Polypharmacy and Drug-Drug İnteractions Among Patients With Diabetes Mellitus

Diabet Hastalarında Polifarmasi ve İlaç İlaç Etkileşimleri

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Geliş Tarihi / Received : 23.11.2023 Kabul Tarihi / Accepted: 08.12.2023

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Hippocrates Medical Journal / Hippocrates Med J 2023, 3(3):7-15 DOI: https://doi.org/10.58961/hmj.1394987

Abstract

Introduction Diabetes mellitus is a chronic disease. The aim of our study was to evaluate drug- drug interactions and polypharmacy in diabetic patients.

Materials and Methods Patients with type 2 diabetes attending our internal medicine and endocrinology policlinics from April 2019 to July 2019 were included to the study. It was designed as a prospective, descriptive and cross-sectional study. The socio-demographic characteristics of diabetic individuals, the drugs they use in the treatment of diabetes, and other accompanying diseases were evaluated according to the ATC classification. In this study, interactions between multiple drugs and polypharmacy were examined.

Results The study population consisted of 526 patients between the ages of 18-87/years (59 ± 11). 69.6% of the patients were women.83.8% of the patients had chronic diseases accompanying diabetes. The most common chronic diseases were hypertension (53.6%), hyperlipidemia (41.4%) and coronary artery disease (27.2%), respectively. 45.01% of the patients were using five or more drugs. The mean number of drugs was found to be 4.49 ± 1.93. Among the drugs used by the patients, 787 drug-drug interactions were found in a total of 429 (81.5%) patients. The average number of interactions was 3.89 ± 3.6 for interaction A 15.2% (n = 81), 16.2% (n = 85) for interaction B, 69.8% (n = 367) for interaction C was, 47.9% (n = 252) for interaction D, and 0.4% (n = 2) for interaction X. The most frequent interaction was found between acetylsalicylic acid and insulin and metformin and angiotensin converting enzyme inhibitors.

Conclusion Both the polypharmacy rate and drug-drug interaction rate are high in diabetic patients. The most common type of interaction is type C and type D drug-drug interaction. Attention should be paid to drug-drug interactions in the treatment of diabetes patients.

Keywords Diabetes Mellitus, Polypharmacy, Drug-Drug Interactions

Özet

Amaç Diabetes Mellitus kronik bir hastalıktır. Çalışmamızın amacı diyabetik hastalarda ilaç-ilaç etkileşimlerini ve polifarmasiyi değerlendirmektir.

Gerec ve Yöntemler Nisan 2019 ile Temmuz 2019 tarihleri arasında dahiliye ve endokrinoloji polikliniğimize başvuran tip 2 diyabetli hastalar çalışmaya dahil edildi. Prospektif, tanımlayıcı ve kesitsel bir çalışma olarak tasarlandı. Diyabetli bireylerin sosyo-demografik özellikleri, diyabet tedavisinde kullandıkları ilaçlar ve eşlik eden diğer hastalıkları ATC sınıflamasına göre değerlendirildi. Bu çalışmada çoklu ilaç ve polifarmasi arasındaki etkileşimler incelenmiştir.

Bulgular Araştırmanın evrenini yaşları 18-87/yıl (59±11) arasında değişen 526 hasta oluşturdu. Hastaların %69,6'sı kadındı. Hastaların %83,8'inde diyabete eşlik eden kronik hastalıklar vardı. En sık görülen kronik hastalıklar sırasıyla hipertansiyon (%53,6), hiperlipidemi (%41,4) ve koroner arter hastalığı (%27,2) olarak belirlendi. Hastaların %45,01'i beş ve daha fazla ilaç kullanıyordu. Ortalama ilaç sayısı ise 4,49±1,93 olarak belirlendi. Hastaların kullandığı ilaçlardan toplam 429 (%81,5) hastada 787 ilaç-ilaç etkileşimi tespit edildi. Ortalama etkileşim sayısı 3,89 ± 3,6, etkileşim A için %15,2 (n = 81), etkileşim B için %16,2 (n = 85), etkileşim C için %69,8 (n = 367), %47,9 (n = 252) idi. Etkileşim D için ve etkileşim X için %0,4 (n = 2). En sık görülen etkileşim asetilsalisilik asit ve insülin ile metformin ve anjiyotensin dönüştürücü enzim inhibitörleri arasında bulundu.

