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RESEARCH ARTICLE

A Case-Control Study on Risk Factors affected Peripherals Neuropathic complication in Elderly with Type 2 Diabetes Mellitus

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ABSTRACT

Background: Diabetic Peripheral Neuropathy (DPN) is a microvascular complication that commonly occurs in people with diabetes mellitus. Geriatrics with type 2 diabetes mellitus is one of the populations most vulnerable to this complication. An epidemiological study states that geriatrics has a 32% greater risk of developing this complication compared to other age groups. There have not been many studies conducted to evaluate the risk factors that influence this DPN complication, so it needs to be done an individual evaluation for the elderly population. **Objective:** This study aims to explore the risk factors that influence the incidence of DPN in elderly patients with type 2 diabetes mellitus. **Methods:** A case-control study design was carried out on 70 geriatrics with type 2 diabetes mellitus. The outcome determined was the incidence of DPN to track the cause of DPN exposure retrospectively. Influential risk factors are determined by the Odds Ratio (OR) with a 95% confidence interval (CI). All statistical analyzes were two-tailed, and p-values <0.05 were considered as statistically significant. **Results:** Seven factors influence the incidence of DPN in the elderly consisting of smoking history (OR=13.1), uncontrolled lipid profile (OR=5.1), non-neuroprotector users (OR=5.6), uncontrolled blood glucose (OR=42.7), history of heart disease (OR=9.0), uncontrolled blood pressure (OR=4.3), and BMI above normal (OR=5.1). **Conclusion:** Strong recommendation for medical personnel to focus attention on seven significant risk factors affected complications of DPN to reduce its progression or prevent upcoming complications.

KEYWORDS: DPN, Elderly, Complication, Diabetes, Risk Factor.

INTRODUCTION:

Diabetic Peripheral Neuropathy (DPN) is one of the most common complications in diabetics.[1,2] All patients with diabetes, both type 1 and type 2, have the same risk of developing neuropathy complications[1–3]. More than 60% of patients with uncontrolled diabetes are found to have DPN[1,4,5]. DPN is defined as a disorder that occurs in the nervous system due to diabetes mellitus. This disorder appears caused by microvascular damage due to high blood glucose levels. If this complication goes on chronically, it will damage the peripheral nerve fibers, which will affect the ability of the peripheral nervous system to work normally[6–8].

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Patients who experience DPN will experience paresthesia with a sensation of tingling or numbness, skin crawling, or itching[3,6,9–11].

An epidemiological study presents the results that the elderly have the highest incidence of DPN, which is 32% higher than other populations[2,5,10,12]. The elderly should get more attention related to this problem. If these DPN complications are not seriously treated, the patients will have a higher risk of disability due to foot ulceration and amputation, gait disturbance, and fall-related injuries[6,11–14]. DPN in the elderly will also reduce the quality of life and increase the cost of treatment in the future[5,11,13,15,18].

Many studies have been carried out to identify the factors that cause DPN, but there is still minimal data examining the geriatric population. Further research is needed to identify risk factors for DPN in geriatrics. This study will provide an overview for clinicians to be able to intervene in the risk factors that cause DPN, especially

risk factors that can be modified to prevent the progression of DPN in geriatrics.

METHODS:

1. Study Design and Sample Size:

This study was a case-control conducted at a government hospital in the province of Bali, Indonesia. This research was part of a larger research, in which the data collection process has been carried out from 2016 to 2019. This study has been approved by the ethics commission and hospital permits with ethical clearance number 185/UN.14.2/R&D/2015. All patients included in this study had a good understanding of the aims and objectives of the study and agreed to be involved after completing and signing informed consent. Based on a minimum sample calculation for a case-control study, a minimum sample of 35 patients was obtained in both the case and control groups, so that the total number of patients analyzed were 70 subjects.

