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Original Article

Effect of pharmacist-led intervention on predictors of diabetic neuropathy at two different hospitals of Malaysia

[Efecto de la intervención dirigida por farmacéuticos sobre los predictores de neuropatía diabética en dos hospitales diferentes de Malasia]

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Abstract

Context: Diabetes mellitus is a progressive disease. In poor glycemic control, it can cause severe and non-reversible complications. A proper educational intervention from health care providers is needed for patients to decrease the progression of diabetes and its complications.

Aims: To evaluate the effect of pharmacist-led educational intervention on predictors of diabetic neuropathy in patients.

Methods: From two tertiary care hospitals, diabetic patients were randomly selected and divided into the control and intervention groups. The control group contained 200 patients who were getting traditional treatment from hospitals. In contrast, the intervention group included 200 patients who were receiving conventional treatment together with separate counseling sessions with pharmacists. The study continued for one year, and four follow up visits for both groups. A pre-validated data collection form was used to collect data for the signs and symptoms of diabetic neuropathy. Statistical Package for the Social Sciences version 24 was used to analyze the data.

Results: The average HbA1c values decreased by up to 1.96% in the control group and 3.41% in the intervention group from baseline data. A statistically significant ($p<0.05$) difference in HbA1c among both of the study groups at every follow-up. The results of univariate and multivariate regression analysis showed that a statistically significant difference was observed in the improvement of signs and symptoms of diabetic neuropathy among both of the study groups.

Conclusions: Statistically significant reduction in the sign and symptoms of diabetic neuropathy was observed in the intervention group at the end of one year.

Keywords: diabetic complications; diabetes mellitus; diabetes medication therapy adherence clinic program; neuropathy; pharmacist intervention.

Resumen

Contexto: La diabetes mellitus es una enfermedad progresiva. Un mal control glucémico puede provocar complicaciones graves e irreversibles. Se necesita una intervención educativa adecuada de los proveedores de atención médica para que los pacientes disminuyan la progresión de la diabetes y sus complicaciones.

Objetivos: Evaluar el efecto de la intervención educativa dirigida por farmacéuticos sobre los predictores de la neuropatía diabética en pacientes.

Métodos: De dos hospitales de atención terciaria, los pacientes diabéticos fueron seleccionados al azar y divididos en grupos de control e intervención. El grupo de control estaba formado por 200 pacientes que recibían tratamiento tradicional en hospitales. Por el contrario, el grupo de intervención incluyó a 200 pacientes que estaban recibiendo tratamiento convencional junto con sesiones de asesoramiento separadas con farmacéuticos. El estudio continuó durante un año y cuatro visitas de seguimiento para ambos grupos. Se utilizó un formulario de recopilación de datos, validado previamente, para recopilar datos sobre los signos y síntomas de la neuropatía diabética. Se utilizó el paquete estadístico para Ciencias Sociales versión 24 para analizar los datos.

Resultados: Los valores medios de HbA1c disminuyeron hasta 1,96% en el grupo de control y 3,41% en el grupo de intervención con respecto a los datos iniciales. Una diferencia estadísticamente significativa ($p<0.05$) en HbA1c entre ambos grupos de estudio en cada seguimiento. Los resultados del análisis de regresión univariante y multivariante mostraron que se observó una diferencia estadísticamente significativa en la mejora de los signos y síntomas de la neuropatía diabética entre ambos grupos de estudio.

Conclusiones: Se observó una reducción estadísticamente significativa de los signos y síntomas de la neuropatía diabética en el grupo de intervención al cabo de un año.

Palabras Clave: complicaciones diabéticas; diabetes mellitus; intervención farmacéutica; neuropatía; programa de adherencia clínica a la terapia de medicamentos para la diabetes.

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INTRODUCTION

Diabetes mellitus became a prolonged upsetting public health issue throughout the world for the last few decades (Tabish, 2007). For achieving rigorous glycemic control, not only the physician adherence and compliance to the given guideline are important, but patient adherence to medication regimens also plays a vital role (Polonsky and Henry, 2016). Patient adherences toward the medication, dosage regimens, proper use as well as storage of insulin devices are the key factors in patient compliance. Patient compliance can be increased with appropriate counseling and education of patients about the consequences of uncontrolled disease by healthcare providers (Polonsky and Henry, 2016).

