ORIGINAL ARTICLE

Comparison of Neutrophyl Lymphocyte Ratio and Nerve Conduction Study Between Male Type 2 Diabetes Mellitus With or Without Peripheral Neuropathy Complication

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ABSTRACT

Background: Diabetic Peripheral Neuropathy (DPN) is one of the type 2 Diabetes Melitus (T2DM) complication, which may lead to diabetic foot ulcer and lower extremity amputation. Inflammation plays a role in the pathogenesis of this type 2 DM complication. Recent studies showed neutrophyl-lymphocyte ratio (NLR) is a potential inflammation marker. Early screening for neuropathy is an important part of the medical rehabilitation management of this condition.

Material and methods: This study uses data analysis independent sample T-2 test with a significant ($p<0.05$). This study is a analytic observation cross-sectional study with type 2 diabetic male subjects, screened with Michigan Neuropathy Screening Instrument then divided into 2 groups, with DPN group (11 subjects) and without DPN group (7 subjects). This was followed with complete blood count laboratory testing (neutrophyl and lymphocyte level) and NCS to measure distal latency, amplitudo, and NCV of the tibial, peroneal, and sural nerve on both lower extremities.

Result: There were 18 subjects in this study. Independent T-2 test showed that there was no significant difference in neutrophils ($p=0.679$), lymphocytes ($p=0.127$), and NLR ($p=0.190$) in the DM group without or with neuropathy. NCS showed that there were significant differences on the amplitude of the three nerves peroneal ($p=0.003$), tibial ($p=0.017$), sural ($p=0.033$), also in NCV of peroneal ($p=0.001$) and tibial ($p=0.008$). There were no significant differences found on the three distal latency of peroneal ($p=0.074$), tibial ($p=0.151$), sural ($p=0.294$), and NCV of sural ($p=0.262$).

Conclusions: This study shows that there is no significant difference in NLR on both groups. There were significant differences in the amplitude of the three peroneal, tibial, and sural nerves and the conduction velocity of the peroneal and tibial nerves. However, there was no significant difference in the distal latency of the three peroneal, tibial, sural, and the NCV of the sural nerves.

Keywords: diabetes melitus, diabetic peripheral neuropathy, nerve conduction studies, neutrophyl-lymphocyte ratio, rehabilitation management.

ABSTRAK

Latar belakang: Diabetic Peripheral Neuropathy (DPN) merupakan salah satu komplikasi Diabetes Mellitus (T2DM) tipe 2 yang dapat menyebabkan ulkus kaki diabetik dan amputasi ekstremitas bawah. Inflamasi berperan dalam patogenesis komplikasi DM tipe 2 ini. Studi terbaru menunjukkan rasio neutrofil-limfosit (NLR) adalah penanda peradangan potensial. Skrining dini untuk neuropati adalah bagian penting dari manajemen rehabilitasi medis dari kondisi ini.

Metode: Studi ini menggunakan data analisis tes Independen Sampel T-2 dengan nilai ($p<0.05$) signifikan. Studi ini termasuk studi observasional analitik cross-sectional dengan subjek laki-laki diabetes tipe 2, diskrining dengan Instrumen Skrining Neuropati Michigan kemudian dibagi menjadi 2 kelompok, dengan kelompok DPN (11 subjek) dan kelompok tanpa DPN (7 subjek). Ini diikuti dengan pemeriksaan laboratorium hitung darah lengkap (tingkat neutrofil dan limfosit) dan NCS untuk mengukur distal latensi, amplitudo, dan kecepatan hantar saraf (KHS) saraf tibialis, saraf peroneal dan saraf sural pada kedua ekstremitas bawah.

Hasil: Terdapat 18 subjek dalam penelitian ini. Uji T-2 Independen menunjukkan bahwa tidak ada perbedaan bermakna pada neutrofil ($p=0.679$), limfosit ($p=0.127$), dan NLR ($p=0.190$) pada kelompok DM tanpa maupun dengan neuropati. NCS menunjukkan terdapat perbedaan yang signifikan pada amplitudo ketiga saraf peroneal ($p=0.003$), tibialis ($p=0.017$), dan sural ($p=0.033$) serta KHS peroneal ($p=0.001$) dan tibialis ($p=0.008$). Tidak terdapat perbedaan bermakna pada ketiga saraf distal latensi yaitu peroneal ($p=0.074$), tibialis ($p=0.151$), sural ($p=0.294$), dan KHS sural ($p=0.262$).

