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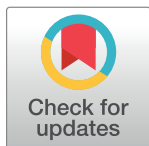
RESEARCH ARTICLE

Impact of medication therapy management service on selected clinical and humanistic outcomes in the ambulatory diabetes patients of Tikur Anbessa Specialist Hospital, Addis Ababa, Ethiopia

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Abstract

Background

Diabetes mellitus (DM) patients are at increased risk of developing drug therapy problems (DTPs). The patients had a variety of comorbidities and complications, and they were given multiple medications. Medication therapy management (MTM) is a distinct service or group of services that optimize therapeutic outcomes for individual patients. The study assessed the impact of provision of MTM service on selected clinical and humanistic outcomes of diabetes patients at the diabetes mellitus clinic of Tikur Anbessa Specialized Hospital (TASH).

Methods

A pre-post interventional study design was carried out at DM clinic from July 2018 to April 2019. The intervention package included identifying and resolving drug therapy problems, counseling patients in person at the clinic or through telephone calls, and providing educational materials for six months. This was followed by four months of post-intervention assessment of clinical outcomes, DTPs, and treatment satisfaction. The interventions were provided by pharmacist in collaboration with physician and nurse. The study included all adult patients who had been diagnosed for diabetes (both type I & II) and had been taking anti-diabetes medications for at least three months. Patients with gestational diabetes, those who decided to change their follow-up clinic, and those who refused to participate in the study were excluded. Data were analyzed using Statistical Package for the Social Sciences (SPSS). Descriptive statistics, t-test, and logistic regressions were performed for data analyses.

Results

Of the 423 enrolled patients, 409 fulfilled the criteria and included in the final data analysis. The intervention showed a decrease in average hemoglobin A1c (HbA1c), fasting blood

sugar (FBS), and systolic blood pressure (SBP) by 0.92%, 25.04 mg/dl, and 6.62 mmHg, respectively (p<0.05). The prevalence of DTPs in the pre- and post-intervention of MTM services was found to be 72.9% and 26.2%, respectively (p<0.001). The overall mean score of treatment satisfaction was 90.1(SD, 11.04). Diabetes patients of age below 40 years (92.84 (SD, 9.54)), type-I DM (93.04 (SD, 9.75)) & being on one medication regimen (93.13(SD, 9.17)) had higher satisfaction score (p<0.05).

Conclusion

Provision of MTM service had a potential to reduce DTPs, improve the clinical parameters, and treatment satisfaction in the post-intervention compared to the pre-intervention phase.

Introduction

Globally, an estimated 422 million adults were living with diabetes mellitus (DM) in 2014, with prevalence of 8.5% in the adult population, which is expected to rise to 641.8 million by 2040 [1]. An estimated 14.2 million adults in Africa had diabetes, with a regional prevalence of 2.1–6.7%. In Ethiopia about 2.6 million adults had diabetes in 2017 [2]. Global health spending to treat diabetes and prevent complications accounted for 11.6% of the total health expenditure in 2015 and this value was between $80–200 millions in Ethiopia [1].

Based on etiopathogenesis of the disease, diabetes can be classified as type I diabetes(5 to 10%), type II diabetes($\sim$ 90–95% of diabetes), gestational diabetes mellitus (GDM) and monogenic diabetes and secondary diabetes(less common) [3]. The management of diabetes depend on understanding of the pathophysiology of the disease. In type I diabetes mellitus, there is a significant insulin deficiency and the only therapeutic option is the administration of insulin or insulin analog. Metformin in combination with insulin may help type I DM patients who are overweight, taking high doses of insulin, or have a HbA1c of more than 8%, according to recent research [3,4].

While in type II diabetes mellitus individuals, have relative insulin deficiency and peripheral insulin resistance that require either oral medication or insulin/insulin analog or both. The currently available class of oral antidiabetes medication include sulphonylurea(SUs) and metiglinides, which function as insulin secretagogues and promote insulin secretion directly; biguanides (such as metformin) and thiazolidinediones (TZD), which improve insulin sensitivity; and alpha glucosidase inhibitors, which minimize the need for post-prandial insulin secretion by slowing intestinal carbohydrate absorption [2].

The management of diabetes is complex, requiring more than plasma glucose control. It comprises managing DM-related complications and modifying risk factors [5]. The management involves combining lifestyle modification with the pharmacological agents to address the multiple pathophysiological defects [6]. Due to coexistence of comorbidities and complications, DM management is challenged by the occurrence of drug therapy problems (DTPs). DTPs can occur at different stages of medication use starting from prescriber to patients and often deleterious and costly [7–9]. DTPs are significant public health issue worldwide and have been significantly increasing overtime [1,10].

Studies conducted in different parts of the world showed that DTPs are highly prevalent. Those carried out in Asia and Africa reported an average of 1–3 DTPs per patient [10–13]. A similar rate of DTPs has been reported by various studies conducted in Ethiopia [14–16]. Drug-related hospital admissions are also significantly increasing overtime. It account for

5–10% of admissions and more than 50% of which were avoidable [17]. In the USA, an estimated 100,000 deaths occur annually due to DTPs, costing taxpayers approximately $201.4 billion per annum [18].

To reduce such drug therapy issues and attain targeted therapeutic outcomes, implementation of medication therapy management (MTM) service is crucial. MTM is a pharmacist-provided standard practice for assessing patient's drug-related needs as well as identifying and resolving DTPs.

MTM service involves providing self-management education, addressing medication adherence issues, and considering preventative health strategies to optimize therapy and improve clinical outcomes [8]. It begins by comprehensive medication review to ensure if the patient's medication-related needs have been met and all of his/her medications are appropriate, effective, safe, and convenient. At the end of the review, a care plan is developed and shared with the patient and the primary care provider to resolve and prevent any DTPs [7,19].

A meta-analysis of 44 studies assessing the effectiveness of MTM services in patients with chronic diseases showed that MTM improved prescribing, use and adherence related issues [20]. The Asheville project showed that more than 50% of patients achieve optimal hemoglobin A1c (HbA1c) at each follow-up assessment, indicating the long-term clinical and economic gains [21]. In a prospective pre-post longitudinal study, HbA1c levels decreased on average by 0.27, while systolic and diastolic blood pressure decreased by 6.0 and 4.2 mmHg, respectively [22]. In a pragmatic randomized controlled trial of telephonic MTM to reduce hospitalization in home health patients, the intervention group was three times less likely to be hospitalized compared to the usual care group [23]. Even though many studies are available on the implementation of MTM service in different countries, no study exists about this service in diabetes patients of Ethiopia. Thus, the aim of this study was to assess the impact of introduction of MTM service at the diabetes clinic of Tikur Anbessa Specialized Hospital (TASH).

Methods

Design and patients

A pre-post interventional study was carried out from 6 July 2018 to 30 April 2019 (6-month intervention and 4-month assessment) to assess the effectiveness of MTM in patients attending the diabetes clinic of TASH. TASH is the largest referral hospital that offers a comprehensive health care service for more than 500,000 patients per year through its 20 specialty clinics and 5 main inpatient service departments. The diabetes clinic provides outpatient service for 6,000 adult patients annually, with an average of about 250 patients per week.

All adult patients diagnosed with DM (both type I &II) and on anti-diabetes drugs for at least three months in diabetes clinic of TASH were included in the study. Gestational DM patients, patients planning to change the follow up clinic, and patients unwilling to participate in the study were excluded. The study was approved by the Institutional Review Board (IRB) of the School of Pharmacy, Addis Ababa University (Ref. No.: 002/17/SPharma). Written informed consent was obtained from participants before collecting the required data.

Sampling

A sample size(n) of 423 were computed based on single proportion formula assuming DTPs prevalence(p) 50%. A critical value for normal distribution at 95% confidence interval, z-value of 1.96 was used with a margin of error(d) 5% in sample size calculation.

$$n = \frac{Z^2 p(1-p)}{d^2} = \frac{(1.96)^2 x(0.5)(0.5)}{(0.05)^2} = 384.16$$

Therefore, with adjustment for 10% contingency (for non-response), the total sample size were 423.

