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Review

Management of Type 2 Diabetes Mellitus with Overweight: Focus on SGLT–2 Inhibitors and GLP–1 Receptor Agonists

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ABSTRACT

GLP-1 receptor agonists (GLP-1RAs) and SGLT-2 inhibitors, along with the widely used metformin, are the drug classes discussed in this mini-review. GLP-1RAs stimulate insulin secretion and slow down gastric emptying, thereby contributing to weight loss. SGLT-2 inhibitors lessen renal glucose reabsorption, lower blood pressure, and contribute to body weight reduction. A similar effect on body weight should be anticipated from the intestinal alpha-glucosidase inhibitor (acarbose), but its efficiency depends on the carbohydrate contents of diet. Notably, the hypoglycemic effects of the two drug classes are unrelated to the stimulation of insulin secretion by beta cells. An exhaustion of beta cells as a result of a prolonged stimulation is regarded as possible. Insulin hypersecretion contributes to an increase in body weight. This indicates that, other things being equal, drugs acting without the stimulation of insulin secretion may be preferable. In conclusion, the goals of glycemic control need to be individualized based on age, prognosis, the presence of macrovascular disease, and the risk of hypoglycemia.

Keywords: Anti-diabetic drugs, glycemic control, type 2 diabetes mellitus

INTRODUCTION

There have been innovations in the management of type 2 diabetes mellitus (T2DM) in the last decades. In this mini-review, only those medications that are not associated with weight gain are discussed. Metformin is the first-line medication for T2DM, but sooner or later, a second-line treatment may be needed (1, 2). It reduces the demand for insulin, thereby improving the sensitivity of peripheral tissues and inhibiting hepatic glucose production. It does not stimulate insulin secretion by pancreatic beta cells, thus not inducing hypoglycemia (3-8). It is not only indicated for the treatment of T2DM with obesity but also benefited patients with a normal body weight. Among the beneficial effect of metformin is appetite suppression, which contributes to weight loss. However, not all studies confirm the weight reduction after a prolonged intake of metformin; some authors classify metformin as neutral with regard to body weight (3, 6, 8). The main contraindication to metformin use is a significant reduction of the glomerular filtration rate because of the risk of lactic acidosis. Further contraindications include conditions associated with hypoxia and the risk of metabolic acidosis, as well as severe liver disease (4). Furthermore, metformin treatment is associated with gastrointestinal side effects, such as diarrhea, nausea, vomiting, bloating, indigestion, abdominal discomfort, or pain, in 20%–30% of patients, whereas approximately 5% of patients have severe symptoms and discontinue the treatment (9, 10). New extended-release metformin preparations have better gastrointestinal tolerability and adherence (11). In case of contraindications or intolerance of metformin, other drugs are administered.

Dipeptidyl peptidase 4 (DPP-4) inhibitors suppress the degradation of glucagon-like peptide 1 (GLP-1), which stimulates insulin secretion and inhibits the synthesis of glucagon. DPP-4 inhibitors do not enhance the risk of hypoglycemia and have no impact on body weight. The hypoglycemic effect of GLP-1 receptor agonists (GLP-1RAs) is more pronounced than that of DPP-4 inhibitors. In addition to the stimulation of insulin secretion, these drugs slow down gastric emptying, suppress appetite, and contribute to weight loss (12, 13). The delayed gastric emptying is associated with eructation and regurgitation (14, 15), which might be disturbing, in particular, for older patients. There are experimental data about an increase in beta cell mass and reduction of their apoptosis under the influence of GLP-1RA; however, direct evidence in humans is lacking (13, 16, 17). At the same time, an exhaustion of beta cells due to excessive stimulation by GLP-1RA is deemed possible (18). Disadvantages include delivery by injection and relatively high costs. An oral preparation of semaglutide (Oral sema; Novo Nordisk, Bagsvaerd, Denmark)

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is currently under evaluation (19). A combination of a GLP-1RA with metformin is efficient, being associated with weight loss and low risk of hypoglycemia (4). The intestinal alpha-glucosidase inhibitor acarbose (Glucobay; Bayer, Leverkusen, Germany) hampers the digestion of carbohydrates, lowers postprandial hyperglycemia and, secondarily, hyperinsulinemia, whereas the risk of hypoglycemia is low. Side effects include meteorism and other intestinal symptoms (20). According to one meta-analysis, acarbose does not influence body weight (21); however, another meta-analysis indicated that it contributes to weight loss especially in patients with T2DM with obesity (22, 23). In experiments, acarbose reduced the body weight of animals (20). The hypoglycemic effect of acarbose depends on the carbohydrate contents of food; therefore; it can be used occasionally during violations of a low-carbohydrate diet. Pramlintide (Symlin; AstraZeneca, Cambridge, United Kingdom), a synthetic amylin analog, lowers the glycated hemoglobin (HbA1c) level in patients with type 1 and 2 diabetes, slows down gastric emptying, reduces appetite, and exerts favorable effects on body weight. It is administered subcutaneously before meals and is comparatively expensive. Adverse effects may include nausea and headache (1).