Kesimpulan: Studi ini menunjukkan bahwa tidak ada perbedaan NLR yang signifikan pada kedua kelompok. NCS menunjukkan terdapat perbedaan yang signifikan pada amplitudo ketiga saraf peroneal, tibialis, sural, serta KHS peroneal dan tibialis. Namun, tidak ada perbedaan yang signifikan dalam latensi distal dari tiga saraf peroneal, tibialis, sural dan KHS sural.

Kata kunci: diabetes melitus, manajemen rehabilitasi, neuropati perifer diabetik, rasio neutrofil-limfosit, studi konduksi saraf

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INTRODUCTION

Diabetes Mellitus (DM) is a chronic metabolic disturbance with an increasing number of prevalency worldwide. Type 2 DM is the most common occured with hyperglycemia as its character caused by insulin resistance and relative insulin deficiency.[1]

Diabetic peripheral neuropathy (DPN) is one of the most common chronic complications

of diabetes mellitus (DM).[2-3] Prevalence of neuropathy on diabetic patients is around 30-50%, with 50% DPN being asymptomatic.[1,3] DPN increase the risk of foot infection, foot ulcer, non traumatic amputation, long term disability, may affect quality of life and productivity. Peripheral neuropathy is also one of the three culprits causing fall on diabetic paients, aside from vestibular disturbance and diabetic retinopathy.[1,5,6]

DPN is a complex condition because the nerve fiber damaged varies among patients, which attacks sensory and motoric nerve fibers of different diameters thus the difficulty in DPN diagnosis and early screening. Diagnosing DPN depend on clinical examination, nerve conduction study, questionnaire, and biopsy. Recent years showed the rise of electrodiagnosis as a tool for early diagnosis of DPN. NCS examination may help in determinining location, type, and severity of the neuropathy. NCS is a sensitive, dependable, non invasive, and objective gold standard examination for peripheral neuropathy diagnosis.[4,7,8] Availability of NCS examination should consider. Its unavailability may hinder its role to be set as routine examination. This needs for the search of another indicator for prevention and early diagnosis of DPN.[6,9]

Subclinical inflammation has a role in type 2 DM progressitivity and chronic complication. Recent years also showed NLR as a potential new marker of chronic inflammation. Neutrophyl count will elevate and lymphocyte will decline in the condition of chronic inflammation.[6]

Previous study showed higher NLR of diabetic patients with complication, compared to study control.[10] NLR also found to be correlated with diabetic ulcer from another study.[11] Based on previous studies, this study will compare NLR and NCS of type 2 DM subjects with peripheral neuropathy and without peripheral neuropathy. The ethical feasibility has been approved by the Ethics Commission for basic science/clinical research at RSUD Dr. Soetomo Surabaya with ethical clearance number 1116/KEPK/IV/2019.

MATERIAL AND METHODS

This study is an analytic observation cross-sectional study comparing Neutrophyl-Lymphocyte Ratio and nerve conduction study datas done on Medical Rehabilitation Outpatient Clinic of Dr. Soetomo General Hospital from May 2019 to June 2019. Etchical clearance for this study approved by the Ethical Committee of Dr. Soetomo General Hospital.

Inclusion criterias were Type 2 Diabetes Mellitus male patient, 35-50 years old, body mass index of 23-29.9 kg/m2, willing to be study subject and follow the examination procedure. Exclusion criterias were history of lower extremity injury or surgery, neuromusculoskeletal disease of the lower extremity, diabetic ulcer of the foot, umor or malignancy. DPN was diagnosed by using Michigan Neuropathy Screening International (MNSI), positive diagnosis with questionnaire score >7 or clinical examination score >2.5. Nerve conduction study was done with Cadwell Sierra Wave (version 11.0.116) electrodiagnosis device to measure distal latency, amplitudo, and NCV on tibial, sural, and common preoneal nerve on both lower extremities.

STATISTIC ANALYSIS

Data analysis was done using SPSS 22.0, using an Independent Sample T-2 Test to compare NCS and NLR in male type 2 DM patients with and without complications of peripheral neuropathy.

RESULT

Target population of this study is type 2 DM male aged 35-50 years old. Study subject's characteristics in table 1 showed that the average of the age (p=0.616) and BMI (p=0.497) were not significantly different, but the years of DM (p=0.03) was significantly different with the mean years of DM subjects with neuropathy is longer than the one without neuropathy.