2. Study Population and Procedures:

The population of this study was all geriatric patients with age criteria ≥60 years who were diagnosed with type 2 diabetes mellitus in the geriatric ward of a government hospital in the province of Bali, Indonesia. The research sample was part of the population that meets the inclusion criteria. Subjects will be included in the study if they have complete medical record data for at least the past year. The intended medical record data consists of at least: diagnosed with type 2 diabetes mellitus, having primary identity data, smoking history, blood pressure (SBP/DBP), lipid profile (TC, LDL, HDL, TG), duration of diabetes, height, body weight, random blood glucose profile, history of outpatient drugs being used, and the presence/absence of cardiovascular diseases (CVD)[15–19]. The patient will be excluded from this study if: the patient is not willing to be included in the study, and there are data records that are not clearly reported, such as unreadable data, scattered, exchanged data, and duplicated data.

Medical records were taken randomly for review. The case-control study begins with the determination of patient outcomes in the form of DPN and non-DPN to be further seen retrospectively predictors that have the potential to cause outcomes[20]. The review process was carried out by four reviewers. Reviewers hold open meetings to discuss the results of the review. If there are differences of opinion, an evaluation phase will be carried out until an agreement is reached.

3. Case-Control Assessment:

Part of the population of geriatric patients diagnosed with Type 2 Diabetes Mellitus, according to established criteria, will be the subject of this study. Geriatrics who were diagnosed with DPN would be included in the case group, while geriatrics who were not diagnosed with DPN would be included in the control group. DPN, in this case, is an outcome that has been observed. Reviewers retrospectively explore factors that have the potential to be outcome predictors. Predictors that went through the review stage were: smoking history, lipid profile, gender, neuroprotector users, duration of diabetes, blood glucose profile, history of heart disease, blood pressure, and BMI[20].

4. Data Collection and Measurements:

All data in this study were collected through patient medical record text data. Baseline data on the demographic characteristics of subjects in both the case and control groups included age, gender, smoking history, blood pressure, lipid profile, duration of diabetes, BMI, random blood glucose profile, and the number of drug items used by the patient. The characteristics of neuropathy symptoms in the case group are also described[15–19]. The main data in this study were measured by the following criteria: smoking history (have a history/not), lipid profile (controlled if TC<200mg/dL; LDL<100mg/dL; HDL>40mg/dL; TG<150mg/dL. Uncontrolled was the opposite), sex (male/female), neuroprotector users (users/not users of vitamin B complex or high dose vitamin B12>500mcg/day), duration of diabetes (longer/shorter than ten years), blood glucose profile (random blood glucose on average controlled if it is <200mg/dL. Uncontrolled was the opposite), history of heart disease (Have a history of heart disease if they have undergone a coronary heart attack or stroke. Have no history was the opposite), blood pressure (controlled if SBP and DBP <130/100mmHg, uncontrolled was the opposite), and BMI (having a normal BMI if <25kg/m^2. Being overweight to obesity when>25kg/m^2)[15–19].

Patients included in this study were being treated in the ward. Informed consent was signed at the hospital. For patients who are not being treated at the hospital (outpatient), informed consent was signed online with initial telephone follow-up.

5. Statistical Analysis:

Data analysis in this study was assisted with IBM SPSS 21 version. The analysis included baseline demographic characteristics using Chi-Square and Mann Whitney U to analyze differences in characteristics between groups (case and control). The primary data were analyzed by binary logistic analysis with odds ratio parameters and used 95% confidence intervals. The case group that had DPN complications was continued analyzed for access to the degree of pain felt. The degree of pain was categorized into “mild pain” with a visual analog scale (VAS) value of 1-3, “moderate pain” with VAS 4-7, and “severe pain” with VAS 8-10[3,13,14]. The neuropathic pain data were analyzed using binary conditional logistic regression. Other numerical data in this study were

presented with numerical and percentage data. All statistical analyses were two-tailed, and p-value <0.05 was considered as statistically significant.

