Evaluation of the Relationship Between Polypharmacy and Malnutrition in Diabetic Elderly

Diyabetik Yaşlılarda Polifarmasi ve Malnütrisyon İlişkisinin Değerlendirilmesi

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ABSTRACT

Aim: Type 2 diabetes mellitus (T2DM) is one of the most common chronic diseases in older adults. With advancing age, polypharmacy and protein-energy malnutrition associated with chronic diseases can be seen frequently in T2DM patients due to metabolic causes and may adversely affect the prognosis. In this study, it was aimed to evaluate the relationship between polypharmacy and malnutrition in T2DM patients.

Materials and Methods: Three hundred and twenty-one patients aged 65 years and over, diagnosed with T2DM and receiving oral anti-diabetic drug therapy, who applied to the Internal Medicine and Geriatrics outpatient clinic between February and November 2021, were included in the study. The data of the patients were obtained retrospectively from their medical files. The use of 5 or more drugs was considered as polypharmacy. Mini Nutritional Assessment-short form (MNA-SF) was used for nutritional status assessment.

Results: The median number of concomitant medications used in patients followed up with the diagnosis of T2DM was 5. Polypharmacy was found in 209 (65.1%) patients, and severe polypharmacy was found in 21 (6.5%) patients. Malnutrition was found in 43 (20.6%) patients with polypharmacy, while 17 (80.1%) of 21 patients with severe polypharmacy had malnutrition. A positive correlation was found between the number of drugs and HbA1c, and a negative correlation with the MNA-SF score (r=0.792, p<0.001, r=-0.317, p<0.001, respectively). According to the logistic regression analysis, the presence of HbA1c and polypharmacy were found to be effective factors in the development of malnutrition (p=0.009, p=0.002).

Conclusion: Current findings show that polypharmacy is quite common in elderly T2DM patients and often accompanies malnutrition. It is important to review the drugs used in each visit and to evaluate malnutrition that may be related to newly started or currently used drugs so that intertwined polypharmacy and malnutrition are not overlooked in elderly patients.

Keywords: Diabetes mellitus, polypharmacy, malnutrition, elderly patients

ÖZ

Amaç: Tip 2 diabetes mellitus (T2DM), yaşlı yetişkinlerde sık rastlanan kronik hastalıklardandır. İlerleyen yaşla birlikte kronik hastalıklarla ilişkili polifarmasi ve protein-enerji malnütrisyonu metabolik nedenlere bağlı olarak T2DM hastalarında sık görülebilir ve prognozu olumsuz etkileyebilir. Bu çalışmada T2DM hastalarında polifarmasi ve malnütrisyon ilişkisinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Şubat-Kasım 2021 tarihleri arasında İç Hastalıkları ve Geriatri Polikliniği'ne başvuran, 65 yaş ve üzeri T2DM tanısı olan ve oral anti-diyabetik ilaç tedavisi alan 321 hasta çalışmaya dahil edildi. Hastaların verileri tıbbi dosyalarından retrospektif olarak elde edildi. Beş ve üzeri ilaç kullanımı polifarmasi olarak kabul edildi. Beslenme durum değerlendirmesinde Mini Nutrisyonel değerlendirme- kısa form (MNA-SF) kullanıldı.

Bulgular: T2DM tanısı ile takip edilen hastalarda eşzamanlı kullanılan ilaçların medyan sayısı 5 idi. Hastaların 209'unda (%65,1) polifarmasi, 21'inde (%6,5) ise şiddetli polifarmasi saptandı. Polifarmasisi olan hastaların 43'ünde (%20,6) malnütrisyon saptanırken şiddetli polifarmasisi olan 21 hastanın 17'sinde (%80,1) malnütrisyon vardı. İlaç sayısı ile HbA1c arasında pozitif, MNA-SF puanı ile negatif korelasyon saptandı (sırasıyla r=0,792, p<0,001, r=-0,317, p<0,001). Yapılan lojistik regresyon analizine göre HbA1c ve polifarmasi varlığı malnutrisyon gelişiminde etkili faktörler olarak bulundu (p=0,009, p=0,002).

