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Assessment of Potential Drug-Drug Interactions in Obese Patients

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ABSTRACT

Aim: Polypharmacy may cause life-threatening adverse effects due to drug-drug interactions (DDIs). It is possible to observe DDIs due to polypharmacy in obese patients who is known to have many co-morbid diseases that necessitates multiple drug use. The aim of the present study is to determine the frequency and severity of potential DDIs (pDDIs) in obese patients.

Material and Methods: This cross-sectional study analyzed the patient charts that admitted to obesity outpatient clinic of tertiary care hospital from April 1, 2016 to July 1, 2017. The severity of DDIs was interpreted using the Lexi-comp® drug interaction database. A chi-square test was performed for the comparison of the presence of DDIs based on patients' demographic characteristics [gender (male/female), age categories (18-44, 45-64 and ≥65 years) and BMI (30-34.9, 35-39.9 and ≥40 kg/m2)], co-morbid clinical conditions and number of drugs. The comparisons were considered as statistically significant at $p< 0.05$.

Results: Out of 476 patient data evaluated, a total of 781 drugs were prescribed. Among 190 patients who were prescribed two or more drugs, 35 (18.4%) patients had one or more pDDIs. We determined 48 (70.6%) C, 12 (17.6%) B, 7 (10.3%) D and 1 (1.5%) X risk category interactions. The most common pDDIs were between metformin and nonsteroidal anti-inflammatory drugs (7.4%). The presence of pDDIs was significantly associated with the number of prescribed drugs ($p<0.001$).

Conclusion: The pDDIs in obesity outpatient clinic were relatively low. Nevertheless, in order to minimize DDIs, it is vital for physicians to be aware of the interactions between the frequently prescribed drugs in obesity outpatient clinic and monitor patients for the safe use of drugs.

Keywords: *Drug interactions, Polypharmacy, Obesity*

Obez Hastalarda Olası İlaç-İlaç Etkileşimlerinin Değerlendirilmesi

ÖZ

Amaç: Polifarmasi, ilaç-ilaç etkileşimlerine bağlı yaşamı tehdit eden yan etkilere neden olabilmektedir. Çoklu ilaç kullanımını gerektiren birçok ko-morbid hastalığı olduğu bilinen obez hastalarda polifarmasiye bağlı ilaç-ilaç etkileşimlerini gözlemlemek muhtemeldir. Bu çalışmanın amacı, obez hastalarda olası ilaç-ilaç etkileşimlerinin sıklığını ve şiddetini belirlemektir.

Gereç ve Yöntemler: Bu kesitsel çalışmada, 1 Nisan 2016- 1 Temmuz 2017 tarihleri arasında üçüncü basamak bir hastanenin obezite polikliniğine başvuran hastaların reçete verilerini analiz edildi. İlaç-ilaç etkileşimlerinin şiddeti, Lexi-comp® ilaç etkileşimi veri tabanı kullanılarak yorumlandı. Hastaların demografik özellikleri [cinsiyet (erkek/kadın), yaş kategorileri (18-44, 45-64 ve ≥65 yaş),VKİ'leri (30-34,9, 35-39,9 ve ≥40 kg/m2)], eşlik eden hastalıkları ve ilaç sayısına göre ilaç ilaç etkileşimi varlığının karşılaştırılması için ki-kare testi uygulandı. $p <0,05$ değeri istatistiksel olarak anlamlı kabul edildi.

Bulgular: Değerlendirilen 476 hasta verisinde, toplam 781 ilaç reçete edildi. İki veya daha fazla ilaç reçete edilen 190 hasta arasında, 35 (%18,4) hastada bir veya daha fazla olası ilaç-ilaç etkileşimi vardı. 48 (%70,6) C, 12 (%17,6) B, 7 (%10,3) D ve 1 (%1,5) X risk kategorisi ilaç-ilaç etkileşimi tespit edildi. En sık olası ilaç-ilaç etkileşimi metformin ve nonsteroidal antiinflamatuvar ilaçlar arasındaydı (%7,4). Olası ilaç-ilaç etkileşimlerinin varlığı, reçete edilen ilaçların sayısı ile anlamlı düzeyde ilişkiliydi ($p<0,001$).

