

INVESTIGATION OF FACTORS AFFECTING ADHERENCE TO METFORMIN THERAPY IN TYPE 2 DIABETES

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Abstract: Adherence is the degree to which the patient's behavior (taking medication, following a diet, and/or changing lifestyle) matches the agreed recommendations of the prescriber. Adherence is influenced by socio-economic factors, factors related to the health system, factors related to the disease, factors related to the patient and factors related to therapy. Many methods have been developed to measure adherence. Methods are divided into direct and indirect. Adherence is usually lower in patients with chronic conditions than in patients with acute conditions. More recent studies show adherence values to oral antidiabetic therapy of 65-85%. Adherence is usually considered optimal when patients take at least 80% of their prescribed medication. The research conducted on the sample made up of middle-aged, non-adherent respondents (35-65), who have been using metformin for a minimum of 6 months in the treatment of type 2 diabetes mellitus showed the influence of different factors on adherence. The factors that showed the greatest influence on the low degree of adherence are: lower education, passive life, low physical activity, smoking, long-term therapy, change of therapy, concomitant therapy, metformin dosing more than 2 times a day, forgetting to take therapy. The average value of blood sugar for all subjects is 10.5 mmol/L, which indicates the ineffectiveness of the prescribed therapy, and which can be directly linked to the determined non-adherence of subjects to metformin therapy.

Keywords: diabetes, adherence, patients, factors, metformin

Field: Pharmacoeconomics, Pharmacy

1. INTRODUCTION

Until relatively recently, the most commonly used term for adherence to prescribed therapy in the English-language literature was compliance (Haynes et al., 1980). Compliance is defined as the extent to which the patient's behavior is in accordance with the prescriber's instructions. This term is used less and less because it is associated with the patient's passive role, i.e. poor compliance implies the patient's incompetence to follow the doctor's instructions.

As an alternative to this term, the term adherence is used. According to the definition of the World Health Organization (WHO), adherence is the degree to which the patient's behavior (taking medication, following a diet, and/or changing lifestyle) matches the agreed recommendations of the prescriber (Pladevall et al., 2004). Adherence is, in the true sense of the word, a partnership between the patient and the prescriber (Boccuzzi et al., 2001). In addition to adherence to the method and frequency of taking the prescribed medications, adherence also implies adherence to the prescribed diet, lifestyle changes, regular check-ups and other recommendations given in order to prevent or treat diseases. It affects the success of achieving positive therapeutic outcomes and reducing the frequency of side effects.

Lack of patient adherence to treatment of chronic diseases, such as diabetes, has become a global public health and economic problem. Even the best treatment can become ineffective if the patient does not follow the recommendations given. Conclusions from numerous studies have shown that only 50% to 60% of patients use medications for chronic diseases as prescribed (Sackett & Snow, 1979). This problem is particularly present in the countries of the European Union, where the availability of health services as well as their utilization is very high (ABC Project, 2012).

The degree of adherence is an individual characteristic of the patient and reflects the difference between the patient's awareness of the need for therapy and concern about side effects or failure of therapy (Horne & Weinman, 1999). If the disease causes pain or discomfort to the patient, the degree of adherence to therapy is higher. In chronic diseases that generally do not have pronounced symptoms,

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adherence is significantly lower because the ratio of apparent benefit and risk is lower. Adherence is influenced by a large number of factors that can be divided into 5 groups: socio-economic factors, factors related to the health system, factors related to the disease, factors related to the patient and factors related to therapy.

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When it comes to social and economic factors, it must be emphasized that the patient's knowledge about medicines and his own illness can significantly help in taking therapy more regularly. Often, patients do not know which drugs they are taking and why they are taking them in their therapy, but distinguish the drugs by their shape and color. They take them "because the doctor prescribed it", but they are not aware of their illness and therapy (Borgsteede et al., 2011). Factors that increase the degree of adherence are: higher level of education, employment, middle and older age of the patient, better communication with doctors and masters of pharmacy, acute illness, simpler therapeutic regimen. Factors that reduce the degree of adherence are: payment for the drug, high price of the drug, more complex therapeutic regimen, frequent changes of therapy or drug manufacturer, failure of previous therapy, rapid onset of side effects, chronic and asymptomatic diseases, rapid improvement of symptoms. Gender and financial or material status of the patient do not significantly affect the degree of adherence.

