

Impact of pharmacist-led interventions on diabetes management at a community pharmacy in Pakistan: A quasi-experimental study

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Abstract

Objective: To determine the impact of pharmacist-led interventions on satisfaction, disease state knowledge and perception of self-management of diabetes patients.

Method: The interventional, quasi-experimental study was conducted in Bahawalpur, Pakistan, from December 1, 2018, to June 30, 2019, and comprised data from a community pharmacy of patients who had diagnosed type 2 diabetes for at least one year. Both non-pharmacological and pharmacological interventional tools were used as part of a care package administered by pharmacists. The modified version of the Diabetes Disease State Management Questionnaire was used to assess patient satisfaction, disease state knowledge and perception of self-management. Data was analysed using SPSS 20.

Result: Of the 100 patients initially enrolled, 80(80%) completed the follow-up. The mean age of the sample was 49.33±8.31 years. Of the total, 63(78.8%) patients had diabetes for <10 years. A significant improvement was seen in patient satisfaction ($p=0.04$), disease state knowledge ($p=0.009$) and self-management of diabetes ($p=0.02$) scores after the intervention.

Conclusions: Interventions by pharmacists in a community pharmacy resulted in significant improvement in patient satisfaction, disease state knowledge and perception of self-management among type 2 diabetes patients.

Keywords: Type 2 diabetes mellitus, Community pharmacists, Patient satisfaction, Disease state knowledge, Self-management. (JPMA 71: 1924; 2021) DOI: <https://doi.org/10.47391/JPMA.2220>

Introduction

Globally, diabetes mellitus (DM) is one of the most common non-communicable diseases and the 7th leading cause of death in both developed and developing countries. As per a global survey conducted by the International Diabetes Federation (IDF), the prevalence of diabetes in 2015 was 415 million which was expected to be as high as 642 million in 2040.¹ In Pakistan, approximately 6.9% of adults suffered from DM in 2015 and it is estimated that this number will rise to 8.2% by 2040.¹ DM management is a challenge since it demands multiple self-care behaviours by patients, including modification in dietary habits, physical activity, weight reduction, adherence to medicines, and monitoring glycaemic levels. Several studies have shown a major lack in self-care behaviours among DM patients.² Thus, a multidisciplinary team comprising physicians, pharmacists, nurses and dieticians, with expertise in the education about and management of DM patients could help to alleviate the burden associated with this disease.³

It has been seen that beyond the traditional role of dispensing, community pharmacists in developed countries have expanded their professional roles to care, screen and manage diabetics.⁴ Domains of pharmacist-led DM care include DM education along with reinforcement of nutrition/exercise, adequate foot/eye care, monitoring and ensuring adherence to medicines, identification of drug-related problems and optimisation of pharmacotherapy.⁵

The majority of people in Pakistan visit public and private-sector hospitals for the management and treatment of DM. Studies relating to a range of diseases, such as insomnia, acute respiratory tract infection, diarrhoea etc., have been conducted at community pharmacies in Pakistan to demonstrate the impact of pharmacist-led interventions^{5,6} and the findings are encouraging. However, to the best of our knowledge, no study has been conducted in the context of diabetes. The current study was planned to fill the gap by determining the impact of pharmacist-led interventions on patient satisfaction, disease state knowledge and perceptions of self-management of DM patients.

Patients and Methods

The interventional, quasi-experimental study was conducted in Bahawalpur, Pakistan, from December 1, 2018, to June 30, 2019, and comprised data from a community pharmacy. After approval from the Pharmacy Research Ethics Committee (PREC) at the Islamia University