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Sonuç: Obezite polikliniğindeki olası ilaç-ilaç etkileşimlerinin oranı nispeten düşüktü. Bununla birlikte, ilaç-ilaç etkileşimlerini en aza indirmek için, hekimlerin obezite polikliniğinde sık reçete edilen ilaçlar arasındaki etkileşimlerin farkında olması ve ilaçların güvenli kullanımı için hastaları izlemesi hayati önem taşımaktadır.

Anahtar Sözcükler: *İlaç etkileşimleri, Polifarmasi, Obezite*

INTRODUCTION

The aging of the population and the fact that certain patients have numerous co-morbid diseases result in chronic prescription of multiple drugs at the same time (polypharmacy), (1). Although polypharmacy may aim to improve therapeutic outcomes, various drug combinations may be harmful. Namely, polypharmacy may cause undesirable consequences such as inadequate treatment or life-threatening adverse effects due to drug-drug interactions (DDIs), (1, 2).

DDI is described as the changes in the effect of one drug with the addition of another drug utilized for the same or different diseases. DDIs may be minor enough to be undetectable, or they may be severe enough to impact the health negatively (1). The term 'potential drug-drug interaction' (pDDI) denominates the probability that one drug may alter the effects of another when used concomitantly (3). The prevalence of pDDIs has been reported to vary between 16% and 96% in various researches conducted on different patient groups and settings (1, 3-9). DDIs have been found to be associated with the increase in the length of hospital stay (10). In addition, mortality rate due to DDIs has been reported as 4% (11).

Particularly, the elderly population using multiple drugs are at high risk for DDIs due to age-related pharmacokinetic and pharmacodynamic changes (12, 13). Apart from age, gender and co-morbid diseases have been also found to be related to polypharmacy and DDIs (2, 10).

Obesity is known to be associated with many co-morbid diseases like diabetes mellitus, hypertension, hyperlipidemia, coronary heart disease, which usually necessitate many drug use (14). Obesity has been reported to be among the major determinants of starting polypharmacy and strongly associated with maintaining polypharmacy (15). In this regard, it is possible to observe drug-drug interactions due to polypharmacy in obese patients.

The frequency of DDIs can be used as a quality indicator that indicates the safety of prescribing. As such, the main purpose of this study is to detect the frequency and severity of pDDIs in the prescriptions at the obesity outpatient clinic of a tertiary care hospital and assess whether the presence of pDDIs was associated with patients' demographic characteristics and clinical conditions.

MATERIAL and METHODS

Study Design

This cross-sectional, retrospective study analyzed the patient charts that admitted to obesity outpatient clinic of Istanbul Medeniyet University Goztepe Training and Research Hospital from April 1, 2016 to July 1, 2017. This study was approved by Istanbul Medeniyet University Goztepe Training and Research Hospital Ethics Committee (IRB No: 2020/0464, July 22, 2020). The files of the patients were assessed retrospectively following getting approval from the ethics committee.

Sample

Patients ≥ 18 years and with a body mass index (BMI) ≥ 30 kg/m^2 were included in the study. All prescriptions that have at least one or more drugs were included in the assessment. Variables such as age, gender, BMI and co-morbid diseases (hypertension, diabetes mellitus, depression etc.), number of drugs prescribed, drug names, the Anatomical Therapeutical Chemical (ATC) codes, dosage forms, route of administration, number of the pDDIs and risk category of the interaction (B, C, D and X category) were assessed. The ATC (Anatomical Therapeutic Chemical) methodology is a significant universally approved comparison practice which is used in drug utilization studies in order to extinguish the challenges with respect to the discrepancies of quantity, dose, duration etc. and make comparisons (http://www.whocc.no/atc_ddd_index/). ATC-1, ATC-2 and ATC-5 classifications of the prescribed drugs were analyzed. Repetitious prescriptions of the same person were not assessed. Duplications were avoided by taking into consideration about the first encountered prescription in the system for a patient.

Analysis of pDDIs

The seriousness of pDDIs was interpreted according to cthe Lexi-comp® drug interaction database, which categorizes the interaction as A, B, C, D and X. Lexi-comp® online interaction risk rating levels are as follows (16):

A: No interaction.

B: The indicated agents may interfere with each other, but there is little to no evidence of clinical significance.

C: The indicated agents may interfere with each other in a clinically significant way. Monitor the therapy.

D: The two drugs may interfere with each other in a clinically significant way. Monitor the therapy aggressively and consider therapy modification.

