Assessment of adverse drug reaction reports : metformin and metformin fixed drug combinations

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Diploma thesis

Academic year:
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Assist. Prof. Joško Božić, MD, PhD

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Table of contents

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1. INTRODUCTION

1.1. Diabetes definition

Diabetes mellitus is a chronic syndrome of disordered metabolism of carbohydrate, protein and fat, secondary to an absolute or relative deficiency of insulin, due to impaired insulin secretion, reduction in biological effectiveness of insulin or decreased insulin sensitivity of tissues (1, 2).

There are two main types of diabetes mellitus: type 1 diabetes – formerly known as insulin dependent diabetes mellitus, and type 2 diabetes – known as non-insulin dependent diabetes mellitus. The latter accounts for more than 90% of all diabetes cases (1, 3). Diabetes type 2 is characterized by partial insulin deficiency due to dysfunction of pancreatic B-cells and variable insulin resistance in target organs (3). Other major categories of diabetes mellitus are: other specific causes, such as endocrinopathies, drug-induced, infections, genetics and defects of B cell function and gestational diabetes mellitus (4).

1.2. Epidemiology

Diabetes mellitus type 2 is a growing public health problem because of a global rising tide of physical inactivity, unhealthy diet and obesity among adolescents and young adults. It is one of the fastest growing diseases worldwide. Although nowadays it is increasingly diagnosed in children, adolescents, and young adults it is still mostly diagnosed in elderly (5).

The epidemiology of type 2 diabetes is influenced by genetic and environmental factors. Incidence and prevalence of diabetes are different in various geographical regions, where over 80% are living in low-middle-income countries. In 2017 it was estimated that 415 million people were diagnosed with diabetes, and 193 million people had undiagnosed diabetes. The number of people affected by diabetes is expected to reach 642 million by 2040 worldwide. The global prevalence is approximately 8%, and it is expected to have an increase of more than 10% by 2040, with the African region having the greatest increase (3, 6, 7).

1.3. Diagnostic criteria

To make a diagnosis of diabetes the person must fulfill some criteria. According to World Health Organization (WHO), a person is at high risk if having one or both prediabetic conditions: impaired fasting glucose (IFG), defined as fasting plasma glucose (FPG) concentration 6.1-7.0 mmol/L, and/or impaired glucose tolerance (IGT), defined as taking 75 g oral glucose and measure 2 h post-load plasma glucose concentration 7.8-11.1 mmol/L.

Additionally, prediabetes is defined if HbA1c is 6.0-6.4%. If some of the diagnostic criteria's is reached (fasting glucose ≥7.0 mmol/L or glucose after OGTT ≥11.1 mmol/L or HbA1c is ≥ 6,5%) the patient is diagnosed with diabetes (4, 8).

IFG indicator in prediabetes is often more developed in men, whereas IGT is more often showed in women (9).

1.4. Pathophysiology

Diabetes mellitus type 2 is a progressive, complex metabolic disease, resulting in defects of multiple organs. In healthy people the blood glucose levels are well regulated. While in diabetics, changes in glucose and insulin concentration occur gradually over many years. It was observed increased glucose values due to reduced insulin sensitivity even 13 years before diagnosis, with a sudden fall of insulin sensitivity 5 years before diagnosis. This shows us that insulin resistance begins 5-10 years before symptomatic diabetes occurs, and that decreased B-cell function already starts in the prediabetic stage (3, 10).

The pathophysiology of diabetes type 2 is characterized by impaired regulation of hepatic production of glucose, peripheral insulin resistance, and decreased B-cell function, which will eventually lead to B-cell failure (11).

1.4.1. Impaired insulin secretion

The relative insulin deficiency is a consequence of both functional and quantitative factors (2). This means they have decreased responsiveness to secretagogues due to B-cell exhaustion, that will lead to less intracellular insulin pool available, and decreased B-cell mass (2, 8).

In diabetes type 2 the B-cell mass is reduced up to 60%. However, decline in B-cell mass alone cannot cause insulin deficiency. Evidence shows in otherwise healthy individuals who need to undergo 50% surgical pancreatectomy does not lead to hyperglycemia. B-cell defect is multifactorial with both genetic influence and environmental exposure. Emerging evidence suggest that loss of B-cell function has a more aggressive course in young onset patients (2, 5, 8).

1.4.2. Impaired insulin sensitivity

Insulin resistance is commonly seen in individuals that are physical inactive, obese, aging, use certain medications, and the presence of higher amount of free-fatty acid and blood

glucose concentration. In all age groups, insulin resistance is directly associated to a proportional increase of fat in muscles and liver (5).

It frequently occurs as a part of metabolic syndrome, which also includes abdominal obesity, dyslipidemia (high cholesterol, high LDL, low HDL), glucose intolerance and hypertension. All these parts increase the risk of cardiovascular disease even more. Insulin resistance can also be associated with polycystic ovary syndrome. Another factor that mitigates insulin resistance is body fat distribution. Accumulation of adipose tissue in the liver and abdominal region especially has a large negative impact on insulin resistance (2, 8, 12, 13).

1.5. Risk factors

The steep rise of diabetes mellitus is contributed by many factors. Some factors are modifiable (e.g. lifestyle) while others are non-modifiable, such as genetics. They can be divided into several groups: biological, health behavior and psychosocial risk factors. There are clinically important gender differences. In men, the body mass index (BMI) and younger age has a greater impact for diagnosis of diabetes type 2, while obesity is the most prominent risk factor in women. The strongest risk factors in general are family history of diabetes, older age, obesity (especially abdominal obesity) and physical inactivity (9, 14).

