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Prospective Study

Diabetic Neuropathy Results in Vasomotor Dysfunction of Medium Sized Peripheral Arteries

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Abstract

BACKGROUND

The effect of sympathetic nervous system on peripheral arteries is that vasoconstriction occurs when smooth muscle cells in the walls of blood vessels contract, which leads to narrowing of arteries and reduction of the blood flow

AIM

The purpose of this study is to compare the sympathetic vasomotor activation of the brachial arteries in healthy subjects and painful diabetic neuropathy patients; and therefore, to assess whether there is a significant vasomotor dysfunction of medium sized arteries in diabetic neuropathy.

METHODS

The study included 41 diabetic neuropathy patients and 41 healthy controls. Baseline diameter and flow rate of the brachial arteries are measured. Then, using a bipolar stimulus electrode, we administered a 10 mA, 1 Hz electrical stimulus to the median nerve at the wrist level for 5 s. The brachial artery's diameter and blood flow rates were remeasured after the stimulation.

RESULTS

In the control group, the median flow rate was assessed to be 70.0 mL/min prior to stimulation and 35.0 mL/min after stimulation, with a statistically significant drop ($p < 0.001$) which is consistent with the sympathetic nervous system functioning (vasoconstriction). In diabetic neuropathy group, median flow rate before the stimulation was 35.0 mL/min. After stimulation, the median flow rate was 77.0 mL/min; in other words, no significant drop of the flow rate was detected. In the control group, the median brachial artery diameter, which was 3.6 mm prior to stimulation, decreased to 3.4 mm after stimulation, and this drop was also statistically significant ($P = 0.046$). In diabetic neuropathy group, the median brachial artery diameter increased from 3.4 mm to 3.6 mm following nerve stimulation. Once again, no narrowing was observed.

CONCLUSION

Our research suggests that diabetic neuropathy results in significant vasomotor dysfunction of medium sized peripheral arteries. Physiological vasoconstriction in response to sympathetic activation is impaired in diabetic neuropathy.

INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder that affects millions of people worldwide [1]. One of the most common complications associated with diabetes mellitus is distal symmetrical peripheral neuropathy, which affects the peripheral nerves and can result in variety of symptoms, including pain, paraesthesia, numbness, tingling, discomfort, and sensations of burning or cold *etc.* Diabetic neuropathy with painful symptoms, also known as painful diabetic neuropathy (PDN), is particularly debilitating form of the condition.

There are several factors associated with PDN, which have been extensively studied in scientific literature. One of the main factors associated with PDN is hyperglycaemia, or dysregulation of blood sugar levels. Chronic hyperglycaemia may harm the nerves

through variety of mechanisms, including oxidative stress, inflammation, and advanced glycation end products (AGEs) [2]. Additionally, hyperglycaemia can impair the microcirculation of the nerves, leading to ischemia and further nerve damage [3]. Other factors associated with PDN include dyslipidaemia, which results in nerve damage through similar mechanisms as hyperglycaemia [4]; chronic inflammation, which can contribute to nerve damage and sensitization of pain pathways [5]; and genetic factors, which may predispose individuals to develop PDN [6].

In patients with diabetic neuropathy, autonomic nervous system dysfunctions have also been observed. Signs and symptoms related to cardiovascular, sudomotor, gastrointestinal and thermoregulatory systems are frequently reported [7]. Cardiovascular autonomic neuropathy and sympathetic failure as orthostatic hypotension secondary to diabetes mellitus can be diagnosed with multiple autonomous tests today [8]. As to a report, sympathetic skin response (SSR) amplitudes were significantly lower in diabetics than in the controls [9]. Additionally, SSR test is suggested to be a sensitive indicator of autonomic dysfunction in diabetes [10]. All this data indicates that sympathetic nervous system dysfunction is frequently complicated with PDN.

The sympathetic nervous system (SNS) plays crucial role in regulating blood flow to peripheral vascular structures [11]. The effect of the system on peripheral arteries is that vasoconstriction occurs when smooth muscle cells in the walls of blood vessels contract, which leads to narrowing of arteries and reduction of the blood flow [12]. On the other hand, peripheral vasodilator response of extremities is not mediated with parasympathetic nervous system but by the local nitrergic mechanisms [13]. The SNS induces vasoconstriction through the release of norepinephrine from sympathetic nerve terminals, which binds to alpha-adrenergic receptors on smooth muscle cells. Activation of alpha-adrenergic receptors triggers the opening of calcium channels in smooth muscles, vessel wall contraction, and arterial vasoconstriction [14]

There are several tests that can be used to diagnose autonomic dysfunction in diabetic neuropathy. Heart rate variability (HRV) test, Tilt table test, Valsalva Ratio,

Quantitative sudomotor axon reflex testing (QSART) and Sympathetic Skin Response (SSR) are such of them [15].

