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Review Article / Преглед литературе

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Impact of currently used oral antihyperglycemic drugs on dysfunctional adipose tissue

Утицај савремених оралних антихипергликемијских лекова на дисфункционално масно ткиво

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SUMMARY

Obesity is a disease with pandemic frequency, often accompanied by chronic metabolic and organic complications. Type 2 diabetes (T2DM) is among the most common metabolic complications of obesity. First step in the treatment of T2DM is medical nutrition therapy combined with moderate physical activity and with advice to patients to reduce their body weight. Pharmacotherapy starts with metformin, and in the case of inadequate therapeutic response, another antihyperglycemic agent should be added. The most clinical experience exists with sulfonylurea agents, but their use is limited dueto high incidence of hypoglycemia and increase in body weight. Based on the fact that dysfunction of adipose tissue can lead to development of chronic degenerative complications, precise usage of drugs with a favorable effect on the functionality of adipose tissue represents an imperative of modern T2DM treatment. Antihyperglycemic drugs of choice in obese individuals are those which cause maturation of adipocytes, improvement of secretion of protective adipokines, and redistribution of fat mass from visceral to subcutaneous depots. Oral antihyperglycemic agents that can affect the functionality of adipose tissue are metformin, SGLT-2 inhibitors, DPP-4 inhibitors, and thiazolidinediones.

Keywords: adipose tissue; adipokines; type 2 diabetes; treatment

САЖЕТАК

Гојазност је болест са пандемијском учесталошћу, коју прате хроничне метаболичке и ораганске компликације. Међу најчешће метаболичке компликације гојазности спада тип 2 шећерне болести, а први корак у њеном лечењу је нутритивна терапија уз дозирану физичку активност и редукцију телесне масе. Медикаментно лечење се започиње метформином, а у случају неадекватног успеха додају се и други антихипергликемијски лекови. Са дериватима сулфонилуреје постоји највеће клиничко искуство, али је њихова употреба ограничена јер изазивају учестале хипогликемије и пораст телесне масе. У светлу сазнања да је масно ткиво ендокрини орган и да управо дисфункција овог ткива доводи до хроничних компликација, императив у савременој терапији је употреба лекова са снажним ефектом на функционалност овог ткива. Антихипергликемијски лекови избора ког гојазних особа су они који доводе до матурације адипоцита, лучења протективних адипоцитокина и редистрибуције масне масе из висцералних у субкутане депое. Орални хипогликемијски агенси који утичу на функционалност масног ткива су метформин, СГЛТ-2 инхибитори, ДПП-4 инхибитори и тиазолидиндиони.

Кључне речи: масно ткиво; адипоцитокини; тип 2 диабетеса; терапија;

INTRODUCTION

Obesity is a disease characterized by the excessive accumulation and storage of adipose tissue in body, that presents a risk to health and can lead to many complications [1-3]. Adipose tissue is a metabolically active organ with both endocrine and paraendocrine effect [3]. Dysfunction of this tissue is clearly associated with more frequent occurrence of visceral obesity, type 2 diabetes (T2DM), insulin resistance (IR) and chronic subclinical inflammation [3-5]. Namely, fat tissue makes approximately 10-20% of total body mass, while that percentage in obese persons can be 4 to 5 times greater [6,7]. Reduction in adenosine monophosphate-activated protein kinase α (AMPKα), peroxisome proliferator-activated receptor gamma, coactivator 1 α (PPARGC1A, PGCα) and peroxisome proliferator-activated receptor α (PPARα) genes expression decrease oxidative capacity of adipocytes, and thereby inhibite the possibility of energetic metabolism turnover in the adipose tissue, which represents the main pathophysiological model that causes obesity [8]. Knowing this fact,

current therapy of T2DM and development of modern antihyperglycemic drugs are based on the stimulation of those impaired pathways in the adipose tissue.