1.5.1. Genetics/Biological

The heritable genetic correlation is not yet completely understood, but we know that the genetic component plays a major role in the disease. Young-onset phenotype has usually a stronger family history. It is higher concordance rate between monozygotic twins than dizygotic twins. Also, first-degree relatives of patients with diabetes type 2 has 40% chance to develop the disease, while the incident rate in the general population is only 6% (15).

Other biological factors are high BMI, prediabetic state and gestational diabetes. The latter biological risk factor is a strong female risk factor, but not only for the mother but also for the fetus, especially if she is carrying a male fetus (9).

1.5.2. Health behavior

An extensive variety of lifestyle factors have a great impact on diabetes type 2, such as physical inactivity, sugar-sweetened beverages, unhealthy diet, smoking and alcohol consumption. The most important risk factor for this disease is obesity, which may influence and contribute to even faster progression of insulin resistance. According to the WHO, 90% of

diabetic patients who develop diabetes type 2 is due to excessive body weight and increased BMI (15, 16).

Many studies have also shown that obstructive sleep apnea (OSA) is much more prevalent (36-60%) in diabetes type 2 patients than in the general population. Furthermore, soft drinks and metabolic syndrome are directly associated with higher BMI. In addition, diet, especially low fiber diet with a high glycemic index, is a modifiable risk factor, which is positively associated with an increased risk for diabetes type 2 (15, 17, 18).

1.5.3. Psychosocial factors

Psychosocial risk factors are particularly seen in women. These factors are often modifiable, such as: low educational level and income, unhealthy lifestyle behavior, social disparities and stress. All of them can lead to increased risk of depression and obesity. Even psychological stress is of great importance to the development of the disease onset and progression. Depression is the most common investigated type of psychological factor, and may have a large influence on diabetes. Increased amount of glucose and lipids relative to energy demands is a type of metabolic stress that can encourage insulin resistance and weight gain (9).

1.5.4. Other factors

Other factors that could influence the course of diabetes type 2 are decreased vitamin D and vitamin K. Vitamin D deficiency has negative effect on glucose tolerance and insulin secretion. Vitamin K influences the glucose homeostasis, by increasing insulin sensitivity and glycemic status. It is especially noted poor glycemic control and bone quality in diabetic patients with vitamin K1 deficiency (15).

1.6. Complications

Diabetes type 2 can affect different organ systems, and lead to serious complications that are responsible for the majority of deaths related to the disease. These complications can be divided into short-and long-term complications, where long-term complications can be further classified as micro- and macrovascular complications (13).

Short-term complications also called metabolic acute complications, include: ketoacidosis, hyperosmolar non-ketogenic coma and hypoglycemia, whereas long-term microvascular complications are: diabetic nephropathy, retinopathy and neuropathy (e.g. diabetic foot). Microvascular complications have a much higher prevalence than macrovascular

complications. Macrovascular complications are cerebrovascular and cardiovascular diseases (6, 15).

Evidence shows that young-onset diabetes type 2 patients have a much greater chance to develop complications, than those with diabetes type 1 or late-onset type 2 diabetes. It increases with longstanding hyperglycemia. When a patient develops complications it results in even lower quality of life, increased mortality risk and increased medical care costs (5, 19).

1.6.1. Microvascular complications

The burden of microvascular complications is significantly increased, especially if the patient is diagnosed before age of 20 years. Not only is the chance to develop complications at an earlier age increased, but also the severity of the complications will present in a worse form, as well as they have a faster progression of the complications. The high prevalence of microvascular complications is a consequence of longstanding untreated hyperglycemia. These complications are the leading cause of renal failure, nontraumatic lower extremity amputation and new onset blindness in adults (1, 5).

1.6.1.1. Nephropathy

Diabetic nephropathy is the leading cause of chronic kidney disease and end-stage renal disease. Unfortunately, younger onset patients have a 4 times greater risk of renal failure, and an increased rate of progression from microalbuminuria to macroalbuminuria, which is defined as the earliest manifestation of the complication. Patients with diabetic nephropathy are at increased risk to develop cardiovascular disease and stroke as well as die from macrovascular disease, then those without nephropathy. Usually patients with nephropathy have already been diagnosed with retinopathy (5, 6, 15).

1.6.1.2. Retinopathy

Diabetic retinopathy is the leading cause of blindness in adults, and is the most common microvascular complication. Because rods and cones in the retina need high oxygen to convert light into electrical energy, it needs to have a large vascular supply. Chronic hyperglycemia increases the vascular permeability in the retina and vitreous humor that will eventually lead to macular edema and hemorrhage, which is the reason to blindness. Blindness can be prevented if diabetes is detected in an early stage. Therefore, regular eye examination is recommended (15).

1.6.1.3. Peripheral neuropathy

The neuropathic complication can be classified into polyneuropathy, mononeuropathy and autonomic neuropathy, and affects 30-50% of individuals with long-lasting diabetes mellitus. The risk factors that influence the diabetic neuropathy are smoking, sustained hyperglycemia, high BMI, hypertension and elevated concentration of triglycerides. The most common form of diabetic neuropathy is the chronic sensorimotor distal symmetric polyneuropathy. The patient will present with symptoms and signs like loss of sensation, tingling, numbness, foot ulcers (that frequently leads to amputations due to gangrene), non-healing skin wounds (extreme infections, cellulitis) and sexual dysfunction. The latter one usually occurs in young-onset diabetic patients due to increased oxidative stress in the cavernous tissues (1, 13, 15).

