The Correlation Between HbA1c and Neuropathy Disability Score in Type 2 Diabetes

Ilsa Hunaifi[1], I Gusti Ngurah Ommy Agustriadi[2], I Gede Yasa Asmara[2], Catharina Budyono[2]

[1] Department of Neurology, Faculty of Medicine, University of Mataram - West Nusa Tenggara General Hospital, NTB, Indonesia.
[2] Department of Internal Medicine, Faculty of Medicine, University of Mataram - West Nusa Tenggara General Hospital, NTB, Indonesia.

Corresponding Author:
Ilsa Hunaifi, MD. Department of Neurology, Faculty of Medicine, University of Mataram-West Nusa Tenggara General Hospital. Jl. Prabu Rangkasari, Dasan Cermen, Mataram, NTB 83232, Indonesia. email: ilsahunaifi@unram.ac.id.

ABSTRAK

Latar belakang: *World Health Organization (WHO) memperkirakan angka kejadian DM tipe 2 di Indonesia sebesar 21.3 juta jiwa pada tahun 2030. Diabetes Melitus mempunyai komplikasi kronis. Salah satu komplikasi kronis adalah terjadinya neuropati perifer. Untuk mengetahui terjadinya neuropati, pemeriksaan fisik yang direkomendasikan adalah menilai Neuropathy Disability Score (NDS). Haemoglobin A1c (HbA1c) adalah glycated haemoglobin yang digunakan untuk menilai status kadar gula dalam 2 atau 3 bulan terakhir. Hubungan antara HbA1C dengan derajat keparahan neuropati DM dilakukan dengan pemeriksaan elektrodiagnostik menunjukkan bahwa peningkatan kadar HbA1c dan usia menjadi prediktor utama terjadinya neuropati DM namun pemeriksaan elektrodiagnostik mahal. Untuk itu diperlukan penelitian untuk mengetahui hubungan antara kadar HbA1c dengan NDS sehingga morbiditas neuropati DM dapat diminimalisir. Penelitian ini bertujuan untuk mengetahui hubungan antara derajat keparahan neuropati diabetes yang diukur dengan Neuropathy Disability Score dengan nilai HbA1c pada penderita diabetes melitus tipe 2.* ***Metode*****:** *penelitian analitik korelatif dengan metode cross sectional. Setiap penderita DM yang memenuhi kriteria inklusi dan eksklusi dimasukkan sampai jumlah sampel terpenuhi. Data yang terkumpul dianalisis dengan uji korelasi Spearman.* ***Hasil:*** *didapatkan 56 subyek penelitian. Rerata usia 59.55 (SB 9.48) dengan 57.1% berjenis kelamin wanita, median lamanya menderita DM 5.5 tahun. Median nilai skor NDS sebesar 7.5 dan median nilai HbA1c sebesar 8.65. Analisa korelasi Spearman menunjukkan koefisien korelasi sebesar 0.487 dengan nilai p=0.000.* ***Kesimpulan:*** *terdapat hubungan antara kadar HbA1c dengan derajat keparahan neuropati pada pasien DM tipe 2.*

Kata Kunci*: Haemoglobin A1c, neuropati, diabetes melitus.*

ABSTRACT

Background: *World Health Organization (WHO) estimates the incidence of type 2 diabetes in Indonesia would increase to 21.3 million in 2030. Diabetes has a chronic complications, including peripheral neuropathy. The degree of neuropathy was assessed through the Neuropathy Disability Score (NDS). In contrast, haemoglobin A1c is glycated haemoglobin used to monitor the glucose levels of diabetic patients in the last 2 or 3 months. The relationship between HbA1c and diabetic neuropathy carried out by electrodiagnosis showed that HbA1c and age were the main predictors of diabetic neuropathy. However, electrodiagnosis is still considered costly. Research is needed to determine the relationship between HbA1c and NDS to reduce morbidity. This study aims to determine the relationship between the severity of diabetic neuropathy as measured by NDS with HbA1c*

level in type 2 Diabetes. ***Methods:*** *this cross-sectional study involved correlation analysis.. The collected data were analyzed with the Spearman correlation test.* ***Results:*** *approximately 56 diabetic patients were involved in this study. Patients were recruited from the internal medicine outpatient ward from the West Nusa Tenggara General Hospital. The mean age was 59.55 (SD 9.48) with 57.1% female; the median duration of diabetes was 5.5 years. The median NDS score is 7.5 and the median HbA1c value is 8.65. Spearman correlation analysis shows a correlation coefficient of 0.487 with a value of p = 0.000* ***Conclusion:*** *there is a relationship between HbA1c level and the severity of diabetic neuropathy in Type 2 DM.*