RESULTS:

1. The Flow of Study Subjects Data Selection:

In the study period, there were 155 medical records of patients who went through the review process. A total of 74 medical records were not included in the analysis because they did not meet the specified inclusion criteria. A total of 81 medical records that met the inclusion criteria consisted of 46 medical records included in the case group and 35 medical records included in the control group. A total of 11 medical records from the case group during the review process were excluded because as many as eight patients who owned the medical records were not willing to be involved in the study, and three other medical record data had unclear records. This case-control study finally succeeded in analyzing 70 medical records consisting of 35 data in patients with complications of DPN (case group) and 35 data of patients without complications of DPN (control group).

2. Demographic Characteristics of Study Subjects:

Demographic characteristics of study subjects can be seen in Table 1. Demographic characteristics that include age, gender, blood pressure, lipid profile, duration of diabetes, BMI, random blood glucose profile, and the number of drug items used by the patient both in the case group and control shows results that are not significant. Only the smoking history characteristics show a significant difference with the chi-square analysis. Subjects who had a history of smoking had a greater tendency to be in the case group in this study. This condition can describe that smoking history can be one of the strong predictors that will influence DPN complications in study subjects. In general, it can be summarized that the study subjects have uniform characteristics except for the smoking history parameter.

Table 1: Study subject characteristics

S. No	Subject Characteristics	Neuropathic Complication (Case) n= 35	No Neuropathic Complication (Control) n= 35	p-Value
1	**Age (year ± SD)**	62 ± 4	63 ± 5	0.658
2	**Gender [n (%)]**			
	Male	21 (60)	24 (69)	0.454
	Female	14 (40)	11 (31)	
3	**History Smoking [n (%)]**	22 (63)	4 (11)	0.001*
4	**Blood Pressure (mmHg ± SD)**			
	SBP	142 ± 20	135 ± 16	0.403
	DBP	86 ± 11	83 ± 9	0.513
5	**Lipid Profile (mg/dL ± SD)**			
	TC	165 ± 55	166 ± 47	0.827
	LDL	97 ± 35	88 ± 30	0.485
	HDL	43 ± 14	43 ± 12	1.000
	TG	152 ± 95	147 ± 72	0.727
6	**Diabetes Duration (year ± SD)**	7 ± 4	5 ± 4	0.083
7	**BMI (kg/m^2 ± SD)**	27 ± 4	26 ± 4	0.814
8	**Average Random Blood Glucose (mg/dL ± SD)**	188 ± 80	172 ± 88	0.729
9	**Number of drug items used (n ± SD)**	4 ± 1	4 ± 1	1.000

Table description: *=statistically significant using chi-square analysis; n=subjects; SD=standard deviation; SBP=systolic blood pressure; DBP=diastolic blood pressure; TC=total cholesterol; LDL=low density lipoprotein; HDL=high density lipoprotein; TG=triglycerides; BMI=body mass index.

All patients in the case study group identified the characteristics of DPN that occurred in them. These characteristics are shown in Table 2. All patients in the case group experienced paresthesia consisting of tingling, numbness, prickling, burning, and chilling. Almost all patients feel tingling and numbness as the main complaints.

Table 2: Study subject diabetic peripheral neuropathic pain characteristics

No	DPN Pain type problems	Total n (%) n=35
1	Tingling	33 (94)
2	Numbness	30 (86)
3	Pricking	16 (46)
4	Burning	13 (37)
5	Chilling	6 (17)

Table description: n=subjects; DPN=diabetic peripheral neuropathy.

3. Risk Factors Related To The Incidence of Diabetic Peripheral Neuropathy:

The results of the binary logistic analysis for the factors that influence the incidence of DPN can be seen in Table 3. Based on the analysis of seven exposures consisting of smoking history, lipid profile, neuroprotector users, blood glucose profile, history of heart disease, blood pressure, and BMI, found to affect the incidence of complications of DPN in geriatrics, whereas two other exposures in the form of gender and duration of diabetes were found that did not affect DPN complications in this study.

