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Research Article

Comparative analysis of newer classes of antidiabetics and the concept of pharmaceutical care – dealing with therapeutic problems

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Abstract

The prevalence of obesity is increasing rapidly. The latest World Health Organization – WHO report declares the disease as an epidemic. After pharmacodynamic, pharmacokinetic, clinical and pharmacoepidemiologic data analysis and comparison of the three classes of antidiabetic medicinal products: GLP-1 receptor agonists, DPP-4 inhibitors and SGLT2 inhibitors, a literature review of the topic, patient education and the concept of pharmaceutical care emerged as methods for dealing with the most common adverse drug reactions, safety concerns, and drug interactions.

Keywords

obesity, metabolic syndrome, antidiabetic products

Introduction

The prevalence of obesity is increasing rapidly. The latest WHO report declares the disease as an epidemic. Various cultural, genetic, behavioral, and environmental factors play a role in the development of obesity. Obesity is a serious medico-social disease that is directly associated with type 2 diabetes mellitus, arterial hypertension, osteoarthritic changes, various types of cancer, as well as a high risk of cardiovascular diseases. Although genetic predisposition is a major factor, a sedentary lifestyle and a high-calorie diet contribute to in the development of obesity. Current treatment includes lifestyle changes such as increased physical activity and a low-energy diet. New approaches in the pharmacotherapy of obesity are very important to achieve long-lasting effects.

The latest classes of antidiabetic medicinal products are: GLP-1 receptor agonists, DPP-4 inhibitors and SGLT2 inhibitors. Glucagon-like peptide-1 (GLP-1) agonists (also known as GLP-1 receptor agonists, incretin mimetics, or GLP-1 analogs) are a class of drugs used to treat type 2 diabetes in adults. Their representatives are: exenatide, lixisenatide, liraglutide, albiglutide, dulaglutide and semaglutide. According to current guidelines for the treatment of type 2 diabetes, metformin still remains the first line of treatment and GLP-1 agonists should be considered in patients with contraindications or intolerance to metformin, in patients with HbA1c higher than 1.5% above target values, or in patients who do not reach their HbA1c target values after three months of treatment, especially in patients with atherosclerosis, heart attack or chronic kidney disease (Graaf 2016; Isaacs 2016; Drucker 2018; Hirsch 2019).

Moreover, high doses of liraglutide are approved for the treatment of obesity or can be prescribed to patients with comorbidities. The use of GLP-1 analogs has been the subject of studies with a more favorable effect on HbA1c and body weight loss in patients with type 1 diabetes. It is important to note that their high cost and side effects are a limiting factor in their prescription (Grieco 2019; Hirsch 2019; Bakbak 2021; Wen 2021).

GLP-1, in a glucose-dependent way, also reduces the secretion of glucagon from the a-cells of the pancreas, respectively the production of glucose from the liver. As a cumulative effect when blood sugar rises, GLP-1 enhances insulin secretion and inhibits glucagon secretion, leading to normalization of glycemia. Conversely, when fasting and lowering blood sugar, no GLP-1 is released, which leads to suppression of insulin secretion and an increase in glucagon secretion – the production of glucose by the liver increases as a natural defense mechanism against the onset of hypoglycaemia.

GLP-1 acts by binding to its receptors, expressed on islet and in the central and peripheral nervous system, gastrointestinal tract, heart, lung, kidney, adipose and muscle tissues, vascular endothelium. This determines their multiple pleiotropic actions, including cardioprotective ones – reduction of the endothelial dysfunction, the size of atherosclerotic plaques, the ischemia and myocardial lesions, improvement of dyslipidemia, myocardial function, hypertension.

GLP-1RA slow gastric emptying by inhibiting pyloro-duodenal motility and, in a dose-dependent manner, delays the passage of food into the lower gastrointestinal tract. This appetite-regulatory action is also enhanced by appetite inhibition in the fasting state through a central brain action.

