

Glycemic Control and Peripheral Nerve Function after Healed of Plantar Foot Diabetic Ulcer in Semarang, Indonesia

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Glycemic Control and Peripheral Nerve Function after Healed of Plantar Foot Diabetic Ulcer in Semarang, Indonesia

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ABSTRACT

Background: Poor glycemic control and diabetic neuropathy cause the plantar foot diabetic ulcer. Glycemic control improvement has been done to heal the plantar foot diabetic ulcer. Thus, knowing the glycemic control and peripheral nerve function after plantar foot diabetic ulcer is very important. However, the study to evaluate the glycemic control and peripheral nerve function assessment after healed of plantar foot diabetic ulcer has not been conducted yet in Indonesia.

Purpose: The purpose of the study was to evaluate the levels and correlation of glycemic control and peripheral nerve function after healed of plantar foot diabetic ulcer in Semarang, Indonesia.

Methods: A cross-sectional study was conducted in patients with healed plantar foot diabetic ulcers selected consecutively at two hospitals in Semarang Indonesia. Data on glycemic control was measured using HbA1c levels. Peripheral nerve functions were measured using the Diabetic Neuropathy Examination (DNE) scores. Data were analyzed using the Pearson correlation test.

Results: Fifty patients with recently healed plantar foot diabetic ulcer (≤ 12 months) were included in this study. About 42% of the subject had very poor glycemic control ($\text{HbA1c} > 10\%$) and 92 % had dysfunction of peripheral nerve. There was a significant correlation of glycemic control and function of peripheral nerve after healed plantar foot diabetic ulcer ($r = 0.328, p = 0.006$).

Conclusion: Most of the patients with healed plantar foot diabetic ulcers had very poor glycemic control and peripheral nerve dysfunction. There was a positive correlation between glycemic control and peripheral nerve functions significantly in patients with healed plantar foot diabetic ulcers. This study recommends that have to make an intensive intervention to improve glycemic control and peripheral nerve function after healed of plantar diabetic foot ulcer.

Keywords: HbA1c, Diabetic Neuropathy, peripheral nerve function, glycemic control, diabetic foot ulcer

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BACKGROUND

Plantar foot diabetic ulcer is one of the diabetes mellitus (DM) complications (Armstrong et al., 2017). Plantar foot diabetic ulcer can be found in neuropathy diabetic foot ulcers, ischemic diabetic foot ulcers, and neuroischemic diabetic foot ulcers (Alavi et al., 2014). Plantar foot diabetic ulcer often occurs in diabetic patients with peripheral neuropathy (Dubsky et al., 2013). The most of diabetic foot ulcer in Semarang, Indonesia is neuropathy diabetic foot ulcer up to 49,1% and the least is ischemic diabetic foot ulcer up to 10,7 % (Pemayun & Naibaho, 2017).

The prevalence of plantar foot ulcer diabetic is 45.1 – 61.22% of the overall diabetic foot ulcer (Younis et al., 2018; Zaine et al., 2014). The majority of diabetic foot ulcer will heal for a longer duration rather than another wound (Alexiadou & Doupis, 2012). Some interventions are given for faster the healing process of diabetic foot ulcers, including glycemic control (Lepántalo et al., 2011). Thus, a diabetic foot ulcer gives a big burden on the patients (Raghav et al., 2018).

The preventive action of a diabetic foot ulcer is very important. International Working Group of Diabetic Foot

(IWGDF) has suggested that patients have to check their conditions at least once in one to three months after a diabetic foot ulcer healed to prevent a diabetic foot ulcer incident (S A Bus et al., 2016). The history of diabetic foot ulcer may influence the conditions of the patients after diabetic foot ulcer has healed (Sicco A Bus & van Netten, 2016). Not only glycemic control, but also peripheral nerve function are included in the assessment of the patients with diabetic foot ulcer history to make some preventive intervention of the diabetic foot ulcer in the future (Alexiadou & Doupis, 2012; S A Bus et al., 2016). Most of the patients with diabetic foot ulcers have poor glycemic control. Glycemic control can be demonstrated with the HbA1c level (Association, 2018). Diabetic patients are recommended to check HbA1c at least two times a year (Association, 2018). HbA1c may exhibit the condition of glycemic control of the patient within the previous three months (Tavares Ribeiro et al., 2016). The health care provider in Indonesia makes a target of the HbA1c level for diabetic patients is $< 7\%$ to prevent diabetic foot ulcers (Endocrinology, 2015). Previous studies in some countries founded vary in the result assessment of the patients with diabetic foot ulcer