The patient's motivation to adhere to prescribed therapy is influenced by the importance that the patient attaches to the therapy and the patient's degree of self-confidence in being able to adhere to it (Miller & Rollnick, 1999).

In order to increase the level of adherence, predictors of poor adherence to drug therapy are monitored. They include: the presence of psychological problems (depression), the presence of cognitive disorders, the treatment of an asymptomatic disease, inadequate planning of the patient's discharge and follow-up, side effects of drugs, the patient's lack of trust in the benefit of therapy, the patient's ignorance of the disease, an underdeveloped patient-doctor relationship, the existence of obstacles to the drug or treatment, missing scheduled visits, treatment complexity, drug price or co-payment for drugs from the essential drug list.

Many methods have been developed to measure adherence. Methods are divided into direct and indirect. Direct methods obtain data on adherence by observing the patient or measuring the concentration of the drug in the blood. They are very precise, but they are expensive and can only be carried out under controlled conditions. Indirect methods access data indirectly. These include: patient surveys, pill counting, prescription monitoring, clinical sign monitoring, electronic therapy monitors and patient diaries. Indirect methods are cheaper and easier to implement, but also less objective (Osterberg & Blaschke, 2005).

Diabetes mellitus is a metabolic disease characterized by hyperglycemia caused by a disorder in insulin secretion, a disorder in its action, or due to the presence of both of these disorders (American Diabetes Association, 2010). It can be a consequence of the absolute absence of insulin when it manifests as insulin-dependent diabetes mellitus or diabetes mellitus type 1, or a relative lack of insulin and insulin resistance at the level of target tissues, i.e. insulin-independent diabetes mellitus or diabetes mellitus type 2 (Rašković, 2015; Morsi et al., 2018; Petersen et al., 2017; Leiter & Nauck, 2017). Diabetes mellitus type 1 occurs most often in children and young people, while diabetes mellitus type 2 is characteristic of adults, with more frequent diagnoses in children as well, due to the increase in the obesity rate. The cause of diabetes is numerous factors, the most important of which are genetic factors, lifestyle and external environment. According to estimates by the International Diabetes Federation (IDF), 415 million (8.8%) adults (aged 20-79) globally have diabetes, and 75% of them live in low- and middle-income countries. One in 11 adults (aged 20-79) has diabetes. According to IDF data, 542,000 children (aged 0-14) have type 1 diabetes (Idf Diabetes Atlas, 2015).

Diabetes therapy includes non-medicinal and medicinal treatment of glycoregulation disorders, as well as complications caused by diabetes. Five forms of treatment are used, which are intertwined with each other: diet, physical activity, education and self-monitoring, oral antihyperglycemic agents and insulin. Medical therapy includes therapy with oral antihyperglycemic agents, combined therapy and insulin therapy.

Oral hypoglycemics can be divided into: sulfonylurea derivatives (I generation - chlorpropamide, II generation - glibenclamide, gliquidone and gliclazide, III generation - glimepiride), meglitinides (repaglinide, nateglinide), biguanides (metformin), glucosidase inhibitors (acarbose), thiazolidinediones or glitazones (pioglitazone, rosiglitazone).

Metformin is used in the treatment of type 2 diabetes mellitus when controlled diet and exercise are not sufficient to maintain normal blood glucose levels, especially in obese patients. The mechanism of action of metformin is based on:

1. reducing glucose production in the liver by inhibiting gluconeogenesis and glycogenolysis,
2. increasing the sensitivity of muscles to insulin and improving the entry and use of glucose in peripheral cells,
3. delaying the absorption of glucose in the intestine.

Adult patients usually start therapy with 500 mg or 850 mg of metformin two or three times a day, with meals. The maximum daily dose is 3000 mg divided into three separate doses.