GLP-1RA also demonstrated an improvement of body weight loss up to 2.9 kg compared to placebo, reduction in both systolic and diastolic blood pressure and total cholesterol, additionally. Regarding cardiovascular effects, GLP-1 receptor agonists can improve left ventricular ejection fraction, myocardial contractility, coronary blood flow, cardiac output, and endothelial function, while reducing infarct size and overall cardiovascular risk (Monami 2009; Zheng 2018). Other effects are: to increase muscle glucose uptake, to reduce liver glucose production, neuroprotection, and decreased appetite by hypothalamic mechanism of action. GLP-1 RA may also show lower all-cause mortality as well as a reduction in HbA1c of about 1% compared to controls in patients with type 2 diabetes (Seufert 2014; Hinnen 2017).

Many formulations of GLP-1 agonists, all injectable and administered subcutaneously due to poor oral bioavailability, are currently available.

Dipeptidyl peptidase 4 (DPP-4) inhibitors (gliptins) are designed to suppress the activity of the key enzyme in incretin degradation and indirectly increase the levels of the intact, physiologically active, endogenous forms of GLP-1 and GIP. The first oral selective DPP-4 inhibitor is sitagliptin, approved for monotherapy or for combination therapy with metformin or thiazolidinediones. Currently available medicinal products sitagliptin, vildagliptin, saxagliptin, alogliptin, linagliptin vary in their molecular structure and metabolism.

DPP-4 inhibitors increase insulin secretion by a glucose-dependent mechanism and do not increase the risk of hypoglycaemia, except in combination with insulin or SU (sulfonylureas). DPP-$ inhibitors reduce the level of HbA1c (0.5–0.9%) to a more moderate extent, as their action depends on the endogenous production of GLP-1, which can be reduced in type 2 diabetes. They do not affect gastric emptying or satiety; therefore, they have a neutral effect on weight.

DPP-4 inhibitors (except linagliptin) are mainly excreted by the kidneys, their dose is reduced in renal impairment, and they are not recommended in patients with moderate to severe renal insufficiency (creatinine clearance <50 ml/min).

They are effective in combination with insulin and other oral antidiabetics. They are most often administered together with metformin (including fixed combinations) or with SU in cases of intolerance or contraindications to metformin (Drucker 2006).

In addition to beneficially influencing insulin secretion, DPP-4 inhibition has been found to improve insulin sensitivity (Ahren 2005). This effect may be related to reduced glucagon levels combined with influencing insulin action due to improved metabolic control (Ahren 2005). DPP-4 inhibitors have no additional cardiovascular benefits for patients, but also do not lead to additional risks, i.e. they are neutral.

DPP-4 inhibitors – sitagliptin and vildagliptin – available in clinical practice are effective medicinal products with extremely few side effects, comparable to placebo. Most studies have found they do not affect the blood pressure. Both medicinal products are well tolerated and safe. Due to the glucose-dependent effect of GLP-1, the risk of hypoglycaemia with DPP-4 inhibitors is very low (Ahren 2004, 2005; Barnett 2006). DPP-4 inhibitors are weight neutral, which is extremely important given that over 80% of patients with type 2 diabetes are overweight and obese.

Glycosuria has been studied for more than 150 years using the plant extract phlorizin (Ehrenkranz 2005). Phlorizin was later identified as a non-specific inhibitor of sodium-glucose co-transporter (SGLT) proteins, and several types of SGLT proteins have since been identified. These proteins function independently of insulin. Inhibition of these proteins has been observed to lead to changes that favorably improve carbohydrate metabolism, thus becoming an attractive concept for the treatment of diabetes (Mudaliar 2015; Sheen 2015; Shubrook 2015).

Sodium-glucose cotransporter-2 (SGLT-2) proteins are expressed in the proximal convoluted tubules of the kidney. These transporters are an ideal target for the treatment of diabetes because they are responsible for approximately 90% of the reverse reabsorption of glucose (Fioretto 2015; Sheen 2015; Shubrook 2015; Triplitt 2015).

