

## Evaluation of factors influencing adherence to treatment with sodium-glucose cotransporter type 2 inhibitor

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### ABSTRACT

**Background.** Despite the emergence of new groups of drugs for the treatment of type 2 diabetes mellitus (DM2), the issue of optimal adherence to treatment remains of interest.

**The aim** of this study was to investigate the factors that influence the adherence to treatment with sodium glucose co-transporter type 2 inhibitor, empagliflozin (Jardiance, Boehringer Ingelheim, Germany), in patients with DM2.

**Materials and methods.** The study included 102 patients with DM2 (58 of them were women); the observation time was 24 weeks. The mean age was  $58.3 \pm 10.4$  years.

**Results.** Patients without cognitive impairment had a lower level of glycated hemoglobin (HbA1c) (7.76%, 6.18–9.34) than patients with mild dementia (8.51%, 7.02–10;  $p = 0.032$ ). In the group of patients who noted the impossibility of purchasing even a part of the drugs, the level of HbA1c was 9.73% (8.95–10.51), while patients who had no difficulties in purchasing drugs HbA1c was 8.83% (7.85–9.81;  $p = 0.036$ ). Empagliflozin was discontinued in 38.2% of patients for the following reasons: cost of the drug (16.6%), development of side effects (10.7%), lack of effectiveness (7.8%), other reasons (2.9%).

**Conclusion.** Thus, the main factors influencing the adherence to treatment were the cost of the drug, development of adverse events, and lack of effectiveness from the therapy. At the same time, the opportunity of purchasing all the necessary drugs was associated with both better glycemic control and a higher quality of life.

**Key words:** diabetes mellitus, adherence to treatment, sodium glucose co-transporter type 2 inhibitor, empagliflozin.

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# Оценка факторов, влияющих на приверженность к лечению ингибитором натрий-глюкозного ко-транспортера 2-го типа

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## РЕЗЮМЕ

**Актуальность.** Несмотря на появление новых групп препаратов для лечения сахарного диабета 2-го типа (СД2), вопрос оптимального соблюдения режимов терапии остается в центре внимания.

**Цель.** Изучить факторы, влияющие на приверженность к лечению ингибитором натрий-глюкозного ко-транспортера 2-го типа – эмпаглифлозином (Джардинс, Берингер Ингельхайм, Германия) у пациентов с СД2.

**Материалы и методы.** В исследование были включены 102 пациента с СД2 (из них 58 женщин), время наблюдения – 24 нед. Средний возраст составил  $(58,3 \pm 10,4)$  лет.

**Результаты.** Пациенты без нарушения когнитивных функций имели меньший уровень гликированного гемоглобина (HbA1c) – 7,76 (6,18–9,34)%, чем пациенты с деменцией легкой степени выраженности – 8,51 (7,02–10)%,  $p = 0,032$ . В группе пациентов, которые отметили невозможность приобретения даже части препаратов, уровень HbA1c составил 9,73 (8,95–10,51)%, в то время как пациенты, не испытывающие финансовых затруднений в приобретении препаратов, имели HbA1c 8,83 (7,85–9,81)%,  $p = 0,036$ . Терапия эмпаглифлозином была прекращена у 38,2% пациентов по следующим причинам: стоимость препарата – 16,6%, развитие побочных эффектов – 10,7%, отсутствие эффективности от терапии в виде улучшения гликемического контроля – 7,8%, другие причины – 2,9%.

**Заключение.** Таким образом, основными причинами, влияющими на продолжение лечения, оказались финансовые затруднения в приобретении препарата, возникновение побочных эффектов и отсутствие эффективности от терапии. При этом возможность приобретать всю необходимую терапию ассоциировалась как с лучшим гликемическим контролем, так и более высоким качеством жизни.

**Ключевые слова:** сахарный диабет, приверженность к лечению, ингибиторы натрий-глюкозного ко-транспортера 2-го типа, эмпаглифлозин.

**Конфликт интересов.** Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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## INTRODUCTION

Diabetes mellitus (DM) is one of the most widespread non-infectious diseases worldwide. In 2017, 425 million people worldwide were reported to have DM, which is a global prevalence of 8.3% [1]. At the same time, the majority of cases are of DM2, which represents a problem in modern healthcare because of a significant social burden and major financial cost of treatment for chronic complications like nephropathy,

retinopathy, and neuropathy that can finally lead to terminal kidney failure, blindness, and amputation of lower extremities. The risk of death from cardiovascular or cerebrovascular events in patients with DM2 is significantly higher in comparison with people without diabetes [2].

