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Age, disease duration and multimorbidity as predictors of hypoglycemia in elderly women with type 2 diabetes mellitus

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Abstract

Aim – to study the correlations between age, disease duration, concomitant chronic non-infectious pathology and the risk of developing hypoglycemia in patients with type 2 diabetes mellitus (T2DM).

Material and methods. The study involved 90 elderly women (mean age 70.5 ± 6.2 years) with T2DM. The medical history of all study participants collected during the interviews was supported by the following analysis of their medical documentation. Additionally, we analyzed the results of clinical and biochemical blood tests and calculated the Charlson comorbidity index for all participants.

Results. The prevalence of hypoglycemia among patients with T2DM was: 47% in patients aged 65–74 years, and 75% in older patients (75–85 years). The significant correlation was found between the indicators "Patient's age" and "Presence of hypoglycemia" r = 0.2489 (p = 0.018). When calculating χ^2 (chi-square), the value obtained was $\chi 2$ = 5.513 (p = 0.018). One-way analysis of variance of these values resulted in F-ratio = 5.811 at the significance level p = 0.018, which confirmed a significant relationship between the two variables. The significant correlation was found for the indicators "Existing cases of hypoglycemia" and "Duration of diabetes mellitus" (r = 0.3512 with a significance level of p = 0.0007). The data allowed us to draw a conclusion about the statistical dependence of these values. The result of the χ^2 test for the trend was χ^2 (trend) = 10.982 (p = 0.0009). The data obtained might indicate the relationship between these variables. The correlation between the indicators "Existing cases of hypoglycemia" and "Charlson Comorbidity Index score" was confirmed by the value r = 0.4020 (p = 0.0001). The relationship between these variables was revealed by calculating χ^2 = 16.336 (p = 0.0059). Based on the χ^2 test for the trend, the value χ^2 (trend) = 14.544 (p = 0.0001) was obtained. One-way analysis of variance for these indicators presented F-ratio = 3.734 (p = 0.004).

Conclusion. The patient's age, duration of T2DM and multimorbidity were significantly associated with the risk of hypoglycemia in patients with T2DM.

Keywords: type 2 diabetes mellitus, hypoglycemia, risk factors of hypoglycemia, multimorbidity, Charlson Comorbidity Index, CCI, gerontology.

Conflict of interest: nothing to disclose.

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Abbreviations
DM – Diabetes Mellitus; T2DM – Type 2 Diabetes Mellitus; CVDs – cardiovascular diseases; CCI –Charlson Comorbidity Index; ESR – erythrocyte sedimentation rate; HDL – high-density lipoproteins; LDL – low-density lipoproteins; ALT – alanine aminotransferase; AST – aspartate aminotransferase.

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Возраст, длительность заболевания и полиморбидность как предикторы гипогликемии у женщин пожилого и старческого возраста с сахарным диабетом 2 типа

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Аннотация

Цель – изучить взаимосвязь возраста, длительности заболевания и сопутствующей хронической неинфекционной патологии с риском развития гипогликемии у женщин с сахарным диабетом 2 типа (СД2).

Материал и методы. В исследовании участвовали 90 пациенток пожилого и старческого возраста (средний возраст 70,5 ± 6,2 года) с СД2. У всех участников исследования собран анамнез заболевания, изучена медицинская документация. Исследованы показатели клинического анализа крови и биохимического анализа крови, а также вычислен индекс коморбидности Charlson.