Sonuç: Mevcut bulgular yaşlı T2DM hastalarında polifarmasinin oldukça yaygın olduğunu ve sıklıkla malnütrisyona eşlik ettiğini göstermektedir. Yaşlı hastalarda birbiri ile iç içe geçmiş polifarmasi ve malnütrisyonun gözden kaçırılmaması için her vizitte kullanılan ilaçların gözden geçirilmesi, yeni başlanan veya kullanılmakta olan ilaçlarla ilişkili olabilecek malnütrisyonun değerlendirilmesi önemlidir.

Anahtar Kelimeler: Diabetes mellitus, polifarmasi, malnütrisyon, yaşlı hastalar

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is one of the most common chronic diseases among older adults due to aging and the gradual increase in life expectancy[1]. Elderly patients have multiple comorbidities such as hypertension, dyslipidemia, coronary heart disease and chronic kidney disease[2]. As the most important consequence of this, more than one drug is often needed to adequately and appropriately treat T2DM and associated comorbidities. Commonly, the "use of five or more drugs per day" is defined as polypharmacy[3]. Polypharmacy increases the risk of increased hypoglycemia, decreased medication adherence, drug-drug interactions, and higher hospitalization, mortality, and healthcare costs[4]. In these patients, individualized treatments should be applied to control/balance other comorbid conditions and/or complications besides T2DM and to minimize and/or prevent drug-related risks; therefore, it is a complex process[5]. Although non-pharmacological interventions for the management of T2DM and related comorbidities are an integral part of the treatment plan, pharmacotherapy actually remains the cornerstone of management.

Malnutrition is defined as "a nutritional state in which a lack of energy, protein and other nutrients causes measurable adverse effects on tissue and body form (body shape, size and composition) and function and clinical outcomes"[6]. With advancing age, especially protein-energy malnutrition is common, and it also causes personal, social and economic burden[7]. The number and scope of drugs used in the elderly, especially symptoms such as loss of appetite or constipation related to the drugs used, are the most important factors that directly or indirectly affect the risk of malnutrition through the development of tolerance/unwillingness for food in patients[8]. A positive correlation has been observed between polypharmacy and malnutrition in cross-sectional studies[9].

Many factors have been associated with malnutrition in older adults and the most notable of them in recent years is undoubtedly polypharmacy. Since the emergence of diseases that require pharmacological treatment is more common with aging, the prevalence of polypharmacy is likely to increase in advanced ages[10]. The relationship between malnutrition and polypharmacy is quite striking, especially in elderly T2DM patients using different drugs that affect appetite[11].

Therefore, in our study, we aimed to evaluate the frequency and relationship of polypharmacy and malnutrition in elderly T2DM patients who applied to the Internal Medicine and Geriatrics Outpatient Clinic.

MATERIALS AND METHODS

Participants of the Study

In this study, 321 patients aged 65 years and over, who applied to İnönü University Medical Center Internal Medicine and Geriatrics Polyclinic between February 2021 and November 2021, were diagnosed with T2DM and were using oral anti-diabetic (OAD) drug therapy, were included. The study was designed as a retrospective, cross-sectional study. The demographic (age, gender, comorbidities), anthropometric, clinical and laboratory data of the patients and the comprehensive geriatric examination test results performed at each patient visit were retrospectively scanned from the medical files of the patients and recorded in the forms. The files of 450 patients who applied to the outpatient clinic were evaluated. According to this evaluation, 129 patients who were not diagnosed with T2DM, were diagnosed with T2DM but received insulin therapy and could not complete comprehensive geriatric tests (due to neurological or psychiatric diseases) were excluded from the study. Body weight was measured in kilograms. Body mass index (BMI) was calculated with the formula of body weight/height^2 (kilogram/meter^2).

