Glucagon-like peptide-1 (GLP-1) receptor agonist as cardio- and nephroprotection in a patient with diabetic kidney disease and proximal myotonic myopathy type 2 (PROMM MD2)

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Abstract:

We present a 42-year old male patient, with diabetic kidney disease, progressing proximal myotonic myopathy type 2 (PROMM MD2), metabolic syndrome and several comorbidities. Due to POMM MD2, the patient had a mixed restrictive-obstructive disorder of pulmonary ventilation, a large ventral hernia, along with weakening of the anterior abdominal wall musculature, relaxation of the paravertebral musculature, discopathy and radiculopathy of the lumbosacral spine. The patient had an extremely high cardiometabolic risk for cardiovascular and cerebrovascular accidents. The patient was treated with a glucagon-like peptide-1 (GLP-1) receptor agonist for cardio- and nephroprotection, along with treatment of all associated conditions, specific diet and adapted physical therapy. In the subsequent follow-ups at 3 and 6 months after the treatment start an improvement in several components of the metabolic syndrome and renal function was noted. The patient had a significant reduction in body weight, better glucoregulation, a significant reduction of proteinuria, maintained renal function, and better lipid profile. The overall cardiovascular risk was significantly reduced. GLP 1 receptor agonists could be used as effective cardiorenal protection in patients with progressive neuromuscular diseases.

Keywords: Diabetic Nephropathies, Myotonic Dystrophy Type 2, Metabolic Syndrome, Glucagon-Like Peptide 1 Receptor Agonists, Cardiovascular Diseases

Sažetak:

Agonist receptora peptida-1 nalik glukagonu (GLP-1) kao kardioprotekcija i nefroprotekcija u bolesnika sa šećernom bolešću bubrega i proksimalnom miotoničnom miopatijom tipa 2 (PROMM MD2)

Predstavljamo 42-godišnjeg muškog bolesnika sa šećernom bolešću bubrega koji napreduje proksimalnom miotoničnom miopatijom tipa 2. (PROMM MD2), metabolički sindrom i nekoliko komorbiditeta. Zbog MD2 PROMJERA, bolesnik je imao mješoviti restriktivno-opstruktivni poremećaj plućne ventilacije, veliku ventralnu herniju, zajedno sa slabljenjem muskulature prednje abdominalne stijenke, opuštanjem paravertebralne muskulature, diskopatijom i radikulopatijom lumbosakralne kralježnice. Bolesnik je imao izuzetno visok kardiometabolički rizik od kardiovaskularnih i cerebrovaskularnih incidenata. Bolesnik je liječen agonistima receptora glukagonu sličnog peptida-1 (GLP-1) za kardiozaštitu i nefrozaštitu, zajedno s liječenjem svih povezanih stanja, posebnom prehranom i prilagođenom

fizikalnom terapijom. U naknadnim kontrolama 3. i 6. mjeseca nakon početka liječenja zabilježeno je poboljšanje nekoliko komponenti metaboličkog sindroma i bubrežne funkcije. Bolesnik je imao značajno smanjenje tjelesne težine, bolju regulaciju glukoze, značajno smanjenje proteinurije, održanu funkciju bubrega i bolji profil lipida. Ukupni kardiovaskularni rizik bio je značajno smanjen. Agonisti receptora GLP 1 mogu se koristiti kao učinkovita kardiorealna zaštita u bolesnika s progresivnim neuromuskularnim bolestima.

Ključne riječi: Dijabetičke nefropatije, Miotonična distrofija tipa 2, Metabolički sindrom, Agonisti receptora peptida 1 sličnog glukagonu, Kardiovaskularne bolesti

Introduction:

Diabetes mellitus type 2 (T2DM) is the main cause of chronic kidney disease (CKD) and end-stage kidney disease (ESKD), and diabetic kidney disease (DKD) is the main cause of morbidity and mortality in diabetes. Despite advances in the nephroprotective treatment of T2DM, DKD remains the most common complication, leading to the need for renal replacement therapy (RRT) (1). Until recently, prevention of DKD progression was based on strict blood pressure control, using renin-angiotensin system blockers that simultaneously reduce blood pressure and proteinuria, adequate glycemic control and control of cardiovascular risk factors (1).