Statistical tests analysis using Independent Sample T-2 Test showed no significant difference of neutrophyl level (p=0.679), lymphocyte level (p=0.127), and neutrophyl-lymphosit ratio (p=0.127) on both groups as shown in Table 2 and Figure 1. The comparison of NCS values in the group without and with peripheral neuropathy examination in Table 3 showed that distal latency retardation of the three nerves on type 2 DM with DPN group compared to type 2 DM only group, but the difference was not statistcally significant on the three nerves distal latency of peroneal (p=0.074), tibial (p=0.151), sural (p=0.294) and also nerve conduction velocity (NCV) of sural (p=0.262).

Table 1. Subject Characteristics (Age, BMI, Years of DM)

	DM without Neuropathy (n=7)	DM with Neuropathy (n=11)	p-value
Age (tahun)	45.14 + 2.79	45.90 + 3.75	0.616
BMI (kg/m2)	26.46+2.16	25.67+2.70	0.497
Years of DM (years)	2 + 1.19	7.10 + 6.29	0.03

*Independent Sample T-2 Test, significant if p<0.05

Tabel 2. Comparison of Neutrophil, Lymphocyte, and Neutrophil to Lymphocyte Ratio in the Group Without and With Peripheral Neuropathy

	DM without Neuropathy (n=7)	DM with Neuropathy(n=11)	p-value
Neutrofil (x103/uL)	5.40 + 2.15	4.96 + 2.16	0.679
Limfosit (x103/uL)	1.99 + 0.75	2.69 + 0.96	0.127
Neutrophil Lymphocyte Ratio	3.34 + 2.59	1.88 + 0.59	0.190

*Independent Sample T-2 Test, significant if p<0,05

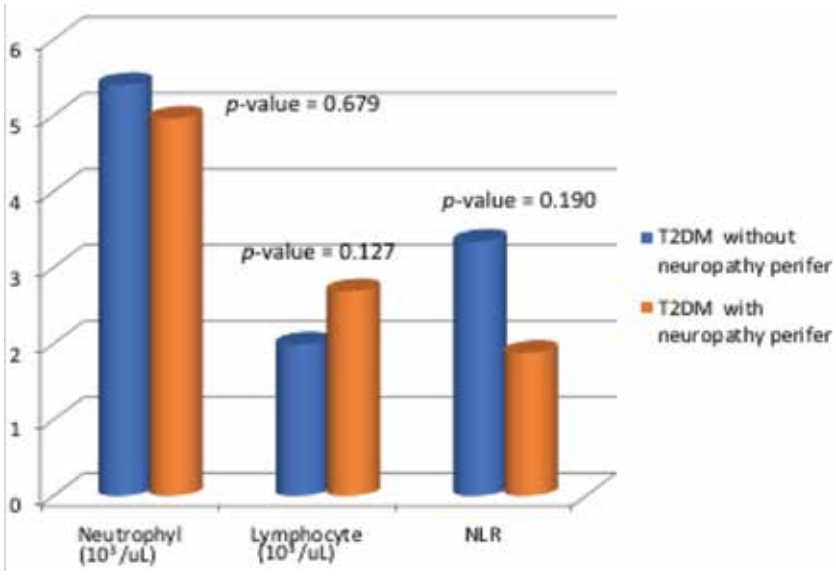

Figure 1. Comparison of Neutrophyl, Lymphocyte, and NLR

The amplitudes of the three nerves were significantly smaller on the type 2 DM with DPN group compared to type 2 DM only group of the three nerves peroneal (p=0.003), tibial (p=0.017), and sural (p=0.033) as shown in Table 3. The NCV were slower of the three nerves on type 2 DM with DPN group compared to type 2 DM only group, but only the peroneal (p=0.001) and tibial (p=0.008) nerve were statistically significant. There were no significant differences found.

Tabel 3. Nerve Conduction Studies Comparison

	DM without Neuropathy (n=7)	DM with Neuropathy (n=11)	p-value
Peroneal			
Distal latency (ms)	4.20 + 0.53	4.94 + 0.93	0.074
Amplitude (mV)	4.67 + 1.38	1.91 + 1.73	0.003*
NCV (m/s)	47.42 + 4.15	36.45 + 6.21	0.001*
Tibial			
Distal latency (ms)	4.21 + 0.97	4.91 + 0.89	0.151
Amplitude (mV)	11.78 + 4.14	6.11 + 4.52	0.017*
NCV (m/s)	44.14 + 3.02	36.45 + 6.28	0.008*
Sural			
Distal latency (ms)	3.11+ 0.16	6.43 + 10.48	0.294
Amplitudo (mV)	15.28 + 9.23	7.66 + 4.61	0.033*
NCV (m/s)	44.45 + 2.67	41.63 + 6.9	0.262

*Independent Sample T-2 Test, significant if p<0.05,
ms = milisecond, mV= miliVolt, m/s = meter per second.

