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OVERTREATMENT AND HYPOGLYCEMIA PREVALENCE IN GERIATRIC PATIENTS WITH TYPE-2 DIABETES IN THE TURKISH POPULATION

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Abstract

Objective. To determine the prevalence of over-treatment and hypoglycemia in Turkish type-2 diabetes patients and to identify the risk factors.

Methods. Patients ≥ 65 years, having a minimum 5 years of type-2 diabetes, were included in the study. Patients' body mass index, mean HbA1c level, disease onset and medications related with their co-morbidities were recorded. Over-treatment is defined as the use of non-metformin therapies despite having HbA1c levels < 7%. A history of hypoglycemia episodes in the last three months and patients' home blood glucose measurements were recorded. Factors relating to hypoglycemia and over-treatment were analyzed.

Results. After applying criteria, 755 patients were included in the study: 728 patients (96.4%) had at least one comorbidity. 257 patients (34%) were found to have HbA1c levels < 7%. 217 of them (84.4%) were using non-metformin therapies. 497 patients (65.8%) were using insulin. The over-treatment prevalence in the ≥ 65 years group was 28.7%. The over-treatment ratio in ≥ 80 years group was 28.2%. Hypoglycemia prevalence in the last three months was 23.3%. It was 22.7% for patients ≥ 80 years. Mean age, disease duration, body mass index, insulin usage and doses were found to be significantly different in over-treated patients compared to the others.

Conclusions. This study showed that despite recent guidelines, there is still a considerable amount of over-treated geriatric patients who are at risk of hypoglycemia and related morbidity and mortality. Insulinization rate was high. Physicians should not avoid de-intensifying the treatment of geriatric patients who have multiple co-morbidities.

Key words: diabetes, epidemiology, hypoglycemia, over-treatment, Turkey.

INTRODUCTION

Diabetes prevalence is on the increase and by 2030, an estimated 350 million people will have type-2 diabetes worldwide (1). Tight glycemic control may benefit some patients. However, older persons, particularly those with complex medical problems, may benefit less or even be harmed by intensive treatment to lower glucose levels (2-5). The elderly are also more susceptible to hypoglycemia and its consequences than younger healthier persons (6, 7).

Three consecutive studies showed that tight glycemic control (HbA1c<7%) had no effect on decreasing microvascular complications (8-10). The ACCORD study also recorded an increase in cardiovascular and all-cause mortality risk caused by tight glycemic control (8). As a result, higher HbA1c level targets were recommended in elderly patients (11). The American Diabetes Association (ADA) has published a framework for the treatment of glycemia, with HbA1c targets in the range of < 7.5% to < 8.5% (12). In addition, the American Geriatrics Society (AGS) has updated their guidelines for improvement in the care of the elderly who have diabetes. They recommend that a treatment other than metformin should be avoided when treating elderly patients who have HbA1c of <7.5% (13).

Despite this information, we still frequently observe over-treatment in older patients with multiple serious co-morbidities. As far as we know, there are no studies investigating over-treatment and hypoglycemia in Turkey. The aim of this study is to determine the prevalence of over-treatment and hypoglycemia in elderly type 2 diabetes patients and to identify related factors. With these results, we aim to raise awareness and to contribute to changing customary treatment strategies in Turkey.

MATERIALS AND METHODS

The study was designed as a retrospective, descriptive, epidemiological study. It was approved by

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the Local Ethics Committee at the University of Health Sciences "Dr. Lütfi" Kırdar Kartal Training and Research Hospital. It was carried out over 7 months between June 2018 and January 2019. Approval number: 2018/514/127/7. Patients who were regularly admitted to our diabetes center were retrospectively analyzed.

