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PRACA POGLĄDOWA
REVIEW

The use of metformin in patients with chronic kidney disease

Stosowanie metforminy w przewlekłej chorobie nerek

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ABSTRACT

Diabetes is a disease that affects about 4% of the population, and its incidence has been growing steadily. Increasingly more young people have to face this illness, and therefore more people suffer from chronic complications. The most frequent disorder of diabetics is diabetes nephropathy. This complication makes people's lives very difficult – not only the life of the patients but also the doctors who must strongly restrict the base of pharmaceuticals which can be used by these patients. Metformin has become a hope for people suffering from diabetes. This medicine has many advantages such as a decrease in glycaemia through many mechanisms. Simultaneously, it does not expose diabetics to hypoglycaemia. It reduces the death rate and protects patients' hearts. Additionally, it positively influences body weight, and it is taken orally. Currently, this medicine is also recommended in pre-diabetes states. Unfortunately, the chronic disease of the kidneys which usually occurs during diabetes does not enable the use of metformin. According to the Polish Diabetes Association, the dose of metformin should be reduced by half in the third phase of chronic kidney disease. In next phases, metformin should be thoroughly abandoned. There are opinions about the positive influence of metformin on people suffering from kidney disorders.
The above article summarizes the current knowledge of using metformin and analyzes the latest research which describe its functioning. Additionally, it confronts two stances about the use of metformin in chronic kidney disease.

KEY WORDS
hypoglycemia, diabetes, chronic kidney disease, metformin, diabetic nephropathy

STRESZCZENIE

Cukrzyca jest chorobą, która dotyka około 4% populacji, a częstość jej występowania stale rośnie. Chorują coraz młodsze osoby, stąd problem przewlekłych powikłań dotyczy coraz większej liczby osób. Najczęstszym powikłaniem osób z cukrzycą jest nefropatia cukrzycowa, która stanowi problem nie tylko chorych, lecz także lekarzy, którzy muszą w dużym stopniu ograniczyć bazę leków stosowanych u tych pacjentów. Nadzieją dla osób chorych na cukrzycę stała się metformina – lek o wielu zaletach. Obniża glikemię drogą wielu mechanizmów, jednocześnie nie narażając na epizody hipoglikemii, zmniejsza śmiertelność, działa kardioprotekcyjnie, wykazuje korzystny wpływ na masę ciała i jest

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stosowana doustnie. Obecnie wskazana również w stanach przedcukrzycowych. Barierą do stosowania metforminy okazała się przewlekła choroba nerek, która rozwija się w przebiegu cukrzycy. Według Polskiego Towarzystwa Diabetologicznego powinno się zredukować dawkę metforminy o połowę w III stadium przewlekłej choroby nerek, natomiast powyżej tego stadium, odstawić całkowicie. Pojawiły się również doniesienia o pozytywnym wpływie tego leku u chorych z powikłaniami nerkowymi.
Artykuł podsumowuje obecny stan wiedzy na temat zastosowania metforminy, analizuje najnowsze badania, które opisują mechanizmy jej działania, a także konfrontuje dwa stanowiska odnośnie do stosowania metforminy w przewlekłej chorobie nerek.

SŁOWA KLUCZOWE
cukrzyca, metformina, nefropatia cukrzycowa, hiperglikemia, przewlekla choroba nerek

INTRODUCTION

Diabetes is called the first, non-infectious epidemic in human history. It has accompanied people for centuries. Diabetes is not an isolated disease entity, but a set of metabolic disorders arising from elevated blood glucose values. Hyperglycemia contributes to late complications in the form of macro- and microangiopathy, resulting in the damage of multiple organs, particularly the eyes, heart, and kidney [1].
The IDF (International Diabetes Federation) estimates that currently diabetes affects more than 250 million people in the world, including 90% of them that are diagnosed with type 2, and it is expected that in 2025 this number will increase to approximately 380 million of people. 4.9 million people die from diabetes every year, namely one person every 7 seconds [2,3,4,5]. In Poland, diabetes affects 2.73 million people. Despite the intensification and personalization of therapy, diabetes in Poland is still the most common cause of blindness, limb amputation and kidney failure [6].
Metformin is a commonly used medicine in the treatment of type 2 diabetes mellitus. Moreover, according to the latest indications of diabetes associations – European (EASD – European Association for the Study of Diabetes) and American (ADA – American Diabetes Association) it should be used at every stage of the disease [7]. In addition, the usage of metformin in preventing the progression of prediabetes i.e. impaired fasting glucose and impaired glucose tolerance should be considered [8].
Due to the frequent use of metformin in patients with chronic kidney disease, it was decided to summarize this subject.