During the three months recruitment periods, patients who had an appointment at the diabetes clinic of TASH were made the sampling frame and the sampling fraction was calculated. The average 125 daily attendees were used for calculation of constant (k). The total sample size (423) was divided by the number of days the clinic provide service within three months (24 days) of the recruitment period to get the estimated sample of participants per day. Based on this calculation about 18 patients were sampled each day. This was made for the purpose of participant distribution throughout the study period for better representativeness. A systematic random sampling technique was used based on list of patients' appointment record by calculating sampling interval as $K = N/n$ (where N (125) average number of patients per day; n (18) is sample to be taken per day). Then participant's medical card number (ID) were taken every seventh interval for comprehensive chart review. A colored sticker was posted on the patient chart to identify easily during follow up and to avoid double recruitments.

Intervention

On the day of appointment, recruited patients were interviewed for additional information (social habit, economic status, educational and marital status, physical activity etc) and provided with MTM services after they got usual care from the primary physician. Based on the standard diabetes treatment guideline [2,24] trained pharmacists reviewed patients' medication regimen and rendered verbal education and training on medication use and best administration sites with the goal of optimizing medication therapy. The interventions also involved identifying DTPs, such as medication duplications, drug interactions, dosing for renal and liver impairment, suspected adverse drug reactions (ADRs), therapeutic drug monitoring and inappropriate non-pharmacological managements. DTPs were identified and classified using the Cipolle's [7] tools.

The pharmacists also provided brochures prepared in a local language (Amharic) as intervention package to increase patients' awareness about their disease condition and lifestyle modification. The package also included delivering personal medication data book comprising personal information, personal medication record (PMR), medication action plan (MAP), investigation value recorder (blood pressure (BP), fasting blood sugar (FBS), random blood sugar (RBS) and HbA1c) as well as additional information about hypoglycemia symptoms and its management.

In DTPs identification, age, comorbidities and complications, glycemic control, drug safety profile and proper drug selection, dosage titration, indication for therapy, untreated indication, clinical characteristic, and organ function tests were considered. After reviewing, the pharmacists provided recommendations after consultation with the treating physician and patients. They then documented any interventions provided during each visit and made follow up through telephone calls. Interventions required during the follow-up were made following consultations with the treating physicians.

For both pre- and post-MTM assessment, a recent HbA1c and an average consecutive FBS were considered. Time spent with each patient was 15–20 min for interview as well as for medication review, and 15–20 min for intervention, patient medication record, and documentation. All patients recruited for the intervention were used for post-MTM assessment study.

Outcome measures

The main outcome measured were the change in DTPs, clinical and humanistic (treatment satisfaction) outcomes from pre-MTM (baseline) to post-MTM after intervention. The clinical

outcomes include glycemic control (HbA1c, FBS, RBS), blood pressure, lipids profile (HDL, LDL, triglycerides) levels. DTP were determined by modified Cipolle [7] while the humanistic outcome treatment outcome were measured by satisfaction with medicines questionnaire (SATMED-Q) [25,26].

Hyperglycemia was defined as an average FBS level of above 130 mg/dl for patients between 18 and 60 years old with no comorbid with disease duration of below 8years and values above 150 mg/dl for those above 60 years of age and patients with multiple comorbid and also those with disease duration more than 8 years. Controlled hypertension: if patient diagnosed as hypertension and initiated with medication or lifestyle modification achieve therapeutic goal of SBP/DBP< 130-140/90 mmHg. Controlled lipid profile: if dyslipidemic patients achieve lipid profile of HDL-C >40 mg/dL, LDL-C <100 mg/dL, TG <150 mg/dL, and TC <200mg/dL [2,24,27].

The most commonly used HbA1c goal for many nonpregnant adults is less than 7% (53 mmol/mol). The more stringent HbA1c goals (such as less than 6.5% [48 mmol/mol]) were also used for selected individual patients if it can be achieved without significant hypoglycemia or other adverse effects of treatment (i.e., polypharmacy). Appropriate patients might include those with short duration of diabetes, type 2 diabetes treated with metformin only, long life expectancy, or no significant cardiovascular disease. In addition less stringent HbA1c goals (such as less than 8% [64 mmol/mol]) were also considered for patients with a history of severe hypoglycemia, limited life expectancy(eg, <10 years), advanced microvascular or macrovascular complications, extensive comorbid conditions, or long-standing diabetes in whom the goal is difficult to achieve despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin [2,24,27].

Data collection and management

Data were collected using a pre-tested data abstraction format, modified Cipolle DTP identification tools[7], and satisfaction with medicines questionnaire (SATMED-Q) [25,26] as instruments. In DTP assessment, categories (1–6) associated with indication, effectiveness, and safety were used (Appendix I in S1 File). However, the seventh category that assesses medication adherence was removed, as it had to be assessed by Morisky medication adherence scale (MMAS) tool. During reporting each value (frequency) was recorded as prevalence of the specific category and then converted to percentage.

A self-administered SATMED-Q questionnaire was used to measure patients' treatment satisfaction in persons with any chronic disease treated with medicines (Appendix I in S1 File). It is a brief, feasible and easy to self-administer that has 17 items, assessing six treatment satisfaction domains; undesirable side effects (3 items), treatment effectiveness (3 items), convenience of use (3 items), impact on daily activities (3 items), medical care (2 items) and global satisfaction (3 items) each of which is computed as a score. Each item in the scale uses a five-point Likert scale (not at all (0), a little bit (1), some-what (2), quite a bit (3), very much (4)); overall and domain scores range from zero to 68, with higher scores indicating greater levels of treatment satisfaction. The resultant total composite score could be transformed to a more intuitive and easier to understand metric with a minimum of 0 and a maximum of 100, using the following expression

$$Y' = \frac{Yobs - Ymin}{Ymax - Ymin} * 100 = Yobs*1.471$$

Where Y max is 68 (maximum total score), Ymin is zero (minimum total score), Yobs is the total patient score, and Y' is the transformed score. A similar expression can be used to change the metric of each individual domain [25,26].

Demographic (age, sex, marital status, education, residence, and occupation status) and clinical information (disease type, duration of the disease, comorbidity & complication, type of medications, source of medication, and lifestyle (physical activity, alcohol use, smoking and dietary status)) were collected using the data abstraction format (Appendix I in S1 File). Online resources (Micromedex, Launch Lexi-Interact™) and Standard textbooks [28,29] were used for DTP identification. Other variables, including weight, height, body mass index (BMI), waist circumference (WC), BP were also recorded.

For the intervention phase, two clinical pharmacists and two nurses were recruited and provided with a 2-day intensive theoretical and practical training on the procedure followed during intervention, intervention implementation, and mitigation of challenges. For the post-intervention assessment, another two nurses and two pharmacists were recruited and trained for data collection based on their interest and full commitment to the MTM project. The role of the pharmacists was identifying DTPs and providing intervention package, while the nurses were involved in facilitating and coordinating activities during intervention and assessment.

Data analysis

Data were checked, cleaned, entered and analyzed using SPSS version 25. Descriptive analysis was computed as frequency and percent for categorical variable, and mean and standard deviation (SD) for continuous variables. To examine the influence of different variables on DTPs logistic regression analysis was used. To control potential confounders, the variables in bivariate analysis with p-value ≤ 0.20 were further analyzed in multivariate logistic regression. Paired sample t-test was used to compare the difference between the mean of pre- and post-intervention continuous variables while McNemar test was for categorical variables. Association between treatment satisfaction (mean scores of SATMED-Q) and socio-demographic and clinical characteristics was determined using independent t-test for mean values of two continuous variables and one-way analysis of variance (ANOVA) with post hoc analysis for mean values of more than two continuous variables. A 95% CI and p-value of <0.05 was considered statistically significant for all data analysis.

