

The Role of Clinical Pharmacist in Initiation and/or Dose Adjustment of Insulin Therapy in Diabetic Patients in Outpatient Clinic in Jordan

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ABSTRACT

Glycemic control in diabetic patients is a challenging issue and requires pharmacist involvement in the patient care plan and patient's awareness to optimize diabetic regimen.

Objectives: The aim of this study is to investigate the role of clinical pharmacist on glycemic control of diabetic patients by insulin therapy management in the endocrine outpatient clinic in a teaching hospital in Jordan.

Method: This is a prospective, randomized controlled study carried out in the Endocrine-outpatient clinic in Jordan University Hospital (JUH). Patients with type 1 or type 2 diabetes were randomly assigned to intervention (n=50) or control group (n=50). Newly diagnosed patients with (HbA1c > 10%); or those who are diabetic with (HbA1c >7%) and taking insulin with or without oral hypoglycemic agents; or patient with (HbA1C > 7%) and on two or more oral hypoglycemic gents for ≥ 6 months were recruited either in the intervention group or the control group. Follow up started concurrently with data collection; patients were followed up for 3 months after enrollment. During the first visit demographic data, history of diabetes and diabetes assessment, other chronic disease, anti-diabetic medications and current medications used, adherence to medications, diabetes life style adherence and baseline data for HbA1c, FBG and weight were obtained. Moreover, the patients' medical records were reviewed by the pharmacist to obtain other related information. Data analysis was performed using SPSS software version (17.0). Glycosylated hemoglobin A1C (HbA1c), fasting blood glucose (FBG), frequency of hypoglycemic episodes and weight gain were measured.

Results: 88 patients completed the study; clinical pharmacist interventions resulted in a significant reduction in HbA1c by 1% (p-value <0.001) and fasting blood sugar by (28.44±84.62) mg/dl compared to the baseline (p-value=0.029) with a statistically significant difference between both groups (p-value <0.05). Insignificant difference in weight gain was found between the 2 groups (p-value = 0.117), but with higher significant weight increase in the intervention group from baseline (p-value=0.001). Although hypoglycemic episodes frequency was significantly higher during the first month in the intervention group compared to the control group (p-value=0.016), none of these episodes required hospitalization.

Conclusion: This study supports the role of clinical pharmacist in glycemic control in diabetic insulin users', in a country like Jordan in which clinical pharmacy practice is relatively new.

Keywords: The role of Clinical Pharmacist, Diabetic patients, Outpatient Clinic in Jordan.

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1. INTRODUCTION

Diabetes Mellitus (DM) is a group of metabolic diseases resulting from inability of the body to secrete insulin, resistance to its action, or both. DM is characterized by high level of blood glucose; this chronic high glucose level is associated with different organs damage, like the eyes, kidneys, nerves, heart, and blood vessels⁽¹⁾. DM is a common disease; 346 million people in the world having DM. An estimated 3.4 million people died in 2004 from elevated blood glucose consequences It is projected that DM death will double between 2005 and 2030⁽²⁾. In Jordan, age-standardized prevalence of Type 2 diabetes mellitus(T2DM) and impaired fasting glucose (IFG) among Jordanians is 17.1% and 7.8% respectively, no significant differences were found between women and men⁽³⁾.

Diabetes has common consequences; according to World Health Organization (WHO) diabetes increases the chance of heart disease and stroke. About 50% of people with diabetes die from cardiovascular disease. Combined with decrease blood flow, diabetes damage of nerves (neuropathy) in the feet increases the risk of foot ulcers and limb amputation. Diabetes damages the small blood vessels in retina (retinopathy), which is an important cause of blindness with about 2% of patients becoming blind and about 10% having severe visual impairment after 15 years of diabetes. Diabetes is one of the leading causes of kidney failure with 10-20% of diabetic patients' dying of kidney failure. The risk of dying in diabetic patients is at least double the risk of their non-diabetic peers⁽²⁾.

Insulin is the most effective agent at decreasing glucose level. It can reduce any level of HbA1C to the recommended goals when given in adequate doses. Insulin differs from other sugar lowering agents in that it does not have a maximum dose after which the effect will not occur. Higher doses of insulin (≥ 1 unit/Kg) may be required in T2DM compared with T1DM to achieve HbA1C goal and overcome insulin resistance⁽⁴⁾.

Study indications

Pharmacists' role has been assessed on glycemic

control and other health aspects have been evaluated through several studies. Most of these studies showed the positive effects of pharmacists' interventions, but few of them did not. These studies have different study designs, different methodology and different follow up period with most of them targeting type 2 diabetic oral hypoglycemic agents' users, insulin users or both. Fewer studies targeting only diabetic insulin users with or without oral hypoglycemic agents including both T1DM and T2DM and some of these studies have no control group or have historical control group⁽⁵⁻¹⁹⁾. In Jordan the impact of clinical pharmacist on glycemic control, lipid values, blood pressure, self-care activities and self-reported medication adherence for patients with T2DM have been assessed in outpatient diabetes clinic through randomized control trial and showed the positive impact of clinical pharmacist intervention⁽²⁰⁾. In addition, clinical pharmacist interventions in the management of oral medications in type 2 diabetic patients resulted in a significant improvement in HbA1c, FBG, lipid profil, diabetes knowledge, diabetes self-care activities and self-reported medication adherence after 6 months of follow up⁽²¹⁾.

This indicates that there is a need for a prospective randomized controlled study in diabetic patients (T1DM or T2DM) targeting insulin users specifically; with an intervention that combines pharmacotherapy changes and patient education to evaluate the role of clinical pharmacist in initiation and/or dose titration of insulin therapy in diabetic patients in Jordan.

Objectives

The aim of this study was to assess the role of clinical pharmacist on glycemic control in uncontrolled diabetic patients who already take insulin or newly started on insulin therapy.

Methodology

This is a prospective, randomized controlled study carried out in the Endocrine-outpatient clinic in Jordan University Hospital (JUH). An approval from Institutional Review Board (IRB) committee was

obtained before patients' recruitment. Data collection and patients interviewing were carried out in the endocrine outpatient clinic of this teaching Hospital. Patients' recruitment started from the 27th of September 2011 until 9th of January 2012, follow up started concurrently with data collection and ended in 7th of May 2012. Endocrine outpatient clinic operates 4 days weekly from Sunday to Wednesday. The average number of patients visiting this clinic is about 70 patients/day, of these about 45 patients/day are diabetic, and most of them are T2DM.

A sample size of 35 patients in each research arm would be enough ($\beta = 0.20$ and $\alpha = 0.05$) to detect a difference in HbA1c of 1% (14). Our target was to have 50 patients in each research arm.