X: The indicated agents may interact with each other in a clinically significant manner. Avoid drugs' concurrent use.

IBM SPSS v25.0 software was used for the statistical data analyses.Frequency tables were used to show qualitative data. Categorical data were stated as percentages. A chi-square test was used to compare DDIs based on patients' demographic characteristics [gender (male/female), age groups (18-44, 45-64 and ≥65 years) and BMI (30-34.9, 35-39.9 and ≥40 kg/m^2)], co-morbid clinical conditions and number of drugs. The comparisons were considered as statistically significant at $p< 0.05$. In the power analysis performed with 80% power and 5% margin of error, the minimum sample size was 454.

RESULTS

Demographic and Clinical Characteristics of the Patients

A total of 761 patient charts that admitted to obesity outpatient of clinic of Istanbul Medeniyet University Goztepe Training and Research Hospital between the specified time interval (April 1, 2016 - July 1, 2017) were assessed. Among them, 476 (62.5%) patients who were prescribed at least one or more drugs were further analyzed. The mean age was 47.5±12.5 years and 88% of them were female (Table 1). Most of the patients were between 45 - 64 years (57.6%), (Table 1). Mean BMI values were 37.1±5.7 kg/m^2. The most frequent co-morbid disease was essential hypertension (34.7%), followed by diabetes mellitus (32.8%), depression (11.6%) and cardiovascular diseases (8.8%), (Table 1).

Prescribing Pattern of Drugs in Obese Patients

A total of 781 drugs were prescribed to 476 patients. More than half of the patients (60.1%) were prescribed one drug per encounter and only 1.9% of the prescriptions contained ≥ 5 drugs (Table 1). The average number of drugs per patient was 1.6±1.0 with a minimum of 1 and a maximum of 8 drugs (Table 1).

When the ATC-1 distributions of the prescribed drugs were analyzed, "Alimentary tract and metabolism drugs" (ATC-1 code: A; 62.2%) were the most frequent group, followed by "Cardiovascular system drugs" (C; 9.3%), (Table 2). According to the ATC-2 group distributions of the prescribed drugs, "Vitamins" (ATC-1 code: A11; 30.7%) and "Drugs Used in Diabetes" (A10; 25.1%) were the most commonly prescribed drugs (Table 2).

The most common drug in the prescriptions was Vitamin D3 (cholecalciferol), (ATC-5 code: A11CC05; 26.4%), followed by metformin (A10BA02; 20.4%) and levothyroxine sodium (H03AA01; 5.1%), (Table 3). Oral route (93.5%) was the most common way of application, followed by the drugs administered subcutaneous (3.2%) and intramuscular (3.2%) ways. Tablets (49.5%) and oral drops (32.3%) were the most common drug forms.

Table 1: Patients' demographic characteristics and clinical conditions [Number of patients (n)=476].

Variables	n (%)
Gender	
Female	419 (88.0)
Male	57 (12.0)
Age groups (in years)	
18-44	176 (37.0)
45-64	274 (57.6)
≥65	26 (5.4)
Co-morbid diseases	
Hypertension	165 (34.7)
Diabetes mellitus	156 (32.8)
Depression	55 (11.6)
Cardiovascular diseases	42 (8.8)
Chronic obstructive pulmonary disease	24 (5.0)
Rheumatic diseases	21 (4.4)
Polycystic ovary syndrome	20 (4.3)
Obstructive sleep apnea syndrome	13 (2.7)
Number of drugs per patient	
1	286 (60.1)
2	121 (25.4)
3	38 (8.0)
4	22 (4.6)
≥5	9 (1.9)
	Mean± SD (Min-Max)
Age (years)	47.5±12.5 (18-80)
BMI (kg/m^2)	37.1±5.7 (30.0-57.0)
Average number of drugs per patient	1.6±1.0 (1-8)

BMI: Body mass index

Table 2: ATC-1 and ATC-2 classification of the prescribed drugs [Number of drugs (n)=781].

