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Evaluation of Drug Related Problems in Patients with Type 2 Diabetes

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ABSTRACT

Objective: Diabetic patients usually have co-morbidities requiring the use of multiple medications, making them more vulnerable in experiencing drug related problems (DRPs) that may affect their quality of life (QOL). The objective of this study was to asses DRP in type 2 diabetes (T2D) patients and factors associated with its occurrence and the DRPs that affect QoL.

Methods: A cross-sectional study was conducted among T2D patients who were attending a tertiary care teaching hospital, Lebanon. The identification and assessment of DRPs were based on the Pharmaceutical Care Network Europe tool version 8.03. The QoL was assessed using Health Related Quality of Life Brief Clinical Inventory.

Results: The total number of DRP was 313 with a mean of 2.05 ± 1.03 per patient. The most common DRPs encountered were adverse drug event (31.3%), untreated symptoms or indication (10.54%), effect of drug treatment not optimal (7.34%) and high drug dose (7.34%). Logistic regression showed that polypharmacy and several comorbidities such as stroke, dyslipidemia, heart failure, coronary artery disease, renal and liver impairment were common factors significantly associated with different types of DRPs ($p<0.005$). The risk of having problems" No effect of drug treatment"," Effect of drug treatment not optimal" and "Adverse drug event (possibly) occurring" was significantly increased in patients with abnormal HbA1c. The use of sulfonylurea increases the risk of" Inappropriate duplication of therapeutic group" ($p= 0.047$). Following a low sugar diet showed to decrease the probability of having problem" Patient uses/takes more drug than prescribed" by 99.99%. On the other hand, insulin administration showed to increase 7.63 times this probability ($p=0.006$). The average HRQoL was 40 ± 9.900. Linear regression showed that problems "Untreated indication and "Patient uses unnecessary drug" were associated with poor QoL score. Having a medical insurance was found to be associated with better HRQoL scores.

Conclusion: Early identification of DRPs and factors associated with them are essential to pre- vent and resolve them in diabetic patients by engaging clinical pharmacist, which may ultimately improve patient's QoL.

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Introduction

Diabetes is a chronic metabolic disease characterized by elevated blood glucose level, caused by defects in insulin secretion, insulin action, or both [1]. It is widely recognized as an emerging epidemic that has a cumulative impact on almost every country, age group, and economy across the world. According to the International Diabetes Federation (IDF), in 2017, there were 425 million people with diabetes worldwide, or 8.8% of adults aged 20-79 years. Seventy nine percent of diabetic patients live in low and middle-income countries [2]. It is projected that diabetes will be the seventh leading cause of death in 2030 [3]. In Lebanon, as of 2017, there were 585,400 cases of diabetes reported by the IDF Middle East and North Africa Members, with a prevalence of 14.6% [4]. The World Health Organization (WHO) noted that in Lebanon, diabetes accounts for 4% of total deaths [5]. The American Diabetes Association (ADA) classifies diabetes into four general categories: Type 1 diabetes (T1D), type 2 diabetes (T2D), gestational diabetes mellitus, and others [1].

Diabetic patients usually have coexisting chronic health conditions including, hypertension, dyslipidemia, coronary artery disease, depression and chronic kidney disease, which require the use of multiple medications for treatment [6]. All of this put patients with diabetes at high risk of polypharmacy, with an estimated prevalence of 57%-84% of patients with diabetes using five or more medications, thus, making these patients more vulnerable in experiencing drug-related problems (DRPs) [7, 8]. DRPs is defined by the Pharmaceutical Care Network Europe (PCNE) as an event or circumstance involving drug therapy that actually or

potentially interferes with desired health outcomes [9]. There is a high prevalence of DRP in diabetic patients, with an average of about 4 DRPs occurring in one patient [10].

DRPs is divided into both intrinsic and extrinsic toxicity. Intrinsic toxicity is a toxicity caused by the chemical and/or pharmacological characteristics of the drug and the human biosystem. Therefore, intrinsic toxicity is the synonymous of adverse drug reactions (ADRs). Whereas the extrinsic toxicity refers to any problem caused by medication handling, either by the healthcare professional or by the patient. Improper use of drug means that a medication error has been made [11]. In diabetic patients, in addition to being poly-medicated and having co-morbidity, risk factors such as age, medical conditions, and renal impairment have been associated with the development of DRP [12]. There are a number of consequences associated with DRPs, which include hospitalizations, long-term care admissions, increase in the number of emergency room visits, additional physician clinic visits, additional prescriptions, and increase fundamental costs [13]. In addition to these, DRPs have been shown to negatively influence quality of life (QoL). A worse QoL was significantly associated with the occurrence of errors (mainly in the dose), where Patient's medication errors occurs between 19% and 59%, noting that elderly patients makes more errors than others, especially with the dosage [14, 15].

In Lebanon, there is a lack of studies assessing DRPs in patients with T2D and its different factors and the effect of DRPs on QoL. Most studies have focused on medication prescribing errors without mentioning specific disease or all type of DRPs that may occur, with a study assessing the prevalence of potentially inappropriate medications [16, 17]. The objective of this study was firstly, to evaluate DRPs and its risk factors in patients with T2D who attended a tertiary hospital in Lebanon and secondary, to assess the impact of socio-demographic factors along with DRPs on diabetic Patient's QoL.

Methods

Study Design and Population

A cross-sectional observational study was conducted in a tertiary care teaching hospital in Lebanon. All Lebanese adult patients (≥ 18 years), diagnosed prior to admission as T2D with or without co-morbidity, taking at least one antidiabetic drug (oral antidiabetic drug or insulin), admitted to the hospital between March 1st and July 31st, 2019 were included. All patients with diabetes other than T2D including Type 1 diabetes were excluded from the study.

