Cukurova Medical Journal

Araştırma Makalesi / Research Article

# Evaluation of Blink Reflex in Patients with Steatosis

## Steatozlu Hastalarda Blink Refleksin Değerlendirilmesi

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*Cukurova Medical Journal 2015;40(4):714-722.*

### ABSTRACT

**Purpose:** The blink reflex (BR) is a useful electrodiagnostic method for evaluating neuropathies. The aim of our study was to investigate the role of the BR in the early diagnosis of neuropathy in simple steatosis.

**Material and Methods:** A total of 86 subjects were enrolled in this study: 56 patients (29 female, 27 male) with simple steatosis and 30 healthy controls (17 female, 13 male). After the electrical stimulation of the supraorbital nerve, two responses in the orbicularis oculi muscle occur, the early ipsilateral response and the late bilateral response latencies, which were recorded.

**Results:** The triglyceride levels and lipid accumulation products were higher in the patients with steatosis than in the controls. When compared to the control group, the patient group had early right ipsilateral latency, late right ipsilateral latency, late right contralateral latency, early left ipsilateral latency, late left ipsilateral latency, and late left contralateral latency.

**Conclusion:** There is a slowdown of the BR in the steatosis stage; therefore, by performing the BR, neuropathy can be detected at an early stage in patients with steatosis.

**Key words:** Blink reflex, neuropathy, steatosis, non-alcoholic fatty liver disease, hypertriglyceridemia

### ÖZET

**Amaç:** Blink refleks (BR) nöropatileri değerlendirmek için kullanılan yararlı bir elektrodiagnostik yöntemdir. Biz bu çalışmada basit steatozda nöropatinin erken tanısında BR'in rolünü incelemeyi amaçladık.

**Materyal ve Metod:** Çalışmaya basit steatozlu 56 hasta (29 kadın, 27 erkek) ve 30 sağlıklı kontrol (17 kadın, 13 erkek) olmak üzere toplam 86 kişi dahil edildi. Supraorbital sinirin elektriksel uyarımından sonra orbikularis okuli kasında ortaya çıkan iki cevap, erken ipsilateral cevap ve geç bilateral cevap gecikme zamanları kaydedildi.

**Bulgular:** Trigliserid düzeyi ve lipid akümülasyon skoru steatozlu hastalarda kontrol grubundan daha yüksekti. Kontrol grubuyla karşılaştırıldığında hasta grubunda erken sağ ipsilateral gecikme, geç sağ ipsilateral gecikme, geç sağ kontralateral gecikme, erken sol ipsilateral gecikme, geç sol ipsilateral gecikme ve geç sol kontralateral gecikme zamanı uzundu.

**Sonuç:** Steatoz aşamasında BR'de yavaşlama vardır. Steatozlu hastalarda BR ölçülerek nöropati gelişimi erken aşamada tespit edilebilir.

**Anahtar kelimeler:** Blink refleks, nöropati, steatoz, non-alkolik yağlı karaciğer, hipertrigliseridemi

## INTRODUCTION

Peripheral neuropathies have a wide variety of symptoms, such as paresthesia or hyperesthesia of the extremities, loss of sensation, muscle weakness, atrophy, and autonomic symptoms. An accurate diagnosis of peripheral neuropathy can require electrodiagnostic investigations, such as nerve conduction studies and electromyography (EMG). Furthermore, many conditions can lead to peripheral neuropathy, including hyperglycemia, insulin resistance, dyslipidemia, and oxidative stress[1,2].

Hyperglycemia, insulin resistance, dyslipidemia, and oxidative stress may cause steatosis[3], and non-alcoholic fatty liver disease (NAFLD) includes a spectrum of liver histopathologies, from simple steatosis to non-alcoholic steatohepatitis (NASH)[4]. Simple steatosis has a relatively favorable clinical course, while NASH can progress to cirrhosis and hepatocellular carcinoma[5]. NASH is common in patients with obesity, diabetes and metabolic syndrome[6,7].

The eye-blink is a self-generated process or spontaneous reflex that protects the eye. The blink reflex (BR) constitutes a bilateral electromyographic reaction of the orbicularis oculi muscle in response to unilateral electrical stimulation of the supraorbital nerve, which is a branch of the trigeminal nerve[8]. In this study, the right and left supraorbital nerves were stimulated electrically with bipolar surface electrodes according to the method described by Kimura[9]. The stimulation of the supraorbital nerve revealed two reflex responses with early R1 and late R2 components[10,11]. Therefore, the BR is an easy and non-invasive technique that can provide information on peripheral and central neurological functions[9], and as such, the BR is a good electrodiagnostic method for evaluating neuropathies[9,12]. Thus, we can detect silent extra-axial lesions, like polyneuropathies, using this technique.