Glucagon-like peptide-1 receptor agonists (GLP-1RA) are a new class of antihyperglycemic drugs that have been shown to improve cardiovascular and renal events in DKD. GLP-1RAs have a nephroprotective effect, which is expressed through both indirect (improvement of blood pressure and glycemia control, weight loss) and direct action (establishment of normal intrarenal hemodynamics, prevention of the effects of ischemic and oxidative damage) (2,3).

Myotonic dystrophy (MD) is an autosomal dominant muscle disease with a variable overlap of the characteristics of muscular dystrophy and myotonia, and a multiorgan affection dominated by endocrine disorders and cataracts (4). Myotonic dystrophy type 2 (PROMM, MD2) is a multisystem disease in which glucose intolerance or diabetes mellitus and cardiomyopathy are common (4). The diagnosis of MD2 is established in a proband by identification of a heterozygous pathogenic expansion of a CCTG repeat within a complex repeat motif, (TG)n(TCTG)n(CCTG)n in CNBP. The number of CCTG repeats in a pathogenic expansion ranges from approximately 75 to more than 11,000, with a mean of approximately 5,000 repeats. The detection rate of a CNBP CCTG expansion is more than 99% with the combination of routine PCR, Southern blot analysis, and the PCR repeat-primed assay. (5).

There is insufficient experience in the use of GLP 1 RAs in patients with MD, but some previous studies suggest that GLP-1R agonists reduce muscle wasting by suppressing muscle atrophic factors and enhancing myogenic factors via GLP-1R-mediated signaling pathways. These new findings suggest that activation of GLP-1R signaling may be beneficial for the treatment of muscle atrophy-related diseases (6).

Case presentation:

A male patient, 52 years old, diagnosed with PROMM MD2 20 years ago with a nerve biopsy and genetic confirmation, due to impaired mobility and significantly reduced physical activity, along with the progression of the underlying disease, had a significant increase in body weight during the last 3 years, with a body mass index (BMI) of 38.6 kg /m2, development of peripheral edema, arterial hypertension, and poor tolerance of physical exertion.

The initial work-up in the urine analysis verified proteinuria 2+ with normal values of serum creatinine, fasting hyperglycemia (over 7.2 mmol/l), with a significant mixed dyslipidemia (total serum cholesterol level 7.7 mmol/l, LDL 6.88 mmol/l, serum triglycerides 9.9 mmol/l) and hyperuricemia. Endocrinology examination verified T2DM with proper thyroid, adrenal and pituitary function, hypovitaminosis D, with normal serum concentrations of calcium and phosphate. Renal function tests verify renal hyperfiltration (creatinine clearance 2.05 ml/s, GFR 115 ml/min/1.73m^2) with subnephrotic proteinuria (1.58 gr/24h), predominantly albuminuria (1.11 gr/24h). Additional processing verified unregulated systolic and diastolic hypertension (ABPM ambulatory blood pressure monitoring analyses), along with an enlarged thoracic segment of the aorta, still without signs of cardiomyopathy and coronary disease. Spirometry showed a mixed restrictive obstructive ventilation disorder of second degree. Additionally, on clinical examination a large ventral hernia was found, along with weakening of the anterior abdominal wall, relaxation of the paravertebral musculature, discopathy and radiculopathy in the lumbosacral spine. Laboratory and radiological tests have shown steatosis of the liver with elevated serum transaminases (NAFLD), fibrosis level 3 on transient elastography.

The patient was treated with a fixed combination of antihypertensives, ACE inhibitor/diuretic/Ca channel antagonist, selective beta blocker, simvastatin in accordance with the results of individual studies in which it was shown to be safe in the treatment of patients with muscular dystrophies (7), fibrate, LAMA/LABA inhalation bronchodilator, allopurinol, cholecalciferol, GLP-1 RA liraglutide in doses according to body weight, with a gradual dose increase and monitoring by an endocrinologist, diabetic diet, reduction of salt, lipid and purine intake and diet, and adapted physical therapy.

