

**RELATIONSHIP OF HYPERTENSION AND THE SEVERITY OF NEUROPATHY SYMPTOMS IN TYPE II DIABETES MELLITUS PATIENTS AT SIDHI SAI MEDICAL CLINIC**

**I Putu Aris Govindha Putra<sup>1</sup>, Intan Lestari Putri<sup>2</sup>, I Wayan Artana<sup>3</sup>**  
Medical Doctor of Sidhi Sai Medical Clinic, Badung, Bali, Indonesia

**ABSTRACT**

Neuropathy is one of the chronic microvascular complication of diabetes mellitus disease that often occurs and causes a decrease in the quality of diabetes mellitus patient's life. Hypertension is a cardiovascular disease that can worsen and accelerate the emergence of neuropathy in diabetes mellitus. The purpose of this study is to see that hypertension is related to causes of the severity in diabetic neuropathy symptoms. Subject of this study were type 2 of diabetes mellitus patients with neuropathy who visited the Sidhi Sai Medical Clinic in February to July 2019, subject consisted of 50 people with type 2 diabetes mellitus with neuropathy. The test equipment used to determine presence of neuropathy was Diabetic Neuropathy Symptom Score (DNS) and to determine the severity of diabetic neuropathy symptom using Modified Neuropathy Disability Score (MNDS). The Statistical test used Chi-Square test with significance  $p < 0.05$ . The results showed that women and age over 55 years suffered a lot of neuropathy. Symptoms of severe neuropathy were dominant in samples with hypertension, but in the statistical test results showed that there was no a significant relationship with the severity of diabetic neuropathy symptoms ( $p = 0.260$ )

**KEYWORDS:** Type 2 diabetes mellitus, Hypertension, Diabetic Neuropathy

**INTRODUCTION**

Diabetes mellitus is a group of metabolic disease characterized by hyperglycemia that occurs due to abnormalities in insulin secretion, insulin action or both. In Rikesdas 2018, based on doctor diagnose, the prevalence of Diabetes Mellitus in Indonesia on  $\geq 15$  years old is about 2%, which increases 0,5% from 2013.

The classification according to ADA are: 1. Type 1 diabetes mellitus caused by autoimmune that damage the pancreatic beta cell, 2. Type 2 diabetes mellitus caused by the loss of insulin secretion due to insulin resistance, 3. Gestational diabetes mellitus is a diabetes that occurs during the 2nd and 3rd trimester of pregnancy, 4. Specific type of diabetes caused by another factors, such as : monogenic diabetes syndrome, pancreatic exocrine gland disease, the influence of drugs and chemicals.

In diabetes mellitus, there are acute and chronic complication. Acute complication is hypoglycemic coma and hyperglycemic (diabetic ketoacidosis and hyperglycemic hyperosmolar state), whereas for chronic complication can be divided into 2, those are macrovascular complication (coronary heart

disease, cerebrovascular disease and peripheral vascular disease) and microvascular complications (neuropathy, nephropathy, and retinopathy)

The occurrence of neuropathy can happen 40-50% after 10 years onset of the diabetes mellitus diagnose is confirmed. For type 1 diabetes mellitus seldom occurs when 5 years onset, whereas in type 2 diabetes mellitus can occur since patient is diagnosed to suffer diabetes mellitus or pre diabetes.

Neuropathy causes morbidity and decrease the quality of patient's life if it is not managed properly. Diabetic neuropathy can develop asymptomatic and undetectable, show symptoms and signs slowly, and can be a serious complication as well. The most common neuropathy in diabetes mellitus is a distal symmetric polyneuropathy (DSPN). The risk factor such as: duration of the diabetes, hyperglycemia, glycemic variability, prediabetic, age, hypertension, dyslipidemia, smoking, obesity, metabolic syndrome, insulin resistance, alcohol consumption, hypoinsulinemia, oxidative stressed, platelet activation, deficiency of vitamin D, genetic factor, lack of physical activity, growth factor depletion. Furthermore, there are some related factors such as level of HbA1c and Body Mass Index.