1.6.2. Macrovascular complications

Cardiovascular diseases are the major macrovascular complication and the primary cause of mortality and morbidity in prediabetics and diabetes type 2 patients. It accounts up to 65% of deaths in patients with diabetes. Mortality rates due to heart disease or stroke are 3-4 times increased in diabetics compared to non-diabetic people. Also 70% of patients with diabetes has hypertension, and need to take drugs to regulate blood pressure level. A potential mechanism that plays a major role for cardiovascular complications is oxidative stress, as mentioned earlier (15).

There are three important risk factors that have an enormous influence on the complications in a patient with diabetes: hyperglycemia, hypertension and hypercholesterolemia. By controlling the high blood pressure, glycaemia and cholesterol, the patient can decrease its risk for complications. Complications do not only affect the morbidity and mortality, but it also affects the healthcare system by contributing to large financial cost and unnecessary work that could have been prevented). Diabetes mellitus in general, but especially after developing any complication, the quality of life will significantly decrease. The best way to reduce this risk worldwide is to prevent diabetes in the first place (20).

1.7. Treatment

1.7.1. Lifestyle changes

The cornerstone of treatment for diabetes mellitus type 2 is lifestyle modification. The lifestyle changes should be focusing on the diet, 7-10% weight loss, and moderate physical exercise for at least 150 min per week. The goal of treatment is to reduce weight, decrease the use of diabetes medications, and reduce the risk of comorbidity and psychological distress (21).

It has been acknowledged that it is difficult to maintain weight loss and physical activity over an extended period in diabetic patients. An interesting study was performed with obese children and adolescents with type 2 diabetes, who had to undergo only lifestyle changes (low caloric diet) for 2 months. During this period some improvement of weight loss was seen, but still after cessation of the low caloric diet they gained back weight immediately (5, 8).

One of the largest challenges for a diabetic patient is changing the eating habit. There is no "diabetic diet", but different types of dietary regimens are available and has been shown to have a beneficial effect in metabolic conditions, such as: the Mediterranean diet, a vegan or vegetarian diet, or a low-carbohydrate/high-protein diet. In all overweight (BMI 25-30) or obese (BMI >30) diabetes type 2 patients, weight loss is recommended and is the key treatment of the disease. Weight loss has been shown to decrease insulin resistance. As mentioned previously, a high fiber diet has a protective effect on diabetes (22, 23).

Exercise, especially aerobic, either alone or in combination with diet is crucial. It will reduce the systolic blood pressure and total cholesterol and increase HDL concentration. All subtypes of activity have a beneficial effect, even light exercise like walking is beneficial. Exercise is also shown to be primary prevention in the general population, and reduces the risk of developing diabetes type 2 by 26%. Diabetes type 2 patients should be encouraged to do more physical activity and have a less sedentary lifestyle in order to improve the health outcomes, and secondary prevention of complications (24-26).

1.7.2. Pharmacotherapy

Most patients with diabetes type 2 will eventually need some pharmacological glucose-lowering agents, even though the increased physical activity has been realized but the glucose targets are not met with dietary measures. Pharmacological approach to the management of diabetes type 2 includes glucose-lowering medications, insulin or any kind of medication that improve glucose control. The goal of pharmacological treatment is to find the drug that will improve glucose values and minimize side effects. Insulin therapy is usually initiated when oral glucose-lowering medications and lifestyle changes (exercise and diet) fails, but it can also

sometimes be the first choice in the treatment of diabetes type 2 if hyperglycemia is severe or symptomatic (11).

The glucose-lowering agents can be subdivided dependent on their action:

1. increase insulin secretion
2. increase insulin sensitivity
3. reduce glucose production
4. enhance glucagon like peptide-1 (GLP-1) action
5. promote urinary excretion of glucose
6. replacement therapy with insulin

The glucose-lowering agents for diabetes that can be found on the market today and approved as monotherapy or in combination for type 2 diabetes are biguanides (metformin – representative of this class), sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 inhibitors and insulin (13).

The negative effects of intensive treatment with oral glucose-lowering agents are the high risk of serious hypoglycemic events, weight gain (that occurs with most therapies, but not all), large economic costs for the country, gastrointestinal effects and cardiovascular disease. The major fear in treating diabetes mellitus intensively is hypoglycemia (13, 15).

1.8. Metformin

The most popular oral glucose-lowering drug is metformin, chemically a synthetic biguanide. Metformin is derived from a plant called *Galega officinalis*. It was originally described in 1922. Almost 30 years later in 1950, Stern et al. saw its clinical potential and in 1957 it was accepted as a drug and introduced in humans as a medication in diabetes type 2 patients. Metformin can be used as monotherapy and in combination with other oral glucose-lowering drugs or with insulin (27, 28).

It is recommended as a first-line treatment because of its safety, known side effects, it promotes modest weight loss, cardiovascular benefits and is low in cost, and a well-tolerated drug in majority of patients. A stepwise approach regime treatment is recommended with one single agent at the beginning, and if the glycemic target can´t be achieved, add a second or maybe even a third agent (29).

A study published in prestigious scientific journal The New England Journal of Medicine compared the reduction in incidence of diabetes type 2 by lifestyle modification (diet

and exercise) and metformin. The authors of this publication came to a conclusion that modification of lifestyle was more effective than metformin therapy (30).

Other indications for metformin have been extensively investigated. It can be used as a cardiovascular protective agent, anticancer agent, it can be neuroprotective, and a potent drug for polycystic ovary syndrome and endometrial hyperplasia. The most important non-glycemic effect is the cardiovascular benefit of the drug, and so far it the only diabetic drug with clear cardiovascular benefits. It is clear that metformin is cardioprotective in diabetic patients, but what about non-diabetic patients? Do they have any cardioprotective benefits by metformin? Plenty of theories are set but it still remains unclear. Research has shown some benefits by metformin in patients with heart failure such as preservation of ejection fraction. A proper understanding of metformin action of mechanism on the heart requires further research (31, 32).