Inclusion Criteria

- Being ≥ 65 years
- Having type 2 diabetes
- Having a minimum of 5 years disease duration
- Having perfect attendance in routine controls in the last two years

Exclusion Criteria

- Having type 1 diabetes
- Having malignancies
- Skipping routine controls

Data Collection

Patients' age, body mass index (BMI), disease onset, co-morbidities (hypertension, hyperlipidemia, coronary heart disease, stroke, thyroid disease, renal failure, chronic obstructive pulmonary disease), HbA1c levels at the last visit, types of oral antidiabetic drugs (OAD), types of insulins and doses, other medications relating to their co-morbidities were recorded. A history of hypoglycemia episodes in the last three months and home blood glucose measurements were also recorded.

Hypoglycemia was defined as a combination of experiencing Whipple's triad (symptoms of hypoglycemia, low circulating glucose and relief of symptoms instantly after taking glucose) additional to patients' at home self-measurements below 54 mg/dL, which is recommended by The International Hypoglycemia Study Group (14).

Over-treatment was defined as having HbA1c levels under 7% together with using insulin or oral antidiabetic medications other than metformin. Patients with HbA1c levels under 6% are defined as hyper-overtreated.

Patients' ages, gender, body mass index, duration of disease, glomerular filtration rate (GFR), types of oral antidiabetic treatments, types and doses of insulins and their relationship to hypoglycemia and over-treatment results were was analyzed.

Statistical Analyses

Statistical analyses were performed using PASW Statistics 18.0 software. Frequency distributions and percentages were calculated. T-test and chi-square tests were performed. Results were considered to be statistically significant at the level of $p<0.05$.

RESULTS

We retrospectively analyzed 1294 patient files: 297 patients were excluded due to non attendance of routine visits in the last two years; 26 patients were excluded due to malignancy; 39 patients were excluded because of having type-1 diabetes; 177 patients were excluded as a result of missing data in their files.

In total, 755 patients were included in the study: 458 F and 297 M, with mean age of 70.9±5.9 years. Patients' demographical characteristics are shown in Table 1.

Among 755 patients, 728 patients (96.4%) had one or more co-morbidities. The most common co-morbidities were hypertension (86.6%), hyperlipidemia (60%), coronary heart disease (39.6%) and renal impairment (23.8%).

A number of 641 patients (84.9%) were using oral antidiabetic medications; 258 patients (34.2%) were using OAD only, whereas 383 patients (50.7%) were using OAD combined with any type of insulin. The distribution of the use of oral antidiabetic agents is shown in Table 2.

Insulin was used in 497 patients (65.8%); 114 patients (15.1%) were using insulin alone, whereas 383 patients (50.7%) were using insulin with any type of OAD. The distribution of the use of insulin types is shown in Table 3.

Due to their co-morbidities, 700 patients (92.7%) were using additional medications. The distribution of additional drug types is shown in Table 4.

Table 1. Demographic characteristics of patients

	MALES	FEMALES	p values
Age (y)	70.7±5.6	71.1±6.1	0.490
Height (cm)	166.1±13.4	153.6±8.5	**0.001**
Weight (kg)	82.1±11.9	79.6±13.8	**0.007**
Disease onset (y)	18.3±8.5	18.7±9.1	0.508
HbA1c (%)	7.8±1.6	7.6±1.4	0.022

Table 2. Distribution of oral antidiabetic agents

AGENTS	n, (%)
Metformin	589, (91.9)
Sulfonylurea	127, (19.8)
Glinide	24, (3.7)
Pioglitazone	5, (0.8)
Acarbose	35, (5.4)
GLP-1 a	7, (1.1)
DPP4 i	257, (40.1)
SGLT2 i	20, (3.1)

Table 3. Distribution of using insulin types

INSULIN TYPE	n, (%)	Mean Dosage (IU)
Short acting	144, (28.9)	35.4±15.8
Basal	339, (68.2)	32.5±17.1
Mix	158, (31.8)	48.5±19.3

Table 5. Hypoglycemia and overtreatment data

Findings	≥65 Years	≥80 years
Hypoglycemia in last 3 months	23.3%	22.7%
Overtreatment prevalence	28.7%	28.2%
Hyper-overtreatment prevalence	5.6%	8.7%

Hypoglycemia and Over-treatment Data

Hypoglycemia prevalence was 22.7% for patients ≥ 80 years. 176 patients (23.3%) were found to have experienced hypoglycemia in the last three months.

