Original Article

Drug-related Problems Among Type 2 Diabetic Patients With Hypertension in a Tertiary Care Hospital in Lebanon: A Cross-sectional Study

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ABSTRACT

Background: Patients with type 2 diabetes (T2D) often have other associated comorbidities, making them susceptible to drug-related problems (DRPs) which can adversely affect their quality of life. Understanding these problems can provide baseline data to allow informed health decisions and effective management of patients.

Objectives: This study aims to investigate DRPs in T2D patients with hypertension and find the predictors of these problems.

Methods: This cross-sectional study was conducted for six months in the internal medicine department of a tertiary care hospital in Lebanon. Participants were 135 adult T2D patients with hypertension who were receiving one or more anti-diabetes drugs, and at least one medication for hypertension. Pharmaceutical care network europe classification system was used to classify the DRPs. Data were collected by two clinical pharmacists using a self-report tool.

Results: Most of patients were female. Most of them (94.1%) had at least one DRP (1.43±0.72 per patient). "Non-optimal drug treatment effect" was the most frequent problem (48.2%). Achieving the HbA1C target reduced the odds of this problem by 66.6%, while the increased serum creatinine level caused a two-fold increase in this problem. The use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers reduced the odds of DRPs by 86.2% and 83.3%, respectively, while lipid-lowering and anti-anginal drug use caused a four-fold increase in DRPs.

Conclusion: Early identification of DRPs in diabetic patients with hypertension and their associated factors can help improve their management and reduce the associated mortality and morbidity rates.

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Introduction

The prevalence of type 2 diabetes (T2D) have significantly increased, having upward trend [1] and high clinical and public health burden [2]. There are several modifiable risk factors for T2D. Adequate management of these risk factors can reduce mortality and the occurrence of comorbidities [3]. T2D is associated with an increased risk of cardiovascular diseases (CVD) such as myocardial infarction, ischemic stroke, heart failure, and aortic valve stenosis [4]. Drug-related problems are common among T2D patients and can negatively affect their quality of life [5]. The T2D patients with hypertension are at a higher risk of drug-related problems (DRPs), considering the number of medications used for their treatment [6]. These problems can induce mortality and morbidity among patients and extend their hospitalization due to the challenges in controlling their blood pressure and the diabetes-related complications [7].

The DRPs can be prevented [8] and lead to significantly lower health expenditures [9]. Several factors can increase the risk of DRPs in T2D patients with hypertension. The main reported factors are polypharmacy, older age, and underlying diseases [10]. A recent cross-sectional study found that, for every one unit increase in the number of medications, the odds of DRPs increased by 10% [11]. Inappropriate prescribing, over-the-counter drug use, and low adherence to treatment can also increase the risk of DRPs [12]. Older patients are more prone to DRPs and require interventions to manage some problems, such as the use of expired medications and drug storage issues [13]. Inpatients and those with many chronic conditions are also at a higher risk of developing DRPs [14].

A recent study investigated DRPs among T2D patients in Lebanon [15]. However, no study was found on hospitalized T2D patients with hypertension in Lebanon. There are few studies investigated them in other countries. Understanding DRPs can help make informed health decisions and effectively manage these patients. Therefore, this study aims to investigate DRPs and their causes among T2D patients with hypertension and to find the predictors of these problems.

Materials and Methods

Study design and samples

This is an observational cross-sectional study that was conducted for six months (March-September 2021) on patients diagnosed with T2D and hypertension admitted to the internal medicine department of a tertiary care hospital in Lebanon. Adult patients receiving one or more anti-diabetes drugs and at least one medication for CVD or hypertension were included. The criteria based on sex, age, and ethnicity were not used. The sample size was determined using the Epi Info software, version 7. Based on findings from a previous study [16], 90.5% of T2D patients had at least one DRP. Considering a 95% confidence interval and a 5% margin of error, the minimum sample size was 133.

Data collection

After explaining the study objectives orally to the patients for 15 minutes and inviting them to participate in the study, their written informed consent was obtained. For surveying their characteristics, a questionnaire was developed in English based on the literature review [14, 17]. It was tested in a pilot study on 10 patients, and the items that needed more clarity were either modified or deleted. The adequacy of the instrument was examined based on a technique recommended in a previous study [18]. Positive inter-item correlations [ranging 0.25-0.35), test re-test reliability of 0.807, and a Cronbach α of 0.737 were obtained, indicating the adequacy of the designed questionnaire. The first part surveys the general characteristics of participants such as sex, age (<65 or ≥65), height, weight, educational level (illiterate, primary school, secondary school, academic), employment status, marital status, medical insurance coherence, and lifestyle habits such as smoking, alcohol and coffee consumption, physical activity and its frequency, and the recommended type of diet (low-carbohydrates, low-salt, or low-fat). The second part surveys the medical and medication history: Duration of diabetes and CVD, glycosylated hemoglobin A1C (HbA1C) level (target level <7%) [19], other associated diseases, name, dosage, and administration of used medications, and the reason for hospitalization.

