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Satilmis Bilgin , Gulali Aktas , Ozge Kurtkulagi , Burcin M. Atak , Gizem Kahveci ,  
 Muhammed E. Demirkol , Tuba T. Duman   
 Abant Izzet Baysal University Hospital, Department of Internal Medicine, Bolu, Turkey

## Characteristics of the type 2 diabetic patients with hypoglycemia in a tertiary referral hospital

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**Abstract. Background.** Hypoglycemia is an important complication of the treatment of type 2 diabetes mellitus, which constitutes a barrier in stringent diabetic control. Beside it constitutes nearly 10 % of emergency department admissions that caused by adverse drug events, it may also increase morbidities and mortality by inducing, cardiac arrhythmias, neurological impairment and ischemic events. Hypoglycemia is the most common side effect of insulin treatment, however, oral antidiabetic agents may also induce hypoglycemic complications. In present retrospective study, we purposed to observe general characteristics and laboratory data of the type 2 diabetic patients whom presented with mild or moderate/severe hypoglycemia. **Materials and methods.** Patients with type 2 diabetes mellitus whom presented to our institution with hypoglycemia between January 2019 and January 2020 were retrospectively analyzed. General characteristics and laboratory data of the subjects recorded. Patients grouped into two groups, group I consisted of subjects with mild hypoglycemia and group II consisted of patients with moderate/severe hypoglycemia. Data of the subjects in groups I and II were compared. **Results.** There were 15 subjects in group I and 23 in group II. HbA1c and other laboratory markers were not significantly different in study groups. Similarly diabetes duration and anti-diabetic treatment were not significantly different in study groups. The rate of geriatric patients was significantly higher in group II compared to group I ( $p = 0.04$ ). **Conclusions.** Subjects with moderate/severe hypoglycemia tend to be more frequently in geriatric age and HbA1c not correlates with the degree of the hypoglycemia. Since neither duration of diabetes, nor anti-diabetic treatment were associated with the severity of the hypoglycemia, each case should be evaluated individually to prevent further episodes which could increase morbidity and mortality in diabetic population.

**Keywords:** hypoglycemia; type 2 diabetes mellitus; glycated hemoglobin

### Introduction

Hypoglycemia is an important barrier for tight glucose control during treatment of diabetic subjects since it is a severe and life threatening acute complication of anti-diabetic therapy [1]. Beside it constitutes nearly 10 % of emergency department admissions that caused by adverse drug events [2], it may also increase morbidities and mortality by inducing, cardiac arrhythmias, neurological impairment and ischemic events [3]. Hypoglycemia is the most common side effect of insulin treatment [4], however, oral antidiabetic agents may also induce hypoglycemic complications.

A plasma glucose level equal to or lower than 70 mg/dl is referred as hypoglycemia according to the suggestions of American Diabetes Association [5]. In a further classification, a plasma glucose level between 54 mg/dl and 70 mg/dl

is considered as mild, and lower than 54 mg/dl is considered as moderate hypoglycemia. Severe hypoglycemia is defined as significant cognitive impairment that requires external assistance for recovery. Hypoglycemia, whether mild, moderate or severe, may increase morbidity and mortality via excess sympathetic activation [6].

Symptoms of the hypoglycemia may include deterioration in mood and/or memory, being anxious and/or sweaty, feeling angry and hungry [1]. Neuroglycopenic symptoms may include fatigue, cognitive deterioration, irritability, visual failure, seizures and coma [7].

In present retrospective study, we aimed to observe general characteristics and laboratory data of the type 2 diabetic patients whom presented with mild or moderate/severe hypoglycemia.

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For correspondence: Gulali Aktas, M.D., Abant Izzet Baysal University Hospital, Department of Internal Medicine, 14280, Golkoy, Bolu, Turkey; e-mail: draliaktas@yahoo.com; contact phone: +903742534656, fax: +903742534615.

Full list of authors information is available at the end of the article.

## Materials and methods

### Study Design

After obtaining approval from local ethics committee (no: 2018/297), we retrospectively analyzed type 2 diabetic subjects whom presented to our institution with hypoglycemia between January 2019 and January 2020. Age, gender, duration of type 2 diabetes mellitus, duration of hospitalization due to hypoglycemia, symptoms on admission, presence of consciousness disturbance, treatment for type 2 diabetes mellitus, type of insulin therapy of the patients received insulin treatment were carefully recorded from patients' files and institutional database. Patients with hypoglycemia of other reasons (i.e., insulinoma, advanced cancer) were not included to the study.