SGLT-2 inhibitors are the newest class of antidiabetic drugs. They block the reabsorption of glucose in the proximal tubules of the kidney, leading to the loss of a greater amount of glucose in the urine and a decrease in its levels in the blood. This mechanism of action is fundamentally different from all others and provides several significant

advantages: independent of insulin and a reliable glucose-lowering effect, tolerance to practically all widely used diabetic drugs, few systemic side effects, low risk of hypoglycaemia and weight gain, etc. Of the currently known side effects, an increase in the frequency of genital infections, mainly in women, can be noted. The kidneys are involved in the control of blood sugar by increasing its levels when it is not enough and reducing them when it is in excess.

Positive aspects of SGLT-2 inhibitors include primarily a low risk of hypoglycaemia. The effect of SGLT-2 inhibitors depends on the level of glycemia and glomerular filtration rate (GFR). This means that the more decompensated BP and preserved HF, the more pronounced the therapeutic effect will be. They do not completely block SGLT-2. While glycemia approaches normal values, less and less glucose is lost, which means a lower risk of hypoglycaemia. Another advantage is non-insulin-dependent mechanism of action and the renal reduction of glycose is unique and makes them applicable in all situations, practically, as there is adequate GFR – over 60 (dapagliflozin) and 45 (canagliflozin) ml/min/1.73 m^2. Their effectiveness, assessed by the reduction of HbA1c, is in the range of 0.5–1% (Cefalu 2014). They decrease the body weight by 1–5 kg due to the calories' loss with glycosuria. A decrease in blood pressure (especially systolic) with 3–7 mmHg is found, the mechanism being primarily related to osmotic diuresis. No significant changes in the RAAS system that could be assumed in relation to natriuresis were found. Even if it exists, they would favorably balance the increased renal sodium retention found in DM2 (type 2 diabetes mellitus). There are no alarming signs of orthostatic hypotonia, but caution is required in patients on diuretic treatment and the elderly. They can be combined with practically all other antidiabetics, and there is evidence for combinations with metformin, SU, insulin. They cause an increase in HDL. Although they are currently indicated for DM2, in the future they will probably be able to be used together with insulin in (type 1 diabetes) DM1 (Henry 2013; Perkins 2014).

Aims and objectives

The aim of the present study is to review and compare the pharmacodynamic, pharmacokinetic, clinical and pharmacoepidemiologic data for the three classes of antidiabetic medicinal products, and to provide methods to address the most common adverse drug reactions, safety concerns and drug interactions through the methods of patient education and the concept of pharmaceutical care.

Materials and methods

Scientific methods of analysis are applied to achieve the scientific research objective. Documental, comparative, and statistical analysis are performed. The SPC of the products are examined and compared.

Documental method – review and systematization of the results obtained from SPCs, normative acts and other literary sources in Bulgaria and in the European Union, reports of international organizations, etc. – to identify specific challenges related to pharmacovigilance. The selection and research of the scientific publications was carried out using certain keywords (obesity, metabolic syndrome, diabetes, adverse drug reaction, pharmaceutical legislation, risk minimization measure, benefit/risk ratio, rationale drug use, pharmaceutical care), and searching the scientific databases: PubMed, Scopus, Google Scholar, ScienceDirect for a period of 20+ years (1993–2022).

Statistical analysis was performed using the statistical package SPSS version 14.0.

Results

Against the background of the defined problems that may arise with the considered three newest classes of antidiabetic medicinal products, the role of the pharmacist and the implementation of pharmaceutical care for patients undergoing therapy with them is concentrated in the following main guidelines:

1. Avoiding application and dosing errors;
2. Acquaintance and treatment of side effects;
3. Drug interactions;
4. Contraindications;
5. Encouraging lifestyle changes and increasing physical activity, harmful habits and risk factors.

Injectable dosage forms, their dosage (daily, weekly) and peculiarities, despite training in the endocrinology office, sometimes give rise to questions and problems for solution, which may be the subject of pharmaceutical care and discussion in the pharmacy. Patients with DM2, unlike those with DM1, less often use insulin in their therapy and somehow associate the inclusion of an injectable form as an aggravation of the disease and are against their use, also self-injection by the patient is also a potential fear that should be overcome. Therefore, the acquisition of knowledge about the methods of administration and dosage of the different dosage forms of antidiabetic drugs is of paramount importance for the implementation of pharmaceutical care. A good knowledge of the subject matter by the pharmacist is key to correct and timely pharmaceutical care for the patient with type 2 diabetes. The pharmacist must have, in addition to knowledge and practical experience in the application of the different dosage forms, a careful assessment of individual differences in communication with different patients and their degree of awareness, knowledge and intellectual features. The collaboration of the pharmacist with endocrinologists and other health professionals involved in the prescribing, education, and care of patients with DM2 would be very beneficial.

