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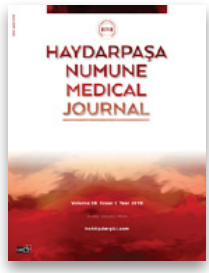

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ORIGINAL ARTICLE

Glycemic Control and Hypoglycemia Prevalence in Elderly Patients with Type 2 Diabetes Mellitus

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Abstract

Introduction: Optimal glycemic control is known to reduce the frequency of complications and mortality rates in elderly patients. The aim of this study is to evaluate the glycemic control and hypoglycemia frequency in elderly patients with type 2 diabetes mellitus (T2DM).

Methods: This single-center cross-sectional study was conducted in the endocrinology and metabolic diseases outpatient clinic. A total of 103 patients with T2DM older than 65 years without psychiatric disorders, end-stage renal disease, cancer and dementia were included in the study. The cognitive and functional status of the patients, their comorbidities and the anti-diabetic drugs they were using were evaluated, and the general health status of the patients (categorized simply as good, moderate, or poor) was determined according to the 2019 Endocrine Society guidelines. The patients were divided into 3 groups according to the HbA1c levels as; overtreated (HbA1c below target value, n=14), optimally controlled (those achieving HbA1c goals, n=36), and undertreated (HbA1c above target values, n=53). Demographic characteristics, frequency of hypoglycemia, antihyperglycemic therapies they used and complications were compared between the groups.

Results: According to glycemic targets, 13.6% of the patients were overtreated, 35% were optimally treated, and 51.4% were undertreated. Diabetic retinopathy was higher and glomerular filtration rate was lower in the overtreated patient group ($p<0.05$). It has been shown that 39.8% of the patients had a hypoglycemic event in the last 4 weeks. Hypoglycemia was more common in patients with diabetic retinopathy ($p<0.01$). Although it was not statistically significant, half of the patients who had hypoglycemia were in the undertreatment group.

Discussion and Conclusion: Treatment should be tailored in each visit according to comorbidities, complications, life expectancy, and neurocognitive status of the patients in order to minimize both hypoglycemia and hyperglycemia.

Keywords: Elderly; diabetes mellitus; hypoglycemia; overtreatment; undertreatment; glycemic control.

Diabetes mellitus is one of the most important chronic illnesses worldwide. Its prevalence shows an increase with age. According to TURDEP-II trial, diabetes prevalence was 34.7% in elderly population[1]. Since life expectancy is increasing and the world population is getting older, diabetes prevalence among elderly people is predicted to be higher in the future[2].

Frailty, longer duration of diabetes, polypharmacy, alterations in physiological responses and comorbidities make elderly patients more vulnerable to complications of both hyperglycemia and hypoglycemia[3]. Tight glycemic control and strict HbA1c targets were recommended in the past, but studies showed increased rates of hypoglycemia secondary to intensive treatment with little benefits[4,5].

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Hypoglycemia can lead to cognitive impairment, decrease in quality of life, falls, fall related fractures, seizures and increase cardiovascular disease risk[6-8]. Therefore, an optimal glycemic control is essential to minimize all these risks of morbidity and mortality. Current guidelines recommend individualization of glycemic targets based on functional status, comorbidities, non-diabetes chronic illnesses, and life expectancy[9,10].

The aim of this study is to evaluate the achievement of glycemic control according to current guidelines and detect the frequency of hypoglycemia in elderly patients. We also aimed to define contributing factors which facilitates development of hypoglycemia in this patient group.

Materials and Methods

The present study was an observational cross-sectional one, conducted in endocrine outpatient clinic in Haydarpaşa Numune Training and Research Hospital. We evaluated all the patients with type 2 Diabetes Mellitus (T2DM) older than 65 years-old from September 2020 to December 2020. Patients with type 1 diabetes mellitus, psychiatric disorders, end-stage renal disease, cancer and dementia were excluded from the study. One-hundred three patients were included in this study. The informed consent was obtained from all of the patients. Eligible patients were enrolled consecutively to minimize selection bias.

Age (years), sex, duration of diabetes, height and weight (measured with their underwear on), medications used, comorbid diseases, history of severe hypoglycemia requiring hospitalization for last 6 months and any hypoglycemia for last 4 weeks before admission were evaluated. Oral antidiabetic agents and their dosages, insulin usage and total insulin requirements (IR) were assessed. IR was calculated as U/kg/day (current weight).

Body mass index was calculated as the ratio of weight to the square of height (kg/m^2). Body-mass-index (BMI) categories were defined according to the World Health Organization (WHO): normal weight (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2), and obesity (BMI ≥30 kg/m^2).