Laboratory parameters, including fasting plasma glucose (FPG), serum creatinine, glomerular filtration rate (GFR), plasma sodium (Na), potassium (K), and chloride (Cl) levels, aspartate transaminase (AST), alanine transaminase (ALT), glycated hemoglobin (HbA1c), serum uric acid, white blood cell count (WBC), hemoglobin (Hb), platelet count (PLT), thyroid stimulating hormone (TSH), vitamin B<sub>12</sub>, C-reactive protein (CRP) levels were also recorded.

Patients divided into two groups according to the severity of hypoglycemia either as mild hypoglycemia group (group I) or moderate or severe hypoglycemia group (group II). Clinical and laboratory parameters of the groups compared.

### Statistical Analyses

Statistical analyses were held with SPSS software (SPSS 15.0 for Windows, IBM Co., Chicago, IL, USA). Distribution of the variables in study groups were analyzed with Kolmogorov-Smirnov test. Variables with normal distribution were compared with independent samples t test and expressed as mean  $\pm$  standard deviation. On the other hand, variables without normal distribution were compared with Mann Whitney U test and expressed as median (interquartile range — IQR). Categorical variables were compared with chi-square test.

## Results

There were 15 subjects in group I while there were 23 patients in group II. Median age of the groups I and II were 64 (18) and 72 (14) years, respectively. The age was not significantly different between groups I and II ( $p = 0.06$ ).

Six (40 %) of 15 subjects in group I and 13 (56.5 %) of 23 subjects in group II were women, while 9 (60 %) of 15 subjects in group I and 12 (43.5 %) of subjects in group II were men. Gender was not statistically different between groups I and II ( $p = 0.32$ ).

Plasma glucose on hospital admission of groups I and II were  $60 \pm 4$  mg/dL and  $35 \pm 10$  mg/dL, respectively ( $p < 0.001$ ). However, HbA1c of groups I ( $8.4 \pm 1.9$  %) and II ( $7.5 \pm 1.2$  %) were not statistically different ( $p = 0.19$ ). Similarly, duration of hospitalization of groups I (4 (3) days) and II (4 (2) days) were not statistically different ( $p = 0.91$ ).

Serum uric acid ( $p = 0.07$ ), serum creatinine ( $p = 0.41$ ), GFR ( $p = 0.96$ ), plasma Na ( $p = 0.19$ ), K ( $p = 0.26$ ), chloride ( $p = 0.48$ ), aspartate transaminase ( $p = 0.98$ ), alanine transaminase ( $p = 0.08$ ), TSH ( $p = 0.31$ ), ferritin ( $p = 0.68$ ),

vitamin B<sub>12</sub> ( $p = 0.98$ ), CRP ( $p = 0.46$ ), hemoglobin ( $p = 0.53$ ), WBC ( $p = 0.75$ ) and PLT ( $p = 0.71$ ) levels were not significantly different between groups I and II. General characteristics and laboratory data of the study population is shown in table 1.

Six (40 %) of 15 subjects in group I and 17 (74 %) of 23 subjects were geriatric patients who were older than 65 years of age ( $p = 0.04$ ). 2 (13.3 %) of 15 subjects in group I and 10 (43.5 %) subjects in group II had consciousness disturbance on admission ( $p = 0.051$ ). Six (40 %) of subjects in group I and 12 (52 %) of subjects in group II were on oral antidiabetic treatment, 4 (27 %) of subjects in group I and 6 (26 %) of subjects in group II were on insulin treatment, and 5 (33 %) of subjects in group I and 5 (22 %) of subjects in group II were on oral antidiabetic plus insulin treatment ( $p = 0.69$ ).

## Discussion

Hallmark results of the present study are as follows: (a) neither age, nor gender were associated with the severity of the hypoglycemia in type 2 diabetic patients, (b) neither the duration of the diabetes mellitus and the rate of consciousness disturbance on admission nor laboratory parameters including serum creatinine, GFR and even HbA1c were significantly different in mild hypoglycemia patients compared to moderate/severe hypoglycemia, and (c) despite age was not statistically different between study groups, patients over 65 years of age was more common in moderate/severe hypoglycemia group compared to the subjects with mild hypoglycemia.

About one to 3 of every 10 type 2 diabetic subjects that received insulin therapy develop severe hypoglycemia annually [8, 9]. Hypoglycemia is considered when plasma glucose level is lower than 70 mg/dL, which refers as mild hypoglycemia. Moderate hypoglycemia is defined as a plasma glucose lower than 54 mg/dL. There is no plasma glucose threshold for severe hypoglycemia which is defined as hypoglycemia with significant cognitive impairment that requires external assistance for recovery. Hypoglycemia increases the mortality in diabetic population. Mortality of every 4 to 10 subjects of for 100 diabetic patients is caused by hypoglycemia [10–12]. Causes of hypoglycemia are either insulin or oral antidiabetics; such as, sulfonylureas or glinides, in the treatment of T2DM [10, 13].