Sample Size Calculation

The sample size was calculated using the Epi Info version 7, based on a study of DRPs in T2D patients where 90.5% had at least one DRP [18]. Considering a 95% confidence interval with an absolute precision of 5%, a number of 133 patients was estimated as a minimum sample needed to obtain a 95% probability for measuring the prevalence of DRP. A total of 135 patients were included in this study.

Data Collection

Data were collected from patient's medical files. Demographic characteristics (age, gender, and body mass index), social history (place of residence, educational level, marital status, monthly income, presence of caregiver at home, and medical insurance), and lifestyle characteristics (cigarette and waterpipe smoking, alcohol consumption, physical activity, and diet) were recorded. Health status characteristics (duration of T2D, level of HbA1c, presence of comorbidities), and patient's medication history were also collected. DRP identification was performed by a clinical pharmacist. The Pharmaceutical Care Network Europe (PCNE) classification of DRPs version 8.03 was used to categorize DRPs [9]. It is an established system that has been revised several times and tested for validity and reproducibility [19, 20]. This instrument consists of separated codes. Three problem domains (P1-P3), eight cause domains (C1-C8), five intervention domains (I0-I4), three intervention acceptance domains (A1-A3) and four outcome domains (O0-O3). Several categories are generally available for each domain. In this study, the problem, cause and intervention domains of the PCNE classification were used. The different type of DRPs were identified from the Patient's medical records, with reference to the standard guidelines. Three main references were used to assess the appropriateness of drug indications, appropriateness of drug and dosage, possible drug interactions, adverse drug reactions and contraindications [21-23].

The Patient's health related quality of life was assessed using the DQoL-BCI instrument. It was inspired from the 60-item DQoL questionnaire, which was developed for both T1D and T2D as part of the Diabetes Control and Complications Trial. The new inventory showed good internal consistency (alpha = 0.85). The instrument consist of 15 items, which cover a broad range of issues related to diabetes. They range from satisfaction with various aspects of the diabetes regimen to fears and concerns to frequency of diabetes problems. Items were ranked in a 5-point Likert scale in two general formats. The total score range was 15-75 (15 is the best QoL) [24].

Statistical Analysis

The data analysis was carried out using the "Statistical Program for Social Sciences" (SPSS) version 22. The descriptive data were analyzed using mean/standard deviation for quantitative data and frequency/percentage for qualitative data. Multivariate logistic regression was conducted to investigate the relationship between the different DRPs (dependent variables) and other factors in order to identify variables that best predict DRPs. Multiple linear regression was used to identify the types of DRPs affecting DQoL-BCI scores. Any variable with a p value of < 0.2 was entered and all socio-demographic factors were controlled in both analyses. A P-value < 0.05 was considered statistically significant.

Results

Patient's Characteristics

A total of 135 patients were enrolled as subject cases for this study. Their ages ranged from 36 to 92 years old, with a mean age of 86.20 years (± 11.51). More than half of the sample patients (56.9%) were elderly (age 65 years or older). About 60.7% of the patients were females and 45.2% overweight. The vast majority of the subjects was married (74.1 %) and lives in South Lebanon (78.5 %). The majority of the subjects were non-cigarette and waterpipe smokers, 71.1 and 96.3%, respectively. About 81.4% of patients were physically inactive. Ninety seven percent of included patients reported that they follow a low sugar diet. In addition, 38.5% and 30.4% consumed beverages containing sugar such as coffee and tea respectively (Table 1). Around 41.5% of patients lived with diabetes for 21 to 30 years, and 41.5% had a normal HbA1c level. Comorbidities were present in 99.3% of the subjects. The most common being hypertension (88.1 %) followed by coronary artery disease (48.1 %). The study population had an average of 2.91± 1.20 comorbidities per patient (Table 1).

Tables

Table 1. Patient's Characteristics

Variables		Number (%) / Mean (SD)
Gender		
	Males	53 (39.3)
	Females	82 (60.7)
Age (years) [Mean (SD)]		
	Adults (18-64 years)	46 (34.1)
	Elderly (≥ 65 years)	89 (65.9)
BMI		
	Underweight (< 18.5 kg/ m2)	2 (1.5)
	Normal Weight (18.5-24.9 kg/m2)	38 (28.1)
	Overweight (> 25 kg / m2)	61 (45.2)
	Obese (> 30 kg /m2)	34 (25.2)
Residence		
	Beirut	4 (3.0)
	Mount Lebanon	21 (15.6)
	North	2 (1.5)
	South	106 (78.5)
	Bekaa	2 (1.5)
Education Level		
	Illiterate	31 (23)
	Reads and write	52 (38.5)
	School level	39 (28.9)
	University level	13 (9.6)
Marital Status		
	Single	9 (6.7)
	Married	100 (74.1)
	Divorced	3 (2.2)
	Widow/er	23 (17.0)
Employment		
	Unemployed	45 (33.3)
	Employee	37 (27.4)
	Private work	9 (6.7)
	Retired	44 (32.6)
Monthly Income		
	500,000 L.L-1,000,000 L.L	23 (17.0)
	1,000,000 L.L- 2,000,000 L.L	58 (43.0)
	> 2,000,000 L.L	12 (8.9)
	No answer	42 (31.1)
Help at home		127 (94.1)
Medical Insurance		128 (94.8)
Cigarette smoking		39 (28.9)
Waterpipe smoking		5 (3.7)
Alcohol Consumption		3 (2.2)
Physical activity		110 (81.4)
	< 3 times/week	21 (15.6)
	>3 times/week	4 (3.0)
Diet		
	Low sugar	131 (97)
	Low lipid	57 (42.2)
	Low salt	34 (25.2)
	Coffee	52 (38.5)
	Tea	41 (30.4)
Diabetes Duration		
	< 10 years	35 (25.9)
	11-20 years	44 (32.6)
	>20 years	56 (41.5)
Level HbA1c		
	Abnormal	53 (39.3)
	Normal	56 (41.5)
	Unknown	26 (19.3)
Presence of comorbidities		134 (99.3)
Number of comorbidities [Mean (SD)]		2.91 (1.20)
Comorbidities		
	Hypertension	119 (88.1)
	Coronary artery disease	65 (48.1)
	Renal disease	52 (38.5)
	Dyslipidemia	30 (22.2)
	Heart failure	25 (18.5)
	Nervous system disorder	21 (15.6)
	Atrial fibrillation	18 (13.3)
	Cancer	18 (13.3)
	Chronic obstructive pulmonary disease	11 (8.1)
	Thyroid disease	10 (7.4)
	Asthma	9 (1.7)
	Benign prostatic hyperplasia	6 (4.4)
	Stroke	6 (4.4)
	Liver disease	3 (2.2)
	Pulmonary embolism	3 (2.2)
	Deep venous thrombosis	2 (1.5)
	Peripheral artery disease	2 (1.5)
	Arrhythmia	1 (0.7)
	Osteoporosis	1 (0.7)
	Others	16 (11.9)