Keywords: *Haemoglobin A1c, neuropathy, diabetes mellitus.*

INTRODUCTION

Based on the International Diabetes Federation, 425 million people would suffer from Diabetes Mellitus (DM) by 2045. In a developing country, including Indonesia, it is predicted that 4 out of 5 have Diabetes.[1] According to the Basic Health Research conducted by the Ministry of Health Indonesia in 2013, DM is the 4th most non-communicable disease after cancer in Indonesia. Furthermore, in West Nusa Tenggara, the estimated number of people having DM is 0.9% of the total population.[2]

Diabetes is a metabolic disease with an abnormal hyperglycemic index that occurs due to abnormal insulin secretion, insulin action, or combined. DM type 2 has several classic symptoms, including polyuria, polydipsia, polyphagia, and weight loss. DM diagnosis requires several laboratory examinations: fasting blood glucose level, 2 hours after postprandial blood glucose level, and Haemoglobin A1c (HbA1c).[3] Diabetes Mellitus has several acute and chronic complications that may affect various organs and cause morbidity and mortality. Chronic complications are categorized into vascular (microvascular and macrovascular) and non-vascular complications. Microvascular complications include neuropathy, nephropathy, and retinopathy, whereas macrovascular complications include cerebrovascular, coronary heart disease, and peripheral arterial disease.[4]

DM neuropathy affects 50% of people with both type 1 and type 2 DM. Diabetic neuropathy can be in the form of polyneuropathy, mononeuropathy, or autonomic neuropathy. The occurrence of neuropathy is related to the duration of DM and control of blood glucose. The most type of neuropathy is distal symmetric polyneuropathy and the most common symptoms are such sensory disorders as hyperesthesia, paresthesia, and dysesthesia.[4] To identify the complications of neuropathy in diabetes, it is necessary to screen and then stratify for the degree of neuropathy. Screening the occurrence of neuropathy is conducted through a series of questions to patients to find out whether there is neuropathy. A series of physical examinations such as the Neuropathy Disability Score (NDS) can be used to determine the degree of neuropathy so that complications can be prevented. NDS include pinprick examination, Achilles reflex examination, temperature, and vibration perception on patients.[5,6] NDS examination is performed on both sides and a score ≥ 6 points are considered abnormal.[6]

Haemoglobin A1c (HbA1c) is glycated haemoglobin used to monitor the status of glucose levels in the previous 2 or 3 months. Recommendation from the American Diabetes Association (ADA), HbA1c levels must be maintained at 7% in all diabetics patients. HbA1c levels above 7% increase the risk of complications, especially microvascular complications. Koening and colleagues first reported the relationship between HbA1c and blood glucose control in uncontrolled diabetic patients. Many studies indicate an association between HbA1c and diabetes complications. However, few studies have focused on HbA1c levels with diabetic polyneuropathy.[7] Early detection of diabetes polyneuropathy can prevent morbidity. Neuropathy Disability Score (NDS) has been widely accepted and validated as an assessment tool to identify the presence of diabetic neuropathy.[8] The relationship between HbA1c and the severity of diabetic neuropathy is

done by electrodiagnosis examination, showing that increased HbA1c levels and age are the main predictors of diabetes neuropathy.[9] The electrodiagnosis examination is a sophisticated examination and not all hospitals in low resource settings have this device so that validated physical testing is needed to establish the severity of the diabetic neuropathy.[9] For this reason, research is required to explore the correlations between HbA1c and the severity of diabetic neuropathy as assessed by the Neuropathy Disability Score (NDS) among diabetes mellitus patients.

METHODS

This cross-sectional study was conducted from March to August 2019 with criteria of type 2 diabetes mellitus who experienced neuropathy symptoms selected by examining neuropathy symptom scores. Patients were recruited from the internal medicine outpatients ward of West Nusa Tenggara General Hospital. Patients who experience symptoms of neuropathy were examined for neuropathy disability scores and HbA1c levels. Neuropathy disability scores include vibration sensation with a 128 Hz tuning fork, temperature sensation with a cold tuning fork, pinprick examinations, and Achilles reflex examinations on both sides of the body (**Table 1**). The maximum NDS score is 10 and the abnormal score is ≥ 6.[6]

Table 1. Neuropathy disability score (NDS).[6]

NDS Items	Description
Vibration Sensation (128 Hz tuning fork)	0 = present, 1 = reduced/absent per side
Temperature sensation (cold tuning fork)	0 = present, 1 = reduced/absent per side
Pin-prick	0 = present, 1 = reduced/absent per side
Ankle reflex	0 = present, 1 = present with reinforcement, 2 = absent per side

This study has been approved by the Ethical Committee of Mataram University (Reference number 41/UN18.F7/ETIK/2019).