DISCUSSION

Neutrophyl count and NLR were higher on the type 2 DM without neuropathy group compared to the group with neuropathy, while lymphocyte count was higher on the peripheral neuropathy group, but these differences were all not statistically different.

The increased neutrophil- lymphocyte ratio is related to the pathophysiological mechanism of endothelial dysfunction. The mechanism of the relationship of neutrophils in cardiovascular disease is mainly atherosclerosis from the early to the late phase, while the decrease in the number of lymphocytes is associated with progression. Atherosclerosis caused by apoptosis, on the other hand, increased neutrophils due to atherogenic processes, lipid mediation, necrosis and inflammation, secretion of chemokines and cytokines.[12]

Lipid profile imbalance, marked by HDL decrease, increase of LDL, c-reactive protein, proinflammatory cytokine, endotoxin, homocystein, and coagulation factors increase leading to endothel dysfunction with atherome plaque, other heart conditions, and neutrophyl lymphocyte ratio increase.[12] This fit with subject characteristics of this study of having hypertension, heart disease, as coexisting disease which may affect neutrophyl count, lymphocyte count, and neutrophyl–lymphocyte ratio.

NLR reflects both the lymphocyte and neutrophyl counts. The power of NLR as an inflamatory factor stem from both a reduction in the lymphocyte count and an increase in the neutrophyl count. The mean body mass index of the non neuropathic group was more than the neuropathy group in this study. This may affect the neutrophyl, lymphocyte count, and neutrophyl–lymphocyte ratio as stated by previous.[13] Tanaka et al showed that T lymphocytes were reduced in obese people and that lymphopenia appeared to be related to inflamation.[14]

NCS examination was done on the three lower extremity nerves, peroneal, tibial, and sural nerves. The examination was intended to measure the distal latency (the time gap from stimulation to response), amplitude, and NCV.

Table 3 shows prolonged distal latency, reduced amplitude and NCV of the nerves from the type 2 diabetic with neuropathy group compared to the type 2 diabetic only group, although the difference of distal latency was insignificant. These indicate myelin and axonal disturbance of the peroneal nerve in the peripheral neuropathic group. Duration of diabetes associated with low NCV and response amplitude. The presence of nephropathy, retinopathy, or a clinical diagnosis of neuropathy was associated with low nerve conduction velocity and amplitude.[15]

There were also marked differences of tibial nerve amplitude ($p=0.017$) and NCV ($p=0.008$) were significantly lower in the neuropathic group. The sural nerve examination showed only significant lower amplitude in the neuropathic group. The results showed that amplitudes were significantly affected in all motor as well as sensory nerves, while nerve conduction studies were not affected in the sural nerve. The results from this study concur with previous studie, research by Jin and Park showed that there are changes in nerve function in patients with peripheral neuropathy which are initially subclinical and can be detected by NCS examination. Diabetic peripheral neuropathy can

damage sensory, motor and autonomic nerves. Specifically, the symptoms of impaired function of the three nerves are due to damage of several different types and sizes.[16]

NCS is a valid method of clinical examination of the peripheral nerves. Previous NCS studies stated that it can be affected by multiple factors. These factors are divided into biologic factors (age, height, sex) and physical factors related to physical condition of the nerve and muscle, such as conditions caused by metabolic disease.[17] Other study, compare the parameters of NCS found that motor distal latency of both the nerves were statistically significantly different and higher in diabetics group. Results also show decreased amplitude and conduction velocities on both nerves in diabetic patients. All the parameters of NCS were found correlated with blood sugar levels in diabetics.[18]

STUDY LIMITATION

Limitations of this study were the small sample size and some confounding factors were not evaluated, such as the duration of diabetes mellitus, and also the consumption of the drugs.

CONCLUSION

This study showed that the nerve function of DPN patients is worse than the ones without eripheral neuropathy. There was no significant difference of NLR on both groups. There were significant differences in the amplitude of the three peroneal, tibial, and sural nerves and the conduction velocity of the peroneal and tibial nerves. However, there was no significant difference in the distal latency of the three peroneal, tibial sural nerves, and the NCV of the sural nerves. Nerve conduction study examination reveal axonal in motor in motor and sensory and dmyelinzation in motor nerves. Prolonged distal latency, decline of amplitude and Nerve Conduction Velocity on type 2 Dibetes Mellitus with or without peripheral neuropathy.

CREDIT STATEMENTS

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