The risk of developing diabetes in adults is more in developing countries such as Malaysia (Chan et al., 2019). According to the National Health and Morbidity Survey 2018 by the Ministry of Health Malaysia (Elderly Health), the total prevalence of diabetes mellitus (self-reported diabetes) was 18.8% (Ministry of Health Malaysia, 2018). The prevalence of diabetes mellitus is continuously increasing, and many of them are still undiagnosed. The highest prevalence is in Kedah, Perlis, and Johor states of Malaysia.

Type 2 diabetes mellitus is an important endocrine and metabolic disorder affecting different body organs of diabetic patients when their glycemic control is not good (Ekoru et al., 2019). Uncontrolled diabetes mellitus usually results in short and long-term complications, including hypoglycemia, heart problems, neuropathy, nephropathy, retinopathy, and diabetic foot (Chawla et al., 2016; Goel et al., 2019; Huang et al., 2020). Poor control of diabetes is a major public health issue and a considerable hazard aspect for the progression of its complications. Thus, glycemic control remains the key therapeutic goal for the stoppage of these organ damages and any other problems due to diabetes (Haghighatpanah et al., 2018).

The HbA1c has become a benchmark for determining the control of diabetes and is helping in predicting short or long-term diabetic complications (Rohlfing et al., 2000; Bennett et al., 2007). The control of HbA1c is complex in clinical practice; thus, both patient and health care provider-related factors are equally important in good control of HbA1c (Rhee et al., 2005; Greenapple, 2011).

From the literature, it has been proven that the teamwork of physicians and pharmacists resulted in improved glycemic control in diabetic patients (Iqbal et al., 2014; 2019). In Malaysia, pharmacists are directly working together with physicians in all tertiary hospitals by Diabetes Medication Therapy Adherence Clinic (DMTAC) program. In DMTAC the pharmacists are working with physicians. DMTAC is ambulatory care and value-added service provided by pharmacists in collaboration with physicians to help diabetic patients to accomplish better medication adherence and good glycemic control. Patients enrolled under DMTAC followed-up for a minimum of 8 visits, where they receive medication adherence evaluation, identification and solving of drug-related problems, counseling for prescribed medication, evaluating the clinical outcomes, and diabetes education by the pharmacist. In this arrangement, physicians recommend medication regimens, and the pharmacists are educating the patient about diabetes mellitus, lifestyle modifications, dosages regimens, proper use, and storage of insulin devices. They also taught about the disease progression if not control properly with its complications.

The present study was conducted to appraise the impact of pharmacist educational intervention on the improvement of signs and symptoms that belonged to diabetic neuropathy.

MATERIAL AND METHODS

Sample size and study approvals

The current study was a prospective non-clinical, multicenter randomized control study and

was conducted in two hospitals of Malaysia. The present study was approved by hospital authorities as well as the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia, with approval reference [KKM/NIHSEC/P18-1307 (13)]. The sample size was estimated using the previous data from a study by Butt et al. (2016) to compare the mean of HbA1c between the intervention and control group. A total of 65 patients in each study group were needed to detect the difference of 0.79% (8.47% *versus* 9.26% HBA1c) with 80% certainty (power) and using an alpha level of 0.05 and SD was σ = 1.61. The type I error probability associated with the test of this null hypothesis was 0.05. With an additional 20% dropout rate, the sample size was about 80 samples per group.

Study procedure

For recruiting the estimated sample size from study locations, 3 to 4 months' time capsule frame was set, depending on the patient's inflow in each hospital. Initially, the informed consent form was given and signed by 150 patients in each hospital. The patient's hospital identification numbers from each selected hospital were listed as a control group and, similarly, an interventional group. Upon completing 150 record numbers of patients in each hospital, that list was entered into Microsoft Excel, and randomization was carried out to select randomly 100 from each 150 record numbers to consider them as participants of the current study in each hospital (Fig. 1).