Patients were recruited as per the following criteria:

Inclusion criteria:

- Male or female ≥ 18 years.
- Patients who have been diagnosed with DM.
- Patient with HbA1C according to one of the following criteria:
 1. HbA1c $> 7\%$ in a patient who takes insulin with or without oral hypoglycemic agents.
 2. Patient with HbA1C $> 7\%$ and on 2 or more oral hypoglycemic agents for ≥ 6 months.
 3. Patient with HbA1C $> 10\%$ at initial diagnosis.
- Patient willing to perform self-monitoring of blood glucose (SMBG).
- Patient is a candidate for insulin therapy and physician plans to prescribe insulin.
- Patient who accepts to be a part of this study and provides written informed consent to his participation.

Exclusion criteria:

- Pregnant or nursing women.
- Patient who refuses insulin initiation.
- Patient not willing to do self-monitoring of blood glucose (SMBG).
- Patient with serious renal or hepatic disease.
- Patient with dementia or cognitive impairment.
- Patient who needs emergency care.

Patients were randomly allocated either as intervention or as control group after providing consent form; randomization was carried out by asking the patients to draw from a closed envelope of equal even and odd numbers. Data were collected from patients by the clinical pharmacist including demographics, medical history, current medications used, adherence to medications, DM life style adherence, and baseline data for HbA1c, fasting blood glucose (FBG) and weight. Patients' medical records were reviewed by the clinical pharmacist to obtain other related information. The medication adherence questionnaire⁽²²⁾ and life-style adherence questionnaire⁽²³⁾ were used to obtain other data from the patients themselves or by the accompanied care giver.

Intervention group

For patients in the intervention group, the clinical pharmacist collaborated with physician in the management of insulin therapy. During the first interview of patients and after collecting essential data, clinical pharmacist recommendations regarding insulin therapy were discussed with their responsible physician, these recommendations were (based on Texas Diabetes Council Insulin algorithm 2010⁽²⁴⁻²⁵⁾).

In addition, the clinical pharmacist asked the physician to prescribe extra amounts of insulin and the clinical pharmacist was responsible to follow the patients closely through the phone calls during the first 2-4 weeks to guide the patients through insulin dose adjustment (patients assessed on average of 3 days, no interventions were done after week 4) based on patients' SMBG record that was provided by the clinical pharmacist.

Moreover, during the first visit the clinical pharmacist provided the following to the

patients:

- Explained the clinical course of the disease including sign and symptoms.
- Described the recommended goals of glycemic control [based on Texas Diabetes Council 2010]⁽²⁴⁻²⁵⁾.
- Justified the role of insulin therapy in their medications.
- Education about appropriate use of antidiabetic

medications [Based on Clinical Drug Information, Lexi-Comp Online, Adult patient education]⁽²⁶⁾.

- Education about hypoglycemia and the proper way to deal with it [based on American Diabetes Association-standards of medical Care in diabetes-2011]⁽²⁷⁾.
- Education about lifestyle changes including diet and exercise. [Based on American Diabetes Association-Standards of Medical Care in Diabetes, 2011; and Texas Diabetes Council- Nutrition Recommendations and Interventions for Diabetes, 2011]^(27, 28).
- Education about importance of adherence to pharmacological and non-pharmacological treatments, and encouraged patients' compliance by explaining to them that they are the key element in their disease management.
- Provided the patients with Accu-Chek® Performa devices [note that not all patients provided with this device, some used their own devices], SMBG record sheet and educated them how to use the device. The patients were asked to self-monitor their blood glucose several times a day.

Control group

Patients in the control group received their usual care from clinic team. However, they were provided with Accu-chek Performa® devices [note that not all patients provided with this device some used their own devices]; they were asked to record their FBG at each month and to record hypoglycemic episodes if any.

Follow-up

All patients were followed up for 3 months after enrollment.

During the follow up the following were obtained from both groups:

- First month: FBG and frequency of hypoglycemic episodes.
- Second month: FBG and frequency of hypoglycemic episodes.
- Third month: HbA1C, FBG, weight, frequency of hypoglycemic episodes.

Outcome measures

- Glycosylated hemoglobin A1C (HbA1c). (primary outcome)
- Fasting blood glucose (FBG). (secondary outcome)
- Frequency of hypoglycemic episodes. (secondary outcome)
- Weight gain.(secondary outcome)

Instruments:

Hemoglobin A1C measurement

The HbA1c measurements at baseline and after 3 months were measured by two laboratory workers (both of them were blinded regarding patients group). The Bio-Rad D-10™ Dual program was used to determine HbA1C level. The D-10 dual program performs 400 tests for the determination of HbA1c or 200 tests for the determination of HbA₂/F/A_{1c}. The Bio-Rad D-10™ Dual program is intended for the percent determination of HbA1c in human whole blood using ion-exchange high-performance liquid chromatography (HPLC).

Weight measurement

The weight measurements at baseline and after 3 months were measured by the attending nurse (she was blinded regarding patients group).

Fasting blood glucose measurement

Fasting blood glucose measurements were conducted using 2 methods. First one; fasting blood glucose were measured at baseline and 3 months later by using (Glucocard II™ device, Embee Diagnostics) taking a venous sample by the two endocrine lab workers, blood glucose was measured in the whole blood. Second method by using patients' SMBG devices (most of them using Accu-Chek® Performa, Roche Diagnostics GmbH); this meter delivers results that correspond to blood glucose concentrations in plasma as per the recommendation of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC), therefore; it displays blood glucose concentrations that refer to plasma although whole blood apply to the test strip. Taking samples by finger stick at baseline, month 1, month 2 and month 3.

Hypoglycemia episodes recording

We asked the patients to record their episodes of hypoglycemia. These episodes included: Documented symptomatic hypoglycemia; any episode during which typical symptoms of hypoglycemia are associated with a measured plasma glucose level ≤ 70 mg/dl. Or, Sever

hypoglycemia; any episode needing assistance of another person to actively administer carbohydrate, or other resuscitative actions, plasma glucose level may be not available during such episode, but neurological recovery considered a sufficient evidence⁽²⁹⁾.