The etiology of steatosis and neuropathy are very similar; therefore, patients with steatosis may be remarkably accompanied by neuropathy in high numbers. The aim of our study was to investigate the role of BR in the early diagnosis of neuropathy in simple steatosis with neuropathy.

## MATERIAL and METHODS

This study was carried out in the Internal Medicine Department of the Faculty of Medicine at Recep Tayyip Erdogan University, from September until December of 2012. This study was performed according to the guidelines of the Helsinki Declaration, was approved by the local ethics committees, and informed consent from each participant was obtained (approval numbers: 2012/127). A total of 56 patients, 29 female and 27 male, were included in the patient group, which received a diagnosis of grade 1 or 2 simple steatosis according to the ultrasonographic (USG) evaluations. The study excluded patients with a history of neuropathy, neurologic disorders, diabetes, $B_{12}$ deficiency, thyroid disease, chronic renal failure, pregnancy, acute or chronic infection, the use of drugs that might cause steatosis and hyperglycemia, hypertension or pre-hypertension (systolic blood pressure 135–139 mmHg, diastolic blood pressure 85–89 mmHg), alcohol consumption, and any other known chronic disease. All of the participants (patients and control group) without brainstem lesions, such as multiple sclerosis, tumors, or strokes in the pons and medulla, were diagnosed by a neurological specialist.

Elevated levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transferase, and alkaline phosphatase were considered to be “other liver diseases” and excluded from the study. Healthy subjects who did not have any known diseases and normal USG findings were selected for the control group (17 females and 13 males). All of the patients underwent a 75 gr oral glucose tolerance test

(OGTT), and the patients were excluded from diabetes based on those results. An insulin resistance score, Homeostasis Model Assessment + Insulin Resistance (HOMA+IR), was computed using the following formula: HOMA-IR = fasting plasma glucose (FPG) (mmol/L) × fasting serum insulin (mU/mL)/22.5. The cut-off value was 2.7 for the HOMA-IR[13].

In order to measure the waist circumference (WC) accurately, the weight and height were measured using standard procedures, and the WC was measured midway between the lower rib margin and iliac crest, as recommended by the World Health Organization. The Body Mass Index (BMI) was calculated as the weight/height$^2$ (kg/m$^2$), with overweight defined as a BMI of 25–29.9 kg/m$^2$, and severe obesity defined as a BMI ≥ 35 kg/m$^2$.

The lipid accumulation product (LAP) for men = (WC [cm] – 65) × (triglycerides [TG] [mmol/L]), while the LAP for women = (WC [cm] – 58) × (TG [mmol/L])[14].

**Measures of Laboratory Tests**

The biochemical parameters were measured after a 12-h fast, and all blood samples were collected into tubes and centrifuged at 4500 rpm for 10 min, then the serums were stored at −30°C. The biochemical tests were performed using the photometric assays of the Abbott Architect C16000 analyzer (Abbott Diagnostics, USA); while the thyroid stimulating hormone and vitamin $B_{12}$ tests were performed using the Chemiluminescent Microparticle Immunoassay (CMIA) method of the Abbott Architect I 2000 immunology analyzer (Abbott Diagnostics, USA).

The HBsAg, anti-HCV, and anti-HIV were tested with the Roche Cobas E 601 microelisa device (Roche Diagnostics, England). Finally, the insulin levels were measured using the CMIA (Abbott, Architect system, USA).

**Ultrasonography**

Although the gold standard test for diagnosing steatosis is a liver biopsy, the most appropriate approach is a noninvasive method, such as USG[15]. Therefore, USGs of the liver were performed using a standard technique by the same radiologist, and hepatic steatosis was quantified using a method very similar to that recently formalized by Hamaguchi et al.[16].

Hepatic steatosis was diagnosed by a characteristic liver echo pattern showing diffuse hyperechogenicity of the liver relative to the right kidney. The patients were divided into three groups according to the USG appearance of hepatosteatosis: mild (grade 1), moderate (grade 2), and severe (grade 3) fatty liver. In grade 1, the echogenicity was increased slightly, with normal visualization of the diaphragm and intrahepatic vessel borders. Grade 2 (moderate) fatty infiltration was established when the echogenicity was increased moderately, with slightly impaired visualization of the diaphragm or intrahepatic vessels. In grade 3 (severe) fatty infiltration, the echogenicity was increased markedly, with poor visualization of the diaphragm, intrahepatic vessels, and posterior portion of the right lobe.