A meta-analysis including metformin therapy concluded that it decreases the overall cancer incidence and mortality by 31% and 34% respectively in patients with diabetes. Yet the mechanism involved in the anti-cancer therapy is not fully understood. Furthermore, it has a great benefit in colorectal and prostate cancer treatment, especially in those undergoing radiotherapy (32).

Grade four astrocytic brain tumor, glioblastoma, is the most common brain tumor in adults. Recently, combining chemo – or radiotherapy with drugs targeting cell metabolism has become attractive. Metformin exhibits anti-tumoral effects by inhibiting glioma cell proliferation through cell cycle arrest, induces autophagic process and cell death. And in combination with chemo- or radiotherapy it will enhance its effect (33).

Endometrial cancer is the second most common gynecological cancer in the world today, and affect mostly young women. Some studies about metformin preventing endometrial hyperplasia development into endometrial cancer have been done, but they are insufficient to support any kind of evidence in prevention of cancer development yet. The same issue is stated for polycystic ovarian syndrome (PCOS), long-term data is missing, but there is a potential of metformin having a positive effect in both PCOS and endometrial cancer. Both conditions activate insulin/IGF-1 signaling and PI3K/AKT/mTOR signaling, on which metformin also has some cellular metabolic effect (33-35).

In females with metabolic disease (insulin resistance together with PCOS), metformin has become a useful drug to improve fertility outcomes, as well as in obese males with reduced fertility and metabolic syndrome. It can act directly through adenosine monophosphate (AMP)

dependent or independent mechanisms that will improve sperm function and fertilization, and oocyte quality with a decreased miscarriage rates and birth defect (36).

It is also important to take into consideration that metformin passes the placenta, and the fetal concentration of the drug is almost like in the mother in a pregnant woman. Also the pharmacokinetics of metformin will be different in a pregnant woman because they have a higher glomerular filtration rate than non-pregnant women. But sill no evidence has shown any incline in congenital malformations or miscarriages (37, 38).

1.8.1. Mechanism of action

Several different glucose lowering mechanisms of metformin has been studied, but still its mechanism of action is not fully understood. The target organ for metformin act is liver through a complex mechanism of action. The most consistent finding is that metformin reduces the hepatic glucose production, by suppression of gluconeogenesis. Metformin does not only act on the liver, but it also improves insulin´s action in skeletal muscles, by increasing glucose consumption in the muscle tissue. In addition, metformin increases anaerobic metabolism in the intestinal wall, and glucagon-like peptide-1circulating levels. Metformin also improves the lipid profile, and it may improve pancreatic insulin secretion (37, 39, 40).

1.8.2. Pharmacokinetics

Because metformin has a slow onset of action and gastrointestinal symptoms are seen with high dose, the initial dose should be low and slowly increased over time. Absorption of metformin is low and incomplete, and the active pharmacologically dose needs to be higher, 0,5-2 g/day (maximally effective dose is 2mg daily) taken 2-3 times daily. There are different preparations of metformin, in tablets form they are found in 500, 850 and 1000 mg. The most popular preparation is immediate-release formulation. Its bioavailability is 40-60%, with a maximum concentration after 2-3 h. It has renal clearance and is therefore contraindicated in people with chronic renal disease. As described above the higher dosage is associated with pronounced gastrointestinal side effects, like diarrhea, nausea, vomiting, anorexia, abdominal pain, metallic taste and loss of appetite. Fortunately, these side effects occur mostly when initiating metformin and resolves spontaneously, but on the other hand it is also the main reason for discontinuation of the therapy (13, 27, 37).

The pharmacological and therapeutic concentration of metformin has its inter-individual variations. Some factors should be taken in consideration when prescribing the drug, like genetic factors, patient's age, the indication for metformin usage, other comorbidities and drug-

drug interaction if the patient takes other medications. During treatment with metformin patients will get approximately 30% lower vitamin B12 levels (13, 41).

1.8.3. Contraindications

Contraindications to initiate metformin treatment are in patients with renal insufficiency (with a glomerular filtration rate (GFR) <60 mL/min), any kind of acidosis, liver disease, pronounced hypoxia or unstable congestive heart failure. Also in some situations metformin treatment needs to be changed to insulin therapy, such as in patients who cannot take medication orally, and in those who need to receive radiographic contrast material (13).

1.8.4. Adverse reactions of metformin

Luckily, side effects of metformin are mostly mild, and rarely they present as severe. The most common adverse effects are gastrointestinal (GI) and occur in up to 50% of patients taking metformin. The patient will present with nausea, vomiting, diarrhea and abdominal discomfort. The cause could be from drug accumulation in intestinal enterocytes. Mostly GI side effects are transient and dose-related, so slowly increase in the dosage when starting the drug is recommended. The most common preparation used is the fast-releasing formulations, but to reduce the GI side effects it is better to use slow-release formulations (27).

A potentially life-threatening side effect is lactic acidosis. The risk is extremely small, with an incidence of 3-10/100,000 persons per year. When the concentration of metformin exceeds the toxic range (>5 mg/l) the patient develops a greater risk of developing lactic acidosis, especially if the patient has chronic kidney disease which is a contraindication for metformin. According to recent studies, metformin can be prescribed in individuals with mild to moderate kidney function impairment (GFR > 30 ml/min). Other conditions that could lead to increase lactate production, are alcoholism, sepsis and cardiogenic shock. Even hyperglycemia alone, if not threated is a great risk factor for development of lactic acidosis (27, 31, 40).