The most common side effects of the new classes of antidiabetic drugs: GLP-1 receptor agonists, DPP-4 inhibitors and SGLT-2 inhibitors are from the gastrointestinal tract. Their frequency and prevalence are specific to their various

members, but in general they are emergent in mechanism of action and, at least in the first two classes, are caused by a blunted sense of hunger, and in the last one by increased glucose elimination. Gastrointestinal effects include nausea, vomiting and diarrhoea, which can cause dehydration leading to deterioration of kidney function. These reactions are usually mild or moderately severe and don't last long. Acute pancreatitis has been observed with the use of GLP-1 receptor agonists. Patients should be informed about the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, they should be discontinued, and if suspicion is confirmed, treatment should not be resumed. It should be approached with caution in patients with a history of pancreatitis. With the appearance of the first medicinal products GLP-1 agonists, the first cases of pancreatitis were described. A long-term study was conducted, the analysis of which showed that users of incretins were younger, had higher HbA1c values, had a longer duration of antihyperglycemic treatment, were more likely to be overweight, and were more likely to have used antidiabetic therapy in the year prior to the start of the study compared to those who received SU. There was no difference in the potential risk of developing pancreatitis between the two groups being compared in the study. There is no conclusive evidence that incretins increase the risk of acute pancreatitis. Hypoglycemia is a rare side effect with members of these drug classes. Another side effect of GLP-1 receptor agonists may be dizziness and mild tachycardia, diabetic retinopathy, infections, headache, dyspepsia, itching and erythema at the site of administration. A rare side effect is pancreatic carcinoma and incretin therapy. SGLT-2 inhibitors have a fourfold increased incidence of genital infections as side effects of therapy. The increased amount of glucose in the urine facilitates the occurrence of infections due to osmotic diuresis; it is accompanied by frequent urination, thirst and less often by orthostatic hypotension. Fungal infections, urinary infections, and osmotic diuresis-related side effects also become more frequent, but they are mild to moderate and rarely lead to discontinuation. Another, more dangerous side effect of SGLT-2 inhibitors, is ketoacidosis. It occurs after one day of therapy up to 1 year of therapy (average 43 days), according to various sources. The explanation of diabetic ketoacidosis lies in the insufficiency of insulin to reduce glucose metabolism, due to which lipolysis increases, free fatty acids in the liver increase, and high levels of glucagon enhance the oxidation of fatty acids and the production of ketone bodies. It is manifested by hyperglycemia, glycosuria, and hyperketonemia. SGLT-2 inhibitors induce a rapid increase in urinary glucose excretion. It enhances blood glucose and causes a decrease in insulin level and increases glucagon level. This leads to inhibition of gluconeogenesis in the liver and enhances endogenous glucose production. The impaired insulin/glucagon ratio stimulates lipolysis and ketogenesis. Because of the low glucose levels (caused by increased glycosuria) in patients on SGLT-2 inhibitors, ketoacidosis is difficult to detect and its diagnosis and treatment may be delayed.

Management of the GIT side effects includes patients' education of a mechanism of action of the drugs and the application and dosing. On the other hand, warning about certain anticipated side effects can concentrate patients' minds on avoiding certain dietary habits and avoiding their occurrence. It can also make patients more patient in overcoming temporary side effects and avoid incompliance, adherence, and discontinuation due to intolerance. Also, part of the pharmaceutical care is the treatment of the more severe side reactions with the corresponding medicinal products: for example, antiemetics and others.

Table 1. Most common side effects in the three classes of antidiabetics – comparison.