Drug Therapy and Drug Related Problems

The total number of medications taken per day by included patients was 5.23 ± 2.71. The average number of home and hospital medications was 8.66 ± 2.94 and 10.78 ± 3.93 drugs, respectively. Eighty-one patient (60%) were taking oral antidiabetic drugs; 25.2 % took insulin with oral antidiabetic medication. In this category, insulin with two oral antidiabetic was the most common combination (13.3 %). The most commonly used oral antidiabetic

drugs were metformin (65.9%) and DPP4 inhibitors (40.8%). About 69.6% were on beta-blocker therapy, 63.7%were on anti-platelet, followed by 57% and 49.6%users of ARA and diuretics, respectively (Table 2).

The total number of DRP was 313 ranging between one and six with a mean of 2.05 ± 1.03 for each patient. Adverse drug event (possibly) occurring was the main DRP encountered (31.3%), followed by untreated symptoms or indication (10.54 %), with 7.34 % of the patients having non-optimal effect of drug treatment and too high drug dose. There was no or incomplete drug treatment despite an existing indication in 7 % of the patients. About 5.43% of patients have inappropriate drug combinations (Table 2).

Most DRPs was without pharmacist intervention (51.4 %). Intervention at the prescriber level came in second with 34.1% with the majority on informing the prescriber (16.7 %) (Table 2).

Quality of Life Score: Diabetes Quality of Life Brief Clinical Inventory

The average HRQoL-BCI score for the study participant was 40.24 ± 9.9, raging between 21 and 69 (Table 2).

Table 2: Drug Therapy and Drug Related Problems

Variables		Number N (%) / Mean (SD)
Number of home medication per patient [Mean (SD)]		8.66 (2.94)
Number of hospital medication per patient [Mean (SD)]		10.78 (3.93)
Antidiabetic therapy		
	Insulin [N (%)]	20 (14.8)
	Oral antidiabetic [N (%)]	
	Insulin + Oral antidiabetic [N (%)]	
Type of antidiabetic therapy		
	DPP4 Inhibitor [N (%)]	55 (40.8)
	Vildagliptin [N (%)]	31 (23)
	Linagliptin [N (%)]	12 (8.9)
	Saxagliptin [N (%)]	4 (3)
	Sitagliptin [N (%)]	8 (5.9)
	Metformin [N (%)]	89 (65.9)
	Sulfonylurea [N (%)]	34
	Gliclazide [N (%)]	14 (10.4)
	Glimepiride [N (%)]	15 (11.1)
	Glibenclamide [N (%)]	6 (4.4)
Meglitinides		
	Pioglitazone [N (%)]	1 (0.7)
	SGLT2 inhibitor	
	Dapagliflozin [N (%)]	3 (2.2)
Number of antidiabetic medication/patient [Mean (SD)]		1.325 (0.87)
Number of medication for other pathologies/ patient [Mean (SD)]		6.13 (3.01)
Comorbidities medications		
	Beta Blockers [N (%)]	94 (69.6)
	Anti-platelet [N (%)]	86 (63.7)
	ARA [N (%)]	77 (57.0)
	Diuretics [N (%)]	67 (49.6)
	ARB [N (%)]	60 (44.4)
	Anti-coagulant [N (%)]	61 (45.2)
	Lipid lowering [N (%)]	50 (37.0)
	Digoxin [N (%)]	30 (22.2)
Total number of Drug-Related Problems [N (%)]		313 (100)
Total number of DRPs / person [Mean (SD)]		2.05 ±1.03
PCNE classification for DRP		
	P – Problems [N (%)]	174 (54.84)
	P 1.1 - No effect of drug treatment [N (%)]	10 (3.2)
	P 1.2 - Effect of drug treatment not optimal [N (%)]	23 (7.3)
	P 1.3 - Untreated symptoms or indication [N (%)]	33 (10.5)
	P 2.1 - Adverse drug event (possibly) occurring [N (%)]	98 (31.3)
	P 3.1 - Problem with cost-effectiveness of the treatment [N (%)]	2 (0.63)
	P 3.2 - Unnecessary drug-treatment [N (%)]	6 (1.9)
	C – Causes [N (%)]	139 (45.16)
	C 1.1 - Inappropriate drug according to guidelines/ formulary [N (%)]	8 (2.6)
	C 1.2 - Inappropriate drug (within guidelines but otherwise contra-indicated) [N (%)]	14 (4.5)
	C 1.3 - No indication for drug [N (%)]	11 (3.5)
	C 1.4 - Inappropriate combination of drugs [N (%)]	17 (5.4)
	C 1.5 - Inappropriate duplication of therapeutic group or active ingredient [N (%)]	8 (2.6)
	C 1.6 - No or incomplete drug treatment in spite of existing indication [N (%)]	22 (7.02)
	C 1.7 - Too many drugs prescribed for indication [N (%)]	7 (2.2)
	C 3.1 - Drug dose too low [N (%)]	4 (1.2)
	C 3.2 - Drug dose too high [N (%)]	23 (7.3)
	C 7.1 - Patient uses/takes less drug than prescribed or does not take the drug at all [N (%)]	6 (1.9)
	C 7.2 - Patient uses/takes more drug than prescribed [N (%)]	9 (2.9)
	C 7.3 - Patient abuses drug (unregulated overuse) [N (%)]	3 (0.9)
	C 7.4 - Patient uses unnecessary drug [N (%)]	5 (1.6)