Sonuç Diyabetik hastalarda hem polifarmasi oranı hem de ilaç-ilaç etkileşimi oranı yüksektir. En sık görülen etkileşim türü C tipi ve D tipi ilaç-ilaç etkileşimleridir. Diyabet hastalarının tedavisinde ilaç-ilaç etkileşimlerine dikkat edilmelidir.

Anahtar Kelimeler Diabetes Mellitus, İlaç ilaç etkileşimleri, polifarmasi

INTRODUCTION

The prevalence of Type 2 diabetes mellitus (T2DM) is increasing worldwide [1,2]. In parallel to this increase in diabetes accompanying comorbidities are also more frequently observed in the last years. This leads to consumption of a lot of medicaments, which is called polypharmacy [3,4]. Accompanying microvascular and macrovascular complications are important. Especially, cardiovascular system diseases are frequently observed in diabetic patients. In addition, hypertension, hyperlipidemia, depression, anxiety disorder and immune system diseases are among the chronic diseases frequently seen in individuals with diabetes. Therefore, this condition increases the risk of drug interactions and, accordingly, undesirable drug effects in individuals with diabetes [1,3,5]. The excess of the number of drugs used in the treatment is defined as the concept of polypharmacy. In the literature, polypharmacy is generally defined as the simultaneous use of five or more drugs [6,7]. Therefore polypharmacy may cause important clinical problems in terms of drug interactions, adverse drug reactions, drug errors and increased risk of hospitalization, which may develop in the patient, in terms of pharmacoeconomics [8]. Multi-drug treatments can inevitably cause drug-drug interactions. This situation may cause serious health problems and makes physicians responsible for malpractice if patients are harmed. When two drugs are used together, the situation that occurs as a result of changing the pharmacological effect of one of the drugs by the other is defined as "drug-drug interaction". Polypharmacy, which is the most important reason for the prevalence of drug interactions, is the use of multiple drugs at the same time [9,10]. The principles of rational drug use aims to be able to treat a disease with few drugs or single drug or to plan effective treatment with the least drug and lowest cost, and to keep drug interactions to a minimum [11]. In our study, it was aimed to analyze the active ingredients of drugs used to treat chronic diseases in individuals with diabetes, to detect the presence of polypharmacy, and to determine interactions between drugs.

MATERIAL and METHODS

Our study is a prospective study, and 526 diabetic individuals with a history of drug use, and who applied to our Internal Medicine and Endocrinology Outpatient Clinics between April 2019 and July 2019, were recruited. Questionnaires including sociodemographic characteristics of diabetic individuals such as age and gender, medications used, comorbidities and family histories were asked. Those who were not diagnosed with diabetes mellitus, had no history of drug use, diabetic individuals under the age of 18, and those who did not volunteer to participate in the study were excluded from the study.For our study, permission was obtained from the Local Ethics Committee (Ethics Committee No/Date:2019-04/19.03.2019). The drugs used were divided into groups according to anatomical, therapeutic and chemical classification (ATC).While evaluating the definition of polypharmacy, the use of five or more drugs was evaluated as polypharmacy in the light of the information in the literature [12,13]. Lexi-Comp (Lexi-Comp.Inc.Hudson, Ohio) electronic database was used for potential drug-drug interactions (pDDI) [14]. Mean, standard deviation, percentage, maximum and minimum values were used as descriptive statistics. Chi-square test was used to compare non-numerical categorical variables. Statistical analyzes and demographic data tables were made. The results were evaluated at the 95% confidence interval, at the $p<0.05$ significance level.