Doppler ultrasound combined with low-dose electrical stimulation of a peripheral nerve with "electroneuromyography, evoked potential" (ENMG/EP) system to evaluate the autonomous system functioning can also be used as an alternative test model to these procedures. This test specifically measures the sympathetic vasomotor response to peripheric neural activation and already defined by us in active and healthy subjects in elsewhere. As to our previous study, it is demonstrated that after electrical stimulation of the median nerve, blood flow and diameter of brachialis artery is decreased in healthy subjects [16]. We before also designated that the sympathetic fibres in the median nerve contribute on brachial artery's vasomotor functioning [17]. Hence, the purpose of this study is to compare the sympathetic vasomotor activation of the brachial artery in response to median nerve activation in healthy subjects and PDN patients; and therefore, to assess whether there is a significant vasomotor dysfunction in PDN patients or not. In this study, our main purpose is to find out diabetic neuropathies impact on medium sized arteries. [

MATERIALS AND METHODS

Subjects: This experimental study is conducted at VM Medicalpark Ankara Hospital in 2022. The studies adhered to the most recent version of the Declaration of Helsinki, and the No. 2 Clinical Research Ethics Committee of Ankara City Hospital allowed the operations. The ethics committee at the Ankara City Hospital is the most approved ethics body within the Turkish Ministry of Health. Due to the nature and significance of our research, we deemed it necessary to get ethical approval from the Ankara city hospital. (Approval number: E3-22-1307) Each participant and/or guardian gave informed consent (s).

Our study included 41 diabetic individuals with painful neuropathy and 41 healthy controls. Diabetic patients are randomly chosen from the follow up patients of Endocrinology Clinic who have neuropathic symptoms. These subjects were diagnosed

as Diabetes Mellitus due to abnormal fasting and postprandial glucose levels and high HbA1c values. Diabetic neuropathy was diagnosed by interrogation of neuropathic symptoms, neurological examination, and electrophysiological methods performed by experienced Neurologist.In both group, participants with heart disease, essential hypertension, and carpal tunnel syndrome; and in the control group, diabetes mellitus and polyneuropathy from any cause were eliminated. The ratio of females to males was maintained in both the patient and control groups. For each patient in the patient group, age-matched controls were assigned to the control group.

Experimental Design: Similar methods to "sensory nerve conduction studies" are composed. Such non-invasive methods are routinely applied for the diagnosis of peripheral sensorial neuropathies in electrophysiology laboratories. There was a four-hour period before the experiment in which smoking, consumptions of coffee, tea and alcohol, and exercise are discouraged. At the beginning of the experiment, individuals sat quietly for 10 minutes with their right forearms supinated. Their blood pressure, heart rate, and body temperature were then measured, and individuals with abnormal results (hypertension, fever, tachycardia *etc.*) were taken out of the research again. So, the normal hemodynamic parameters required for the experiment are maintained. After a 10-minute break, individuals were told to stay as still as possible as they were given an oral briefing on what to expect at each stage of the test. In this study, we used a 9-Hz linear probe of a General Electric (GE) LOQIC P9 Doppler device to measure the baseline diameter and flow rates of the right brachial artery 2 cm above the antecubital fossa. These measurements were taken by a radiologist who has worked in the field of doppler for eight years. Doppler sensor was stationary during the experiment so that continuous data could be collected. Then, using the bipolar stimulus electrode of Nihon Kohden MEB-9400A EMG/EP system, we administered a 10 mA (milliampere), 1 Hz (Hertz) electrical stimulus orthodromically (that is, through the physiological transmitting way of the sensorial nerve fibres) to the median nerve at the wrist level for 5 s. The artery's diameter and blood flow rates were remeasured immediately after the sixth stimulation.

Statistical analysis: The variables were investigated using analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to determine whether they are normally distributed. Descriptive analyses were presented using frequencies and percentages for the categorical variables, mean ± SD for normally distributed variables and median (25P-75P) for the non-normally distributed variables. Student-t Test or Mann Whitney U test was used for the comparison of continuous variables in independent groups, and Paired-Sample T-test or Wilcoxon test was used in dependent groups.