	C 7.5 - Patient takes food that interacts [N (%)]	1 (0.3)
	C 7.7 - Inappropriate timing or dosing intervals [N (%)]	1 (0.3)
	C 7.8 - Patient administers/uses the drug in a wrong way [N (%)]	1 (0.3)
	C 8.1 - No or inappropriate outcome monitoring (incl. TDM) [N (%)]	1 (0.3)
PCNE classification of interventions on DRPs V 8.03		
	I - Intervention [N (%)]	138 (100)
	I 0 - No intervention [N (%)]	71 (51.4)
	I 1 - At prescriber level [N (%)]	47 (34.1)
	I 1.1 - Prescriber informed only [N (%)]	23 (16.7)
	I 1.3 - Intervention proposed to prescriber [N (%)]	20 (14.5)
	I 1.4 - Problem with cost-effectiveness of the treatment [N (%)]	20 (14.5)
	I 3 - At drug level [N (%)]	4 (2.9)
	I 3.1 - Drug changed to [N (%)]	4 (2.9)
	I 3.5 - Drug paused or stopped [N (%)]	9 (6.5)
	I 3.6 - Drug started [N (%)]	7 (5.1)
Quality of life HRQoL-BCI score [Mean (SD)]		40.244 ± 9.900

Multivariate Logistic Regression for Factors Associated with DRPs

In this analysis, each component of the PCNE classification for DRP was considered separately as the dependent factor and the analysis was repeated for each component.

The result of the multiple linear regression showed that: (Table 3)

1. Abnormal level of HbA1c increases the risk of problem "no effect of drug treatment".
2. Patients with abnormal level of HbA1c are likely to have problem "not optimal effect of drug treatment".
3. Having more than three medications for different pathologies increases the risk of problem "untreated symptoms of indication".
4. Abnormal level of HbA1c increases the risk of having problem "Adverse drug event (possibly) occurring".
5. Having a higher education level decreases the chance of problem "unnecessary drug-treatment".
6. Dyslipidemia increases the risk of problem "inappropriate drug according to guidelines/formulary and inappropriate combination of drugs".
7. Heart failure increases the risk of problem "inappropriate drug (within guidelines but otherwise contra-indicated)".
8. Coronary artery disease (CAD) decreases problem "having no indication for drug".
9. Sulfonylurea increases the risk of problem "inappropriate duplication of therapeutic group or active ingredient".
10. The risk of problem "no or incomplete drug treatment in spite of existing indication" decreases with the place of residence and employment while increases with low lipid diet and liver impairment.
11. Atrial fibrillation and renal disease increases the risk of having problem "drug dose too high".
12. Taking oral antidiabetic and being overweight decrease the risk of problem "patient using/taking less drug than prescribed or not taking the drug at all".
13. The risk of problem "patient using/taking more drug than prescribed" decreases with low sugar diet and increases with insulin administration.
14. Having a help at home decreases the risk of problem "patient using unnecessary drug".

Table 3: Multivariate Logistic Regression for Factors Associated with Drps

Dependent variable	Factors associated with DRPs	Adjusted OR	95% CI	p-value
P 1.1 "No effect of drug treatment"*				
	Abnormal HBA1c level	11.33	1.19-107.47	0.034
P 1.2 "Effect of drug treatment not optimal"µ				
	Abnormal HBA1c level	78.7	3.95-1568.99	0.004
P 1.3 "Untreated symptoms of indication"§				
	Number of medications for other pathologies (>3)	51.16	1.01-2588.3	0.049
P 2.1 "Adverse drug event (possibly) occurring"£				
	Abnormal HBA1c level	4.02	1.01-16.02	0.048
P 3.2 "Unnecessary drug-treatment"Ø				
	Education level	0.11	0.01-0.98	0.049
C 1.1 "Inappropriate drug according to guidelines/formulary"€				
	Dyslipidemia	9.64	1.22-76.16	0.032
C 1.2 "Inappropriate drug (within guidelines but otherwise contra-indicated)¥				
	Heart failure	24.34	1.06-560.36	0.046
C 1.3 "No indication for drug"Ð				
	CAD	0.08	0.01-0.55	0.01
C 1.4 "Inappropriate combination of drugs"¶				
	Dyslipidemia	32.5	2.85-370.96	0.005
C 1.5 "Inappropriate duplication of therapeutic group or active ingredient"†				
	Sulfonylurea	217.08	1.09-43417	0.047
C 1.6 "No or incomplete drug treatment in spite of existing indication"‡				
	Place of residence	0.56	0.33-0.95	0.031
	Employment	0.62	0.38-0.99	0.045
	Low lipid diet	4.53	1.35-15.16	0.014
	Liver impairment	56.02	2.56-1226.39	0.011
C 3.2 "Drug dose too high"¤				

