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Analysis of determinant diabetic neuropathy symptom score factors in diabetes mellitus patients

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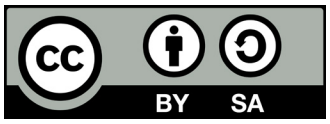

ABSTRACT

Background: Diabetes peripheral neuropathy (DPN) is a set of signs and symptoms of peripheral nervous system dysfunction in diabetes mellitus patients. Abdominal obesity is one of the main risk factors for DPN. Diabetic neuropathy symptom (DNS) is a reliable instrument with consistent results for the diagnosis of neuropathy.

Objective: This study aimed to determine the correlation of abdominal obesity with scores.

Methods: This research was a quantitative study with a cross-sectional approach. The sample of this study was 92 type 2 diabetes mellitus (T2DM) patients aged range 30-60 years who participated in the chronic disease management program (*Prolanis*) and the integrated healthcare center (*Posbindu*) for people in the area of three public health centers (*Puskesmas*) in Pekalongan Regency which purposively selected. Instruments used to measure DPN were DNS sheets, and abdominal obesity was measured by waist circumference using a midline. The bivariate analysis was performed using the Pearson correlation and linear regression tests.

Results: There was a correlation between abdominal obesity and DNS scores with a p value of 0.043 with a correlation coefficient of 0.212. The DNS score was influenced by age, gender, duration of diabetes, and body mass index by 13.4%.

Conclusion: There was a correlation between abdominal obesity and DNS scores. It indicated that the higher the value of abdominal obesity was, the higher DNS scores increased.

Latar Belakang: *Diabetes peripheral neuropati didefinisikan sebagai tanda gejala disfungsi sistem saraf perifer pada pasien diabetes melitus. Obesitas Abdominal adalah salah satu faktor risiko utama terjadinya DPN. Salah satu instrumen yang diandalkan dengan hasil konsisten untuk diagnosis neuropati adalah DNS merupakan instrumen yang dapat diandalkan dengan hasil yang konsisten untuk diagnosis neuropati.*

Tujuan: *Tujuan penelitian ini adalah untuk mengetahui korelasi obesitas abdominal dengan skor DNS.*

Metode: *Penelitian ini merupakan penelitian kuantitas dengan pendekatan cross-sectional. Sampel dalam penelitian ini sejumlah 92 orang usia antara 30 – 60 tahun, penderita Diabetes melitus (DM) tipe 2 peserta prolanis dan posyandu lansia di tiga wilayah puskesmas Kabupaten Pekalongan yang dipilih dengan teknik purposive sampling dengan kriteria inklusi mengalami gejala DNS ≥ 1. Instrumen yang digunakan untuk mengukur DPN adalah lembar DNS. Obesitas abdominal diukur dengan lingkar pinggang. Analisis bivariat menggunakan tes korelasi Pearson dan regresi linear.*

Hasil: *Terdapat korelasi antara obesitas abdominal dengan skor DNS dengan nilai p value sebesar 0.043 dengan koefisien korelasi 0.212. Skor DNS secara simultas diperngaruhi oleh usia, jenis kelamin, lama menderita diabetes dan indeks massa tubuh sebesar 13.4%.*

Kesimpulan: *Terdapat korelasi positif antara obesitas abdominal dengan skor DNS artinya semakin tinggi nilai obesitas abdominal semakin beresiko mengalami peningkatan skor DNS.*

INTRODUCTION

Type 2 diabetes mellitus is a metabolic syndrome with hyperglycemic characteristics due to decreased insulin secretion with reduced cellular response to insulin (insulin resistance). Elevated blood sugar levels in T2DM lead to the development of complications. The most common complication experienced by T2DM patients is microvascular disorders, one of which is DPN.[1] The DPN complications are the earliest microvascular complications suffered by T2DM patients that cause treatment difficulties, increase foot complications such as amputations, and reduce patient quality of life.[2]