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history in the word (Khalifa, 2018; Molines-Barroso et al., 2019; Monami et al., 2015; Waaijman, De Haart, et al., 2014). HbA1c levels of patients with diabetic foot ulcer history of all foot locations in Italy was 7.35% and in Egypt was 10.24%, but the HbA1c level of patients with plantar foot diabetic ulcer history in Spain was 7.4% and in Amsterdam was 7.6% in healed of plantar foot diabetic ulcer patients (Khalifa, 2018; Molines-Barroso et al., 2019; Monami et al., 2015; Waaijman, de Haart, et al., 2014). There is no study in Indonesia about glycemic control in healed plantar foot diabetic foot ulcers. Giving the data about glycemic control in patients with healed plantar foot diabetic ulcers is very important to prevent vascular complications more severe and to reduce the incidence of the dead. Poor glycemic control may result in the impact of death for patients if not treated intensively (Mader et al., 2019). Healed plantar foot diabetic ulcer patients with poor glycemic control have a 9.9 times higher risk of dying compared to those with good glycemic control (Mader et al., 2019).

Based on pathophysiology, chronic hyperglycemia can cause peripheral nerve damage that decreases the nerve conduction and function of the nerve in diabetic patients (Alavi et al., 2014; Pop-Busui et al., 2017). The previous study has found the correlation of HbA1c variability and the conduction of nerve in diabetic patients (Lai et al., 2019). The study to evaluate the levels and correlate glycemic control and peripheral nerve function after healed of plantar foot diabetic foot ulcer have not been conducted yet. The large and small nerve fiber function on the lower limb were conducted using clinical scores that can be done in all setting.

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OBJECTIVE

The objective of the study was to evaluate the levels and correlation between HbA1c levels with peripheral nerve function.

METHODS

Design and Sample

A cross-sectional study was conducted on subjects who healed plantar foot diabetic ulcers at two hospitals in Semarang Indonesia from September 2019 to February 2020 that selected consecutively. The study's inclusion criteria were 40-60 years old and have recently healed plantar foot diabetic ulcer (<12 months to study entry) and had written informed consent. Subjects were excluded if they have lower limb contracture, Parkinson's, stroke with lower limb paresis/plegia, lower limb pos-amputation.

Data Collection

Data on glycemic control and peripheral nerve function were obtained at the same time. Glycemic control was identified by the HbA1c level. Data of HbA1c was obtained by analyzing a sample of venous blood inserted in a tube that has been given EDTA. Samples were analyzed with high-performance liquid chromatography (HPLC) ion exchanger methods in NGSP certified laboratories (National Glycohemoglobin Standardization Program). HbA1c is the gold standard for glycemic control in diabetic patients. Glycemic control was divided into four categories such as good glycemic control if HbA1c levels <7%, fair glycemic control if HbA1c levels 7.1-8%, poor glycemic control if HbA1c levels 8.1-10%, and very poor glycemic control if >10%. Peripheral nerve function was identified by clinical scores. Meijer et

al developed a diabetic neuropathy examination (DNE) scoring to diagnose peripheral nerve fiber dysfunction and its severity in diabetic patients (J.-W. Meijer et al., 2000; J.-W. G. Meijer et al., 2003). Peripheral nerve function was divided into 2 categories such as normal function if DNE scores 0-3 and dysfunction of peripheral nerve if DNE score >3. DNE scores obtained by physical assessment of the small and large nerve fiber function. DNE contains 8 items that can assess the function of small and large nerve of peripheral nerve function. Each measurement DNE item is rated 0 to 2 (0 if normal and 2 if severely disturbed). (20,21)

Statistical Analysis

Statistical analysis using SPSS 23.00. Univariate analysis was performed to describe the subject characteristics. Continuous variables were reported in mean $\pm$ standard deviations (SD), and variable categorical variables are reported in frequency and percentage. Shapiro Wilk's test was used to determine the distribution of data. Pearson correlation test was used to analyze the correlation of HbA1c levels and peripheral nerve function, with a significant level $p < 0.05$.

Ethical Clearance

This study was approved by the ethics committee of the faculty of medicine at Diponegoro University, Semarang Indonesia (Number 395/EC/KEPK/FK UNDIP/IX/2019). The permission from the hospital authorities in Semarang was secured prior to the study. The subject gave informed consent before the research begin.