It is known that in the presence of excessive obesity the possibility of prediabetes development increases, which can, in the later course, lead to the onset of T2DM, which imposes the need for implementation of the active screening procedures among populations with a great propensity to develop diabetes , like among obese individuals, but also a need to intensify their treatment [9]. Populations with greater susceptibility for T2DM development include subjects with prediabetes, obese and overweight individuals, subjects with established cardiovascular diseases (CVD), and persons older than 45 years [9]. In these cases it is indicated to perform 2-hour oral glucose tolerance test with 75 g of glucose [9, 10].

The consequence of dysfunctional adipose tissue is sustained lipid toxicity, then IR and associated metabolic complications. These metabolic alterations negatively affect global metabolic homeostasis. The adipose tissue distribution optimization and its functional metabolic flexibility are promoting insulin sensitivity and metabolic control in patients with T2DM. These therapeutic approaches require a deep understanding of adipose tissue in all broad aspects. In this article we will discuss the influence of the different glucose-lowering agents on adipose tissue depots with respect to adipokines production, plasticity, cellular composition, as well as metabolic signatures of pharmacotherapy of T2DM [9, 10].

Randomized controlled studies showed that in persons with higher risk of developing T2DM, lifestyle changes and/or drug therapy can prevent progression of the disease [11]. Considering that at the moment of diabetes diagnosis, 80 to 90% of patients are overweight or obese, American Diabetes Association (ADA) guidelines recommend,introductionof antihyperglycemic drugs with weight-reducing or at least weight-neutral properties in patients with body mass index (BMI) $\geq$27 kg/m^2, whenever other circumstances allow it [10]. Antihyperglycemic drugs that stimulate weight reduction are metformin, α-glycosidase inhibitors, glucagon-like peptide-1 (GLP-1)receptor agonist, amyline mimetics, and sodium-glucose cotransporter-2 (SGLT-2) inhibitors. Dipeptidyl peptidase-4 inhibitor (DPP-4) inhibitors areweight-neutral to weight'reducing, while secretagogues, thiazolidinediones and insulin are related to significant increase in body weight [9,10].

THERAPY

Initial therapy for T2DM surely includes lifestyle changes such as intensification of physical activity to minimum of 150 min/week and changes in dietary habits [9-11]. Metformin is the first line of drug therapy, according to current recommendations [9, 10]. If this treatment fails to give expected results in a period of 3 months, combination therapy should be introduced [9,10]. While choosing the right additional antihyperglycemic drug, it is neccessary to bear in mind its effect on the body weight. [9, 10, 12].

List of available glucose-lowering agents are shown in table 1.

Table 1. Properties of available glucose-lowering agents that may tailor the individualized treatment choice in patients with T2DM.

Class	Compound(s)	Cellular mechanism(s)	Primary physiological action(s)
Biguanides	Metformin	activates AMP-kinase	↓ hepatic glucose production
Sulfonylureas	2nd generation: Glyburide Glipizide Gliclazide Glimepiride	closes K_{ATP} channels on β-cell plasma membranes	↑ insulin secretion
Meglitinides	Repaglinide Nateglinide	closes K_{ATP} channels on β-cell plasma membranes	↑ insulin secretion
Thiazolidinediones	Pioglitazone Rosiglitazone	activates the nuclear transcription factor PPARγ	↑ insulin sensitivity
α-Glucosidase inhibitors	Acarbose Miglitol	inhibits intestinal α-glucosidase	slows inestinal carbohydrate digestion/absorption
DPP-4 inhibitors	Sitagliptine Vildagliptine Saxagliptine Linagliptine Alogliptine	inhibits DPP-4 activity, increasing postprandial active incretin (GLP-1) concentrations	↑insulin secretion ↓secretion of glucagon
Bille acid sequestrants	Colesevelam	binds bille acids in intestinal tract, increasing hepatic bile acid production	?↓hepatic glucose production ?↑ incretin levels
Dopamine-2 agonists	Bromocriptine	activates dopaminergic receptors	modulates hypothalamic regulation of metabolism ↑insulin sensitivity
SGLT-2 inhibitors	Canagliflozin Dapagliflozin Empagliflozin	inhibits SGLT-2 receptors in the proximal nephron	blocks glucose reabsorption by the kidney, increasing glucosuria
GLP-1 receptor agonists	Exenatide Liraglutide Albiglutide Lixisenatide Dulaglutide	activates GLP-1 receptors	↑insulin secretion ↓glucagon secretion slows gastric emptying ↑satiety
Amylin mimetics	Pramlintide	activates amylin receptors	↓glucagon secretion slows gastric emptying ↑satiety
Insulins	Lispro Aspart Glulisine Human regular Human NPH Glargine Detemir Degludec	activates insulin receptors	↑glucose disposal ↓hepatic glucose production

