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THE ROLE OF ANTI-OBESITY DRUGS IN THE MANAGEMENT OF OBESE DIABETICS

Abstract: Obesity contributes to type 2 diabetes and worsens its control. 5-10% weight loss among obese diabetics significantly improves glucose control, lipids and blood pressure. Weight loss should be a key goal of diabetes care for all overweight and obese patients with type 2 diabetes. Adjunctive therapy with weight loss drugs is indicated among obese diabetics who can not achieve weight maintenance with lifestyle alone. Metformin use is associated with weight loss during management of diabetics. Metformin may reduce BMI by 5.3 % in comparison with placebo and it is considered as first-line agent in obese patient with type 2 diabetes. SGLT-2 inhibitors may reduce body weight for 3 to 5 kg during management of type 2 diabetes. Orlistat use resulted in a significant reduction of cumulative incidence of type 2 diabetes after 4 years of treatment of obese subjects. Phentermine and topiramate combination use in patients with diabetes and prediabetes results in greater reduction in HbA_{1c} values and fewer prediabetes patients progression to type 2 diabetes. Therapy with combination of bupropione and naltrexone sustained-release among diabetic patients with obesity resulted in reduction of HbA_{1c} and improvements in triglycerides and HDL cholesterol values. In BLOOM-DM study lorcaserin decreased weight by 4.5-5 % together with reductions in HbA_{1c}. Liraglutide has a therapeutic potential for both obesity and type 2 diabetes, due to its dual benefits on body weight and glycemic control. Semaglutide is a new GLP-1 analogue that reduces HbA_{1c} and body weight and improves obesity related complications. Combination of GLP-1/glucagon dual agonist theoretically may decrease food intake and body weight according the preclinical experience. In case where patient does not lose 5 % or more of his body weight on prescribed drug, after three months of treatment, therapy with this drug should be stopped and changed with some other.

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Introduction

Obesity contributes to type 2 diabetes and worsens its control. 5-10% weight loss among obese diabetics significantly improves glucose control, lipids and blood pressure. Weight loss should be a key goal of diabetes care for all overweight and obese patients with type 2 diabetes. It is difficult to achieve weight maintenance with lifestyle alone and some patient may need adjunctive therapies with weight loss medications. Recently, weight reducing effect of some new antidiabetic medications were demonstrated, so the combinations of weight reducing antidiabetic drugs with weight loss drugs were suggested as a favourable treatment for the management of the diabetic patients that are overweight or obese.

Metformin

Metformin is associated with weight loss during management of diabetics and differs from a number of other antidiabetic medications that are associated with weight stability or weight gain. Long term follow-up from the Diabetes Prevention Program gave evidence that metformin produces durable weight loss (1). Mechanism of weight loss on metformin is based on decreased food intake. Metformin effect on appetite is likely to be multifactorial and includes changes in hypothalamus physiology, changes in insulin and leptin sensitivity and effects on gastrointestinal physiology and changes of fat oxidation and storage in liver, skeletal muscle and adipose tissue (2).

However, metformin is not approved by drug regulatory agencies for weight management. Metformin may reduce BMI by 5.3 % in comparison with placebo and it is considered as first-line agent in obese patient with type 2 diabetes. Recently it was hypothesized that metformin may exert its anti-obesity effect by altering the composition of the gut microbiome (3) .

SGLT-2 inhibitors

It was shown that therapy with SGLT-2 inhibitors may reduce body weight for 3 to 5 kg during management of type 2 diabetes. SGLT-2 induce loss of about 75 g (approximately 300 kcal) of glucose in the urine due to inhibition of renal glucose transport (4).

Specific anti-obesity medications can improve metabolic control for patients with type 2 diabetes and obesity.

Orlistat

Orlistat is the only weight-loss medication that acts outside the brain and it inhibits pancreatic lipases, leading to 30 % less fat absorption in the gut. Orlistat use resulted

in a significant reduction of cumulative incidence of type 2 diabetes after 4 years of treatment of obese subjects (9% with placebo vs 6.2% with orlistat). Reduction of LDL cholesterol was also observed during Orlistat use (5). Kidney and liver function should be controlled during Orlistat therapy.