In order to identify the occurrence of neuropathy in diabetic mellitus patient easily and quickly, Diabetic Neuropathy Symptom (DNS) score can be applied.

The patients were asked some questions to know the score:

**Table 1 Diabetic Neuropathy Symptoms Score**

No	Questions	Positive	Negative
1	Symptoms of imbalance when walking	1	0
2	Feelings of burning, aches and pains in the legs and feet	1	0
3	Feeling like being punctured in the area of the legs and feet	1	0
4	Feeling numb in the legs and feet	1	0

One (1) is for positive result and zero (0) is for negative result. Range 1-4 point is identified as neuropathy, and 0 point is identified as not neuropathy.

In order to identify the severity level of neuropathy symptoms in diabetes, we can use Modified Neuropathy Disability Score (MNDS)

**Table 2. Modified NDS Score**

Symptoms: legs / lower legs	Yes	No
Burning sensation	2	0
Numb	2	0
Tingling sensation	2	0
Feeling of exhaustion	1	0
Cramps	1	0
Pain	1	0
Location		
Legs	2	
Lower legs	1	
Other parts	0	
Exacerbation		
Appears at night	2	
Appears at day and night	1	
Appears merely at day	0	
The patient wakes up from sleep because of these symptoms	1	0
Make symptoms worse		
Walking	2	
Standing up	1	
Sitting and laying	0	
Neuropathic symptom scores are 3-4 mild, 5-6, moderate and 7-10, severe	Total score	

Hypertension is one of the risk factors for neuropathy in diabetes mellitus patient, hypertension classification according to JNC 7 (Joint National Committee) can be divided into 4 categories among others normal, prehypertension, stage 1 hypertension, and stage 2 hypertension.

**Table 3. Classification of Hypertension in Adults**

The mechanism of neuropathy in diabetes is inseparable from hyperglycemic state that can activate polyol lane, AGEs lane (Advanced Glycation End Products), PKC (Protein Kinase C), and excessive release of oxidative stress and cytokines. Hyperglycemia in diabetic causes excessive activation of these lanes, where glucose is converted into sorbitol with aldose reductase enzyme followed by the oxidation of NADPH to NADP. The sorbitol is oxidized to be fructose by sorbitol dehydrogenase, followed by oxidation of NADP to NAD<sup>+</sup>. Aldose reductase enzyme bonds with glucose are so strong, leading to the occurrence of accumulation of sorbitol in intracellular which triggers the osmotic stress of nerve cell, the other thing that has to be concern is increasing of cofactor change such as NADPH and NAD<sup>+</sup>, decreasing of reduction and regeneration of glutathione. Decrease level of glutathione can be major cause of oxidative stress and related with the accumulation of toxic

substances, it can initiate the auto-oxidation of glucose and its metabolite, increase the formation of AGEs in intracellular, changes in mitochondrial function, PKC activation and excessive activity of hexosamine lane. The increases of oxidative stress is said to be caused by the high free radical produced by oxidation of glucose and its metabolites and reduction of antioxidant protection reserves.

All of that things can trigger microvascular damage which results in hypoxia and ischemia of nerve tissue lead to the vascular nerve structure breakdown. While the mechanism of diabetes neuropathy in hypertension is almost the same, it just can worsen the damage of structure and function of blood vessels that have already occurred in diabetes patient. It can cause the damage of axon, myelin and other parts of the nerve, that finally can result in the reduction and damage the structure as well as function of the nerve. This is suspected as a mechanism of neuropathy in hypertension, although this mechanism is not yet fully understood.