Comprehensive Geriatric Evaluation

Among the comprehensive geriatric assessment tests, the Katz Index of Independence in Activities of Daily Living, Lawton Instrumental Activities of Daily Living Scale (IADL), Mini-Mental State Examination (MMSE), Geriatric Depression Scale (short form consisting of 15 questions) (GDS) and the Mini Nutritional Assessment Short Form (MNA-SF) were used. The activities of daily living were evaluated with the Katz ADL. This index evaluates the functions of dressing, bathing, going to the toilet, getting out of bed, eating and urinary incontinence over 6 points[12]. Instrumental activities of daily living were evaluated using the Lawton IADL. In this scale, activities such as phone use, shopping, meal preparation, housework, laundry, urban transportation, and correct drug use are evaluated over eight points[13,14]. Cognitive functions were investigated by MMSE. Low scores obtained from this test, which is evaluated over

30 points, indicate deterioration in cognitive functions[15,16]. In the non-cognitive evaluation, the 15-item short form GDS of Yesevage was used[17]. Nutritional status was investigated with MNA-SF. Considering the Turkish validity and reliability of this test, 0-7 points indicate malnutrition, 8-11 points indicate malnutrition risk, and 12-14 points indicate normal nutrition[18].

Data on the number of drugs prescribed were recorded during the patient visit. Medications taken daily or at regular intervals were defined as regular use. Occasionally taken drugs were defined as drugs taken when needed and were not included in the number of drugs in the study. Polypharmacy status was defined as two subgroups. Severe polypharmacy was defined as the use of ten or more drugs, and polypharmacy was defined as the use of five to nine drugs[8].

Biochemical Measurements

Blood samples taken from the patients after at least 8 hours of fasting were taken into a 4 cc gel biochemistry tube and a hemogram tube containing 2 cc citrate. Fasting blood glucose, urea, creatinine, total protein, albumin, complete blood count, 25 hydroxy vitamin D (25-OH Vit D), C reactive protein and HbA1c levels were studied in these tubes.

Statistical Analysis

Statistical analyses were performed with SPSS for Windows version 22.0 (IBM SPSS Statistics, Armonk, NY). The distribution of normality was checked using the Shapiro-Wilk test. The Mann-Whitney U test was employed to compare two groups of independent variables that did not have normal distribution, the chi-square test was used to evaluate the relationship between categorical variables, and the Spearman's rank correlation coefficients were used to evaluate the relationship between numerical variables. In order to determine the independent predictors of malnutrition, first of all, linear regression analysis was performed to calculate the variance inflation factor, and the factors causing the multicollinearity problem were removed from the model, then multivariate logistic regression analysis was performed.

Ethical Principles

The study was approved by the Ethics Committee of Non-Interventional Clinical Researches of İnönü University with the date of 14.12.2021 and the decision number of 2021/2837. This study was carried out in accordance with the ethical standards of the Declaration of Helsinki. Volunteer participants were included in the study and their personal identity information was kept confidential. A voluntary consent form was obtained from each of the participants.

RESULTS

The demographic information of the patients is summarized in Table 1. A total of 321 patients, 105 of whom were male, were included in the study. The mean age of the patients was 71.66±6.17 years. The median number of concomitant medications used in patients followed up with the diagnosis of T2DM was 5 (IQR 2-12), and 209 (65.1%) of the participants had polypharmacy and 21 (6.5%) had severe polypharmacy (Table 1). The laboratory and comprehensive geriatric evaluation results of the groups with and without polypharmacy are shown in Table 2. Accordingly, 67.9% (n=147) of the patients with polypharmacy were women. Fasting blood glucose and HbA1c were found to be significantly higher in the polypharmacy group (Table 2).

Grouping according to the number of drugs used by the patients is shown in Table 2. Of 188 patients with polypharmacy (number of drugs 5-9), malnutrition was found in 22 (11.7%) and malnutrition risk was found in 65 (34.6%) patients. On the other hand, of 21 patients with severe polypharmacy, 17 (80.1%) had malnutrition and 4 (19.9%) had malnutrition risk.

Table 1. Socio-demographic characteristics of the patients	
Age (year)	**71.66±6.17**
	n (%)
Gender	
Male	105 (32.7%)
Female	216 (67.3%)
Educational status	
Illiterate	130 (40.8%)
Primary school	116 (36.4%)
Middle school	33 (10.3%)
High school	19 (6.0%)
University	21 (6.6%)
Marital status	
Married	218 (68.3%)
Single	24 (7.4%)
Widow	72 (22.6%)
Divorced	5 (1.6%)
With whom they live	
Alone	36 (11.2%)
With spouse	181 (56.4%)
With relatives	80 (24.9%)
With caregiver	21 (6.5%)
Aged care facility	3 (1.0%)
Number of drugs used	
1-4	112 (34.8%)
5-7	157 (48.8%)
8-9	31 (9.6%)
≥10	21 (6.5%)