In this study, a minimum sample of 51 patients was determined and sampling was carried out by the method according to the case that came sequentially (sampling from consecutive admission) until a predetermined sample size was reached. Data were analyzed through the Pearson correlation test or Spearman if the requirements for the Pearson correlation test were not obtained. All data were analyzed using SPSS version 22.0.

RESULTS

Fifty-six individuals met the criteria of this study, see **Table 2**. The mean age of the study subjects was 59.55 (SD 9.48) years. The youngest patient was 43 years old and the oldest was 79 years old. Demographic data of research subject are shown in **Table 2**.

Table 2. Baseline characteristic (n: 56).

Characteristic	Value	p
Age (years), mean (SD)	59.55 (9.48)	0.757
Sex, n		0.396
- Male	24	
- Female	32	
Type of therapy, n		
- Medical	36	
- Insulin	15	
- Others	5	
Length of diabetes, mean (SD)	6.95 (5.07)	0.238
NDS value, mean (SD)	6.77 (2.55)	
HbA1c value, mean (SD)	9.13 (2.36)	

The correlation between NDS values and HbA1c levels was tested with the Spearman correlation test because the data were not normally distributed even though the data transformation was done. From the Spearman correlation test results obtained a correlation coefficient of 0.487 with a value of p = 0.000 (**Table 3**)

Table 3. Correlation of HbA1c with NDS.

Variable	Coefficient correlation	*p*	n
NDS vs HbA1c	+ 0,487	0,000	56

Spearman correlation test

DISCUSSION

Research subjects were predominantly female. This was similar to the previous study in China showing that DM in women was mostly found in rural area and male in urban areas.[10] Based on age, the mean age of study subjects was 59.55 (SD 9.48) years. The CDC (*Centers for Disease Control and Prevention*) report shows the average age of DM sufferers was 53.8 years

in 1997 and 54.2 years in 2011. Furthermore, previous studies reported that the average age of DM in Hong Kong was 52 years and in China was 40-59 years.[10]

Patients with DM for more than five years have a higher risk of neuropathy. The results of this study indicate that the median duration of DM is 5.5 years. Reports in the United Kingdom (UK), DM neuropathy, occurs in 36% of people with diabetes for more than ten years compared with people with diabetes less than five years and nerve denervation damage increases with the length of DM.[11]

Various scores were developed to assess the degree of neuropathy in people with DM. One of the score that are often used is NDS (*Neuropathy Disability Score*). The median value of NDS in the study was 7.5. NDS assesses Achilles reflexes, vibration sensations, prick pin tests, and temperature sensations on both feet with a maximum score of 10 where a score of 6 or more indicates a severe degree of neuropathy. Data reports in the UK show that 50% of people with DM show neuropathy symptoms and 7% have diabetic foot after 1 year.[12]

This study aims to find the relationship between DM neuropathy severity by measuring the NDS scale with HbA1c levels. Spearman correlation analysis results show there is a significant relationship between HbA1c and NDS. This indicates that the higher the HbA1c value in patients with type 2 DM, the higher the NDS value was. In other words, the higher the HbA1c level, the higher the severity of the neuropathy. Zilliox *et al*.[11] research showed that NDS values in DM neuropathies were 6.26 (SD 0.34). The electrodiagnosis examination found in patients with large fiber neuropathy showed a heavier NDS value compared to patients with small fiber neuropathy [(7.23 (SD 0.91) vs 4.77 (SD 0.53)]. The research of Stem *et al*.[12] showed that complications of DM (neuropathy, retinopathy, or nephropathy) occur in patients with HbA1c 8.5 (SD 1.5). The higher levels of HbA1c will further accelerate and worsen the complications of neuropathy. Control of glucose levels is very important to prevent and decrease the complications from DM. High levels of HbA1c have associated with high microvascular complications in people with DM. Limitations of this study were HbA1c was only evaluated once and electrodiagnosis examination was not performed as a gold standard to determine the severity of neuropathy.

CONCLUSION

HbA1c level is related to the severity of neuropathy in patients with type 2 diabetes. The higher the HbA1c value, the higher the Neuropathy Disability Score. Monitoring of HbA1c level is crucial to prevent further complications of DM both in the nervous system and in other organs.

