VIA MEDICA
CASE REPORT
ISSN 2450–7458
e-ISSN 2450–8187

Marcin Kleibert, Beata Mrozikiewicz-Rakowska, Leszek Czupryniak
Department of Diabetology and Internal Diseases, Medical University of Warsaw, Poland

A patient on parenteral nutrition: the problem of insulin therapy and more

ABSTRACT

The management of diabetic patients after resection of large intestinal sections is a significant clinical problem, particularly when parenteral nutrition is required, which increases the risk of hyperglycaemia. On the example of a patient who underwent subtotal resection of the small intestine due to mesenteric artery embolism, possible approaches to blood glucose lowering treatment in such patients in the perioperative period were discussed. We presented the current perspective on insulin therapy during parenteral nutrition and proposed a regimen for such treatment. Potential use of glucagon-like peptide 2 analogues in patients with short bowel syndrome was also highlighted. (Clin Diabetol 2021; 10; 3: 310–315)

Key words: parenteral nutrition, diabetes mellitus, short bowel syndrome, hyperglycaemia, insulin therapy

Introduction

In many clinical situations, there is a need to modify existing drug therapy in patients with diabetes type 2, e.g., in the perioperative period, when changing the nutrition mode, and during an infection. Persisting hyperglycaemia is associated with an increased predisposition for thromboembolic events [1]. The latter, in addition to commonly occurring acute coronary syndromes and central nervous system ischaemic events, also include mesenteric embolism which is also a life-threatening condition. Its treatment involves urgent revascularization or resection of a necrotic intestinal segment [2]. A reduced intestinal absorption surface often requires initiation of parenteral nutrition. Resection of the small intestine which is the main organ responsible for incretin secretion results in worsened control or induction of diabetes. Both these factors, i.e., use of parenteral nutrition and disruption of the incretin axis, necessitate a modification of the existing therapy.

Case report

A 46-year-old obese patient (body weight 140 kg, height 1.72 m, body mass index 47.3 kg/m^2) with permanent atrial fibrillation (AF), hypertension, and diabetes type 1 was admitted on an acute basis to a surgical ward due to abdominal pain persisting for several hours, accompanied by nausea and elevated body temperature.

The patient had a history of AF diagnosed two years earlier and reported irregular intake of rivaroxaban (20 mg once daily). Before a cardioversion attempt, coronary angiography was performed and showed no hemodynamically significant coronary lesions. Ultimately, sinus rhythm was not restored, and the likely cause for AF in a relatively young patient was hypertrophic cardiomyopathy, as indicated by the echocardiographic findings during the hospital stay. In addition, the patient was treated for hypertension for 10 years, and his regimen included telmisartan (40 mg once daily), amlodipine (5 mg once daily), and indapamide (1.25 mg once daily).

Previous history of diabetes

Diabetes was diagnosed 15 years earlier in the settings of classical symptoms of hyperglycaemia (polydipsia, polyuria, weight loss by about 20 kg). Investigations at that time included antibody testing for an autoimmune aetiology of diabetes and the patient was presumptively diagnosed with diabetes type 1

Address for correspondence:
Beata Mrozikiewicz-Rakowska
Department of Diabetology and Internal Diseases
Medical University of Warsaw, Poland
e-mail: rakowskab123@gmail.com
Translation: dr n. med. Piotr Jędrusik
Clinical Diabetology 2021, 10; 3: 310–315
DOI: 10.5603/DK.a2021.0005
Received: 29.12.2020 Accepted: 05.02.2021