RESULTS

A total of 526 diabetic patients were included in our study.69.6% (366) of DM individuals were female and 30.4% (160) were male. The ages of the patients were (18-87) and the mean age was (59±11/years) **(Table: 1).**

The mean age of the women was (59±10/years) and the mean age of the men was (58±12).40.3% (212) of the patients did not have a family history of diabetes, 55.9% (294) of the patients had a history of diabetes in their first-degree relatives and 3.8% (20) in their distant relatives.83.7% (440) of the patients were married, 14.3% (75) were widowed, and 2.1% (11) were single. There was an accompanying disease in 83.8% (441) of diabetes patients. The most common chronic diseases were hypertension 53.6% (282), hyperlipidemia 41.4% (218), coronary artery disease 27.2% (143), depression 5.3% (28), osteoporosis 4.2% (22), COPD 3% (16), and cancer 1% (6), consecutively. Most of our patients had cardiovascular diseases and hyperlipidemia. When polypharmacy was considered as five or more drug use, the sociodemographic data of diabetic individuals with and without polypharmacy are shown in **Table 2.**

Table 1. Clinical information.

Variable	Subgroups	Number (n=526)	Percent (%)
Gender	Male Female	160 366	30,4 69.6
Diabetes history in relatives	None Primer relative Seconder relative	212 294 20	40,3 55,9 3,8
Age (years) 18-87 (59±11)years	Male Female	(58±12) (59±10)	
Diabetes Duration (years)	Under 10 years 10 years and above	309 213	58,7 41,3
Treatment Type	OAD OAD and Insulin together Insulin	283 157 86	53,8 29,8 16,4
Education	Illiterate Primary education High school University	51 383 79 13	9,69 72,8 15,0 2,47
Marital status	Married Single Divorced	440 11 75	83,65 2,09 14,25
BMI	BMI 1 (low) BMI 2 (high)	63 463	88,02 11,97
Total Drugs Number	2367(1-11)	(4,49±1,93)	
Total DDI Number	787 (0-30)	(3,89±3,6)	33,24
Risk category of the interactions	C D X	367 252 2	69.8 47.9 0.4
Pharmacological data	Categories	n	%
	1–4 5–8 9-11	289 217 20	54,94 41,25 3,80
Number of detected interactions	None 1 2 3 >3	98 94 66 42 226	18,63 17,87 12,54 7,98 42,96

Our polypharmacy rate was 45.01%.The drugs used by individuals with DM and the interactions between these drugs were examined. The most commonly used drug in the treatment of diabetes was metformin. Metformin usage rate was 42%.

Oral antidiabetic drugs and insulin usage data used by the patients and other drugs used during diabetes treatment (**Table 3, Table 4**) are shown together with their ATC (Structural therapeutic chemicals classification) codes.

Table 2. Immunohistochemical data

		Polypharmacy			
		Present (n %) (n: 237, %45,01)	**Absent (n %) (n: 289, % 54,99)**	**X2**	**p**
Gender	**Female**	168 (45,9)	198 (54,1)		
	Male	69 (43,1)	91 (56,9)	0,347	0,556
Marital Status	**Married**	192 (43,6)	248 (56,4)		
	Singe	1 (9,1)	10 (90,9)		**0,003***
	Divorced	44 (58,7)	31 (41,3)	11,71	
Education	**İlliterate**	31 (60,8)	20 (39,2)		
	Primary School	175 (45,7)	208 (54,3)		
	High School	26 (32,9)	53 (67,1)	10,09	0,018*
	University	5 (38,5)	8 (61,5)		
Family type	**Core Family**	180 (43,2)	237 (56,8)		
	Cowded family	52 (54,2)	44 (45,8)	4,09	0,132
	Fragmented Family	5 (38,5)	8 (61,5)		
Diabetes Year	**0-10 years**	122 (39,5)	187 (60,5)		
	11 years and above	113 (53,1)	100 (46,9)	9,38	**0,002***
Age	**0-64 years**	156 (42,2)	214 (57,7)		
	65- years and above	81 (51,4)	75 (48,1)	4,22	0,040*
BMI	**BMI 1**	42 (33,3)	21 (66,7)		
	BMI 2	247 (46,7)	216 (53,3)	3,97	0,046*
Income Status	**Low**	20 (40,8)	29 (59,2)		
	Moderate	205 (46,4)	237 (53,6)	2,30	0,315
	Good	12 (34,3)	23 (65,7)		
Additional Diseases	**Yes**	226(51,2)	215 (48,8)		
	None	11 (12,9)	74 (87,2)	42,24	**0,000***