Diabetes peripheral neuropathy is the riskiest complication of T2DM, affecting 50-70% of people with T2DM.[3,4] Diabetic patients commonly suffer from DPN due to chronic hyperglycemia and metabolic abnormalities such as the increase of polyols, for example, the development of advanced glycation end products (AGEs), and the rise in oxidative stress. Another mechanism of DPN in T2DM is the occurrence of cell damage as a result of the polyol pathway activation, production of reactive oxygen species (ROS), nitrogen, and AGEs, as well as their buildup, which can activate the inflammatory cascade, causing cell death and injury. Another cause of DPN in T2DM patients is the decrease in endothelial nitric oxide (NO) that causes an ischemic, a trigger of DPN.[5]

Diabetes peripheral neuropathy damages the somatic and autonomic nervous systems, resulting in symptoms such as sensory loss, numbness, tingling, burning sensation in the feet, and pain. Over time, these symptoms progress to more severe complications such as foot ulceration, gangrene, and amputation, which increase morbidity and mortality.[6] According to studies, patients with T2DM had a four times increased prevalence of amputations, where 25 - 90% of amputations are associated with a combination of DPN and infection in T2DM, a result of impaired peripheral arterial flow in DPN.[7]

Metabolic problems and insulin resistance are common in abdominal obesity. Numerous studies have demonstrated that obesity with abdominal fat distribution is a risk factor for T2DM.[8] Those studies demonstrate how adipokines and inflammatory markers are affected abnormally by adipose tissue. Leptin and adiponectin are adipokines suspected of causing metabolic problems. Resistin and Tumor Necrosis Factor Alpha (TNF-α), released by adipose tissue, are also believed to have a role in regulating insulin resistance. Visceral (intra-abdominal) fat is associated with insulin resistance by increasing fatty acids via a lipolytic mechanism that lowers insulin activity.[9] The development of metabolic disease and visceral to abdominal fat accumulation in adipose tissue are factors in diagnosing central obesity. A better criterion to gauge visceral and abdominal fat distribution is waist circumference.[10] Waist circumference is a quick and easy way to diagnose abdominal obesity and spot those who could become type 2 diabetes.[8]

Early diagnosis and management of DPN is essential as it may lower the prevalence of foot ulcers and amputations in various populations.[11] Effective foot care surveillance and education have been shown to reduce the incidence of infection and amputation by 50%.[12] The American diabetes association (ADA) recommends annual DPN screening in adults diagnosed with DM.[13] Consequently, it is crucial to pinpoint DNP risk factors. The demographic literature studies reveal that age, duration of DM, smoking habit, and metabolic syndrome, including obesity, are the risk factors for DPN.[14] One of the five metabolic syndrome components linked to T2DM is a major pathophysiologic factor of metabolic syndrome.[15] Studies reveal that abdominal obesity increases the risk of DPN.[16]

Diabetes peripheral neuropathy is a sensory nerve disorder. Its initial symptoms usually appear on the lower extremities sensory system, such as pain, tingling, and pricking sensations (paresthesia), negative symptoms such as numbness and pain whenever being touched (allodynia), and increased sensitivity to stimuli (hyperalgesia). As the disease progresses, the motor system symptoms start to appear in the form of weakness of the distal toes or ankles and calves that further cause balance disorders, falls, and numbness in the feet.[16]

The DNS is one of the screening instruments for neuropathy in diabetes. Several studies have pointed out a correlation between DNS and DPN.[17] The DNS instrument consists of questions about neuropathy symptoms such as instability in walking, burning sensation, tingling, pain, stabbing sensation, and numbness in the leg or foot. These symptoms are the manifestations of microvascular

disorders in DM affecting the nerve fibers starting from the longest; hence, it is called long-dependent diabetic polyneuropathy (LDDP).

Three preliminary studies at three health centers in Pekalongan Regency found that 8 out of 10 (80%) T2DM patients had waist circumference ≥ 94 cm with complaints of pain and tingling in the foot and leg areas. The symptoms felt by the patients were in line with the symptoms of DPN. This study would identify the correlation between DNS scores and abdominal obesity.

