuropathy is a descriptor for a spectrum of clinical and subclinical symptoms with varying clinical histories, anatomical distributions, and perhaps underlying pathogenetic mechanisms.[3] Distal symmetrical sensorimotor polyneuropathy DPN is prevalent, frequently chronic, and frequently progressive. It is believed that chronic, sensorimotor, length-dependent, symmetrical, polyneuropathy is the most prevalent form of DPN.[4] Electro diagnostic studies are important for estimating peripheral neuropathy, and nerves are compared bilaterally to determine if a significant asymmetry exists.[5] It is frequently assumed that the occurrence of cranial neuropathies in diabetic patients is greater than in the general population. The oculomotor and facial nerves are typically afflicted, although the trigeminal, glossopharyngeal, and vagus nerves are affected less frequently. The blink reflex is an objective measure of the CNS and cranial nerves conduction routes.[6] Few investigations focused on the central nervous system and cranial nerves in previous electrophysiological research. So, early injury to the central nervous system in diabetic individuals is more likely to be overlooked and misdiagnosed.[7] Lesions of the trigeminal nerve influence the efferent nerve of the reflex arc and cause absence or delay of both the initial ipsilateral and late bilateral reflex responses to supraorbital nerve stimulation on the affected side, whereas lesions of the facial nerve influence the efferent limb of the reflex arcs. Regardless of whether side of the supraorbital nerve is stimulated, the late reflex response on the side of the lesion is changed, whereas the late reflex response on the side opposite the lesion is intact.[8] Unilateral medullary lesion reveals a normal R1 and contralateral R2 with an absent or

*Author for Correspondence: solaf.Emad1208e@comed.uobaghdad.edu.iq

delayed ipsilateral R2 when stimulating the affected side, but stimulating the unaffected side results in normal ipsilateral R1 and R2 potentials with an absent or delayed contralateral R2.[9] Pontine lesions result in unilateral or bilateral R1 prolonged; however, R2 may be affected or intact, based upon whether or not delayed reflex pathways are obstructed as they pass via the pons along the trigeminal spinal cord.[8] Generalized polyneuropathy may generate blink trigeminal reflex abnormalities.[10]

## METHODOLOGY

### Patients and Methods

This research included a group of 60 patients with T2DM: 12 females and 48 males in the age range of 30 to 75 years served study group. The mean glycosylated hemoglobin value was 9.4 ± 2.3.

Another 60 healthy individuals (non-diabetic) without any pain, paresthesia, or weakness in either limb. The mean glycosylated hemoglobin value was 5.8 ± 0.3% served as a control group.

This study is conducted at the neurophysiology unit in Ghazi Al-Hariri Hospital in Baghdad during the period from the first of November 2021 to February 2022. This included 120 patients who attended the neurophysiology unit after a referral from the Neurology Department.

Patients having cranial nerve lesions, a history of stroke, receiving drugs recognized as potentially causing neuropathy and other diseases related to polyneuropathy were excluded.

### Medical History and Examination

At the beginning of patient reception, a brief medical history is obtained. It includes questions to collect information on specific socio-demographic variables (age and gender), smoking, disease duration, the history of DM with specified details (the type of DM, and type of management), and clinical characteristics (burning pain, numbness, paresthesia, and dry skin).

The clinical examination was conducted in accordance with a recognized procedure, which included examination of muscle atrophy, muscular weakness, deep tendon reflexes, the light touch sensation, pinprick, and sensation of position. The vibration sensation was evaluated using a tuning fork with a frequency of 128 hertz.[11]

### Electrophysiological Tests

Nerve conduction studies were done using a Dantec Natus electromyography device (KEYPOINT.NET Software v. 2.40) surface recording electrodes were used. Studies were conducted in a warm room, with extremity skin temperature between 36 and 37°C, at the side where nerve conduction study was done.

Blink reflex analysis will be performed for them, including latencies of (R1, ipsilateral R2, and contralateral R2) and durations of (ipsilateral R2 and contralateral R2).

Nerve conduction studies of the limbs will be performed for both upper and lower limb, including (Distal motor latency, Motor, and sensory conduction velocity, latency, and amplitude).