ATC-1 classification	n (%)	ATC-2 classification	n (%)
Alimentary Tract and Metabolism (A)	486 (62.2)	Stomatological Preparations (A01)	2 (0.3)
		Drugs for Acid Related Disorders (A02)	30 (3.8)
		Drugs for Functional Gastrointestinal Disorders (A03)	8 (1.0)
		Antiemetics and Antinauseants (A04)	1 (0.1)
		Drugs for Constipation (A06)	3 (0.4)
		Antidiarrheals, Intestinal anti-inflammatory/anti-infective Agents (A07)	1 (0.1)
		Digestives, including Enzymes (A09)	1 (0.1)
		Drugs Used in Diabetes (A10)	196 (25.1)
		Vitamins (A11)	240 (30.7)
		Mineral Supplements (A12)	4 (0.5)
Blood and Blood Forming Organs (B)	32 (4.1)	Antianemic Preparations (B03)	32 (4.1)
Cardiovascular System (C)	73 (9.3)	Cardiac Therapy (C01)	2 (0.3)
		Antihypertensives (C02)	3 (0.4)
		Diuretics (C03)	1 (0.1)
		Vasoprotectives (C05)	1 (0.1)
		Beta Blocking Agents (C07)	10 (1.3)
		Calcium Channel Blockers (C08)	7 (0.9)
		Agents Acting on the Renin-Angiotensin System (C09)	29 (3.7)
		Lipid Modifying Agents (C10)	20 (2.6)
Dermatological (D)	7 (0.9)	Antifungals for Dermatological Use (D01)	4 (0.5)
		Corticosteroids, Dermatological Preparations (D07)	3 (0.4)
Genitourinary System and Sex Hormones (G)	1 (0.1)	Urologicals (G04)	1 (0.1)
Systemic Hormonal Prep. excluding Sex Hormones (H)	61 (7.8)	Corticosteroids for Systemic Use (H02)	19 (2.4)
		Thyroid Therapy (H03)	42 (5.4)
General Anti infectives for Systemic Use (J)	44 (5.6)	Antibacterials for systemic use (J01)	42 (5.4)
		Vaccines (J07)	2 (0.3)
Antineoplastic and Immunomodulating Agents (L)	2 (0.3)	Antineoplastic agents (L01)	2 (0.3)
Musculoskeletal System (M)	21 (2.7)	Anti-inflammatory and antirheumatic product (M01)	18 (2.3)
		Muscle relaxants (M03)	3 (0.4)
Nervous System (N)	31 (4.0)	Analgesics (N02)	15 (1.9)
		Antiepileptics (N03)	3 (0.4)
		Anti-parkinson Drugs (N04)	1 (0.1)
		Psycholeptics (N05)	2 (0.3)
		Psychoanaleptics (N06)	10 (1.3)
Antiparasitic Products (P)	2 (0.3)	Antiprotozoals (P01)	1 (0.1)
		Anthelmintics (P02)	1 (0.1)
Respiratory system (R)	21 (2.7)	Nasal preparations (R01)	6 (0.8)
		Throat preparations (R02)	1 (0.1)
		Drugs for obstructive airway diseases (R03)	5 (0.6)
		Cough and cold preparations (R05)	4 (0.5)
		Antihistamines for systemic use (R06)	5 (0.6)

ATC: Anatomical Therapeutical Chemical

Assessment of pDDIs

A total of 190 patient charts who were prescribed ≥ 2 drugs were analyzed in detail regarding pDDIs. Among 190 patients, 35 (18.4%) patients had one or more pDDIs with a maximum of 6 pDDIs (Table 4). A total of 68 pDDIs were detected of which 48 (70.6%) were C, 12 (17.6%) were B, 7 (10.3%) were D and 1 (1.5%) were X risk category interactions (Table 4). The average number of pDDIs per patient was 0.1.

Table 3: The most frequently prescribed 10 drug at obesity outpatient clinic [Number of drugs (n)=781].

Drugs (ATC-5 Code)	n (%)
Vitamin D3 (A11CC05)	206 (26.4)
Metformin (A10BA02)	159 (20.4)
Levothyroxine sodium (H03AA01)	40 (5.1)
Vitamin B complex combinations (A11EA)	34 (4.4)
Phosphomycin (J01XX01)	23 (2.9)
Dexamethasone (H02AB02)	18 (2.3)
Atorvastatin (C10AA05)	15 (1.9)
Iron glycine sulfate (B03AA01)	13 (1.7)
Paracetamol (N02BE01)	13 (1.7)
Exenatide (A10BJ01)	12 (1.5)

ATC: Anatomical Therapeutical Chemical

Table 4: Frequency and the severity of pDDIs [number of patients who were prescribed two or more drugs (n)=190].