Another potential non-life-threatening side effect, but can cause irreversible neurological sequelae is vitamin B12 deficiency. Therefore, regular biochemical testing in patients on long-term metformin therapy or even prophylactic oral vitamin B12 is advisable, particularly in patients with additional conditions like anemia or peripheral neuropathy as a disease itself or as a complication from diabetes (27).

1.9. Pharmacovigilance and adverse drug reactions

The definition of adverse drug reaction (ADR) is when a patient gets noxious and unintended drug reaction as a response of medication at normally tolerated dosage. ADR is a serious global burden and health problem that leads to unnecessary hospital admission and economic burden (42).

In 1968 World Health Organization (WHO) established WHO Programme for International Drug Monitoring for Globalization of Pharmacovigilance to improve the safety of pharmaceutical products, especially after thalidomide disaster. The purpose of reporting the ADR was to improve the recognition of serious and fatal spontaneous ADR, and patient´s quality of life. In fact, there are different reasons for not reporting ADRs. The most common reason is that the reaction is well known from before (43, 44).

ADR is a common cause of hospitalization in elderly, even though more than 50% of ADR can be prevented. Elderly are especially prone to ADR compared to the pediatric patients because of polypharmacy and multimorbidity (42).

The understanding and building knowledge of pharmacovigilance and the importance of preventing, recognizing, managing and reporting ADRs should raise even higher awareness and more education should be provided, because the spontaneous reporting is the keystone for efficient post-marketing safety surveillance. Serious and non-serious ADRs should be prevented because they can all negatively influence patient´s quality of life and decline treatment satisfaction and drug compliance (45).

2. OBJECTIVES

The aim of this study was to compare adverse drug reaction reports for metformin and metformin in fixed combinations in Croatia from 2007 to 2018.

Hypothesis:

1. There will be higher number of adverse drug reaction reports for metformin, than metformin in fixed combinations.
2. Adverse drug reaction reports of metformin and metformin combinations will have equal distribution in patient gender, age, reporter qualification, seriousness criteria and other medication in therapy.

3. SUBJECTS AND METHODS

3.1. Study drugs

In Croatia, only drugs with marketing authorization granted by either the Agency for Medicinal Products or European Commission may be on the market. For this study the adverse drug reactions attributed to metformin, irrespective of indication of use, were selected. During the study period the followed drugs containing metformin, or metformin in fixed-dose combinations, had authorization for Croatian market:

- Metformin
- Metformin; Vildagliptin
- Metformin; Empagliflozin
- Metformin; Linagliptin
- Metformin; Dapagliflozin
- Metformin; Sitagliptin
- Metformin; Alogliptin
- Metformin; Pioglitazone
- Metformin; Glibenclamide
- Metformin; Rosiglitazone

3.2. Data source

Agency for Medicinal Products and Medical Devices of Croatia (HALMED) manages the national spontaneous reporting system which contains all spontaneously reported suspected adverse drug reactions. HALMED established this database of adverse drug reactions in 2007. Electronic database allows for a retrieval of adverse drug reactions data. Therefore, the data received from 1 January 2007 to 31 December 2018 was analyzed in this retrospective study. In Croatia, both consumer and health care professionals can report adverse drug reactions. The suspected adverse drug reactions could be reported by sending the completed form to HALMED by mail or fax, via e-mail, using an on-line application available on the HALMED web site or via a mobile app that was released on January 2016.

3.3. Data analysis

Metformin reports were categorized into two main groups: single-drug formulations and fixed-dose combinations of drugs. The data of the year of the adverse drug reaction report, reporter qualification, patient age and gender, adverse drug reaction seriousness and other medication in therapy was included. All the aforementioned data were inserted into the

electronic spreadsheet and descriptive statistics was calculated using MedCalc (version 11.5.1.0, MedCalc Software, Ostend, Belgium). For statistical comparisons between metformin monotherapy and metformin in combinations the chi-squared test was used. For all analyses a P value <0.05 was defined as the threshold for significance.

4. RESULTS

From 2007 to 2018 period the number of the metformin adverse drug reactions reports was 377 (70.3%) and metformin in combinations had 159 (29.7%) reported adverse drug reactions. Overall, this accounts for 536 adverse drug reaction reports included in this study. Distribution of the reports by the study years is presented in Figure 1. Only in 2018 combinations of metformin were reported equally as metformin alone, 44 of the reports each.