Table 2. Laboratory findings and comprehensive geriatric evaluation results of the patients according to their polypharmacy status

	Polypharmacy		
	Yes (n=209)	No (n=112)	p
Female (%)	142 (44.2%)	74 (23.1%)	0.034*
Male (%)	67 (20.9%)	38 (11.8%)	0.020*
Waist circumference (cm)	106.52±7.92	101.14±6.68	0.448
BMI (kg/m²)	29.56±1.03	28.44±1.81	0.599
Number of drugs	6.62±0.14	3.61±0.05	<0.001*
Laboratory values			
Fasting blood glucose (mg/dL)	211.56±14.42	135.85±8.74	0.001*
Creatinine (mg/dL)	0.87±0.57	0.85±0.84	0.285
Uric acid (mg/dL)	5.92±0.33	5.98±0.81	0.941
Albumin (g/dL)	3.91±0.13	3.71±0.11	0.360
Hemoglobin (g/dL)	13.44±0.31	13.72±1.79	0.649
25 hydroxy vitamin D (ng/mL)	16.08±7.96	17.64±6.27	0.247
HbA1c (%)	8.11±0.44	5.98±0.23	<0.001*
C-reactive protein (mg/L)	3.74±0.70	3.75±1.24	0.653
ADL	4.98±1.93	5.03±1.80	0.258
IADL	6.27±2.04	6.63±1.91	0.056
MMSE	24.50±4.59	24.69±4.79	0.976
GDS	5.54±4.20	4.83±4.60	0.2670
MNA-SF	11.19±2.29	11.24±2.90	0.689
Comorbid diseases			
Hypertension	134 (64.1%)	60 (53.6%)	0.066
Coronary artery disease	89 (42.6%)	20 (17.9%)	<0.001*
Hyperlipidemia	74 (35.4%)	25 (22.3%)	<0.016*
Asthma/COPD	33 (15.8%)	11 (9.8%)	0.138
Dementia	17 (8.1%)	1 (0.9%)	0.007*

*p<0.05 statistically significant.

BMI: Body mass index, ADL: Katz index of independence in activities of daily living, IADL: Lawton instrumental activities of daily living scale, MMSE: Mini-mental state examination, GDS: Geriatric depression scale (short form consisting of 15 questions), MNA-SF: Mini Nutritional Assessment Short Form

Table 3. Evaluation of the groups according to the MNA-SF score

	Malnutrition (n=48)	Malnutrition risk (n=103)	Normal (n=170)	p
Age (year)	73.22±8.95	72.02±6.31	70.98±5.43	0.062
BMI (kg/m²)	24.09±6.12	26.22±5.22	27.54±5.83	0.035*
Waist circumference (cm)	92.96±15.15	96.17±10.57	100.70±12.46	0.013*
Albumin (g/dL)	3.55±0.67	3.58±0.34	3.65±0.47	0.397
Hemoglobin (g/dL)	14.58±0.65	14.93±0.62	14.67±0.67	0.415
C-reactive protein (mg/L)	1.65±1.79	1.49±1.69	1.60±1.58	0.614
HbA1c (%)	7.41±1.89	7.33±1.83	7.21±2.01	0.780
Polypharmacy n (%)				
Yes	39 (81.3%)	69 (67.0%)	101 (59.4%)	0.017*
No	9 (18.7%)	34 (33.0%)	69 (40.6%)	

*p<0.05 statistically significant.

MNA-SF: Mini nutritional assessment short form, BMI: Body mass index

According to MNA-SF scores, patients were divided into three groups as normal, malnutrition risk and malnutrition. Accordingly, 48 (14.9%) patients were diagnosed with malnutrition, while 103 (32.1%) patients were considered to be at risk for malnutrition. Thirty-five (72.9%) of 48 patients with malnutrition and 73 (70.9%) of 103 patients with malnutrition risk were female. A statistically significant difference was found among the three groups in terms of the number of drugs used, BMI, and waist circumference (p<0.001, p<0.007, and p<0.013, respectively) (Table 3). The number of drugs in the malnutrition group was found to be significantly higher than the malnutrition risk group and the normal group (p<0.001, p<0.001, respectively).