METHODS

Study design

Cross-sectional design methodology was used in this quantitative research.

Population and sampling

There were 92 subjects with type 2 diabetes, aged around 30-60 years, who took part in the *Prolanis* and *Posbindu* for people in the work area of three *Puskesmas* in Pekalongan Regency. The sampling of linear regression (multivariate) formula was used to determine the sample size, which was 5 to 10 times the number of parameters in the model; the number of variables in this study was seven, therefore the minimum sample was 70 respondents.[18] These participants were chosen by a purposive sampling technique with the inclusion criteria: T2DM patients who experienced more than one symptom of DNS, came to Posbindu or Prolanis, without any history of diabetic ulcers. Explanations about the study were performed before enrollment and the participants were independent to be involved in the study. All 92 respondents have signed their willingness to become respondents in written consent.

Data collection

Data was collected one-time using questionnaires and measurement techniques. The questionnaire consisted of a demographic data questionnaire containing questions about the initial name, age, gender, and length of time with DM. Age and disease duration were presented as numerical data, and gender in categorical data. Initial names are used to ensure data confidentiality and ensure the privacy of respondents. Another questionnaire used is to measure the DNS score. The questionnaire was used to identify the neuropathy symptoms. Interviews were conducted to identify DNS scores by asking the respondents about their symptoms, including unsteadiness in walking, burning sensation, tingling, pain, stabbing, and numbness in the foot or leg. Each 'yes' answer was counted as 1 point. The maximum score was four points where 0 points indicated no neuropathy, and 1-4 points indicated neuropathy.[19] A person was diagnosed with neuropathy with at least one symptom of DNS.[20] The instrument was valid in identifying the symptoms of neuropathy, according to the correlation score between DNS and nerve conduction studies (NCV), whose rho was 0.51.[19]

The other measurements were height and weight to obtain the respondent's Body Mass Index (BMI) score, and waist circumference, expressed in centimeters. Body mass index and waist circumference were presented as a total score or numerical data. The tool used to measure height is a stature meter with a length range of 0-200 cm with the OneMed®. The tool for measuring body weight uses OneMed® digital body scales EB-974 1pc series. The OneMed® medline tape measure 150 cm was used to measure waist circumference, as an indicator of abdominal obesity. The waist's midline was located above the upper lateral boundary of the iliac crest, and the circumference was measured during normal breathing.

Data analysis

The data analysis was performed with SPSS series 24 software. Univariate analysis presented demographic data of respondents including age, duration of DM, waist circumference, and DNS score. Bivariate analysis started by carrying out a normality test, using a skewness test. Afterward, a bivariate analysis was done to determine the correlation between DNS scores and abdominal obesity by applying the Pearson correlation test. To determine the contribution of factors other than waist circumference to DNS score, multivariate tests were conducted with linear regression tests.

Ethic

This study obtained ethical clearance from the Health Research Ethics Committee of the Faculty of Medicine, University of Muhammadiyah Surakarta, No. 3964/B.2/KUPK-FKUMS/I/2022.

RESULTS

The risk factors for DPN examined in this study included age, duration of DM, and gender. The total respondents were 92 people with T2DM who joined Prolanis and Posbindu, the majority of them were women (83.7%). The mean waist circumference was 92.92 cm, their age range was 56.92 years, and they had T2DM for 5.62 years on average. Table 1 presents the risk factors in this study.

Table 1. Respondent characteristics based on gender, age, history of DM, BMI, WC, and DNS

Variable	n (%)	Mean	Median	Std. deviation	Minimum-Maximum
Gender					
Male	15 (16.3)				
Female	77 (83.7)				
Age		56.92	58	7.54	36-77
Duration of DM		5.62	4	4.24	1-22
BMI		25.27	25.25	4.08	14.3-36.2
WC		92.93	92.5	8.58	63-115
DNS Score		2.7	3	0.82	1-4

DM: Diabetes Mellitus, BMI: Body Mass Index, WC: Waist Circumference, DNS: Diabetic Neuropathy Symptom