AMP-kinase: adenosine monophosphate-kinase; K_{ATP} channels: adenosine triphosphate-sensitive potassium channels; PPARγ: peroxisome proliferator-activated receptor gamma; DPP-4: dipeptidyl peptidase-4; GLP-1: glucagon-like peptide-1; SGLT-2: sodium-glucose cotransporter-2; NPH: neutral protamine Hagedorn;

Sulfonylureas are drugs that are now used for a several decades. They show high efficiency in HbA1c reduction and evidence from earlier landmark studies indicates their positive effect on the delay of chronic microvascular complications development. However, nowadays, at least in developed countries, they are replaced with other drugs, because they cause high rates of

hypoglycemia, tend to increase body weight, and have a negative effect on spontaneous vasodilatation of coronary arteries [12].

α-Glucosidase inhibitors have limited usage, considering their modest efficiency in HbA1c reduction accompanied with gastrointestinal side effects (diarrhea, flatulence) [12]. However these drugs found their place in the treatment of obese patients after the bariatric surgery. Number of patients treated with bariatric surgery procedures report so-called "dumping syndrome", and usage of acarbose showed decrease in incidence of this complication thus leading to improvement in quality of in these patients [13].

Bile acid sequestrants are used mainly in treating hypercholesterolemia, since their main effect is low density lipoprotein (LDL)-cholesterol lowering [14]. However, they demonstrate satisfying glucose-lowering effect (HbA1c reduction in the range from 0.3 to 1.1% is reported), in particularlycolesevelam [14]. Their physiological actions remain unknown, with the assumption that it is based on the incretin effect through the stimulation of incretin secretion (GLP-1 and other) and on the impact on the hepatic glucose production [14].

Bromocriptine is one of the newer antihyperglycemic agents, with unique central mechanism of action. Normal weight individuals have maximum prolactin secretion during the night, because of the low dopaminergic activity, while after waking up prolactin level decreases [15]. Obese individuals with IR have two times higher prolactine levels during the day comparing to healthy persons [15]. The main mechanism of the bromocriptine antihyperglycemic action is an increase in the daily dopaminergic activity and lowering prolactine level [15]. Previous experiences show that bromocriptine monotherapy or its combination with other oral antihyperglycemic agents, lead to HbA1c reduction ranging from 0.4% to 0.7% [15]. Even though it shows low/mild HbA1c reduction effect, benefits of bromocriptine usage are weight reduction combined with low incidence of hypoglycemia [12,15]. The side effects of bromocriptine (ortostatic hypotension, nausea, vertigo and possible interactions with other plasma protein-binding drugs) limit its usage [12,15]. Since postprandial glycemia is equally important indicator of glycoregulation, as well as HbA_1c and fasting glycemia, large efforts are made recently in therapeutic targeting of this particular aspect of diabetes management. Efficiency in reduction of postprandial glycemia are shown by meglitinides, GLP-1 receptor agonists (mainly short acting ones), DPP-4 inhibitors, SGLT-2 inhibitors, and amyline mimetics. [16].