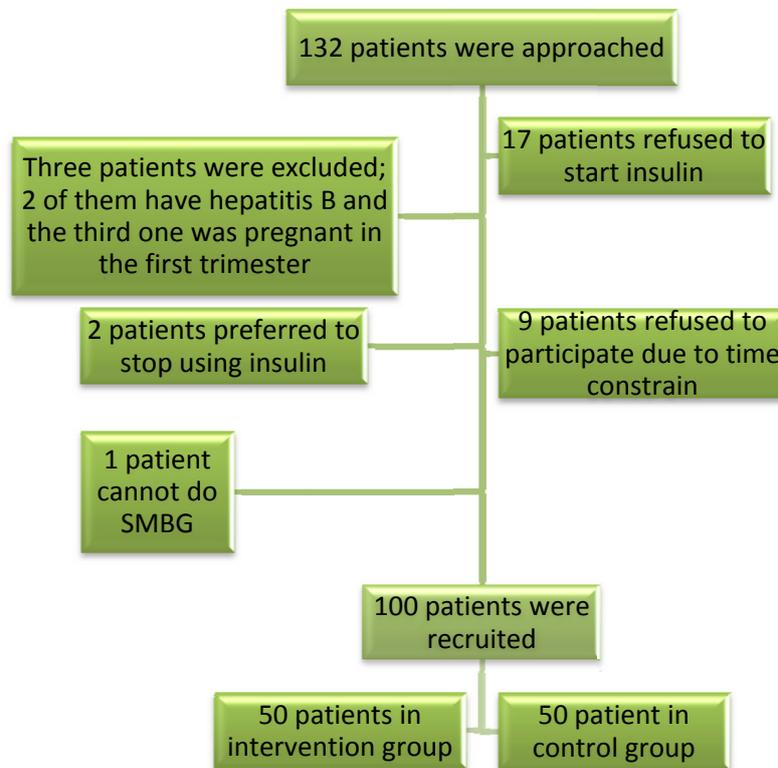


Figure 1. Patients' selection chart

Self-reported medication adherence questionnaire

Patients' adherence to their medications were assessed using Morisky, *et al.* (1986) self-reported medication adherence questionnaire⁽²²⁾.

Self-reported adherence to self care activities questionnaire

Patients' adherence to self-care activities were assessed by using The Summary of Diabetes Self-Care Activities (SDSCA) Scale by Toobert, *et al.* (2000). This questionnaire includes items assessing general diet, specific diet, exercise, blood-glucose testing, foot care, and smoking⁽²³⁾.

Data analysis

Data analysis was performed using SPSS software version (17.0). A *p*-value < 0.05 was considered statistically significant. Appropriate test were used depending on variables type and function required. For continuous variables, either independent samples t-test or paired sample t-test were used; the first test to compared data from two unrelated groups, the second test to compared follow-up values with baseline values. In addition, Chi-square test or McNemar test were used for categorical variables. Pearson test was used for correlation.

RESULTS

Out of 132 patients who were approached, 100 patients were recruited, 50 patients in the intervention group and 50 in the control group; patients' selection chart are shown in Figure 1.

12 patients were lost from follow up (7 from the control group and 5 from the intervention group) as they did not return back to their clinic visits.

The baseline demographic and clinical characteristics

of the study participants are presented in Table 1 and Table 2, respectively.

Numbers of co-morbidities of the study sample were almost similar for both the intervention as well as the control groups with a range from 0-5 chronic diseases (mean 2.10 diseases per patient). The majority of the participants had hypertension (84%), more than half (62%) had dyslipidemia, and 26% had ischemic heart disease.

Table 1. Demographic characteristics (N=88)

Parameter	Total (%)*	Intervention (%)†	Control (%)†	P-value‡
Research group, N	88	45	43	
Gender, N (%): Male	37 (42)	19 (42.2)	18 (41.9)	0.973
Female	51 (58)	26 (57.8)	25 (58.1)	
Age (years), mean (SD)	55.59 (10.2)	54.71 (10)	56.51 (10.4)	0.410
Weight (Kg), mean (SD)	90.54 (15.6)	88.54 (15.8)	92.64(15.2)	0.218
Body mass index (Kg/m ²),mean (SD)	32.80 (5.30)	32.28 (5.5)	33.34 (5.1)	0.347
Body mass category, N (%) Normal	5 (5.7)	4 (8.9)	1 (2.3)	0.306
Overweight	21 (23.9)	13 (28.9)	8 (18.6)	
Obese	54 (61.4)	24 (53.3)	30 (69.8)	
Morbid obesity	8 (9.1)	4 (8.9)	4 (9.3)	
Education level, N (%) Primary	23 (26.1)	9 (20.0)	14 (32.6)	0.622
Secondary	13 (14.8)	7 (15.6)	6 (14.0)	
High school	18 (20.5)	11 (24.4)	7 (16.3)	
Middle college	11 (12.5)	7 (15.6)	4 (9.3)	
College	11 (12.5)	6 (13.3)	5 (11.6)	
Post-graduated	5 (5.7)	3 (6.7)	2 (4.7)	
Not educated	7 (8.0)	2 (4.4)	5 (11.6)	
Marital status, N (%) Single	4 (4.5)	2 (4.4)	2 (4.7)	0.919
Married	73 (83.0)	38 (84.4)	35 (81.4)	
Widowed	11 (12.5)	5 (11.1)	6 (14.0)	
Divorced	0 (0.0)	0 (0.0)	0 (0.0)	
Employment status, N (%) Employed	20 (22.7)	12 (26.7)	8 (18.6)	0.631
Retired	24 (27.3)	11 (24.4)	13 (30.2)	
Non	44 (50.0)	22 (48.9)	22 (51.2)	

* Percent within total.

† Percent within research group.

‡ P-value by independent samples t-test for age, weight, & BMI, and by Chi-square test for gender, marital status, education level, employment status & BMI category.

Table 2. DM assessment (N=88)

parameter	Total (%)*	Intervention (%)†	Control (%)‡	P-value‡
DM type, N (%)				1.00 ^c
T1DM	6 (6.8)	3 (6.7)	3 (7.0)	
T2DM	82 (93.2)	42 (93.3)	40 (93.0)	
DM duration (years), mean (SD)	13.44 (7.08)	13.16 (6.42)	13.74 (7.8)	0.699
Insulin duration (years), mean (SD), (N=76)	5.69 (6.16)	4.83 (5.39)	6.56 (6.8)	0.222
Presence of retinopathy, N (%)	46 (52.3)	19 (42.2)	27 (62.8)	0.053
Presence of neuropathy, N (%)	65 (73.9)	34 (75.6)	31 (72.1)	0.712
Presence of nephropathy, N (%)	25 (28.4)	12 (26.7)	13 (30.2)	0.711
Baseline HbA1c, mean (SD)	9.43 (1.42)	9.52 (1.66)	9.34 (1.1)	0.554
Baseline FBG (worker) (mg/dl), mean (SD)	193.92 (78.4)	196.89 (71.13)	191 (86)	0.718
Baseline FBG (SMBG) (mg/dl), mean (SD)	164.91(64)	167.58(58.00)	162 (70)	0.691
Patients No. wit hypoglycemic episodes, N(%)	44 (50.0)	23 (51.1)	21 (48.8)	0.831
Patients No. hyperglycemic symptoms N (%)	61 (69.3)	29 (64.4)	32 (74.4)	0.331
Smoking, N (%)				0.923
Current smoker	21 (23.9)	10 (22.2)	11 (25.6)	
Never smoked	57 (64.8)	30 (66.7)	27 (62.8)	
Quitted (≥ 3 months)	10 (11.4)	5 (11.1)	5 (11.6)	
General health status**				0.266
According to the patient, N (%)				
Excellent	1 (1.1)	0 (0.0)	1 (2.3)	
Very good	10 (11.4)	6 (13.3)	4 (9.3)	
Good	38 (43.2)	17 (37.8)	21 (48.8)	
Fair	22 (25.0)	15 (33.3)	7 (16.3)	
Poor	17 (19.3)	7 (15.6)	10 (23.3)	

* Percent within total.