Phentermine

Phentermine is another agent which was approved in 1959 and can be prescribed for a maximum of 3 months and its mechanism of action is mediated by reduction in hunger perception. Weight loss might be mediated through the release of catecholamines in the hypothalamus which leads to reduced appetite and decreased food consumption (6). It is recommended for use in patients with low to intermediate cardiovascular risk in combination with lifestyle changes.

Phentermine and topiramate

Combination of phentermine and topiramate extended-release was introduced in 2012 and its anorexigenic mechanism is based on regulation of various brain neurotransmitters. Use of this combination in patients with diabetes and prediabetes results in greater reduction in HbA_{1c} values and fewer prediabetes patients progression to type 2 diabetes. Phentermine and topiramate extended-release combination is contraindicated in pregnancy, uncontrolled hypertension, coronary artery disease, glaucoma and hyperthyroidism and in patients treated with MAO inhibitors (7).

Bupropione and naltrexone

Combination of bupropione and naltrexone sustained-release was approved in 2014. Bupropion is a dopamine and norepinephrine reuptake inhibitor while naltrexone is an opioid receptor antagonist. Bupropione was initially used for management of depression and smoking cessation, while naltrexone was approved for therapy of alcohol and opioid dependence. Therapy with combination of bupropione and naltrexone sustained-release among diabetic patients with obesity resulted in reduction of HbA_{1c} and improvements in triglycerides and HDL cholesterol values. Combination of bupropione-naltrexone is contraindicated in patients with seizures or diagnosis of anorexia or bulimia and in those who are on chronic opioid therapy (8).

Lorcaserin

Lorcaserin was approved for chronic weight management in 2012. Activation of the serotonin 2C receptor decreases food intake by increasing satiety and decreasing hunger. Lorcaserin is a selective 5-H_{2c} receptor agonist which acts as appetite

suppressant. In BLOOM-DM (Behavioral Modification and Lorcaserin for Obesity and Overweight Management in Diabetes Mellitus) study lorcaserin decreased weight by 4.5-5 % together with reductions in HbA_{1c} (9).

Liraglutide

Liraglutide is an analog of the incretin hormone glucagon-like peptide 1 (GLP-1), with 97 % homology to human GLP-1. It has a therapeutic potential for both obesity and type 2 diabetes, due to its dual benefits on body weight and glycemic control. The dose of 3.0 mg of liraglutide was first approved in December 2014 for the treatment of obesity in the United States of America (10). In March 2015 European Medical Association (EMA) granted marketing authorization for 3.0 mg liraglutide under the FDA approved criteria in all 28 European Union (EU) states. Liraglutide reduces appetite and delays gastric emptying. Obesity is associated with deregulations in both homeostatic and hedonic controls of energy balance potentially facilitated by impaired glucagon-like peptide 1 (GLP-1) signaling (11). GLP-1 receptors have been localized in the arcuate nucleus and periventricular nucleus in rodents and their stimulation reduce food intake and induce weight loss. GLP-1 receptors are also located in the dopaminergic neurons of the ventral tegmental area where activation inhibits neural firing, potentially reducing hedonic drives toward food consumption (11). In SCALE Diabetes trial liraglutide at a dose of 3.0 mg resulted in 6% weight reduction and significant improvement in HbA_{1c} (1.3%). Therapy with Liraglutide among obese diabetic patients with elevated cardiovascular risk factors resulted in a significant reduction of major cardiovascular events. Due to this data, liraglutide was suggested as a favourable choice for high-risk patients with type 2 diabetes, obesity and cardiovascular disease (12).

Semaglutide

Semaglutide is a new glucagon-like peptide-1 (GLP-1) analogue for the treatment of type 2 diabetes, with 94% amino acid sequence homology to native GLP-1 and with a half-life of approximately 1 week (13). It was demonstrated for Semaglutide that beside reduction of HbA_{1c}, that its application contribute to the reduction of body weight and improvement of obesity related complications. According the results of the SUSTAIN clinical trial programme, consisting of seven global clinical trials, semaglutide demonstrated superior reductions from baseline in both HbA_{1c} and body weight versus placebo and active comparators (14).