After 6 months, more than one third of patients, and after one year about 50% of patients with chronic diseases stop the initial treatment (Naderi et al., 2012). Studies that followed the trend in the use of antidiabetic drugs showed that the use of these drugs is increasing, which is in line with the increase in the prevalence of this disease all over the world (Doro et al., 2005).

According to data from the World Health Organization, adherence to therapy for chronic diseases in developed countries is on average around 50% (WHO, 2003). Adherence is usually lower in patients with chronic conditions than in patients with acute conditions. More recent studies, however, show adherence values to oral antidiabetic therapy of 65-85% (Schechtman et al., 2002; Spoelstra et al., 2003). Adherence is usually considered optimal when patients take at least 80% of their prescribed medication, but the cut-off can be as high as 90% according to some studies (Carro et al., 2004; Donnan et al., 2002).

In patients on oral antidiabetic therapy, in a review of eleven retrospective studies conducted between 1966 and 2003, adherence (defined in these studies as taking 90% of prescribed medication) followed for 6-24 months ranged from 36% to 93% (Cramer, 2004). Adherence monitoring using electronic monitors (MEMS) showed that patients took 61-85% of prescribed doses of oral antidiabetic drugs (García-Pérez et al., 2013). Determination of adherence by MEMS showed nonadherence in 47% of patients, 29% by pill counting, and 31% when self-report was used (Mason et al., 1995; Matsuyama et al., 1993). These variations between different studies depend on a number of factors such as: type of method for determining adherence, patient population, socio-economic conditions and differences in the value of the cut-off point. Medication dosage also has a great influence on the degree of adherence. Although patients with type 2 diabetes usually start treatment with metformin, in order to maintain glycemic control, it is often necessary to introduce more than one drug. Most studies show that the level of adherence decreases as the number of drugs in therapy increases. Adherence is reduced by taking more doses of oral antidiabetic drugs per day, such that patients on a once-daily dosing regimen have higher adherence (61%) compared to patients on a twice-daily dosing regimen of oral antidiabetic medications (52%) (Dezzi et al., 2002). A study from 1997 monitored patient adherence over 6 months and reported adherence of 79% for once-daily dosing, 66% for twice-daily dosing, and 38% for thrice-daily dosing of oral antidiabetic medications. (Paes et al., 1997). However, 33% of patients who use medication once a day take more medication than prescribed. Patients

using fixed-dose drug combinations use less health care resources, have lower health care costs, and live longer compared to those using single-dose combinations (Hutchins et al., 2011). A very important factor in achieving optimal adherence is the patient's understanding of the prescribed therapy regimen. In doing so, the patient's unfamiliarity with medical terms, the patient's age, the perception and duration of the disease, the complexity of the dosage regimen, polytherapy, psychological factors, safety, tolerance and costs must be taken into account. The following factors contribute to the increase in adherence to type 2 diabetes mellitus therapy: a reduction in the complexity of dosage regimens, the use of drugs with an improved safety profile, educational initiatives, improvement in doctor-patient communication, and social support. The costs of poor adherence rates for developed countries are enormous, so improving adherence provides enormous health savings.