Based on the information obtained by the instruments as well as those extracted from the patients' medical records, effectiveness of diabetes and CVD treatment, drug indication, drug contraindication, drug dosage, drug combinations, and adverse drug reactions (ADR) were evaluated [20-22]. The Pharmaceutical Care Net-

work Europe (PCNE) classification system, version 7 was used to categorize the DRPs [23]. Three domains of problems (treatment effectiveness, adverse safety, and other) and three domains of causes (drug selection, dose selection, and other) based on the PCNE classification were assessed.

Statistical analysis

Statistical analyses were performed in SPSS software, version 27 (SPSS Inc, Chicago, Illinois). Based on the values of the skewness (0.027) and kurtosis (0.470), the data were found to have normal distribution and met the expected values [24]. The body mass index (BMI) of patients was calculated by dividing the weight (in kilograms) by the height (in meters squared). Then, the patients were categorized based on BMI according to the recommended criteria [25]. Categorical variables were presented by frequency and percentage. The data related to age, duration of diabetes and other comorbidities, and number of drugs per patient were described by Mean±SD. Bivariate analysis was conducted on the dichotomous dependent variable (DRPs). Independent-sample t-test was performed over continuous independent variables, and chi-square/Fisher's exact test were used for categorical variables. Binary logistic regression was done on the two most frequent DRPs producing odd ratios (ORs) at a 95% confidence interval (CI). The Risk factors with $P<0.20$ were in bivariate analyses. A $P<0.05$ was considered statistically significant. The statistical model for finding the predictors of non-optimal treatment effect had a $P<0.001$ in Omnibus test, (Nagelkerke R square=0.411). The model for finding the predictors of an untreated indication also had a $P<0.001$ in Omnibus test (Nagelkerke R square=0.919).

Results

General characteristics of the patients

Overall, 146 eligible patients participated, out of whom 135(92.5%) completed the survey. Table 1 represents their general characteristics and lifestyle. Most of them were female (57% vs. 43% male). Their mean age was 70.2±11.1 years; 100(74.1%) <65 years, and 35 (25.9%) ≥65 years. About 25% of patients had a normal BMI; most of them were overweight (31.9%) or obese (40%). Most patients were married (60.7%) and illiterate (47.4%) or with a primary school education (35.6%). Almost 80% were unemployed, and 92.6% had a family caregiver. Regards lifestyle factors, only 23.7% were smokers; 20.7% had physical activity for less than 150 minutes per week, and 67.4% were coffee consumers. Low-carbohydrate, low-salt, or low-fat diets were adopted by about one-third of patients

Medical and medication history

Table 2 shows the statistics for medical and medication history of the patients. Most of patients (64.4%) had been hospitalized for seven days or less. Hospitalization rate related to diabetes and CVD was 17.0% and 26.7%, respectively. The mean duration of diabetes was 12.5±7.8 years, and only 38.6% achieved the target level of HbA1C. Retinopathy was the most common associated complication (57.0%), followed by diabetic foot (17.0%). The mean duration of hypertension was 10.0±7.0 years. The CVDs were coronary artery disease (62.2%), heart failure (13.3%), and stroke (11.9%). Other comorbidities were renal insufficiency (77.0%) and dyslipidemia (20.0%). Sixty percentage of patients were treated by insulin alone in the hospital, and the rest (40%) by combination of insulin and oral antidiabetics including dipeptidyl peptidase-4 (DPP4) inhibitors (24.4%) and metformin (23.7%). The most common antihypertensive and CVD drugs were beta blockers (69.6%), antiplatelet agents (63.7%), lipid-lowering drugs (57.8%), and diuretics (49.6%).