The most commonly used drug group is diabetes drugs by 48.24% (n=1142).The patients used a total of 2367 active substances. The mean number of active substances used was (4.49±1.93). Patients were using(1 to 11) drugs, of which 3.4% were using one drug, 10.7% using two drugs, 19.7% using three drugs, and 21.6% using four drugs. One patient was using eleven drugs, 18 patients were using one drug. The number of drugs used by the patients is shown in (Figure-1). 787 drug-drug interactions were found in 429 (81.5%) of 526 patients included in our study. Mean number of drug

interactions was (3.89±3.6) (0-30). Interaction A was 15.2% (n=81), interaction B was 16.2% (n=85), interaction C was 69.8% (n=367), interaction D was 47.9% (n=252), interaction was X 0.4% (n=2) **(Table 5).**

Table 3. Drugs used in the treatment of diabetes and ATC (Anatomic Therapeutic Chemical Classification) (Structural classification of therapeutic chemicals codes)

ATC Code: Oral Antidiabetic Drug		Prescription Frequency %	Number of drugs prescribed n
(A10BA02)	**Metformin**	42	221
(A10BH02)	**Vildagliptin**	25,66	135
(A10BB09)	**Gliclazid**	21,48	113
(A10BD07)	**(Metformin+Sitagipti**	9,31	49
(A10BH01)	**Sitagliptin**	9,12	48
(A10BK01)	**Dapagliflozine**	8,74	46
(A10BH05)	**Linagliptin**	7,03	37
(A10BF01)	**Acarbose**	4,18	22
(A10BG03)	**Pioglitazone**	3,23	17
(A10BK03)	**Empagliflozin**	3,04	16
(A10BJ01)	**Exenatide**	2,66	14
(A10BH03)	**Saxagliptin**	0,95	5
(A10BB12)	**Glimepiride**	0,57	3
(A10BX03)	**Nateglinide**	0,57	3
(A10BB01)	**Glibenclamid**	0,19	1
ATC Code: İnsülin			
(A10AE04)	**İnsülin Glargine**	29,84	157
(A10AB05)	**İnsülinAspart**	17,87	94
(A10AD30)	**İnsülinlispro+ İnsülinAspart**	15,72	83
(A10AB06)	**İnsülinGlusiline**	7,41	39
(A10AE05)	**İnsülinDetemir**	4,75	25
(A10AD06)	**İnsülinAspartand Degludec**	2,66	14

Table 4: Drugs used in non-diabetes treatment and ATC codes

ATC Code: Other drugs		Prescription Frequency %	Number of prescribed drugs (n)
(C10)	**Lipid metabolism drugs**	**44,10**	**232**
(C09)	**Medicines that regulate blood pressure**	**31,93**	**168**
(N02)	**Analgesics**	**17,87**	**94**
(C07)	**Beta Blockers**	**17,11**	**90**
(H03)	**Thyroid Drugs**	**15,58**	**82**
(C08)	**Calcium channel blockers**	**12,54**	**66**
(C03)	**Diuretics**	**5,70**	**30**
(B01)	**Antithrombotic**	**5,70**	**30**
(N06)	**Psycho- analeptics**	**5,13**	**27**
(A02)	**Proton pump inhibitors**	**4,75**	**25**
(R03)	**Respiratory System Drugs**	**2,47**	**13**