Side effects	GLP-1 RA	DPP-4 I	SGLT-2 I
Frequent			
Nausea	+	+	+
Vomiting	+	+	+
Diarrhea	+	+	+
Acute pancreatitis	+		
Urogenital infections			++
Fungal infections			+
Ketoacidosis			+
Rare			
Hypoglycemia	+		
Dizziness	+		
Mild tachycardia	+		
Headache	+		
Dyspepsia	+		
Itching and erythema	+		
Carcinoma of the pancreas	+		
Orthostatic hypotension			+

Patients with DM2 often have co-morbidities or metabolic syndrome ie. arterial hypertension, dyslipidaemia, kidney diseases, polycystosis and others. Often, they take various medicines for each disease, and they may be prescribed by different specialists who do not always manage to follow the complete drug therapy and sometimes this is missed by the general practitioner. The pharmacist providing pharmaceutical care is in a unique position to monitor the final polytherapy of such patients and can provide a competent opinion and screen for possible drug interactions.

Examples of drug interactions and their resolution

An unacceptable combination is the use of a GLP-1 agonist and a DPP-4 inhibitor, due to their similar effect on incretins. Also, both groups of drugs delay the emptying of gastric contents, as well as provoke side reactions on the part of the GIT and thus can affect the rate of absorption of concomitantly administered oral medicinal products. They should be used with caution in patients taking oral medicinal products that require rapid gastrointestinal absorption. In most cases, this has no clinical manifestation, but should be considered and may be in the scope of pharmaceutical care. More sensitive medicinal products may be paracetamol, digoxin, atorvastatin, antibiotics, and oral contraceptives. Also, frequent monitoring of INR is recommended when taking anticoagulants – for example, warfarin or other coumarin derivatives.

The risk of clinically significant drug-drug interactions with DPP-4 inhibitors is low. In vitro studies show that the

main enzyme responsible for their metabolism is CYP3A4 with the participation of CYP2C8. In patients with normal renal function, metabolism, including through CYP3A4, plays a minor role in their clearance. Metabolism may play a more significant role in elimination in severe renal impairment or end-stage renal disease (ESRD). For this reason, it is possible that potent CYP3A4 inhibitors (such as ketoconazole, itraconazole, ritonavir, clarithromycin) may alter the pharmacokinetics of DPP-4 inhibitors in patients with severe renal impairment or ESRD. They are also substrates of p-glycoprotein and organic anion transporter-3 (OAT3). OAT3-mediated transport is inhibited in vitro by probenecid, although the risk of clinically relevant interactions is estimated to be low. A study was conducted to evaluate the effect of cyclosporine, a potent inhibitor of p-glycoprotein, on the pharmacokinetics of sitagliptin. A study was conducted to assess the effect of ciclosporin, a potent inhibitor of p-glycoprotein, on the pharmacokinetics of sitagliptin. Co-administration of a single 100 mg oral dose of sitagliptin and a single 600 mg oral dose of ciclosporin increased the AUC and Cmax of sitagliptin by approximately 29% and 68%, respectively. These changes in sitagliptin pharmacokinetics were not considered to be clinically meaningful. The renal clearance of sitagliptin was not meaningfully altered. Therefore, meaningful interactions would not be expected with other p-glycoprotein inhibitors. In vitro data suggest that sitagliptin does not inhibit or induce CYP450 isoenzymes. In clinical studies, DPP-4 inhibitors did not meaningfully alter the pharmacokinetics of metformin, glyburide, simvastatin, rosiglitazone, warfarin, or oral contraceptives, providing in vivo evidence of a low propensity for causing interactions with substrates of CYP3A4, CYP2C8, CYP2C9, and organic cationic transporter (OCT).

SGLT-2 inhibitors may have the following pharmacodynamic interactions: With diuretics, they may increase the diuretic effect of thiazides and loop diuretics and may increase the risk of dehydration and hypotension. Insulin and insulin secretagogues, such as sulphonylureas, cause hypoglycaemia, therefore, when used in combination with dapagliflozin in patients with type 2 diabetes mellitus, a lower dose of insulin or an insulin secretagogue may be required to achieve reduction of the risk of hypoglycemia.