Drug-related problems and causes

The identified DRPs and their causes are presented in Table 3. The most reported problems were related to treatment effectiveness (88.1%). Most of these problems were related to the non-optimal effect of drug treatment (48.2%), and untreated indication (38.3%). The causes of these problems were primarily related to drug selection or dose selection (72.0% and 21.8%, respectively). One of the reported causes was the lack of receiving a synergistic medication (46.0%). In this study, 31 patients did not receive angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), despite having a history of atherosclerotic CVD or microalbuminuria. The absence of primary or secondary prevention of CVD without contraindication was also reported in patients with lower limb edema. Moreover, 12 patients received moderate-intensity statin instead of high-intensity statin. Other patients received inadequate medications (enoxaparin, saxagliptin, trandolapril, and moxonidine). The most prescribed drugs in the presence of contraindication were six moxonidine cases with a creatinine clearance (ClCr) <30 mL/min, two metformin cases (ClCr <30 mL/min), and three trimetazidine cases (ClCr <30 mL/min, Parkinson disease). Other problems were also reported such as hypotension (due to the combination of several antihypertensive drugs), hyperkale-

Table 1. General and lifestyle characteristics of the patients (n=135)

General Characteristics		No. (%)
Sex	Male	58(43.0)
	Female	77(57.0)
Age (y)	<65	100(74.1)
	≥65	35(25.9)
BMI (kg/m^2)	Underweight (<18.5)	3(2.2)
	Normal weight (18.5-24.9)	35(25.9)
	Overweight (≥25)	43(31.9)
	Obese (≥30)	54(40.0)
Marital status	Married	82(60.7)
	Single/Divorced/Widowed	53(39.3)
Level of education	Illiterate	64(47.4)
	Primary school	48(35.6)
	High school	12(8.9)
	University degree	11(8.1)
Employment	Unemployed	107(79.3)
	Employed/Retired	28(20.7)
Family caregiver	Yes	125(92.6)
Medical insurance	Yes	104 (77.0)

Lifestyle		No. (%)
Smoking	No	103(76.3)
	Yes	32(23.7)
Coffee consumption	Yes	91(67.4)
	No	44(32.6)
Physical activity	≥150 min/week	9(6.7)
	<150 min/week	28(20.7)
	No activity	98(72.6)
Reported diet	Low in carbohydrates	47(34.8)
	Low in fat	45(33.3)
	Low in salt	52(38.5)

Table 2. Statistics for medical and medication history of the patients (n=135)

Medical History		No. (%)/Mean±SD
Length of hospitalization (day)	≤7	87(64.4)
	8-14	37(27.4)
	≥15	11(8.2)
Reason for hospitalization	Diabetes	23(17.0)
	CVDs	36(26.7)
	Other	76(56.3)
HbA1C target level achievement	Yes	49(38.6)
	No	78(61.4)
Diabetes complications	Retinopathy	77(57.0)
	Diabetic foot	23(17.0)
	Nephropathy	18(13.3)
	Neuropathy	14(10.4)
CVD-related complications	Coronary artery disease	84(62.2)
	Heart failure	18(13.3)
	Stroke	16(11.9)
	Atrial fibrillation	11(8.1)
	Peripheral artery disease	6(4.4)
Comorbidities	Chronic kidney disease	104(77.0)
	Dyslipidemia	27(20.0)
	Benign prostatic hyperplasia	15(11.1)
	Chronic obstructive pulmonary disease	13(9.6)
	Thyroid dysfunction	10(7.4)
Number of comorbidities/patient	4.6±1.2	

Medication History		No. (%)
Antidiabetic drugs	Insulin	81(60.0)
	Insulin+oral antidiabetics	54(40.0)
	DPP4 inhibitors	33(24.4)
	Metformin	32(23.7)
	Sulfonylurea	16(11.8)
	Meglitinides	3(2.2)

Medication History		No. (%)
Antihypertensive and CVD-related drugs	Beta blockers	94(69.6)
	Anti-platelet agents	86(63.7)
	Lipid-lowering agents	78(57.8)
	Diuretics	67(49.6)
	Anticoagulants	50(37.0)
	Calcium channel blockers	46(34.1)
	Anti-anginal agents	46(34.1)
	Angiotensin-converting enzyme inhibitors	38(28.1)
	Angiotensin receptor blockers	38(28.1)
	Peripheral vasodilators	15(11.1)
	Moxonidine	9(6.7)
	Digoxin	7(5.2)

mia, hyponatremia (due to the combination of diuretics), and hypoglycemia (due to insulin). Serum creatinine level was significantly higher in patients who had DRPs (1.35 vs. 0.94 mg/dL; P=0.004) and those with the problem "non-optimal effect of drug treatment" (1.44 vs. 1.07 mg/dL; P=0.006).