Результаты. Распространенность гипогликемии среди пациенток с СД2 составила 47% у пожилых и 75% у пациенток старческого возраста. Индекс корреляции между показателями «возраст пациента» и «наличие случая гипогликемии» составил r = 0,2489 (p = 0,018), что свидетельствует о статистической зависимости данных величин. При вычислении χ^2 (хи-квадрат) получено значение χ^2 = 5,513 (p = 0,018). Однофакторный дисперсионный анализ данных величин демонстрирует результат F-отношения = 5,811 при уровне значимости (p = 0,018), что подтверждает значительную связь между двумя переменными. Был вычислен индекс корреляции по показателям «наличие случаев гипогликемии» и «стаж сахарного диабета» (r = 0,3512 при уровне значимости p = 0,0007). Данные позволяют сделать вывод о статистической зависимости данных величин. Результат теста χ^2 для тренда получено значение χ^2 (тренд) = 10,982 (p = 0,0009). Приведенные данные свидетельствуют о взаимосвязи данных переменных. Корреляция между показателями «наличие случая гипогликемии» и «индекс коморбидности Charlson (баллы)» подтверждается значением r = 0,4020 (p=0,0001). Связь между данными переменными выявлена вычислением χ^2 = 16,336 (p = 0,0059). На основании теста χ^2 для тренда получено значение χ^2 (тренд) = 14,544 (p = 0,0001). Однофакторный дисперсионный анализ данных показателей демонстрирует результат F-отношения = 3,734 (p = 0,004).

Заключение. Возраст пациента, стаж СД2 и полиморбидность достоверно связаны с риском гипогликемии у пациенток с СД2.

Ключевые слова: сахарный диабет 2 типа, гипогликемия, факторы риска гипогликемии, полиморбидность, индекс коморбидности Charlson, CCI, геронтология.

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Список сокращений
СД – сахарный диабет; СД2 – сахарный диабет 2 типа; ССЗ – сердечно-сосудистые заболевания; СКФ – скорость клубочковой фильтрации.

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INTRODUCTION

Diabetes Mellitus (DM) is one of the most prevalent non-infectious pathologies and a global problem of healthcare worldwide. Over 500 million people internationally and almost 5 million Russians have Diabetes Mellitus [1, 2]. More than 90% of all cases of the disease are Type 2 Diabetes Mellitus (T2DM) diagnosed in 4.58 million people in Russia [2]. Vital importance of T2DM problem is related to the overall trend of population aging resulting from combined increased expectancy of life and decreasing birth rate [3]. More than a half of all cases of T2DM are found in patients over 65, and the greater prevalence of the pathology is observed in the cohort of 65–70 years olds [4]. The pathogenesis of T2DM is related to insulin resistance combined with dysfunction of beta cells of the pancreas and reduced synthesis of insulin resulting in a persistent hypoglycemia, which, in its turn, affects the vascular endothelium and causes damage to various organs and systems [5]. With advancing age, the tissue sensitivity to insulin decreases on the post-receptor level. Loss of muscle mass and development of sarcopenia result in the decreased glucose consumption by muscles, increase of insulin resistance, and increase of hypoglycemia [6–8]. Sedentary lifestyle, high-calorie processed foods and intake of some medications additionally assist increased insulin resistance. Elderly and old patients demonstrate an involution of the pancreatic beta cells and a decrease of their sensitivity to incretins, which leads to insulin secretion disorder [7, 8]. Thus, the T2DM is an age-associated disease.

Elderly patients with T2DM often take antihyperglycemic agents of such groups as sulfonyl urea and insulin [2, 9]. Being effective and available to patients under reimbursement programs, these agents are also characterized with a higher frequency of hypoglycemia occurrence versus other groups of antihyperglycemic agents [10, 11]. Glycaemia values of 3 to <3.9 mmol/l in DM patients receiving antihyperglycemic therapy are predictors of hypoglycemia development and require measures to manage this condition regardless of the presence or absence of symptoms. The blood glucose below 3 mmol/l points at clinically significant hypoglycemia. In cases of severe hypoglycemia, depression of consciousness and cognitive functions is observed, the management of which requires assistance from third persons or medical professionals [10]. The hazard of hypoglycemia, especially for patients of advanced age, lies in the increased risk of adverse cardiovascular events and death [12, 13]. Hypoglycemia initiates a cascade of reactions forming a counter-regulatory response. One of components of this response is the activation of the sympathoadrenal system whereby adrenalin is released; under hypoglycemia, it reduces glucose consumption by muscles and stimulates its production by the liver [14]. The activation of the sympathoadrenal system result in the patient developing adrenergic effects such as increased sweating, tremor of the upper extremities; these symptoms allow for a timely identification of a hypoglycemic event and prevention of development of severe hypoglycemia by the patient. Changes in the hemodynamics related to hypoglycemia and reactive increased secretion of adrenaline are manifested in an increased heart rate and systolic blood pressure, increased myocardial contractility, stroke and ejection volume [15]. Hypoglycemia also causes changes in the hemostasis shown in the increase of activity of platelets and blood coagulation factors, viz. Factor VII and von Willebrand Factor. Increased