	Atrial fibrillation	55.67	1.38-2248.88	0.033
	Renal disease	7.57	1.01-56.59	0.049
C 7.1 "Patient uses/takes less drug than prescribed or does not take the drug at all"¿				
	Oral antidiabetic	0.04	0.002-0.8	0.035
	Being overweight	0.01	0.01-0.75	0.036
C 7.2 "Patient uses/takes more drug than prescribed"¢				
	Low sugar diet	0.01	0.01-0.35	0.011
	Insulin administration	7.63	1.03-56.6	0.047
C 7.4 "Patient uses unnecessary drug"Œ				
	Help at home	0.03	0.001-0.83	0.038

*Factors included in the analysis: place of residence, marital status, BMI group, HBA1c level, asthma, other comorbidities, oral anti diabetic therapy, insulin + oral diabetic treatment, number of home medication / patient, and number of hospital medication/ patient. Factors controlled place of residence and marital status.

µFactors included in the analysis: age, employment, HBA1c level, number of comorbidity, CAD, COPD, number of home medication / patient, number of medications for other pathologies. Factors controlled age and employment.

§Factors included in the analysis: employment, cigarette smoking, hypertension, dyslipidemia, HF, CAD, nervous system problems, low lipid diet, low salt diet, number of comorbidities / patient, and number of medications for other comorbidities / patient. Factors controlled employment.

£Factors included in the analysis: marital status, water pipe smoking, alcohol, stroke, renal disease, number of hospital medications / patient, HBA1c level. Factors controlled marital status.

ØFactors included in the analysis: gender, place of residence, education level, age, cigarette smoking, low sugar diet, low salt diet, hypertension, heart failure, atrial fibrillation, COPD, and insulin + oral diabetic treatment. Factors controlled gender, place of residence, education level, and age.

€Factors included in the analysis: Employment, cigarette smoking, dyslipidemia, PAD, nervous system problems, and insulin + oral diabetic. Factors controlled employment.

¥Factors included in the analysis: gender, education level, employment, heart failure, atrial fibrillation, stroke, number of home medication / patient, and number of medications for other comorbidities / patient. Factors controlled gender, education level, and employment.

ÐFactors included in the analysis: gender, marital status, employment, waterpipe smoking, physical activity, low sugar diet, coffee, tea, CAD, stroke, renal disease, COPD, and cancer. Factors controlled gender, marital status, and employment.

¶Factors included in the analysis: age, education level, employment, waterpipe smoking, alcohol, hypertension, dyslipidemia, CAD, DVT, arrhythmia, renal disease, number of home medication / patient, and number of hospital medication / patient. Factors controlled age, education level, and employment.

†Factors included in the analysis: Gender, place of residence, number of comorbidities / patient, number of orally admitted medications / patient, insulin + oral antidiabetic therapy, and sulfonylurea. Factors controlled gender and place of residence.

‡ Factors included in the analysis: place of residence, employment, waterpipe smoking, low lipid diet, arrythmia, liver impairment, and number of comorbidities / patient. Factors controlled place of residence and employment.

¤Factors included in the analysis: gender, education level, employment, age, heart failure, atrial fibrillation, CAD, renal disease, number of comorbidities / patient, number of medication for other comorbidities / patient, number of home medication / patient, and number of hospital medication / patient. Factors controlled gender, education level, employment, and age.

¿Factors included in the analysis: income, help at home, water pipe smoking, physical activity, low lipid diet, dyslipidemia, heart failure, oral antidiabetic, insulin + oral antidiabetic treatment, and BMI group. Factors controlled income, and help at home.

¢Factors included in the analysis: place of residence, marital status, income, low sugar diet, drinking tea, HBA1c level, heart failure, CAD, nervous system problems, and insulin administration. Factors controlled place of residence, marital status, and income.

ŒFactors included in the analysis: income, help at home, cigarette smoking, physical activity, low sugar diet, afib, stroke, renal disease, asthma, nervous system problems, and insulin + oral antidiabetic therapy. Factors controlled income, and help at home.

Multiple Linear Regression Analysis of the Actual DRPs Affecting HRQoL-BCI Scores

In order to assess the impact of socio-demographic factors and DRPs on diabetic Patient's QoL, only variables showing significant correlation with HRQoL-BCI ($p<0.05$) such as medical insurance, C1.4, C1.6, and C7.4, or a $p<0.2$ such as age, help at home, P1.2, P1.3, P2.1, C1.1, and C1.2 were included in the multiple linear regression. Age, help at home, and medical insurance were controlled in the analysis. The result of the multiple linear regression showed that the model containing four variables was the best to predict HRQoL-BCI scores (P-value <0.05) (Table 4). Among those four variables, problems "Untreated symptoms or indication" and "Patient uses unnecessary drug" were significantly associated with poor HRQoL-BCI scores, while "having medical insurance" and "No or incomplete drug treatment in spite of existing indication" were found to be associated with better HRQoL-BCI scores.