Table 3: Risk factors related to diabetic peripheral neuropathy complications

S. No	Variable	Even in Case Group n= 35	Even in Control Group n= 35	OR	CI95%	p-Value
1	History of smoking (n=26)	22	4	13.115*	3.770-45.629	0.001*
	Non-smoking history (n=44)	13	31			
2	Uncontrolled lipid profile (n=29)	21	8	5.063*	1.791-14.310	0.002*
	Controlled lipid profile (n=41)	14	27			
3	Male (n=45)	21	24	0.688	0.257-1.838	0.455
	Female (n=25)	14	11			
4	Non neuroprotector user (n=15)	12	3	5.565*	1.409-21.987	0.014*
	Neuroprotector user (n=55)	23	32			
5	DM duration < 10 years (n=53)	26	27	0.856	0.287-2.556	0.781
	DM duration >10 years (n=17)	9	8			
6	Uncontrolled BG (n=31)	28	3	42.667*	10.064-180.891	0.001*
	Controlled BG (n=39)	7	32			
7	CVD history (n=26)	21	5	9.000*	2.812-28.809	0.001*
	Non CVD history (n=44)	14	30			
8	Uncontrolled BP (n=40)	26	14	4.333*	1.569-11.967	0.005*
	Controlled BP (n=30)	9	21			
9	BMI > 25 kg/m^2 (n=41)	27	14	5.063*	1.791-14.310	0.002*
	BMI < 25 kg/m^2 (n=29)	8	21			

Table description: *=statistically significant; OR=odd ratio; CI95%=confidence interval 95%; n=subjects; SD=standard deviation; DM=diabetes mellitus; BG=blood glucose; CVD=cardiovascular diseases; BP=blood pressure; BMI=body mass index.

Table 4. Determination analysis of the strongest risk factors causing diabetic peripheral neuropathic pain in high-risk study subjects

S. No	Variable	Mild DPN Pain [n (%)]	Moderate DPN Pain [n (%)]	Severe DPN Pain [n (%)]	p-Value
1	History of Smoking* (n=22)	2 (9.09)	12 (54.55)	8 (36.36)	0.001*
2	Uncontrolled lipid profile (n=21)	7 (33.33)	12 (57.14)	2 (9.52)	
3	Non neuroprotector user (n=12)	4 (33.33)	7 (58.33)	1 (8.33)	
4	Uncontrolled BG* (n=28)	3 (10.71)	16 (57.14)	9 (32.14)	
5	CVD history (n=21)	8 (38.09)	12 57.14)	1 (4.76)	
6	Uncontrolled BP (n=26)	7 (26.92)	18 (69.23)	1 (3.85)	
7	BMI > 25 kg/m^2 (n=27)	6 (22.22)	20 (74.07)	1 (3.70)	

Table description: *=statistically significant; n=subjects; DPN=diabetic peripheral neuropathy; BG=blood glucose; CVD=cardiovascular diseases; BP=blood pressure; BMI=body mass index.

Table 5. Pooled analysis of the strongest risk factors causing diabetic peripheral neuropathic pain in high-risk study subjects

S. No	Strong Risk Factor Cause Painful DPN	Other Risk Factor Cause Painful DPN	p-Value
1	History of Smoking (n=22)	Uncontrolled BG (n=28)	1.000
		Uncontrolled lipid profile (n=21)	0.005*
		Non neuroprotector user (n=12)	0.010*
		CVD history (n=21)	0.004*
		Uncontrolled BP (n=26)	0.013*
		BMI > 25 kg/m^2 (n=27)	0.013*
2	Uncontrolled BG (n=28)	History of Smoking(n=22)	1.000
		Uncontrolled lipid profile (n=21)	0.006*
		Non neuroprotector user (n=12)	0.012*
		CVD history (n=21)	0.005*
		Uncontrolled BP (n=26)	0.015*
		BMI > 25 kg/m^2 (n=27)	0.0

Table description: *=statistically significant; DPN=diabetic peripheral neuropathy; n=subjects; BG=blood glucose; CVD=cardiovascular diseases; BP=blood pressure; BMI=body mass index.