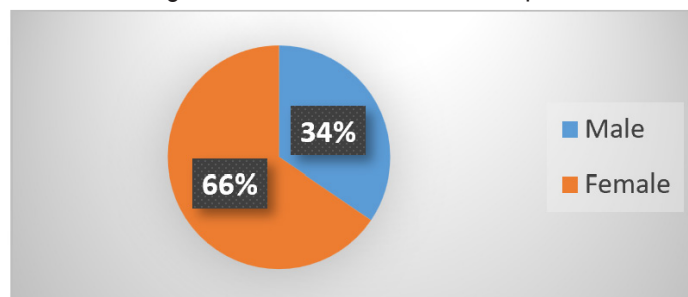
2. MATERIALS AND METHODS

The research was conducted in the family medicine centers of the Health Centers Lukavac and Banovići. The sample was made up of middle-aged, non-adherent respondents (35-65), who have been using metformin for a minimum of 6 months in the treatment of type 2 diabetes mellitus. The criteria for the inclusion of subjects in the research are: information that the subject suffers from diabetes mellitus type 2 for at least 6 months, that the subject uses metformin for more than 6 months, that the subject uses metformin irregularly during the last 6 months, that the patient does not suffer from a malignant disease, that the patient does not suffer from a severe mental disorder and voluntary written consent to participate in the research. The criteria for exclusion from the study are: non-consent to participate in the research, age under 35 and over 65, information that the subject does not suffer from type 2 diabetes mellitus for more than 6 months, the subject uses metformin for less than 6 months, the subject regularly uses metformin in treatment type 2 diabetes mellitus in the last 6 months, the subject does not use metformin in the treatment of type 2 diabetes mellitus, the patient suffers from malignant diseases, the patient suffers from a severe mental disorder, pregnancy. The instrument used in the research is a questionnaire modified on the basis of the Morisky scale. It was used to examine individual factors that influence adherence (socio-economic, health system factors, environmental factors, therapy-related factors, patient-related factors). The research was carried out according to the principles of the current revision of the Declaration of Helsinki. Considering that the survey of respondents was included, all subjects were also given an explanation to sign the appropriate form for agreeing to be included in the study and only after voluntary consent were the respondents surveyed. The survey questionnaire that was offered to respondents consists of a total of 60 closed-ended questions and 2 open-ended questions. The first part of the questionnaire concerned demographic and professional information. The second part contained questions related to the assessment of the patient's current behavior related to daily exercise and lifestyle, as well as to the disease - diabetes itself. The third part is a modified Morisky scale that dealt with the patient's self-assessment of his own behavior towards taking the therapy, and the fourth part was related to the patient's satisfaction with the therapy. Through the questionnaire we assessed the evaluation of certain factors that influence adherence (socio-economic, health system factors, environmental factors, factors related to therapy, factors related to the patient). The survey was conducted using the "face to face" method, where the interviewer asked questions to the respondent, following the specified instructions. The survey was anonymous and it was not possible to determine the identity of the respondents from the answers provided. Respondents themselves were marked with a code and the documentation did not contain identification data about the respondents. The subjects were informed about the purpose of the research, and it was explained to them that the obtained data will be used exclusively for research purposes. After the survey, all respondents had their blood glucose level measured.

3. RESULTS AND DISCUSSION

The survey included 58 diabetics from health centers Lukavac and Banovići, who are on metformin therapy and whose non-adherence was determined on the basis of a delay in arriving for the prescribed prescription, or on the basis of a delay in picking up therapy at the pharmacy for at least 6 days in the last 6 months. The respondents were surveyed in March and April 2024. The first part of the questionnaire refers to the demographic characteristics and professional orientation of the respondents. Out of 60 respondents, 38 (65.52%) respondents are female, while 20 (34.48%) respondents are male (Figure 1). Based on the obtained results, the influence of gender on the degree of adherence cannot be determined with certainty, and the aforementioned should be further investigated.

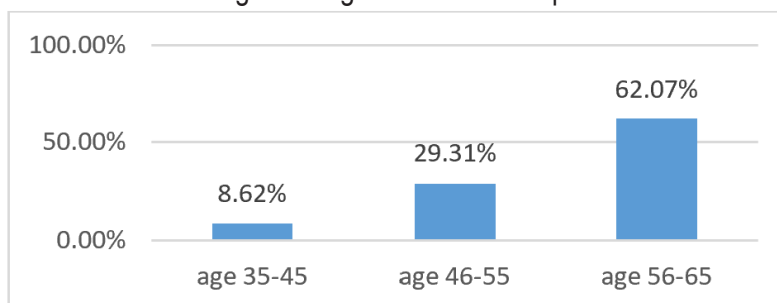
Figure 1. Gender structure of respondents



Source: Authors

Regarding the age of respondents, 5 (8.62%) respondents are aged 35-45 years, 17 (29.31%) respondents are aged 46-55 years, while 36 (62.07%) respondents are aged 56-65 year (Figure 2). Although the research included a group of middle-aged respondents, based on the results obtained, it can be seen that the largest number of respondents are 56-65 years old, and this research did not confirm the relationship between better adherence to therapy with middle-aged and older people.