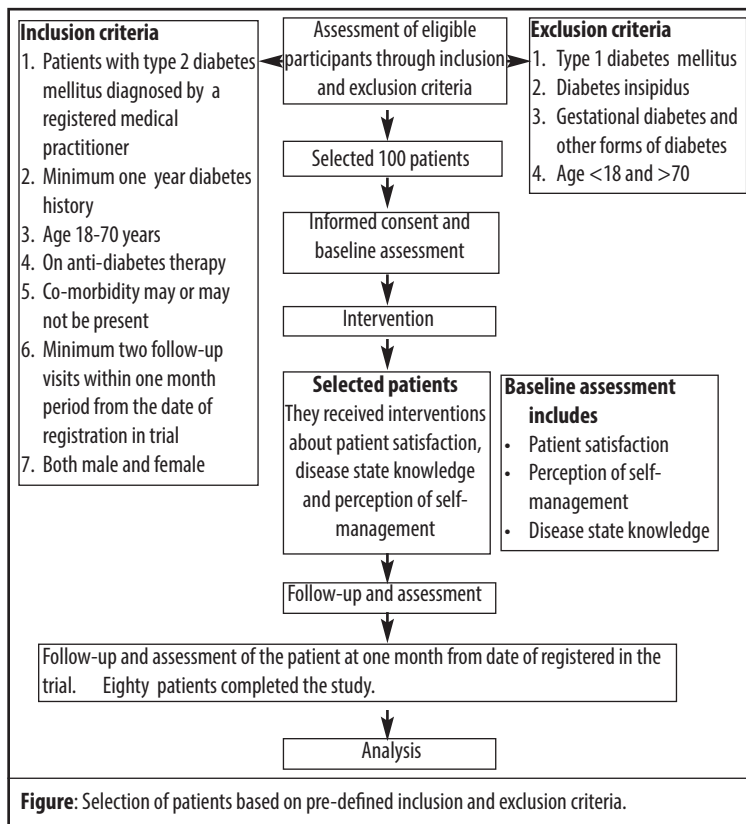
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Annexure A: Modified Diabetes Disease State Management (DDSM) questionnaire for basic characteristics.

Age				
Gender	Male	Female		
Marital status	Single	Married		
Employment	Yes	No		
Occupation	Public	Private	Self employed	Unemployed
Family history of DM	Positive	Negative		
Duration of diabetes	< 10 years	≥ 10 years		
Regular exercise	Yes	No		
Get support for diabetes	Health care provider	Family	Co-worker	Others
Types of medication	Diabetes pills	Injection	Both	
Co-morbidities	Hypertension	High cholesterol	Kidney problems	Others

DM: Diabetes Mellitus.

of Bahawalpur, the sample size was calculated using an online calculator⁷ based on effect size 0.5 ± 1.3 , power 80% and level of significance 0.05.

The sample was raised using purposive sampling technique from among patients of either gender aged 18-70 years who had diagnosed type 2 diabetes mellitus (T2DM) for at least one year and who were on anti-diabetes therapy with the ability to read and understand English. Patients excluded were those with type 1 DM, diabetes insipidus, gestational diabetes or any other form of DM

except T2DM (Figure).

Subjects meeting the inclusion criteria visiting the community pharmacy were approached and enrolled after getting due consent. During the 7-month study period, data was collected from each of the enrolled patients after one month and included in the study provided they completed a minimum of two follow-up visits within a one-month period from the date of registration in the trial.

In order to maintain uniformity of intervention, single pharmacist conducted the intervention. Another pharmacist was involved in administering the questionnaires to the patients at the baseline and after one month of intervention. The outcome variables included patient satisfaction, disease state knowledge and perception of self-management. Data related to demographics, diabetes history, meal plan, exercise routine, smoking status, history of co-morbidities and medications for diabetes was collected using the modified version of the Diabetes Disease State Management Questionnaire (DDSM-Q)⁸ (Annexure A).

DDSM-Q is an instrument targeting DM self-care designed to assess behaviours associated with metabolic control within common treatment regimens for type 1 and type 2 diabetes in adult patients. It is a valid data-collection tool used in multiple studies.^{8,9} DDSM-Q is based on questions related to patient characteristics, whereas its modified version contains statements about patient satisfaction, disease state knowledge and perception of self-management. The modified DDSM-Q consists of 17 statements across the three domains of services of pharmacist, self-management and knowledge of patient about diabetes. Each statement is answered on a 6-point Likert scale from 1 = strongly disagree to 5 = strongly agree (Annexure B). The first domain contains eight items about the services the pharmacist provided with a total possible score of 40. Reverse coding (1 = strongly agree and 5 = strongly disagree) is used for items 4 and 8 as these are negative statements. The second domain has five items addressing the perceptions of self-management of patient regarding DM with a possible score of 25. The last domain contains four items relating to DM disease state knowledge of the patient with a possible score of 20. Reverse coding is used for the last item (1= strongly agree and 5= strongly disagree) as it is a negative statement. The self-reporting modified DDSM-Q was administered to all participants before and after the intervention.

Annexure B: Modified form of Diabetes Disease State Management (DDSM) questionnaire.