Table 5. Drug-Drug interactions

Interacting drug pair	Patient number (%)	Risk Classification (A-X)	Probable effects
ASA-Insulin	54(10,26)	C	Increase in hypoglycemia risk
Metformin-ACE inhibitor	52 (9,88)	C	Lactic acidosis and increase in hypoglycemia risk
Gliclazide-Vildagliptin	49 (9,31)	D	Increase in hypoglycemia risk
ASA-ACE inhibitor	37 (7,03)	C	Decrease in ACE inhibition activity and increase in nephrotoxicity risk
Linagliptin-Insulin	36 (6,84)	D	Increase in hypoglycemia
Metformin-ASA	36 (6,84)	C	Increase in hypoglycemia
Metformin + Sitagliptin-ASA	32 (6,08)	C	Increase in hypoglycemia
ASA-Gliklazid	24 (4,56)	C	Salicylates can enhance the hypoglycemic effect of agents that lower blood sugar
Metformin+ Sitagliptin-Atorvastatin	14 (2,66)	C	Increased adverse / toxic effects , Rhabdomyolysis
ASA-Clopidogrel	13 (2,47)	C	Increase in the antiplatelet effect
Sitagliptin-Atorvastatin	12 (2,28)	C	Increased adverse / toxic effects , Rhabdomyolysis
Carvedilol-Insulin	10 (1,90)	C	Increased hypoglycemia
Thioctic acid-Insulin	7 (1,33)	C	Increased hypoglycemia
Metformin-Sertraline	7 (1,33)	C	Increased hypoglycemia
Atorvastatin-Fenofibrate	5 (0,95)	C	Increased adverse / toxic effects
ASA-Diclofenac	3 (0,57)	C	Increase in the antiplatelet effect, bleeding risk
Paroxetine-Rasagiline	1 (0,19)	X	Seratonin syndrome
Etodolac-Dexketoprofen	1 (0,19)	X	Increase adverse / toxic effects

Gender distribution results are shown in **(Table 6).**

Table 6. Drug-drug interaction: Gender distrubition

		Interaction A		Interaction B		Interaction C		Interaction D		Interaction X	
		n	%	n	%	n	%	n	%	n	%
Gender	Female	66	81,2%	62	72,9%	258	70,3%	175	69,4%	2	0,4 %
	Male	15	18,8%	23	27,1%	109	29,7%	77	30,6%	0	0,0%

We aimed to draw the attention of clinicians to this issue by revealing polypharmacy and potential drug-drug interactions in diabetic patients who applied to the internal medicine and endocrinology outpatient clinic.