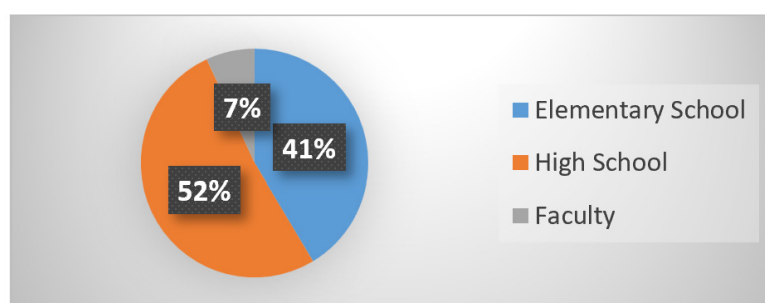
Figure 2. Age structure of respondents



Source: Authors

The largest number of respondents are married, 47 (81%). While the rest of the respondents stated that they were not married (divorced or widowed). The survey revealed that 24 (41.40%) of the respondents had completed only primary school, while 30 (51.70%) of the respondents stated that they had completed secondary school. Only 4 (6.90%) respondents state that they have completed higher education or university. Data on the completed education of the respondents are presented graphically (Figure 3). Regarding employment, the majority of respondents, 40 (69%) state that they are not employed (unemployed or retired), while only 18 (31%) state that they are employed. The impact of the respondent's marital status on adherence cannot be assessed with certainty based on the data obtained, and further analysis of the impact of the aforementioned factor is needed. The data that only 6.90% of the respondents have completed higher school or university speaks in favor of the fact that a lower level of adherence is also associated with a lower level of education of the respondents. Analyzing data on the respondents' employment leads to the conclusion that although 69% of the respondents indicated that they are employed, and 31% indicated that they are unemployed, employment does not affect the increase in the degree of adherence.

Figure 3. Data on completed education of the respondent

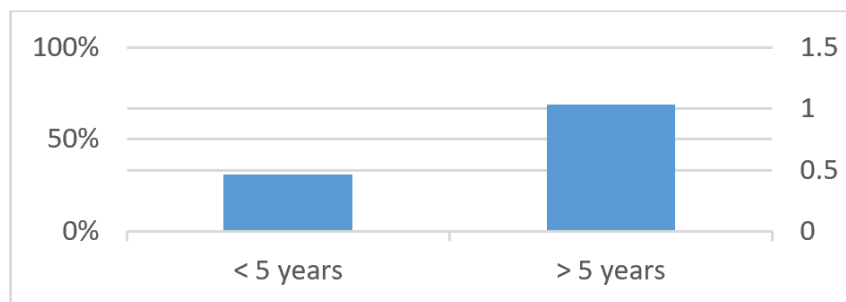


Source: Authors

In the second part of the questionnaire, the respondents' behavior was analyzed in relation to eating habits, physical activity, alcohol and cigarette consumption. 28 (48.30%) respondents state that on average they walk less than 1 hour a day, while 55 (94.80%) of them state that they do not have any physical activity - training. 30 (51.70%) respondents state that they walk more than 2 hours a day. In terms of eating habits, smoking and alcohol consumption, the following results were obtained: 21 (41.38%) respondents stated that they had 1-2 meals a day on average, while 34 (58.62%) stated that they had 3-4 meals a day. 20 (34.48%) respondents are smokers, while only 12 (20.68%) respondents state that they occasionally consume alcohol. Based on the obtained data on nutrition, physical activity and eating habits of the respondents, it can be concluded that a large number of respondents lead a passive life, with very little physical activity and that we have a large percentage of smokers. A passive lifestyle with unhealthy habits such as smoking, regardless of the diagnosis of diabetes, can be associated with poor adherence to therapy in the majority of respondents.