The respondents had an average length of time with DM of 5.62 years, with a minimum length of time with DM of 1 year and a maximum of 22 years. The average body mass index of respondents reached 25.27 with the highest BMI reaching 36.2. The waist circumference of the respondents ranged from 63-115 cm with an average of 91.93 cm with a considerable variation of 8.58 cm. The average DNS score ranged from 1 to 4, with 2.7 being the mean. The results of statistical test analysis proved a correlation between abdominal obesity and DNS score with a p-value of 0.043. It indicated that the higher the value of abdominal obesity was, the higher the DNS scores increased with a coefficient correlation of 0.212 or weak correlation (Table 2).

Table 2. The correlation between waist circumference and DNS Score

Variable	Mean±SD	Coefficient Correlation	p
Waist circumference	92.92±8.583	0.212	0.043*
DNS Score	2.59 ±0.841		

*Pearson correlation test (p<0.05), DNS: Diabetic Neuropathy Symptom

Other factors that are simultaneously associated with DNS are age, gender, duration of DM, and body mass index (p-value 0.028). Waist circumference with age, gender, duration of DM, and boy mass index were simultaneously associated with DNS Score by 13.4% (R square= 0.134 are shown in Table 3), the others were associated with other factors outside this study. Increasing 1 cm waist circumference increased 4.4% DNS Score, and increasing 1 BMI increased 3.2 DNS Score.

Table 3. Analysis of factors influencing DNS score

Variable	r	R Square	p-value
Effect of age, gender, duration of DM, BMI, WC on DNSS	0.366	0.134	0.028

BMI = Body Mass Index; WC = Waist Circumference; DNSS = Diabetic Neuropathy Symptom Score

DISCUSSION

As in this study, the average age was 56.92 years old, or in the early elderly category. Thus, this study showed that increasing age among T2DM patients leads to an increased risk of DPN. Age is one of the risk factors for DPN. The incidence of DPN in T2DM is significantly linked with age, the most prominent non-modifiable risk factor for DPN.[21] This study found that age was not partially related

to DNS, and modeling age reduced the risk of DNS by 1.3%. However, other studies proposed that the increasing age is associated with the prevalence of DPN.[12] Age as a risk of DPN is closely related to the degenerative process that causes decreased body function, including decreased pancreatic β-cell function in producing insulin as a trigger for glucose intolerance.[22] The aging process can also reduce mitochondrial activity in muscle cells by 35% so that it can increase muscle fat levels by 30% and ultimately increase the risk of insulin resistance.[23]

The other risk factor of DPN is gender, where women are more at risk of suffering from DPN. This study found that females were the majority of the respondents (83.7%), which makes gender a notable risk factor for DPN. Female respondents have a 14.3% risk of increasing DNS score. Research revealed that there were more female DPN sufferers than male ones.[23] Physically, women tend to be less active than men, and this raises the risk of suffering DPN.20 The decreasing estrogen and progesterone hormones during menopause can also bring possible effects to increase the risk of DPN. It has been shown that estrogen plays a central and peripheral role in the control of glucose homeostasis. In both human and animal models, estrogen insufficiency or defective estrogen signaling is linked to insulin resistance, disturbed metabolic balance, and the development of T2DM and obesity.[24]

The mean duration of suffering diabetes of the respondents was 5.62 years, as this study result who have long time suffering from T2DM adds another risk factor for DPN. The results showed that the DNS score increased by 2.3% for every length of time with DM increase. The risk factor of length of DM increased the risk of DNS by 1.39 times in patients diagnosed with DM for 1-5 years and by 4.5 times in patients with DM for more than 25 years. DM for more than 25 years. Research mentioned that suffering from T2DM ≥ 5 years was associated with the incidence of DPN.[2] Long-time suffering from T2DM can cause DPN since chronic hyperglycemia may cause endothelial damage to capillaries that are directly related to nerve structures and can cause DPN.[5] Chronic hyperglycemia can also increase AGEs, protein kinase-C (PKC), Interleukin-6 (IL-6) and TNF-α as risk factors for peripheral nervous system damage and can cause increased oxidative stress as a result of AGEs secretion which causes ischemia in peripheral organs.[25]