Results

Socio-demographic and clinical characteristics of patients

Of the 423 patients recruited, 14 were excluded as per the eligibility criteria. Two patients changed their follow up site, one patient became pregnant, and eleven patients refused to participate in the post-intervention assessment. Patients had a mean age of 52.3(SD, 15.6) years and most (42.5%) were in the age range of 40–60 years. Majority of them were females (54.5%), married (71.4%) and resident of Addis Ababa (84.4%) (Table 1).

Greater proportion (78.2%) of the patients had type-II DM. Comorbidity and complication were found in 73% (299) and 37% (151) of the study participants, respectively. Hypertension (56.2%) and neuropathy (30.1%) were the two most common comorbidities and complications, respectively (Table 1).

Majority (77%) of the patients had 1–2 pharmacist visits and the rest had three or more visits. McNemar test revealed a significant decrease (p<0.001) in the proportion of hyperglycemic patients from 68% in the pre-intervention to 40.3% in the post-intervention phase. Likewise, hypoglycemia occurrence came down from 18.3% to 5.6% (p<0.001). The intervention also produced an improvement in the clinical characteristics of patients, including BMI, WC, BP, HbA1c and FBS. Based on the paired sample t-test, significant improvement (p<0.05) was noted in the post-intervention values for SBP, HbA1c, and FBS compared to the corresponding pre-intervention values (Table 2).

Table 1. Socio-demographic and clinical characteristics of adult patients.

Variables	Categories	N (%)
Age(Years)	Mean ± SD	52.3 ±15.6
	< = 40	99(24.2)
	40–60	174(42.5)
	>60	136(33.3)
Sex	Male	186(45.5)
	Female	223(54.5)
Marital status	Married	292(71.4)
	Single	69(16.9)
	Divorced	19(4.6)
	Widowed	29(7.1)
Education	Unable to write & read	28(6.8)
	Informal education	25(6.1)
	Primary school	74(18.1)
	Secondary school	131(32.0)
	Diploma and above	151(36.9)
Residence	Addis Ababa	345(84.4)
	Out of Addis Ababa	64(15.6)
Occupational status	Employed	115(28.1)
	Unemployed	82(20.1)
	self-employed	59(14.4)
	Others[a]	153(37.4)
Source of medication	Buying	78(19.1)
	Free	331(80.9)
Allergy to any medication	Known	29(7.1)
	No/Not known	380(92.9)
Social drug use	X-smoker	4(1.0)
	Smoker	6(1.5)
	Alcohol consumption	59(14.4)
	Caffeine intake	280(68.5)
	Khat chewing	10(2.4)
Type of physical activity	No	56(13.7)
	Walking	193(47.2)
	Exercise	31(7.6)
	Daily activity	129(31.5)
Family history	No/Unknown/ Other[b]	349(85.3)
	Mother/Father/Sister/Brother	60(14.7)
Type DM	Type I	89(21.8)
	Type II	320(78.2)
Number of comorbidities	No	110(26.9)
	1–2	240(58.7)
	> = 3	59(14.4)
Types of comorbidity	Hypertension	230(56.2)
	Dyslipidemia	96(23.5)
	IHD	52(12.7)
	CKD	26(6.4)
	RVI	15(3.7)
	Asthma	9(2.2)
	Others[c]	105(25.7)

(*Continued*)

Table 1. (Continued)

Variables	Categories	N (%)
Number of complications	No	258(63.1)
	1–2	141(34.5)
	> = 3	10(2.4)
Types of complications	Neuropathy	123(30.1)
	Nephropathy	30(7.3)
	Retinopathy	29(7.1)
	Diabetic foot ulcer	5(1.2)
	Others[d]	14(3.4)
Number of Medications	Mean ± SD	4.3±2.4
	One	76(18.6)
	Two-Four	137(33.5)
	Five and above	195(47.7)
Duration of diabetes (Years)	Mean ± SD	13.9± 8.6
	<5	41(10.0)
	5–10	59(14.4)
	10–15	69(16.9)
	> = 15	129(31.5)

[a]Retired

[b]Grandparents, Relative

[c]Thyroid disorders, osteoarthritis, psychotic disorder, infection, cancer, seizure, obesity

[d]Peripheral arterial disease, autonomic gastroparesis; CKD: Chronic kidney disease; IHD: Ischemic heart disease; RVI: Retroviral infection; SD: Standard Deviation.

Patients received an average of 1.49 anti-diabetes medications per patient. Insulin (41.3%) was the most prescribed medication followed by Metformin + Insulin (29.6%). Apart from anti-diabetes medications, antihypertensive agents (53.8%) were also the predominantly prescribed medications. Among the total patients, 18.6% used one, 33.5% used 2–4, and 47.7% used ≥5 medications.

Drug therapy problems

During the pre-intervention phase, 578 DTPs were identified in 298 (72.9%) patients, with a mean of 1.94 (SD, 1.06) DTPs per patient. Of this, one DTP occurred in 130 (43.6%) and two DTPs in 92 (30.9%) patients (Fig 1). In the post-intervention phase, the number of DTPs was reduced to 128 and identified in 107 (26.2%) patients (p<0.001) (Table 3). The most frequent type of DTP was ADRs. ADRs occurred in about 38.2% (221) of patients and were undesired in 25.3% (n = 146) of the cases. The second most commonly encountered DTP was needs additional drug therapy (26.5%, 152) followed by dosage too low (25.4%, 147). Among anti-diabetes drugs used for management, insulin (41.3%) was the most frequently involved in DTPs followed by the combination of metformin and insulin (32.1%). Statin (65.2%) and angiotensin converting enzyme inhibitors (ACEI)/ angiotensin-receptor blockers(ARBs)(49.8%) were the most common drugs involved in DTPs among other class of drugs.

Once the DTPs were identified, discussions were held with physicians (about the treatment regimen), nurses (about patient education), pharmacists (about dispensing the medications), and patients (about adherence to interventions). The clinical pharmacists made interventions as appropriate and the acceptance rate was 86.3%.

Table 2. Clinical measures for mean scores and paired samples t-test for clinical outcome measures among adult diabetic patients.

Variables	Descriptive Statistics		Paired Differences			t	p-value
	(Mean ± SD)		Mean±SD	95% CI of the Difference			
	Pre MTM	Post MTM		Lower	Upper		
BMI	25.0±4.3	24.7±4.3	0.13±1.6	-0.03	0.28	1.61	0.108
WC	36.8±5.7	35.7±6.7	-1.53±10.55	-2.56	-0.51	-2.94	0.003
SBP	141.2±18.7	134.5±15.9	6.62 ± 26.75	4.02	9.22	5.01	0.000
DBP	80.9±10.5	79.3±9.3	-2.85±16.76	0.83	-4.48	-3.441	0.001
HbA1c	9.3±1.7	8.2±1.6	0.92±3.04	0.63	1.22	6.13	0.000
FBS	167.0±61.4	141.7±47.5	25.04±62.93	18.93	31.16	8.05	0.000

Key: BMI: Body mass index; DBP: Diastolic blood pressure; FBS: Fasting blood sugar; HbA1c: Hemoglobin A1c; MTM: Medication therapy management; SBP: Systolic blood pressure; SD: Standard deviation of mean; WC: Waist circumference.