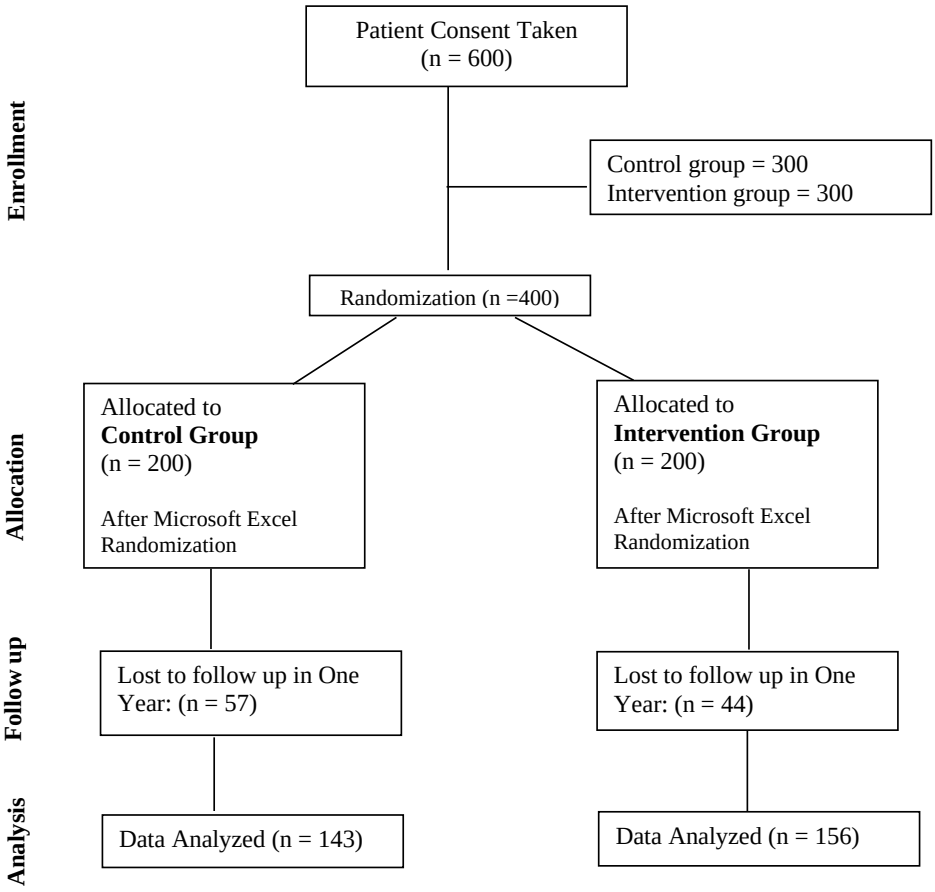

Figure 1. Flow diagram of the study.

The informed consent form was given and signed by 300 patients in each study group. After randomization, 200 patients were left behind in each study group. Then, follow-ups were made for these patients every 3-4 months in both the control and intervention groups.

Control group

This group included adult outpatients of diabetes mellitus with Type 2 Diabetes Mellitus (T2DM) for at least five years, HbA1c more than 8%, and receiving usual treatment from diabetic clinics selected hospitals.

Intervention group

This group included adult patients of diabetes mellitus who were having Type 2 Diabetes Mellitus (T2DM) for at least five years, HbA1c more than 8%, and receiving treatment from diabetic clinics with the intervention of pharmacists from selected hospitals.

Baseline data was taken for the control group and intervention group from each selected hospital. Then, follow-ups were made for these patients every 3-4 months in both the control and intervention groups. After baseline, a total of four follow-ups were made for both control and intervention groups in each hospital. At every follow-up, the laboratory outcomes and the sign and symptoms of diabetic neuropathy were taken on data collection forms.

The control group patients were receiving usual treatment from diabetic clinics in selected hospitals. The intervention group patients were also receiving treatment from diabetic clinics with the intervention of pharmacists from selected hospitals. All the included T2DM patients were having Type 2 diabetes mellitus (T2DM) for at least five years and HbA1c more than 8%. There was no difference in the pharmacotherapy of the patients in both of the study groups. All the patients were receiving the same recommended treatment as per the Malaysian guideline for diabetes mellitus. All the patients were on combination therapy (insulin with oral antidiabetics). Thus, there was no difference in the standard treatment in both of the study groups. The only difference was the educational interventions from the pharmacist for the intervention groups.

Study tool

The patient information was collected by a prevalidated data collection tool. This tool contained demographic details and clinical outcomes in the form of HbA1c of patients. Hospital laboratories determined the HbA1c of patients in both study groups as both the selected study hospitals belonged to the government; thus, the laboratory investigations and all medications were provided by Malaysia's government under the Ministry of Health Malaysia. All the laboratory investigations and medicines were free of cost to the patients. The researchers only collected the details of data in the form of information from the patients. Additionally, the study tool also carried various signs and symptoms list related to diabetic neuropathy to evaluate diabetic complications in selected patients.