In clinical practice, the maintenance of target values of glycated hemoglobin (HbA1c) remains one of the main therapeutic tasks to prevent complications as-

sociated with DM2, especially microvascular events. This data is based on the results of three major experimental studies (ACCORD, ADVANCE and VADT) and UKPDS study that showed that lower levels of HbA1c are associated with later onset and progression of microvascular complications [3–6].

Although drug therapy for DM2 achieved significant development in the past years, some factors decrease the effectiveness of this therapy. Among them are low awareness of the disease and insignificant adherence to the therapy [7, 8].

Adherence to therapy is an important factor that determines the disease outcome in patients with chronic diseases. In 2003, the WHO reported that “an increase in the effectiveness of interventions to the adherence to therapy can have a more beneficial effect on the population health than the improvement of single types of treatment” [9]. Still, the majority of studies indicate that the adherence to drug therapy remains suboptimal for patients with multiple chronic diseases, including DM2 [10–14]. In 2004, Cramer published a systematic review aimed at comparing the parameters of adherence to anti-hyperglycemic drugs and insulin [15]. The results of the review showed that many patients with diabetes did not adhere to the recommended pharmacotherapy, which led to non-optimal control of glycemia. Besides, the review on the adherence to DM2 showed that the level of education in patients, especially regarding self-management during treatment, was the most important factor that predicted the improvement of glycemic control, the quality of life and possible outcomes [16]. Among the reasons for non-optimal adherence to the treatment of DM2, there were factors like the complexity of the dose regimen and adverse events associated with the treatment. A meta-analysis that included 40 studies published from 2005 to 2015 showed that only 67.9% of patients with DM2 adhered to their anti-hyperglycemic drugs [17]. Still, the adherence to treatment of diabetes mellitus is known to be associated with better glycemic control, lower rates of hospitalizations, lower expenses on health care, and lower mortality rate [18].

Despite the emergence of numerous anti-hyperglycemic drugs on the market that are characterized by high efficiency and good tolerance, the issue of adherence remains acute. Although it is suggested that there is a positive association between the adherence to treatment, patients' awareness of their disease and their levels of HbA1c, few studies on anti-hyperglycemic drugs evaluate the association between the described variables factually and performed the analy-

sis of factors that influence these processes [19, 20]. This study is focused on the factors that influence the adherence to treatment with sodium-glucose co-transporter type 2 inhibitor (SGCI2) empagliflozin (Jardiance, Boehringer Ingelheim, Germany) in patients with DM2.

## MATERIALS AND METHODS

The study included patients with DM2 (men and women aged 18 to 70) who started their therapy with sodium-glucose co-transporter type 2 inhibitor (SGCI2) empagliflozin at a daily dose of 10 mg. Signing the patient's informed consent form for participation in the study and stable anti-hyperglycemic therapy for a minimum of 12 weeks before being included in the study were obligatory study entry criteria. The criteria of exclusion were diabetes mellitus type 1, acute coronary syndrome, acute cerebrovascular condition within the past two months, verified kidney diseases (glomerulonephritis, pyelonephritis, amyloid disease) or chronic kidney disease with  $GFR < 45 \text{ ml/min/1.73 m}^2$ . Additionally, the study excluded patients with leg ulcers in cases of diabetic feet and patients that underwent bariatric operations and treatment with medications for weight loss within the past 3 months.

In the beginning of the study, the authors collected patients' personal information like age, sex, level of education, height and body weight (BMI), duration of diabetes, chronic complications with the stage of retinopathy and nephropathy, if any, and a history of infections of the urinary tract and reproductive organs. The authors evaluated such parameters as arterial blood pressure (BP), heart rate (HR), glycated hemoglobin (HbA1c), fasting plasma glucose, and creatinine in the blood with the calculation of GFR. During the first visit, patients filled in the EQ5D and life quality evaluation forms. The Hospital Anxiety and Depression Scale (HADS) was used to identify the presence and severity of depression. The cognitive condition of every patient was evaluated with Mini-Mental State Examination (MMSE). Patients additionally filled in a questionnaire that included the questions on peculiarities of disease development and the presence or absence of diabetic chronic complications. The questionnaire also included questions that allowed the authors to evaluate the level of patients' trust toward the attending physician and the awareness of their disease.