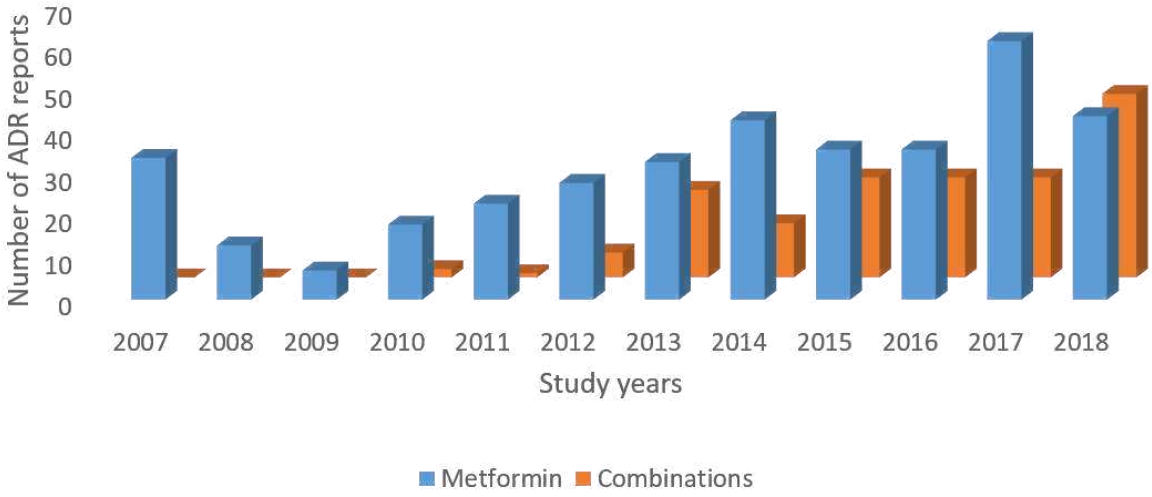

Figure 1. Distribution of adverse drug reaction reports by the study years

The main characteristics of metformin and metformin combinations adverse drug reaction reports are presented in Table 1. Majority of all the reports were provided from physicians. Furthermore, no differences were observed in number of reports provided from consumers and other health care when metformin and combinations reports are compared. Overall, female consumers reported a largest proportion of adverse drug reactions when compared to male consumers. However, combination drugs reports were more frequently reported by male consumers. Most of the reports were obtained by elderly and only in group of consumers aged >70 difference was observed between metformin and combination drugs.

Table 1. Main characteristics of adverse drug reaction reports

Characteristic	Metformin (N=377)	Combinations (N=159)	P value*
Reporter qualification			
Pharmacist	166 (44.0)	71 (44.6)	0.751
Physician	184 (49.0)	74 (46.5)	
Consumer/non health professional	17 (4.5)	11 (7.0)	
Other health professional	10 (2.5)	3 (1.9)	
Patient gender			
Male	135 (35.8)	81 (50.9)	< 0.001
Female	242 (64.2)	78 (49.1)	
Patient age (years)			
<10	3 (0.8)	1 (0.6)	0.124
10-19	2 (0.5)	0 (0)	
20-29	3 (0.8)	0 (0)	
30-39	11 (2.9)	1 (0.6)	
40-49	18 (4.8)	9 (5.7)	
50-59	71 (18.8)	37 (23.3)	
60-69	122 (32.4)	49 (30.8)	
>70	123 (32.6)	37 (23.3)	
missing	24 (6.4)	25 (15.7)	

* chi-square test

Data is presented as number and percentage.

Table 2. Number and proportion of adverse drug reaction reports of combination drugs

Combination drugs	N (%)
Metformin; Vildagliptin	55 (34.6)
Metformin; Empagliflozin	10 (6.2)
Metformin; Linagliptin	4 (2.5)
Metformin; Dapagliflozin	21 (13.2)
Metformin; Sitagliptin	44 (27.7)
Metformin; Alogliptin	16 (10.0)
Metformin; Pioglitazone	3 (1.8)
Metformin; Glibenclamide	4 (2.5)
Metformin; Rosiglitazone	2 (1.3)

The drug combinations that were most frequently reported to HALMED during the examined period were metformin and vildagliptin, followed by sitagliptin and dapagliflozin.

In 403 out of 536 reports, 75% of the cases, suspected adverse drug reactions report included concomitant drug in the therapy, other than suspected metformin or metformin in combination. Table 3 shows number of concomitant drugs in therapy of the reported adverse drug reactions. Majority of patients had additional 3 drugs in therapy, other than suspected metformin (23.6%). Interestingly, 20.6 % of the patients used 5 or more drugs in addition to metformin or metformin combinations.

Table 3. Number of concomitant drugs included in the reports of adverse drug reactions

Number of concomitant drugs in therapy	N (%)
1	83 (20.6)
2	90 (22.3)
3	95 (23.6)
4	52 (12.9)
5	38 (9.4)
6	21 (5.2)
7	5 (1.2)
8	7 (1.7)
9	7 (1.7)
10	3 (0.7)
11	1 (0.2)
13	1 (0.2)

Majority of reported adverse drug reactions (87.1 %) were classified as non-serious. However, 4 deaths were reported in metformin group and 1 in combination group. The stratification of adverse drug reaction by seriousness criteria for each group is presented in Figure 2. Both groups had similar proportions of each criteria, and no statistically significant difference was observed. The expected life-threatening adverse drug reaction, lactic acidosis, associated with metformin use, was reported in less than 1% of all the reports.