## METHODS

This study is an analytical study with a cross-sectional approach. This study is located in Sidhi Sai Medical Clinic, Abiansemal sub-district, Badung district. The data source of this study is primary data with quantitative data. The study population was all the patients who diagnosed with type II diabetes mellitus. Purposive sampling was used in determining sample. There were two criteria, those are inclusion, in this study were all patients with type II diabetes who have neuropathy, are willing to participate in the study and sign an informed consent. Exclusion were patients who did not have a neuropathy, refused to participate in the study and patients who had difficulty in communicating. The study was conducted in February 2019 until July 2019. The test equipment used to determine neuropathy was Diabetic Neuropathy Symptom Score (DNS) and Modified Neuropathy Disability Score (MNDS) was used to assess the severity of neuropathy symptoms.

Measuring blood pressure was conducted by using a mercury sphygmomanometer. The collected data were analyzed using the chi square test with SPSS version 24.

## RESULTS

The study was conducted on Type 2 diabetes mellitus patient with neuropathy at Sidhi Sai Medical Clinic, involved 50 patients, the result obtained as the following:

**Table 1. Characteristics of Type 2 diabetes mellitus patients with neuropathy at Sidhi Sai Medical Clinic, categorized by sex**

Sex	Frequency	Percentage
Male	22	44 %
Female	28	56 %
Total	50	100%

From the table, it is obtained that most patients with type 2 diabetes mellitus with neuropathy are women by 56% and men are only 44%.

Table 2. Characteristics of type 2 diabetes mellitus patients with neuropathy at Sidhi Sai Medical Clinic, categorized by age

Age	Frequency	Percentage
<55 years	23	46 %
>55 years	27	54 %
Total	50	100%

From the table 2, it is obtained that most people with type 2 diabetes mellitus with neuropathy are > 55 years old by 54% and the age of <55 years by 46%.

**Table 3. Characteristics of type 2 diabetes mellitus patients with neuropathy at Sidhi Sai Medical Clinic based on the presence of hypertension**

Blood Pressure	Frequency	Percentage
Hypertension	26	52 %
Non-Hypertension	24	48 %
Total	50	100%

From the table 3, it is found that the characteristics of the sample are based on the presence of hypertension, in this study most people with type 2 diabetes mellitus with neuropathy also have hypertension with percentage of 54% and those without hypertension are 48 %

**Table 4. Cross Tabulation between the severity of neuropathy symptoms and hypertension**

	Neuropathy symptoms			Total	P Value
	Mild	Moderate	Severe		
Blood Pressure					
	Hypertension	7	10	9	0.206
	Non-Hypertension	12	5	7	
Total		19	15	16	

From the table 4, it can be seen that the symptoms of moderate and severe neuropathy mostly occurred in the group diabetic neuropathy with hypertension, while most of the group that is not with hypertension symptoms are mild neuropathy.

In the statistical test that has been done using chi-square shows the value of  $p = 0.206$  ( $p \geq 0.05$ ) therefore it shows that there is no significant relationship between the severity of diabetic neuropathy symptoms with hypertension.

## DISCUSSION

In this study we know that women with type 2 diabetes mellitus experience more neuropathy symptoms than men, this is due to the influence of the estrogen and progesterone hormones. For women who experience menopause the hormone level decreases., the decline in the hormone levels causes a decrease in the speed of motor nerve conduction lead to neuropathy<sup>21</sup>. In accordance with previous study conducted by Suyanto et al (2016) in Semarang with 79 samples, it was found that 59% of neuropathy patients were women<sup>22</sup>. The study from Fargol et al (2005) with 110 samples found that 61.8% of neuropathy patients were women. <sup>23</sup>

It was obtained that patients who are over 55 suffer more neuropathy than patients who are under 55 years. This is because at that age neurological function has begun to progressively decline, due to the degeneration of nerve axon fibers <sup>11,24</sup>. In accordance with previous study by Fargol et al (2005) in Iran with 110 samples of neuropathy patients, more than 50% were found in patients over the age of 55 years. In the case-control study conducted by Arini et al (2017) in Surabaya showed that out of 72 samples, most neuropathies occur in people over 50 years. <sup>23,25</sup>