Sodium glucose co-transporter-2 (SGLT-2) inhibitors reduce the renal reabsorption of glucose. Osmotic diuresis lowers blood pressure, thereby reducing the risk of cardiovascular (CV) complications. Thus, the loss of glucose reduces the potential glucotoxicity and the risk of beta cell failure (24). High levels of glycosuria induced by SGLT-2 inhibitors increase the risk of genital infections, such as vulvovaginitis and balanitis. A slight risk increase of urinary tract infections (UTIs) was reported in some studies; other studies found no statistically significant increase of UTI risk in patients receiving SGLT-2 inhibitors compared with placebo. Usually, these infections are mild to moderate, being successfully treated with standard therapies (25-28).

Clinical and Research Consequences

Owing to their insulin-independent action mechanism, SGLT-2 inhibitors can be combined with other anti-diabetic drugs and insulin (12, 29). In particular, a combination of SGLT-2 inhibitors with metformin or GLP-1RAs was reported to be favorable for patients with T2DM also with obesity and insulin resistance (2, 30, 31). The ketogenic effect of SGLT-2 inhibitors, in consequence of switching from carbohydrates to lipids as a source of energy, should be pointed out (30). A similar effect has low-carbohydrate–high-fat diet (LCHFD), which at a carbohydrate content ≤50 g/day is called ketogenic (32). Under its impact, the amount of glucose absorbed from food does not suffice to maintain glycogen stores, which results in a lowering of glucose and insulin levels in blood, reduction of glycogen stores, and burning of fatty acids with the production of ketones. These ketones are used by the brain and muscles along with glucose as sources of energy. The literature shows that diet studies with LCHFD in patients with T2DM and obesity do induce favorable effects on weight loss, blood glucose, and insulin. However, there is a lack of data supporting the long-term efficacy, safety, and health benefits of LCHFD (32). The LCHFD and SGLT-2 inhibitors act partly in parallel lowering the availability of glucose so that their combination would probably be efficient for the purpose of weight loss. However, caution is needed because of the potential risk of euglycemic ketoacidosis, whose incidence was slightly increased with SGLT-2 inhibitors mainly in type 1 diabetes, sometimes provoked by alcohol excess, surgery, or intercurrent disease (30, 33, 34). A combination of SGLT-2 inhibitors with a strict LCHFD is regarded as a contraindication (35). Notably, the development of mild ketosis has been hypothesized to contribute to the beneficial effects of SGLT-2 inhibition on cardiac and renal outcomes (30). Considering that a prolonged adherence to LCHFD is difficult for patients, a combination of LCHFD with SGLT-2 inhibitors might contribute to the catabolism of fat depots causing less discomfort than a strict LCHFD alone. Such an experimental therapy would require a tight clinical control.

Furthermore, the SGLT-2 inhibitors decrease the risk of heart failure and other CV complications due to their diuretic action with the reduction of blood pressure. Notably, the prevalence of heart failure is increased in patients with T2DM receiving various glucose-lowering agents, such as thiazolidinediones and probably also DPP-4 inhibitors. As for GLP-1RAs, their positive effect on left ventricular ejection fraction, if any, appears to be inconsistent and rather modest in most patients with heart failure (36). In the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial, the rates of nonfatal myocardial infarction and stroke, as well as hospitalization for heart failure, were insignificantly lower in the liraglutide group than in the placebo group, whereas patients in the liraglutide group had lower rates of CV events and death from any cause than those in the placebo group (37). In the ELIXA (Evaluation of Lixisenatide in Acute coronary syndrome) trial, there was no significant difference in the rates of CV events, including heart failure, and of death from any cause, between the lixisenatide and placebo groups of patients with T2DM after a recent acute coronary event (38). The CV protection by GLP-1RA has been hypothesized to act via anti-atherogenic/anti-inflammatory actions (31, 36). However, the mechanisms remain largely unexplained (36). Based on recent trials with SGLT-2 inhibitors, especially the EMPA-REG OUTCOME (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes) trial, a paradigm shift in the management of T2DM has been proposed. It implies a transition from current algorithms based primarily on glucose and HbA1c control to a strategy additionally focused on the secondary prevention of CV complications using SGLT-2 inhibitors earlier in the management of T2DM. This may be of particular importance for patients with a pre-existing macrovascular disease (39-41).