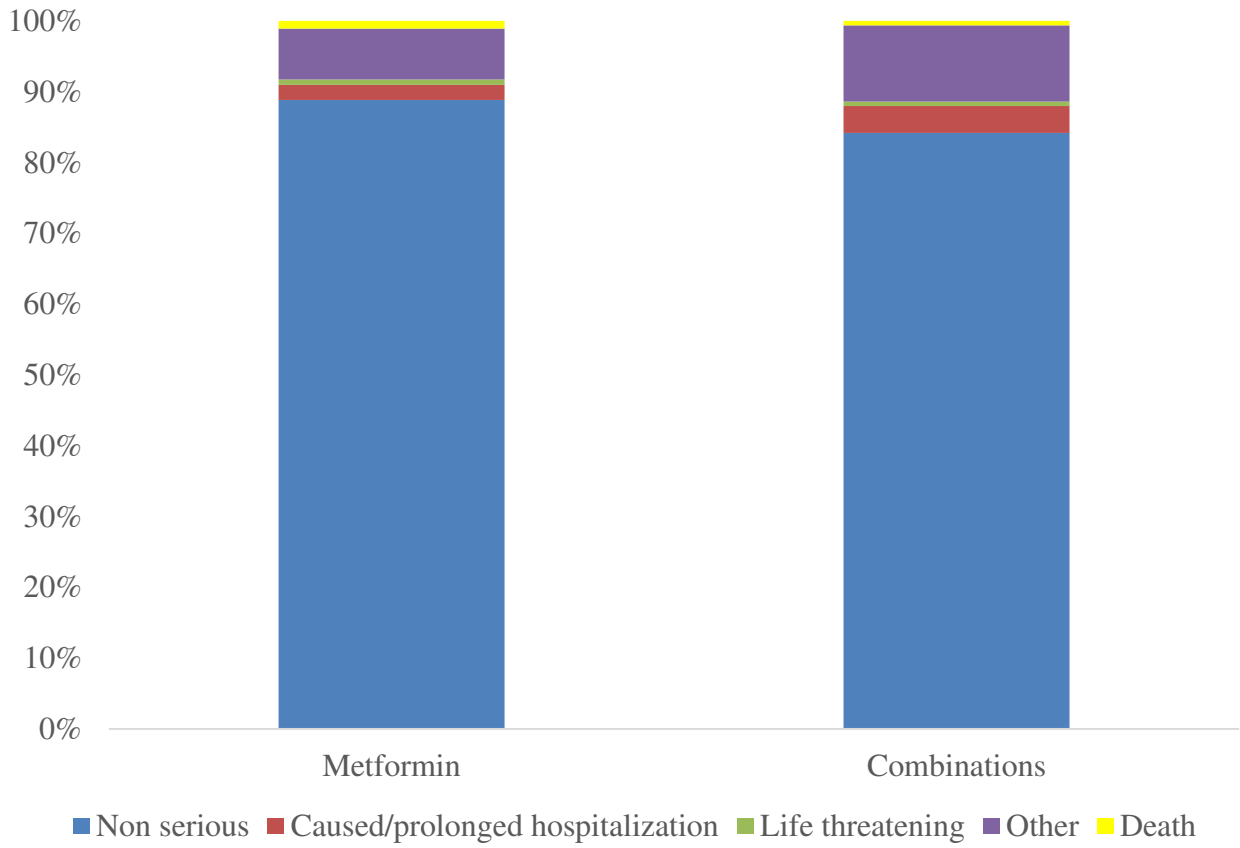

Figure 2. Proportions of seriousness criteria of adverse drug reactions in metformin and combination drugs

5. DISCUSSION

In the examined period a higher number of reports for metformin than metformin in combinations was observed. However, this observation could be due to the fact that metformin has been marketed in Croatia for a longer period when compared to all of the currently available combination drugs. Furthermore, metformin has been suggested as a first line therapy in diabetes type 2 and therefore it can be assumed that metformin consumption is higher than consumption of other diabetic drugs. However, the comparison of drug consumption and reported adverse drug reaction exceeds the scope of this study.

Further, the number of reports for both metformin and metformin drug combinations was increased during the examined period. It should be acknowledged that in 2018 the number of reports for single and combination metformin were identical. There is a possibility that with approval of the new drug combinations on the market their number of adverse drug reaction reports will increase.

Data of spontaneously reported adverse drug reactions of metformin or metformin in combinations is limited. However, several reviews or randomized control trials have compared safety profiles of metformin alone or metformin and sitagliptin. In study by Hayes *et al.* the authors concluded that the coadministration of metformin and sitagliptin was generally well tolerated and that the most commonly reported adverse drug reactions were similar to the adverse drug reaction profiles seen with monotherapy. Furthermore, Dalal *et al.* addressed the value of spontaneously reported adverse drug reaction data and how it adds to current data of metformin and metformin/sitagliptin safety (46, 47).

The similar profile of serious adverse drug reactions between metformin and metformin in combinations was observed in the present study. Furthermore, the well-known life-threatening adverse drug reaction, lactic acidosis, associated with metformin use, was reported in less than 1% of the reports. The observed low prevalence of lactic acidosis is in concordance with previously published data of risk of lactic acidosis in metformin users (48).

Polypharmacy was observed in majority of the reports. Polypharmacy can affect not only occurrence of adverse drug reaction and hospitalization, but also patients' adherence to pharmacotherapy and patients' quality of life. Moreover, polypharmacy increases health care costs and risks of drug interactions. The majority of consumers included in this study were elderly, and this age group is especially vulnerable in terms of polypharmacy. Previous research conducted by Maher *et al.* has established a strong relationship between polypharmacy and negative clinical consequences in elderly. Moreover, the authors proposed inter-professional (frequently including clinical pharmacist) collaboration in order to effectively improve the overall quality of prescribing in elderly (49).

The adverse drug reaction reports were most commonly provided by physicians. As most of the patients switch between drugs when adverse drug reaction is experienced this observation was expected. In Croatia, physicians are recognized as most common reporters . Further, it is praiseworthy that primary care or hospital physicians are introduced to pharmacovigilance practice. However, the consumers reported only a small proportion of adverse drug reaction during the same period, and it would account for nearly 2 consumers report in each year (50).

In Croatia, consumers can send an adverse drug reaction report via post office, and use either internet or smartphone application. In 2016, Web-Recognising Adverse Drug Reactions (WEB-RADR), a smartphone application based on a simplified reporting form, was introduced in Croatia. However, as most of the consumers included in this study could be classified as elderly it can be assumed that their knowledge and practice of pharmacovigilance is low. Future educational activities available for wide population should aim to provide elderly with all of the possibilities and their use in practice (51).

Male consumers reported more adverse drug reaction for metformin in combinations when compared to female consumers. Contrary to this, number of female reports for metformin alone was significantly higher. In most of the previously published data of adverse drug reaction spontaneous reporting, females were always dominant reporters (52).