This study also shows that hypertension is almost always present in neuropathy patients. The symptoms in diabetic neuropathy patients with hypertension are more severe than those without hypertension, although the statistical tests do not show significant results, but the group with hypertension experienced more severe symptoms. This is because hypertension occurs in dysfunction of blood vessel endothelial cells. Normally endothelial cells will excrete 2 factors, namely relaxation factors and contraction factors. Those modulate tone from vascular smooth muscle, relaxation factor imbalances such as nitric oxide, endothelium derivatives and prostacyclin and contraction factors such as endothelin-1, prostanoid vasoconstrictor, angiotensin II and superoxide anion, will cause hemodynamic failure of blood vessels.<sup>26</sup> Therefore, this causes organ vascularity disorders including micro vascularization of nerve cells. It brings damage to axons, myelin and other parts of the nerve, which ultimately results in a decrease to damage the structure and function of blood vessels. It causes hypertension worsen the damage of structure and function of blood vessels in diabetes patients and neuropathic symptoms in patients.<sup>18</sup>

The results of this study are consistent with previous study conducted by Goutham et al in 2015 in India with a comparative study. It was found that most neuropathy in samples with hypertension compared with those without hypertension<sup>27</sup>. Similarly, a research conducted by Chan-pai et al (2003-2011) in Taiwan revealed that blood pressure  $> 135/85$  mm / hg increased the risk of neuropathy occurrence compared to normal blood pressure<sup>28</sup>. Another study conducted by De Visser et al in Canada in 2014 revealed that hypertension in diabetic neuropathy add nerve cell damage,

especially the myelin section. therefore, the symptoms are getting worse<sup>29</sup>. In addition to a study by Georgios et al in 2019, showing an association between hypertension and abnormalities in nerve fiber conduction.<sup>30</sup>

## CONCLUSION

From this study it can be concluded that the most common diabetic neuropathy occurs in women, aged over 55 years, and there is no significant relationship between the severity of diabetic neuropathy symptoms with hypertension. This shows that the severity of neuropathy is influenced by many other factors such as the duration of diabetes, the state of blood sugar, medication adherence, lack of physical activity, smoking, dyslipidemia and alcohol consumption, so that it can be used as a reference to prevent the severity of diabetic neuropathy symptoms that ultimately can maintain quality of life which is good in people with diabetes mellitus. There are still many weaknesses of this study therefore other research is needed to see the factors that influence the severity of neuropathy symptoms.

## REFERENCES

1. PERKENI. 2015. Konsensus Pengelolaan dan Pencegahan Diabetes melitus tipe 2 di Indonesia 2015. PB. PERKENI. Jakarta
2. KEMENKES RI. 2018. Hasil Utama RISKESDAS 2018. Kementrian Kesehatan Badan Penelitian dan Pengembangan Kesehatan. Jakarta
3. KEMENKES RI. 2013. Riset Kesehatan Dasar 2013. Kementrian Kesehatan Badan Penelitian dan Pengembangan Kesehatan. Jakarta
4. American Diabetse Association. 2018. Standards Of Medical Care In Diabetes-2018. The journal of clinical and applied research and education, volume 41. Supp 1. USA
5. Arleta Rewers. 2010. Acute Metabolic Complications In Diabetes. Diabetes In America 3RD Edition, Chapter 17. USA
6. American Diabetse Association. 2016. Acute And Chronic Complication. [https://diabetes.diabetesjournals.org/content/diabetes/65/Supplement\\_1/A541](https://diabetes.diabetesjournals.org/content/diabetes/65/Supplement_1/A541).
7. Konstantinos Papatheodorou, Maciej Banach, Eleni Bekiari, Manfredi Rizzo, Michael Edmond. 2018. Complications of Diabetes 2017. Hindawi. Journal of Diabetes Research Volume 2018, Article ID 3086167, 4 pages. <https://doi.org/10.1155/2018/3086167>
8. Aastha Chawla, Rajeev Chawla, Shalini Jaggi. 2016. Microvascular and macrovascular complications in diabetes mellitus: Distinct or continuum?. Indian J Endocrinol Metab. 2016 Jul-Aug; 20(4): 546–551. doi: 10.4103/2230-8210.183480: 10.4103/2230-8210.183480
9. Michael J. Fowler. 2008. Microvascular and Macrovascular Complications of Diabetes. Diabetes Foundation. Clinical Diabetes. Volume 26. Number 2, 2008
10. Vera Bril MD, FRCPC, Ari Breiner MD, FRCPC, Bruce A. Perkins MD, MPH, FRCPC, Douglas Zochodne MD, FRCPC. 2018. 2018 Clinical Practice Guidelines Neuropathy. Canadian Journal Diabetes 42 (2018) S217–S221