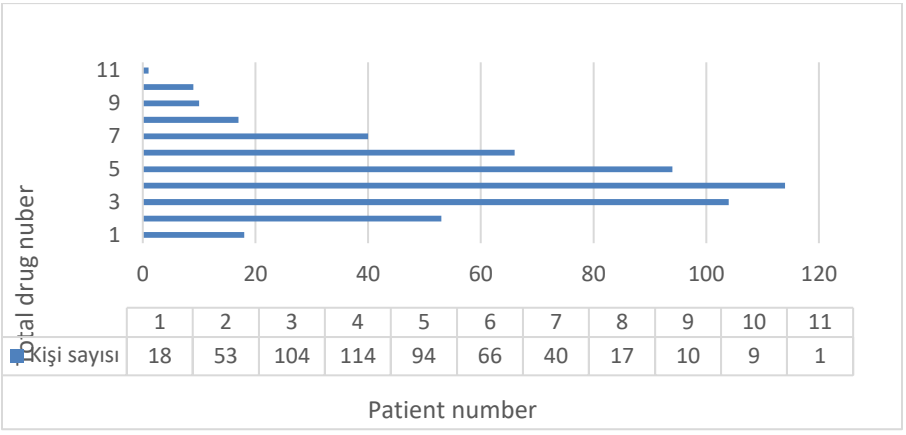

Figure 1. Number of drugs used by patients

DISCUSSION

Polypharmacy is a common condition in patients with diabetes. In terms of pharmacoeconomic, adverse drug reactions, drug-drug interactions, drug-nutrient interactions, it paves the way for serious clinical consequences for patients. When polypharmacy was defined as the number of drugs used daily as 5 or more, the rate of polypharmacy was found to be 45.1% in our study. Polypharmacy was 31.9% in female patients and 13.1% in males. No significant difference was observed in the presence of polypharmacy between men and women. Polypharmacy rates in patients with diabetes are reported to be between 26.7% and 56.5% in the literature. We can say that the rate we found is similar to the literature data [15-18]. Of the diabetic individuals included in our study, 69.6% were female and 30.4% were male. Although there are different results regarding the incidence of DM in the literature, we found that diabetes is more common in women [18, 20-23]. The mean age of our study group was (18-87) and the mean age was (59±11). The mean age of the women was (59±10) and the mean age of the men was (58±12). According to studies, we can say that our average age is higher [22, 23]. Additional diseases seen with aging lead to the use of multiple drugs. Feng and colleagues' studies have revealed that polypharmacy is common in those with additional diseases. Polypharmacy was more common in those with non-diabetic additional diseases in the study group (p=0.000).

Polypharmacy was observed more frequently in individuals aged 65 years and older compared to younger age groups and this was statistically significant (p=0.0040). When we evaluate the relationship of marital status and polypharmacy, the rate of polypharmacy was higher in those who divorced their spouse (p=0,003). As in the whole world, the vast majority of polypharmacy patients in our study were patients aged 65 and older [24]. Polypharmacy is reported to be more common in patients with low levels of education. The fact that those with low levels of education also have low health

literacy explains this situation. It is pointed out in the literature that low level of education is associated with polypharmacy. In our study, polypharmacy rate was high in the illiterate group [20,25]. The number of drugs used in diabetic individuals enrolled in the study was the lowest 1, the highest 11. Our study group used drugs on average (4.49±1.93).

Although the average number of drug use varies between 5.3 and 8.1 in the literature, it is recognized that there is a significant risk for polypharmacy of diabetes. Our results are similar to literature [21,22, 26-28]. In patients with diabetes, the age of diabetes is an important criterion for the development of complications. The incidence of polypharmacy in our patients with diabetes age under 10 years was 39.5%, while this rate was 53.1% in those with diabetes age over 10 years. Polypharmacy was found to be more common in patients aged 11 years and older with diabetes (p=0.002). This can be explained by the use of more medications for diabetic patients to prevent diabetes [29].

High body mass index (BMI) in patients with DM is one of the underlying factors for polypharmacy reasons such as insulin resistance and accompanying diseases. In our study, it was found that the frequency of polypharmacy was higher in those with high BMI. In our study, 918 of antidiabetic drugs were used by individuals under the age of 65, while 329 were used by individuals over the age of 65. Studies indicate that the frequency of antidiabetic drug use decreases as age increases in patients with diabetes [29, 30].