### Statistical Analysis

Using the Shapiro test and histogram, the distribution of the data was examined for normality. Depending primarily on whether the distribution was normal or skewed, continuous variables were reported as means standard deviations (SD) or medians with interquartile ranges (IQRs). Categorical variables were reported as percentages. Using the Welch two-sample t-test, the means of two groups were compared. As applicable, the difference between categorical variables was investigated using the 2 test or Fisher's exact test. The correlation analysis used Pearson's correlation analysis. The risk of diabetic neuropathy was evaluated using univariate logistic regression analysis. *p-values* 0.05 were deemed statistically significant. R software and related statistical packages were used for data administration and statistical analysis (R version 4.1.3, R Foundation for Statistical Computing, Vienna, Austria).

## RESULTS

The research involved a group of 60 patients with type 2 DM: 12 females and 48 males aged 30–75 years (mean: 50 ± 10.2 years). The average duration of DM was 1–20 years (mean: 6.8 ± 4.2 years) served as a study group.

The mean glycosylated hemoglobin value was 9.4 ± 2.3% (normal: 4.2–6.4).

Another 60 healthy individuals (non-diabetic) the mean age was 47 ± 16.3 years without any pain, paresthesia, or weakness in either limb. The mean glycosylated hemoglobin value was 5.8 ± 0.3% served as a control group.

Table 1 shows the baseline characteristics of the cases and control groups. A statistically significant difference between the cases and control was found regarding blood HbA1c level and for all blink reflex parameters (R1 latency, IR2 latency, CR2 latency, IR2 duration, CR2 duration) with a *p-value* $< 0.001$.

Parameters of the blink reflex were correlated with age, BMI, duration of DM, and glycosylated hemoglobin. (Table 2). No statically significant correlation was found between the duration of diabetes mellitus and the blink reflex parameters. Regarding HbA1c, a significant positive association with I.R.2 latency and CR2 latency was noted ($r = 0.3$, *p-value* $<0.001$), and also, a negative correlation that is statistically significant was found with IR2 duration and CR2 duration (*p-value* $< 0.001$). Negative associations were found between the sural nerve amplitude and blink reflex latencies and positive associations with blink reflex duration

## DISCUSSION

R1 and R2 are the two most prominent components of the blink reflex waveform (including IR2 and CR2). R1 has an initial phase. Nerve impulses are transmitted via the trigeminal nerve branch to the trigeminal sensory nucleus of the pons, then to the ipsilateral nerve nucleus via adjacent interneurons, and finally to the facial nerve. There are only one to three interneurons involved in the process.[12] IR2 and CR2 are late, multiphase waves. The blink reflex pathway involves both peripheral and central nerves (Trigeminal, and Facial nerves) (Pons, and Medulla oblongata). By evaluating the parameters

**Table 1:** Clinical data of the study participants

| *Characteristics* | *Diabetes cases N = 60* | *Control N = 60* | *p-value* |
|---|---|---|---|
| Age, years | 50 ± 10.2 | 47 ± 16.3 | 0.2 |
| Gender | | | |
| Male | 48 (80%) | 46 (78%) | 0.8 |
| Female | 12 (20%) | 14 (22%) | |
| Smoking | 20 (33%) | 12 (20%) | 0.3 |
| BMI, kg/m$^2$ | 25.5 ± 4.0 | 22 ± 4.2 | 0.04 |
| DM duration, year | 6.8 ± 4.2 | | |
| HbA1C (%) | 9.4 ± 2.3 | 5.8 ± 0.3 | <0.001 |
| Blink Reflex parameters | | | |
| R.1 latency, ms | 12.1 ± 1.9 | 11.4 ± 0.7 | 0.011 |
| I.R.2 latency, ms | 42.7 ± 5.7 | 35.1 ± 4.3 | <0.001 |
| C.R.2 latency, ms | 42 ± 6.2 | 35.0 ± 4.2 | <0.001 |
| I.R.2 duration, ms | 24.8 ± 8.6 | 36.5 ± 3.1 | <0.001 |
| C.R.2 duration, ms | 25.4 ± 8.7 | 37.4 ± 2.6 | <0.001 |

[1]Mean ± SD; n (%)
[2]Welch Two Sample t-test; Pearson's Chi-squared test; Fisher's exact test.
Abbreviations:I.R.1: ipsilateral R1; I.R.2: ipsilateral R.2; C.R.2: contralateral R2; BMI: body mass index; HbA1c: hemoglobin A1c

of the bilateral blink reflex, the extent of this pathway's damage can be determined (including peripheral and central nerves).