ORAL ANTIHYPERGLYCEMIC AGENTS AND DYSFUNCTIONAL ADIPOSE TISSUE

Metformin

Metformin is used in the treatment of T2DM since 1950`s.As it is already known, metformin reduces body weight [9,10]. However, the greatest reduction of fat mass was actualy detected in subcutaneous abdominal depots [17]. Also, it is shown that metformin causes the highest insulin stimulated glucose uptakein the visceral adipose tissue [17]. Fujita et al. have questioned the positive

effect of this drug on dysfunctional adipose tissue, showing that *in vitro* model, metformin actualy blocks a diferentiation of visceral tissue preadipocytes into mature adipocytes and that it does not reduce size or number of adipocytes, which could be expected as the positive effect [17]. This way maturation of preadipocytes and secretion of adipocyte final maturation indicators , such as adiponectin, which demonstrates strong antiinflammatory and antidiabetic effect, are supressed [17]. On the other hand, positive effects of metformin are shown among women with polycystic ovary syndrome. Tan et al. published that metformin usage significantly lowers level of chemerine, adipocytokine involved in pathogenesis of IR and hypertriglyceridemia [18]. Metformin's main mechanism of action in adipose tissue is activation of adenosine monophosphate (AMP)-kinase and lipogenesis supression in preadipocytes, and the greatest antihyperglycemic effect is achieved through lowering the hepatic glucose production [19].

DPP-4 inhibitors

DPP-4inhibitors are among newer antihyperglycemic agents, and according to the current diabetes guidelines are referred as weight-neutral [9, 10]. DPP-4 are proteases located on the cell surface, but there is also a soluble fraction of this proteases in plasma [20]. Recently, this enzyme was recognized as an adipocytokine, responsible for development of metabolic syndrome and T2DM [20]. DPP-4 interfere with insulin signalization through paracrine and endocrine ways [20].

Although until now they were referred as weight-neutral, recent studies on DPP-4 inhibitor, evogliptin, in animal model, indicate possible benefit effects in term of body weight reduction. Namely, this drug shows the possibility of changing energy balance within the white adipose tissue [21]. Evogliptin in animal model does not increase thermogenesis in white adipose tissue, but contrary reduces uncoupling protein-1(UCP-1) level in mitochondria of adipocytes [21]. It is shown in animal model that evogliptin induces energy consumption with the help of increased expression of cytochrome c oxidase subunit 4 isoform 1(Cox4I1)which correlates with increased concentration of protein molecule PPARGC1A [21]. This protein is directly involved in the transcription processes, that stimulate production of enzymes necessary for mitochondrial biogenesis and energy consumption [21]. Also, PPARGC1A stimulates diferentiation of muscle fibers, and has protective effect in terms of obesity development [20,21]. Evogliptin usage led to decrease in leptin level, which can be a result of weight reduction or possible consequence of decrease in the level of leptin resistance [21]. The effect of decreasing leptin resistance is just a hypothetical one, since authors did not measure the expression of leptin receptor [21]. Similar effect in humans is caused byvildagliptin [21].

SGLT-2 inhibitors

In the last 10 years, a new therapeutic approach has been developed, which does not include use of insulin in treatment of T2DM. In physiological conditions, glucose that is excreted in primary urine, is being entirely reabsorbed back to plasma in renal tubules, so less than 1% of glucose is being excreted by urine [21]. In condition of SGLT-2 receptor inhibition major part of excreted glucose,

does not go through the reabsorption process, it stays in the urine and through that way is eliminated from body [21].

Until now there has been some concern over the fact that use of SGLT-2 inhibitors increases LDL-cholesterol level. However, this group of agents demonstrate positive effect on lipid profile through decreasing level of triglycerides and increasing level of C2 sub-fraction of high density lipoprotein (HDL)-cholesterol, thus reducing overall atherogenic risk. One of the explanations for their antiatherogenic effect lays in the fact that SGLT-2 inhibitors suppress transformation of large LDL particles into small dense LDL particles, which carry great atherogenic potential, but are difficult to detect in the everyday routine laboratory diagnostics [22]. Additionally, use of dapagliflozin reduces BMI level, hepatic transaminases level, and increases adiponectin level [22]. Non-alcoholic fatty liver disease (NAFLD) is the most common cause of elevated liver enzymes in obese people. It is known that subjects with high level of small dense LDL particles, NAFLD and low adiponectin level have additionally increased cardiovascular risk [21, 22]. Considering positive effects of dapagliflozin on all mentioned risk factors and also an impact on decreasing level of triglycerides, it is clear why it should be used in people with cardiometabolic complications of dysfunctional adipose tissue. Ludkvist et al. conducted a trial among 50 obese individuals with prediabetes, based on previous favorable experiences in body weight management among obese patients with T2DM [19]. Results showed possibility of dapagliflozin use in this population, due to significant weight reduction, reduction of systolic blood pressure and improved glucose tolerance that has been achieved [19].