Doctors explain that liver and kidney function in the elderly works more slowly than in young people, and again, because more frequent episodes of hypoglycemia occur in the elderly, they use fewer medications. This also indicates that young people use more antidiabetic drugs to prevent complications that can develop due to diabetes. The results of our study are similar to the literature [31]. 83.8% of our patients with diabetes had a concomitant disease. The most common accompanying disease was 53.6% hypertension and 41.4% hyperlipidemia. Other drugs used during the treatment of diabetes included 44.10% lipid-lowering drugs, 31.93% antihypertensive drugs, 17.84% analgesics decayed. Atorvastatin was most commonly used in lipid-lowering drugs [20]. 42% of our study group was on Metformin. Although this rate was reported as 11.2% in Prado et al studies, the percentage of metformin use was lower than in other studies [19-22]. Hypertension and hyperlipidemia increase the incidence of cardiovascular diseases in patients with diabetes, leading to more drug use. Studies indicate that cardiovascular disease is the most common cause of death in 80% of patients with diabetes [32]. In our study, the most commonly used group of drugs other than diabetes drugs was found to be lipid-lowering and cardiovascular system drugs. Potential drug drug interaction (pDDI) is the simultaneous prescribing/taking of two interacting drugs, regardless of whether an adverse outcome occurs in the patient. In the literature [33] , it is reported that there is a relationship between the presence of polypharmacy and pDDI. In our study, a statistically significant association was found between polypharmacy and pDDI (p=0.000).

The average number of active substances used in the study was (4.49±1.93), while the pDDI value per patient was (0-30), (3.89±3.6). It is mentioned as 5 in the work of Marusic et al [34].

Our pDDI incidence was 33.4%. This value is thought to be a predisposing factor for pDDI in patients with polypharmacy. It bears similarities to the studies carried out [35, 36].

In Type C interactions, it is recommended to follow on the treatment, if the benefit from the joint use of the two interacting drugs is usually greater than the risk caused by the interaction. According to the literature, Type C interactions are most commonly observed in pDDI interactions [37, 38]. In our study, it was also shown that the most common type interaction is Type C interaction with a percentage of 69,8% (367). In different studies, Type C interaction is the most common form as reported in the Savran et al study (47.5%) [39].

In D-type pDDI interactions, it may be necessary to modify the treatment by evaluating the risks and benefits caused by simultaneous use of drugs. Among p DDI's, our rates of D- and X-type interactions, which are considered important for their association with clinical manifestations, were found to be 47.9% (252) and 0.4% (2) . Type D p DDI interaction rates in the literature range from 5.1% to 21.4% in diabetic patients [19,29,40].

In our study results, we found that both Type C and Type D interactions were high compared to the values stated in the literature. Aspirin was one of the most interacting drugs in our study. There is an interaction between Aspirin and antidiabetic drugs such as insulin, metformin, gliclazide. The effect of hypoglycemia may occur when used together. Again, there is an interaction between Aspirin and angiotensin Converting enzyme inhibitor drugs. Aspirin leads to a decrease in the effectiveness of acei medications.Important drugs that cause Group D interaction were found between gliclazide-vildagliptin and linagliptin-insulin. Group X interactions that we identified in our study are between Paroxetine-rasagiline and Etodolac-Decketoprofen. An increase in the number of chronic diseases with aging increases the incidence of both polypharmacy and drug-drug interactions.

CONCLUSION

In our study, in diabetic patients, the rate of chronic disease is high and the associated polypharmacy rate is high. A higher percentage of Type C drug-drug interactions were observed compared to other studies when drug-drug interactions were grouped together. Our D-type drug interaction rate was found to be higher than in other studies. Both patients and physicians have great responsibility for the prevention of polypharmacy and drug-drug interactions. Before issuing a prescription, doctors should check websites, textbooks and databases according to the age, education and knowledge levels of patients and evaluate the medications they will use in treatment.

Ethıcal Declerations

The approval for this study was obtained from Kütahya Health Sciences University Non-invasive Clinical Research Ethics Committee19.03.2019 (Protocol no: 2019/04).

InformedConsent:

Because the study was designed retrospectively, no written in formed consent form was obtained from patients.

Conflict of Interest Statement:

The authors have no conflicts of interest to declare.

Financial Disclosure:

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Author Contributions:

All authors contributed to the study's conception and design. FO, TPK, KO, and FO, TPK performed study preparation, data collection, and analysis. FO, KO wrote the first draft of the manuscript, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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