Variables	n (%)
DDIs	
Yes	35 (18.4)
None	155 (81.6)
Number of DDIs	
1	24 (12.6)
2	2 (1.1)
3	2 (1.1)
4	2 (1.1)
5	4 (2.1)
6	1 (0.5)
Risk category of DDIs	
B	12 (17.6)
C	48 (70.6)
D	7 (10.3)
X	1 (1.5)

DDIs: Drug-drug interactions

Patients who were prescribed ≥ 5 drugs were significantly more likely to have pDDIs than did those receiving 2-4 drugs (p<0.001). Patients with diabetes mellitus were found to have higher possibility of pDDIs compared to their non-diabetic counterparts (p=0.041). Age groups, gender, BMI groups, and other comorbidities evaluated in the study were not found to be significantly associated with the presence of DDIs (Table 5).

The most common pDDIs were between metformin and nonsteroidal anti-inflammatory drugs (NSAIDs), (7.4%), It was followed by the pDDIs between metformin and hydrochlorothiazide (4.4%), and between metformin and angiotensin converting enzyme (ACE) inhibitors (4.4%), (ACE Inhibitors may increase the adverse effect of Metformin such as hypoglycemia and lactic acidosis). The most common ten pDDIs and estimated clinical outcomes are depicted at Table 6.

Table 5: Comparison of the presence of DDIs based on patients' demographic characteristics, clinical conditions and number of drugs.

Variables	DDIs		P value
	Yes n (%)	None n (%)	
Gender			
Female	32 (91.4)	133 (85.8)	p=0.374
Male	3 (8.6)	22 (14.2)	
Age			
18-44	12 (34.3)	49 (31.6)	p=0.341
45-64	19 (54.3)	97 (62.6)	
≥65	4 (11.4)	9 (5.8)	
BMI			
30- 34.9	12 (34.3)	62 (40.0)	p=0.821
35-39.9	13 (37.1)	53 (34.2)	
≥40	10 (28.6)	40 (25.8)	
Number of drugs			
2-4	27 (77.1)	154 (99.4)	p<0.001
≥5	8 (22.9)	1 (0.6)	
Co-morbid diseases			
Hypertension	17 (48.6)	51 (32.9)	p=0.081
Diabetes mellitus	18 (51.4)	50 (32.3)	p=0.041
Depression	1 (2.9)	16 (10.3)	p=0.162
Cardiovascular diseases	5 (14.3)	8 (5.2)	p=0.053
Polycystic ovary syndrome	1 (2.9)	6 (4.0)	p=0.755
Obstructive sleep apnea syndrome	1 (2.9)	3 (1.9)	p=0.732

DDIs: Drug-drug interactions, **BMI:** Body mass index.

Table 6: The most common 10 DDIs between drugs prescribed at the obesity outpatient clinic [Number of pDDIs (n)=68].

DDIs	Risk category	n (%)
Metformin-NSAIDs (Metformin-Flurbiprofen) (Metformin-Dexketoprofen)	C	5 (7.4)
Metformin- Hydrochlorothiazide	C	3 (4.4)
Metformin-ACE inhibitors (Metformin-Ramipril) (Metformin-Perindopril) (Metformin-Lisinopril)	C	3 (4.4)
Metformin-Ciprofloxacin	C	2 (2.9)
Levothyroxine-Esomeprazole	B	2 (2.9)
Levothyroxine-Iron Sulfate	D	2 (2.9)
ACE inhibitors- NSAIDs (Perindopril-Flurbiprofen) (Trandolapril-Piroksikam)	C	2 (2.9)
Hydrochlorothiazide- NSAIDs (Hydrochlorothiazide-Indomethacin) (Hydrochlorothiazide-Ibuprofen)	C	2 (2.9)
Beta Blockers-NSAIDs (Nebivolol-ibuprofen) (Metoprolol-indomethacin)	C	2 (2.9)
Angiotensin Receptor Blockers (ARBs)-NSAIDs (Valsartan-Ibuprofen) (Olmesartan-Indomethacin)	C	2 (2.9)

DDIs: Drug-drug interactions, **NSAIDs:** Nonsteroidal Anti-Inflammatory Drugs, **ARBs:** Angiotensin receptor blockers, **ACE:** Angiotensin converting enzyme

DISCUSSION

DDI is an important public health issue which may have life-threatening consequences and it is predicted to lead to almost 2.8% of all hospitalizations annually (17). Therefore, it is crucial for physicians to be aware of these pDDIs and common pDDIs should be taken into consideration by physicians for safety of the patients.