Out of SGLT-2 inhibitors, empagliflozin emerged as the most significant agent. The results of the recently completed Empagliflozin Removal of Excess of Glucose Outcome (EMPA-REG OUTCOME) study indicate that empagliflozin significantly reduces cardiovascular mortality and hospitalization rate because of heart failure in patients with T2DM [23]. This is due to antihyperglycemic effect of the SGLT-2 inhibitors but also because of their effect on natriuresis, body weight reduction, blood pressure and lipid profile. Even though protective effect of empagliflozin in diabetic patients is established, effect of SGLT-2 inhibitors on this specter of cardiovascular risk factors in condition of prediabetes is known only from animal models [23]. Kusak et al. study was conducted among rats with prediabetes, and they clearly showed that after 7 weeks of treatment with empagliflozin weight reduction was gained despite increased food intake when compared to the control group [24]. Regarding the fact that there was no difference in the amount of fat mass between study group and control group, and that size of subcutaneous fat mass was smaller in the study group a question on protective role of empagliflozin has imposed [24]. This study has demonstrated that there is a significant difference in the size of adipocytes [24]. Empagliflozin use leads to the histological changes in the structure of the adipose tissue, in the sense of reducing the diameter of adipocytes, which have more favorable metabolic impact than insufficiently differentiated adipocytes with large diameter [24]. In relation to metabolic parameters, reduction of HbA1c, lowering of

postprandial glycemia and decrease in insulin level were observed [24]. Although it was noted that empagliflozin does not lower level of total cholesterol and free fatty acids (FFA), it certainly reduces the rate of lipid peroxidation [24]. On the other hand people with prediabetes have a high risk of developing CVD [1-5]. Taking into account the favorable effect of empagliflozin on preventing hypertrophy and fibrosis of the left ventricle, SGLT-2 inhibitors could also be used in the treatment of individuals with prediabetes [23,24].

Thiazolidinediones

It was clearly proven by now that there is a correlation between IR, T2DM and adipose tissue dysfunction [1,2,4,5]. One of the key genes responsible for function of adipose tissue is PPARγ [25]. Previous studies have shown that PPARγ plays a role in numerous functions of adipose tissue such as preadipocytes differentiation and secretion of adipocytokines, and also controls the level of inflammation and insulin sensitivity within the adipose tissue [25]. As it was mentioned beforehand, important markers of dysfunction and inadequate differentiation of adipose tissue are larger diameter of adipocytes, reduced expression and low level of circulating adiponectin and reduced expression of PPARGC1A [25,26].Thiazolidinediones are PPARγ agonists, and by that they increase glucose uptake in adipocytes, and prevent FFA release and possible subsequent lipotoxicity, which represents one of the key physiopathogenetic mechanisms in T2DM development [27].

