Učinkovitost zdravljenja sindroma policističnih jajčnikov z metforminom

Efficacy of metformin treatment in polycystic ovary syndrome

Avtor / Author

Ustanova / Institute

Katja Jerenec[1], Maša Samojlenko[1], Ksenija Geršak[2], Polonca Ferk[1]

[1]Univerza v Mariboru, Medicinska fakulteta, Maribor, Slovenija; [2]Univerza v Ljubljani, Medicinska fakulteta, Katedra za ginekologijo in porodništvo, Ljubljana, Slovenija; Univerzitetni klinični center Ljubljana, Ljubljana, Slovenija

[1]University of Maribor, Faculty of Medicine, Maribor, Slovenia; [2]University of Ljubljana, Faculty of Medicine, Department of Obstetrics and Gynaecology, Ljubljana, Slovenia; University Medical Centre Ljubljana, Ljubljana, Slovenia

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Naslov za dopisovanje / Correspondence
doc. dr. Polonca Ferk, Univerza v Mariboru, Medicinska fakulteta, Taborska ulica 8, SI–2000 Maribor, Slovenija
Telefon + 386 22345821
Fax + 386 22345820
E–pošta: polonca.ferk@guest.arnes.si

Izvleček

Metformin je peroralni antidiabetik, potencialno učinkovit tudi v terapiji bolnic s sindromom policističnih jajčnikov (PCOS). Med bolnicami s PCOS prihaja do opaznih razlik v farmakološkem odzivu na metformin, kar je verjetno posledica kliničnih, biokemijskih, genetskih in drugih dejavnikov. V prispevku navajamo kratek pregled ugotovitev dosedanjih kliničnih študij učinkovitosti zdravljenja bolnic s PCOS z metforminom ter hkrati povzemamo preliminarne rezultate retrospektivne farmakogenetske študije na vzorcu slovenskih bolnic s PCOS. Sodobno znanje farmakogenetike si počasi, a vztrajno utira pot v klinično prakso ter postaja pomemben segment obravnave bolnikov in eden od temeljev osebne medicine – medicine prihodnosti.

Abstract

Metformin is an oral antidiabetic drug with potentially beneficial effects in patients with polycystic ovary syndrome (PCOS). Different pharmacological responses to metformin have been reported in PCOS patients, which may be attributable to various clinical, biochemical, genetic and other factors. Here, we have outlined a short review of the results from current clinical studies on metformin efficacy in PCOS patients. Additionally, preliminary results from a retrospective pharmacogenetic study by our group on a sample of Slovene PCOS patients are presented. Pharmacogenetics is an emerging science that should provide options for individualized medicine, the future of healthcare.

DEFINITION, ETIOPATHOGENESIS AND DIAGNOSIS OF POLYCYSTIC OVARY SYNDROME

Polycystic ovary syndrome (PCOS) is one of the most common female endocrine disorders. The disease affects approximately 7% of the female population at the reproductive age (1) and is the most common cause of anovulatory infertility (2). PCOS is defined by excessive androgen biosynthesis and action with distinct chronic oligo– or anovulatory cycles and morphologically polycystic ovaries (2). Despite extensive previous and ongoing studies, the etiology of this multifactorial syndrome remains unclear.

Excessive release of luteinizing hormone (LH) is still considered to have an important role in PCOS pathogenesis (3, 4, 5, 6, 7); however, androgen overproduction, anovulation and formation of multiple ovarian cysts are nowadays considered to be predominantly causatively linked with intraovarian hyperandrogenism. In addition, at least adrenal dysfunction may contribute to hyperandrogenic features in PCOS (8, 9, 10). Insulin resistance and compensatory hyperinsulinaemia are also linked to PCOS, resulting in further elevation of serum androgen levels (11, 12, 13). Long–term complications of PCOS include metabolic syndrome, cardiovascular disease and diabetes mellitus type 2 (DM2), accompanied by psychological issues (2, 8, 14). PCOS diagnosis is based on the Rotterdam diagnostic criteria approved in 2003 (15), specifically: (i) oligo– or anovulation, (ii) clinical or biochemical signs of hyperandrogenism, and (iii) polycystic ovaries on ultrasound (US). For confirmation of PCOS diagnosis, two out of three criteria must be fulfilled, and all other causes of similar clinical problems excluded (e.g., congenital adrenal hyperplasia, androgen–secreting tumors, Cushing's syndrome) (15).