Fasting blood glucose, creatinine, HbA1c, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, sodium and potassium levels were recorded. Estimated glomerular filtration rate (eGFR) was calculated by using MDRD formula.

Comorbidities, cognitive status and functional status [activities of daily living (ADL) such as bathing, dressing, eating, toileting, and transferring and instrumental ADL such as preparing meals, shopping, managing money, using the telephone, and managing medications] were evaluated to define patient's overall health status according to the 2019 Endocrine Society guideline criteria[10]. Overall health status was classified as follow: good (no comorbidities or ≤2 non- diabetes chronic illnesses, and no basic ADLs impairments and ≤1 instrumental ADL (IADL) impairment), intermediate (3 or more non-diabetes chronic illnesses, and/or any one of the following: mild cognitive impairment or early dementia or ≥2 IADL impairments), or poor (end-stage medical condition, moderate/severe dementia). In our study none of the patients were in poor health status. The HbA1c should be kept above the lower limit in patients who are receiving hypoglycemic agents (insulin, sulfonylureas (SU) or glinides). In patients with good health status, the HbA1c target range is <7.5% in the absence of hypoglycemic agents and 7.0–7.5%in presence of hypoglycemic treatment. In patients with intermediate health status, the HbA1c target range is <8.0% in the absence of hypoglycemic agents and 7.5–8.0% in the presence of hypoglycemic treatment.

Three groups were defined in light of the recommendations of the 2019 Endocrine Society guideline, named as overtreatment (HbA1c value lower than target range), optimal (HbA1c value in the patient's target range), and undertreatment (HbA1c value higher than the patient's target range). Lower limit of HbA1c has been established only for patients using hypoglycemic agents. Therefore, overtreatment group consisted of patients receiving hypoglycemic therapy. Hypoglycemia was defined based on patient reports of typical adrenergic symptoms of hypoglycemia, with a concomitant capillary glucose level of less than 70 mg/dL.

SPSS 20.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. In addition to descriptive statistical methods (mean, standard deviation) one-way ANOVA, The Pearson Chi-Square or Fisher's Exact tests were used to examine group differences. The results were expressed within a 95% confidence interval and $p<0.05$ level of significance.

Results

Mean age at the time of study was 71.7±4.9 years and 27.2% of the patients were more than 75 years old. 63.1% of the patients were female, 36.9% of the patients were male. The mean diabetes duration was 13.5±7.1 years. Hypertension, coronary heart disease, cerebrovascular disease, hyperlipidemia, and diabetic retinopathy were presented in 90%, 35%, 2.9%, 56%, and 47 % respectively. Considering overall health status of the patients 74 of the patients were clas-

sified as good (72%) and 29 as intermediate (28%). None of the patients was in poor health as we excluded patients with end-stage renal disease, cancer or dementia. According to glycemic targets; 14 (13.6%) were overtreated, 36 (35%) were optimally treated, and 53 (51.4%) were undertreated. Demographic and metabolic characteristic of patients were shown in Table 1.

The groups did not differ in age, gender, diabetes duration, BMI, overall health category, and hypoglycemia history. Diabetic retinopathy was found to be significantly higher in overtreatment group. Mean GFR was 59.6±21 mL/min/1.73 m^2 in overtreatment group which was significantly lower than the mean GFRs measured in other groups ($p<0.05$).

Overall 14 patients were using insulin without oral antidiabetic agents (OAD), 38 were using both OAD and insulin, and 51 of the patients were using only OAD treatment. Metformin (68%), dipeptidyl peptidase-4 (DPP-4) inhibitors (49%), sodium-glucose co-transporter 2 (SGLT-2) inhibitors (19%), and SU (13%) were the most frequently used OADs. 71.8% of the patients were using