Table 4: Multiple Linear Regression Analysis of the Actual Drps Affecting Hrqol-Bci Scores

Variables	Unstandardized Beta	95% CI	Standardized Coefficients Beta	p-value
Age	0.115	[-0.016,0.245]	0.133	0.084
Help at home	-0.592	[-7.242,6.058]	-0.014	0.860
Medical Insurance	8.889	[1.800,15.977]	0.200	0.014*
P 1.2 "Effect of drug treatment not optimal"	-3.770	[-7.678,0.137]	-0.144	0.058
P 1.3 "Untreated symptoms of indication"	-5.565	[-10.332,-0.797]	-0.242	0.023*
P 2.1 "Adverse drug event (possibly) occurring"	-3.218	[-6.537,-0.101]	-0.146	0.057
C 1.1 "Inappropriate drug according to guidelines/ formulary"	-3.864	[-10.163,2.434]	-0.092	0.227
C 1.2 "Inappropriate drug (within guidelines but otherwise contra-indicated)	-3.287	[-8.261,1.687]	-0.102	0.193
C 1.4 "Inappropriate combination of drugs"	2.912	[-1.779,7.604]	0.098	0.221
C 1.6 "No or incomplete drug treatment in spite of existing indication"	11.674	95.996,17.353]	0.437	0.000*
C 7.4 "Patient uses unnecessary drug"	-10.588	[-18.709,-2.467]	-0.203	0.011*

CI , Confidence Intervals; *, statistically significant.

Discussion

In this study, a total of 313 DRPs were identified in 135 patients. The frequency of DRPs was 2.05 ± 1.03 per patient. This is in agreement to a study conducted in Nigeria in which the mean of DRP was 2.1 ± 1.4 per patient.12 Moreover, this reported mean is higher compared to 1.8 and 1.9 DRPs per patient in two studies conducted in Ethiopia and Malaysia, respectively [18, 25]. However, a number of 4 DRP per patient has been detected by other studies in patients with T2D [10, 26]. This difference could be due to the different methods and references used to identify DRPs as well as the clinical knowledge of the investigator that could also influence the evaluation and identification of DRPs. In addition, an explanation is the different version of the PCNE classification system used (6 domains for problems with 22 categories) or the different DRP classification tools used which are more general compared to the PCNE classification system which could affect the results. The most prominent DRP was found to be "adverse drug event (possibly) occurring" (31.3 %) followed by "untreated symptoms or indication" (10.5 %), in agreement with study conducted in Ethiopia [25]. Evidence indicates that diabetic patient's needs aggressive medication treatment in order to prevent morbidity, mortality and unnecessary hospital stay and disability [1]. The third most commonly observed DRP was "Effect of drug treatment not optimal" and "drug dose too high" with (7.3 %) each. This is in contrast with other studies, which showed that" Effect of drug treatment being not optimal", and" Lack of appropriate monitoring", were the most prevalent DRP, respectively [8, 25]. These differences could be due to the different methods and references used to identify DRPs. Regarding the factors affecting different type of DRPs, when examining DRPs with several factors, a statistical significant associations were observed. These associations should receive the attention of the health care providers in order to minimize preventable DRPs.

Among studied patients, 58.5% had good glycemic control (HbA1c < 0.05). In this study, patients who had poor glycemic control were significantly more likely to have problems including, "No effect of drug treatment" and "Effect of drug treatment not optimal". By the fact patients who had poor glycemic, control had lower adherence to their drugs so this could explain why they do not have optimal treatment effect [27]. In addition, abnormal glycemic control increase susceptibility to problem "Adverse drug event occurring". Patients with poor glycemic control need an increase in monotherapy dose or addition of other agents, which in turn will place patients at a greater risk of ADEs [28].

In this study, there was a significant correlation between the total number of medications and the problem "Untreated symptoms or indication". This is in agreement with the findings of other researchers who found that the number of medications was significantly correlated with having DRPs in diabetic patients [29]. It can be explained by the fact that multiple medications put patients at greater risk for ADEs in which most of the case left untreated by the physicians, where the selection of drug therapy is admitted to the main cause where the minor condition is unobserved [30]. Patient's education level was shown to decrease the probability of having problem unnecessary drug treatment. Researches found that low literacy level is associated with poor physician-patients communication, which involve miscommunication of important information about patient's symptoms and condition and poor information documentation [31]. This issue can result in misdiagnoses and prescribing wrong medications. Having dyslipidemia was shown to have a statistically significant association with the occurrence of DRP. The current study showed that patients with poor lipid control were at a higher risk of developing problems" Inappropriate drug according to