TREATMENT OPTIONS FOR POLYCYSTIC OVARY SYNDROME

PCOS is treated symptomatically and individually, considering therapeutic goals that vary with each patient (16). Due to the importance of specific symptoms in different age groups, the therapy should be appropriately adjusted to individual patients (17). Treatment options in PCOS women can be divided into "urgent" (improving menstrual cycle abnormalities, ovulatory dysfunction, infertility, symptoms of hyperandrogenism) and "long–lasting" (dealing with insulin resistance and its consequences, preventing subchronic inflammatory processes and oxidative stress) (16, 17, 18, 19). The first therapeutic approach always involves changes to promote a healthy lifestyle (including regular and healthy diet, physical activity), especially in overweight patients (20). The next step is pharmacological treatment, which includes oral contraceptives, clomiphene citrate, metformin, antiandrogens, progestagens and gonadotropin–releasing hormone agonists (Table 1). In the case of pharmacotherapeutic insufficiency, surgical options need to be considered, such as ovarian laparoscopic resection or ovarian electrocoagulation (18, 20).

PHARMACOLOGICAL CHARACTERISTICS OF METFORMIN

Metformin is an oral antidiabetic drug belonging to the biguanide class. Its formal and crucial indication for prescription is DM2, particularly in overweight patients (21). The standard single dose is 500 or 850 mg two to three times a day during meals. To avoid unwanted effects, a gradual increase in dosage is recommended over the first 10 to 15 days until the therapeutic daily dose is achieved, which is usually around 2000 mg (21). Many previous studies have shown beneficiary therapeutic effects of metformin in PCOS patients. In addition to improving insulin sensitivity (consistent with its formal indication for prescription), metformin exerts other positive effects on metabolic, hormonal and reproductive irregularities in different PCOS subphenotypes (22). The latter findings were additionally confirmed by preliminary results of our pharmacogenetic study on Slovene non–insulin resistant PCOS patients (data not published yet).

Pharmacodynamics of metformin

The primary target organ for metformin action is liver, although other tissues are affected as well (skeletal muscle, visceral fat, endothelium, ovaries) (1).

Table 1: *Management options for polycystic ovary syndrome (obtained from (17))*

Clinical features of PCOS	Management options	
Irregular menstrual cycles	Oral contraceptives	
	Lifestyle modification, weight loss	
	Metformin	
Hyperandrogenism	Biochemical	Decreasing testosterone production
		• Oral contraceptives
		• Metformin
		• Lifestyle modification, weight los
		Decreasing testosterone action
		• Antiandrogens (spironolactone)
		• Metformin
		• Lifestyle modification, weight loss
	Mechanical	Shaving, electrolysis, laser, 13.9% eflornithine hydrochloride cream
Infertility	Clomiphene citrate	
	Lifestyle modification, weight loss	
	Metformin	
Insulin resistance, risk of type 2 diabetes mellitus	Lifestyle modification, weight loss	
	Metformin	

The key mode of metformin action is inhibition of gluconeogenesis in hepatocytes. Furthermore, metformin slows down glycogenolysis, enhances peripheral insulin sensitivity, promotes uptake and utilization of glucose in peripheral tissues, reduces gastrointestinal glucose absorption, and has a beneficial effect on fat metabolism (20).

On a molecular level, the majority of effects of metformin occur as a result of adenosine–monophosphate–dependant protein kinase (AMPK) activation. AMPK activation is a trigger for phosphorylation of key metabolic enzymes, transcription factors and co–activators, which leads to a switch from anabolic to catabolic cell metabolism (synthesis of glucose, fat, proteins and cell growth are stalled, while fatty acid oxidation and cell glucose uptake are promoted) (23). However, the exact mechanism of action of metformin on AMPK is currently unclear. Recent studies have demonstrated that the primary target of metformin action is the mitochondrial cellular respiratory chain, specifically the respiratory complex I (RCC1), and not AMPK. Activation of RCC1 leads to reduction of adenosine–triphosphate (ATP) production, which temporarily results in energy reduction in cells. Consequently, the AMP/ATP ratio is raised, and AMPK activated. For successful activation of AMPK, phosphorylation with serine–threonine kinase 11 (STK11) and Ca^{2+}/calmodulin–dependant kinase β (CaMKKβ), proposed to be allosterically activated by AMP (23), is also required.