The HbA1c is considered as a marker of mean glycemia for last 3 months and higher levels of HbA1c are associated with chronic complications of the T2DM [14]. Despite a threshold of lower than 7 % for HbA1c is warranted for better metabolic control in T2DM [14], some other studies suggest individual targets of HbA1c in diabetic subjects [12, 15, 16]. This suggestion is a consequence of that hypoglycemia was the main limiting factor for targeting lower HbA1c values. Besides tight glycemic control improve HbA1c levels, it also increase the rate of hypoglycemia episodes. The lower HbA1c levels are associated with the higher risk of hypoglycemia [17]. In contrast, HbA1c levels of groups I and II in present study were not statistically different.

Hypoglycemia is more common in older type 2 diabetic subjects compared to their younger counterparts.

**Table 1. General characteristics and laboratory data of the study population**

| Parameter                       |              | Group I    | Group II   | p       |
|---------------------------------|--------------|------------|------------|---------|
| Gender                          | Women (n, %) | 6 (40)     | 13 (56.5)  | 0.32    |
|                                 | Men (n, %)   | 9 (60)     | 12 (43.5)  |         |
| <b>Mean ± SD</b>                |              |            |            |         |
| Plasma glucose (mg/dL)          |              | 60 ± 4     | 35 ± 10    | < 0.001 |
| HbA1c (%)                       |              | 8.4 ± 1.9  | 7.5 ± 1.2  | 0.19    |
| Uric acid (mg/dL)               |              | 5.3 ± 1.5  | 6.4 ± 1.9  | 0.07    |
| GFR (%)                         |              | 71 ± 31    | 71 ± 25    | 0.96    |
| Cl (mmol/L)                     |              | 106 ± 3    | 105 ± 6    | 0.48    |
| WBC (k/mm <sup>3</sup> )        |              | 8.6 ± 5.0  | 8.2 ± 2.9  | 0.75    |
| Hb (g/dL)                       |              | 12 ± 3     | 12 ± 2     | 0.53    |
| PLT (k/mm <sup>3</sup> )        |              | 243 ± 96   | 232 ± 93   | 0.71    |
| <b>Median (IQR)</b>             |              |            |            |         |
| Age (years)                     |              | 64 (18)    | 72 (14)    | 0.06    |
| Hospitalization duration (days) |              | 4 (3)      | 4 (2)      | 0.91    |
| Creatinine (mg/dL)              |              | 0.94 (0.5) | 0.99 (0.5) | 0.41    |
| AST (U/L)                       |              | 19 (11)    | 19 (10)    | 0.98    |
| ALT (U/L)                       |              | 17 (13)    | 12 (8)     | 0.08    |
| Ferritin (mcg/L)                |              | 81 (25)    | 78 (10)    | 0.68    |
| Vitamin B <sub>12</sub> (ng/L)  |              | 331 (145)  | 294 (190)  | 0.98    |
| TSH (mIU/mL)                    |              | 2.21 (2.4) | 1.4 (1.9)  | 0.31    |
| CRP (mg/L)                      |              | 4 (2.1)    | 6.5 (2.4)  | 0.46    |
| Na (mmol/L)                     |              | 138 (2)    | 136 (7)    | 0.19    |
| K (mmol/L)                      |              | 4.5 (0.7)  | 4.4 (1)    | 0.26    |

The risk of development of hypoglycemia is increased in elderly population mainly because of deteriorated adaptive mechanisms to decreased plasma glucose [18]. When blood glucose fall below 70 mg/dl in healthy individuals, a number of physiological mechanisms triggered to restore blood glucose up to none dangerous levels. These mechanisms include inhibition of insulin secretion and increased secretion of glucagon from pancreas, increased hepatic glycogenolysis and gluconeogenesis, increased adrenaline release from adrenal glands [18]. However, these mechanisms are deteriorated in diabetic subjects and even lost in elderly diabetics [19]. Counter regulatory mechanisms against hypoglycemia are even impaired in non-diabetic older adults [20]. This is primarily because of the altered metabolism of counter regulatory hormones, and possibly due to the changed metabolism of antidiabetic medications [19, 21]. In present study, the age of subjects with mild hypoglycemia was not different from the age of the subjects with moderate/severe hypoglycemia, however, the rate of the subjects over 65 years of age was higher in moderate/severe hypoglycemia group than that of the mild hypoglycemia group.

There are two main limitations of present study. First, retrospective design and second, maybe more important, small study population. Enhanced diabetic control in 21<sup>th</sup>

century clinics might reduce the hypoglycemic events, thus, caused decreased hospital admissions due to hypoglycemia. Nevertheless, present study provide significant information about hypoglycemic diabetics treated in a tertiary referral hospital.