Subjects in this study who had "uncontrolled lipid profiles," "non-neuroprotector users," and "overweight" had a five times greater risk of developing DPN complications compared to the control group. Geriatric who have "uncontrolled blood pressure" have four times the risk of developing a DPN. Remarkable findings in this study were exposed to "smoking history," "uncontrolled blood glucose," and "CVD history" in geriatric found higher than five times the risk of DPN complication. Almost all geriatric patients who have exposure to "smoking history," "uncontrolled blood glucose," and "CVD history" in this study have DPN complications.

The exposure of "gender" and "duration of diabetes" did not affect the incidence of geriatric DPN complications. In this study found that gender and duration of diabetes are not absolute factors that influence DPN complications during the exposure of "smoking," "lipid profile," "neuroprotector user," blood glucose," "heart disease," "blood pressure," and "BMI" were well controlled. Thus, if those seven risk factors can be

controlled, the risk of DPN complications can be prevented, or DPN progression can be slowed.

4. Binary Conditional Logistic Regression Analysis To Determines The Dominant Risk Factor Caused Diabetic Peripheral Neuropathic Pain:

Every patient who has DPN complications, in general, will feel neuropathic pain. Neuropathic pain often appears as a sign that there is abnormal nerve function[2,19]. Binary conditional logistic regression analysis was carried out to look further into the influence of the seven significant factors previously elaborated on the degree of neuropathic pain felt by geriatrics. The results of the analysis are shown in Table 4.

Table 4 shows the average degree of neuropathic pain in patients grouped by risk factors that affect the incidence of DPN. The average patient who had mild neuropathic pain was 24.81%, moderate pain 61.09%, and severe pain 14.09%. There is a significant relationship between risk factors that cause DPN to the degree of pain. The pooled analysis found that the risk factors of "smoking history" and "uncontrolled blood glucose" contributed the most to the cause of the severity of neuropathic pain. Table 5 showed the two most influential risk factors for diabetic neuropathic pain compared to other risk factors.

A comparison of the two strongest risk factors, "smoking history" and "uncontrolled blood glucose" on the degree of pain in neuropathy in study subjects showed no significant results ($p > 0.05$). The relationship between the other risk factors with the two strongest factors showed significantly different results ($p < 0.05$). These data indicate that "smoking history" and "uncontrolled blood glucose" are the most influential factors on the degree of neuropathic pain by study subjects in case groups with high-risk factors.

DISCUSSION:

Neuropathic complications in diabetes mellitus is a microvascular complication that often arises in sufferers[7,21]. Geriatric itself is a special population that is very susceptible to this complication when suffering from diabetes mellitus with an uncontrolled condition[25–27]. Geriatrics is a vulnerable population because this group of patients has decreased physiological functions such as decreased functional ability and in maintaining homeostasis[21,22,26–28]. This makes it difficult for older people to deal with stressful situations that will affect the nervous, musculoskeletal, and cardiovascular systems[29–32]. Neuropathy complications in diabetes, if not treated seriously, can bring greater problems in the future for sufferers[25–27]. The risk of getting foot ulcers until amputation becomes the most difficult problem that sufferers will have in addition to reducing the quality of life due to neuropathic pain[2,4,7,10].

In this study, a case-control study approach was carried out to find any risk factors that could potentially cause DPN complications, especially in the elderly population. The results of the study show that there are seven factors that influence the incidence of DPN complications, among others having a smoking history, uncontrolled lipid profile, non-neuroprotector users, uncontrolled blood glucose, having a history of heart disease, uncontrolled blood pressure, and body mass index (BMI) above normal. Seven of the nine factors analyzed showed that these risk factors contributed five times to fold to complications than the control group. The most powerful and dominant risk factors are found in "smoking history" and "uncontrolled blood glucose." History of smoking and high blood glucose levels are associated with high levels of Reactive Oxygen Species (ROS), which will cause impaired blood vessel function in the form of thickening of the basement membrane of blood vessel walls, endothelial hyperplasia, endothelial dysfunction, increased expression of endothelin and increased levels of vascular endothelial growth factor (VEGF). If this is left unchecked, there will be an increased inhibition of axonal transport and inhibition of Na +/ K+ ATPase activity[26–28]. This condition will contribute to capillary damage and will ultimately cause axonal degeneration and nervous system dysfunction[2,4,5,7,10,11,22].