Determination of HbA1c

Laboratories of hospitals determined the entire laboratory investigations, including HbA1c. The researchers only collected data in the form of information from patient files.

Determination of diabetic neuropathy predictors

The physicians conducted all the determinations of diabetic neuropathy predictors in both hospitals as per the recommendations of Malaysian Clinical Practice guidelines for diabetes mellitus. The researchers only collected data in the form of information from patient files.

Statistical analysis

The data analysis was done using SPSS version 24. Descriptive data were expressed as mean ± standard deviation (SD). The normality of the data was checked by SPSS using skewness and kurtosis testing. The univariate and multivariate regression analysis was used to evaluate the association between independent variables and pharmacist intervention in the current study. A value of $p<0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

At the end of one year, out of 400 eligible recruited patients, 299 patients had completed four required follow-ups after baseline for the current study's total one-year duration. Overall, 26.5%

(intervention arm: 29.5% vs. control arm: 23.5%) patients dropped out of the study due to various known and unknown reasons. Data in the form of information was collected from the patients on the validated data collection tool. The first follow-up was taken 3-4 months of baseline and followed by every 3-4 months. The total period of data collected was one year from the date of patient recruitment.

The socio-demographic characteristics of finally included 299 patients are presented in Table 1. From these 299 patients, 149 patients were from Hospital A, and 150 patients were from Hospital B. Overall, the portion of Malay ethnicity was more in both of the study locations.

The changes and improvements in HbA1c in both of the study groups are shown in Fig. 2.

At baseline, all the signs and symptoms belong to diabetic neuropathy were checked for statistically significant to observe the differences at baseline. Statistically, non-significant differences were observed between all the signs and symptoms that belonged to diabetic neuropathy. The number and percentage of patients among study groups having each sign and symptom of complications were measured by cross-tabulation. Regression analysis was performed to examine the effect of a pharmacist-led education intervention on each diabetic neuropathy signs and symptom improvement on every follow-up visit.

The baseline characteristics of the control and intervention groups can be seen in Table 2 and the follow-up characteristics of the control and intervention groups can be seen in Table 3.

At follow-up 1, in the control group, patients without signs and symptoms were 33.6% (Table 2), which was improved up to 35.7% (Table 3). In contrast, in the intervention group at baseline, this percentage was 35.9%, which was improved at follow-up one up to 44.9%. Similarly, the improvements were noted in 'numbness or reduced ability to feel pain/temperature change'. A statistically significant (p=0.048) difference was observed between the control and intervention group on 'numbness or reduced ability to feel pain/temperature change'. However, no improvements were found in the dry skin symptom of diabetic neuropathy at follow up 1 in both study groups.

At follow-up 2, in the control group, the patients without signs and symptoms were 35.7% at follow-up one, which was improved up to 43.4% at follow-up 2. In contrast, at follow-up 1, this percentage was 44.9% in the intervention group, which was improved at follow up two up to 56.4%. Similarly, the improvements were noted in 'numbness or reduced ability to feel pain/temperature change'. A statistically significant (p=0.020) difference was observed between the control and intervention group on 'numbness or reduced ability to feel pain/temperature change'. In the same way, the improvements were noted in all signs and symptoms of diabetic neuropathy at the end of follow up 2 in control and intervention groups.

At follow up 3, a significant improvement was observed between the control group and intervention group in various signs and symptoms of the complication. Regression analysis showed that the statistically significant improvement changes between both of the study groups in 'numbness or reduced ability to feel pain/temperature change' (p=0.005), and 'increased sensitivity to touch' (p=0.038). Whereas statistically non-significant difference (p=0.694) was observed in 'loss of balance/coordination' symptom of diabetic neuropathy in both of the study groups at third follow up.

At follow-up 4, a noteworthy improvement was observed between the control and intervention groups in various signs and symptoms of neuropathy. Regression analysis showed that the statistically significant improvement changes between both of the study groups in 'numbness or reduced ability to feel pain/temperature change' (p=0.003), 'tingling or burning sensation' (p=0.007), and 'increased sensitivity to touch' (p=0.032). Notably, the patients without any sign and symptom of diabetic neuropathy became 90.4%, which was 35.9% at baseline. Whereas this percentage in the control group was 65.7% at the fourth follow-up, but this percentage was 33.6% at baseline.