S. No.	Statement	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
Service						
1.	I am satisfied with being able to reach my current pharmacist when needed					
2.	I appreciate receiving the service from my current pharmacist.					
3.	I am pleased with the service I receive.					
4.	The appointment site is too hard to get to					
5.	I am satisfied that my current pharmacist is helpful during the service.					
6.	I am thankful for the time my current pharmacist gives up to provide the service					
7.	I am satisfied with the convenience of the location during the service					
8.	My current pharmacist is unfriendly and unsupportive during the service					
Self-management						
9.	The service motivates me to stay in control of my disease state(s)					
10.	I am more compliant with my medications since participating in the service					
11.	The service gives me confidence to deal with my disease state(s)					
12.	I feel a sense of accomplishment after achievement of my goals and participating in the service					
13.	I have improved my lifestyle (diet and exercise habits) since participating in the service					
Knowledge						
14.	I am satisfied with my understanding of what I should eat to control my disease state.					
15.	I am satisfied with my understanding of the types and amounts of physical activity I can do to control my disease state(s)					
16.	I am satisfied with my understanding of how things (e.g., stress, obesity and blood pressure) can change my blood sugar.					
17.	I do NOT know what types of exercise are beneficial to control my disease state(s)					

Both non-pharmacological and pharmacological interventional tools were used as part of a care package. The intervention was administered to patients at the time of their registration in the trial after the assessment of baseline parameters. The non-pharmacological intervention was based on charts with pictorial representation and verbal communication. Charts included

a diet chart, a foot-care chart, charts about symptoms of hypoglycaemia and hyperglycaemia, as well as on the correct way to administer insulin. The diet chart contained information related to food items which must be avoided, taken with care or consumed according to the medical needs of the individual patient. The foot-care chart outlined various exercises that are expected to increase blood circulation in the periphery. The third chart was related to glycaemic control and contained information related to symptoms of hypoglycaemia and hyperglycaemia and the appropriate steps to overcome these scenarios. The final chart had step-by-step information related to the correct administration of insulin. All of these charts were predefined by Novo Nordisk pharmaceutical company and approved by the Ministry of National Health Services Regulation and Coordination of Pakistan.¹⁰ The importance of exercise, time to take medications, frequency of medications and other medication-related information was provided through verbal conversation with the patients by the pharmacist. Cross-questioning was undertaken with patients during consultation to ensure that they fully understood the meanings of the counselling. The pharmacological intervention was based on adjustment of dose, frequency of insulin and oral anti-diabetic medicines only in cases where it was not according to the standard¹¹ and method of insulin administration. The pharmacological intervention comes under the role of the community pharmacist in Pakistan in accordance with government legislation.¹²

Data was analysed using SPSS 20. Descriptive statistics were applied. Outcomes of continuous variables were analysed using paired sample t-test to study the effect at Tone month versus T baseline (time/intervention effect). Independent sample t-test was used to compare each independent variable with dependent variable. P<0 .05 was considered statistically significant.

The study was registered under the clinical trial protocol (No: ISRCTN10671625) with the International Standard Randomised Controlled Trial Number¹³ (ISRCTN) registry.

Results

Of the 100 patients initially enrolled, 80(80%) completed the follow-up. The mean age of the sample was 49.33±8.31 years. Of the respondents, 54(67.5%) were male; 78(97.5%) were married; 48(60%) did not have a family history of DM;

Table-1: Socio-demographic and clinical characteristics of the respondents.

Characteristics	n (%)
Mean age in years (SD)	49.33 ± 8.31
Age ranges (years)	(31-67)
Gender	
Male	54 (67.5)
Female	26 (32.5)
Marital status	
Single	2 (2.5)
Married	78 (97.5)
Employment	
Yes	22 (27.5)
No	58 (72.5)
Occupation	
Public	16 (20)
Private/ Self employed	6 (7.5)
Unemployed	58 (72.5)
Family history of Diabetes Mellitus	
Positive	32 (40)
Negative	48 (60)
Duration of diabetes	
< 10 years	63 (78.8)
≥ 10 years	17 (21.2)
Regular exercise at baseline	
Yes	27 (33.8)
No	53 (66.2)
Regular exercise after one month	
Yes	69 (86.2)
No	11 (13.8)
Get support for diabetes	
Health care provider	79 (98.8)
Others (family and co-worker)	1 (1.2)
Types of medication	
Diabetes pills	64 (80)
Injection	11 (13.8)
Both pills and injection	5 (6.2)
Number of pharmacy visits (study site)	
< 5	56 (70)
> 5	24 (30)
Co-morbidities	
Hypertension	33 (41.3)
High cholesterol	30 (37.5)
Kidney problems	8 (10)
Sexual problems	6 (7.5)
Numbness/tingling/loss of feeling in feet	36 (45)
Dental problems	9 (11.25)

SD: Standard deviation

Table-2: Impact of pharmacist intervention on patient satisfaction, knowledge of disease state and perception of self-management.