**Blink Reflex Test**

The design of this study was created from a similar model in a previous study[17]. The electrophysiological studies were performed with a Dantec Keypoint EMG machine (Natus Medical, Inc., San Carlos, California, USA), and the impedance level was kept below 5 Kohms. The intensity of the stimulus was three times greater than the first R2 threshold and 0.2 ms in duration; four stimuli were applied to each side, every 10 seconds, and the results were averaged.

For the BR recording, the patients and control subjects were supine on a bed in a warm room with slightly closed eyes. The left and right supraorbital nerves were stimulated percutaneously with bipolar surface electrodes placed above the eyebrow, over the site where the

supraorbital nerve emerges from the skull. The reflex responses were recorded using two surface electrodes placed on the cheekbone above the orbicularis oculi muscle, in line with the pupil in a forward gaze to record the muscle response. The reference electrode was placed on the lateral surface of the nose, and the ground electrode was placed on the arm at an electrically inactive site.

The amplitude of a blink EMG rarely exceeds a few hundred microvolts, so recording conditions should facilitate the current flow from the skin surface to the electrodes. Therefore, to reduce the impedance between the skin and electrode, makeup and dead skin cells should be removed from the skin and an electrode gel spread in a thin layer at the recording site. The electrical stimulation of the supraorbital nerve produces two responses in the orbicularis oculi muscle: the early ipsilateral “R1” and late bilateral “R2” responses. The EMG signals were amplified with a frequency response between 20 Hz and 3 kHz, which allowed the accurate analyses of short latency responses, and there was no auditory or visual prepulse stimulation.

**Statistics**

The data were analyzed using SPSS for Windows (ver. 13.1; SPSS, Chicago, IL, USA), and all of the results were analyzed by applying the Kolmogorov Smirnov test for the determination of the normal and non-normal data distributions. The statistical significance of the differences in all of the parameters between the steatosis and control groups were analyzed using independent sample t-tests for normal distribution parameters, such as age, AST, blood urea nitrogen (BUN), creatinine, and high density lipoprotein (HDL), and Mann-Whitney U tests for the non-normal distribution parameters, such as WC, BMI, ALT, total cholesterol (TC), TG, low density lipoprotein (LDL), FPG, LAP, insulin, and HOMA-IR.

The BR findings in the two groups were compared using the Mann–Whitney U test, and the relationship between the variables was analyzed with the Spearman correlation. Stepwise multivariate (MVA) logistic regression analyses were also performed, and the results are given as odds ratios (OR), with a 95% confidence interval (CI). The differences were considered to be significant at $p < 0.05$.

## RESULTS

In the steatosis group, the TG was 190 ± 89 mg/dL, LAP was 77.0 ± 38.6, and HOMA-IR was 2.6 ± 0.6, while in the control group the TG was 92 ± 39 mg/dL, LAP was 32.3 ± 16.1, and HOMA-IR was 2.0 ± 0.3. The TG level ($p < 0.001$), LAP ($p < 0.001$), and HOMA-IR ($p < 0.001$) were higher in the patients with steatosis than in the controls. Additionally, the FPG ($p < 0.001$), TC ($p < 0.001$), and LDL ($p < 0.001$) were significantly higher in the steatosis group. The demographic characteristics and the results of the biochemical parameters of the patients are shown in table 1.

Early right ipsilateral latency (RR1) ($p < 0.05$), late right ipsilateral latency (RR2i) ($p < 0.001$), late right contralateral latency (RR2c) ($p < 0.001$), early left ipsilateral latency (LR1) ($p < 0.05$), late left ipsilateral latency (LR2i) ($p < 0.001$), and late left contralateral latency (LR2c) ($p < 0.001$) were significantly higher in the patients with steatosis than in the controls. The EMG findings are shown in table 2.

Using the Spearman correlation analysis of the BR parameters, there was positive correlation among the RR1 with the RR2i ($r = 0.273$, $p = 0.001$), LR2i ($r = 0.303$, $p < 0.001$), and age ($r = 0.307$, $p = 0.004$). There was also positive correlation among the RR2i with the RR2c ($r = 0.812$, $p < 0.001$), LR1 ($r = 0.297$, $p = 0.004$), LR2i ($r = 0.812$, $p < 0.001$), and LR2c ($r = 0.781$, $p < 0.001$). Additionally, there was positive correlation among the RR2c with the LR1 ($r = 0.271$, $p = 0.012$), LR2i ($r = 0.769$, $p < 0.001$), LR2c ($r = 0.926$, $p < 0.001$), WC ($r = 0.218$, $p = 0.044$), BMI ($r = 0.261$, $p = 0.015$), and glucose ($r = 0.314$, $p = 0.003$); and there was positive correlation among the LR1 with the LR2c ($r = 0.237$, $p = 0.028$) and

glucose (r = 0.284, p = 0.008). There was also positive correlation between the LR2i and the LR2c (r = 0.741, p < 0.001); and there was positive correlation among the LR2c with the WC (r = 0.264, p = 0.014), BMI (r = 0.271, p = 0.011), LDL (r = 0.217, p = 0.044), and glucose (r = 0.282, p = 0.009).