The next section of the questionnaire refers to answers about the characteristics of the disease and therapy, duration of diabetes, current therapy, concomitant therapy and previous changes in the therapy regimen. Based on the answers received, we conclude that 18 (31%) respondents have been suffering from diabetes for less than 5 years, while 40 (69%) respondents state that they have been suffering from diabetes for more than 5 years (Figure 4). Given that diabetes is a chronic disease, it is expected that the subjects' adherence to therapy will be lower, in proportion to the length of therapy use, which was confirmed by this research.

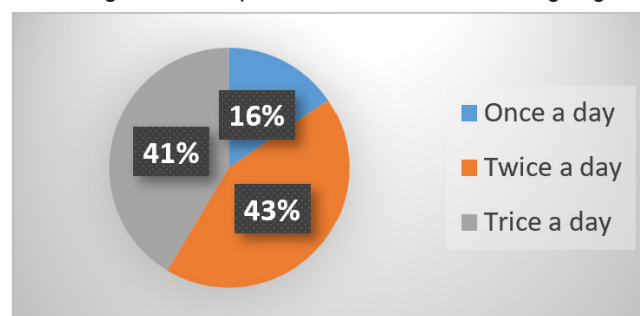
Figure 4. Duration of diabetes in the subjects



Source: Authors

In 24 (41.37%) of the examined patients, there was no change in the therapeutic regimen, while the other subjects stated that their diabetes therapy was changed at least 1 time. In addition to metformin, 20 (34.48%) respondents use another oral antihyperglycemic agent (most often glimepiride) in the treatment of diabetes. Multiple changes in therapy as well as concomitant therapy correlate with a lower degree of adherence to therapy, which can be confirmed by the data obtained in this study, given that non-adherent patients were included, most of whom had at least one other antihyperglycemic agent in addition to metformin, and that most of subjects had a change of therapy at least once. Regarding the dosage regimen of metformin, it was found that 9 (15.50%) respondents use metformin 1 time a day, 25 (43.10%) respondents use metformin 2 times a day, while 24 (41.40%) state that they use metformin 3 times a day (Figure 5). The data that 84.50% of respondents use metformin 2 or 3 times a day confirm the results of earlier research according to which a more complex therapeutic regimen is associated with a lower degree of adherence.

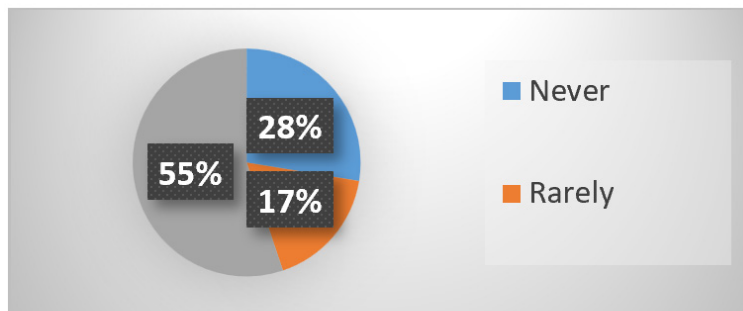
Figure 5. Respondent's metformin dosing regimen



Source: Authors

The section of the questionnaire that analyzed the respondents' attitude towards the regular use of therapy consists of 6 questions and the Cronbach 1 coefficient for it is 0.861. This means that the section particles measure the same attitude towards the use of therapy. The answers to the question "Do you sometimes forget to take your medicine" were obtained and presented graphically (Figure 6). As many as 16 (27.6%) respondents state that they never fail to take medicine, and 10 (17.24%) state that they rarely forget to take medicine. 32 (55.16%) respondents state that they sometimes or often skip taking the medicine. 21 (36.2%) respondents state that they never forget to take medicine with them when they leave home or travel.