However, our finding could be rationalized with possible differences in drug use between female and male patients. Previous studies suggest that metformin use is associated with erectile dysfunction as metformin use causes decreased testosterone level and consequently problems with erection and libido. Therefore, it could be assumed that male patients prefer use of combination drugs. It should be stated that sulfonylureas are drug of choice if this adverse drug reaction occurs. Further, as there is a possibility that patients are ashamed of adverse drug reaction which they are experiencing, there is a possibility that this particular adverse drug reaction is underreported. Moreover, physicians should be competent and comfortable discussing this dysfunction with patients. This patient centered care can make positive contribution to both therapeutic outcome and patients' quality of life. Otherwise, this adverse drug reaction could lead to patient's non-adherence and treatment failure (53).

The greatest limitation of the conducted study is that our data might not represent the real incidence rate, since not all of the adverse drug reactions are reported. The problem of underreporting of adverse drug reactions has been recognized as a bias of all the studies which involve spontaneously reported adverse drug reaction data. However, studies that include

spontaneously reported adverse drug reaction data add value to area of drug safety and should be conducted in the future in order to raise awareness of pharmacovigilance activities.

6. CONCLUSION

1. Higher number of adverse drug reaction reports for metformin (70.3%), than metformin in fixed combinations (29.7%) was observed from 2007 to 2018 in Croatia.
2. Majority of all the reports, 184 for metformin, and 74 for combinations, were provided from physicians.
3. Female patients reported adverse drug reaction in 59.7% of all the cases, but male patients were more prone to report combination drug adverse drug reactions.
4. Metformin and vildagliptin combinations were the most commonly reported combination drug with 55 adverse drug reaction reports during the examined period.
5. In 75% of the cases suspected adverse drug reaction report included concomitant drug in therapy.
6. Majority of the reports, 87.1 %, included adverse drug reaction classified as non-serious.

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8. SUMMARY

Objectives: The aim of the present study was to compare adverse drug reaction reports of metformin and metformin in fixed combination in Croatia from 2007 to 2018.

Materials and Methods: The data of adverse drug reaction reports received from 1 January 2007 to 31 December 2018 was analyzed in this retrospective study. Metformin reports were categorized into two main groups: single-drug formulations and fixed-dose combinations of drugs. The data of the year of the adverse drug reaction report, reporter qualification, patient age and gender, adverse drug reaction seriousness and other medication in therapy was included.

Results: During the examined period the number of the metformin adverse drug reactions reports was 377 (70.3%) and metformin in combinations had 159 (29.7%) reported adverse drug reactions. Overall, this accounts for 536 adverse drug reaction reports included in this study. Majority of all the reports were provided by physicians. Female consumers reported a largest proportion of adverse drug reactions when compared to male consumers. Most of the reports were obtained by elderly, and included concomitant drug in therapy, other than suspected metformin or metformin in combination. Most commonly reported drug combination was metformin and vildagliptin, which were included in 55 of the reports. Majority of the reports, 87.1 %, included adverse drug reaction classified as non-serious and lactic acidosis was reported in 1% of the cases.

Conclusion: Metformin was more frequently reported than metformin in combinations during the examined period. However, as the market of hypoglycemic drug combinations will probably rise in the future, the education of all the interested parties should be proposed in order to monitor safety of newly introduced drugs.

9. CROATIAN SUMMARY

Naslov: Pregled prijava sumnji na nuspojave lijekova – metformin i metformin u fiksnim kombinacijama.

Ciljevi: Usporediti prijave sumnji na nuspojave lijekova metformina i metformina u fiksnim kombinacijama u Republici Hrvatskoj u razdoblju od 2007. do 2018.

Materijali i metode: Podatci o prijavama sumnji na nuspojave lijekova zaprimljeni od 1. siječnja 2007. do 31. prosinca 2018. analizirani su u ovom retrospektivnom istraživanju. Prijave metformina podijeljene su u dvije skupine: metformin i metformin u fiksnim kombinacijama. Podatci o godini prijave, kvalifikaciji prijavitelja, dobi i spolu pacijenta, ozbiljnosti nuspojave i broju ostalih lijekova u terapiji su uključeni u ovo istraživanje.

Rezultati: Tijekom ispitnog razdoblja broj sumnji na nuspojave metformina iznosio je 377 (70,3%), a metformin u kombinacijama imao je 159 (29,7%) prijavljenih sumnji na nuspojave. Sveukupno, to čini 536 prijavljenih sumnji na nuspojavu lijekova koje su uključene u ovo istraživanje. Liječnici su prijavili najviše sumnji na nuspojave ovih lijekova. Ženski pacijenti prijavili su više sumnji na nuspojavu lijekova u usporedbi s muškarcima. Većina zaprimjlenih sumnji uključivala je pacijente starije životne dobi koji su koristili druge lijekove u terapiji, izuzev metformina ili metformina u kombinacijama. Najčešće prijavljena kombinacija lijekova bila je kombinacija metformina i vildagliptina za koju je zaprimljeno 55 prijava. Većina prijava, 87,1 %, nije uključivala kriterije ozbiljnosti te nisu kategorizirane kao ozbiljne nuspojave. Laktička acidoza prijavljena je u 1% svih slučajeva sumnji na nuspojave.

Zaključak: U promatranom razdoblju je prijavljen veći broj sumnji na nuspojave lijekova za metformin, nego za fiksne kombinacije metformina. Međutim, kako će u budućnosti rasti tržište

hipoglikemika potrebna je edukacija svih dionika zdravstvenog sustava kako bi se poboljšalo praćenje sigurnosti novih lijekova.

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