† Percent within research group.

** The patient was asked to self-evaluate his/her general health status by choose one of the following word (excellent, very good, good, fair or poor).

P-value by independent samples t-test for DM duration, insulin duration, HbA1c, FBG, and frequency of hypoglycemia episodes, and by Chi-square test for the reminder variables except that signed by ^cp-value by Fisher's exact test.

Follow up:

Medications changes at first visit are shown in table 3.

Table 3. Medications changes during the first visit

Medication	Intervention (before enrollment medications) N (%)*	Intervention (first visit medications changes) N (%)*	Control (before enrollment medications) N (%)*	Control (first visit medications changes) N (%)*
Insulin	38 (84.4)	45 (100.0)	38 (88.4)	43 (100.0)
Glargine	23 (51.1)	29 (64.4)	19 (44.2)	21 (48.8)
NPH†	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)

Regular insulin	12 (26.7)	12 (26.7)	10 (23.3)	9 (20.9)
Glulisine	2 (4.4)	2 (4.4)	1 (2.3)	1 (2.3)
Premixed (70% NPH+ 30% regular) insulin	15 (33.3)	15 (33.3)	19 (44.2)	22 (51.2)
Metformin	42 (93.3)	40 (88.9)	39 (90.7)	38 (88.4)
Glimipride	10 (22.2)	14 (31.1)	13 (30.2)	11 (25.6)
Gliclazide	1 (2.2)	1 (2.2)	0 (0.0)	0 (0.0)
Glibinclamide	4 (8.9)	0 (0.0)	0 (0.0)	0 (0.0)
Vildagliptin	2 (4.4)	1 (2.2)	1 (2.3)	1 (2.3)
Sitagliptin	0 (0.0)	0 (0.0)	1 (2.3)	1 (2.3)

* Percent within research group.

† NPH: Neutral Protamine Hagedorn.

Table 4. Outcomes measured (Changes from baseline)

N=88 (45 intervention, 43 control)		Mean (SD)		P value † between groups
		Intervention	Control group	
HBA₁C (%)	At enrollment	9.52 (1.66)	9.34 (1.13)	
	After 3 months	8.52 (1.04)	9.11 (1.42)	
	Change	-1.00 (1.58)	-0.23 (1.27)	
	P-value *	< 0.001	0.241	0.013
FBG [workers] (mg/dL)	At enrollment	196.89 (71.13)	190.81 (85.99)	
	After 3 months	168.44 (65.27)	204.26 (76.77)	
	Change	-28.44 (84.26)	13.44 (108.23)	
	P-value *	0.029	0.420	0.045
FBG [SMBG] (mg/dL)	At enrollment	167.58 (58.00)	162.12 (69.95)	
	After 1 months	133.36 (41.66)	158.35 (58.21)	
	Change	-34.22 (56.84)	-3.77 (76.57)	
	P-value *	< 0.001	0.749	0.036
	After 2 months	128.00 (37.62)	175.49 (81.64)	
	Change	-39.58 (72.81)	13.37 (78.70)	
	P-value *	0.001	0.272	0.002
	After 3 months	141.00 (53.11)	177.98 (73.14)	
Change	-26.58 (69.63)	15.86 (94.36)		
P-value*	0.014	0.277	0.018	
Weight (kg) i.e. gain	At enrollment	88.54 (15.85)	92.64 (15.16)	
	After 3 months	90.10 (16.31)	93.33 (15.38)	
	Change	1.56 (2.84)	0.69 (2.29)	
	P-value*	0.001	0.056	0.117

Patients with hypoglycemic Episodes §	At enrollment	23	21		
	After 1 month	30	20		
	<i>P</i> -value within group ‡	0.167	1.000		
	After 2 months	26	19		
	<i>P</i> -value within group ‡	0.607	0.824		
	After 3 months	22	13		
	<i>P</i> -value within group ‡	1.000	0.096		
	Frequency of hypoglycemic episodes	After 1 month	2.49 (3.23)	1.12 (1.84)	0.016
		After 2 months	1.22 (1.70)	0.95 (1.34)	0.415
After 3 months		1.27 (1.86)	1.00 (2.53)	0.573	

* *P*-value by paired sample t-test.

† *P*-value by independent sample t-test.

‡ *P*-value by McNemar test.

§ Percent within group

Outcome measures; Changes from baseline

HbA1c decreased significantly in the intervention group (mean 1.00 ± 1.58 SD, p -value < 0.001) and insignificantly in the control group (mean 0.23 ± 1.27 SD, p -value = 0.241) with a statistically significant difference between the 2 groups (p -value = 0.013).

FBG either measured by lab workers or by patients' decreased significantly in the intervention group with a

statistically significant difference between the 2 groups. However, there was a statistically significant increase in the mean weight from baseline in the intervention group patients (p -value 0.001), as well as the control group patients (p -value 0.056). However, there was no statistically significant difference between the 2 groups (p -value 0.117), details are shown in table 4 and figures 2, 3 and 4).