Table 1. Laboratory test results during the hospitalization

Parameter	Reference range	D 0	D 1	D 2	D 3	D 4	D 5	D 6
Albumin [g/dL]	3.5–5.3	5			3.2			3
GPT [U/L]	7–56	66	46	57	47			49
GOT [U/L]	5–40	113	70	72	54			69
GGTP [U/L]	7–50	65	44	51	53			79
APTT [s]	26–37	35.2	33.2	34.4	32.1			30.8
INR	0.9–1.3	1.31	1.55	1.34	1.22			1.16
CRP [mg/dL]	< 10	37	190.4	264.4	116.1			39.7
Creatinine [mg/dL]	0.5–1,1	1.41		1.44	1.27			1.07
eGFR [mL/min/1.73m^2]	> 60	59		58	67			83
Potassium [mmol/L]	3.6–5	4.94	5.36		3.86			3.52
Sodium [mmol/L]	137–145	139			143.3			138.8
Glucose [mg/dL]	70–99	452			216			353
WBC [10^3/μL]	4–11	29.69	22.99	23.9	15.63			11.76
NEU [10^3/μL]	1.9–8	27.27	20.04					
LYM [10^3/μL]	0.9–5.2	0.82	0.87					
RBC [10^6/ μL]	4,2–5.7	4.92	4.06	4.21	4			4.39
HGB [g/dL]	14–18	14.3	11.6	12.1	12			13.1
pH	7.32–7.42	7.14	7.43	7.4	7.43	7.43	7.44	
pCO_2 [mmHg]	41–51	33.4	30.8	37.4	42.3	43.1	41.8	
PO_2 [mmHg]	25–40	36.9	69.5	41.4	31.3	38.6	25.6	
SBE [mmol/L]	–3.3–3.0	–16.5	–3.2	–1.4	3.8	4.1	3.7	
HCO^{3-} [mmol/L]	24–28	10.8	20.3	22.7	27.8	28.2	27.7	
H^+ [mmol/L]	—	73	36.7	39.8	36.9	37	36.6	
Lactate [mmol/L]	0.5–2.2	11.6	2.7	2.2	2.1	1.9	1.8	

D — day

pending the results. Intensive insulin therapy was initiated, and the patient required large insulin doses for a long time after the diagnosis. Following hospital discharge, the patient's body weight increased by 40 kg, which resulted in an increasing insulin requirement (28 units of a rapid-acting analogue at meals and 36 units of a long-acting analog at bedtime, overall 120 units per day). The above insulin regimen was maintained until the current admission, with only minor dosing modifications following visits to a diabetes clinic. The patient reported that the diagnosis of diabetes type 1 was ultimately confirmed, although the course of the current illness made it questionable. Periodic follow-up testing indicated inadequate metabolic control of diabetes (the most recent HbA_{1c} level, measured about 12 months earlier, was 13.4%). Over the last several years, the patient was not investigated for other complications of diabetes.

On admission, abdominal pain was accompanied the laboratory findings of lactic acidosis and significant hyperglycaemia (452 mg/dL). The laboratory test results are shown in Table 1. An acute coronary syndrome was excluded based on the absence of elevated biomarkers of myocardial necrosis. Elevated lactate level and increased leukocyte count along with abdominal pain prompted the managing team to perform computed angiotomography of the mesenteric arteries which showed upper mesenteric artery embolism (Figures 1 and 2). An urgent surgery was agreed upon. Due to a very high periprocedural cardiovascular risk, a preoperative cardiology consultation was requested. In the perioperative period, low-molecular-weight heparin at a therapeutic dose was substituted for rivaroxaban. Due to an urgent indication for surgery, preoperative echocardiographic evaluation was not possible. As imaging showed small intestine necrosis, endovascular revascularization was not attempted and subtotal small intestinal resection was performed (only 50 cm of the small intestine was preserved).

In the perioperative period, the patient was managed with an intravenous insulin pump. Due to short bowel syndrome (SBS), parenteral nutrition was used after the surgery to correct nutritional deficiencies due to inability of oral food intake and reduced intestinal absorption surface. Due to osmotic diarrhoea, loperamide was used as needed. A persistent high