We compared the characteristics of the blink reflexes of the two groups. Patients with type 2 diabetes reported greater latencies of the blink reflex compared to healthy individuals. Our findings revealed that R1 characteristics change significantly between the diabetic and control groups, except with the findings of Kazem and Behzad[13] and Y. Lian-hong[14], and in contrast to the findings of Guney *et al.* (2008), who observed no difference between diabetes patients and controls. It is demonstrated that certain thick fibers perish prior to the onset of neuropathy. This idea may explain the delayed R.1, R2I, and R2C latencies seen in our investigation across all diabetes patients with or without polyneuropathy.[10]

In addition, R2 durations (ipsilateral and contralateral) of diabetic patients were shorter than those of normal individuals. There are multisynaptic links between the reflex arc of R2 and the intermediate neurons of the reticular structure, which are subject to several variables such as thalamic and brain injuries, and mental state.[15] Additionally, the reduction of ipsilateral R2 and contralateral R2 durations suggests a reduction in the number of interneurons linked with multisynaptic reflex activity and excitability.[7] In individuals with T2DM, in addition to the latency of the blink reflex, the length of R2 might represent the severity of lesions of the central nervous system, including the brainstem, thalamus, and brain. This was similar to Li Xiao *et al.* 2021, who discovered that R2 durations (ipsilateral and contralateral) of diabetic patients were shorter than those of normal participants.[7]

In this study, we evaluated the affecting factors of the blink reflex in DM patients, including duration of DM, body mass index, HbA1c, and peripheral neuropathy. We noticed that R2 latency and R2 duration are useful indicators of blink reflex abnormalities. This study demonstrated a negative correlation between BMI and latencies of the blink reflex (including R1 latency, ipsilateral and contralateral and R2 latency). This means blink reflex is more aberrant the lower the body mass index. This finding indicates that patients with poorly controlled T2DM have a low body mass index.[14]

**Table 2:** Correlation analysis of blink reflex with age, BMI, duration of DM, HbA1C, and sural nerve amplitude

| | | *Age* | *BMI* | *Duration* | *HbA1c* | *Sural amplitude* |
|---|---|---|---|---|---|---|
| R.1 latency | r[1] | 0.2 | - 0.2 | 0.01 | 0.1 | - 0.2 |
| | *p-value*[2] | 0.02 | 0.1 | 0.9 | 0.3 | 0.1 |
| I.R.2 latency | r[1] | 0.3 | - 0.1 | 0.5 | 0.3 | - 0.3 |
| | *p-value*[2] | <0.001 | 0.4 | 0.6 | <0.001 | 0.02 |
| C.R,2 latency | r[1] | 0.3 | - 0.08 | 0.4 | 0.3 | - 0.23 |
| | *p-value*[2] | <0.001 | 0.5 | 0.7 | <0.001 | 0.07 |
| I.R.2 duration | r[1] | 0.03 | -0.1 | -0.1 | - 0.3 | 0.3 |
| | *p-value*[2] | 0.6 | 0.4 | 0.2 | <0.001 | 0.01 |
| C.R.2 duration | r[1] | - 0.01 | - 0.05 | - 0.2 | - 0.4 | 0.3 |
| | *p-value*[2] | 0.8 | 0.6 | 0.1 | <0.001 | 0.009 |

[1]Pearson's correlation coefficient
[2]Pearson's product-moment correlation

The length of DM is not linked with the blink reflex latency. These results inconsistent with those published by Elkholy *et al.*[16] and those reported by Kazem and Behzad,[12] who discovered a stronger association for R1 latency. We also discovered that the amplitude of the sural nerve was inversely associated with blink reflex latencies (including R1 latency, ipsilateral and contralateral R2 latencies). Accordingly, the abnormality of the blink reflex increases as amplitude decreases. The dorsal sural nerve is utilized to identify polyneuropathy in its early stages. As the most distant sensory nerve of the foot, the dorsal sural nerve may be damaged by early or subclinical peripheral neuropathy.[17]

## CONCLUSIONS

The blink reflex parameters (including R1 latency, and ipsilateral and contralateral R.2 latencies and durations) could assist in the evaluation of cranial nerve and CNS damage in T2DM patients.