concentration of C-reactive protein and proinflammatory cytokines under hypoglycemia may lead to damage of vascular endothelium [16]. The above mentioned changes in the hemostasis and hemodynamics contribute to the ischemia of the myocardium, especially in elderly and old patients, in the presence of atherosclerotic coronary disease. In the structure of mortality of T2DM patients in the Russian Federation, cardiovascular diseases (CVDs) are leading [2]. The patient's age and presence of CVDs are the factors determining the individual targets of glycemic control [10, 17]. Hypoglycemia elevates the risk of development of dementia and, respectively, functional dependence of advanced age patients with T2DM, whereas the existing cognitive deficiency increases the risk of the onset of severe hypoglycemic events [17, 18].

The primary physiological reaction to hypoglycemia is reduction of insulin secretion by pancreatic beta cells. Possibly, due to paracrine interrelation between the cells of the pancreatic islets, the alpha cells then release the glucagon, an insulin counter-regulatory hormone stimulating development of hypoglycemia by activating breakdown of glycogen in the liver. As the duration of DM increases, chronic hypoglycemia leads to damage and loss of beta cells, and cross-reactions between alpha and beta cells are disrupted as well as glucagon secretion in response to decrease of glycaemia [19, 20]. This results in an elevated risk of the onset of a severe hypoglycemic event. It may be suggested that a long duration of DM may be a risk factor of severe hypoglycemia.

Geriatric practices are closely related to the problem of polymorbidity or two or more chronic conditions found in the same patient [21]. Among patients aged over 65, the prevalence of polymorbidity reaches 95.1%. Some scientists believe that the processes of aging and development of chronic diseases are based on similar mechanisms, and polymorbidity may be viewed as a marker of accelerated aging [22]. To assess stratification of patients against the level of comorbidity and to ensure individual approaches to treatment and follow-up various indices and scales are used [23]. One of such widely used indices is the Charlson Comorbidity Index (CCI) developed in 1987. It is expressed in points and allows identification of the patient's comorbidity and to predict the probability of 10-year mortality [23, 24].

Considering the aforementioned adverse outcomes of hypoglycemia on T2DM patients of advanced age groups, the evaluation of the patient's age, duration of T2DM and the value on the Charlson comorbidity index as predictors of a hypoglycemic event is of interest.

AIM

To determine the significance of age, duration of T2DM and polymorbidity as predictors of hypoglycemia in elderly and old women with T2DM.

MATERIAL AND METHODS

The cross-sectional study included 90 elderly and old female patients. The minimum age of the participant was 60 years, the maximum was 85 years, and the average age was 70.5 ± 6.2 years.

Inclusion Criteria: female sex, age of 60 and above, history of T2DM, signing of informed voluntary consent by the patient to participate in the study.

Exclusion Criteria: history of T1DM, presence of diabetic ketoacidosis at the time of examination, acute infectious diseases, severe cognitive impairment that makes it difficult to collect complaints and anamnesis, a history of cancer, severe renal impairment (GFR below 15 ml/min/1.73m2 calculated using the CKD-EPI equation), severe liver failure (increase in liver transaminase activity by more than 5 times the upper limit of reference values). The participants of the study were divided into two groups. The first group were the patients who experienced a hypoglycemic event within the past year (49 people, 54.4%), average age of 72.1 ± 5.9 years. The second group were patients without history of hypoglycemia (41 people, 45.6%), average age of 68.5 ± 6.1 years.