Parameter	Intervention group (n =80)			p-value
	Baseline Mean ± SD	One month Mean ± SD	Mean change* (Range)	
Patient satisfaction	38.05 ± 2.67	38.84 ± 2.13	0.79 (0.04 to 1.53)	0.04
Disease state knowledge	18.74 ± 1.79	19.39 ± 1.18	0.65 (0.17 to 1.13)	0.009
Perception of self-management	23.69 ± 2.22	24.48 ± 1.53	0.79 (0.15 to 1.42)	0.02

SD: Standard deviation. *Paired sample t-test for time effect within the group

and 63(78.8%) had DM for <10 years (Table 1).

The majority 77(96.3%) of patients strongly agreed that they would appreciate continue receiving services from pharmacists after one month compared to 75(93.8%) at baseline. Similarly, 74(92.5%) patients strongly agreed that they were pleased with the services provided by pharmacists after one month compared to 73(91.2%) at baseline.

A significant improvement was seen in patient satisfaction scores post-intervention ($p=0.04$).

Regarding disease state knowledge, 67(83.8%) participants strongly agreed with the diet plan suggested by the pharmacist post-intervention compared to 61(76.3%) at baseline, and 67(83.8%) patients strongly agreed with the obesity, stress and blood pressure management strategies compared to 60(75%) at baseline.

A significant improvement was seen in patient knowledge scores after the intervention ($p=0.009$).

In terms of perception of self-management, 72(90%) participants strongly agreed that the service motivated them to control their disease state post-intervention compared to 66(82.5%) at the baseline, and 74(92.5%) patients strongly agreed that their compliance towards medication increased as a result of the services compared to 60(75%) at the baseline. A significant improvement was seen in the perception of self-management of participants post-intervention ($p=0.02$) (Table 2).

Discussion

The current study aimed at understanding the impact of a pharmacist-led intervention on DM management in a community pharmacy in Bahawalpur, Pakistan. People find health services accessible at community pharmacies due to short waiting times, ease of location, free advice and extended opening hours. The rising prevalence of DM along with its complex management poses a huge burden on physicians who are expected to meet the medical and psychosocial needs of DM patients.¹⁴ This burden could be shared by engaging the services of community pharmacists. Effective interventions by community pharmacists may pave the way towards increased patient satisfaction, better disease state knowledge and perception of self-management leading to improved management of diabetes.¹⁵⁻¹⁷ It has been reported that community pharmacists are regarded by DM patients as reliable healthcare professionals capable of providing medicine-related information and advice, and referrals to physicians and nurses when needed.⁵ This notion is supported by the current study which found significant improvements in

patient satisfaction, disease state knowledge and perceptions of self-management.

The initial step in managing DM is to develop a proper understanding of the relationship between the disease and patient characteristics. The current findings revealed that the majority of participants were male with mean age of <50 years. This is in line with another study.² Studies have reported that sedentary lifestyle, genetic factors and poor eating behaviour among males make them more prone to DM compared to their female counterparts.¹⁸ Most participants in the current study had co-morbidities and this is in line with the fact that diabetes is a major risk factor for multiple co-morbidities, particularly cardiovascular problems.¹⁹

It has been reported that increased patient satisfaction with diabetes care is directly related with improved compliance to treatment which facilitates better glycaemic control.²⁰ The current study showed that the mean score for most of the items of the patient satisfaction component of the questionnaire improved at the end of the intervention. This is in line with the findings of a study conducted in the United States.¹⁵ The current study also found significant improvement in patient satisfaction scores after the intervention and this finding is not surprising since pharmacist interventions were not solely based on non-pharmacological DM education, but also included pharmacological intervention of adjusting dose frequency. Although it cannot be determined specifically which components of the intervention resulted in increased patient satisfaction; it can be assumed that a combination of non-pharmacological and pharmacological components yielded beneficial effect on patient satisfaction. Similar findings have also been reported in a study.¹⁷ Provision of sufficient consultation time, attention and the imparting of disease-related knowledge to patients by community pharmacists are the likely contributing factors of increased patient satisfaction.¹⁶

Sufficient disease-related knowledge can help DM patients to assess the risk of disease-related complications, encourage them to look for adequate care and treatment, and steer them to take charge of their disease for the remainder of their lives.²¹ In line with the findings of other studies,^{15,22} the current study found significant improvement in disease-related knowledge scores after the intervention. Overall improvement was seen in the mean scores of each item of the knowledge questionnaire. The pharmacist is considered to be an expert on medicines, and imparting therapeutic information to patients which not only leads to improved knowledge about their disease, but it also enhances medicinal compliance amongst patients.²³ Thus, improved disease-related knowledge of patients

ultimately leads to better health outcomes in DM patients.