Table 1. Demographic and metabolic characteristics of patients

Variable	All Mean±SD or n (%)	Over-treatment n=14 (13.6%)	Optimal treatment n=36 (35%)	Under-treatment n=53 (51.4%)	p
Age (years)	71.7±4.9	73.5±5.0	70.8±4.4	71.8±5.1	
<75 years	75 (72.8)	8 (57.1)	27 (75)	40 (75.5)	NS
≥75 years	28 (27.2)	6 (42.9)	9 (25)	13 (24.5)	
Gender					
Female	65 (63.1)	9 (64.3)	24 (66.7)	32 (60.4)	NS
Male	38 (36.9)	5 (35.7)	12 (33.3)	21 (39.6)	
BMI (kg/m^2)	28.7±4.5	27.1±5.3	28.6±4.4	29.3±4.4	
Normal	22 (21.4)	5 (35.7)	10 (27.8)	7 (13.2)	NS
Overweight	49 (47.6)	6 (42.9)	16 (44.4)	27 (50.9)	
Obesity	32 (31)	3 (21.4)	10 (27.8)	19 (35.8)	
DM duration (years)	13.5±7.1	16.2±7	11.6±6	14±7	NS
Health category					
Good Health	74 (72)	9 (64.3)	27 (75)	38 (71.7)	NS
Intermediate Health	29 (28)	5 (35.7)	9 (25)	15 (28.3)	
Diabetic retinopathy	49 (47.6)	9 (64.2)	11 (30.1)	29 (54.7)	<0.05
Hypoglycemia in last 4 weeks	41 (39.8)	7 (17.1)	13 (31.7)	21 (51.2)	NS
Hypoglycemic agent [a] usage	61 (59.2)	14 (100)	6 (16.7)	41 (77.4)	<0.01
Drug combination OAD only	51 (49.5)	2	33	16	
Insulin only	14 (13.6)	4	2	8	NS
OAD + insulin	38 (36.8)	8	1	29	
Glucose (mg/dL)	149±43	134±38	129±27	165±46	NS
HbA1c (%)	7.8±1.4	6.79±0.4	6.69±0.71	8.9±1.1	
<6.5	18 (17)	2 (14)	16 (44)	-	
6.5-6.9	20 (19)	11(79)	9 (25)	-	<0.01
7-7.9	22 (21)	1 (7)	10 (28)	11 (21)	
8-8.9	20 (19)	-	1 (3)	19 (36)	
≥9	23 (22)	-	-	23 (43)	
Creatinine (µmol/L)	1.02±0.3	1.14±0.4	0.94±0.2	1.04±0.3	NS
GFR (ml/min)	70.2±21	59.6±21	75.9±22	69.1±19	<0.05
HDL cholesterol (mg/dl)	48.5±13	45±13	49±13	48±13	NS
LDL cholesterol (mg/dl)	114±39	114±47	121±42	110±35	NS
Triglycerides (mg/dl)	151±72	164±83	137±62	158±75	NS

Data presented as mean±standard deviation or n (%); [a] Hypoglycemic agents include insulin, sulfonylureas and glinides; BMI: Body mass index; DM: Diabetes Mellitus; GFR: Glomerular filtration rate; HbA1c Glycated hemoglobin; HDL: High-density lipoprotein; LDL: Low-density lipoprotein cholesterol; NS: Not significant; OAD: oral antidiabetic drugs; SD: Standard deviation.

1-2 OADs, 14.5% were using 3-4 OADs. Metformin plus DPP-4 inhibitors were the most frequently used combination. Within the treatment regimens of patients in the overtreatment, optimal treatment and undertreatment groups, metformin was used by 57.1%, 86.1%, and 58.5%, respectively (p<0.01); SU by 28.6%, 8.3%, and 13.2%, respectively (p>0.05); DPP-4 inhibitors by 50%, 36.1%, and 58.5%, respectively (p<0.05); pioglitazone by 0%, 0%, and 3.8%, respectively (p >0.05); SGLT-2 inhibitors by 7.1%, 8.3%, and 30.2%, respectively (p <0.05); basal insulin by 71.4%, 8.3% and 56.6%, respectively (p<0.01); bolus insulin 42.9%, 5.6%, and 28.3%, respectively (p<0.05). Fifty two (50.5%) patients were using insulin and mean IR was 0.53±0.4 U/kg/day (range 0.1-1.5). When we evaluate the drug regimens in the overtreatment group; two of them were on metformin and SU treatment, 4 of them were on basal insulin plus OADs, and 8 of them were using basal-bolus insulin regimen.

Forty-one (39.8%) of the patients had hypoglycemia in last 4 weeks. Patients with retinopathy were more prone to hypoglycemia (p<0.01). No difference was detected in terms of age, diabetes duration, BMI, type of hypoglycemic agent used, and GFR between patients with or without hypoglycemia. Although it did not reach statistical significance, insulin treatment duration and IR were higher in patients with hypoglycemia history (5.3 vs 7.9 years, and 0.4 vs 0.6 U/kg, respectively).

Two of the patients reported to have hypoglycemia requiring hospitalization in last 6 months. These two patients' HbA1c levels were 11 and 7.7%, and they both had G3b chronic kidney disease (GFR 41 and 34 mL/min/1.73 m^2). They were on basal insulin plus OAD treatment. Lipid profiles of the groups were similar. LDL cholesterol was higher than 100 mg/dL in 64%, less than 70 mg/dL in 9.7%, and less than 55 mg/dL in only 2.9% of the patients. Triglyceride levels were less than 150 mg/dL in 59% of the patients. These levels did not differ between groups.