A p-value of less than 0.05 was considered to show a statistically significant result. Statistical analyses were performed using the SPSS (20.0. Armonk, NY).

In addition to sociodemographic data such as age and gender, the diameters and flow rates of the brachial arteries were recorded as final values before and after electrical stimulation in patients with diabetic neuropathy and control groups.

RESULTS

The study included 82 participants, 41 of whom had PDN and 41 of whom were in the control group. The mean age of the 82 participants was 59.7±11.2 years, and 54 (65.9%) of the participants were female (min. 38 - max. 84)

Table 1 displays the flow measurements of the brachial artery before and after stimulation of the median nerve in PDN and control groups. In the control group, the median flow rate was assessed to be 70.0 mL/min prior to stimulation (Min:23 mL/min and Max:204 mL/min) and 35.0 mL/min after stimulation (Min:7 mL/min and Max:103 mL/min), with a statistically significant drop detected with stimulation ($p< 0.001$) (Table 1). Before the nerve stimulation, median flow rate in the PDN group was 35.0 mL/min (Min:8 mL/min and Max:103 mL/min). After stimulation, the median flow rate was 77.0 mL/min (Min:23 mL/min and Max:201 mL/min); in other words, no significant drop of the flow rate was detected (besides, significant higher values are observed).

In the control group, the median brachial artery diameter, which was 3.6 mm prior to stimulation (Min: 2.8 mm and Max: 4.4mm), decreased to 3.4 mm after stimulation (Min: 2.3 mm and Max: 4.7mm), and this drop was statistically significant (P = 0.046). (Table2). In PDN group, the median brachial artery diameter increased from 3.4 mm (Min: 2.1mm and Max: 5.1mm) to 3.6 mm following nerve stimulation (Min: 2.9 mm and Max: 4.6mm). Once again, no narrowing was observed.

Table 3 summarizes the changes in brachial artery flow and diameter measurements induced by stimulation of the median nerve. In diabetic neuropathy group, the brachial artery output increased by a median of 39.0 mL/min, whereas it decreased by a median of 34.0 mL/min in the control group ($p<0.001$). In PDN group, the average diameter increased by 0.2 mm, whereas the diameter decreased by 0.2 mm in the control group (P = 0.007). These variations were deemed statistically significant (Table3).

Tables 4 and 5 give the findings of the investigation undertaken to identify the effect of gender on the change in flow and diameter according to chronic illness status. In the presence of diabetic neuropathy, the change in flow between men and women was statistically substantially different (P = 0.004), but there was no statistically significant difference between the changes in flow between men and women in the control group (P = 0.137). Increases in circumference were observed to be statistically equivalent between both sexes in both the diabetic and control groups ($p>0.05$).

DISCUSSION

Our results indicate that medium sized arteries vasomotor responses are impaired in diabetic neuropathy.In peripheral diabetic neuropathy, initially the distal sensory and autonomic fibres are damaged [18]. Therefore, autonomic involvement with differing degrees is frequently complicated with diabetic distal painful neuropathy. Diabetic autonomic neuropathy (DAN) is a complication of diabetes that affects the autonomic nervous system, which controls the involuntary functions of the body such as heart rate, blood pressure and digestion. [19]. There are several tests used in the detection of DAN, including much more standardized cardiovascular reflex tests [20] and less

standardized quantitative sensory tests and sudomotor tests [19]. However, autonomic dysfunction measured by vasomotor response of medium sized arteries has not been reported in the literature.

Cardiovascular reflex tests are the most used tests for the diagnosis of DAN. These tests measure the heart rate and blood pressure responses to various stimuli such as deep breathing, standing up, and the Valsalva manoeuvre. Abnormal responses to these tests indicate dysfunction of the autonomic nervous system. The most widely used cardiovascular reflex tests are the heart rate response to deep breathing (HRDB), the heart rate response to standing (HRS), and the blood pressure response to standing (BPS). A reduction in HRDB, HRS or BPS is indicative of autonomic dysfunction [15, 19, 21].

Quantitative sensory tests measure the ability of a person to perceive changes in temperature, pressure, and vibration. These tests are useful for detecting early changes in peripheral autonomic nerve functioning. Abnormalities in these tests suggest damage to small sensory nerves, which is a common manifestation of DAN [20].

Sudomotor tests measure the function of the sweat glands, which are controlled by the sympathetic nervous system. These tests assess the ability of the sweat glands to produce sweat in response to a stimulus such as heat or electrical stimulation. Abnormal results in those suggest dysfunction of the autonomic nervous system [15, 21].