Table 1. Demographics and clinical characteristics of patients at baseline.

Variables	Frequency (%)
Hospital	
Hospital A	150 (50.2)
Hospital B	149 (49.8)
Gender	
Male	144 (48.2)
Female	155 (51.8)
Ethnicity	
Malay	231 (77.3)
Chinese	48 (16.1)
Indian	20 (6.7)
Age (mean, SD)	60.25 ± 6.31
Duration of diabetes (years, SD)	9.96 ± 2.87
Residence status	
Urban	145 (48.5)
Rural	154 (51.5)
Employment status	
Unemployed	145 (48.5)
Employed	154 (51.5)
Educational status	
No Education	96 (32.1)
Primary	97 (32.4)
Secondary	78 (26.1)
College/University	28 (9.4)
Type of daily diet	
Vegetarian	159 (52.2)
Non-vegetarian	140 (46.8)
Smoking status	
Yes	53 (17.7)
No	246 (82.3)
Exercise status	
Yes	78 (26.1)
No	221 (73.9)
Type of anti-diabetic therapy	
Oral only	116 (38.8)
Insulin	129 (43.1)
Oral + insulin	54 (18.1)

SD: Standard deviation, Hospital A: Hospital Sultan Abdul Halim, Sungai Petani, Kedah; Hospital B: Hospital Sultanah Bahiyah, Alor Setar, Kedah.

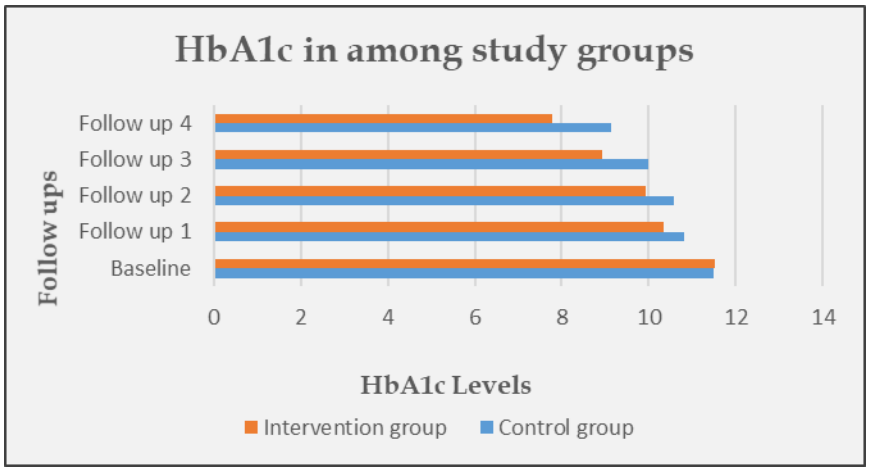

Figure 2. Changes in the HbA1c in both of the study groups at all follow-ups.

Data are expressed as mean ± SD (n = 299). HbA1c of respondents in both of the study groups are expressed in percentage (%). Follow-ups were taken after every 3-4 months. The HbA1c in control group at follow-up 1 was decreased up to 0.5%, and at follow-up 4 was decreased up 1.8%, but this decrease in the intervention group was 1.4% and 3.8%, respectively. The differences were statistically significant among the study groups ($p \leq 0.001$).

Table 2. Diabetic neuropathy predictors at baseline (n = 299).

Predictors	Study groups		Univariate analysis	
	C. G N (%)	I. G N (%)	Crude OR (95% CI)	p-value
Diabetic Neuropathy				
No symptom	48 (33.6)	56 (35.9)	Referent	
Numbness or reduced ability to feel pain/temperature change	32 (22.4)	30 (19.2)	0.804 (0.428–1.509)	0.503
Tingling or burning sensation	21 (14.7)	20 (12.8)	0.816 (0.396–1.683)	0.640
Increased sensitivity to touch	18 (12.6)	21 (13.5)	1.000 (0.478–2.092)	0.823
Dry skin	18 (12.6)	21 (13.5)	1.000 (0.478–2.092)	0.823
Loss of balance/coordination	6 (4.2)	8 (5.1)	0.143 (0.370–3.526)	0.703

Assumption: Simple Logistics Regression assumed that there must be at least two cases for each category of the dependent; OR: Odds Ratio; 95% CI: 95% Confidence Interval; C.G: Control group; I.G: Intervention group.