In the subsequent follow-up of the patient in controls at 3 and 6 months after the introduction of therapy, a significant reduction in body weight (26 kg), good glucoregulation (HbA1c - glycosylated hemoglobin 5.4%), with a significant reduction in proteinuria (total proteinuria 0.54 gr/ 24h, microalbuminuria 380mg/24h), with maintained renal function (creatinine clearance 1.73 ml/s, GFR 104 ml/min/1.73m2).
The overall cardiovascular risk is significantly reduced, because of better metabolic regulation achieved with lipid profile values (total serum cholesterol 5.31 mmol/l, LDL 2.54 mmol/l, serum triglycerides concentration 2.4 mmol/L), uric acid concentration in referent range, with regulation of serum transaminases.
Significant reduction of peripheral edema, better regulation of arterial hypertension with regular therapy, according to the findings of 24-hour ambulatory blood pressure monitoring, improvement of spirometry findings, greater ability to perform daily activities with reduction of body weight and physical therapy were clinically observed.

Discussion:

Obesity is related to the loss of skeletal muscle mass and function (sarcopenia). The co-existence of obesity and sarcopenia is called sarcopenic obesity (SO). Glucagon like peptide-1 receptor agonists (GLP-1RA) are widely used in the treatment of diabetes and obesity. However, the protective effects of GLP-1RA on skeletal muscle in obesity and SO are not clear. In a study of Xiang et al. liraglutide and semaglutide reduced HFD-induced body weight gain, excessive lipid accumulation and improved muscle atrophy in obese mice animal model. Liraglutide and semaglutide eliminated the increase of muscle atrophy markers in skeletal muscle and C2C12 myotubes. Liraglutide and semaglutide restored impaired glucose tolerance and insulin resistance. These beneficial effects were attenuated by inhibiting SIRT1 expression (8).
In Yamada et al. study the effect of liraglutide, a glucagon-like peptide-1 receptor agonist, on skeletal muscles in rats with type 2 diabetes was investigated. Male SDT fatty rats (8-week-old) were provided liraglutide, or insulin-hydralazine for 8 weeks; control SDT fatty rats and SD rats were administered a vehicle. At 16 weeks of age, muscle strength of limbs was significantly lower in all SDT fatty rats compared to SD rats. While cross-sectional areas of type IIb muscle fibers in extensor digitorum longus muscle were significantly lower in SDT fatty rats than in SD rats, those of type I muscle fibers in soleus were similar in all rats. In the soleus of SDT fatty rats, liraglutide led to greater citrate synthase activity and cytochrome c oxidase subunit 5 B protein expression, independently of blood glucose and blood pressure levels. Study showed that liraglutide may contribute to preservation of mitochondrial content on soleus muscle in type 2 diabetes (9).
GLP-1R agonists could be a novel therapy for PM (polymyositis) that recovers muscle weakness and suppresses muscle inflammation through inhibiting muscle fibre necroptosis according to the results of Kamiya et al study in vitro model (10).
Another considered option in nephroprotection in our patient was the introduction of sodium-glucose transport protein 2 (SGLT2) inhibitors, which we have not yet introduced, given the satisfactory response to GLP-1 RA therapy. SGLT-2 inhibitor would be the next option in glucoregulation, reduction of proteinuria and nephroprotection, if there is progression of proteinuria or deterioration of glucoregulation.

Conclusion:

GLP-1RAs offer the potential for adequate glycemic control in multiple stages of DKD without an increased risk of hypoglycemia and with additional benefits in weight reduction, cardiovascular outcomes, and renal outcomes of treatment. Research data also provide evidence for the therapeutic effects of GLP-1R agonists on muscle atrophy. These findings highlight the potential application of GLP-1R agonists for the treatment of diseases accompanied by muscle atrophy.

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