guidelines/formulary" and" Inappropriate combination of drugs" by 9.64 and 32.5 times, respectively (p-value < 0.05). This result agrees with a study conducted in the Malaysia where patients with poor lipid control were at a higher risk of developing DRPs (95.5%) (OR= 9.840, p= 0.002) [18]. Regarding the association with problem "Inappropriate combination of drugs", it can be explained by the fact that patients with poor lipid control have a high risk of developing macro vascular complications, and theoretically, the development and progression of complications lead to more drugs being prescribed and used in order to control these complications. Thus, this lead to increase in the probability of having inappropriate combination of drugs [32]. Moreover, possible reasons could be related to the inappropriate timing of drug administration, or dosing intervals, polypharmacy, multiple diagnoses, or associated comorbidity, drug characteristics of potential incompatibility, and lack of appropriate information and knowledge about the drug pharmacokinetics [30]. The multiple logistic regression showed that heart problems were associated with the likelihood of having DRPs among diabetic patients. Heart failure was associated with an increased likelihood of having the problem" Inappropriate drug (within guidelines but otherwise contra-indicated)" (OR = 24.34, p= 0.046). In this study, potentially inappropriate medication use in elderly people was assessed using beers criteria, which gives a list of medications that pose potential risks outweighing potential benefits whenever used in elderly patients. This association maybe because in this study we observed the use of digoxin in elderly patients with heart failure and at a dose > 0.125 mg/d , although according to the Beer's criteria it is recommended to avoid it as first line therapy for heart failure and if used avoid dosages > 0.125 mg/d. Beer's criteria stated questionable effects on risk of hospitalization and increased mortality in older adults with heart failure, in addition to that , higher dosages is not associated with more benefit and may increase risk of toxicity. Our result agrees with what was found in a study conducted in India, where amiodarone and digoxin showed a high risk for DRPs and prolonging hospital stay of the patient [30]. Similarly, one more study reported that amiodarone and digoxin were responsible for the greatest numbers of unplanned hospitalizations [33]. Patients with CAD were less likely to have problem "No indication for drug" (OR=0.08, p=0.01). This observation was in contrast to other study were 5.66 % of DRP in patients with cardiovascular disease accounts for drug use without indication [18]. Patients with cardiovascular events add an additional burden to patient's conditions and complicate the drug regimens, which increase the risks of patients for iatrogenic ADEs [34]. Patients with cardiovascular events that have complex drug treatment and receives more than 5 drugs are at a high risk of developing DRPs [35]. In addition to the lack of physicians follow up and medical treatment reassessment [18].Therefore, attention must be paid to treatment instructions in order to limit the use of unnecessary drugs. Using Sulfonylurea as an oral antidiabetic; was associated with the probability of having problem" Inappropriate duplication of therapeutic group or active ingredient". Where the use of Sulfonylurea increase the risk of having this problem by times 217.08 (p < 0.05). However, another study showed different drugs that were associated with the occurrence of this problem, where 1.92% of the studied population have therapeutic duplication in amlodipine, ondansetron, midazolam, furosemide, rabeprazole, metformin and others. The possible reason for this drug duplication episodes maybe due to physician busy schedule, failure to update of case sheets by nursing staff, failure to recognize different brands names with same active ingredient, illegible handwriting in prescribing medication orders, switch over to oral from parental or vice versa, unclear communication, look alike, sound alike and spell alike drugs, monotherapy and combo therapy of similar medications [30]. This study observed that liver impairment increase the risk of having problem" No or incomplete drug treatment in spite of existing indication" by 56.02 times (p= 0.011). Similarly to another studies conducted on diabetic patients who found that the problem" Indication without Drug" comprises of 1.04 and 1.75 as an average of DRP per patient, respectively [30, 36]. The causes of such problem could be attributed to the physicians lack of time due to busy schedules, high patient load to the clinic, patients with a severe comorbid conditions, lack of documentation of patient underlying co-morbidity, past medical and medication history, selection of drug therapy to the main cause where the minor condition is unobserved [30]. In addition to liver impairment, low lipid diet was found to increase the problem "No or incomplete drug treatment in spite of existing indication". Patients who follow low lipid diet are usually patients with chronic diseases and specifically dyslipidemia. Appropriate treatment of dyslipidemia in diabetic patients offers clear benefit but adds to polypharmacy in these patients, which in turn increase the probability of under prescription [37]. It can be speculated that physicians are unwilling to prescribe more drugs to patients with polypharmacy, due to complexity of drug regimens, fear of ADRs, interactions and poor adherence, where a so-called risk treatment mismatch exists meaning that patients at highest risk for complications, have the lowest chance to receive the recommended pharmacological treatment [38].

However, this study found that employment and place of residence may decrease the problem "No or incomplete drug treatment in spite of existing indication". This may be due to the fact that Patient's place of residency offers accessibility to obtain medications from nearby pharmacies and employment may provide patients with medical insurance which reduce this problem.

According to our results, patients with renal disease have 7 more times risk of having problem "Drug dosage too high" than those without this disease. This findings was similar to what was found by a study conducted in Malaysia, where renal impairment was associated with drug dosing problem (p = 0.027) [18]. The severity of dosing selection might be underestimated where dosage adjustment was commonly ignored by physicians [39]. Additionally, the lack of assessment of patient's renal functions before prescribing the medication and lack of dosage regimen information by physicians may have contributed to this problem [30]. DRPs were common among patients with renal impairment due to co-existing morbidities, where most of them were taking multiple medications, which requires dosage adjustment and routine monitoring in order to decrease drug toxicity or sub therapeutic effect. The chance of having this problem increased as well with the presence of atrial fibrillation, which is quite common in patients with T2D. In contrast to other study that showed that, patients with atrial fibrillation were at increased risk of low drug dosage. In every day practice, physicians are more concerned about bleeding from anticoagulant medications in atrial fibrillation patients than about the evolution of the disease such as stroke and systemic embolism, leading to high rate of prescribing inadequately low doses [40]. Patients who follow up the low sugar diet recommended by their physician were less likely to have problem" Patient uses/takes more drug than prescribed" than those who do not by 99% (p= 0.011). Similar result was observed in a recent study carried out the Arabic region too, where patients who were non adherent to healthy diet were two times more non adherent to their medications (p= 0.05) [41]. This is maybe because patients who follow non-pharmacologic treatments and lifestyle modifications recommended by their physician are also more likely to follow their pharmacologic treatment. Moreover, it was