The pharmacokinetics of SGLT-2 inhibitors are not affected by metformin, pioglitazone, sitagliptin, glimepiride, voglibose, hydrochlorothiazide, bumetanide, valsartan, or simvastatin. Administration with other enzyme inducers (eg carbamazepine, phenytoin, phenobarbital) is also not expected to have a clinically significant effect.

SGLT-2 inhibitors did not affect the pharmacokinetics of metformin, pioglitazone, sitagliptin, glimepiride, hydrochlorothiazide, bumetanide, valsartan, digoxin (p-gp substrate), warfarin (Swarfarin, CYP2C9 substrate) or the anticoagulant effects of warfarin as measured by INR.

Monitoring of glycemic control by 1,5-AG test is not recommended because measurement of 1,5-AG is unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. The use of alternative methods to monitor glycemic control is recommended.

Table 2. Comparison of the most common drug interactions.

Drug interactions	GLP-1 RA	DPP-4 I	SGLT-2 I
Bad combinations	DPP-4 I	GLP-1 RA	
That may affect absorption	yes	yes	
paracetamol, digoxin, atorvastatin, antibiotics, and oral contraceptives	yes	yes	
anticoagulants	yes	yes	yes
strong CYP3A4 inhibitors (such as ketoconazole, itraconazole, ritonavir, clarithromycin		yes	
substrates of p-glycoprotein		yes	no
That are substrates of organic anion transporter-3 (OAT3)		yes	
diuretics			yes
Insulin and SU	yes	yes	yes

First, all three classes of antidiabetic drugs are contraindicated in case of hypersensitivity to the active ingredient or excipients. Also, all three classes are contraindicated in pregnancy and lactation and their effect on fertility is unknown. The most common contraindications to GLP1 agonists are type 1 diabetes mellitus or the treatment of diabetic ketoacidosis. Diabetic ketoacidosis has been reported in insulin-dependent patients who experienced rapid withdrawal of insulin or reduction in insulin dose when treatment with a GLP 1 receptor agonist was initiated. DPP-4 inhibitors are also not recommended in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. GLP-1 receptor agonists may be associated with gastrointestinal side effects. This should be considered in treatment of patients with impaired renal function, as nausea, vomiting and diarrhea may cause dehydration leading to deterioration of renal function. In patients with severe kidney diseases, including those on dialysis, lower doses of DPP-4 inhibitors are recommended due to their impaired renal excretion. In patients treated with semaglutide in combination with sulphonylureas or insulin, there may be an increased risk of hypoglycaemia. The risk of hypoglycaemia can be lowered by reducing the dose of sulfonylurea or insulin when initiating treatment with semaglutide.

GLP-1 receptor agonists and DPP-4 inhibitors are associated with a risk of acute pancreatitis. Patients should be informed about the characteristic symptom of acute pancreatitis: persistent, very severe abdominal pain. After therapy discontinuation, resolution of pancreatitis has been observed (with or without supportive care), but in very rare cases necrotizing or haemorrhagic pancreatitis and/or death have been reported. If pancreatitis is suspected, their intake and other potentially suspected medicines should be stopped; if acute pancreatitis is confirmed, the intake should not be resumed. Caution should be exercised in patients with a history of pancreatitis.

There is a lack of experience in patients with NYHA class IV congestive heart failure and therefore GLP-1 receptor agonists and DPP-4 inhibitors are not recommended in these patients. In patients with diabetic retinopathy treated with insulin and semaglutide, an increased risk of developing diabetic retinopathy complications has been observed. Due to its mechanism of action, SGLT2 inhibitors increase diuresis which may lead to the modest decrease in blood pressure