257 patients (34%) were found to have HbA1c levels under 7%. 217 of them (84.4%) were using at least one non-metformin therapies. Over-treatment ratio in the ≥ 65 years group was 28.7%. Hypoglycemia-overtreatment ratio in the ≥ 65 years group was 5.6%. Over-treatment ratio in the ≥ 80 years group was 28.2%. Hypo-overtreatment ratio in the ≥ 80 years group was 8.7%. The findings are summarized in Table 5.

The mean age of over-treated patients was 71.6±6.1 whereas the mean age of the others was 70.3±5.4 and it was significantly higher in the over-treatment group (p=0.01). There was no difference between the mean age of the patients who had experienced hypoglycemia and those who had not (71.2±6.3, 70.9±5.8, p=0.501). Gender had no effect on over-treatment or the experience of hypoglycemia (p=0.190, p=0.547 respectively).

The mean disease duration was 16.5±9.0 years in over-treated patients whilst it was 18.8±8.9 years in other patients. There is a significant difference in mean disease duration between the two groups (p=0.003). Mean disease duration in those who had experienced hypoglycemia was 20.3±8.8 and it was 17.9±8.5 in those who had not. The difference between the two groups is significant (p=0.002).

Table 4. Additional medications list

MEDICATIONS	n, (%)
ACE Inhibitors	287, (41)
ARB	298, (42.6)
Thiazide diuretics	238, (34)
Furosemide	26, (3.7)
Spironolactone	11, (1.6)
Ca Channel Blockers	240, (34.3)
Beta Blockers	252, (36)
Alpha Blockers	28, (4)
Statins	415, (59.3)
Fibrates	42, (6)
Antiaggregants	401, (57.3)
Alpha Lipoic Acid	30, (4.3)
Pregabalin/Gabapentin	30, (4.3)
Proton Pump Inhibitors	79, (11.3)
Levothyroxine	100, (14.3)

In general 23.8% of all patients had GFR<60 mL/min/1.73m^2. The mean glomerular filtration rate was 70.6±23.6 mL/min/1.73m^2 in over-treated patients whereas it was 71.3±21.8 mL/min/1.73m^2 in others. There is no statistical difference between the two groups (p=0.704). The difference is also not significant in patients who had experienced hypoglycemia or those who had not (p=0.345).

The mean BMI was 32.7±5.4 kg/m^2 in patients with HbA1c levels ≥7 whilst the mean BMI was 30.4±4.9 in patients with Hba1c levels <7. It was significantly lower in over-treated patients (p<0.001). However, the mean BMI did not differ in patients who had experienced hypoglycemia and those who had not (31.9±5.3 kg/m^2, 32.3±5.8 kg/m^2 respectively, p=0.338).

The mean HbA1c levels were significantly higher in insulin users (p<0.001). Insulin usage except basal insulin was found to be very significantly associated with the experience of hypoglycemia (p<0.001). Only basal insulin usage was not statistically different between patients who had experienced hypoglycemia and those who had not (p=0.34). Total insulin dosage was found to be significantly higher in patients who had experienced hypoglycemia. The mean insulin dose was found to be 41.6 IU in patients who experienced hypoglycemia whilst it was found to be 28.3 IU in other patients (p<0.001).

Factors and their relationship to over-treatment and hypoglycemia are summarized in Table 6. The relationship between the types of oral antidiabetic medications and over-treatment is shown in Table 7. Only the use of glinide, DPP4i and SGLT2i were found to be significantly higher in the high HbA1c (≥7) group.