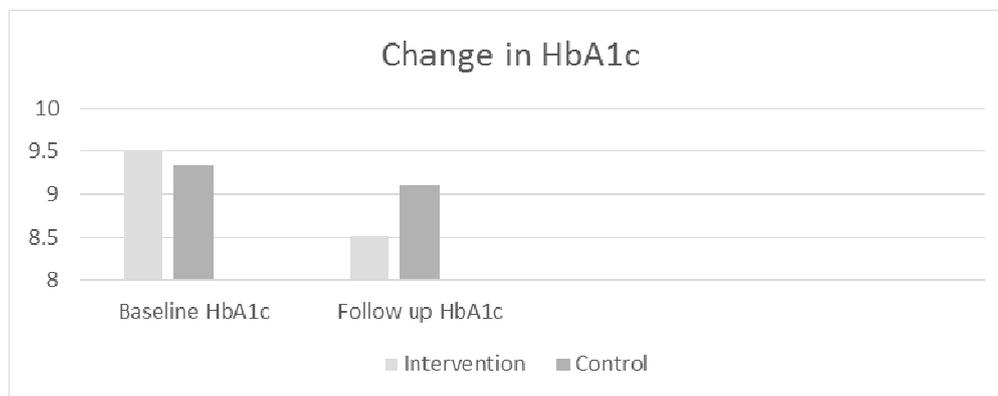


Figure 2. Change in HbA1c

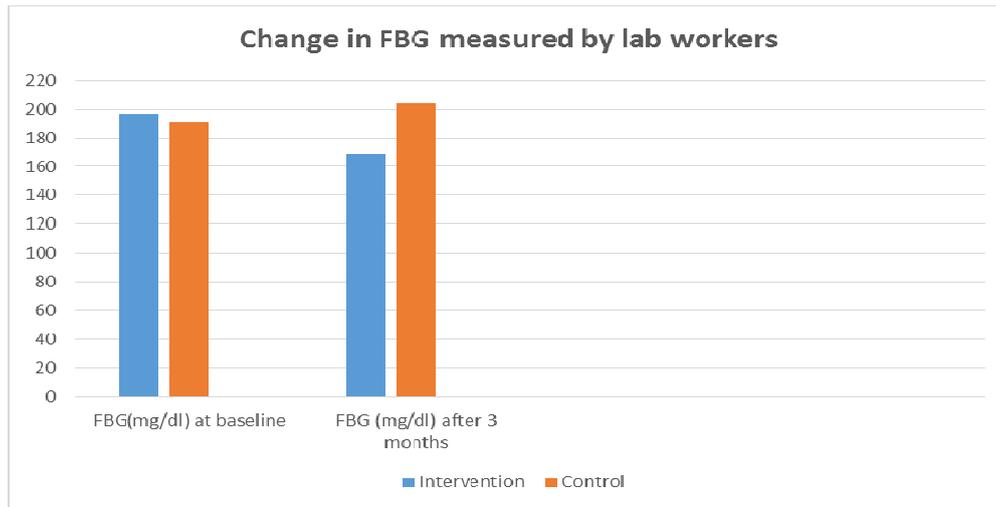


Figure 3. Change in FBG measured by lab workers

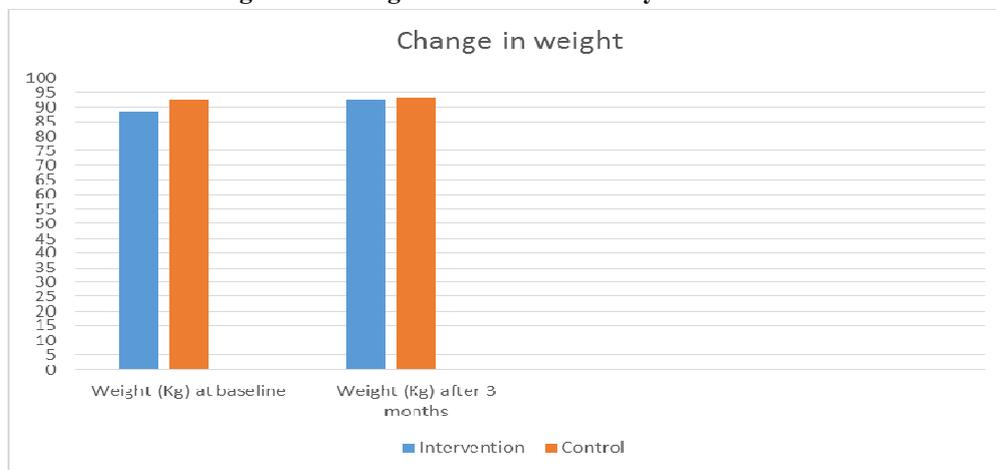


Figure 4. Change in weight

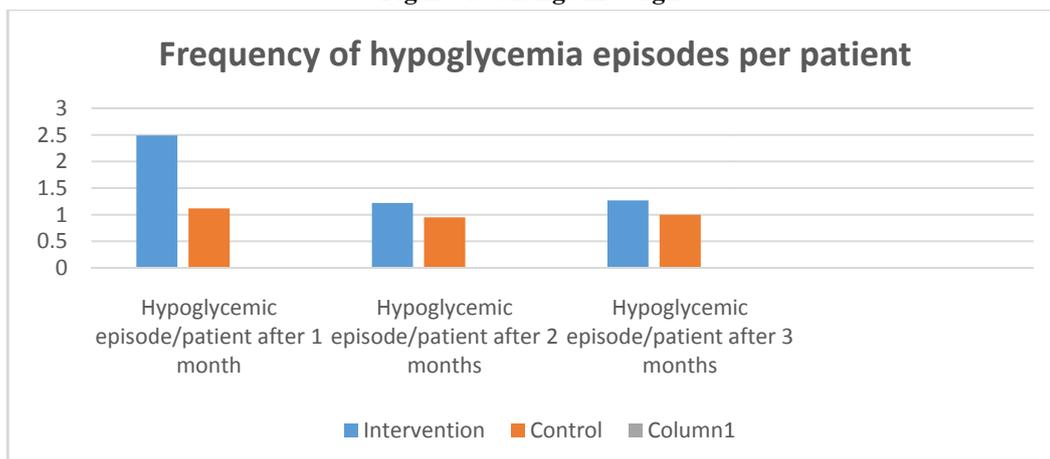


Figure 5. Frequency of hypoglycemia episodes per patient

Table 5. Insulin doses changes

N=88 45 intervention, 43 control		Mean (SD)		P value between groups †		
		Intervention	Control			
Total insulin dose changes compared to baseline dose (units / kg) 45 intervention 43 control	Baseline	0.594 (0.455)	0.791 (0.548)	0.385		
	Week 0 ^c	0.708 (0.483)	0.878 (0.543)			
	Change	0.114 (0.154)	0.088 (0.122)			
	Week 1 ^c	Week 1 ^c	0.730 (0.492)	0.878 (0.543)	0.115	
		Change	0.136 (0.16)	0.088 (0.122)		
	Week 2 ^c	Week 2 ^c	0.747 (0.504)	0.878 (0.543)	0.043	
		Change	0.153 (0.171)	0.088 (0.122)		
	Week 3 ^c	Week 3 ^c	0.762 (0.506)	0.878 (0.543)	0.016	
		Change	0.168 (0.177)	0.088 (0.122)		
		Week 4 ^c	Week 4 ^c	0.775 (0.509)	0.874 (0.549)	0.004
			Change	0.181 (0.183)	0.083 (0.117)	
	Glargine dose changes compared to baseline dose (units / kg) 29 intervention 21 control	Baseline	0.261 (0.210)	0.346 (0.255)	0.661	
Week 0 ^c		0.333 (0.164)	0.407 (0.219)			
Change		0.072 (0.098)	0.061 (0.069)			
Week 1 ^c		Week 1 ^c	0.354 (0.160)	0.407 (0.219)	0.261	
		Change	0.092 (0.112)	0.061 (0.069)		
Week 2 ^c		Week 2 ^c	0.361 (0.158)	0.407 (0.219)	0.162	
		Change	0.100 (0.111)	0.061 (0.069)		
Week 3 ^c		Week 3 ^c	0.369 (0.155)	0.407 (0.219)	0.104	
		Change	0.107 (0.113)	0.061 (0.069)		
Week 4 ^c		Week 4 ^c	0.375 (0.151)	0.401 (0.225)	0.031	
		Change	0.114 (0.121)	0.056 (0.060)		
Premixed (70% NPH+ 30% regular) insulin dose changes compared to baseline dose (units / kg) 15 intervention 22 control		Baseline	0.711 (0.409)	0.803 (0.448)	0.864	
	Week 0 ^c	0.857 (0.358)	0.936 (0.417)			
	Change	0.146 (0.216)	0.133 (0.224)			
	Week 1 ^c	Week 1 ^c	0.871 (0.369)	0.936 (0.417)	0.726	
		Change	0.159 (0.215)	0.133 (0.224)		
	Week 2 ^c	Week 2 ^c	0.877 (0.376)	0.936 (0.417)	0.672	
		Change	0.165 (0.228)	0.133 (0.224)		
	Week 3 ^c	Week 3 ^c	0.896 (0.384)	0.936 (0.417)	0.482	
		Change	0.184 (0.227)	0.133 (0.224)		
	Week 4 ^c	Week 4 ^c	0.898 (0.392)	0.932 (0.425)	0.444	
		Change	0.187 (0.229)	0.129 (0.222)		
	Regular insulin dose (units/kg) changes compared to baseline dose	Baseline	0.514 (0.324)	0.774 (0.397)	0.684	
Week 0 ^c		0.601 (0.305)	0.887 (0.306)			
Change		0.087 (0.154)	0.113 (0.123)			
Week 1 ^c		0.624 (0.312)	0.887 (0.306)			