observed in clinical studies. It may be more pronounced in patients with very high blood glucose concentrations. Caution should be exercised in patients for whom a SGLT2 inhibitors-induced drop in blood pressure could pose a risk, such as patients on antihypertensive therapy with a history of hypotension or elderly patients. In case of intercurrent conditions that may lead to volume depletion (e.g. gastrointestinal illness), careful monitoring of volume status (e.g. physical examination, blood pressure measurements, laboratory tests including haematocrit and electrolytes) is recommended. Temporary interruption of treatment with SGLT2 inhibitors is recommended for patients who develop volume depletion until the depletion is corrected. Rare cases of diabetic ketoacidosis (DKA), including life-threatening and fatal cases, have been reported in patients treated with SGLT2 inhibitors. In a number of cases, the presentation of the condition was atypical with only moderately increased blood glucose values, below 14 mmol/L (250 mg/dL). The risk of diabetic ketoacidosis must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness. Patients should be assessed for ketoacidosis immediately if these symptoms occur, regardless of blood glucose level. In patients where DKA is suspected or diagnosed, treatment should be stopped immediately. Treatment should be interrupted in patients who are hospitalized for major surgical procedures or acute serious medical illnesses. Monitoring of ketones is recommended in these patients. Measurement of blood ketone levels is preferred to urine. Treatment may be restarted when the ketone values are normal and the patient's condition has stabilized. Before initiating, factors in the patient's history that may predispose to ketoacidosis should be considered.

Postmarketing cases of necrotising fasciitis of the perineum (also known as Fournier's gangrene) have been reported in female and male patients taking SGLT2 inhibitors. This is a rare but serious and potentially life-threatening event that requires urgent surgical intervention and antibiotic treatment.

Patients should be advised to seek medical attention if they experience a combination of symptoms of pain, tenderness, erythema, or swelling in the genital or perineal area, with fever or malaise. Be aware that either uro-genital infection or perineal abscess may precede necrotising fasciitis. If Fournier's gangrene is suspected, treatment should be discontinued and prompt treatment (including antibiotics and surgical debridement) should be instituted. Urinary glucose excretion may be associated with an increased risk of urinary tract infection; therefore, temporary interruption of therapy should be considered when treating pyelonephritis or urosepsis. Elderly patients may be at a greater risk for volume depletion and are more likely to be treated with diuretics. Elderly patients are more likely to have impaired renal function, and/or to be treated with anti-hypertensive medicinal products that may cause changes in renal function such as angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin II type 1 receptor blockers (ARB). The glucose lowering efficacy of SGLT-2 inhibitors depends on renal function and is reduced in patients with GFR < 45 ml/min, and is likely absent in patients with severe renal impairment. Therefore, they are not recommended for use in patients with severe chronic kidney disease. An increase in the incidence of lower limp amputation (predominantly of a toe) has been observed in long-term clinical trials in type 2 diabetes mellitus with SGLT2 inhibitors. Urine laboratory tests will be positive for glucose in patients taking it due to the mechanism of action of SGLT-2 inhibitors.

The treatment of DM2 and metabolic syndrome is not only an object of pharmacotherapy. Without a change in lifestyle and an increase in physical activity and avoiding certain harmful habits, the treatment of these patients is doomed to failure and serious consequences. Therefore, the pharmacist's role in promoting non-pharmacological therapy of DM2 and MS is important. It is recommended that each pharmacy be able to provide materials on metabolic syndrome, the most common acute and chronic complications, as well as materials promoting healthy diet and an active lifestyle.

Table 3. Comparison of contraindications and special indications for the three classes of antidiabetic medicinal products.

Contraindications	GLP-1 RA	DPP-4 I	SGLT-2 I
Hypersensitivity to the active ingredient or excipients	yes	yes	yes
Pregnancy and breastfeeding	yes	yes	yes
ZD1	yes	yes	
Diabetic ketoacidosis	yes	yes	
Special attention for:	GLP-1 RA	DPP-4 I	SGLT-2 I
Impaired renal function	yes	yes (dose decrease)	
Combination with SUP	yes	yes	
Risk of acute pancreatitis	Combination with DPP-4 I	Combination with GLP-1 RA	
Congestive heart failure class IV	yes	yes	
Diabetic retinopathy	yes (comb. with insulin)		
Risk of hypotension			yes
Intercurrent diseases leading to volume depletion			yes
Major surgical procedures or acute serious illnesses requiring hospitalization			yes (risk of DKA)
Fournier's gangrene			yes
Urinary tract infections			yes
Elderly (≥65 years), taking ACE or ARB, GFR<45ml/min, severe chronic kidney disease			yes

Table 4. List of measures to solve the problems with metabolic syndrome.