It appears that the adverse effects of SGLT-2 inhibitors are sometimes exaggerated to promote more expensive drugs. In a previous analysis of nationwide registers from two countries, the use of SGLT-2 inhibitors, as compared with GLP-1RAs, was associated with an increased risk of lower limb amputation and diabetic ketoacidosis (25). This study sounds impressive also for patients if they read the abstract (25). This information has been repeated in Ref. (41). The complication rates of lower limb amputation and diabetic ketoacidosis per 1000 patient-years were 2.7 versus 1.1 and 1.3 versus 0.6, respectively (30), which is a rather low incidence rate. For amputations, these figures are within the usual range (1.5–5.0 per 1000 patient-years) of amputation incidence

in patients with diabetes (42). Ketoacidosis has been discussed above. The reason for the enhanced amputation rate remains speculative; it is unclear whether it concerns all SGLT-2 inhibitors or particular ones (43). Existing records are not sufficient to prove a cause–effect relationship (44, 45). A retrospective cohort study and meta-analysis of four observational databases found no evidence of the increased risk of below-knee lower limb amputations for patients with T2DM treated by SGLT-2 inhibitors, in particular, with canagliflozin (42, 46). The EMPA-REG OUTCOME trial did not report any increased risk of amputation with empagliflozin (46). The putative mechanism of the increased risk of amputation is an intravascular volume depletion due to diuretic effect (25, 41). This is in agreement with studies suggesting that diuretics are generally a risk factor for amputations (47). Therefore, it is essential for patients receiving SGLT-2 inhibitors to maintain adequate hydration. Fortunately, the frequency of more general diabetic foot-related complications was significantly lower in reports for SGLT-2 inhibitors than in those for non-SGLT-2-inhibitor drugs with the diabetes indication, although this difference was tapered after the exclusion of reports listing insulin as a concomitant drug (44). Importantly, the study found no association between the use of SGLT-2 inhibitors and the risk of serious UTIs, venous thromboembolism, acute pancreatitis, and bone fractures, which are adverse events of current concern (25).

The following considerations are sometimes excluded in comparing the GLP-1 RA and SGLT-2 inhibitors. The hypoglycemic effect of the latter is unrelated to the stimulation of insulin secretion. The beta cell failure is a known factor of the T2DM progression (48). A protection from excessive stimulation may arrest the beta cells exhaustion (49, 50). Some experts regard the reduction of beta cell workload to be an effective therapeutic strategy (16). In contrast, e.g., to sulfonylureas, GLP-1RAs potentiate glucose-dependent insulin secretion, but do not stimulate secretion at basal glucose levels (48). GLP-1RAs were reported to induce significant changes of fasting insulin level neither in patients with T2DM nor in healthy volunteers (51, 52); sitagliptin, a DPP-4 inhibitor, did not affect the fasting insulin level in obese prediabetic spontaneously hypertensive rats (53). In addition, there have been reports on the elevation of the fasting serum insulin level and its reduction or modulation under the influence of GLP-1RAs or DPP-4 inhibitors, depending on doses and glucose concentrations (54-56). An exhaustion of beta cells as a result of prolonged stimulation by GLP-1RA is regarded as possible (18). For example, in "humanized mice," a long-term administration of liraglutide resulted in progressive deterioration of glycemic control (57). Further studies, shielded from conflicts of interest, are needed. The elevated insulin level is associated with weight gain, insulin resistance, and mortality risk (50, 58-60). Therefore, other things being equal, drugs acting without the stimulation of insulin secretion appear to be preferable.

CONCLUSION

It is preferable for the treatment of T2DM with overweight to use medications diminishing body weight. Along with the widely used metformin, the following drug classes should be mentioned. The GLP-1RAs stimulate insulin secretion and slow down gastric emptying, thereby contributing to weight loss. The SGLT-2 inhibitors reduce the renal glucose reabsorption, thereby lowering blood pressure and contributing to weight loss. A similar effect on body weight should be anticipated from the intestinal alpha-glucosidase inhibitor (acarbose); however, its efficiency depends on the carbohydrate contents of diet. Importantly, the hypoglycemic effects of the latter two drug classes are unrelated to the stimulation of insulin secretion, which may be an advantage. In conclusion, the management of T2DM and goals of glycemic control need to be individualized considering age, prognosis, the presence of CV disease, hypertension, dyslipidemia, and other risk factors.

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