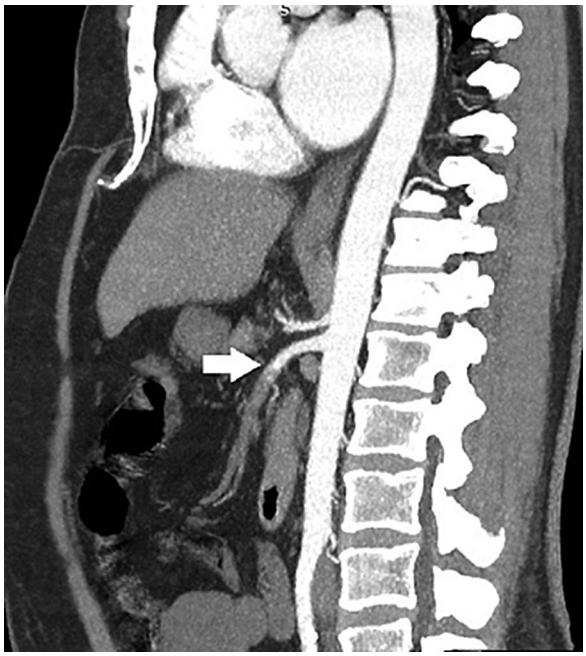

Figure 1. Computed tomography imaging with contrast enhancement, arterial phase, a filling defect is seen in the upper mesenteric artery (arrow), consistent with arterial occlusion, is seen in the sagittal plane

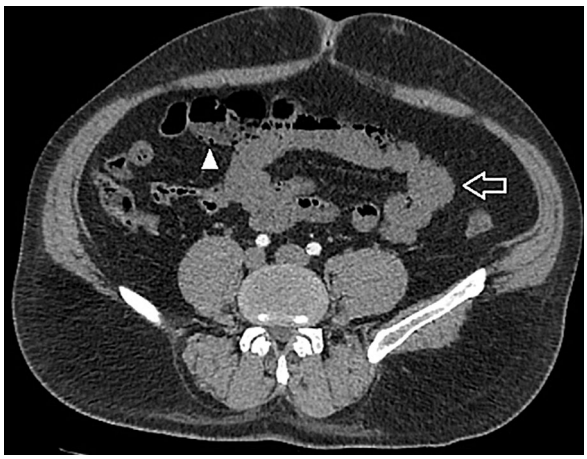

Figure 2. Transverse plane imaging shows lack of small intestine contrast enhancement (empty arrow) and intramural gas (arrowhead), indicating ischaemia and necrosis

insulin requirement, on average 12–15 units/hour, was initially observed but it gradually decreased over the next days, which could be attributed to body weight reduction and uncomplicated surgical wound healing. Ultimately, subcutaneous insulin was used at 6 weeks after the surgery in doses significantly lower compared to the preoperative period (8–10 units of short-acting human insulin in 4 injections during the awake period and 16–19 units of a long-acting analogue at bedtime, overall 48–58 units per day). Such a significant reduction in the insulin requirement over a relatively short time suggests diabetes type 2. The initial diagnosis of diabetes type 1 was likely made based on C-peptide level and not its immunological markers.

The nutrition team at the surgical unit decided to continue parenteral nutrition indefinitely. The patient was managed with subcutaneous human insulin in fractionated doses adjusted to the composition of the nutritional formula. Table 2 shows selected nutritional formulas prescribed during the hospitalization. Previous drug treatment was also modified; telmisartan, amlodipine and indapamide were withdrawn, and the patient was started on zofenopril 30 mg twice daily, bisoprolol 5 mg twice daily, furosemide 40 mg three times daily, rosuvastatin 10 mg once daily, and omeprazole 40 mg once daily.

Anticoagulation with low-molecular-weight heparin at a therapeutic dose was also continued due to the presence of indwelling parenteral nutrition Broviac catheter. The patient was also scheduled for left atrial appendage occlusion (LAAO). Warfarin was substituted for low-molecular-weight heparin while the patient was awaiting the latter procedure following a cardiology consultation. LAAO was rescheduled several times due to two thromboembolic events that ensued, first ischaemic stroke and then acute lower limb ischaemia due to femoral artery embolism.

Discussion

The above case calls for a discussion regarding the optimal approach to blood glucose control in patients requiring parenteral nutrition and those with SBS.