GLP-1/glucagon dual agonist

Recently, combination of GLP-1/glucagon dual agonist was developed by the groups of Richard DiMarchi and Mathias Tschop. The rationale to combine the

pharmacology of GLP-1 and GIP in a single entity was based on the hypothesis that such a dual incretin hormone action would maximise the glycemic benefits while the anorexigenic effect of GLP-1 would restrain any obesogenic potential of GIP (15). In a preclinical testing evidence was obtained for decreased food intake and decrease in body weight primarily through the loss of fat mass and lowering of blood glucose levels. Whether the promising preclinical results translate into clinical weight-loss benefits remains to be seen in the future.

Conclusion

In an approach to the management of obese diabetic patient, it is important to start treatment with lifestyle intervention which should be continued during all the next steps. After lifestyle intervention, one should introduce metformin as a first line treatment, and if no improvements are seen, GLP-1 receptor agonist or SGLT-2 inhibitor should be added as a second line therapy. In case that HbA_{1c} and BMI after these drugs are not in a satisfactory range, weight loss medication should be added, depending on patient status and possible contraindications. If patient does not lose 5 % or more of his body weight on prescribed drug, after three months of treatment, therapy with this drug should be stopped and changed with some other.

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Acknowledgment:

The authors of the manuscript (DM and SP) was supported by Ministry of Education, Science and Technological Development, Republic of Serbia project No 175067 and by Serbian Academy of Science and Arts project No F34.

REZIME

Gojaznost doprinosi razvoju tipa 2 dijabetesa i pogoršava njegovu kontrolu. Gubitak od 5-10 % u telesnoj težini u gojaznih dijabetičara značajno poboljšava kontrolu glukoze, lipida i krvnog pritiska. Sniženje telesne težine je ključni cilj terapije za sve bolesnike sa tipom 2 dijabetesa koji imaju preteranu telesnu težinu ili gojaznost. Dodatna terapija lekovima za sniženje gojaznosti je indicirana među gojaznim dijabetičarima kada ne mogu da postignu kontrolu telesne težine samo promenom životnog stila. Primena metformina je udružena sa gubitom telesne težine za vreme terapije dijabetesa. Metformin može da redukuje ITM za 5,3% u poređenju

sa placebom i smatra se lekom prve linije u gojaznih bolesnika sa tipom 2 dijabetesa. SGLT-2 inhibitori mogu da redukuju telesnu težinu za 3 do 5 kg za vreme terapije dijabetesa. Korišćenje Orlistata rezultuje u značajnoj redukciji kumulativne incidence tipa 2 dijabetesa posle 4 godine terapije kod gojaznih osoba. Primena kombinacije fentermina i topiramata u bolesnika sa dijabetesom i predijabetesom rezultuje u većoj redukciji vrednosti HbA_{1c} i manjoj progresiji bolesnika sa predijabetesom u tip 2 dijabetesa. Terapija sa kombinacijom bupropiona i naltreksona sa odloženim oslobađanjem kod gojaznih dijabetičara dovodi do redukcije HbA_{1c} i poboljšanja u trigliceridima i vrednostima HDL holesterola. U BLOOM-DM studiji lorcaserin snižava težinu za 4.5-5 % zajedno sa sniženjem HbA_{1c} . Liraglutid ima terapijski potencijal za korekciju gojaznosti i dijabetesa zbog svog dvostrukog efekta na telesnu težinu i kontrolu glikemije. Semaglutid je novi GLP-1 analog koji redukuje HbA_{1c} i telesnu težinu i poboljšava komplikacije nastale usled gojaznosti. Kombinacija GLP-1/glucagon dvostrukog agoniste teorijski može da smanji unos hrane i telesnu težinu prema predkliničkom iskustvu. U slučajevima kada bolesnik ne izgubi 5% ili više od svoje telesne težine posle tri meseca primene leka, terapija tim lekom treba da se prekine i zameni nekim drugim lekom.