Predictors of DRPs

Table 4 presents the predictors of non-optimal treatment effect and the existence of an untreated indication. After adjusting the effect of covariates, the odds of non-optimal drug treatment effect were 2.32 times higher for patients with elevated serum creatinine level compared to those with normal values (OR=2.32; 95% CI, 1.04%-5.21%; P=0.042). These odds were also higher if patients used lipid-lowering agents (OR=3.67; 95% CI, 1.36%-9.89%; P=0.010) or anti-anginal agents (OR=3.71; 95% CI, 1.18%-11.71%; P=0.025), compared to non-users. Moreover, the odds of non-optimal treatment effect were 67% lower among patients with an achieved HbA1C target level compared to those with abnormal levels (OR=0.33; 95% CI, 0.15%-0.76%; P=0.009). They were also lower among patients using ACEIs (OR=0.14; 95% CI: 0.04-0.47; P=0.002) or ARBs (OR=0.17; 95% CI, 0.05%-0.54%; P=0.003), compared to other patients. The odds of having an untreated indication were significantly higher among patients with a history of heart failure (OR=5.7; 95% CI, 3.43%-7.41%; P=0.005), while these odds were 98% lower among those using lipid-lowering agents (OR=0.02; 95% CI, 0.01%-0.24%; P<0.001), compared to other patients.

Discussion

This study investigated the DRPs among T2D patients with hypertension in Lebanon, and assessed the predictors of these problems. The DRPs were mostly related to treatment effectiveness, including the non-optimal effect of drugs and existence of an untreated indication. The most common causes of DRPs were related to drug selection and dose selection. The predictors of non-optimal drug treatment effect were the elevated creatinine level, lipid-lowering drug use, ACEI use, ARB use, and anti-anginal agent use. The odds of untreated indication varied among those with a history of heart failure or those using lipid-lowering agents. The number of DRPs among T2D patients in the present study was significantly lower compared to the results of other similar studies [16, 26]. A recent meta-analysis found more DRPs in T2D patients with hypertension than in those with T2D alone [27]. Although DRPs are common among patients with T2D [28], the difference in the sampling methods and the authors' knowledge can affect their identification and evaluation. Most patients in our study had at least one DRP, similar to other studies [16, 29], but their number was much higher than that reported a hospital-based study in India [30]. This finding can be explained by the presence of underlying diseases, which leads to the use of several treatment options and, as a result, a higher risk

Table 3. DRPs and their causes

DRPs (n=193)	Code	No. (%)
Treatment effectiveness	P1	170(88.1)
Non-optimal effect of drug treatment	P1.2	93(48.2)
Unnecessary drug treatment	P1.3	3(1.6)
Untreated indication	P1.4	74(38.3)
Treatment safety	P2	
Occurance of adverse drug events	P2.1	10(5.2)
Other	P3	
Unclear problem/complaint	P3.2	13(6.7)

Causes (n=211)	Code	No. (%)
Drug selection	C1	152(72)
Inappropriate drug according to the guideline	C1.1	27(12.8)
Inappropriate drug (within guidelines but contraindicated)	C1.2	14(6.6)
No drug indication	C1.3	3(1.4)
Inappropriate combination of drugs, or drugs and food	C1.4	10(4.7)
Inappropriate duplication of a therapeutic group or active ingredient	C1.5	1(0.5)
Synergistic/Preventive medication is required but has not been given	C1.8	97(46)
Dose selection	C3	46(21.8)
Low drug dosage	C3.1	22(10.4)
High drug dosage	C3.2	8(3.8)
Dosage regimen is not frequent enough	C3.3	7(3.3)
Dosage regimen is too frequent	C3.4	9(4.3)
Other	C8.2	13(6.2)

Causes Associated With Each Drp	
DRPs	**Associated causes**
Non-optimal effect of drug treatment	C1.1, C1.2, C1.5, C1.8, C3
Unnecessary drug treatment	C1.3
Untreated indication	C1.8
Occurance of adverse drug events	C1.4
Unclear problem/complaint	C8.2

Table 4. Predictors of non-optimal drug treatment effect and untreated indication among patients