Logistic regression analysis was performed to identify predictors of DTPs (Table 4). From the socio-demographic and clinical characteristic incorporated in the analysis, source of medication and educational status were significantly associated with DTPs
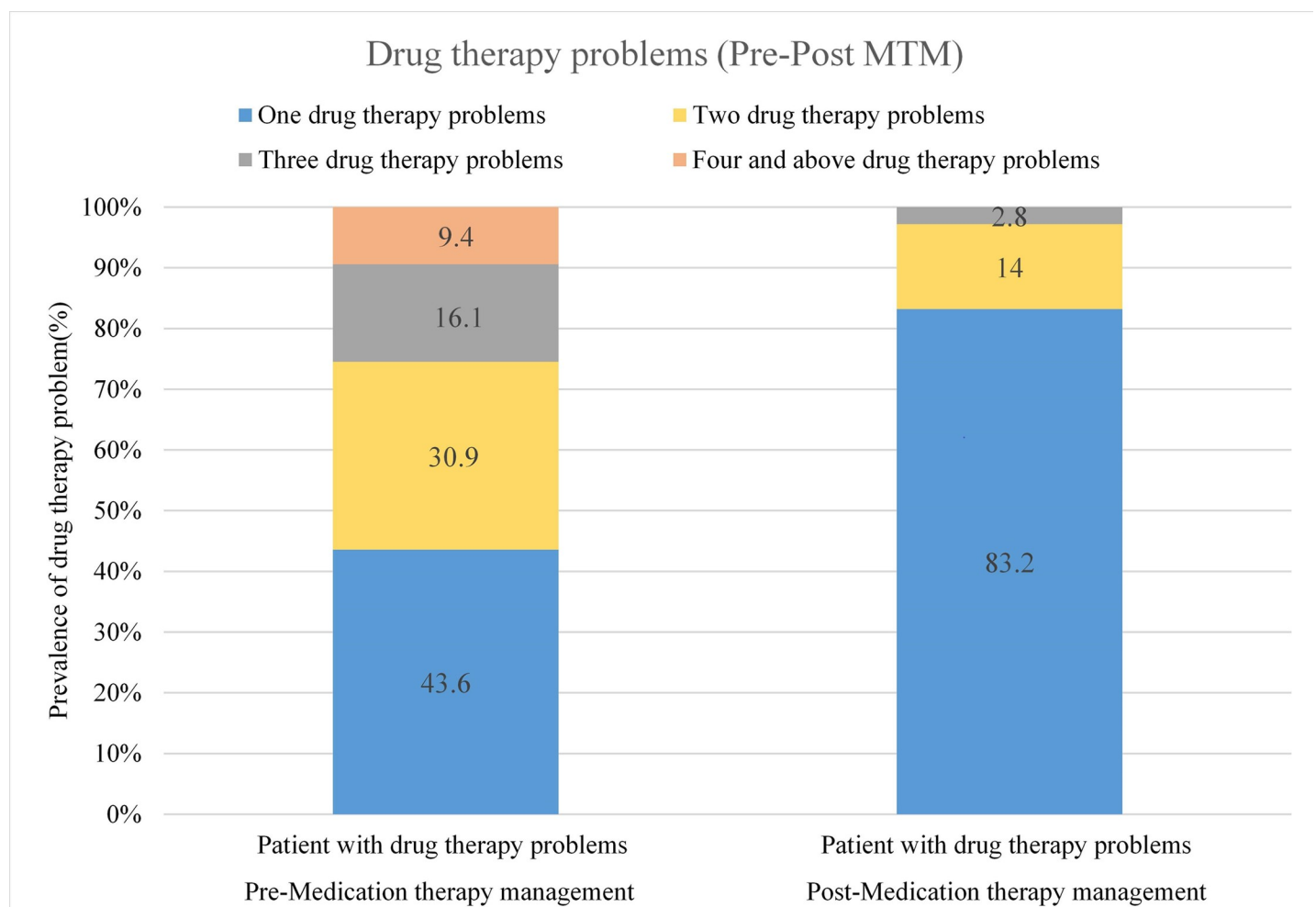
Fig 1. Drug therapy problems among adult patients with diabetes.

Table 3. Drug therapy problems and causes among adult patients with diabetes.

Types of drug therapy problems	Causes	Participants		p-value[*]
		Pre-MTM (N(%))	Post-MTM (N(%))	
Unnecessary drug therapy		28(4.9)	10(7.8)	<0.005
	Inappropriate Duplication of drug therapy	5(0.9)	2(1.6)	0.500
	No medical indication at this time	3(0.5)	1(0.8)	1.000
	Non drug therapy more appropriate	5(0.9)	2(1.6)	0.500
	Addiction/recreational drug use	12(2.1)	4(3.1)	0.125
	Treating avoidable adverse reaction	3(0.5)	1(0.8)	1.000
Needs additional drug therapy		152(26.5)	26(20.3)	<0.001
	Preventive therapy	59(10.2)	12(9.4)	<0.001
	Untreated condition	43(7.4)	8(6.3)	<0.005
	Synergistic therapy	51(8.8)	6(4.7)	<0.001
Ineffective drug product		6(1.0)	0	0.125
	More effective drug available	4(0.7)	0	0.250
	Dosage form inappropriate	2(0.4)	0	1.000
Dosage too low		147(25.4)	19(14.8)	<0.001
	Ineffective dose	54(9.3)	9(7.0)	<0.001
	Frequency inappropriate	32(5.5)	4(3.1)	<0.005
	Incorrect administration	41(7.1)	3(2.3)	<0.001
	Drug interaction	8(1.4)	0	1.000
	Incorrect storage	8(1.4)	3(2.3)	1.000
	Duration inappropriate	4(0.7)	0	1.000
Adverse drug reaction		221(38.2)	65(50.8)	<0.001
	Undesirable side effect	146(25.3)	55(43.0)	<0.001
	Unsafe drug for the patient	3(0.5)	0	0.500
	Drug interaction	58(10.0)	8(6.3)	<0.001
	Incorrect administration	6(1.0)	2(1.6)	0.453
	Allergic reaction	5(0.9)	0	0.125
	Dosage increase/decrease too fast	3(0.5)	0	0.500
Dosage too high		23(4.0)	8(6.3)	0.180
	Dose too high	12(2.1)	4(3.1)	0.219
	Needs additional monitoring	3(0.5)	4(3.1)	1.000
	Frequency too short	4(0.7)	0	0.500
	Duration too long	4(0.7)	0	0.500
Number of patient with DTPs		298(72.9)	107(26.2)	<0.001
Number of DTPs identified		578	128	
Average number of DTPs per participant		1.94±1.06	1.2±0.47	

N: Number of drug therapy problem; DTPs: Drug therapy problems; MTM: Medication therapy management; [*]McNemar test.

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(p<0.05) during the pre-MTM intervention. Patients who paid for their medications had about two-fold risk of developing DTPs as compared to patients who got their medications for free (AOR = 2.27, 95% CI: 1.08–4.77). In addition, patients with primary level of education were also about three times more at risk to develop DTPs as compared to patients who had diploma and above (AOR = 2.94, 95% CI: 1.25–6.91). Following the MTM intervention the male gender was (AOR = 3.06, 95% CI: 1.54–6.07) three times more likely to develop DTPs than female gender.

Table 4. Bivariate and multivariate analysis of factors associated with drug therapy problems among adult patients with diabetes.