Other significant risk factors such as uncontrolled lipid profile, non-neuroprotector use, history of heart disease, uncontrolled blood pressure, and body mass index (BMI) above normal were also found regarding DPN risk. Not optimal control of these risk factors can worsen the homeostatic condition of diabetics[1,7,8,23]. In chronic conditions, the patient's body will increase the synthesis of a molecule called diacylglycerol (DAG), which is a critical activating factor for protein kinase-C, β, α, δ isoforms. Protein kinase C is also activated by oxidative stress and advanced glycation end products. Activation of protein kinase C causes increased vascular permeability, impaired synthesis of nitric oxide (NOs), and changes in blood flow. This event is thought to strongly support damage to the capillaries and peripheral nervous system[1,7,8,21–23]. Another important thing to note from the uncontrolled risk factors is the disruption of the activity of the Nerve Growth Factor (NGF). NGF is a protein that affects the maintenance of nerve fibers and sympathetic neurons. In patients with diabetes, especially the elderly, there is a decrease in NGF so that retrograde axonal transport (from the target organ to the cell body) is disrupted. Decreased levels of NGF are positively correlated with the presence of early symptoms of small fibers sensory neuropathy[21,22].

Risk factors found to be insignificant in this study were gender and duration of diabetes mellitus. Gender in this study is no longer a differentiator in the elderly group because, in general, sufferers in this population tend to have decreased physiological function, so that both men and women when the patient has entered 60 years, then the seven risk factors discussed earlier will be a certain factor[3,16,17,21,22,24]. The interesting thing is precisely found in the long or duration factor suffering from diabetes. In this study, it was found not significant as a contributor to the causes of DPN. This is still not known with certainty the cause. It is suspected that the duration of diabetes will not mean anything when important parameters such as blood glucose levels in diabetics who have been controlled[3,16,17,19,24]. If geriatric patients with diabetes are controlled, then the duration of diabetes is not a determining factor in the progression of the disease. This proves that the progression of diabetes mellitus is not determined by how long a patient has diabetes, but how long they can control their blood glucose profile. When the profile of glucose and other modified risk factors can be controlled, the progression of diabetes, especially neuropathy, will stop or slow down considerably[1,15–19].

This study still has several limitations because this study has a case-control design, all the exposure parameters that were analyzed depending on the medical records available. Parameters such as patient compliance with the drug, their HbA1C profile, what types of medicines they used, the profile of supplements they used, and other important parameters that cannot be observed holistically due to the limitations of available medical records. The number of research subjects also needs to be increased, so that similar research needs to be carried out with a larger number of subjects with experimental study designs. A definite recommendation for clinicians to intervene in seven significant risk factors based on the results in this study for the elderly with type 2 diabetes mellitus. Optimize all modifiable risk factors so that complications of DPN can be prevented or reduced in progression.

CONCLUSION:

Risk factors that affected peripheral neuropathy in elderly patients with type 2 diabetes mellitus are “a smoking history,” “uncontrolled lipid profile,” “non-neuroprotector users,” “uncontrolled blood glucose level,” “having a history of heart disease,” “uncontrolled blood pressure,” and “body mass index (BMI) above normal.” The most dominant risk factor and directly related to the severity of neuropathic pain are “smoking history” and “uncontrolled blood glucose level.”

CONFLICT OF INTEREST:

This paper was written independently. All authors disclose no financial or personal relationships with other people or organizations that could inappropriately influence the work.