Table 6. Factors and their relationship with overtreatment and hypoglycemia

	Hba1c <7%	Hba1c ≥7%	p	Hypoglycemia +	Hypoglycemia -	p
Female/male	1.3	1.6	0.190	1.7	1.5	0.547
Mean age (years)	71.6±6.1	70.3±5.4	**0.01**	71.2±6.3	70.9±5.8	0.501
Disease duration (y)	16.5±9.0	18.8±8.9	**0.003**	20.3±8.8	17.9±8.5	**0.002**
GFR (mL/min/1.73m^2)	70.6±23.6	71.4±21.8	0.704	69.6±22.1	71.5±22.5	0.345
BMI (kg/m^2)	30.4±4.9	32.7±5.4	**0.001**	31.9±5.3	32.3±5.8	0.338
Insulinization rate	47.6%	77.9%	**0.001**	77.3%	62.2%	**0.001**
Mean insulin dosage (U/day)	16.9±24.4	38.6±31.7	**0.001**	41.6±33.5	28.3±30.9	**0.001**

Table 7. Oral antidiabetic agents usage rate in two groups

OAD	HbA1c < 7%	HbA1c ≥ 7%	P	Hypoglycemia (-)	Hypoglycemia (+)	p
Metformin	78.1%	77.4%	0.863	78.3%	76.7%	0.651
Sulphonylurea	20.9%	16.2%	0.153	16.6%	17.0%	0.892
Glinide	**1.0%**	**5.2%**	**0.013**	**2.3%**	**6.3%**	**0.009**
Pioglitazone	1.0%	0.5%	0.370	0.7%	0.6%	0.664
Acarbose	4.7%	3.8%	0,602	4.0%	6.8%	0.124
Glp1a	0.5%	1.2%	0.392	1.2%	0%	0.140
Dpp4i	**24.6%**	**38.6%**	**0.001**	35.3%	29.0%	0.120
Sglt2i	**1.0%**	**4.0%**	**0.048**	2.4%	3.4%	0.489

The relationship between OAD type and hypoglycemia is shown in Table 7. Only glinide was found to be associated with hypoglycemia.

DISCUSSION

This study showed the prevalence of over-treatment and hypoglycemia in one of the biggest diabetes centers in Turkey. Despite recent guidelines, 28.7% of patients ≥ 65 years and 28.2% of patients ≥ 80 years were found to be over-treated. 23.5% of patients were found to have experienced hypoglycemia in the past three months. This result is considerably high.

Among oral antidiabetics, metformin, DPP4 inhibitors and respectively sulfonylurea were the most preferred medications. Among insulins, the most preferred type was found to be basal insulin. The insulinization rate in diabetic geriatric patients (65.8%) is notably high.

The most common co-morbidities were hypertension, hyperlipidemia and coronary heart disease. Among additional medications, the most common used drugs were statins, antiaggregants, ACE inhibitors and ARB.

Over-treatment prevalence was considerable when compared to other studies (15-19). Lipska *et al.* reported that, among older adults with diabetes, 61.5% had an HbA1c level of less than 7% (3.8 million; 95% CI, 3.4–4.2). Among patients with A1c less than 7.0%, 54.9% were treated with either insulin or sulfonylureas. The study results unquestionably showed that many elderly patients with co-morbidities are given treatment with medications to lower their glucose levels. This may be representative of the wide scale usage of over-treatment (15). Another study reported that, of 42,669 individuals with type 2 diabetes mellitus aged 75 and older, 28.1% had diet-controlled diabetes, 37.2% had tight control (16). In KPNC data, of 9786 patients between ages of 70 and 79 years with a duration of diabetes mellitus longer than 10 years, 41% had an HbA1c below 7.0%. Although only 7% of these patients were not receiving any hypoglycemic medication, 61% of these patients were on a course of sulfonylurea and 39% were taking insulin (17). Studies from the Department of Veteran Affairs also indicate a high prevalence of potential over-treatment among adults with diabetes (18,19). In one study, the prevalence of potential over-treatment, defined as an HbA1c level of less than 7%, treatment with insulin or sulfonylurea medications, and coexisting risk factors for hypoglycemia (age ≥75 years; elevated creatinine level of ≥2 mg/dL; or cognitive impairment or dementia), was approximately 50% (19).