Variables	Categories	During MTM Odds Ratios (95% CI)		Post MTM Odds Ratios (95% CI)	
		COR	AOR	COR	AOR
Age(years)	< = 40	1.00		1.00	
	40–60	0.92(0.21–4.01)	0.67(0.16–2.93)	0.74(0.19–2.97)	0.71(0.18–2.80)
	>60	1.37(0.26–7.19)	1.06(0.20–5.55)	0.75(0.15–3.77)	0.75(0.15–3.70)
Gender	Female	1.00		1.00	
	Male	2.04(1.01–4.1)	1.38(0.69–2.76)	4.17(1.96–8.87)	**3.85(1.84–8.07)**
Marital status	Widowed	1.00		1.00	
	Married	2.23(0.47–10.55)	2.15(0.48–9.62)	0.35(0.08–1.63)	0.34(0.08–1.56)
	Single	2.28(0.28–14.97)	2.49(0.40–15.74)	0.31(0.05–1.92)	0.31(0.05–1.89)
	Divorced	3.02(0.32–28.66)	3.15(0.38–25.83)	0.70(0.06–7.5)	0.75(0.07–7.88)
Educational status	Diploma and above	1.00		1.00	
	Unable to write & read	1.22(0.31–4.9)	1.05(0.29–3.86)	3.76(0.8–17.56)	3.51(0.76–16.27)
	Informal education	0.99(0.21–4.47)	0.85(0.20–3.53)	2.91(0.52–16.19)	2.51(0.47–13.4)
	Primary school	3.95(1.52–10.24)	**2.94(1.25–6.91)**	1.5(0.59–3.82)	2.06(0.91–2.76)
	Secondary school	1.96(0.85–4.49)	1.41(0.67–2.99)	2.22(0.96–5.12)	0.35(0.08–4.65)
Residency	Addis Ababa	1.00		1.00	
	Out of Addis Ababa	1.67(0.60–4.71)	1.68(0.62–4.52)	0.6(0.21–1.67)	0.63(0.23–1.73)
Occupation	Employed	1.00		1.00	
	Unemployed	0.32(0.09–1.19)	0.44(0.12–1.58)	1.37(0.38–4.98)	1.42(0.40–5.05)
	Self–employed	0.54(0.16–1.84)	0.80(0.26–2.50)	0.42(0.15–1.19)	0.46(0.17–1.27)
	Others[a]	0.61(0.22–1.71)	0.83(0.309–2.22)	0.99(0.38–2.56)	1.05(0.41–2.69)
Type DM	Type-II	1.00		1.00	
	Type-I	1.58(0.37–6.78)	0.72(0.17–3.10)	1.3(0.38–4.44)	1.28(0.38–4.32)
Number of Comorbidities	No	1.00		1.00	
	1–2	0.91(0.30–2.71)	0.84(0.30–2.38)	1.7(0.64–4.52)	1.65(0.63–4.32)
	> = 3	0.63(0.14–284)	0.75(0.19–3.00)	1.49(0.43–5.23)	1.51(0.43–5.26)
Number of Complications	No	1.00		1.00	
	1–2	0.92(0.40–2.12)	0.88(0.41–1.90)	0.75(0.36–1.56)	0.76(0.37–1.55)
	> = 3	0.25(0.16–4.01)	0.24(0.02–3.20)	2.23(0.19–26.15)	2.26(0.19–26.83)
Duration of DM	<5years	1.00		1.00	
	5-10years	0.70(0.19–2.62)	0.74(0.22–2.46)	0.49(0.15–1.58)	0.49(0.15–1.56)
	10-15years	0.93(0.25–3.47)	0.80(0.24–2.65)	0.61(0.19–1.99)	0.61(0.19–1.94)
	> = 15years	0.82(0.23–2.95)	0.82(0.26–2.62)	0.65(0.21–2.00)	0.61(0.20–1.84)
Source of medication	Free	1.00		1.00	
	Buying	2.49(1.09–5.70)	**2.27(1.08–4.77)**	1.51(0.62–3.66)	1.58(0.65–3.82)

[a]Retired AOR: Adjusted odds ratio; C.I. confidence interval; COR: Crude odds ratio; MTM: Medication therapy management.

Treatment satisfaction

Based on SATMED-Q score tool the treatment satisfaction rate was described in Fig 2 according to the domain score. The satisfaction rate ranged from 88.3 (medical care domain) to 91.6 (convenience domain). The overall mean score of treatment satisfaction was 90.1(SD, 11.04). Socio-demographic and clinical characteristics of the patients also had an effect on treatment satisfaction of patients (Table 5). Diabetic patients of younger age group (below 40 years) (92.84(SD, 9.54)), type-I DM (93.04(SD, 9.75)) and managed by one medication (93.13(SD, 9.17)) had a significantly higher treatment satisfaction score compared to their counterparts (p<0.05).
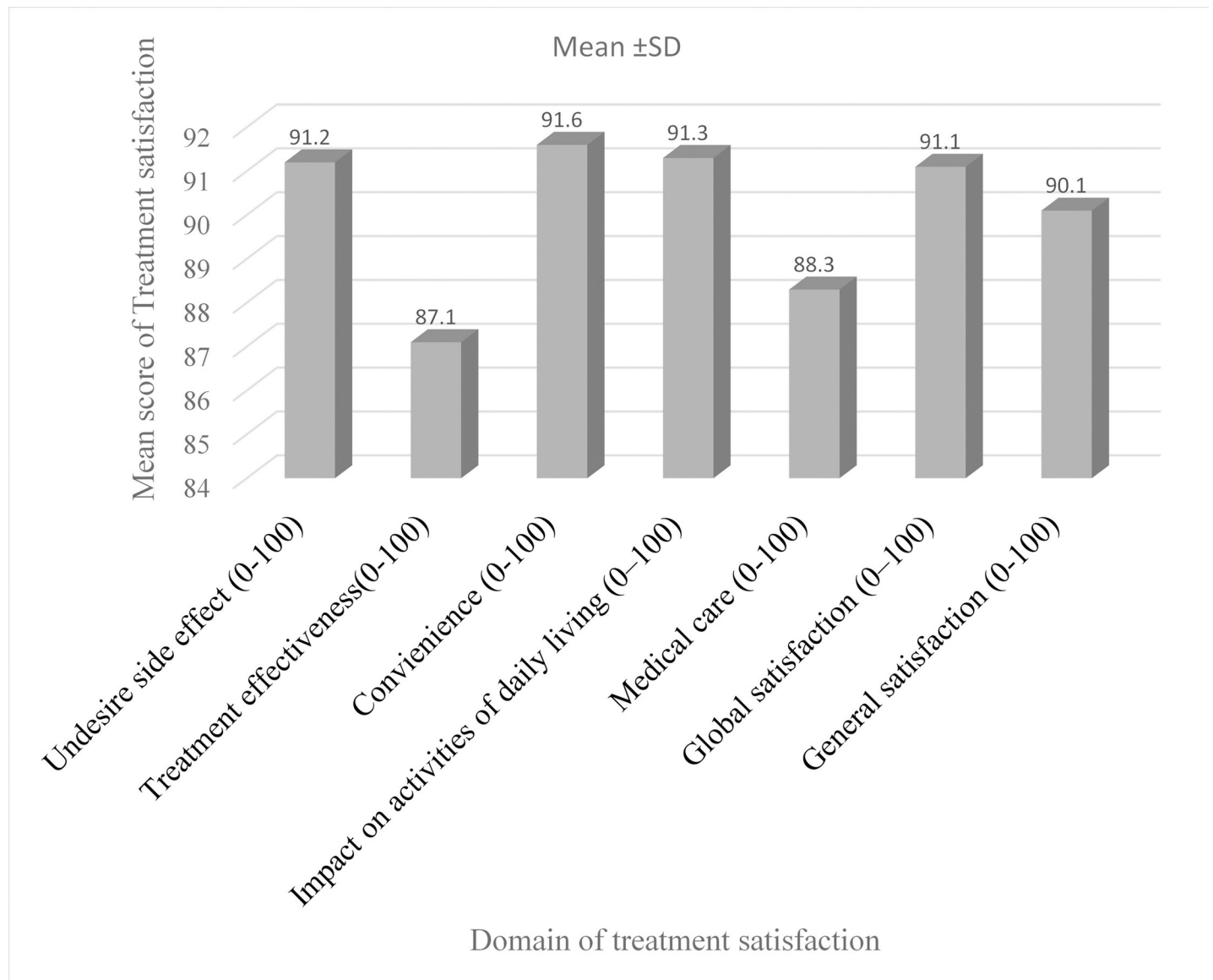
Fig 2. Treatment satisfaction following MTM intervention among adult diabetic patients.