In the present study, we made a detailed analysis of the prescriptions at the obesity outpatient clinic in terms of pDDIs. Earlier studies in the literature have mainly focused on the prevalence of pDDIs among pediatric age group (4, 9, 18) or elderly (7, 8, 12, 14, 19) or pDDIs at different settings (primary care, intensive care units, cardiology, internal medicine outpatient clinics etc), (1, 2, 8, 12, 17) or pDDIs in patients who suffer from cancer (4, 11), chronic kidney disease (5, 20-22) , diabetes mellitus (14, 23) and hypertension (8, 24). To the best of our knowledge, the present study is the first to report the frequency and severity of pDDIs related to drugs prescribed in obesity outpatient clinic.

Patient data from the obesity outpatient clinic showed that 18.4% of the polypharmacy patients had one or more pDDIs, which was closer to the results of previous studies reporting 16% and 16.9% pDDIs in pediatric outpatient departments (9, 18). Frequency rate of pDDIs was lower as compared to studies conducted at different outpatient clinic settings; cardiology & internal medicine outpatient clinic (96%), general outpatient clinic (47.6%) and primary health care outpatient clinic (33%), (1, 8, 12).

In terms of severity, most of the pDDIs were in C risk category (70.6%), while D and X categories constituted 11.8% of the total pDDIs. These results were comparable to previous studies which have reported similar percentages of pDDI risk categories (1, 5, 12, 25). Although a great majority of pDDIs detected in our study were in C risk category and have no critical or fatal clinical implications, it is crucial for physicians to know the frequently encountered pDDIs, monitor the patients or change the drug options if necessary.

Polypharmacy which is commonly defined as prescribing ≥ 5 drugs daily is the most common cause of DDIs (26). In the present study, despite low polypharmacy rates (1.9%), a significant association were found between presence of pDDIs and polypharmacy ($p<0.05$). This significant association between polypharmacy and pDDIs has also been reported by several studies (2, 27, 28, 29).

In contrast to the earlier studies reporting a significant association of age (1, 10, 27), gender (3, 10), BMI (7) with pDDIs, there was no significant association between these variables and pDDIs in our study. As to the type of co-morbid diseases, unlike previous studies reporting a significant association of a number of co-morbid diseases like hypertension (1, 6, 19), dyslipidemia (1), ischemic heart disease (6), stroke (6), with pDDIs, we only found a significant association between diabetes mellitus and pDDIs.

In the present study, the most common pDDIs were between metformin and other agents (NSAIDs, thiazide diuretics and ACE inhibitors). In line with this, a significant association were found between the presence of pDDIs and co-morbid diabetes mellitus. Similar to our results, a study investigating DDIs in Brazilian type 2 diabetes patients reported DDIs due to combined use of metformin with NSAIDs, thiazide diuretics and ACE inhibitors (23) The estimated clinical outcomes related to the most common pDDIs in the present study are as follows: NSAIDs may enhance the adverse/toxic effect of metformin e.g. lactic acidosis, thiazide and

thiazide-like diuretics may diminish the therapeutic effect of antidiabetic agents e.g. hyperglycemia and ACE inhibitors may enhance the adverse effect of Metformin such as hypoglycemia and lactic acidosis (16). However, as a limitation of our study, we don't know whether pDDIs caused these changes in therapeutic efficacy of drugs or not.

CONCLUSION

The present study shows that pDDIs are strongly associated with the number of prescribed drugs and comorbid diabetes mellitus and that pDDIs in obesity outpatient clinic were relatively low. Nevertheless, in order to minimize these DDIs, it is vital for physicians to be aware of the interactions between the frequently prescribed drugs in obesity outpatient clinic and monitor patients for the safe use of drugs.

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None

Author Contributions

First author, performed the creation of the hypothesis and study design, data collection and evaluation, literatüre review and wrting of the article. The co-author contributed to the literatüre review, writing and the revision of the article.

Conflict of Interest

We declare that we have no conflict of interest.

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Ethical Approval

This study was approved by Istanbul Medeniyet University Goztepe Training and Research Hospital Ethics Committee (IRB No: 2020/0464, July 22, 2020).

Peer Review Process

Extremely peer-reviewed and accepted.

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