Since 2003, it has been generally accepted that the glycemic goals should be more flexible in elderly patients according to their life expectancy and co-morbidites (20). Research showed that older patients with multiple comorbid conditions and long standing diabetes with an HbA1c between 6.4% and 6.9% did not have improved macrovascular outcomes or clinically significant improved microvascular outcomes compared with those with an HbA1c of 7.3%

to 8.1%. Given this body of evidence, the physician mantra of "do no harm" would suggest that only a small percentage of patients older than 65 years should have an HbA1c below 7.0% and receive hypoglycemic medications. Similarly the TEMD guide in Turkey also suggests that the HbA1c targets in elderly diabetes patients whose health status is mild to moderately unhealthy should be maintained between 7.1%-8%. As for patients with a severely affected health status, a HbA1c level of 8.5% is satisfactory (21).

Results from an older study conducted by Dr Sussman *et al.*, showed that only one in four of almost 400,000 elderly patients with diabetes had their prescriptions altered after deintensification was indicated (22).

Similarly, another study showed that, despite greater availability of agents that do not typically cause hypoglycemia, insulin or insulin secretagogues continue to be used at high rates in elderly adults, even when HbA1c levels are low (23). Patients treated with sulphonylurea plus insulin, were shown to be at increased mortality risk when compared to metformin-insulin combination (24). A new study showed that in addition to other well-known agents, repaglinide may also be a good candidate for achieving glycemic controls without causing hypoglycemia, especially in patients with renal impairment (25).

Due to a lack of methodologically similar studies in literature, there are no studies available for comparison with our own. The most valuable study up until now concerning diabetes in Turkey is the TURDEP-2 study. According to that study, diabetes prevalence has increased to over 100% in the last ten years (26). Nevertheless, the over-treatment and hypoglycemia rates were not included in this study. According to authors from the Centers for Disease Control and Prevention, Budnitz *et al.*, showed that, in 2011, the second most common medication leading to the hospitalization of an elderly patient in the emergency department due to an adverse drug event was insulin, and the fourth most common medication was an oral hypoglycemic agent, (27). In the ACCORD study, 10% of the intervention group had hypoglycemic events that required medical assistance *vs.* 3% for the control group. 28% of the intervention group experienced weight gain of 10 kgs or more compared to 14% in the control group. An unexpectedly higher death rate was found in the intervention group of the ACCORD study and that hypoglycemic agents often lead to emergency hospitalizations in elderly patients, with hospitalizations frequently leading to lasting disability (8).

Limitations of the study

The main limitation of this study was that it was retrospective. Additionally, due to missing data some patients had to be excluded. Emergency department admissions as a result of hypoglycemia were not investigated in this study. The data concerning hypoglycemia was obtained from the patients in person themselves.

Strengths of the study

This is the first study conducted in Turkey which investigated over-treatment and hypoglycemia in the Turkish elderly population. Data was collected from one of the biggest diabetes centers in Istanbul/ Turkey. The study included a high number of diabetes cases. All patients had a calibrated self-monitoring blood glucose device.

In conclusion, the results of this study indicate a notable prevalence rate of over-treatment in Turkish elderly diabetes patients. Insulin and sulphonylurea treatments should be deintensified when needed and avoided in elderly patients with co-morbidities. Metformin and other agents which do not cause hypoglycemia should be preferred. It is expected that new molecules provide glycemic control without causing hypoglycemia. Wider prospective studies investigating the hypoglycemia and related complications more accurately are needed in order to further shed light on this area which currently lacks data.

Data availability. The dataset used to support the findings of this study are available from the corresponding author upon request.

Conflict of interest. The authors state that they have no conflict of interest.

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