Discussion

Patients with diabetes are at high risk of having DTPs and non-adherence issues due to comorbidities and polypharmacy [30]. Identification and resolution of DTPs contributes to better clinical outcome and reduction of drug-related hospitalizations, morbidity and mortality [10]. Treatment satisfaction is also an important component of the quality of medical care [31]. Therefore, this study evaluated the impact of introducing MTM services on such issues surrounding DM patients.

Clinical outcome

In this study co-morbidities and complications were common among study participants, probably attributed to higher mean age (52 years) and duration of illness (14 years) as well as type

Table 5. Relationship between treatment satisfaction and different characteristics of patients with diabetes.

Variables	Category	N	Mean SATMED-Q score ± SD	F	P-value
Age(years)	< = 40	99	92.84± 9.54	3.060	**0.048**[*]
	40–60	174	88.99± 11.47		
	>60	136	89.51± 11.24		
Gender	Male	186	91.87± 10.32	2.800	0.095[**]
	Female	223	88.61± 11.43		
Marital status	Married	292	89.86± 11.39	0.302	0.824[*]
	Single	69	91.65± 9.76		
	Divorced	19	88.46± 12.66		
	Widowed	29	89.86± 9.22		
Type of DM	Type I	89	93.04± 9.75	5.691	**0.018**[**]
	Type II	320	89.28± 11.25		
Number of Comorbidities	No	110	92.16± 10.26	2.608	0.075[*]
	One-Two	240	89.14± 11.27		
	Three and above	59	90.14± 11.15		
Number of Complications	NO	258	91.17± 10.53	2.028	0.133[*]
	One-Two	141	88.64± 11.39		
	Three and above	10	82.89± 14.85		
Number of medication	One	76	93.13± 9.17	3.064	**0.048**[*]
	Two-Four	138	90.88± 10.83		
	Five and above	194	88.47± 11.50		

SATMED-Q: Satisfaction with Medicines Questionnaire; SD: Standard Deviation.

[*]One-way analysis of variance (ANOVA)

[**]Independent t-test.

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of diabetes they had(most had Type 2 DM). This is consistent with studies conducted in Australia [32] and USA [33] that showed age and duration of diabetes are strongly associated with macro-vascular and microvascular events. Intervention brought about a reduction in HbA1c levels by about 0.92% from baseline and this is concordant with other numerous studies performed in pharmacist-managed ambulatory and community pharmacy diabetes care models [19,34,35]. The reduction is strongly attributed to the intervention, which targeted the optimization of medication therapy need, lifestyle modification and enhanced medication adherence through consultations. The awareness created through brochure, face-face and phone based education about the disease condition and its management; ADR prevention and management could also enhance treatment outcome [36–38].

Intervention was able to reduce proportion of patients with hyperglycemia from 68% to 40%. Similar studies done elsewhere [39,40] reported a decrement following MTM service, with varied extent depending on guideline used for cut-off points, patients' awareness to apply recommendations and other sociodemographic factors. Other clinical parameters including FBS and SBP were also reduced through the intervention as reported elsewhere [34,37,39].

Drug therapy problems

In this study patients having at least one DTP and mean number of DTP per patient decreased after provision of intervention. This finding is concordant with earlier studies that demonstrated pharmacist-provided MTM services would result in lower DTPs prevalence [19,41,42]. This reduction was brought about by increased awareness of patients about lifestyle

modification, side effect prevention and management, medication misuse, and importance of medication adherence [43,44]. In addition, it might be also due to a good communication created between pharmacist and physician during intervention in preventing the occurrence of DTPs [37,45].

ADRs were the most common DTPs encountered as reported elsewhere [46]. The presence of multiple comorbidities and complications as well as the ensuing polypharmacy to curb them might provide an explanation for the observed abundance of ADRs. The increased proportion of elderly population as well as disease duration would also likely increase the risk of ADRs. By contrast, other studies conducted in Gondar [14] and Jimma [15] (Ethiopia), India [10], and USA [18] reported needing additional therapy and taking unnecessary drug therapy were the most prevalent DTPs. Difference in study settings, socio-demographic characteristics, recruitment criteria, pharmacist clinical skills and tools used for DTP assessment might explain the discrepancy.

Patients who paid out of pocket for their medication had a $\geq$ 2-fold risk to develop DTPs compared to those who got their medications for free. This finding is consistent with other studies showing that out of pocket cost of medication affect the medication taking behavior of patients that lead to increased DTPs [47,48]. Optimal management of diabetes, its complications and comorbidities require appropriate medication with affordable cost. If patients are unable to pay for their medications, they try to change the instruction provided or intentionally miss their medication.

Focusing on the problems identified in the pre-intervention phase, the patients were provided with constructive information and education materials. The intervention also targeted improving patients' awareness about pharmacological and non-pharmacological management of their disease condition, the importance of medication adherence and management of adverse drug events. Thus, the only factor that was still significantly associated with DTPs in the post-intervention phase was gender. The male gender was more likely to develop DTPs than the female gender. This was in line with previous studies conducted in Malaysia [12] and Jordan [49]. The likely explanation could be related to differences in health behavior as well as acceptance of recommendation between males and females [50,51].

About 86% of the interventions were accepted and implemented. ADRs, needs additional drug therapy, and dosage too low were the most addressed DTPs. Mining the literature showed a varied range of acceptance rate from 50–55% [10,52] through 70–90% [14,53,54] to 100% [35]. This relatively high acceptance rate reported in the present study might be related to the presence of many comorbidities, complications, and associated polypharmacy that called for teamwork to better manage these conditions.

Treatment satisfaction

The overall mean score of treatment satisfaction was 90.1(SD, 11.04). This was relatively higher than the baseline satisfaction score (80.81(SD, 8.58)) [16]. This finding is consistent with other studies that showed MTM provided by pharmacist had an average score of treatment satisfaction more than 75 composite score [35,55].

Patients with Diabetes below 40 years had high treatment satisfaction score, which is congruent with studies conducted in Qatar [56] and Pakistan [57]. However, it is in stark contrast with the Netherlands study that reported young age is associated with low treatment satisfaction [31]. The lower treatment satisfaction among the elderly might be due to the presence of many comorbidities, complications and long duration of disease. This condition might lead to polypharmacy and economic burden that affects quality of life.

Type-I DM patients had high treatment satisfaction score as compared to type II DM. In contrast to our finding, in the Qatar study [56], type-I DM patients had low treatment satisfaction score. This difference might be due to difference in tool used for assessment, awareness of participants, and perception of participant towards their medication.

There are some limitation in this study. The intervention period is relatively short (six months) which may overestimate the outcome. The study is a single center study that might not allow to make generalization to the whole population. The study also lacks economic evaluation of MTM service due to resource and time limitations. To confirm the current finding and reduce the bias conducting an RCT is important. However, despite the limitations, the study could still provide some tangible evidence about effect of MTM delivery on clinical outcomes, drug therapy problem, and treatment satisfaction in developing nation with limited resource and poor facility.

Conclusion

The study suggest that the provision of MTM service to patients with diabetes, with/without complications and comorbidity had the potential to improve the clinical parameters such as HgA1c, FBS and BP. The study also demonstrate that pharmacist led MTM service reduced the DTPs identified among ambulatory patients with diabetes in TASH. Recruiting patients to MTM service also increased treatment satisfaction among study participants.

Supporting information

S1 File.
(DOCX)

Acknowledgments

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References

1. International Diabetes Federation. IDF Diabetes Atlas. 7th ed. Brussels, Belgium: International Diabetes Federation. 2015. Available at: http://www.idf.org/diabetesatlas. Accessed April 1, 2020.

2. International Diabetes Federation. IDF Diabetes Atlas. 8th ed. Brussels, Belgium: International Diabetes Federation. 2017. Available at: http://www.idf.org/diabetesatlas. Accessed Feb 15, 2020.