An MVA of the BR findings was performed for all of the parameters. Glucose (OR 0.026, 95% CI 0.005-0.047, $p < 0.05$) is an independent risk factor for late RR1; and glucose (OR 0.095, 95% CI 0.028-0.161, $p < 0.05$) is an independent risk factor for late RR2c. Additionally, glucose (OR 0.034, 95% CI 0.013-0.056, $p < 0.05$) and creatinine (OR -1.79, 95% CI -3.47- -0.112, $p < 0.05$) are independent risk factors for late LR1. Also, glucose (OR 0.080, 95% CI 0.016-0.143, $p < 0.05$) is an independent risk factor for late LR2c. The results are shown in table 3. The level of glucose was also found to be a strong predictor of late BR. In addition, the MVA showed that glucose (OR 0.296, 95% CI 0.136-0.430, p < 0.001) and LAP (OR 0.413, 95% CI 0.215-0.499, p < 0.001) are independent risk factors for steatosis, and the results are shown in table 3.

**Table 1. The main characteristics and laboratory parameters of the two groups.**

| Characteristics | | Patients (n=56) | Controls (n=30) | P values |
|---|---|---|---|---|
| Sex (M/F) | | 27/29 | 13/17 | 0.419 |
| Age (years) | | 43±10 | 39±10 | 0.132 |
| Waist Circumference (cm) | M | 99.1±5.4 | 96.9±8.3 | 0.399 |
| | F | 96.3±8.5 | 87.6±5.2 | 0.001 |
| BMI (kg/m$^2$) | | 31.2±3.6 | 28.6±3.1 | 0.001 |
| FPG (mg/dL) | | 99±9 | 91±6 | 0.001 |
| AST (IU/L) | | 21±6 | 18±4 | 0.023 |
| ALT (IU/L) | | 29±14 | 17±6 | 0.001 |
| BUN (mg/dL) | | 29±10 | 29±9 | 0.875 |
| Creatinin (mg/dL) | | 0.74±0.1 | 0.79±0.1 | 0.070 |
| TC (mg/dL) | | 212 ± 37 | 170 ± 34 | 0.001 |
| TG (mg/dL) | | 190 ± 89 | 92 ± 39 | 0.001 |
| LDL (mg/dL) | | 133 ± 32 | 105 ± 28 | 0.001 |
| HDL (mg/dL) | | 41 ± 9 | 45 ± 9 | 0.045 |
| Insulin (µIU/mL) | | 10.7 ± 2.4 | 9.2 ±1.3 | 0.001 |
| HOMA-IR | | 2.6 ± 0.6 | 2.0 ± 0.3 | 0.001 |
| LAP | | 77.0±38.6 | 32.3±16.1 | 0.001 |

**Abbreviations:** ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, Body mass index; BUN, blood urea nitrogen; F, Female; FPG, fasting plasma glucose; HDL, High density lipoprotein. LDL, Low density lipoprotein; M, Male; TC, Total cholesterol; TG, Triglycerides.

**Table 2. EMG findings of the steatosis and control groups.**

| Characteristic | Patients | Control | P values |
|---|---|---|---|
| **RR1 (ms)** | 11.4±1.0 | 11.0±1.0 | 0.015 |
| **RR2i (ms)** | 34.8±3.2 | 31.7±1.7 | 0.001 |
| **RR2c (ms)** | 35.2±3.1 | 32.7±2.0 | 0.001 |
| **LR1 (ms)** | 11.6±1.0 | 11.2±0.8 | 0.027 |
| **LR2i (ms)** | 35.0±2.9 | 32.3±1.7 | 0.001 |
| **LR2c (ms)** | 35.5±2.8 | 33.1±2.1 | 0.001 |

**Abbreviations:** RR1, Early right ipsilateral response; RR2i, Late right ipsilateral response; RR2c, Late right contralateral response; LR1, Early left ipsilateral response; LR2i, Late left ipsilateral response; LR2c, Late left contralateral response.