The observation time was 24 weeks. During the study, the authors evaluated the dynamics of laboratory parameters (HbA1c, creatinine, alanine amino-

transferase (ALT), aspartate aminotransferase (AST), low-density lipoproteins (LDL), and clinical parameters (BP, HR). Patients filled in the same questionnaires that they had during the first visit. The authors analyzed medical documentation provided by patients to reveal the development of urinary tract and reproductive organ infections, cardiovascular conditions (acute myocardial infection), acute coronary syndrome, acute cerebrovascular conditions, and hospitalizations for diabetic ketoacidosis. During the study, the authors recorded data on the development of adverse events and discontinuation of therapy with specifying the reason.

Statistical analysis was performed with the software package STATISTICA 10 (StatSoft Inc, USA). Qualitative parameters were presented as  $n$  (%), quantitative parameters in cases with normal distribution were presented as an arithmetic average and standard deviation ( $M \pm SD$ ), in cases with asymmetric distribution as a median and quartiles ( $Me$ , 25% quartile; 75% quartile). To compare quantitative data, the authors used the Mann – Whitney U-test. The Spearman's rank correlation coefficient was used to identify correlations between the factors. The obtained results were considered statistically significant at  $p < 0.05$ .

## RESULTS

The study included 102 patients with DM2 (Table 1). The mean age of patients was  $58.3 \pm 10.4$  years old, 56.8% of patients were women. By the time of inclusion into the study, 36.2% of the patients received insulin drugs along with anti-hyperglycemic drugs and 23.5% of patients received metformin as a monotherapy.

Table 1

Initial features of patients	
Parameter, units of measurement	Value
Average age, years	$58.3 \pm 10.4$
Women, $n$ (%)	58 (56.8%)
Men, $n$ (%)	44 (43.2%)
Duration of diabetes, years, $M \pm SD$	$9.2 \pm 4.5$
BMI, $kg/m^2$	$28.6 \pm 5.5$
Glomerular filtration rate (eGFR), $ml/min/1.73 m^2$ , $M \pm SD$	$69.7 \pm 20.7$
> 60 $ml/min/1.73 m^2$ , $n$ (%)	58 (55.8%)
< 60 $ml/min/1.73 m^2$ , $n$ (%)	44 (44.2%)
HbA1c, %, $M \pm SD$	$8.8 \pm 1.6$

64.7% of patients had completed a higher education course, 29.4% of patients had secondary vocational education. The comparison of levels of glycated

hemoglobin after 24 weeks in these two groups did not reveal any significant differences with 8.2% (7.3–9.1) and 8.4% (7.4–9.3), respectively ( $p > 0.05$ ). However, patients without cognitive disorders (24–30 points under the MMSE inventory) had lower levels of HbA1c with 7.7% (6.2–9.3) than patients with mild dementia (20–23 points) who had HbA1c levels of 8.5% (7.1–10) ( $p = 0.032$ ).

The mean level of HbA1c after 24 weeks of treatment was 8.4% (7.2–8.9) in patients that did not miss the doses and 9.3 % (7.6–10.8) in patients that missed doses several times per month and more often ( $p = 0.026$ ). Moreover, there was a correlation revealed between the baseline level of HbA1c and the possibility to buy drugs. In the group of patients who had financial difficulties in buying even a part of the drugs, the level of HbA1c was 9.7 % (8.9–10.5), while in patients who did not have financial difficulties, the level of HbA1c was 8.8 % (7.8–9.8), ( $p = 0.036$ ). Similar differences remained after 24 weeks of the therapy: 9.5% (8.7–10.3) and 7.9 (6.8–8.7), respectively ( $p = 0.027$ ). The lipid profile evaluation showed that the baseline level of LDL was 3.9 mmol/L (2.7–4.7) in the group of patients who had financial difficulties when purchasing drugs, and 2.8 mmol/L (2.2–3.3) in patients who had none.

The quality of life self-estimated by patients under the visual-analogue scale of EQ-5D inventory positively correlated with the total score according to the MMSE inventory ( $p = 0.002$ ;  $r = 0.69$ ). At the same time, the quality of life in patients who had no financial difficulties was significantly higher (62.5 (48.4; 75.3)) than in patients who had those difficulties (43.9 (30.1; 59.7)), ( $p < 0.001$ ). In turn, a negative correlation was obtained between the level of HbA1c and the data obtained from EQ-5D inventory ( $p < 0.001$ ;  $r = 0.51$ ). The analysis of the results obtained from HADS inventory revealed a positive correlation between the level of anxiety and HbA1c ( $p < 0.001$ ;  $r = 0.51$ ). A weak but statistically significant positive correlation was found between the level of depression under the HADS scale and the level of HbA1c ( $p = 0.016$ ;  $r = 0.31$ ).