12 intervention 9 control	Change	0.110 (0.164)	0.113 (0.123)	
	Week 2 ^c	0.644 (0.350)	0.887 (0.306)	0.806
	Change	0.130 (0.174)	0.113 (0.123)	
	Week 3 ^c	0.652 (0.347)	0.887 (0.306)	0.733
	Change	0.138 (0.189)	0.113 (0.123)	
	Week 4 ^c	0.675 (0.348)	0.887 (0.306)	0.526
	Change	0.161 (0.196)	0.113 (0.123)	
Basal-Prandial insulin dose changes compared to baseline dose (units / kg) 14 intervention 10 control	Baseline	0.950 (0.529)	1.240 (0.523)	
	Week 0 ^c	1.071 (0.465)	1.394 (0.475)	0.712
	Change	0.121 (0.240)	0.153 (0.145)	
	Week 1 ^c	1.108 (0.483)	1.394 (0.475)	0.961
	Change	0.158 (0.256)	0.153 (0.145)	
	Week 2 ^c	1.141 (0.495)	1.394 (0.475)	0.689
	Change	0.191 (0.264)	0.153 (0.145)	
	Week 3 ^c	1.157 (0.493)	1.394 (0.475)	0.581
	Change	0.207 (0.278)	0.153 (0.145)	
	Week 4 ^c	1.183 (0.485)	1.394 (0.475)	0.420
Change	0.233 (0.280)	0.153 (0.145)		

† *P*-value by independent sample t-test.

^c Week 0 = dose changes at enrollment, week 1= dose by the end of week 1, week 2 = dose by the end of week 2, week 3 = dose by the end of week 3 and week 4 = dose by the end of week 4.

When number of patients who experienced at least one hypoglycemic episode, before and after enrollment was compared; a statistically insignificant difference between the baseline and follow up in both groups was noted. During the first month of follow up, there was a statistically significant difference in hypoglycemic episodes frequency between the two groups (*p*-value =0.016) with mean of (2.49) episodes per patient in the intervention group compared to (1.12) episodes per patient in the control group. But without a statistically significant difference between the 2 groups during the second and third month (*p*-value = 0.415, 0.573; respectively), details are shown in table 4 and figure 5).

Insulin dose changes

Total insulin dose per day (units/Kg) increased significantly from baseline in both groups (*p*-value < 0.001/< 0.001; at the end of week 4). But with higher increment in the intervention group compared to control

group (*p*-value = 0.004; by the end of week 4).

Glargine dose (units/Kg) increased significantly from baseline at weeks (week 0 = dose changes at enrollment, week 1= dose by the end of week 1, week 2 = dose by the end of week 2, week 3 = dose by the end of week 3 and week 4 = dose by the end of week 4) in both groups (details are shown in table 5). There was a statistically significant difference between the 2 groups at week 4(*p*-value = 0.031).

Premixed insulin increased significantly from baseline at weeks 0, 1, 2, 3 and 4 in both groups (details are shown in table 5) without a statistically significant difference between the 2 groups (*p*-values= 0.864, 0.726, 0.672, 0.482, 0.444; respectively). There was a statistically significant increase in regular insulin dose in both groups at week 1, 2, 3 and 4, but without a statistically significant difference between the 2 groups (details are shown in table 5). Basal-prandial insulin (Glargine + regular or glulisine) dose changes were statistically significant from baseline in intervention and control

group (p -value= 0.008 by the end of week 4). Only one patient in the intervention group was started on NPH, so no statistical tests could be performed and a few patients have taken Glulisine (2 patients in the intervention group and 1 patient in the control group) so the comparison is not possible.

Parameter correlation

Among the intervention group, there was a

statistically significant correlation between the increment in total insulin dose (units/Kg) at the end of titration and HbA1c reduction (correlation coefficient= 0.504, p -value< 0.001). Also a significant positive correlation was found between the difference in total insulin dose (units/Kg) at the end of titration and weight gain (correlation coefficient= 0.333, p - value = 0.025), these correlations were not found in the control group.

Table 6. Parameter correlation, (N=88, 45 patients in intervention group and 43 patients in control group)

Group	Parameter	Patient age	Difference in total insulin dose at week 4 (units/Kg)	Difference in HbA1c	Difference in weight (Kg)	Difference in FBG (mg/dl) measured by lab workers
I N T E R V E N T I O N	Patient age	1.000	-0.156	0.009	-0.043	0.372* ($p = 0.012$)
	Difference in total insulin dose at week 4 (units/Kg)	-0.156	1.000	-0.504† ($P < 0.0001$)	0.333* ($p = 0.025$)	-0.193
	Difference in HbA1c	0.009	-0.504† ($p < 0.0001$)	1.000	-0.478† ($p = 0.001$)	0.467† ($P = 0.001$)
	Difference in weight (Kg)	-0.043	0.333* ($p = 0.025$)	-0.478 † ($p = 0.001$)	1.000	-0.266
	Difference in FBG (mg/dl) measured by lab workers	0.372* ($p = 0.012$)	-0.193	0.467† ($p = 0.001$)	-0.266	1.000
C O N T R O L	Patient age	1.000	0.051	-0.157	0.096	-0.131
	Difference in total insulin dose at week 4 (units/Kg)	0.051	1.000	-0.191	0.122	-0.199
	Difference in HbA1c	-0.157	-0.191	1.00	0.254	0.350* ($p = 0.021$)
	Difference in weight (Kg)	0.096	0.122	0.254	1.00	-0.124
	Difference in lab. FBG (mg/dl)	-0.131	-0.199	0.350* ($p = 0.021$)	-0.124	1.00

* Correlation is significant at the 0.05 level (2-tailed).