3. World Health Organization (WHO). Global Report on Diabetes. 2016. Available at:https://apps.who.int/iris/bitstream/handle/10665/204871/9789241565257_eng.pdf;jsessionid=4078DF16BC4D5264F70EE490988E4FBB?sequence=1 Accessed Feb 15, 2020.

4. Meyer L, Guerci B. Metformin and insulin in type 1 diabetes: the first step. Diabetes Care. 2003; 26 (5):1655–6. https://doi.org/10.2337/diacare.26.5.1655-a PMID: 12716857

5. Madhu S, Srivastava S. Diabetes mellitus: Diagnosis and management guidelines. J Int Medi Sci Acad. 2015; 1:47–50.

6. Pharmaceutical Services Division, Ministry of Health Malaysia. Drug Utilization in the Treatment of Diabetes Mellitus in the Ministry of Health Facilities. Kuala Lumpur. 2013; 1–123. Available at: http://www.pharmacy.gov.my. Accessed March 10, 2020.

7. Cipolle RJ, Strand LM, Morley PC. Pharmaceutical care practice: the patient-centered approach to medication management: 3rd ed. McGraw Hill Professional; 2012.

8. Ogallo W, Kanter AS. Using Natural Language Processing and Network Analysis to Develop a Conceptual Framework for Medication Therapy Management Research. AMIA Annu Symp Proc. 2017; 984–993.

9. US Department of Health and Human Services, Office of Disease Prevention and Health Promotion. National Action Plan for Adverse Drug Event Prevention. 2014. Accessed online via http://health.gov/hcq/pdfs/ADE-Action-Plan-508c.pdf on March 14, 2020.

10. Shareef J, Fernandes J, Samaga L. Clinical pharmacist interventions in drug therapy in patients with diabetes mellitus and hypertension in a University Teaching Hospital. Int J Pharm Sci Res. 2015; 6 (10):4424–32.

11. Wong I. Improving Medication Safety and Diabetes Management in Hong Kong–A Multi-disciplinary Approach. Hong Kong Med J. 2017; 23(2): 158–67. https://doi.org/10.12809/hkmj165014 PMID: 28302923

12. Huri HZ, Ling LC. Drug-related problems in type 2 diabetes mellitus patients with dyslipidemia. BMC Public Health. 2013; 13(1192): 1–13. https://doi.org/10.1186/1471-2458-13-1192 PMID: 24341672

13. Ogbonna B, Ezenduka C, Opara C, Ahara L. Drug therapy problems in patients with Type-2 Diabetes in a tertiary hospital in Nigeria. Int J Innov Res Dev. 2014; 3(1):494–502.

14. Abegaz TM, Bhagavathula AS, Tefera YG, Belachew SA, Tegegn HG. Medication therapy management services in emergency and ambulatory care of Gondar University Hospital, northwest Ethiopia. J Pharm Pra Res. 2018; 48(4):320–7.

15. Yimama M, Jarso H, Desse TA. Determinants of drug-related problems among ambulatory type 2 diabetes patients with hypertension comorbidity in Southwest Ethiopia: a prospective cross sectional study. BMC Res Notes. 2018; 11(679):1–6. https://doi.org/10.1186/s13104-018-3785-8 PMID: 30249291

16. Demoz GT, Berha AB, Woldu MA, Yifter H, Shibeshi W, Engidawork E. Drug therapy problems, medication adherence and treatment satisfaction among diabetic patients on follow-up care at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia. PLoS One. 2019; 14(10):e0222985. https://doi.org/10.1371/journal.pone.0222985 PMID: 31574113

17. Nivya K, Kiran VSS, Ragoo N, Jayaprakash B, Sekhar MS. Systemic review on drug related hospital admissions–A pubmed based search. Saudi Pharm J. 2015; 23(1):1–8. https://doi.org/10.1016/j.jsps.2013.05.006 PMID: 25685036

18. Ombengi D, Ndemo F, Noreddin AM, Harris W. The Disease Burden and the Extent of Drug Therapy Problems in an Underserved Minority Population Receiving Medication Therapy Management at an Ambulatory Care Free Clinic. J Pharm Care Health Syst. 2016; 3(2):1–5.

19. Rodis JL, Sevin A, Awad MH, Porter B, Glasgow K, Hornbeck Fox C, et al. Improving chronic disease outcomes through medication therapy management in federally qualified health centers. J Prim Care Community Health. 2017; 8(4): 324–331. https://doi.org/10.1177/2150131917701797 PMID: 28381095

20. Viswanathan M, Kahwati LC, Golin CE, Blalock SJ, Coker-Schwimmer E, Posey R, et al. Medication therapy management interventions in outpatient settings: a systematic review and meta-analysis. JAMA Intern Med. 2015; 175(1):76–87. https://doi.org/10.1001/jamainternmed.2014.5841 PMID: 25401788

21. Cranor CW, Bunting BA, Christensen DB. The Asheville Project: long-term clinical and economic outcomes of a community pharmacy diabetes care program. J Am Pharm Assoc. 2003; 43(2): 173–84. https://doi.org/10.1331/108658003321480713 PMID: 12688435

22. Pinto SL, Kumar J, Partha G, Bechtol RA. Pharmacist-provided medication therapy management (MTM) program impacts outcomes for employees with diabetes. Popul Health Manag. 2014; 17(1):21–7. https://doi.org/10.1089/pop.2012.0124 PMID: 23848476

23. Zillich AJ, Snyder ME, Frail CK, Lewis JL, Deshotels D, Dunham P, et al. A randomized, controlled pragmatic trial of telephonic medication therapy management to reduce hospitalization in home health patients. Health Serv Res. 2014; 49(5): 1537–54. https://doi.org/10.1111/1475-6773.12176 PMID: 24712335

24. American Diabetes Association. Standards of Medical Care in Diabetes-2018. Abridged for Primary Care Providers. Diabetes Care. 2018. Available at: https://clinical.diabetesjournals.org/content/41/Supplement_1. Accessed April 14, 2020.

25. Rejas J, Ruiz MA, Pardo A, Soto J. Minimally important difference of the Treatment Satisfaction with Medicines Questionnaire (SATMED-Q). BMC Med Res Methodol. 2011; 11(1): 1–9. https://doi.org/10.1186/1471-2288-11-142 PMID: 22014277

26. Ruiz MA, Pardo A, Rejas J, Soto J, Villasante F, Aranguren JL. Development and Validation of the "Treatment Satisfaction with Medicines Questionnaire"(SATMED-Q)©. Value Health. 2008; 11(5): 913–26. https://doi.org/10.1111/j.1524-4733.2008.00323.x PMID: 18494753

27. The Society for Endocrinology, Metabolism and Diabetes of South Africa Type 2 Diabetes Guidelines Expert Committee. SEMDSA 2017 guidelines for the management of type 2 diabetes mellitus. J Endocr Metab Diabetes S Afr. 2017; 22(1 Suppl 1):S1-S196.

28. Zeind CS, Carvalho MG. Applied therapeutics: the clinical use of drugs. 2018. Available from: http://pharmacy.lwwhealthlibrary.com/book.aspx?bookid=2324.

29. DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey L. Pharmacotherapy A Pathophysiologic Approach, 10e. New York, NY: McGraw-Hill Education LLC. 2017.

30. Al-Azzam SI, Alzoubi KH, AbuRuz S, Alefan Q. Drug-related problems in a sample of outpatients with chronic diseases: a cross-sectional study from Jordan. Therap clin risk manag 2016; 12: 233–9.