11. Nikolaos Papanas, Dan Ziegler. 2015. Risk Factors and Comorbidities in Diabetic Neuropathy: An Update 2015. The Review of DIABETIC STUDIES Vol 12 No 1-2 2015 Special Edition Microvascular Complications of Diabetes
12. Solomon Tesfate, Andrew J.M. Boulton, Peter J. Dyck. Roy Freeman. Michael Horowitz, Peer Kempler, Giuseppe Lauria, Rayaz A. Malik, Vicenza Spallone, Aaron Vink, Luciano Bernadi, Paul Valensi. 2010. Diabetic Neuropathies: Update on Definitions, Diagnostic Criteria, Estimation of Severity, and Treatments. Review s/Commentaries/ADA Statements. Diabetes Care 33:2285–2293, 2010
13. Meijer, J. W. G., Smit, A. J., van Sonderen, E., Groothoff, J. W., Eisma, W. H., & Links, T. P. 2002. Symptom scoring systems to diagnose distal polyneuropathy in diabetes: the Diabetic Neuropathy Symptom score. Diabetic Medicine, 19(11), 962-965.
14. Shereen R. Kamela, Mona Hamdya, Hanaa A.S. Abo Omara, Amal Kamalb, Lamia H. Alic, Ahmed H. Abd Elkarim. 2015. Clinical diagnosis of distal diabetic polyneuropathy using neurological examination cores: correlation with nerve conduction studies. Egypt Rheumatol Rehabil 42:128–136
15. Joint National Committee. 2004. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. NIH Publication No. 04-5230 August 2004
16. Anne K Schreiber, Carina FM Nones, Renata C Reis, Juliana G Chichorro, Joice M Cunha. 2015. Diabetic neuropathic pain: Physiopathology and treatment. World J Diabetes 2015 April 15; 6(3): 432-444. ISSN 1948-9358 (online)
17. Soroku Yagihashi1, Hiroki Mizukami, Kazuhiro Sugimoto. 2011. Mechanism of diabetic neuropathy: Where are we now and where to go?. Journal of Diabetes Investigation Volume 2 Issue 1 February 2011
18. Rebecca Louise Branch. 2010. Peripheral Neuropathy In Hypertension. A thesis submitted to The University of Birmingham For the degree of Master Of Philosophy. School of Clinical & Experimental Medicine College of Medical & Dental Sciences The University of Birmingham September 2010
19. Jan-Willem G. Meijer, Eelke Bosma, Johan D.Lefandt, Thera P.Links, Andries J.Smit, Roy E. Stewart, Johannes H. Van Der Hoeven, Klaas Hoogenberg. 2003. Clinical Diagnosis of Diabetic Polyneuropathy With The Diabetic Neuropathy Symptom and Diabetic Neuropathy Examination Scores. Diabetes Care 26:697–701, 2003
20. Yuanita Mardastuti. 2013. Uji Realibilitas Dan Validitas Diabetic Neuropathy Symptom 9DNS-INA) Dan Diabetic Neuropathy Examination(DNE-INA) Sebagai Skor Diagnostik Neuropati Diabetik. Universitas Gadjah Mada, 2013 | Diunduh dari <http://etd.repository.ugm.ac.id/>
21. Akansha Singh, Naiyer Asif, Paras Nath Singh, Mohd Mobarak Hossain. 2016. Motor Nerve Conduction Velocity In Postmenopausal Women with Peripheral Neuropathy. Journal of Clinical and Diagnostic Research. 2016 Dec, Vol-10(12): CC13-CC16 16. Available at [www.jcdr.net](http://www.jcdr.net)