† Correlation is significant at the 0.01 level (2-tailed).

Correlation test done by Pearson test.

DISCUSSION

Among 88 patients who completed the study, the patients' demographic characteristics in both groups were generally comparable with 58% of the study sample were female.

The mean age of the participants was (55.59±10.19) years which is lower than the mean age that was found in other studies (5, 14, 17 and 20). For example, the mean age of patients in Coast-Senior, *et al.* (1998) study was (65±9.4) years⁽⁵⁾ and in Jarab, *et al.* (2012) was 63.4 ±10.1 and 65.3±9.2 in intervention and usual care group, respectively (20). Eighty five percent of our study sample was either obese or overweight with mean BMI (32.80±5.30) Kg/m². These findings were close to Rochester's, *et al.* (2010) finding who found that 92% percent of their study sample were either obese or overweight with BMI (31±6) Kg/m²⁽¹⁷⁾.

Ninety three percent of the participants were diagnosed with T2DM and the mean diabetes duration for the total sample was (13.44±7.08) years compared to (8±6) years of having type 2 diabetes in the Veterans Affairs Maryland Health Care System (VAMHCS) at Baltimore insulin initiation clinic⁽¹⁷⁾.

The results of our study are most similar to a study by Rochester's, *et al.* (2010); however their study did not have a control group and targeted T2DM with HbA1c.9%. Their main aim was implementation of an insulin initiation clinic through Collaborative Drug Therapy Management (CDTM). Our study is also comparable to a study by Jarab, *et al.* 2012, the methodology of their study is different from ours. Their aim was to evaluate a pharmacist-led pharmaceutical care program in T2DM. The interventions included initial adjustment of anti-hyperglycemic medications, antihypertensive medications and diabetes education which resulted in a significant reduction in HA1c after 6 months in the intervention group compared with no improvement in the usual care group⁽²⁰⁾. In our study we specifically targeted insulin users, in an effort to evaluate the applicability of clinical pharmacist managed insulin clinic. When comparing baseline HbA1c level, and FBG; our study had a mean comparable HbA1c level (~9.4) and

FBG (~193 mg/dL) in the intervention and the control group. A lower baseline HbA1c was noted in Jarab, *et al.*, 2012 study, in which the HbA1c values were 8.5 and 8.4 in intervention and usual care groups, respectively⁽²⁰⁾. And, a higher baseline (HbA1c 11.2% ± 1.6%) was reported in Rochester, *et al.* (2010) study⁽¹⁷⁾.

Presence of Micro-vascular complications among the study sample was high with 74% having neuropathy and 52.3% percent having retinopathy compared to findings in a study that evaluated the presence of painful diabetic peripheral neuropathy (DPN) in patients with T1DM and T2DM across the Middle East (58%) of diabetic patients in Jordan⁽³⁰⁾.

The main parameter of glycemic control (HbA1c) was decreased significantly in the intervention group by (1.00%) vs. the control group (0.23%). This pharmacist's interventions positive effect was also found in different studies with different degree (0.8-2.6%) in HbA1c reduction and different methodology and follow-up interval^(5, 6, 8, 12, 14, 17, 19 and 20). For example, HbA1c decreased by 2.2% in Coast-Senior, *et al.* (1998) study over 27±10 weeks⁽⁵⁾. Also, in Rochester, *et al.* (2010) study HbA1c decreased by 2.6% over 6 months⁽¹⁷⁾. However, HbA1c reduced by 0.8% in Jarab, *et al.* (2012) study in type 2 diabetic patients over 6 months of follow up⁽²⁰⁾.

Patients' fasting blood glucose was decreased significantly in the intervention group by 28.44 mg/dl compared to the baseline; however, it increased insignificantly by 13.44 mg/dl in the control group. This reduction in FBG was lower than that observed by Coast-Senior, *et al.* (1998) study, in which the reduction in FBG was 65 mg/dl on 27±10 weeks follow up period⁽⁵⁾.

In general, diabetic patients who receive insulin gain weight. As patients propose better glycemic control, reduced glycosuria and intermittent over-insulinization can lead to hypoglycemia, hunger and increased calorie intake⁽³¹⁾. Patients' weight in the intervention group increased significantly compared to the baseline by (1.56) Kg. In addition, it increased in the control group by (0.69) Kg from baseline without a statistically significant difference between the 2 groups (P=0.117). While in

Nkansah, *et al.* (2008) study, no statistically significant change was noted in patients' weight, this is a single group study which included both T1DM and T2DM who were receiving oral or insulin therapy or both⁽¹⁴⁾. Weight gain was also observed in the Treat-to-Target trial which targeting inadequately controlled type 2 diabetic patients on 1-2 oral agents, in this trial weight increased by (3.0±0.2 Kg) in glargine arm and by (2.8±0.2 Kg) in NPH arm⁽³²⁾.

Hypoglycemia is the most common major side effect of insulin therapy⁽³¹⁾. During the follow up period, 66.7%, 57.8% and 48.9% patients in the intervention group experienced at least one episode of hypoglycemia during month 1, 2 and 3, respectively. While in other study symptomatic hypoglycemia episode happened in 35% of the study sample and none of these episodes needed physician intervention⁽⁵⁾. Moreover, the average number of hypoglycemic episodes per patient during month 1, 2 and 3 were (2.49), (1.22) and (1.27) in the intervention group, respectively; and (1.12), (0.95) and (1.00) in the control group, respectively. There was a statistically significant difference between the 2 groups during the first month.

The mean total insulin dose per day at baseline was (0.594 units/Kg in the intervention group vs. 0.791 units/Kg in the control group). A statistically insignificant higher mean of baseline total insulin dose in the control group compared to the intervention group was observed. Mean total insulin dose (units/Kg) increased significantly from baseline in the intervention group and the control group to (0.775) and (0.874) units/Kg by the end of week 4, respectively; but with higher increment in the intervention group. Compared to other studies, the principle of insulin use in insulin deficient T2DM is the same as for T1DM; T2DM often required large dose of insulin about (1-2 units/Kg per day), in clinical practice using lower doses of insulin is a common barrier to effective diabetes control⁽³¹⁾.