Hypoglycemia was determined by the glucose level in the blood below 3.9 mmol/l [10], registered within the past year in the biochemical blood assay or in the patient's self-measurement of glucose in the capillary blood using a glucometer, which is registered in the glycaemia control diary. A detailed history of T2DM was collected from patients: age at the onset of the disease, glycaemia and glycated hemoglobin levels over time, adjustment of antihyperglycemic therapy, history and frequency of hypoglycemic events. The medical histories and electronic outpatient cards of patients in the Unified Medical Information and Analytical System of the Samara Region (EMIAS) were studied in detail. The following laboratory parameters were studied: red blood cell count, mean cell value, hemoglobin, hematocrit, white blood cell count, platelet count, erythrocyte sedimentation rate (ESR), glucose, glycated hemoglobin, creatinine, total protein, total cholesterol, triglycerides, high-density lipoproteins (HDL), low-density lipoproteins (LDL), alanine aminotransferase (ALT) и aspartate aminotransferase (AST). The calculation of GFR was done using the CKD-EPI and MDRD equations widely used in medical practice (KDIGO 2012). Charlson comorbidity index was calculated for all the patients.

The statistical analysis of the obtained data was performed with the MedCalc 20.009 software suite (MedCalc Software Ltd, Belgium). The variables are presented as the average mean (M) with a standard deviation (SD). The normality of the sample distribution was checked using the Kolmogorov-Smirnov criterion. The linear dependence between the indicators was determined using the r-Pearson correlation coefficient. The chi-square ($\chi 2$) criterion was used to analyze the presence of a relationship between categorical variables. One-way ANOVA was used to determine statistically significant intergroup differences. The results were considered statistically significant at $p < 0.05$.

RESULTS

Depending on the age, the patients were divided into groups according to the WHO classification. Out of the 90 participants of the study, the elderly cohort (60–74 years) of patients included 66 people, and the group of old/senile patients (75–85 years) was 24 people. Among the elderly patients, 31 (47%) people had a history of a hypoglycemic event within the past year; in 35 (53%) patients, there was no history of hypoglycemia. In the group of old patients, hypoglycemia was found in 18 (75%) people, the number of patients without hypoglycemic events was only 6 (25%) people. That is, among old patients hypoglycemia is more prevalent than among elderly patients (**Table 1**).

Age category	Group 1 (n=49)		Group 2 (n=41)		p-value
	Number of people, abs.	Percentage from total number in this category	Number of people, abs.	Percentage from total number in this category	
Elderly	31	47%	35	53%	0.0180
Old	18	75%	6	25%	

Table 1. *The prevalence of hypoglycemia in two groups of elderly patients divided by age*
Таблица 1. *Сравнение распространенности гипогликемии среди пациентов пожилого и старческого возраста*

T2DM duration	Group 1 (n=49)		Group 2 (n=41)		p-value
	Number of people, abs.	Percentage from total number in this category	Number of people, abs.	Percentage from total number in this category	
0–10 years	10	33.3%	20	66.7%	0.0007
11–20 years	25	62.5%	15	37.5%	
Over 21 years	14	70%	6	30%	

Table 2. *The prevalence of hypoglycemia in T2DM patients depending on disease duration*
Таблица 2. *Распространенность гипогликемии в зависимости от длительности СД2*

When calculating the correlation coefficient between the indicators "History of a hypoglycemic event" and "Patient age (age group)", a direct correlation was revealed (r=0.2489; p=0.018). These values indicate a statistical dependence of the indicators under consideration. Based on the chi-square criterion, the value of $\chi2 = 5.513$ ($p = 0.018$) was obtained. The one-way ANOVA shows the F ratio = 5.811 ($p = 0.018$). The calculations performed confirm the relationship between two categorical variables.

Depending on the duration of the T2DM, the participants of the study were also divided into groups shown in **Table 2**. It may be pointed out that hypoglycemic events are more frequently observed in patients with the duration of T2DM of 21 years and more (70%). The prevalence of hypoglycemia in patients with disease duration of 11–20 years was 62.5%, and in patients with disease duration of 0–10 years, 33.3%.