All the statistical differences at every follow-up from baseline for each study group can be seen in Table 3.

In the present study, at baseline, the patients in both of the study groups were clinically equal, as all of them followed the inclusion criterion. All the patients were receiving medication from the same hospital under the same laboratory investigations, and the physicians involved were also the same. The only difference was created after the first follow up when the patients were categorized as a control and intervention group. Everything was still the same in intervention groups as in the control group except the pharmacist educational intervention from the DMTAC program. All the laboratory investigations and treatments were given as per the recommendations of Clinical Practice Guideline Malaysia for diabetes mellitus. After the involvement of pharmacist educational intervention, the HbA1c in the intervention group decreased significantly in the intervention group compared to the control group.

A decrease in HbA1c in study groups resulted in improved signs and symptoms of diabetic neuropathy. This improvement was started in the first follow up itself. However, these improvements were more in the intervention group in the presence of pharmacist educational intervention. In the control group, patients without signs and symptoms were 33.6% at baseline, which was improved by up to 35.7% at follow up 1. In contrast, this percentage was 35.9% in the intervention group at baseline, which was improved by up to 44.9% at first follow-up.

Table 3. Diabetic neuropathy predictors at different follow ups (n = 299).

Predictors	Study groups		Univariate analysis		Multivariate analysis	
	C. G N (%)	I. G N (%)	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
At Follow up 1						
No symptom	51 (35.7)	70 (44.9)	Referent		Referent	
Numbness or reduced ability to feel pain/ temperature change	31 (21.7)	22 (14.1)	0.517 (0.269–0.995)	0.048	0.345 (0.118–0.869)	0.087
Tingling or burning sensation	20 (14.0)	18 (11.5)	0.656 (0.315–1.363)	0.258	-	-
Increased sensitivity to touch	18 (12.6)	19 (12.2)	0.769 (0.367–1.610)	0.486	-	-
Dry skin	18 (12.6)	21 (13.5)	0.850 (0.411–1.756)	0.661	-	-
Loss of balance/ coordination	5 (3.5)	6 (3.8)	0.874 (0.253–3.023)	0.832	-	-
At Follow up 2						
No symptom	62 (43.4)	88 (56.4)	Referent	Referent		
Numbness or reduced ability to feel pain/ temperature change	26 (18.2)	16 (10.3)	0.434 (0.215–0.875)	0.020	0.298 (0.162–0.713)	0.049
Tingling or burning sensation	18 (12.6)	16 (10.3)	0.626 (0.296–1.323)	0.220	-	-
Increased sensitivity to touch	16 (11.2)	13 (8.3)	0.572 (0.257–1.275)	0.172	-	-
Dry skin	17 (11.9)	18 (11.5)	0.746 (0.357–1.561)	0.437	-	-
Loss of balance/ coordination	4 (2.8)	5 (3.2)	0.881 (0.221–3.412)	0.854	-	-
At Follow up 3						
No symptom	80 (55.9)	119 (76.3)	Referent	Referent		
Numbness or reduced ability to feel pain/ temperature change	19 (13.3)	8 (5.1)	0.283 (0.118–0.678)	0.005	0.193 (0.096-0.389)	0.014
Tingling or burning sensation	15 (10.5)	10 (6.4)	0.448 (0.192–1.047)	0.064	0.253 (0.085–1.031)	0.203
Increased sensitivity to touch	13 (9.1)	7 (4.5)	0.362(0.138–0.947)	0.038	0.246 (0.108–0.728)	0.111
Dry skin	14 (9.8)	10 (6.4)	0.480 (0.203–1.134)	0.094	0.297 (0.183–1.077)	0.283
Loss of balance/ coordination	2 (1.4)	2 (1.3)	0.672 (0.093–4.871)	0.694	-	-
At Follow up 4						
No symptom	94 (65.7)	141 (90.4)	Referent	Referent		
Numbness or reduced ability to feel pain/ temperature change	14 (9.8)	3 (1.9)	0.143 (0.040–0.511)	0.003	0.121 (0.029–0.397)	0.004
Tingling or burning sensation	13 (9.1)	4 (2.6)	0.205 (0.065–0.648)	0.007	0.142 (0.036–0.458)	0.015
Increased sensitivity to touch	11 (7.7)	5 (3.2)	0.303 (0.102–0.900)	0.032	0.158 (0.092–0.483)	0.085
Dry skin	10 (7.0)	3 (1.9)	0.200 (0.054–0.746)	0.017	0.157 (0.037–0.428)	0.032
Loss of balance/ coordination	1 (0.7)	-	NA[a]			

Assumption: Simple Logistics Regression assumed that there must be at least two cases for each category of the dependent; OR: Odds Ratio, 95% CI: 95% Confidence Interval; C.G: Control group; I.G: Intervention group.