ACKNOWLEDGMENTS

We thank the Language Center University of Mataram for proofreading the manuscript.

CONFLICT OF INTEREST

The author declares no conflict of interest.

REFERENCES

1. International Diabetes Federation, IDF Diabetes Atlas 8ed, 2017, www.idf.org, accessed Oct 14, 2019
2. Departemen Kesehatan Republik Indonesia, Riset Kesehatan Dasar, 2013, www.depkes.go.id. accessed Oct 14, 2019.
3. Perkeni, Konsensus Pengelolaan dan Pencegahan Diabetes Melitus tipe 2 di Indonesia, 2006, www.pbperkeni.or.id, accessed Oct 14, 2019.
4. Powers AC. Diabetes mellitus. In: Fauci AS, Kasper DL, Longo DL, et al (ed). Harrisons principle of internal medicine. 17th ed. New York: Mc Graw-Hill Medical, 2015. p. 2275-304.
5. Boulton AJM, Vinik AI, Arezzo JC, et al. Diabetic neuropathies. Diabetes Care. 2005;28;956-62.
6. Yang Z, Chen R, Zhang Y, et al. Scoring systems to screen for diabetic peripheral neuropathy (Protocol). Cochrane Database of Systemic Reviews. 2014;3:1-31.
7. Lee WJ, Jang S, Lee SH, Lee HS. Correlation between the severity of diabetic peripheral polyneuropathy and glycosylated hemoglobin levels: A quantitative study. Ann Rehabil Med. 2016;40 (2):263-70.
8. Meijer JWG, Sonderen E, Blaauwwikel EE, et al. Diabetic neuropathy examination. Diabetes Care. 2000;23;750-3.
9. Yuan H, Li X, Wan G, et al. Type 2 diabetes epidemic in East Asia: a 35-year systematic trend analysis.Onco Target. 2018;9(6):6718-27.
10. Nisar MU, Asad A, Waqas A, et al. Association of diabetic neuropathy with duration of type 2 diabetes

and glycemic control. Cureus. 2015;7(8):e302.
11. Zilliox LA, Ruby SA, Singh S, Zhan M, Russell JW. Clinical neuropathy scale in neuropathy associated with impaired glucose tolerance. J Diabetes Complication. 2015;29(3):372-7.
12. Stem MS, Blachley TS, Shtein RM, Herman WH, Gardner TW, Stein JD. Impact of diagnosing diabetic complications on future haemoglobin A1c levels. J Diabetes Complication. 2016;30(2):323-8.

Formulir Keputusan Telaah Etik

Komisi Etik Penelitian Kesehatan Universitas Mataram	**Keputusan Penelaahan**	**No:** 41/UN18.F7/ETIK/2019

Judul Penelitian:
Hubungan antara Hemoglobin AIC (HbAIC) dengan *Neurophatic Disability Score* pada Penderita Diabetes Mellitus Tipe 2

Peneliti Utama
dr. Ilsa Hunaifi, Sp.S
Peneliti
dr. IGN Ommy Agsutriadi, SpPD
dr. I Gede Yasa Asmara, Mmed, SpPD
dr. Catharina Budyono, SpPD

Tanggal Penelitian:

Kesimpulan:
☑Disetujui ☐Ditolak ☐Perlu diperbaiki ☐Belum dapat dibahas

Butir alasan, perbaikan/perubahan/keterangan tambahan yang diperlukan:

- Penelitian dapat dilaksanakan, tidak ada potensi pelanggaran etika.

Ketua Panitia Komisi Etik Penelitian Kesehatan Universitas Mataram **Tanggal**

dr. Arfi Syamsun, Sp.KF., M.Si.Med. 21 Februari 2019

Catatan :

1. Peneliti wajib menyerahkan hasil penelitian selambat – lambatnya 1 (satu) bulan setelah selesai penelitian kepada Komisi Etik Penelitian Kesehatan Fakultas Kedokteran Unram. Apabila laporan penelitian tidak diserahkan, maka Komisi Etik berhak untuk membatalkan persetujuan yang diberikan.
2. Apabila pelaksanaan penelitian tidak sesuai dengan usulan kegiatan, Komisi Etik tidak bertanggung jawab terhadap kelayakan etik penelitian tersebut.
3. Apabila ada perubahan prosedur/kegiatan penelitian, mohon agar mengusulkan kembali proposal kelayakan etik kepada Komisi Etik.