Chronic kidney disease

The document 'Kidney Disease: Improving Global Outcomes (KDIGO) 2012', defines chronic kidney disease (CKD) as an irregular construction of the kidneys or kidney problems affecting health, which persists for more than 3 months [9].

CKD advancement is determined on the basis of GFR (glomerular filtration rate):

Category	GFR (ml/min/1.73 m^2)	
G1	≥ 90	Normal or relatively high GFR
G2	60–89	Mild reduction of GFR
G3a	45–59	Moderate reduction of GFR
G3b	30–44	Moderate reduction of GFR
G4	15–29	Severe reduction of GFR
G5	< 15	Established kidney failure

Diabetic nephropathy is a major complication of diabetes. It affects about 30% of patients with type 1 diabetes and 25–40% of patients with type 2 disease [10]. The frequency of renal complications in type 2 diabetes may increase over the following years [11]. Diabetic nephropathy is characterized by the presence of elevated levels of albumin in the urine, progressive deterioration of renal filtration functioning and hypertension [10]. Mortality due to kidney disease is 17 times higher in diabetics compared with people not suffering from diabetes [12]. Screening for diabetic microvascular complications, including diabetic nephronpathy is recommended: an annual preliminary fundus examination and analysis of the urine for albumin. Such studies should be performed in every person with diabetes [13].
Chronic kidney disease in diabetes is a process arising from several disorders. Renin-angiotensin-aldosteron (RAAS) plays an important role in this process. Studies indicate that acute hyperinsulinemia leads to stimulation of the sympathetic nervous system, which is one of the factors inducing the production of renin by the juxtaglomerular apparatus of the kidney [14,15]. Vascular inflammation leads to endothelial dysfunction; it becomes leaky and facilitates the migration of inflammatory cells into the vascular wall [16]. Such vessels demonstrate reduced susceptibility, which results in an increase in the speed of the pulse wave and an increase in blood pressure. Other adverse factors include advanced glycation end products (AGE) generated by the chemical reaction between the reducing sugars and free amino group of proteins, lipids and nucleic acids [17]. In the presence of chronically eleva-

ted levels of glucose, the production of AGE is advanced. This reaction produces an intermediate which contributes to the formation of reactive oxygen species. The binding of the AGE receptor for advanced glycation end products (RAGE) leads to the accumulation of macrophages and T lymphocytes. It develops inflammation by the infiltration of vessels, which contributes to remodeling and atherosclerosis at the location of the receptor [18]. Another mechanism of kidney damage is increased activity of NADPH oxidase, which catalyzes the reduction of oxygen to a superoxide anion; this spontaneously combines with other molecules, producing free radicals. A superoxide anion also reacts with nitric oxide to form peroxynitrite (ONOO), decreasing the pool of free bioactive NO. Free radicals effect the vascular endothelium by inducing inflammation. Additionally, hypertension develops induced by theinhibition of nitric oxide [18,19].

Metformin

Metformin is the most widely used hypoglycemic medication in the world [20]. It is used by about 59–61% of patients with diabetes [21,22]. Its glucose lowering mechanisms result from the inhibition of gluconeogenesis in hepatocytes [23]. Moreover, metformin causes an increase in the sensitivity of peripheral tissues to insulin activation of the insulin IRS-2 receptor and growth in glucose uptake by increasing the translocation of the GLUT-1 receptor [24]. The impact of metformin is also expressed in reducing the absorption of glucose in the middle of the small intestine [25].