The correlation of number of drugs and MNA-SF with age, BMI, HbA1c and albumin was analyzed. Accordingly, there was a positive correlation of HbA1c with the number of drugs and a negative correlation with the MNA-SF score (r=0.792, p<0.001, r=-0.317, p<0.001, respectively).

According to multivariate logistic regression analysis, HbA1c and polypharmacy were found to be independent variables in the development of malnutrition [p=0.009, Odds ratio (OR)=1.41, p=0.002, OR: 1.93, respectively].

DISCUSSION

In our study, we evaluated the relationship between polypharmacy and malnutrition in elderly patients followed up with the diagnosis of T2DM. In addition to the detection of polypharmacy in 209 patients, we found malnutrition in 48 patients and malnutrition risk in 103 patients. In 188 patients with polypharmacy (number of drugs 5-9), malnutrition was found in 22 (11.7%) and malnutrition risk was found in 65 (34.6%) patients. On the other hand, of 21 patients with severe polypharmacy, 17 (80.1%) had malnutrition and 4 (19.9%) had

Table 4. Analysis of independent risk factors affecting malnutrition		
Risk factors	OR (95% CI)	p
Age	1.03 (0.95-1.12)	0.453
Gender (female)	1.67 (0.58-4.83)	0.342
ADL	1.01 (0.98-1.03)	0.593
HbA1c	1.41 (1.09-1.92)	0.009*
Polypharmacy	1.93 (1.21-2.47)	0.002*
Hypertension	1.41 (0.42-4.74)	0.573
Hyperlipidemia	0.62 (0.22-1.75)	0.364
Coronary artery disease	0.62 (0.22-1.71)	0.355
Dementia	1.61 (0.42-6.22)	0.491
GDS	1.12 (0.98-1.28)	0.087

*p<0.05 statistically significant.

ADL: Katz Index of Independence in Activities of Daily Living, GDS: Geriatric Depression Scale (short form consisting of 15 questions), CI: Confidence interval, OR: Odds ratio

malnutrition risk. The BMI and waist circumference of the patients with malnutrition were significantly lower than the other patients, and the number of drugs used was significantly higher. There was a positive correlation between the number of drugs used by the patients and HbA1c, and a negative correlation with the MNA-SF score. In addition, HbA1c and polypharmacy were found to be independent factors in the development of malnutrition in elderly T2DM patients. Our study is the first in our country to evaluate polypharmacy and malnutrition in elderly patients with T2DM.

Both malnutrition and polypharmacy are phenomena that are frequently encountered and that significantly affect the quality of life and mortality rate, especially in older age groups. In addition to age-related physiological, pathological, and environmental changes, polypharmacy put older adults at risk for malnutrition. Apart from these changes, other factors include the increased prevalence of chronic medical conditions, decreased thirst and sense of taste (which may increase the risk of fluid and electrolyte imbalance), dry mouth, and lack of access to a nutritionally adequate diet due to disability or increased difficulty in consuming it[19]. Evaluations have shown an inverse relationship between increased drug use and nutritional status. Accordingly, at least half of the elderly who use 10 or more drugs have malnutrition or malnutrition risk[20]. In our study, we found the malnutrition rate to be 80.1% in patients with severe polypharmacy, which supports this. As increasing age is generally associated with a greater burden of disease, it is associated with increased and often overused medication. A cohort study emphasized that the most important social and health determinants affecting disease-related malnutrition are living alone, polypharmacy and dysphagia, and that these strategies should be focused on to improve patient care[21]. In a large cohort of more than 1300 participants, it was stated that 51% of older adults with T2DM, who participated in the study, were using five or more drugs, and malnutrition and malnutrition risk were twice higher in these patients. In the study, polypharmacy was found to be higher in patients with malnutrition or malnutrition risk[22]. The judgment that it is unclear which is a risk factor for the other, or whether interventions targeting either one will have a significant positive effect, is valid for this study. Another population-based cohort study involving more than 700 community-dwelling older adults in Spain found a statistically significant association between malnutrition or malnutrition risk and increased use of prescription drugs. Furthermore, of the five main predictors of malnutrition (lower BMI, depressive symptoms, frailty, poor self-assessment of health, and polypharmacy), polypharmacy was shown to be a strong predictor in malnutrition assessment for both men and women[23]. A systematic review revealed that severe polypharmacy was a statistically significant risk factor for malnutrition in older women, but not in older men[24]. In

our study, the number of drugs used was found to be higher in the group diagnosed with malnutrition. In addition, the entire group with severe polypharmacy was malnourished or at risk of malnutrition. Our study suggests that polypharmacy significantly increases the risk of malnutrition.