## REFERENCES

1. A. kahdem A, A. DyabAllawi A, Z. Nada S, M. Turki K. Neutrophil gelatinase associated lipocalin (NGAL) in early detection of nephropathy in type 2 diabetic Iraqi patients. J Fac Med. 2017;59(1):74–8.
2. Saber HJ, Daoud AS. Knowledge and practice about the foot care and the prevalence of the neuropathy among a sample of type 2 diabetic patients in Erbil, Iraq. Journal of family medicine and primary care. 2018 Sep;7(5):967.
3. The Validity of Different F Wave Parameters in the Diagnosis of Diabetic Axonal Polyneuropathy Zaineb A. Yaqoub1 MBChB,

Hussein G. Kaddori2 PhD, Farqad B. Hamdan2 PhD
4. Dyck PJ, Albers JW, Andersen H, Arezzo JC, Biessels GJ, Bril V, Feldman EL, Litchy WJ, O'Brien PC, Russell JW, Toronto Expert Panel on Diabetic Neuropathy. Diabetic polyneuropathies: update on research definition, diagnostic criteria and estimation of severity. Diabetes/metabolism research and reviews. 2011 Oct;27(7):620-8.
5. M. Hussein L, H. Ali S, H. Mohammed N. Electrophysiological evaluation of Guillain–Barre syndrome subtypes in childhood. J Fac Med. 2017;59(1):60–4.
6. Sinnreich M, Taylor BV, Dyck PJ. Diabetic neuropathies: classification, clinical features, and pathophysiological basis. The neurologist. 2005 Mar 1;11(2):63-79.
7. Xiao L, Zou K, Zhou D, Ouyang G, Liu S, Luo J. Changes of Blink Reflex in Type 2 Diabetes Mellitus. Journal of Diabetes Research. 2021 Mar 15; 2021.
8. Nazliel Bİ, Yetkin I, Irkec C, Kocer B. Blink reflex abnormalities in diabetes mellitus. Diabetes/metabolism research and reviews. 2001 Sep;17(5):396-400.
9. Preston DC, Shapiro BE. Electromyography and Neuromuscular Disorders E-Book: Clinical-Electrophysiologic-Ultrasound Correlations. Elsevier Health Sciences; 2020 Mar 20.
10. Guney F, Demir O, Gonen MS. Blink reflex alterations in diabetic patients with or without polyneuropathy. International Journal of Neuroscience. 2008 Jan 1;118(9):1287-98.
11. Tesfaye S, Boulton AJ, Dyck PJ, *et al.* Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. Diabetes Care. 2010; 33(10):2285-2293.
12. Guang and T. Xiaofu, "Blink reflex and its clinical application," Chinese Journal of Physical Medicine and Rehabilitation, vol. 23, no. 2, pp. 50-51, 2001.
13. S. S. Kazem and D. Behzad, "Role of blink reflex in diagnosis of subclinical cranial neuropathy in diabetic mellitus type ii," American Journal of Physical Medicine & Rehabilitation, vol. 85, no. 5, pp. 449–452, 2006.
14. Y. Lai, C. Huang, W. Chiu *et al.*, "The role of blink reflex r1 latency as an electrophysiological marker in diabetic distal symmetrical polyneuropathy," Clinical Neurophysiology, vol. 131, no. 1, pp. 34–39, 2020.
15. Schicatano EJ. The effects of attention on the trigeminal blink reflex. Perceptual and Motor Skills. 2016 Apr;122(2):444-51.
16. S. H. Elkholy, H. M. Hosny, N. M. Shalaby, R. A. el-Hadidy, N. T. Abd el-Rahim, and M. M. Mohamed, "Blink reflex in type 2 diabetes mellitus," Clinical Neurophysiology, vol. 31, no. 6, pp. 552–555, 2014.
17. Metwally NA, Elkabeer AM. Clinical utility of facial and dorsal sural nerve conduction studies in patients with type ii diabetes mellitus. Aamj. 2014 jan;12(1).