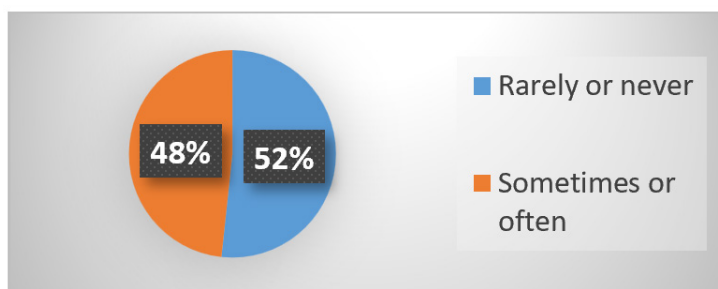
Figure 6. Answers to the question "Do you sometimes forget to take your medicine?"



Source: Authors

44 (75.87%) respondents state that they never have difficulty or rarely have difficulty remembering to take medicine, and only 14 (24.13%) respondents state that they often or almost always have difficulty remembering to take medicine. 30 (51.7%) respondents stated that they rarely or never stopped metformin therapy on their own, while 28 (48.3%) respondents stated that they sometimes or often stopped metformin therapy even though it was not suggested by the doctor (Figure 7). Such answers do not reflect the fact that non-adherent patients were included in the research, which suggests that patients are not objective when assessing their adherence to the prescribed therapy.

Figure 7. Answers to the question "Do you stop therapy on your own even though the doctor did not suggest it?"



Source: Authors

The section of the questionnaire that analyzes patients' satisfaction with the therapy they use consists of 9 questions presented on a Likert-type scale and its Cronbach 1 reliability coefficient is 0.989. Based on the answers received from this section, it can be concluded that the majority of respondents, although they are non-adherent, stated that they are satisfied with the effectiveness of the drug and the simplicity of the therapeutic regimen. As many as 47 (81%) respondents state that they are satisfied with the way the drug works on diabetes, 49 (84.48%) stated that they are satisfied with the time it takes for the drug to work, 56 (96.55%) respondents stated that they believe that is simply to take the drug in the regimen they were using at the time the trial began.

The section of the questionnaire that refers to the assessment of respondents' awareness of therapeutic options, complications of therapy and side effects of the drug has a Cronbach 1 coefficient of 0.906 and consists of 4 questions. 39 (67.24%) respondents state that they are well or very well informed about what they can expect from metformin therapy and that they have been warned by the doctor about possible complications of the therapy. The same percentage of respondents stated that they were actively involved in making the decision on metformin therapy, while 51 (87.93%) stated that they received the doctor's advice to come for regular check-ups. The impact of the patient's information about the therapy

on their adherence cannot be assessed with certainty, although the results obtained speak in favor of the fact that the patients' information was generally good and that it did not have a significant impact on their adherence, considering that patients who are insufficiently adherent were included. 54 (93.1%) subjects had elevated fasting blood sugar values at the time of testing, and only 4 (6.9%) subjects had fasting blood sugar values below 6.1 mmol/L at the time of testing. The average value of blood sugar for all subjects is 10.5 mmol/L, which indicates the ineffectiveness of the prescribed therapy, and which can be directly linked to the determined non-adherence of subjects to metformin therapy.

4. CONCLUSION

There are numerous factors that can affect a patient's adherence to prescribed therapy, especially in the treatment of chronic diseases such as diabetes. Patients are generally not objective when assessing their adherence, which was also confirmed by this research. Numerous interventions have been the subject of research with the aim of improving patient's adhere to a prescribed therapeutic regimen, but it is still unclear how effective these interventions actually are. In their research from 2012, Čulig et al showed how medication adherence affects pharmacoeconomics. They showed the costs of the risks and benefits of the therapy, and measured the cost in monetary terms. The results of the pharmacoeconomics analysis depend on several factors, one of the most common of which is adherence to therapy. Poor adherence to prescribed therapy threatens the effectiveness of treatment, and increases the budget for the introduction of new drugs (Čulig, 2012). Assessment of patient adherence and implementation of interventions aimed at improving it requires health workers to be trained in these skills. If we take into account the fact that the low level of adherence has become a global public health problem and leads to huge health costs, researching the factors that influence the adherence rate and finding the most effective methods that lead to the improvement of adherence to therapy are of great importance.

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