RESULTS

50 subjects of recently healed plantar foot diabetic ulcers were included in the study. Subject characteristics were shown in table 1. Subjects had a mean age of 53.34 ± 5.87 years, mean body mass index (BMI) 24.98 ± 5.63 , and diabetic duration 9.38 ± 7.01 . More than half of subjects were female (52%). Most of the subjects were married (82%), had low education levels (84%), and used oral antidiabetic drugs (82%).

Table 2 shows the mean of HbA1c levels $9.79 \pm 2.02\%$, with majority of the subjects (60%) had very poor glycaemic control (HbA1c > 10%). About 96% of the subject had peripheral nerve dysfunction (DNE score >3), with mean DNE score was 7.68 ± 2.47 .

Table 3 shows a correlation between HbA1c and the DNE score based on the Pearson correlation test ($r = 0.328$, $p = 0.006$).

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DISCUSSION

The objective of the study was to evaluate the levels and correlation of glycaemic control and peripheral nerve function in patients with plantar foot diabetic ulcer history. Plantar foot diabetic ulcer often occurs in diabetic neuropathy patients (Dubsy et al., 2013). Patients with diabetic neuropathy showed the dysfunction of the peripheral nerve (Alavi et al., 2014; Pop-Busui et al., 2017). The dysfunction of the peripheral nerve should be improved and monitored in many ways to prevent diabetic foot ulcers (Pop-Busui et al., 2017). Patients with healed plantar foot diabetic foot ulcers have to monitor the peripheral nerve function in the lower limb at least once everyone to three months. The study evaluated peripheral nerve dysfunction in diabetic patients after healed at least 1 month of plantar foot diabetic ulcer to study entry. The patients may have had

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management for the dysfunction of peripheral nerve after plantar diabetic foot ulcer has healed.

The study found that about 92% of the patients with healed plantar foot diabetic ulcers had dysfunction of peripheral nerve function, with the result of diabetic neuropathy examination scores above three. Only 8% of the patients with healed plantar foot diabetic ulcers had normal peripheral nerve function, with the result of diabetic neuropathy examination score under three. It showed that majority of patients had dysfunction of peripheral nerve. The dysfunction of peripheral nerve at the lower limb involved large and small nerve fibers (Pop-Busui et al., 2017). Patients with dysfunction of small and large nerve fibers showed less sensitivity and movement (Pop-Busui et al., 2017). Patients with healed plantar foot diabetic ulcers showed both small and large nerve fibers dysfunction of peripheral nerve. The study involves the examination of the function of small nerve fibers for pin prick sensitivity and large nerve fibers for vibration perception, monofilament, and movement. Found in this study, the mean DNE score was 7.68.

The normal function of the peripheral nerve is very important for patients with healed plantar foot diabetic ulcers to prevent diabetic foot ulcer recurrence incidence (Armstrong et al., 2017). The peripheral nerve can protect the patients from such injury/trauma that can hurt the skin of the patients (Alavi et al., 2014). Pemayun (2017) found that thermal injury, ill-fitting shoes, walking barefoot, and minor trauma were the precipitating events preceding the diabetic foot ulcer in Indonesia (Pemayun & Naibaho, 2017). Thus, the good function of the peripheral nerve can protect the patients from recurrence of plantar foot diabetic ulcer incidence (Alavi et al., 2014; Armstrong et al., 2017).

The study found the majority of the patients with healed plantar foot diabetic ulcers had HbA1c >7%, even 42% in very poor glycemic control (HbA1c >10%). Only 10% of 50 patients with healed plantar foot diabetic ulcers had HbA1c level <7. It showed that they were far from the HbA1c target level, even though they have had treatment for controlling the glycemic. About 82% of the patients have used antidiabetic oral for controlling the glycaemic, and only 18% have used the combination of antidiabetic oral and insulin injection. As the Association of endocrinologist consensus in Indonesia, insulin injection is given to diabetic patients with HbA1c level >9% to control the glycemic (Endocrinology, 2015). The glycemic control intervention is given to the patients when they are determined as diabetic patients (Association, 2018; Endocrinology, 2015). More intensive glycemic control is given to diabetic patients with diabetic foot ulcer to faster the healing of diabetic foot ulcers (Schaper et al., 2020). Most patients with diabetic foot ulcers have poor glycemic control in Indonesia (Pemayun & Naibaho, 2017). Compare to the Pemayun study, the percentage of very poor glycemic control in patients with active diabetic foot ulcer was higher than patients after diabetic foot ulcer has healed was up to 60% (Pemayun & Naibaho, 2017).