Empagliflozin therapy was discontinued in 39 patients (38.2%) due to the following reasons: cost of the drug (17 patients, 16.6%), adverse effects (11 patients, 10.7%), lack of effectiveness of the therapy as an improvement of the glycemic control (8 patients, 7.8%), other reasons (3 patients, 2.9%). Among patients that discontinued therapy because of financial difficulties, 70% stopped purchasing the drug within the first

90 days of the therapy. The most common adverse effects were urogenital conditions (15.7% of them were registered in female patients – 76.4% of all urogenital infections), mild hypoglycemia (8.8%), and hypotension (5.8%). In 4 patients, the recurrence of urogenital infections (more than 1 time) was observed. Discontinuation of therapy because of recurrent vulvovaginitis was required in 2 female patients.

## DISCUSSION

Poor adherence to treatment was associated with a number of factors that can be grouped in social-economic, therapy-associated, and medical personnel-associated factors [21]. Many of these factors can be interconnected, which makes it difficult to identify the main reasons for failure to adhere to the treatment. For example, patients may report that they simply forgot to take the drug because of “being busy” with their everyday life when, in reality, they lack the motivation to take the drug. This can be associated with failure to understand its importance, concern about unfavorable events, and lack of a possibility to purchase it or any other reason that overweighs the benefits that, in their mind, the therapy would bring. Even the fact of taking the drug on a daily basis can negatively affect adherence since it reminds the patients that they are sick [22].

Since the patients primarily reported good connections with their physician and the study did not include interviewing the medical personnel, it was impossible to evaluate the impact of medical personnel on the adherence to treatment. One of the studies conducted in northern California that included 9 thousand patients showed that patients who had a lower level of trust to their doctor were found to have poorer adherence to the treatment [23]. Some studies showed that there were medical personnel-associated factors that decreased the effectiveness of the treatment as the lack of involvement of patients into making decisions during the therapy and lack of understanding of issues that might arise during the therapy. The results of the present study showed that only 34.3% of doctors discussed financial aspects of the treatment with their patients. Besides, such factors as openness, emotional support, clear and complete information, and possibility to ask questions contribute to the establishment of a trustful relationship between doctors and patients [24].

Social and economic factors influence the adherence to therapy by patients with chronic diseases, including diabetes mellitus. A recent study (a telephone survey) was aimed at evaluating the rate of refusals

to continue the treatment with anti-hyperglycemic drugs. Around 16% out of 1200 patients with DM2 reported on the discontinuation of therapy because of the cost of the drugs (patients were not divided into groups) [25]. Meanwhile, the cost of different drugs varies widely and patients with financial difficulties refuse expensive therapy more often. In this study, the authors evaluated the impact of this factor on the adherence to the therapy with empagliflozin. The rate of refusal because of financial issues was 16.6%, which corresponded to a moderate rate. At the same time, patients who had financial difficulties when purchasing drugs had significantly higher levels of glycated hemoglobin both in the beginning of the study and after 24 weeks of empagliflozin therapy. They also had higher levels of LDL and worse quality of life. The obtained results show that the cost of drugs is an important factor that negatively affects the adherence to the treatment.

The complexity of the drug regimen and high daily rate of drug intake also determine the adherence to the therapy. Several studies described the influence of the rate of dosing on adherence to the treatment recommendations [22, 26]. The analysis of the data of patients with atrial fibrillation and arterial hypertension showed that the adherence to the therapy in patients with single daily administration of a drug was 26% higher than in patients that had to take a drug twice a day [26]. This data indicates a significant impact of the drug regimen on the adherence to the therapy in patients with diabetes mellitus and other chronic diseases. This study did not evaluate the dose regimen because empagliflozin is always administered once a day and this can positively influence the adherence to the treatment.