In addition to what healthcare workers provide, DM self-management is a very important strategy for improving outcomes.²⁴ The current findings demonstrate improvements in self-management of disease among the participants post-intervention. The mean scores of each component of self-management questionnaire were improved as a result of the intervention. A study reported that most patients were highly satisfied with the variety of components of perception of a self-management programme, including improvement in knowledge about disease, quality of life, encouragement and support of pharmacist.²⁵ The positive impact of intervention on self-management of DM patients has been reported in studies from Iran¹⁶ and the US.²² Better self-management of DM ultimately leads to optimal metabolic control, mitigation of complications associated with the disease, improved quality of life and alleviation of economic burden,²⁶ thus having a positive impact on the patient.

Community pharmacists in Pakistan can offer a range of services, including counselling, dispensing of prescription and non-prescription medicines, supply chain management, provision of medicine-related information to patients, participation in health-promotion programmes and diagnostic services by using hand-held household devices, such as glucometer and sphygmomanometer. Multiple non-pharmacological and pharmacological interventions for managing glycated haemoglobin (HbA1c) level, blood pressure, lipid profile and body mass index etc., can also be implemented at community pharmacies. The aforementioned roles of community pharmacists are in line with the Drug Regulatory Authority of Pakistan (DRAP) Act no XXI of 2012.¹²

There are some limitations to the current study. First, it solely focussed on T2DM patients and did not include type 1, gestational and others forms of diabetes. Second, the study had a short duration while the impact of such interventions demands long-term follow-up. It is possible that a longer follow-up period would have resulted in larger detectable differences between the groups, but time constraints and lack of funding did not allow for a larger participant sample or a longer follow-up duration. Another limitation of the study was the absence of a control group. The current study was quasi-experimental. In future, randomised controlled trials (RCTs) shall be undertaken.

The findings of the current study are expected to make policy-makers more aware and help facilitate the implementation of widespread DM care services at community pharmacies in Pakistan. This may start as a pilot project and later be scaled up as a part of extended

pharmacy services based on viable findings.

Conclusions

There were significant improvements in patient satisfaction, disease state knowledge and perception of self-management. Involvement of community pharmacists could help to manage DM, thus simultaneously sharing the burden of physicians in Pakistan as well as having better health outcomes for DM patients.

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Conflict of Interest: None.