31. Redekop WK, Koopmanschap MA, Stolk RP, Rutten GE, Wolffenbuttel BH, Niessen LW. Health-related quality of life and treatment satisfaction in Dutch patients with type 2 diabetes. Diabetes Care. 2002; 25 (3): 458–63. https://doi.org/10.2337/diacare.25.3.458 PMID: 11874930

32. Zoungas S, Woodward M, Li Q, Cooper ME, Hamet P, Harrap S, et al. Impact of age, age at diagnosis and duration of diabetes on the risk of macrovascular and microvascular complications and death in type 2 diabetes. Diabetologia. 2014; 57(12): 2465–74. https://doi.org/10.1007/s00125-014-3369-7 PMID: 25226881

33. Lochner KA, Goodman RA, Posner S, Parekh A. Multiple chronic conditions among Medicare beneficiaries: state-level variations in prevalence, utilization, and cost, 2011. Medicare Medicaid Res Rev. 2013; 3(3): E1–E19. https://doi.org/10.5600/mmrr.003.03.b02 PMID: 24753976

34. Tilton JJ, Edakkunnathu MG, Moran KM, Markel Vaysman A, DaPisa JL, Goen BM, et al. Impact of a Medication Therapy Management Clinic on Glycosylated Hemoglobin, Blood Pressure, and Resource Utilization. Ann Pharmacother. 2019; 53(1):13–20. https://doi.org/10.1177/1060028018794860 PMID: 30099887

35. Ndefo UA, Moultry AM, Davis PN, Askew R. Provision of medication therapy management by pharmacists to patients with type-2 diabetes mellitus in a federally qualified health center. Pharm Therap. 2017; 42(10):632–37.

36. McAdam-Marx C, Dahal A, Jennings B, Singhal M, Gunning K. The effect of a diabetes collaborative care management program on clinical and economic outcomes in patients with type 2 diabetes. J Manag Care Pharm. 2015; 21(6):452–68. https://doi.org/10.18553/jmcp.2015.21.6.452 PMID: 26011547

37. Davis CS, Ross LAR, Bloodworth LS. The impact of clinical pharmacist integration on a collaborative interdisciplinary diabetes management team. J Pharm Pract. 2017; 30(3): 286–290. https://doi.org/10.1177/0897190016631894 PMID: 26888261

38. Boban B, Aswathy K, Athira B, Karthikeyan M, Xavier A, Aravind R. Impact of medication therapy management on knowledge, attitude and practice among diabetic patients. Clinic Epidem Global Health. 2017; 5(2):70–2.

39. Tunpichart S, Sakulbumrungsil R, Somrongthong R, Hongsamoot D. Chronic care model for diabetics by pharmacist home health in Bangkok Metropolitan: A community based study. Int J Medici Medica Sci. 2012; 4(4):90–6.

40. Pathania M, Dutt HK, Gogoi JB, Rathaur V, Singh G, Singh P. Study the Impact of Diabetes Camps on Adherence to Medication and Glycaemic Control in Uttarakhand. J Clin Diagn Res. 2016; 10(2): 22–6. https://doi.org/10.7860/JCDR/2016/16053.7271 PMID: 27042497

41. Barnett M, Frank J, Wehring H, Newland B, VonMuenster S, Kumbera P, et al. Analysis of pharmacist-provided medication therapy management (MTM) services in community pharmacies over 7 years. J Manag Care Pharm. 2009; 15(1):18–31. https://doi.org/10.18553/jmcp.2009.15.1.18 PMID: 19125547

42. Ramalho de Oliveira D, Brummel AR, Miller DB. Medication therapy management: 10 years of experience in a large integrated health care system. J Manag Care Pharm. 2010; 16(3):185–95. https://doi.org/10.18553/jmcp.2010.16.3.185 PMID: 20331323

43. Brummel AR, Soliman AM, Carlson AM, de Oliveira DR. Optimal diabetes care outcomes following face-to-face medication therapy management services. Popun health managt. 2013; 16(1): 28–34. https://doi.org/10.1089/pop.2012.0023 PMID: 23113628

44. Bukhsh A, Nawaz MS, Ahmed HS, Khan TM. A randomized controlled study to evaluate the effect of pharmacist-led educational intervention on glycemic control, self-care activities and disease knowledge among type 2 diabetes patients: A consort compliant study protocol. Medicine. 2018; 97(12):1–6. https://doi.org/10.1097/MD.0000000000009847 PMID: 29561461

45. Strand LM, Cipolle RJ, Morley PC, Frakes MJ. The impact of pharmaceutical care practice on the practitioner and the patient in the ambulatory practice setting: twenty-five years of experience. Curr pharm design. 2004; 10(31):3987–4001. https://doi.org/10.2174/1381612043382576 PMID: 15579084

46. Al Hamid A, Aslanpour Z, Aljadhey H, Ghaleb M. Hospitalisation resulting from medicine-related problems in adult patients with Cardiovascular diseases and diabetes in the United Kingdom and Saudi Arabia. Int J Environ Res Public Health. 2016; 13(5):479. https://doi.org/10.3390/ijerph13050479 PMID: 27171100

47. Viswanathan M, Golin CE, Jones CD, Ashok M, Blalock SJ, Wines RC, et al. Interventions to improve adherence to self-administered medications for chronic diseases in the United States: a systematic review. Ann Intern Med. 2012; 157(11):785–95. https://doi.org/10.7326/0003-4819-157-11-201212040-00538 PMID: 22964778

48. Van Mourik MS, Cameron A, Ewen M, Laing RO. Availability, price and affordability of cardiovascular medicines: a comparison across 36 countries using WHO/HAI data. BMC Cardiovasc Disord. 2010; 10 (25):1–9. https://doi.org/10.1186/1471-2261-10-25 PMID: 20534118

49. Zazuli Z, Rohaya A, Adnyana IK. Drug-Related Problems in Type 2 Diabetic Patients with Hypertension: A prospective Study. J Basic Clini Pharm. 2017; 8(4): 251–254.

50. Campbell AN, Nunes EV, Pavlicova M, Hatch-Maillette M, Hu M-C, Bailey GL, et al. Gender-based outcomes and acceptability of a computer-assisted psychosocial intervention for substance use disorders. J subs abuse treatm. 2015; 53:9–15. https://doi.org/10.1016/j.jsat.2014.12.006 PMID: 25613105

51. Schofield T, Connell RW, Walker L, Wood JF, Butland DL. Understanding men's health and illness: a gender-relations approach to policy, research, and practice. J Ame college health. 2000; 48(6):247–56.

52. Christensen DB, Roth M, Trygstad T, Byrd J. Evaluation of a pilot medication therapy management project within the North Carolina State Health Plan. J Am Pharm Assoc. 2007; 47(4):471–83. https://doi.org/10.1331/JAPhA.2007.06111 PMID: 17616493

53. Barner JC, Lawson KA, Kim Roberson RP, Makhinova T. Clinical and Economic Outcomes of the Texas Medicaid Medication Therapy Management (MTM) Pilot. Center Pharmacoeco Stud. 2015; 1–32.

54. Ploenzke C, Kemp T, Naidl T, Marraffa R, Bolduc J. Design and implementation of a targeted approach for pharmacist-mediated medication management at care transitions. J Am Pharm Assoc. 2016; 56 (3):303–9. https://doi.org/10.1016/j.japh.2016.01.009 PMID: 27150224

55. Sa'ed HZ, Al-Jabi SW, Sweileh WM, Morisky DE. Relationship of treatment satisfaction to medication adherence: findings from a cross-sectional survey among hypertensive patients in Palestine. Health Qual Life Outcomes. 2013; 11(1):1–7. https://doi.org/10.1186/1477-7525-11-191 PMID: 24195638

56. Bener A, Al-Hamaq A, Yousafzai M, Abdul-Ghani M. Relationship between patient satisfactions with diabetes care and treatment. Niger J Clin Pract. 2014; 17(2):218–25. https://doi.org/10.4103/1119-3077.127562 PMID: 24553035

57. Jalil A, Zakar R, Zakar MZ, Fischer F. Patient satisfaction with doctor-patient interactions: a mixed methods study among diabetes mellitus patients in Pakistan. BMC Health Serv Res. 2017; 17(1):1–13. https://doi.org/10.1186/s12913-016-1943-z PMID: 28049468