One of the most widely used tests for sudomotor function is the quantitative sudomotor axon reflex test (QSART), which measures the ability of the sweat glands to produce sweat in response to an electrical stimulus. Other sudomotor tests include the thermoregulatory sweat test (TST), which measures the ability of the body to regulate temperature, and the silicone impression method (SIM), which measures the density of sweat gland openings on the skin [21].

In diabetic neuropathy, peripheral arteries sympathetic vasomotor response is also impaired [22, 23]. However, laser doppler flowmetry utilized in these tests do not have a broad area of use in clinical practise to date. Additionally, they specifically measure the vasomotor alterations in smaller arteries and arterioles, and vasomotor response of the

medium sized arteries are left unanswered. In this work however, we examined the sympathetic vasomotor response of the brachial artery, which is one of the medium size peripheral arteries in human body. In our control subjects, both the diameter and flow rate of the brachial artery are decreased significantly following electrical stimulation of the median nerve, i.e., when peripheral sympathetic fibres are activated. The opposite is true for PDN patients; following the stimulation no significant vasoconstriction response was observed. This result suggests that painful neuropathy is frequently complicated with sympathetic nervous system dysfunction and impaired vasomotor tone of medium arteries. Figures 1 and 2 depict the Doppler parameters of healthy participants and diabetic neuropathy patients (figures 1, 2).

Our research is consistent with the observations that diabetic neuropathy results in sympathetic vasomotor dysfunction. Furthermore, the new non-invasive, cheap, and user-friendly technique that we offer is sensitive to this phenomenon in medium sized arteries. It also has a potential to be used as a tool for early detection of sympathetic dysfunction from other causes (amyloid neuropathy, Guillain Barre Syndrome, transverse myelitis *etc.*). The limitation of this study is that types and duration of diabetes mellitus were not taken into consideration and sub-group of patients were not formed. Further studies are required to make decisions on how vascular tone differs in subtypes.

In conclusion, our research suggests that diabetic neuropathy results in significant vasomotor dysfunction of medium sized peripheral arteries. Moreover, it is the first test that investigates DAN in medium arteries. Physiological vasoconstriction in response to sympathetic activation is impaired in painful diabetic neuropathy.

CONCLUSION

In conclusion, our research suggests that diabetic neuropathy results in significant vasomotor dysfunction of medium sized peripheral arteries. Moreover, it is the first test

that investigates DAN in medium arteries. Physiological vasoconstriction in response to sympathetic activation is impaired in painful diabetic neuropathy.

ARTICLE HIGHLIGHTS

Research background

When the smooth muscle cells lining the blood vessels contract in response to stimulation from the sympathetic nervous system, the result is vasoconstriction and a decrease in blood flow to the extremities.

Research motivation

Trying a different method in the detection of diabetic autonomic neuropathy that does not impair patient comfort

Research objectives

The goal of this research is to determine if there is a major vasomotor dysfunction of medium-sized arteries in diabetic neuropathy by comparing the sympathetic vasomotor activation of the brachial arteries in healthy people and painful diabetic neuropathy patients.

Research methods

For 5 s, we applied a 10 mA, 1 Hz electrical stimulus to the median nerve in the wrist using a bipolar stimulus electrode. After the stimulation, we remeasured the diameter of the brachial artery and the blood flow rates.

Research results

In the control group, the median flow rate was assessed to be 70.0 mL/min prior to stimulation and 35.0 mL/min after stimulation, with a statistically significant drop ($p < 0.001$) which is consistent with the sympathetic nervous system functioning (vasoconstriction). In diabetic neuropathy group, median flow rate before the

stimulation was 35.0 mL/min. After stimulation, the median flow rate was 77.0 mL/min; in other words, no significant drop of the flow rate was detected. In the control group, the median brachial artery diameter, which was 3.6 mm prior to stimulation, decreased to 3.4 mm after stimulation, and this drop was also statistically significant (P = 0.046). In diabetic neuropathy group, the median brachial artery diameter increased from 3.4 mm to 3.6 mm following nerve stimulation. Once again, no narrowing was observed.

Research conclusions

Our study shows that diabetic neuropathy causes medium-sized peripheral arteries to have a lot of trouble moving blood. In diabetic neuropathy, the body can't close off the blood vessels normally when the sympathetic nervous system is activated.

Research perspectives

We have a perspective to try a new method and use it in the clinic in the future.

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