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References

1. Federation I. IDF Diabetes Atlas 6th. 6th ed. Basel, Switzerland: International Diabetes Federation; 2015.
2. Coyle ME, Francis K, Chapman Y. Self-management activities in diabetes care: a systematic review. *Aust Health Rev* 2013; 37: 513-22.
3. Association AD. Standards of medical care in diabetes—2009. *Diabetes care*. 2009; 32(Suppl 1): S13-61.
4. Siu AHY, Krass I, Mitchell B, McNamara K. Implementation of diabetes screening in community pharmacy – factors influencing successful implementation. *Res Social Adm Pharm* 2020; S1551-7411(20)31241-9.
5. Aguiar PM, da Silva CHP, Chiann C, Dórea EL, Lyra Jr DP, Storpirtis S. Pharmacist–physician collaborative care model for patients with uncontrolled type 2 diabetes in Brazil: results from a randomized controlled trial. *J Eval Clin Pract* 2018; 24: 22-30.
6. Hussain A, Ibrahim MI, Malik M. Assessment of disease management of insomnia at community pharmacies through simulated visits in Pakistan. *Pharm Pract (Granada)*. 2013; 11: 179-84.
7. Sample size calculator. Sample size for before-after study (Paired T-test). [Online] 2018 [cited 2018 February 25]. Available from: URL: <http://www.sample-size.net/sample-size-study-paired-t-test/>.
8. Schmitt A, Gahr A, Hermanns N, Kulzer B, Huber J, Haak T. The Diabetes Self-Management Questionnaire (DSMQ): development and evaluation of an instrument to assess diabetes self-care activities associated with glycaemic control. *Health Qual Life Outcomes* 2013; 11: 138.
9. Kamradt M, Bozorgmehr K, Krisam J, Freund T, Kiel M, Qreini M, et al. Assessing self-management in patients with diabetes mellitus type 2 in Germany: validation of a German version of the Summary of Diabetes Self-Care Activities measure (SDSCA-G). *Health Qual Life Outcomes* 2014; 12: 185.
10. Novo Nordisk. Manage your diabetes. [Online] 2017 [cited 2017 November 25]. Available from: URL: <http://www.novonordisk.pk/>.
11. Joint Formulary Committee. British National Formulary London: BMJ Group and Pharmaceutical Press [Online] 2016 [cited 2017 November 22]. Available from: URL: <https://www.bnf.org/products/bnf-online/>.
12. Drug Regulatory Authority of Pakistan. The Gazette of Pakistan. In: government F, editor. Islamabad: Senate secretariat; 2012.
13. ISRCTN registry. Role of pharmacist in diabetes management at community pharmacy: BioMed Central Ltd.Part of Springer Nature. [Online] 2017 [Cited 2020 November 22]. Available from: URL: <https://www.isrctn.com/trialist>.
14. Willens D, Cripps R, Wilson A, Wolff K, Rothman R. Interdisciplinary team care for diabetic patients by primary care physicians, advanced practice nurses, and clinical pharmacists. *Clinical Diabetes* 2011; 29: 60-8.
15. Schuessler TJ, Ruisinger JF, Hare SE, Prohaska ES, Melton BL. Patient Satisfaction With Pharmacist-Led Chronic Disease State Management Programs. *J Pharmacy Practice* 2016; 29: 484-9.
16. Jahangard-Rafsanjani Z, Sarayani A, Nosrati M, Saadat N, Rashidian A, Hadjibabaie M, et al. Effect of a community pharmacist-delivered diabetes support program for patients receiving specialty medical care: a randomized controlled trial. *Diabetes Educ* 2015; 41: 127-35.
17. Frederick A, Juan J, Ivy D, Maldonado YM. Effect of Visit Frequency of Pharmacist-Led Diabetes Medication Management Program. *J Pharmacy Practice* 2020: 0897190020948685.
18. Patterson R, McNamara E, Tainio M, de Sá TH, Smith AD, Sharp SJ, et al. Sedentary behaviour and risk of all-cause, cardiovascular and cancer mortality, and incident type 2 diabetes: a systematic review and dose response meta-analysis. *Eur J Epidemiol* 2018; 33: 811-29.
19. Long AN, Dagogo-Jack S. Comorbidities of diabetes and hypertension: mechanisms and approach to target organ protection. *J Clin Hypertens* 2011; 13: 244-51.
20. Dalal J, Williams JS, Walker RJ, Campbell JA, Davis KS, Egede LE. Association Between Dissatisfaction With Care and Diabetes Self-Care Behaviors, Glycemic Management, and Quality of Life of Adults With Type 2 Diabetes Mellitus. *Diabetes Educ* 2020; 46: 370-7.
21. Shiferaw WS, Gatew A, Afessa G, Asebu T, Petrucka PM, Aynalem YA. Assessment of knowledge and perceptions towards diabetes mellitus and its associated factors among people in Debre Berhan town, northeast Ethiopia. *PLoS ONE* 2020; 15: e0240850.
22. McFarland MS, Wallace JP, Parra J, Baker J. Evaluation of patient satisfaction with diabetes management provided by clinical pharmacists in the patient-centered medical home. *Patients* 2014; 7: 115-21.
23. Conca T, Saint-Pierre C, Herskovic V, Sepúlveda M, Capurro D, Prieto F, et al. Multidisciplinary Collaboration in the Treatment of Patients With Type 2 Diabetes in Primary Care: Analysis Using Process Mining. *J Med Internet Res* 2018; 20: e127.
24. Vongmany J, Luckett T, Lam L, Phillips JL. Family behaviours that have an impact on the self-management activities of adults living with Type 2 diabetes: a systematic review and meta-synthesis. *Diabet Med* 2018; 35: 184-94.
25. Thakur T, Galt KA, Siracuse MV, Fuji KT, Bramble JD. National survey of diabetes self-management program coordinators views about pharmacists' roles in diabetes education. *J Am Pharm Assoc* (2003) 2020; 60: 336-43.
26. American Diabetes Association. 5. Facilitating Behavior Change and Well-being to Improve Health Outcomes: Standards of Medical Care in Diabetes-2021. *Diabetes Care* 2021; 44(Suppl 1): S53-S72. 2021. *Diabetes care*. 2021;44(Supplement 1):S53-S72.