Discussion

To our knowledge, this is the first study in Turkey evaluating the prevalence of overtreatment in elderly diabetic patients according to the 2019 Endocrine Society guideline[10]. We also analyzed the hypoglycemic event for last month before admission. We found that only 1 in every 3 patients was at optimal treatment range. Whereas 13% of the patients had lower HbA1c levels than target range (overtreatment group) but still treated with hypoglycemic agents, mostly insulin. Overtreatment rates reported between 10-66 percent in different studies in the literature. This wide range may be related to different HbA1c levels used as a definition of overtreatment in the literature. In some of the studies patients with HbA1c <7%, in some <6.5% plus use of OAD or insulin were defined as overtreatment[11-13]. Similar to our study, Christiaens et al.[14] also used Endocrine society guideline criteria for defining overtreatment, and found that 52% of the patients were overtreated. Higher rate of overtreatment may be due to inclusion of patients older than 75 years with intermediate and poor health in geriatric ward. None of the patients were in poor health in our study, as we included patients from out-patients clinics, and also we excluded patients with end- stage diseases and dementia as we evaluated hypoglycemia retrospectively. Lower GFR and more diabetic retinopathy seen in overtreatment group may relate to older age and longer diabetes duration.

On the other hand, we detected that half of the elderly patients had HbA1c value higher than the patient's established target range. Although there was a tendency of higher BMI in undertreatment group, this finding did not reach to become statistically significant. Body mass index of patients was higher in current study from reported levels in Thailand and France[11, 13], but lower than a study in Turkey[12]. Sonmez et al.[12] reported undertreatment in 14% of elderly patients and also stated that undertreatment was associated with age over 75 years and the presence of microvascular complications. were independently associated with glycemia undertreatment. Undertreatment rates in our study seems to be higher from this study but their HbA1c cut off values for undertreatment was defined higher than the cut off values in our study (HbA1c more than 9). In our study 22% of patients had HbA1c>9. Undertreatment may be secondary to noncompliance to diet and treatment, or comorbidities in these patients. Moreover, this study was conducted during Covid-19 pandemic. During this period, accessing and receiving health care, obtaining their drugs and maintenance of healthy lifestyle for patients have been affected negatively. Unfortunately, this pandemic will last for an unknown period. For this reason, we should pay attention to strategies including education, glucose monitoring, adjustment of diet and medications, encouraging the patients for compliance to therapy, reducing polypharmacy, and use of telemedicine if possible.

Nearly 40% of the patients experienced hypoglycemia in last 1 month. Half of the patients in undertreatment group had hypoglycemia. Both of these findings are concordant with the literature[12,15]. Pathak et al.[16] found

that the rates of severe hypoglycemia were higher in patients with chronic kidney disease, higher A1c levels, and in users of insulin, SU. Efforts to reduce HbA1c rigorously, more comorbidities, longer diabetes duration, sarcopenia, and polypharmacy may contribute to risk of hypoglycemia. High hypoglycemia rate in undertreatment group also pointed for high glycemic variability in these patients which puts them to high risk for complications[17]. Use of continuous glucose monitoring systems may help us to determine hypo- and hyperglycemic periods and managing treatment modifications more accurately. Lower weight and sarcopenia may increase risk of hypoglycemia[18], but in our study weight was not associated with hypoglycemia. In elderly patients, insulin use, sulfonylurea use, renal disease, and a prior hospitalization for hypoglycemia events were associated with hospitalization[19]. Similarly, two hospitalized patients in our study were on insulin treatment and had renal disease.

Our study has some limitations. This is a cross-sectional study, prospective follow-up studies would clarify the reasons for over- or undertreatment, and hypoglycemia more clearly. We could not perform any tests for cognitive dysfunction, although periodic cognitive screening is recommended in elderly patients with diabetes to identify possible cognitive decline. Patients with poor health status were not included in the study, so that these data cannot be generalized to the elderly population.

Conclusion

Diabetes management in elderly patients relay on multiple factors, notsolely on HbA1c values. We concluded that both over- and undertreatment is high in our study group. Moreover, high rates of hypoglycemia seen in all groups led us to see the picture as a whole. Treatment should be tailored in each visit according to comorbidities, complications, life expectancy, neurocognitive status of the patients in order to minimize both hypoglycemia and hyperglycemia.

Ethical Committee Approval: Haydarpaşa Numune Training and Research Hospital Chief Physician approved. No: 2020/221.

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