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REFERENCES:

1. Arsa P, Ahmadinia-Tabesh R, Mohammadi Y. Assessment of the risk of Coronary Heart Disease in Diabetes Patients Type-II. Asian J Nurs Educ Res. 2019; 9(2): 267.
2. Duby JJ, Campbell RK, Setter SM, White JR, Rasmussen KA. Diabetic Neuropathy: An intensive review. Am J Heal Pharm. 2004 Jan 15; 61(2): 160–73.
3. Han, C.; Whiting, D; Guariguata L. IDF Diabetes Atlas. 6th Edition. Belgium: International Diabetes Federation; 2013. 19–26 p.
4. Juster-Switlyk K, Smith AG. Updates in Diabetic Peripheral Neuropathy. F1000Research. 2016; 5(738): 1–7.
5. Schofield P. The Assessment of Pain in Older People: UK National Guidelines. Age Ageing. 2018 Mar 1; 47(1): 1–22.
6. Katulanda P, Ranasinghe P, Jayawardena R, Constantine GR, Sheriff MHR, Matthews DR. The prevalence, patterns and predictors of diabetic peripheral neuropathy in a developing country. Diabetol Metab Syndr. 2012 Dec 29; 4(21): 1–8.
7. Darivemula S, Nagoor K, Patan SK, Reddy NB, Deepthi CS, Chittooru CS. Prevalence and Its Associated Determinants of Diabetic Peripheral Neuropathy (DPN) in Individuals Having Type-2 Diabetes Mellitus in Rural South India. Indian J Community Med. 2019; 44(2): 88–91.
8. Mao F, Zhu X, Liu S, Qiao X, Zheng H, Lu B, et al. Age as an Independent Risk Factor for Diabetic Peripheral Neuropathy in Chinese Patients with Type 2 Diabetes. Aging Dis. 2019; 10(3): 592.
9. Kawano T. A Current Overview of Diabetic Neuropathy – Mechanisms, Symptoms, Diagnosis, and Treatment. In: Peripheral Neuropathy. In Tech; 2014. p. 1–10.
10. Franklin GM, Kahn LB, Baxter J, Marshall KA, Hamman TF. Sensory Neuropathy in Non-Insulin-Dependent Diabetes Mellitus. Am J Epidemiol. 1990 Apr;131(4): 633–43.
11. Yoo M, Neena S, Mamatha P, Patricia MK. Painful Diabetic Peripheral Neuropathy: Presentations, Mechanisms, and Exercise Therapy. J Diabetes Metab. 2013; 1(10): 1–10.
12. Tracy JA, Dyck PJB. The Spectrum of Diabetic Neuropathies. Phys Med Rehabil Clin N Am. 2008 Feb; 19(1): 1–26.
13. Liu X, Xu Y, An M, Zeng Q. The risk factors for diabetic peripheral neuropathy: A meta-analysis. Palazón-Bru A, editor. PLoS One. 2019 Feb 20;14(2): 212–574.
14. Wild S, Roglic G, Green A, Sicree R, King H. Global Prevalence of Diabetes: Estimates for the year 2000 and projections for 2030. Diabetes Care. 2004 May 1; 27(5): 1047–53.
15. St Onge EL, Miller SA. Pain associated with diabetic peripheral neuropathy: a review of available treatments. P T. 2008 Mar; 33(3): 166–76.
16. Mulla SM, Buckley DN, Moulin DE, Couban R, Izhar Z, Agarwal