As the incidence of diseases requiring pharmacological treatment increases with aging, the prevalence of polypharmacy also increases[25]. It is known that it has the potential to adversely affect the nutritional status due to changes in taste, absorption of vitamins and minerals from the intestines, and changes in the metabolism associated with the drugs used[26]. The content of drug or drugs directly or indirectly affects the risk of malnutrition. In a study, using one or two drugs seems to be protective for the development of malnutrition when compared to not using drugs. The most plausible explanation for this situation is that those who use drugs alone are likely to use preventive drugs for their diagnosis, which can have a beneficial effect on health[27]. However, a positive relationship was observed between the use of multiple drugs and malnutrition. However, many of the findings on polypharmacy are difficult to compare because they are obtained from cross-sectional studies, and many studies do not differentiate between the levels of polypharmacy[24]. We reached similar findings in our study. The rate of malnutrition rate was associated with the number of drug used. Moreover, additional comorbid diseases were found to be higher in the polypharmacy group. Based on this, it can be suggested that the development of additional comorbid conditions affects the development of polypharmacy, and polypharmacy affects the development of malnutrition.

Treatment of T2DM requires prescribing multiple drugs for glycemic control, cardiovascular risk management, and management of common comorbidities. In conclusion, patients followed with the diagnosis of T2DM are at risk for polypharmacy and severe polypharmacy. According to studies, the estimated prevalence of polypharmacy among T2DM patients ranges from 57% to 99%[28-31]. In addition, polypharmacy in T2DM is associated with suboptimal glycemic control, which increases the risk of long-term complications of diabetes[32,33]. Similarly, in our study, while fasting blood glucose and HbA1c levels were found to be significantly higher in the polypharmacy group, there was a positive correlation between the number of drugs and HbA1c. Many studies investigating the prevalence or characteristics of polypharmacy have been performed in selected T2DM populations of older adults[34]. Noale et al.[22] evaluated more than 1300 elderly patients with the diagnosis of T2DM from 57 diabetes centers and found the frequency of polypharmacy to be 57.1%. Moreover, female patients with a BMI ≥30 kg/m^{2} were associated with polypharmacy in the study. In another study in which more than two thousand T2DM and T1DM patients were evaluated, the frequency of polypharmacy was found to be 56%. In addition, according to the results of

the logistic regression analysis, it has been reported that being over 40 years old, having poor or very poor self-perceived health status, the presence of five or more comorbidities, and a mean diabetes mellitus diagnosis of more than ten years are associated with polypharmacy[31]. Polypharmacy in elderly patients should be regularly evaluated at each visit, since it is one of the most common geriatric syndromes, especially in T2DM patients. Examination of drugs at regular intervals should be an absolute part of treatment in elderly patients with T2DM. After a comprehensive geriatric evaluation in the elderly, individual goals should be determined according to the guidelines and potential interactions and adverse reactions should be identified, although it is often not possible to reduce the number of drugs.

Study Limitations

Because the study was conducted in a tertiary health center, the patients who applied to the center may be composed of patients who require more uncontrolled forms of diabetes or more complex medical treatments, or these patients may experience more diabetes-related complications. All these reasons may cause an increase in the prevalence of polypharmacy in patients. The inclusion of only patients using OAD drugs in the study may mean more drug use for T2DM, which is tried to be controlled in these patients.

CONCLUSION

This study, as expected, is important in terms of showing that polypharmacy is common in elderly patients with T2DM and that it often accompanies malnutrition in the elderly. In addition, it underlines that intertwined polypharmacy and malnutrition should not be overlooked in elderly patients, and that malnutrition that may be associated with newly started or currently used drugs should be evaluated, as well as reviewing the drugs used in each visit.

Ethics

Authorship Contributions

Conflict of Interest: No conflict of interest was declared by the authors.

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