The statistic correlation between the parameters under consideration is confirmed by the correlation index ($r = 0.3512$; $p = 0.0007$). In the calculation of the $\chi2$ value, the $\chi2$ (trend) = 10.982 ($p = 0.0009$) value was obtained, which also confirms a significant correlation between these variables.

We collected the history of concomitant non-infectious pathologies (**Table 3**).

According to Table 3, the following chronic non-infectious diseases were most prevalent in the patients of Group 1: arterial hypertension (100% patients), stable angina (65.31%), chronic heart failure (75.51%), osteoarthritis (40.82%), and carotid artery atherosclerosis (32.65%).

In the patients of Group 2, the following picture may be observed: arterial hypertension (100% patients), stable angina (51.22%), chronic heart failure (51.22%), osteoarthritis (43.9%), and carotid artery atherosclerosis (21.95%).

In the process of comparative analysis of morbidity between patients of Groups 1 and 2, we calculated the Charlson comorbidity index, depending on the value of which the patients were distributed as follows (**Table 4**).

The correlation index for the indicators "History of hypoglycemic events" and "Charlson comorbidity index (points)" was $r = 0.4020$ ($p = 0.0001$), which shows the statistic dependence of these variables.

Based on the $\chi2$ test, the $\chi2 = 16.336$ ($p = 0.0059$) was obtained. When calculating the $\chi2$ for the trend, the $\chi2$ (trend)

Disease	Group 1 (n=49)		Group 2 (n=41)		Dynamic (n1%/n2%)	p-value
	No. of people, abs.	No. of people, %	No. of people, abs.	No. of people, %		
Arterial hypertension	49	100.00%	41	100.00%	1,0	1.0000
Stable angina	32	65.31%	21	51.22%	1,28	0.1801
Myocardial vascularization surgery	7	14.29%	7	17.07%	0,84	0.7200
Chronic heart failure	37	75.51%	21	51.22%	1,47	**0.0163**
Atrial fibrillation	5	10.20%	0	0.00%	0,0	**0.0356**
Carotid artery atherosclerosis	16	32.65%	9	21.95%	1,49	0.1190
Bronchial asthma	4	8.16%	3	7.32%	1,11	**0.8830**
Chronic anemia	12	24.49%	3	7.32%	3,35	0.0296
Deep vein thrombosis	1	2.04%	0	0.00%	0,0	0.3633
Pulmonary artery thromboembolia	1	2.04%	0	0.00%	0,0	0.3633
Osteoarthritis	20	40.82%	18	43.90%	0,93	0.7709
Knee arthroplasty	2	4.08%	0	0.00%	0,0	0.1949
Parkinson's disease	0	0.00%	1	2.44%	0,0	0.2768
Alzheimer's disease	0	0.00%	0	0.00%	0,0	1.0000
Trophic ulcers and pressure sores	2	4.08%	2	4.88%	0,84	0.8571
Gouty arthritis	1	2.04%	1	2.44%	0,84	0.8998

Table 3. *Comparison of the prevalence of chronic noncommunicable diseases between patient groups*
Таблица 3. *Сравнение распространенности хронических неинфекционных заболеваний между группами пациентов*

Charlson comorbidity index (points)	Group 1 (n=49)		Group 2 (n=41)		p-value
	No. of people	No. of people, %	No. of people	No. of people, %	
3	1	2.04%	4	9.75%	0.0001
4	2	4.08%	11	26.83%	
5	12	24.48%	10	24.39%	
6	20	40.81%	13	31.71%	
7	13	26.53%	3	7.32%	
8	1	2.04%	0	0%	

Table 4. *Distribution of patients depending on the Charlson comorbidity index*
Таблица 4. *Распределение пациентов в зависимости от индекса коморбидности Charlson*

= 14.544 (p = 0.0001) value was obtained. One-way ANOVA shows the F ratio = 3.734 (p = 0.004). The calculations performed confirm the relationship between two categorical variables.