Similarly, the improvements were noted in 'numbness or reduced ability to feel pain/temperature change'. A statistically significant (p=0.048) difference was observed between the control and intervention group on 'numbness or reduced ability to feel pain/temperature change'. The statisti-

cally significant (p=0.048) difference was observed in 'numbness or reduced ability to feel pain/temperature change', which also became non-significant in multivariate analysis during pure odds ratio calculation. At follow-up 1, in both of the study groups, statistically non-significant differences in the improvements could be due to the priorities of the DMTAC pharmacist. In the first follow-up, the preferences of the DMTAC pharmacist were to control the glycemic level of the patients. Their priorities were not to manage diabetic complications. Because according to various studies, the continuous increase in glycemic levels in patients could result in the demerge of other body organs (Ceriello et al., 2006; Kawahito et al., 2009; Chehregosha et al., 2019). Due to this reason, the diabetic complications did not show any significant differences among both of the study groups.

At follow up two, the mean HbA1c of the control group patients was decreased up to 0.92% since the baseline, whereas in the intervention group, this decrease was 1.58% since baseline. Thus, with this decrease in HbA1c, the sign and symptoms of diabetic complications started to improve in study groups. In the control group, the patients without any signs and symptoms of diabetic neuropathy were 35.7% at first follow-up, which was improved up to 43.4% at the second follow-up. In contrast, in the intervention group at follow-up one, this percentage was 44.9%, which was improved at follow up two up to 56.4%. Similarly, the improvements were noted in 'numbness or reduced ability to feel pain/temperature change'. A statistically significant (p=0.020) difference was observed between the control and intervention group on 'numbness or reduced ability to feel pain/ temperature change'.

These improvements in diabetic neuropathy were probably due to the decrease in the level of HbA1c of patients. According to different studies, if the HbA1c in diabetic patients improved, it results in the improvement of diabetic complications in diabetes mellitus (Ceriello et al., 2006; Lind et al., 2008; Nielsen et al., 2011; Xu et al., 2014). The improvement of glycemic control was more in the intervention group in the presence of diet and lifestyle modification, which was resulted in the pharmacist intervention. On the other hand, the improvement of signs and symptoms belonged to the control group was less as compared with the intervention group due to the less glycemic control in this group of patients.

At follow-up three, the mean HbA1c in the patients' control group was decreased up to 1.51 % since baseline data, whereas in the intervention group, the mean decreased was about 2.59% since baseline. In diabetic neuropathy, statistically significant improvement changes between both of the study groups in 'numbness or reduced ability to feel pain/temperature change' (p=0.005), and 'increased sensitivity to touch' (p=0.038). Whereas the statistical non-significant difference (p=0.694) was observed in 'loss of balance/coordination' symptom of diabetic neuropathy in both of the study groups at third follow up.

The possible reason behind the significant improvement in the sign and symptoms of this included diabetic neuropathy in both study groups could be due to two factors. The first factor was the control of the glycemic levels of the patients. According to various studies, if glycemic levels remain controlled in diabetic patients, it will result in the improvement of diabetic complications (Ceriello et al., 2006; Lind et al., 2008; Nielsen et al., 2011; Xu et al., 2014). The improvement of glycemic control was more in the intervention group in the presence of diet and lifestyle modification, which was resulted in the pharmacist intervention. Thus, the improvement was more in the intervention group. The second factor responsible for the better improvement in the intervention group in the sign and symptoms of diabetic neuropathy was due to the recommendations of DMTAC protocol provided by the Ministry of Health Malaysia. According to the protocol, when the patients are in the fourth module of DMTAC, then the pharmacist elaborates about the diabetic complications to the patients (Ministry of Health Malaysia, 2014). The pharmacist explains to patients in DMTAC about the precautions, diet, and particular recommendations for diabetic complications and their management. So, at this point in time in the third follow up the patients were already gone through the

fourth module of DMTAC that's why the patients were already aware of the lifestyle and diet modifications with do's and don'ts for diabetic complications. That could be the important reason behind the better improvement of diabetic neuropathy at the third follow-up visit in the intervention group as compared to the control group.