## Conclusions

Subjects with moderate/severe hypoglycemia tend to be more frequently in geriatric age and HbA1c not correlates with the degree of the hypoglycemia. Since neither duration of diabetes, nor anti-diabetic treatment were associated with the severity of the hypoglycemia, each case should be evaluated individually to prevent further episodes which could increase morbidity and mortality in diabetic population.

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#### Information about authors

Satilmis Bilgin, MD, Abant Izzet Baysal University Hospital, Department of Internal Medicine, Bolu, Turkey; <https://orcid.org/0000-0003-2811-0052>.  
Gulali Aktas, MD, PhD, Ass.Prof., Abant Izzet Baysal University Hospital, Department of Internal Medicine, Bolu, Turkey; <https://orcid.org/0000-0001-7306-5233>.  
Ozge Kurtkulagi, MD, Abant Izzet Baysal University Hospital, Department of Internal Medicine, Bolu, Turkey; <https://orcid.org/0000-0002-4162-5563>.  
Burcin M. Atak, MD, Abant Izzet Baysal University Hospital, Department of Internal Medicine, Bolu, Turkey; <https://orcid.org/0000-0003-4201-9757>.  
Gizem Kahveci, MD, Abant Izzet Baysal University Hospital, Department of Internal Medicine, Bolu, Turkey; <https://orcid.org/0000-0002-7548-4228>.  
Muhammed E. Demirkol, MD, Abant Izzet Baysal University Hospital, Department of Internal Medicine, Bolu, Turkey; <https://orcid.org/0000-0001-6262-6103>.  
Tuba T. Duman, MD, Abant Izzet Baysal University Hospital, Department of Internal Medicine, Bolu, Turkey; <https://orcid.org/0000-0002-3991-5991>.

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Satilmis Bilgin, Gulali Aktas, Ozge Kurtkulagi, Burcin M. Atak, Gizem Kahveci, Muhammed E. Demirkol, Tuba T. Duman  
Abant Izzet Baysal University Hospital, Department of Internal Medicine, Bolu, Turkey

### Характеристика хворих на цукровий діабет 2-го типу з гіпоглікемією на третинному рівні стаціонарної допомоги

**Резюме. Актуальність.** Гіпоглікемія — важливе ускладнення при лікуванні цукрового діабету 2-го типу, що створює труднощі для досягнення контролю захворювання. Крім того, явища гіпоглікемії зумовлюють майже 10 % випадків госпі-

талізацій у відділення невідкладної допомоги, вони також збільшують захворюваність та смертність шляхом виникнення кардіологічних, неврологічних порушень тощо. Гіпоглікемія залишається найпоширенішим побічним ефектом ліку-

вання інсуліном, однак пероральні протидіабетичні засоби також можуть викликати гіпоглікемічні ускладнення. **Мета дослідження:** у даному ретроспективному дослідженні авторами наведена динаміка клінічних та лабораторних показників хворих на цукровий діабет 2-го типу, у яких спостерігалася гіпоглікемія легкого або середнього ступеня тяжкості. **Матеріали та методи.** Проведено ретроспективний аналіз пацієнтів із цукровим діабетом 2-го типу з явищами гіпоглікемії, які перебували на стаціонарному лікуванні упродовж періоду із січня 2019 року по січень 2020 року. Обстежені пацієнти були розподілені на дві групи. До першої групи увійшли пацієнти з легкою гіпоглікемією, до другої — пацієнти з помірною чи тяжкою гіпоглікемією. Наведено порівняльну характеристику осіб першої та другої груп. **Результати.** У першій групі було 15 хворих на ЦД 2-го типу, у другій — 23. Показники глі-

кованого гемоглобіну (HbA1c) та інші лабораторні маркери істотно не відрізнялися в досліджуваних групах. Аналогічно тривалість ЦД та антидіабетичне лікування істотно не відрізнялися в досліджуваних групах. Частка осіб старшої вікової групи була вірогідно вищою в другій групі порівняно з першою групою ( $p = 0,04$ ). **Висновки.** Пацієнти з помірною чи тяжкою гіпоглікемією належать до старшої вікової групи, а рівень HbA1c не корелює зі ступенем гіпоглікемії. Оскільки ані тривалість цукрового діабету, ані антидіабетичне лікування не були пов'язані з тяжкістю гіпоглікемії, кожен випадок слід оцінювати індивідуально, щоб запобігти подальшим епізодам, які можуть збільшити захворюваність та смертність у діабетичній популяції.

**Ключові слова:** гіпоглікемія; цукровий діабет 2-го типу; глікований гемоглобін