It was found that side effects occur in 28% of patients who take metformin [26]. Gastrointestinal disorders occur most frequently and they are present in approximately 20–30% of patients, of which 5% needs to discontinue treatment with this drug [27]. Lactic acidosis develops in 4.3/100 000 people taking metformin [22,28]. Patients treated with metformin are not exposed to severe hypoglycemia. Its inclusion in the treatment of patients with newly diagnosed diabetes lowers the mortality and morbidity of cardiovascular complications [29].

It is worth noting the additional action of metformin and the resulting new guidelines for its application [8]. Metformin has favorable effects on body weight by reducing visceral adipose tissue and improvement of lipid parameters [30,31]. It also works in a cardioprotective manner by inhibiting platelets, improving endothelial function (the activation of endothelial NO synthase), and reduces the risk of micro and macrovascular complications, regardless of the degree of control of diabetes [7,32,33]. Accordingly, the list of indications for metformin subsidies was expanded by including for instance insulin resistance, characterized by the lack of adequate response of the body to insulin. The factors contributing its development are visceral obesity and abnormal expression of proteins involved in the pathway of insulin action. Insulin resistance may be secondary in the course of other diseases such as cirrhosis, autoimmune diseases, endocrine diseases or cancer. It is also a component of metabolic syndrome, defined as a series of factors that increase the risk of developing hypertension, atherosclerosis and type 2 diabetes [34]. Another indication is PCOS (polycystic ovary syndrome). It is a complex disorder of endocrine clinically manifested ovulation and menstrual disorders consequently leading to infertility. Currently, PCOS is considered to be the most common cause of infertility in Poland [35]. Another important component of the syndrome is insulin resistance and hyperinsulinism secondary to it, which contributes to the development of hyperandrogenism [36]. The beneficial effect of metformin on fertility in PCOS patients and the reduction of insulin resistance changed the regimens of this disease but the safety of use of the above treatment is still under investigation [37].

Despite the many contraindications such as the presence of advanced chronic vascular complications of diabetes, liver failure, kidney failure, heart failure, respiratory failure, severe infections, alcohol abuse, old age (> 75 years) metformin is often used in these patients [38]. In a study conducted in Germany, in up to 73% of patients with type 2 diabetes treated with metformin who reported to hospital admissions had at least one contraindication to metformin usage [39].

Metformin in CDK

Metformin is a drug excreted entirely unchanged by the kidney, therefore it is important to raise the issue of the use of this drug in patients with chronic kidney disease at different stages of its development [38].

According to the current guidelines of the Polish Diabetes Association, 'Guidelines for the clinical management of patients with diabetes' from 2015, treatment with metformin can be continued for an eGFR (estimated GFR) of 60 ml/min/1.73 m^2 [8]. With further deterioration of kidney functioning (eGFR 45–59 ml/min/1.73 m^2) metformin may be further applied, but the patient should be monitored more closely and creatinine levels should be evaluated. The dose of applied metformin should be reduced by half at a glomerular filtration rate at the level of 30––44 ml/min/1.73 m^2, and the discontinuation of the drug should take place at an eGFR less than 30 ml/min/1.73 m^2. To minimize the side effects of metformin which may lead to patient intolerance of the substance, the drug must be introduced slowly, gradually by increasing the dose until a maximum tolerated dose per day (up to 3 g), and divided into 2––3 parts [8]. Similarly, according to the American Geriatrics Society Expert Panel on the Care of Older Adults with Diabetes Mellitus, the use of metformin

should be discontinued at a glomerular filtration rate below 30 ml/min/1.73 m^2. Individually, the use of metformin is allowed at an eGFR of 30–60 ml/min/ 1.73 m^2 with frequent monitoring of renal functioning [40]. According to the US Food and Drug Administration Prescribing Guidelines for Metformin as Related to Kidney Function, metformin usage depends on the concentration of serum creatinine levels. This drug is contraindicated in patients with chronic kidney disease at the moment of achieving a level of createnine ≥1.5 mg/dL for men and ≥1.4 mg/dL for women or an abnormal creatinine clearance (CrCl) [41].