Glycemic control stayed to improve and evaluated even though the diabetic foot ulcer has healed. However, the mean of HbA1c level still high after plantar diabetic foot ulcer has been managed. The mean of HbA1c level of the patients with healed plantar foot diabetic ulcer up to 9,79%. When compared to patients with healed diabetic foot ulcers in the general location, the levels of HbA1c

were lower that reached 10.24%. but when compared to patients with healed plantar foot ulcer diabetic in Amsterdam 7.60% and in Spain 7.4% were higher patients (Khalifa, 2018; Molines-Barroso et al., 2019; Monami et al., 2015; Waaijman, de Haart, et al., 2014).

The causes of HbA1c level in patients with healed plantar foot diabetic ulcer was very complicated. Poor glycemic control in patients with healed plantar foot diabetic ulcers might be related to the sociodemographic and clinical characteristics. The patients with healed plantar foot diabetic ulcers have various demographics and clinical characteristics that may influence the glycaemic control. The previous study found that age, diabetic duration, antidiabetic medication usage of diabetic patients related to the HbA1c of the patients (Cheng et al., 2019). The mean age above 50 years and mean diabetic duration of the subjects was above 9 years may influence the dysfunction of the pancreas to produce the insulin that can control the blood glucose of the patients.

The results of the study showed that there was a correlation between glycemic control and peripheral nerve function in patients with plantar foot diabetic ulcer history. The poorer glycemic control, the poorer function of the peripheral nerve. The hyperglycemia will make the production of some enzymes such as aldose reductase and sorbitol dehydrogenase (Syafriil, 2018). The enzymes will accumulate glucose products that can decrease the synthesis of nerve cell myoinositol. As these nerve cell myoinositol decrease, the conduction or transmission of the impulse along peripheral nerve fibers decreased affecting the function of peripheral nerve performance (Syafriil, 2018). According to previous research, the variability of HbA1c was related to nerve conduction in diabetic patients (Lai et al., 2019). Patients with higher HbA1c levels have dysfunction of nerve conduction (Lai et al., 2019). Good nerve conduction can be indicated the good condition of the nerve and the nerve can have functioned normally (Pop-Busui et al., 2017). Thus, hyperglycemia has an effect on the function of peripheral nerve after healed of plantar foot diabetic ulcers.

However, this study had some limitations. The number of samples in the study was still limited. The cross-sectional design could not know the causal relationship well. This study was the first conducted in patients with healed plantar foot ulcer diabetic so that it could not compare with previous studies with the same population. Some variables were not determined that could influence the HbA1c level and function of the peripheral nerve.

CONCLUSION

Almost all patients study with healed plantar foot ulcer diabetic had HbA1c levels above 7% and dysfunction of the peripheral nerve. Glycemic control was correlated with the function of peripheral nerve. The intensive intervention is necessary to improve the HbA1c levels and peripheral nerve function among patients with a healed plantar foot diabetic ulcer.

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Table 1. Characteristics of the subjects

Characteristics	n (%)	Mean ± SD
Age (years)		53.34 ± 5.87
Gender		
Male	24 (48.00)	
Female	26 (52.00)	
Marital status		
Married	41 (82.00)	
Widow	9 (18.00)	
Educational levels		
College below	42 (84.00)	
College	8 (16.00)	
Medication usage		
Antidiabetic oral	41 (82.00)	
Insulin + antidiabetic oral	9 (18.00)	
BMI (kg/m ²)		24.98 ± 5.63
Diabetic duration (years)		9.38 ± 7.01

Table 2. HbA1c levels and peripheral nerve functions

	n (%)	Mean ± SD
HbA1c (%)		9.79 ± 2.02
Good glycemic control (<7%)	5 (10)	
Fair glycemic control (7,1 -8%)	6 (12)	
Poor glycemic control (8,1-10%)	18 (36)	
Very poor glycaemic control (>10%)	21 (42)	
Peripheral nerve functions		7.68 ± 2.47
Normal peripheral nerve function (DNE scores≤3)	4 (8)	
Peripheral nerve dysfunction (DNE score>3)	46 (92)	
4-8	15 (30)	
9-12	30 (60)	
13-16	1 (2)	

Table 3. Correlation of HbA1c levels and DNE score

HbA1c	DNE
R	0.382
P	0.006

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