A, et al. Management of chronic neuropathic pain: a protocol for a multiple treatment comparison meta-analysis of randomized controlled trials. BMJ Open. 2014 Nov 20; 4(11): 1–7.
17. Geetha V, Sahu SK, Susila C. Assess Quality of Life (QOL) and Glycemic Level among Type 2 Diabetic Patients in Global Hospital and Research Centre and its Units, Sirohi, Rajasthan. Asian J Nurs Educ Res. 2017; 7(4): 577.
18. Joshi R. A Descriptive Study of the Prevalence of Diabetes Mellitus among Peoples residing in Valam Village, Mehsana, Gujarat. Asian J Nurs Educ Res. 2020; 10(1): 23.
19. C. M, Riddle M. Summary of Revisions: Standards of Medical Care in Diabetes—2020. In: Diabetes Care. 2020. p. S4–6.
20. C. M, Riddle M. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2020. In: Diabetes Care. 2020. p. S14–31.
21. C. M, Riddle M. Glycemic Targets: Standards of Medical Care in Diabetes—2020. In: Diabetes Care. 2020. p. S66–76.
22. C. M, Riddle M. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes—2020. In: Diabetes Care. 2020. p. S111–34.
23. C. M, Riddle M. Microvascular Complications and Foot Care: Standards of Medical Care in Diabetes−2020. In: Diabetes Care. 2020. p. S135–51.
24. Lewallen S, Courtright P. Epidemiology in practice: case-control studies. Community eye Heal. 1998;11(28):57–8.
25. Jaya MK, Dwicandra NO. Effectivity Analysis of Neuroprotector (Vitamin B Complex and Mecobalamin) as Neuropathic Pain Supportive Therapy in Elderly with Type 2 Diabetes Mellitus. Asian J Pharm Clin Res. 2017 Dec 1; 10(12): 320.
26. Jaya MKA, Herawati F. Effectivity Comparison of Amitriptyline versus Gabapentin as Neuropathic Pain Therapy in Elderly with Type II Diabetes Mellitus. Int Curr Res. 2017; 9(1): 44769–73.
27. Jaya MKA, Kuswardhani RAT. Safety Comparison between Amitriptyline versus Gabapentin on Neuropathic Pain Therapy in Geriatric with Type II Diabetes Mellitus. Bali Med J. 2016 Oct 12; 5(3): 129.
28. Singh DK, Winocour P, Farrington K. Oxidative stress in early diabetic nephropathy: fueling the fire. Nat Rev Endocrinol. 2011 Mar 14; 7(3): 176–84.
29. N.J M, Joseph T, Dharan SS, S. M. Neuropeptides–A Review. Asian J Pharm Res. 2014; 4(4): 198–200.
30. Khan MY, Gupta P, Bihari B, Verma VK. A Review on Diabetes and Its Management. Asian J Pharm Res. 2013; 3(1): 27–32.
31. Kaur J. A Study to Assess the Knowledge and Attitude related to Diabetic foot and its Prevention among Diabetics Attending Medical Outpatient Department in selected Hospitals of Sri Muktsar Sahib, Punjab. Asian J Nur Edu Res. 2014; 4(1): 50–5.
32. Pareek S. Prevalence of Pre-diabetes and Diabetes mellitus among the Northern Railway Employees: A retrospective study. Int J Adv Nurs Manag. 2017; 5(4): 347.
33. Devi SR, Venkatesan B. Effectiveness of foot reflexology on diabetic peripheral neuropathic pain among patients with diabetes. Int J Adv Nurs Manag. 2018; 6(2): 91.
34. Janet JB, Kanchana K, Nirmala T. Effect of Structured Teaching Programme on knowledge regarding Foot Care among Patients with Diabetes Mellitus at selected Hospital, Coimbatore. Int J Adv Nurs Manag. 2019; 7(4): 336.
35. Prasad J, Netam AK, Sahu MK, Satapathy T. Current Concepts in Clinical Based Management of Diabetic Foot Infections: A Review. Res J Pharmacol Pharmacodyn. 2017; 9(3): 157.
36. Javed S, Petropoulos IN, Alam U, Malik RA. Treatment of painful diabetic neuropathy. Ther Adv Chronic Dis. 2015 Jan 28; 6(1): 15–28.
37. Hu Z, Gao F, Qin L, Yang Y, Xu H. A Case-Control Study on Risk Factors and Their Interactions with Prediabetes among the Elderly in Rural Communities of Yiyang City, Hunan Province. J Diabetes Res. 2019 Feb 18; 1(1): 1–8.

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