Pharmacokinetics of metformin

Passive diffusion of metformin through cell membranes is not possible due to its hydrophilic cation form at physiological pH. Therefore, special cation transporters are needed for metformin distribution. Transporters are expressed in an organ–specific man-

ner (Figure 1). Absorption of metformin after oral administration mainly occurs in the small intestine with the plasma membrane monoamine transporter (PMAT) located on the luminal side of enterocytes. To a lesser extent, the same role is performed by organic cation transporter 3 (OCT3) additionally located in liver, adrenal gland (24), skeletal muscle, heart muscle, brain and placenta (25). Metformin is mainly distributed in the liver, kidneys and skeletal muscles (24). Moreover, metformin has a high volume of distribution and binding to plasma proteins is negligible, implying considerable tissue uptake. The key transporters of metformin into liver and skeletal muscle cells are organic cation transporters 1 (OCT1) and OCT3. After entry into plasma, slow progression of metformin to erythrocytes is observed (24). The metabolites of metformin in humans are not known at present. Excretion of metformin in its unchanged form largely occurs through glomerular filtration and tubular secretion with high clearance (21, 24). The main transporter of metformin uptake in kidneys is OCT2, and on the luminal side, MATE1 and MATE2K predominantly transport metformin into urine (24, 25).

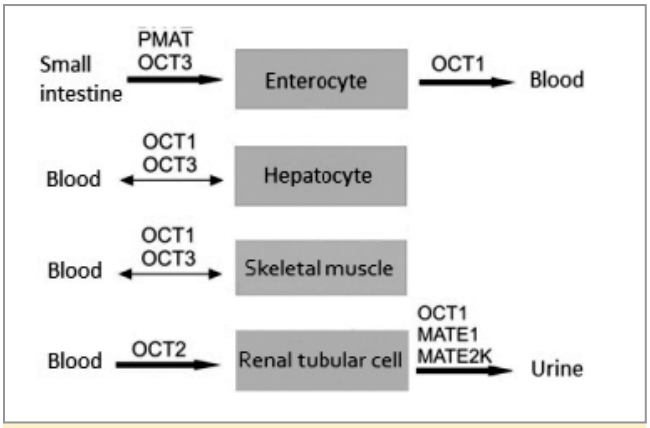

Figure 1. *Major transporters of metformin in human cells (obtained from (24))*

Legend: OCT – Organic Cation Transporter, MATE – Multidrug And Toxin Extrusion, PMAT – Plasma Membrane mono Amine Transporter

MONITORING AND EVALUATION OF EFFICIENCY AND SAFETY OF METFORMIN IN PATIENTS WITH POLYCYSTIC OVARY SYNDROME

Polycystic ovary syndrome is a complex disease with heterogeneous clinical presentations. Therapeutic efficiency is monitored individually according to symptoms and expected goals of treatment. Based on the current knowledge of metformin pharmacology and etiopathogenesis of PCOS, improvement of biochemical, endocrine, reproductive and metabolic features is feasible in metformin–treated PCOS patients (1, 26, 27).

Ideally, the parameters listed in Table 2 should be monitored. However, not all parameters are monitored in practice due to phenotypic differences among patients and specific goals of treatment. Moreover, no common clinical guidelines on the specific parameters and times of monitoring have been presented as yet. Often, the efficiency of metformin treatment is evaluated after 6 months with assessment of menstrual and ovulatory cycles as well as selected metabolic parameters (16).

Reduction of plasma androgen levels and/or improvement of clinical hyperandrogenism have been confirmed in metformin–treated PCOS patients. These effects may be due to the direct inhibition of enzymes involved in ovarian androgen biosynthesis and/or the indirect influence of decreased plasma insulin levels (1). Additionally, more regular menstrual cycles, ovulation and pregnancy rates have been reported in metformin–treated PCOS patients (20). Although our clinical study was performed on a small group of Slovene PCOS patients, the data validated the effectiveness of metformin treatment, revealing a significant reduction in plasma total testosterone (TT) levels, free androgen index (FAI), plasma LH levels, plasma LH vs. follicle–stimulating hormone (FSH) ratio, improvement of clinical hyperandrogenism (acne), and an increase in US visible corpus luteum and pregnancy rates (data not published yet).

Metformin treatment in PCOS patients appears relatively safe. In 10–25% of patients on metformin therapy, minor transient (predominantly gastrointestinal) adverse effects occur. Lactic acidosis is rare, although possible serious complications of adminis-

Table 2: *Important parameters in evaluating the efficacy of metformin in treating polycystic ovary syndrome (16, 20, 26, 29)*

Clinical parameters	• Body mass index
	• Waist–to–hip ratio
	• Menstrual status
	• US visualized ovarian morphology
	• US visualized corpus luteum
	• Pregnancy
	• Hirsutism
	• Acne
	• Male pattern alopecia
Biochemical parameters	• Plasma androgen levels (total and free testosterone, androstendione, DHEAS)
	• Plasma estradiol and progesterone levels
	• Plasma gonadotropin levels (LH, FSH)
	• LH/FSH ratio
	• Plasma SHBG levels
	• FAI
	• Fasting plasma glucose and insulin levels
	• Oral glucose tolerance test
	• HOMA–IR
	• Plasma total cholesterol, HDL, LDL and triglyceride levels