Research recommends the following metformin administration: 500 mg at an eGFR 15 ml/min/1.73 m^2, 1000 mg for a glomerular filtration rate of 30 ml/min/ 1.73 m^2, 2000 mg for 60 ml/min/1.73 m^2 and 3000 mg in the absence of a decrease in glomerular filtration rate. In contrast, for patients on peritoneal dialysis, the dose should not exceed 250 mg and 500mg for people on hemodialysis [42].

The therapeutic levels of metformin have been set at the following level 0.7 (0.3–1.0) mg/L [43]. A study carried out in France found that metformin, as well as serum creatinine concentrations increase with the degree of glomerular filtration impairment. Even lower doses of metformin (1000–2000 mg/d) in patients with chronic kidney disease lead to dangerously high blood levels (above stage III metformin > 1 mg/L) [44]. Frid et al. measured the levels of metformin in 137 patients constantly taking this drug, and with CKD. The average scores were 4.50 μmol/L (deviation 0.10–20.70) for patients with a glomerular filtration rate (eGFR) greater than 60 mL/min/1.73 m^2, 7.71 μmol/L (deviation 0.12–15.15) for an eGFR 30–60 mL/min/1.73 m^2, and 8.8 μmol/L (deviation 5.99–18.60) for an eGFR less than 30 mL/min/1.73 m^2. For The authors established the upper limit of the therapeutic concentration at 20 mmol/L [41].

Research conducted by St. Vincent's Hospital and the University of New South Wales Institutional Ethics Committees on a group of 24 patients indicates that treatment with metformin at such a low creatinine clearance is safe and provides a basis for making larger controlled studies of metformin in patients with chronic kidney disease. However, it is important that the dose should be reduced in renal impairment and increased by taking into account the concentrations of glucose and lactate in blood plasma. Measuring the levels of metformin is useful in order to ensure significant drug accumulation in patients with CKD, but patients need to be aware of warning signs for lactic acidosis, such as nausea and vomiting [45].

Current studies also indicate clinical benefits in patients with chronic kidney disease. Roussel et al. analyzed nearly 20,000 patients with DM2 and diagnosed atherosclerosis. Mortality was 6.3% (95% CI, 5.2%– –7.4%) for patients who take metformin and 9.8% (95% CI, 8.4%–11.2%) for patients without the drug. In the analyzes of predetermined subgroups, there were visible benefits in patients with a creatinine clearance of 30 to 60 ml/min/1.73 m^2 (adjusted HR 0.64 [95% CI 0.48–0.86]). The authors concluded that treatment with metformin can reduce mortality in patients with renal contraindications [46].

Alternative treatment

Despite the many benefits of metformin, there are situations in which the treatment cannot be continued. Usually disorders of the gastrointestinal tract or, less frequently occurring metabolic acidosis, result in treatment discontinuation [27,28]. The most often chosen alternative method of treatment is the use of sulfonylureas, especially in people with normal weight, with preserved functioning of pancreatic beta cells [8]. In patients with impaired renal function, in whom sulfonylureas are contraindicated, or as a result of their use hypoglycemia develops, the solution could be to use DPP-4 inhibitors in a reduced corresponding dose. Linagliptin is a drug which can be used in full doses during reduced GFR [47]. Another group of preferred drugs especially in patients with concomitant obesity and a high risk of occurrence of hypoglycemia are SGLT-2 inhibitors (sodium glucose cotransporter-2 inhibitors). Other alternative drugs are of PPAR-γ agonists (peroxisome proliferator-activated receptor gamma), indicated especially in patients with insulin resistance; however, a contraindication to their use is heart failure [8,48].

SUMMARY

During metformin administration in patients with chronic kidney disease, physicians should be aware of the variability of plasma concentrations. Its growth over the upper limit may result in serious side effects such as lactic acidosis. Summing up PTD and ADA guidelines, diabetics should receive a lower dose of metformin when the creatinine clearance is between 60–30 ml/min/1.73 m^2. However, at a GRF less than 30 mL/min per 1.73 m^2, treatment with this medicine should be discontinued. Metformin in patients with diabetes and CKD also has other benefits than other hypoglycemic ones. A nephroprotective effect is observed and a reduction in the overall mortality in patients taking this drug.

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