Abdominal obesity is associated with DPN. This present study portrayed the average waist circumference of respondents, which was 92.92 cm. It proves that abdominal obesity is a risk factor for DPN ($p<0.05$). The higher DNS scores increased with coefficient correlation by 0.212 or a weak relationship. The results showed that the DNS score increased by 4.4% for every increase in waist circumference and 3.2% for every one point of body mass index. Additional research has found a link between abdominal obesity and DPN.[26] Abdominal obesity is also a risk factor for DPN. Abdominal obesity can be associated with systemic inflammation and endothelial dysfunction that can cause DPN in T2DM. Adipose tissue can induce TNF-α, causing damage to the insulin receptor that leads to endothelial damage.[27] Visceral adipose tissue is a bioactive organ and a source of proinflammatory cytokines causing endothelial dysfunction and microvascular complications.[28] Abdominal obesity is associated with systemic inflammation and endothelial dysfunction that can lead to DPN in T2DM. Abdominal obesity can also increase leptin secretion as a cause of inflammation, increase oxidative stress, and decrease antioxidant capacity, which may lead to microvascular complications in T2DM.[29] Microvascular dysfunction in patients with T2DM is closely related to peripheral nerve dysfunction and poor circulation in the microcirculation, causing peripheral nerve damage.[3]

This present study highlighted the correlation between abdominal obesity and DNS scores. The studies have drawn a positive correlation between abdominal obesity and DPN.[26] Other factors associated with the Diabetic Neuropathy Symptom Score are age, gender, duration of DM, and body mass index. Waist circumference with age, gender, duration of DM, and boy mass index are simultaneously associated with DNS score by 13.4%. Abdominal obesity is also a risk factor for DPN that can be associated with insulin resistance. The insulin resistance represents low-grade inflammation, influences endothelial dysfunction and a microvascular complication.[15]

Diabetes peripheral neuropathy is a neurodegenerative disease starting with the dysfunction of the peripheral nervous system. Impaired sensory axons, axon autonomy, and

motor axons result from nerve dysfunction and cell death caused by oxidative stress and chronic inflammatory processes.[3]

Diabetes peripheral neuropathy is multifactorial. The main risk factors of DPN are age, body mass index, duration of diagnosed diabetes, hypertension, diabetic retinopathy, and smoking.[11] The speed of nerve delivery correlates positively to the length of the nerve, making the toes the first to experience decreasing sensation and loss of reflex compared to other organs. Tingling, burning, and prickling sensations are the predominant symptoms of small fibers damage, meanwhile, numbness is a sensory symptom of both large and small fibers.[20]

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CONCLUSION

This study found a positive correlation between abdominal obesity and DNS score. It indicates that the DNS score increased in proportion to the amount of abdominal fat. The age, gender, duration of T2DM, and body mass index are factors that simultaneously affect the Diabetic Neuropathy Symptom Score. Early detection of diabetic neuropathy is crucial to improve the quality of life of patients with T2DM.

CONFLICT OF INTEREST

The researchers affirm that there are no competing interests in the study's conduct.

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AUTHOR CONTRIBUTION

NA, FF and UBR designed the research and developed the theory. MGS and DF performed analytical calculations and data analysis. All authors discussed the results and contributed in writing the final manuscript.

LIST OF ABBREVIATION

DPN: Diabetes Peripheral Neuropathy; DNS: Diabetic Neuropathy Symptom; T2DM: Type 2 Diabetes Mellitus; AGEs: Advanced Glycation End Products;ROS: Reactive Oxygen Species; NO: Nitric Oxide; TNF-α: Tumor Necrosis Factor-α; ADA: American Diabetes Association; LDDP: Long-Dependent Diabetic Polyneuropathy; NCV: Nerve Conduction; BMI: Body Mass Index; PKC: Protein Kinase-C; IL-6: Interleukin-6

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