Problem	Measures
Application and dosing errors	Pharmaceutical care
Getting to know MS and the medicinal product	Information leaflets
Clarification of side effects and ways to recognize them	Education, pharmaceutical care, information leaflets
Drug interactions	Education, pharmaceutical care, information brochures
Contraindications	Education, pharmaceutical care, information brochures
Promotion of lifestyle change and increased physical activity, rejection of harmful habits and analysis of risk factors	Education, pharmaceutical care, information brochures

Obesity among the adult population, and especially among children, is an alarming problem, which is an independent risk factor for DM2 and metabolic syndrome. Therefore, efforts should be directed not only to patients with a disease, but also as preventive measures in children and young people with obesity.

Discussion

The literature review shows that the problems with adverse reactions and drug interactions from the three newest classes of antidiabetic medicinal products need an interdisciplinary approach and the concept of pharmaceutical care as a way to real solutions in practice and patient-focused therapy of various diseases.

A multidisciplinary team is appropriate for supporting the patient to modify lifestyle and increase physical activity. Statistically significant improvements were observed in several indicators: reduction of abdominal circumference, reduction of arterial pressure, reduction of HbA1c, reduction of triglycerides, increase of HDL-C, reduction of body weight. A multidisciplinary team would make a huge contribution to addressing childhood obesity, which would also reduce the risk of developing metabolic syndrome later in life. The normalization of the individual components of the metabolic syndrome leads to a reduction of the risk factors for the subsequent development of cardiovascular diseases, complications of AH and type 2 diabetes, to increase the quality of life of patients and to extend their life expectancy (Telner 2008; Jardim 2018; Tremblay 2020).

The role of the pharmacist in the multidisciplinary team in supporting patients with metabolic syndrome is fully covered by the concept of pharmaceutical care. Most studies have focused on the contribution of pharmacists to the screening and management of metabolic syndrome. Screening largely involves reporting metabolic parameters to physicians. The management of metabolic syndrome is described by pharmacists collaborating with members of the multidisciplinary team. Positive effects were reported in all studies, including achievement of metabolic syndrome parameter goals, return to non-metabolic syndrome status, and improved adherence. The authors' conclusions are that more in-depth studies and a wider participation of the pharmacist in a multidisciplinary team of doctors and other medical and non-medical specialists – nutritionists, sports instructors, psychologists, etc. – are needed (Al AdAwi 2020).

Similar studies with another disease -e.g. breast cancer – show the role of the multidisciplinary team in increasing compliance and adherence to the pharmacological and non-pharmacological treatment. Compliance and adherence to prescribed treatment is a key point in the management of metabolic syndrome because it is a long-term endeavour aimed at changing the patient's behaviour entirely. The role of society, the media, government institutions, schools, employers and health professionals is huge, and they can offer programs to promote a healthy lifestyle and physical activity in order to reduce the risk factors for the development of metabolic syndrome, especially for children and young people (Samarasinghe 2019).

Conclusion

From the analysis of the three classes of medicinal products for the treatment of DM2, we can make the following conclusions:

The numerous advantages and benefits provided by the last three classes of antidiabetic medicinal products also hide many risks, contraindications, and potential drug interactions.

Their generic replacement is yet to come, which implies an ever-wider use and, accordingly, an ever-greater need for awareness on the part of patients.

Patients prescribed newer antidiabetic medicinal products need support, wider awareness about side effects, contraindications, and methods to solve problems concerning complications, application, and dosage, without always having to consult their physician.

Pharmacists are medical specialists who are specially educated about medicines and the concept of pharmaceutical care, and they are in their position of greatest accessibility, most frequent contact with the patient and have complete pharmacotherapeutic information, including the therapy of accompanying diseases, family characteristics, etc.

Pharmaceutical care can save patients a lot of inconvenience, side effects treatment costs, misuse, and complications. Pharmaceutical care is the tool to promote healthy diet and physical activity, which is a key point recommended in all guidelines for the prevention and treatment of DM2 and metabolic syndrome, as well as in reducing obesity, especially in children, who are the future patients with DM2 and metabolic syndrome if no measures are taken now.

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