	Non-optimal Drug Treatment Effect	OR [95% CI]	P
Employment (unemployment as a reference)	Employed/Retired	0.44 [0.10–1.92]	0.272
	Smoking (no as a reference)	0.35 [0.11–1.08]	0.067
	Chronic Kidney disease (no as a reference)	1.62 [0.49–5.38]	0.427
	Serum creatinine level (normal as a reference)	2.32 [1.04–5.21]	0.042
	Target HbA1C level achievment (no as a reference)	0.33 [0.15–0.76]	0.009
	ACEI use (no as a reference)	0.14 [0.04–0.47]	0.002
	ARB use (no as a reference)	0.17 [0.05–0.54]	0.003
	Lipid-lowering agent use (no as a reference)	3.67 [1.36–9.89]	0.010
	Anti-anginal agent use (no as a reference)	3.71 [1.18–11.71]	0.025
Untreated indication	Heart failure (no as a reference)	5.7 [3.43–7.41]	0.005
	Dyslipidemia (no as a reference)	2.32 [0.17–6.98]	0.476
	Lipid-lowering agent use (No as a reference)	0.02 [0.01–0.24]	<0.001
	Anti-platelet agent use (no as a reference)	0.14 [0.01–1.34]	0.996

of errors. Other studies reported lower percentages of problems related to non-optimal effect of drugs [12, 16], possibly due to the comparison with international treatment guidelines which may not be applied in Lebanese hospitals. The untreated indication problem in our study was significantly higher than in the studies by Rochon et al. and Zaman et al. [12, 16]. This can be related to the unavailability of some drugs in the hospitals [31, 32], leading to their non-prescription despite the needs of patients. Drug selection was the primary cause of DRPs, in agreement with the PCNE classification that links the treatment effectiveness-related problem to drug selection or dose selection [23]. In our study, the number of identified causes was lower than in previous studies [16, 33], possibly due to the adaptation of the problems to the most applicable cause and not to multiple reasons. Comorbidities in T2D patients necessitate the use of polypharmacy [34], which was found to be associated with DRPs [35, 36]. This association was not significant in our study, possibly due to the effect of polypharmacy.

The odds of non-optimal drug treatment were higher among patients with elevated creatinine levels. Renal problems require a dose adjustment and routine monitoring [7] which may cause DRPs. T2D is also a predictor of DRPs [37], and can increase the risk. The odds of non-optimal drug treatment were also higher among those using lipid-lowering or anti-anginal agents, consistent with the findings of a recent study in France [38]. However, the odds were significantly lower among those who achieved the HbA1C target level than other patients. Lower HbA1C level is associated with better metabolic control [39] and, thus, a lower risk of complications and drug use. The odds of untreated indication were significantly higher among patients with a history of heart failure. This can be explained by the cardiac remodeling caused by heart failure resulting in cardiac dysfunction [40] and, as a result, other complications are left untreated [41]. Findings from the present study highlight the importance of hospital pharmacists in assessing DRPs, given that pharmacist-led medication reconciliation was found to be associated with potentially inappropriate medication deprescribing and decreased hospital re-admissions [42]. The clinical integration of a pharmacist in the medical team can improve pharmaceutical and medical care and ensure the production of a reliable medication history [43].

This study had some limitations and strengths. Due to the use of a self-report tool for data collection, there might be recall bias. However, information was validated according to the medical records. The bias was reduced since the pharmacists were uniformly trained and did not interfere with the patient's answers. Moreover,

data coding and analysis were performed by a different researcher, which minimized the subjectivity in data collection. A longitudinal study with larger sample size is recommended in Lebanon and other countries.

Conclusion

There is a high prevalence of DRPs in hospitalized T2D patients with hypertension in Lebanon. The predictors of such problems should be taken into consideration for the management of these patients. Findings of this study emphasize the need for integrating a clinical pharmacist in general practice to detect inappropriate prescriptions and prevent adverse drug events.

Ethical Considerations

Compliance with ethical guidelines

The protocol of this study was approved by the Institutional Review Board of the Faculty of Pharmacy at the Lebanese University and the Hospital's Ethical Committee (Code: 20/21/C; February 19th, 2021). Data were kept confidential. Written informed consent was obtained from the patient. They were free to leave the study at any time.

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Authors' contributions

Conceptualization, formal analysis and validation: Georges Hatem; Project administration: Dalia Khachman; Methodology: Aya Awarkeh, Lynne H Jaffal, Dalia Khachman and Amal Al-Hajje; Data curation: Aya Awarkeh, Lynne H Jaffal and Salam Zein; Review and editing: Georges Hatem, Salam Zein, Dalia Khachman and Amal Al-Hajje; Final approval: All authors.

Conflict of interest

The authors declared no conflict of interest.

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