The tolerance and safety of drugs also influence the adherence to the treatment. The influence of adverse events provoked by anti-hyperglycemic drugs on the adherence to the treatment was evaluated by RECAP-DM [25]. The study included 1709 patients that received monotherapy with metformin as well as sulphonylurea or thiazolidinedione-containing drugs. The study results showed that patients with hypoglycemic episodes missed the doses of the drug and discontinued the therapy more often. The patients assessed the effectiveness, convenience, and satisfaction with the treatment significantly lower than patients that did not have any hypoglycemic conditions. The results of this study show that hypoglycemic conditions in patients who received empagliflozin were observed in 8.8% of patients. All those patients received

insulin therapy and needed dose correction of insulin after the beginning of empagliflozin therapy. Still, the development of hypoglycemic conditions did not lead to discontinuation of the therapy. Urogenital infection was the most common adverse effect (15.7% of patients). In clinical studies, the morbidity rate with genital infections in patients who received empagliflozin was 5% in comparison with the placebo group (1%). The incidence rate of urinary tract infection in the groups that received empagliflozin 10 and 25 mg and the placebo group was similar (9.8%, 10.4%, 9.3%) [27]. The present study revealed a higher rate of urogenital infections in comparison with a randomized controlled study. This can be explained by the fact that only 64.5% of attending physicians told the patients about possible adverse effects and advised on how to prevent them. Among patients who discontinued the therapy because of adverse effects, 72.7% of patients stopped taking the drug after a single event of urogenital infection, although it is recommended to discontinue the therapy with SGCI2 only in case of recurrent urogenital infection.

Apart from social and economic factors, specifics of therapy and factors associated with attending physicians and individual characteristics of patients also have an impact on the low level of adherence to the treatment. Some authors see a low level of awareness as a potential barrier for optimal adherence to the therapy. A survey conducted among 405 patients with DM2 showed that patients with a high level of awareness and strong belief that anti-hyperglycemic drugs are necessary had better adherence to the therapy [28]. And vice versa, patients with a high level of concern about adverse events showed a lower level of adherence to the therapy. In this study, less than a half of the patients were aware of their level of glycated hemoglobin before being included into the study. It should be mentioned that cognitive condition of patients also influenced the adherence to the therapy and the quality of life. Patients without cognitive disorders had lower levels of glycated hemoglobin in comparison with patients with mild dementia. The MMSE score positively correlated with the quality of life according to patients' self-estimation. Depression can be one of comorbid chronic diseases associated with the level of adherence to the therapy. Symptoms of depression were associated with a lower level of adherence in one of the studies [29], which agrees with the results obtained by the authors. Furthermore, it was shown that the level of anxiety and depression (HADS inventory) positively correlated with the level of gly-

cated hemoglobin, which can prove the influence of psychological welfare on adherence to the therapy. There are also other factors that influence the adherence to the therapy, such as alcohol abuse [30] and severity of comorbid diseases [31], but they were not evaluated in this study.

The authors obtained data on adherence to SGCI2 (empagliflozin) therapy in clinical practice. The main reasons that influence the duration of the treatment were financial difficulties, development of adverse effects, and lack of effectiveness of the therapy. The possibility for purchasing the required drug in a volume needed for the therapy was associated with better glycemic control and better quality of life. Among factors that influence the adherence to the therapy, a decrease in the quality of cognitive functions plays an important role. Preventive measures aimed at the maintenance of the cognitive status of patients with chronic diseases, including DM2, are important to improve the adherence to the therapy. At the same time, the obtained data indicates that the psychological status of the patient should be taken into account when evaluating the adherence to the therapy. Therefore, psychotherapy may have a positive influence on adherence to the recommended treatment.

## CONCLUSION

Low adherence to treatment is a crucial issue for patients with chronic diseases like diabetes mellitus. Understanding the factors associated with the failure to adhere to recommendations can help resolve this issue while improving the adherence to the therapy reduces long-term negative consequences in patients with diabetes mellitus. All the factors that influence the adherence can be divided into those that can be corrected (awareness, adverse events) and those that cannot be corrected (cognitive condition, comorbid diseases). When choosing the therapy, doctors should work with factors that can be corrected: educate and instruct patients and discuss financial aspects and adverse events, as well as ways to prevent and treat them. Wide implementation of the above-mentioned inventories can help significantly when evaluating the risk factors of the low level of adherence and developing individual measures to improve it. At the same time, many factors that cannot be corrected tend to have a different nature in the beginning of the therapy. To improve the interaction between doctors and patients, teaching doctors how to communicate with patients and take action to improve the adherence to the therapy should become compulsory in modern



medical education. Patients with diabetes mellitus meet numerous barriers trying to adhere to the therapy, therefore, the researchers need more data to systematize all the factors that influence the adherence and to develop practical advice on how to improve the adherence to the treatment.

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