**Table 3. Multivariate (stepwise) logistic regression analysis of factors related to BR findings.**

| Dependent | Independent | OR (95%Cl) | p values |
|---|---|---|---|
| RR1 | glucose | 0.026 (0.005-0.047) | < 0.05 |
| RR2i | N.S. | | |
| RR2c | glucose | 0.095 (0.028-0.161) | < 0.05 |
| LR1 | glucose | 0.034 (0.013-0.056) | < 0.05 |
| | Creatinine | -1.79 (-3.47- -0.112) | < 0.05 |
| LR2i | N.S. | | |
| LR2c | glucose | 0.080 (0.016-0.143) | < 0.05 |
| Steatosis | glucose | 0.296 (0.136-0.430) | < 0.001 |
| | LAP | 0.413 (0.215-0.499) | < 0.001 |

N.S. not-significant; OR, odds ratio.

## DISCUSSION

Nerve conduction is one of the most frequently used tests for the early detection of damage resulting from hyperglycemic and hyperlipidemic complications. Both steatosis and neuropathy are associated with hyperglycemia and hyperlipidemia; therefore, patients with steatosis determined neuropathy present a very common pattern. The major findings of our study were significant associations between increases in the early (R1) and late blink reflex latency (R2), glucose, and hypertriglyceridemia, which may be attributed to a disorder in the peripheral nerves and steatosis. According to the MVA in the current study, glucose was strongly associated with late BR parameters; therefore, glucose may significantly contribute to the formation of polyneuropathy, while LAP and glucose may strongly subscribe to the formation of steatosis. As a result of increased glucose, the risks of steatosis and polyneuropathy may be elevated, and the LAP may be an important conducive contributor to the formation of steatosis rather than neuropathy.

The hallmark of NAFLD is the accumulation of TG in the cytoplasm of hepatocytes[18,19], and while the accumulation of TG might lead to NAFLD, the generation to free radicals from cytokines and inflammatory mediators might lead to liver damage. The LAP, which is a good marker for steatosis, was significantly high in the patient group[15];

therefore, high TG levels and LAPs might be associated with steatosis and late BR. Obese patients frequently have increased chronic inflammation, insulin resistance, hyperglycemia, and hypertriglyceridemia, and their end products: reactive oxygen species. These can lead to steatosis and neuropathy[20,21,22]. In this study, the WC, FPG, HOMA-IR index, and TG in the patients with steatosis were markedly higher, which might explain steatosis with the later BR.

Hyperglycemia leading to neuropathy has several mechanisms that generate ROS, the polyol pathway and increased advanced glycation end-products (AGE), which can lead to nerve damage[23,24,25]. Dyslipidemia leads to neuropathy by inducing oxidative stress in root ganglia sensory neurons[22,26,27,28], and the contributions of both hyperglycemia and hyperlipidemia to neuropathy development and the late BR, as compared to the control group, might result from a synergistic effect. Interestingly, our MVA results showed that the serum glucose levels are a strong predictive marker, whereas the TG is not a forecast marker. Insulin resistance and dyslipidemia are intertwined processes that are associated with obesity and lipid deposition. Furthermore, released free fatty acids strongly inhibit endothelial nitric oxide synthesis and vasodilation, leading to microvascular ischemia. These processes contribute to obesity, steatosis, insulin resistance, and neuropathy[29,30,31].

According to our results, the early and late phases of the BR were obviously later in steatosis patients, when compared to the control group. In diabetics, cranial nerves III, V, and VII are commonly affected[32,33], and these three nerves control ocular movements. Cranial nerve III (the oculomotor nerve) is the motor nerve for ocular movement, while cranial nerve V (the trigeminal nerve) carries superficial sensation and forms the afferent pathway of the corneal reflex. The reflex eyelid closure is carried out by the motor branches of cranial nerve VII, which form the efferent pathway[34,35,36]. In the current study, steatosis patients showed that these nerves were affected in a fashion similar to that seen in diabetic and metabolic syndrome patients. The later BR in the steatosis patients demonstrates the development of neuropathy and may be used as a screening test.

**Limitations of Study**

The current study was primarily a pilot study, and thus, had certain limitations. First of all, the number of subjects in our study might have been insufficient to represent the general population, and further studies are needed. Additionally, we did not evaluate any other electrophysiological measurements for neuropathy, such as the nerve conduction in the lower and upper extremities.

## CONCLUSION

According to the results of the study, the BR was found to be delayed in the patients with steatosis, and in those patients, by performing the BR, the involvement of cranial nerves V and VII can be demonstrated. Both steatosis and neuropathy are caused by the same mechanisms as hypertriglyceridemia, hyperglycemia, and oxidative stress; therefore, neuropathy can be detected at an early stage by performing the BR in steatosis, which is a simple and uncomplicated test.

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Geliş tarihi/Received on : 07.03.2015
Kabul tarihi/Accepted on: 14.04.2015