At follow-up 4, further HbA1c reduction resulted in the improvement of the sign and symptoms that belonged to diabetic neuropathy in both study groups. Conversely, these improvements were more momentous in the intervention group, with the presence of pharmacist-led intervention. Statistically significant improvements were observed between both of the study groups in 'numbness or reduced ability to feel pain/temperature change' ($p=0.003$), 'tingling or burning sensation' ($p=0.007$) and 'increased sensitivity to touch' ($p=0.032$). Significantly in the intervention group, the patients without any sign and symptom of diabetic neuropathy became 90.4%, which was 35.9% at baseline. Whereas this percentage in the control group was 65.7% at the fourth follow-up, but this percentage was 33.6% at baseline.

There was no difference in the pharmacotherapy of the patients in both of the study groups. All the patients were receiving the same recommended treatment as per the Malaysian guideline for diabetes mellitus. All the patients were on combination therapy (insulin with oral antidiabetics). Thus, there was no difference in the standard treatment in both of the study groups. The only difference was the educational interventions from the pharmacist for the intervention groups.

This study was novel among its types as there was no study evident so far, which measured the effect of pharmacist-led educational intervention on any diabetic complication. Only two studies were evident in the literature regarding the relationship between pharmacist-led education intervention and knowledge of patients (Keban et al., 2017; Krishnaveni et al., 2017). The pharmacist-led educational intervention resulted in the improvement of knowledge of patients on diabetic neuropathy. The results of the present study showed that the pharmacist intervention resulted in improvement in the signs and symptoms of diabetic neuropathy. At baseline, all the predictors of signs and symptoms of diabetic neuropathy were statistically insignificant in both study groups. In follow-up one, it started improving in numbness and tingling. At the fourth follow-up, all the predictors of signs and symptoms of diabetic neuropathy became statistically significant in the intervention group as compared with the control group. Current study results were comparable to the findings of a study conducted by Keban et al. (2017) in India, according to which the patients' knowledge about diabetic neuropathy was improved by pharmacist intervention resulted in the improvement of diabetic neuropathy symptoms in patients. Similar results were also reported by a pilot study conducted in India, according to which even the improvement in knowledge of patients about diabetic neuropathy resulted in improvement in diabetic neuropathy signs and symptoms, which ultimately led to slow down the progression of diabetic neuropathy (Krishnaveni et al., 2017).

There are certain limitations associated with the current study. The present study was conducted in two major hospitals in Kedah state of Malaysia; these findings can generalize to the Kedah state of Malaysia but cannot generalize to the whole Malaysia. Some variations can be expected from different states. Similarly, the follow-ups of the current study were only four, whereas more follow up are required to observe the effects of pharmacist intervention on diabetic complications to see the progression of complications. The comparison of concomitant diseases of patients, degree or type of diabetes in both groups we not done in current study. It is necessary to determine these variables' statistical significance, and future studies can be conducted on these variables.

CONCLUSIONS

This study was novel among its types as there was no study evident so far, which measured the effect of pharmacist-led educational intervention on any complication belong to diabetes mellitus. The sign and symptoms of diabetic neuropathy were significantly improved in the intervention

group as compared with the control group patients. Thus, it proves the pharmacist-led educational intervention has a positive impact on the progression of diabetic complications. These improvements were started from the first follow-up itself.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest among authors with the manuscript's data.

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AUTHOR CONTRIBUTION:

Contribution	Khan AH	Iqbal MZ	Sulaiman SAS	Ibrahim A	Azmi NSBY	Iqbal MS
Concepts or ideas	x	x	x	x	x	x
Design		x				x
Definition of intellectual content	x		x	x	x	
Literature search	x	x				x
Experimental studies	x	x				
Data acquisition	x	x	x	x	x	
Data analysis		x				x
Statistical analysis		x				x
Manuscript preparation	x	x	x	x	x	x
Manuscript editing		x				x
Manuscript review	x	x	x	x	x	x

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