found that patients who uses insulin were 7.63 times more likely to have this problem. Problem "Patient uses/takes more drug than prescribed" can be defined as a third type of non adherence which is known as non conforming, this type includes several ways in which medication are not taken as prescribed, this can range from taking more drugs than prescribed to taking medications at incorrect times or at incorrect doses or skipping doses [42]. Similar to a systematic review, which confirmed that diabetic patients who were prescribed diabetic medications, whether oral agents or insulin where non-compliant to it [43]. Non-compliance among the patients taking insulin agrees with a study conducted in the United Kingdom where it was associated with 50% decrease in adherence [95% CI 0.30:0.81] [44]. In the current study, patients taking oral diabetic were less likely to have problem "Patient uses / takes less drug than prescribed or does not take the drug at all", which is also a third type of non-adherence. Similar to other study that showed adherence to oral hypoglycemic agents by 47.7 %, in contrast to patients on insulin [45]. Patients commonly report nervousness about using injectable with preference for oral diabetic medications. Moreover, insulin is much less available and affordable compared to oral diabetic agents [46]. In this study being overweight, decrease the chance of having this problem Patient uses / takes less drug than prescribed or does not take the drug at all by 99.99 %. Majority of diabetic patients are overweight, which worsen glycemic level and increase the risk of diabetes progression and development of complications [47]. It has been shown that presence of diabetes complications was significantly associated with symptoms of depression or anxiety; as a result, patients become more adherent to their antidiabetic medications in order to prevent further undesirable complications [48]. Social and family support is also important, it was found that patients with help at home have less likely to have problem patient uses unnecessary drug by 99.97 %, where a study showed that lack of family or social support was significantly associated with poor adherence [49]. Having help at home act as a counsellor, which encourage diet and exercise and importantly medication adherence [50]. The majority of the DRPs was without intervention, maybe because some of the problems where detected in the absence of physician or directly before the patient is discharged. The second most pharmacist intervention for DRPs resolutions were conducted at prescriber level, such as informing the prescriber and proposing him intervention. In contrast to what was found by another study, were most of the pharmacists intervention to resolve DRPs were at patient / carer level (60.7%) by providing medication counseling and spoke to the family member/caregiver (38.7 and 21.9% respectively). Intervention at the prescriber level came in second with 27.7% with the majority on informing the prescriber (18.7%) [18]. Pharmacists direct involvement on T2D patient therapy may provide a solution in early detection of DRPs. Previous study showed that the involvement of the clinical pharmacist in diabetic patients helps in identification and prevention of DRPs [51]. Similar to another research which stated that comprehensive and a brief individually targeted intervention for patients with diabetes by pharmacist could improve implementation of drug therapy [52]. Moreover, pharmacist involvement in healthcare team may promote quality improvement in safe medication management [53]. There are many studies investigating factors affecting HRQoL in diabetic patients [54-57]. A study conducted in Emirate, showed that duration of diabetes and the occurrence of diabetes-related complications were identified as factors that significantly influence the total QoL [57]. Another study found that uncontrolled diabetes and gender were the major factors that affect QoL [55]. These studies were using different quality of life measurement tools. In this study, the HRQoL-BCI has been selected since it was tested and validated in diabetic patients in different countries such as. Among the previously mentioned studies, only one study assessed the influence of DRPs on HRQoL in diabetic population [54]. In this study, the HRQoL-BCI average score was 40.244 ± 9.9, which range between 21 and 69. Similar to a study conducted in Iran, where the patients mean HRQoL-BCI score was 41.8 ± 6.2), with the scores ranging from 22 to 59. Which implies that the majority of the diabetic patients had approximately moderate QoL [58]. In contrast to another study findings, where the mean HRQoL-BCI score was equal to 31.85 ± 7.98 and was considered as fairly good [59]. Two classes of DRPs were found to be associated with poor HRQoL-BCI scores (p-value <0.05), including "untreated symptoms or indication" and "patient uses unnecessary drug". It was shown that patients with untreated symptoms or indication have a poor quality of life. This finding is similar to a study, which stated that diabetic patients with undiagnosed and untreated depression showed a decreased quality of life. Painful diabetic peripheral neuropathy can last for years and severely impair quality of life of patients when left untreated [60]. Patients who used unnecessary drug, which is a type of medication non-adherence, have a poor quality of life. Our results were in accordance to a study which showed that patients non-adherence to their medications have reduced quality of life [61]. Interestingly, having a medical insurance was found to be associated with better HRQoL scores ($p < 0.05$). Similar to a study that showed that medical insurance would improve health status and life satisfaction [62]. Moreover, another factor was associated with better quality of life which is problem" No or incomplete drug treatment in spite of existing indication" was found to be associated with better HRQoL scores ($p < 0.05$). This can be explained by the fact that when patients do not know about their undiagnosed medical condition may feel better quality of life, because they will not take medications, will not visit physician and no cost issues will be associated with their treatments [54]. The obtained results in this study should be viewed with consideration of several limitations. First, the study did not cover T2D patients from all over Lebanon. It was conducted on patients admitted to Hammoud Hospital University Medical Center (Saida). It did not consider diabetic patients who visited the clinics during the study period. Thus, the generalizability of the results to countries with similar health care system is limited. In addition, there is a risk of measurement bias since the value of HbA1c was taken from the patient's chart or during direct patient in-terview, which mean that these HbA1c measurement may have been obtained from different laboratories using different techniques. Concerning HRQoL-BCI, there may exist a possibility of respondent and information bias since the results were based on face-to-face questionnaire and this may generate only socially desirable answers. Finally, this was a cross-sectional study, thus it is difficult to establish causality between DRPs and the various factors influencing these problems. In addition, the great ORs and wide 95% CI indicate that a larger sample size is required in order to really define the relationship between some factors and DRPs and some DRPs and HRQoL-BCI such as effect of drug treatment not optimal and adverse drug event (possibly) occurring. Despite these limitations, this study provides valuable information in support of the literature and has several major strengths. Risk factors of DRPs raised by this study were concordant with other studies and can serve as an action plan to intervene and implement effective measures to decrease DRPs. Moreover, this study has the advantage in evaluating the effect of DRPs on QoL in diabetic patients using HRQoL-BCI.

Conclusions

The most common DRPs were adverse drug event, untreated symptoms or indication, effect of drug treatment not optimal and

high drug dose. Several factors were found to have statistically significant associations with the different domains of DRPs.

Some of the interventions made by the clinical pharmacist during the study were accepted. Early identification and management of DRPs would improve the efficacy and outcome of therapy.

Identification and resolving DRPs is a serious and important health care tool in the provision of elderly pharmaceutical care.

Consent: I have read and agree to the privacy policy.

Conflict of Interest: The authors declare that they have no competing interest.

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