Legend: US – ultrasound, DHEAS – dehydroepiandrosterone sulfate, LH – luteinizing hormone, FSH – follicle–stimulating hormone, SHBG – sex hormone–binding globulin, FAI – free androgen index, HOMA–IR – homeostasis model assessment for insulin resistance, HDL – high–density lipoprotein, LDL – low–density lipoprotein; FAi = 100 x plasma total testosterone concentration (nM) /plasma SHBG concentration (nM); HOMA = fasting plasma insulin concentration (mIU/L) x fasting plasma glucose concentration (mmol/L)/22.5

tration may occur when metformin contraindications are not considered. Such complications have been reported mainly in cases of impaired renal function or renal failure (creatinine clearance < 60 ml/min), dehydration, serious infection, shock, use of intravascular radioisotopes containing iodine, liver insufficiency, diabetic ketoacidosis, diabetic coma, acute and chronic illnesses leading to tissue hypoxia (e.g., heart failure, respiratory failure, recent myocardial infarction, shock) and acute alcohol poisoning or chronic alcoholism (16, 21).

In case of no improvement in the clinical and biochemical symptoms of PCOS, the treatment is considered unsuccessful. If serious adverse effects occur that are not resolved during the course of treatment, metformin treatment should be abandoned.

INTERINDIVIDUAL VARIABILITY IN METFORMIN RESPONSE IN PATIENTS WITH POLYCYSTIC OVARY SYNDROME

The complexity of pathophysiological and phenotypic characteristics of PCOS leads to different patient responses to metformin therapy. Application of an equal dose of metformin in the same dosing interval can either lead to: (i) the desired effect, (ii) no or limited therapeutic effects, or (iii) a desired therapeutic effect, but with serious concurrent adverse effects. The goal of modern clinical studies is to identify specific biochemical, clinical, genetic, environmental and other prognostic factors that influence pharmacological responses to the drug to facilitate the selection of the optimal pharmacotherapeutic and dosage regimens for each individual, prior to pharmacotherapy (1, 22). Several studies have shown a lower therapeutic effect of metformin on reproductive and metabolic irregularities in patients with higher ages, long–lasting infertility and higher body mass index (BMI) (22). Metformin–treated PCOS patients with anovulatory periods differ in terms of index of insulin resistance, compared to metformin–treated PCOS patients with ovulatory periods. However, the clinical relevance of this finding is currently unclear (22, 28). In a group of Greek PCOS patients, better response to metformin was observed in women with lower plasma androgen levels (1). We designed a similar study focusing on Slovene PCOS patients. Our preliminary results indicate that lower BMI before treatment is predictive of a higher pregnancy rate after 6 months of metformin therapy (data not published yet).

Recent studies have shown that the efficiency of metformin treatment is largely attributable to genetic factors influencing the pharmacodynamic and pharmacokinetic properties of the drug. Specifically, genetic polymorphisms in genes encoding OCT1 (25, 29, 30, 31), OCT2 (32, 33), MATE1 (34, 35, 36), MATE2–K (35, 37), sex hormone–binding globulin (SHBG), androgen receptor (38) and STK11 kinase (39, 40) appear to play an important role. Our preliminary results on the rs366313 polymorphism in the *NDUFS4* gene encoding RCC1 and rs12943590 polymorphism in the *SLC47A2* gene encoding the MATE2–K transporter indicate that these polymorphisms do not have a significant influence on the efficiency of metformin treatment in PCOS patients. However, it is possible that the results were inappropriately interpreted due to a small number of patients. Notably, the AG genotype of rs366313 and GG genotype of the rs12943590 polymorphism display a tendency towards improving the reproductive function of patients, while a combination of genotypes (AG rs12943590/ AG rs366313) leads to reduction of plasma TT levels after a 6–month treatment period with metformin (data not published yet).

CONCLUSIONS

Owing to the unclear etiology of PCOS, symptomatic treatment of the syndrome is favored. Several studies, including ours, have confirmed that metformin is an effective drug for treating PCOS. However, PCOS is not yet considered a formal indication for metformin administration.

Among PCOS patients, interindividual variability in pharmacological response to metformin treatment is observed, which may be partly alleviated with appropriately designed clinical pharmacogenetic studies. However, for more detailed information and general conclusions, appropriate genome–wide association studies, in combination with evaluation of other relevant clinical, biochemical and environmental factors should be implemented. Based on the known contributions of specific prognostic parameters to metformin efficiency, the final goal is to optimize the therapeutic regimens for individual PCOS patients.

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