In individuals with IR there is a reduction in several key molecules responsible for insulin activity, such as, glucose transporter type 4(GLUT4), PPARGC1A, markers of terminal differentiation of the adipose tissue, and insulin receptor substrate 1(IRS-1) [27, 28]. The use of pioglitazone leads to improvement in insulin sensitivity in non-obese subjects with IR, regardless of its impact on the change in levels of circulating FFA and other lipid and lipoprotein parameters [28]. The explanation of this effect of thiazolidinediones lays in their positive activity on adipose tissue remodeling. Usage of this agents leads to the replacement of the large adipocytes with well differentiated and more insulin sensitive adipocytes with smaller diameter [28]. This kind of adipose tissue remodeling has a positive effect on inflammation, which is one of the leading physiopathogenetic mechanisms of IR and T2DM. In fact, there is a clear correlation between adipocyte size and the level of circulating interleukin-6 (IL-6). Reduction in the size of adipocytes reduces the level of IL-6 in the serum [28]. On the other hand, thiazolidinediones stimulate the production of adiponectin [27,28].It was noted that the level of adiponectin in individuals treated with pioglitazone is the result of increased contribution of high molecular weight adiponectin fraction (HMW)adiponectin [28]. HMW adiponectin is highly protective regarding atherosclerosis and T2DM development [1-3]. PPARγ demonstrates high expression in the adipose tissue. Although the role of thiazolidinediones on PPARγ stimulation is well documented, its role in the expression of this nuclear receptor is still controversial [28]. The beneficial effect of pioglitazone is reflected through the redistribution of fat mass in the body. The use of pioglitazone increases body weight and fat mass.

However, beneficial metabolic effect of pioglitazone is a result of adipose tissue redistribution, reflected through the reduction in visceral adipose tissue amount and increase in the amount of subcutaneous fat depots [28, 29].

Parenteral pharmacotherapy

Among the currently available parenteral therapies for obese patients with T2DM, two classes also promote weight loss. Pramlyntide, a syntetic form of amylin, induces short-term satienty, and may be useful in the combination with other agents. Recent study pointed out improvement in glucose tolerance in diabetic patients in dose-dependent manner, as well as promototion of insulin secretion [30].

On the other hand, GLP-1 receptor agonist associated effects are visceral fat specific. Liraglutid stimulated white adipose tissue browning and thermogenesis independently of nutrient intake [31]. Exenatide redused epicardial, subcutaneous and liver fat in diabetic patients, in a similar way as liraglutide, activating brown adipose tissue and generating clearence of triglycerides and glucose [32]. Treatments of patients with GLP-1 receptor agonists promote weigth loss and increase circulating adiponectin levels. Also, expresion of adiponectin receptors in visceral adipose tissue is increased by exenatide administration [32]. Chronic low-grade inflammation has been reported as connection between obesity and T2DM. The studies suggest that treatment of obese patients with GLP-1 recepror agonists decraeses circulating cytokines including monocyte chemoattractant protein-1 (MCP-1) plasma concentration and inhibits expresion of inflammatory cytokines in 3T3-L1 adipocytes [32].

Most patients with T2DM require insulin and/or insulin analog therapy. Despite the presence of various insulin and/or insulin analog regiments, it is very difficult to achieve an optimal glycemic control in obese patients. Risk of severe hypoglycemia and weight gain have a major impact on metabolic controle during the insulin therapy. Less weight gain and reduced risk of hypoglycemia are benefits offered by using long-acting insulin analogs [33].

How might treatment options look like in the future?

Today we have a wide range of options, so that treatment could be tailored for each patient, in most cases combining two or more drugs to achieve recommended HbA_{1c} targets [10]. In the future, there will be likely 50 or more available oral or parenteral drugs to choose from, for pharmacotherapy of diabetic patients. Because of that, the choice of therapy will be strongly personalized and based on the patient's genetic profile. We could expect that genetic testing will be used to distinguish different types of adipose tissue, different cytokines receptor expression and to diagnose subtypes of adipose tissue maturitation disorder and dysfunction, in order to cope with the direct cause of T2DM.

CONCLUSION

Among variety of oral antihyperglycemic agents, during the tailoring of appropriate individual therapy for overweight and obese patients with T2DM, it is necessary to bear in mind their impact on the function of adipose tissue. Priority should be given to those groups of agents that stimulate the differentiation and maturation of preadipocytes, have a positive effect on the secretion of adipokines and exert a protective effect on the redistribution of fat mass, through reduction of the amount of visceral adipose tissue depots and increase in the amount of subcutaneous adipose tissue departments.

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