The mean dose of Glargine increased significantly from baseline in both groups (0.261 units/Kg to 0.401 units/Kg in the intervention group vs. 0.346 units/Kg to 0.375 units/Kg in the control group). There was a

statistically significant difference between the 2 groups at the end of week 4 (P -value = 0.031). This result may compare with the Treat-to-Target trial, in which the mean daily dose of glargine was 0.48 units/Kg⁽³²⁾. It should be noted that in the Treat-to-Target trial all the patients started either to glargine or NPH insulin in addition to their oral therapy. On the other hand, premixed (70% NPH+ 30% regular) insulin dose increased significantly from baseline in both groups (0.711 U/Kg to 0.898 in the intervention group vs. 0.803 U/Kg to 0.932 in the control group) without statistically significant difference between the 2 groups. These results are lower than that found by other study⁽³³⁾; the latter may be contributed to longer study period as well as using biphasic insulin aspart 70/30 (BIAsp 30).

The mean total insulin dose (units) significantly increased in both groups (54.84±47.45 U to 71.56±56.47 U in the intervention vs. 75.93±54.81 U to 83.42±55.20 U in the control groups). There was a statistically significant difference between the 2 groups $P=0.008$. These results can be compared to Rochester, *et al.* (2010) study, in which the daily units of insulin (mean± SD) at baseline, 3 months and 6 months later, were (37.4 ±12.8), (68.7 ±49.9) and (73.9 ±38.2), respectively⁽¹⁷⁾.

Among the intervention group, there was a statistically significant correlation between the difference in total insulin dose (units/Kg) at the end of titration and HbA1c difference. Also, a significant correlation was found between the difference in total insulin dose (units/Kg) at the end of titration and weight difference (correlation coefficient= -0.504, $P=0.000$ and correlation coefficient= 0.333, $p= 0.025$, respectively). These correlations were not found in the control group. These results are different than Swinnen and DeVries (2009) results, in which the reduction in HbA1c was highly correlated with endpoint insulin dose (U/Kg) ($r^2=0.433$, $p= 0.008$). However, after multivariate regression insulin dose did not remain as an independent predictor of HbA1 reduction ($p=0.270$). Also no dose response relationship between weight gain and end insulin dose was observed ($r^2=0.076$, $p=0.320$)⁽³⁴⁾. This difference can be explained by that, Swinnen and DeVries (2009) only included

studies with duration ≥ 24 weeks which comparing insulin initiation with basal insulin in insulin naive T2DM.

CONCLUSION

The results of this study are complementary to the previous studies' results which support the role of clinical pharmacists on glycemic control in insulin users' diabetic patients in collaboration with their physicians.

Limitation

As all studies, this study has several limitations: first, convenient sample was taken from a single Endocrine

outpatient clinic; however, it does serve a wide range of patients. Second, the short follow up duration of 3 months. Third, some of the outcomes which were measured are based on patients reporting. Fourth, there was a shortage in some insulin types. Finally, funds problems that limited the expansion of the outcomes measurements.

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دور الصيدلاني السريري في بدء و/أو تعديل جرعة الأنسولين في مرضى السكري في العيادات الخارجية في الأردن

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ملخص

تعد مراقبة نسبة السكر في الدم لدى مرضى السكري قضية صعبة وتتطلب مشاركة الصيدلاني في خطة رعاية المرضى وتوعية المريض لتحسين نظام السكري.

وكان الهدف من هذه الدراسة إلى التعرف على دور الصيدلاني السريري في السيطرة على سكر الدم لمرضى السكري عن طريق تنظيم علاج الأنسولين في عيادة الغدد الصماء الخارجية في مستشفى تعليمي في الأردن.

الطريقة: هذه دراسة عشوائية محكمة، أجريت في عيادة الغدد الصماء-العيادات الخارجية في مستشفى الجامعة الأردنية. المرضى الذين يعانون من داء السكري من النوع 1 أو نوع 2، تم توزيع المرضى عشوائياً إما للتدخل (ن = 50) أو المجموعة الضابطة (العناية الصحية التقليدية بدون مشاركة الصيدلاني) (ن = 50).

معايير الإدخال في الدراسة: المرضى الذين تم تشخيصهم حديثاً (نسبة $HbA1c > 10\%$)؛ أو أولئك الذين هم مرضى السكري مع (نسبة $HbA1c > 7\%$) وكانوا يأخذون الأنسولين مع أو بدون أدوية السكري عن طريق الفم، أو المريض مع (نسبة $HbA1c > 7\%$) وعلى اثنين أو أكثر أدوية السكري المأخوذة عن طريق الفم لمدة ≤ 6 أشهر. المتابعة بدأت بالتزامن مع جمع البيانات؛ ومتابعة المرضى تصل لمدة 3 أشهر بعد اشتراكهم في الدراسة. خلال الزيارة الأولى تم جمع البيانات الديموغرافية، تاريخ مرض السكري وتقييم مرض السكري، والأمراض المزمنة الأخرى، وأدوية مرض السكري والأدوية المستخدمة حالياً، والالتزام بالأدوية، والالتزام بنمط الحياة والبيانات الأساسية عن نسبة سكر الدم التراكمي، سكر الدم الصيامي والوزن. وعلاوة على ذلك، تم استعراض السجلات الطبية للمرضى من قبل الصيدلاني للحصول على معلومات أخرى ذات صلة. تم إجراء تحليل البيانات باستخدام برنامج SPSS الإصدار (17.0). تم قياس نسبة السكر التراكمي، وسكر الدم الصومالي، ونوبات هبوط سكر الدم وزيادة الوزن.

النتائج: أكمل الدراسة 88 مريضاً. وأسفرت تدخلات الصيدلاني السريري في تحسين كبير في نسبة $HbA1c$ ($p\text{-value} < 0.001$) ونسبة السكر خلال الصيام في الدم مقارنة مع الأساس ($p\text{-value}=0.029$). كان هناك فرق ضئيل في زيادة الوزن بين المجموعتين ($p\text{-value} = 0.117$) في نهاية الدراسة، ولكن مع ارتفاع زيادة وزن كبير في مجموعة التدخل عن خط الأساس ($p\text{-value}=0.001$). على الرغم من أن نوبات انخفاض سكر الدم كانت أعلى بشكل ملحوظ خلال الشهر الأول في مجموعه التدخل مقارنة مع مجموعة التحكم ($p\text{-value}=0.016$)، علماً بأن هذه النوبات كانت بسيطة ولم تتطلب عناية طبية في المستشفى.

الخلاصة: تدعم هذه الدراسة دور الصيدلاني السريري في السيطرة على سكر الدم في مرضى السكري مستخدمين الأنسولين في بلد مثل الأردن تعد فيه ممارسة الصيدلة السريرية جديدة نسبياً.

الكلمات الدالة: الجسيمات الدهنية الصلبة، ناقلات دهنية نانو تركيبية، مرضى السكري، إندوميثاسين، انطلاق متحكم.

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