22. Suyanto, Andreawan Susanto. 2016. Faktor-faktor Yang Berhubungan Dengan Kejadian Neuropati Perifer Diabetik. *Nurscope. Jurnal Keperawatan dan Pemikiran Ilmiah*. 2(6).1-7
23. Fargol Booya, Fatemeh Bandarian, Bagher Larijani, Mohammad Pajouhi, Mahdi Nooraei, Jamshid Lotfi. 2005. Potential risk factors for diabetic neuropathy: a case control study. *Biomed Central Neurology*. Accepted: 10 December 2005. This article is available from: <http://www.biomedcentral.com/1471-2377/5/24>
24. Lauretani F, Bandinelli S, Bartali B. Axonal degeneration affects muscle density in older men and women. *Neurobiol Aging*. 2006;27:1145–1154.
25. Arini Rahmawati, Arief Hargono. 2017. Faktor Dominan Neuropati Diabetik Pada Pasien Diabetes Melitus Tipe 2. *Jurnal Berkala Epidemiologi* vol. 6 No.1 (2018).60-68. DOI : 10.20473/jbe.v6il.2018.60-68. P-ISSN: 2301-7171; e-ISSN: 2541-092x. available at <http://journal.unair.ac.id/index.php/JBE/>
26. Puddu P, Puddu GM, Zaca F, Muscari A. 2000. Endothelial Dysfunction In Hypertension. *Acta Cardiol* 2000aug;55(4):221-32. DOI : 10.2143/AC.55.4.2005744. available at <https://ncbi.nlm.nih.gov/pubmed/11041120>
27. Goutham Kesavamoorthy. Awnish K Singh, Shruti Sharma, Jyoti Bala Kasav, Surapaneni Krishna Mohan, Ashish Joshi. 2015. Burden of Diabetes Related Complications Among Hypertensive and Non Hypertensive Diabetics: A Comparative Study. *Journal of Clinical and Diagnostic Research*. 2015 Sep, Vol-9(9): LC10-LC14. DOI: 10.7860/JCDR/2015/14461.6452
28. Chan-Pai Yang, Cheng-Chieh Lin, Chia-Ing Li, Chiu-Shong Liu, Wen-Yuan Lin, Kai-Lin Hwang, Sing-YU Yang, Hsuan-Ju Chen, Tsai-Chung Li .2015. Cardiovascular Risk Factors Increase the Risks of Diabetic Peripheral Neuropathy in Patients With Type 2 Diabetes Mellitus. *Medicine* vol.94, number 42, oktober 2015. ISSN: 0025-7974 . DOI:0.1097/MD.0000000000001783. available at [www.md-journal.com](http://www.md-journal.com)
29. De Visser A, Hemming A, Yang C, Zaver S, Dhaliwal R, Jawed Z, Toth C. 2014. The Adjuvant Effect Of Hypertension Upon Diabetic Peripheral Neuropathy in Exsperimental Type 2 Diabetes. *Neurobiol Dis*. 2014 feb;62:18-30. Doi 10.1016/j.nbd.2013.07.019. Epub 2013 Aug 1. Available at <https://ncbi.nlm.nih.gov/pubmed//23938761>
30. Georgios Ponirakis, Ioannis N. Petropoulos, Uazman Alam, Maryam Ferdousi, Omar Asghar, Andrew Marshall, Shazli Azmi, Maria Jeziorska, Ziyad R. Mahfoud, Andrew J.M. Boulton, Nathan Efron, Hitoshi Nukada, and Rayaz A. Malik. 2019. Hypertension Contributes to Neuropathy in Patients With Type 1 Diabetes. *American Journal of Hypertension* 32(8) August 2019. Available at <https://academic.oup.com/ajh/article-abstract/32/8/796/547729>