DISCUSSION

In the course of the study, we analyzed the correlation between the patient's age, duration of the T2DM and polymorbidity with the risk of the onset of hypoglycemia. The results show that the age and the duration of the disease are predictors of the onset of hypoglycemia. Old patients experienced this condition more often than the elderly. We already mentioned that with advancing age the insulin resistance is increasing and the functional reserve of the pancreas is decreasing as the number of beta cells grows lower. This leads to glycaemia levels in elderly patients to go higher, respectively, the antihyperglycemic treatment is intensified, which may lead to the development of hypoglycemia. A large study demonstrated an increase in mortality from CVDs among T2DM patients in the group with intensive glycaemia control as compared to the group in which individual targets of carbohydrate metabolism were observed [25]. Besides, as the age and the duration of the disease advance, the vegetative symptoms of hypoglycemia appear with lower values of hypoglycemia, and the cognitive dysfunction, with higher levels as compared to younger patients. Thus, both the adrenergic symptoms that allow for a timely identification and management of hypoglycemia and the neurology deficiency appear simultaneously in elderly patient. Recurrent hypoglycemic events lead to a further lowering of the threshold of activation of the sypmathoadrenal system. This phenomenon is referred to as 'hypoglycemia unawareness syndrome'. Some authors regard it as a manifestation of autonomous diabetic neuropathy, and some view is as a temporary functional disorder that is potentially reversible with compensation of carbohydrate metabolism and prevention of further hypoglycemia [19, 26].

As per results of our study, patients had differences of prevalence of chronic non-infectious diseases between groups. Among patients with history of hypoglycemia, the increase of atrial fibrillation occurrence was statistically significant (p = 0.0356), as well as chronic heart failure (p = 0.0163) and chronic anemia (p = 0.0296). Contrary to our expectations, the differences in prevalence of stable angina and myocardial vascularization surgery were not statistically significant between the studied groups (p > 0.05), which may be explained by a small sample of patients.

The Charlson comorbidity index is used within the framework of complex geriatric evaluation to assess the risks of negative outcome in patients with polymorbidity from advanced age groups. We found a direct correlation between the score on the Charlson comorbidity index and hypoglycemia. In the group of patients with history of hypoglycemic events, higher scores on the Charlson comorbidity index were found, which is associated with a worse long-term prognosis and lower chance of 10-year survivability. In calculating this index, the following factors are considered: complications of T2DM, history of CVDs, significant decrease of GFR and impairment of the liver function; those are the factors that influence glucose metabolism and pharmacokinetics of antihyperglycemic agents that potentially contribute to the development of a hypoglycemic event.

CONCLUSION

Older patients experienced hypoglycemia more often than the elderly ones. Age of patients and duration of the T2DM are risk factors for the development of hypoglycemia. The choice of antihyperglycemic therapy for patients of advanced age groups requires an assessment of concomitant geriatric syndromes and comorbid conditions increasing the risk of hypoglycemia. The results of our study emphasize, once again, the importance of reaching individual targets of carbohydrate metabolism in elderly patients with T2DM. The targets of treatment of T2DM in such patients should be the maintenance of quality of life and minimization of side effects of antihyperglycemic agents including hypoglycemia.

ADDITIONAL INFORMATION	ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ
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Contribution of individual authors. P.Ya. Merzlova – was responsible for clinical data collection, its systematization and statistical analysis, wrote the first draft of the manuscript. S.V. Bulgakova – developed the study concept, goals and plan. D.P. Kurmaev – provided final manuscript editing. E.V. Treneva – provided the study design and text revision. All authors gave their final approval of the manuscript for submission, and agreed to be accountable for all aspects of the work, implying proper study and resolution of issues related to the accuracy or integrity of any part of the work.	***Участие авторов.*** П.Я. Мерзлова – сбор и обработка клинического материала, написание текста, статистическая обработка данных. С.В. Булгакова – постановка задачи, планирование концепции исследования. Д.П. Курмаев – финальное редактирование текста научной статьи. Е.В. Тренева – дизайн исследования, верстка текста. Все авторы одобрили финальную версию статьи перед публикацией, выразили согласие нести ответственность за все аспекты работы, подразумевающую надлежащее изучение и решение вопросов, связанных с точностью или добросовестностью любой части работы.

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