The reported patient developed mesenteric artery embolism which was a direct consequence of AF. Diabetes is associated with an increased risk of thromboembolic events including mesenteric artery embolism. This is due to endothelial dysfunction leading to hypercoagulability [1]. In addition, oxidative stress enhanced by activation of pathways regulated by the receptor for advanced glycation end-products (RAGE) increased the likelihood of AF [3,4]. This arrhythmia is associated with an increased risk of stroke and peripheral embolism. Both these factors result in diabetic patients being at a higher risk of all embolic complications of AF including systemic embolism [4]. According to population study estimates, about 50% of patients with acute mesenteric ischaemia (AMI) have a history of AF [2]. Our case involved a young patient in whom clinicians rarely expect AMI. However, according to the most recent European Society of Cardiology guidelines, the patient was at a very high risk of cardiovascular events including peripheral arterial

Table 2. Selected nutritional formulas prescribed during the hospitalization

Hospitalization period	After the surgery	Before discharge
Glucose [g]	187.00	135.00
Fat [g]	56.00	54.00
Nitrogen (× 6.25 = protein) [g]	12.00	13.00
Kcal [non-protein]	1300.00	1100.00
Na [mmol]	98.00	92.00
K [mmol]	50.00	56.00
Ca [mmol]	4.50	4.80
Mg [mmol]	6.40	10.00
Cl [mmol]	135.00	107.60
P [mmol]	15.00	20.60
Volume [mL]	1685	2258

disease manifestations such as AMI [5]. This condition should be thus considered when evaluating abdominal pain in this patient group. The differential diagnosis of mesenteric embolism should include other causes than AF, such as malignancy, left ventricular aneurysm, mitral valve disease, and endocarditis [2].

Another clinical problem is irreversible loss of small intestine function. Patients after subtotal small intestine resection are often placed on parenteral nutrition indefinitely, as it was the case in our patient. There are no clear guidelines regarding the approach to correcting hyperglycaemia in patients on parenteral nutrition. Regardless of the previous diagnosis of diabetes, the composition of the parenteral nutrition bag significantly increases the risk of hyperglycaemia, which may require initiation or modification of blood glucose-lowering treatment. Studies are available in the literature that document various approaches to blood glucose normalization in the above clinical settings. During parenteral nutrition, there is a high risk of exceeding blood glucose level threshold considered to induce a cascade of processes affecting dysregulation of repair processes important to control the disease that was the reason for parenteral nutrition, e.g., severe necrotic pancreatitis complicated by systemic inflammatory response syndrome (SIRS). In many studies, the recommended target blood glucose range in these conditions has been set at 80–140 mg/dL. McCulloch et al. analysed disadvantages and advantages of various approaches to correct hyperglycaemia in patients receiving parenteral nutrition, including with insulin added directly to the parenteral nutrition bag, administered intravenously using an insulin pump, injected subcutaneously, or administered using hybrid methods (combination of various forms of insulin therapy depending on the severity of hyperglycaemia). According to these authors, metabolic control also depends on the composition of nutritional formula which affects blood glucose levels. When coupled with preservation of a specific aminoacid composition, vitamin and electrolyte deficiencies result in a significant reduction of insulin bioavailability. An independent analysis focused on the type of bag used for parenteral nutrition which also affects the effectiveness of insulin therapy. Bags made of ethylene and vinyl acetate copolymer (ethylene-vinyl acetate, EVA) are recommended, as this material does not lead to insulin deposition on the internal bag walls, in contrast to glass bottles. The effect of specific insulin therapy regimens on the risk of hypoglycaemia in patients receiving parenteral nutrition was also evaluated [6].

Figure 3 shows an example of insulin therapy regimen in patients receiving parenteral nutrition in the most commonly encountered clinical settings, i.e., in patients without a history of dysglycaemia and in patients with diabetes, including glucocorticosteroid-induced diabetes. Available data indicate that direct insulin administration to the parenteral nutrition bag allows better glycaemic control but long-term randomized studies to evaluate the risk of complications including hypoglycaemia are lacking [7]. For that reason, this approach should be supervised by an experienced personnel. In other cases, continuous subcutaneous insulin infusion using a personal insulin pump should be considered, which in the clinical practice in Poland is limited to young patients with diagnosed diabetes type 1 [6]. This means that subcutaneous insulin injections are used in most patients receiving parenteral nutrition, which does not always allow adequate glycaemic control due to frequently inadequate cooperation between the patient and the managing team.

Oral medications should not be added to parenteral nutrition sets due to possible interactions with components of the nutritional formula [8]. Partial

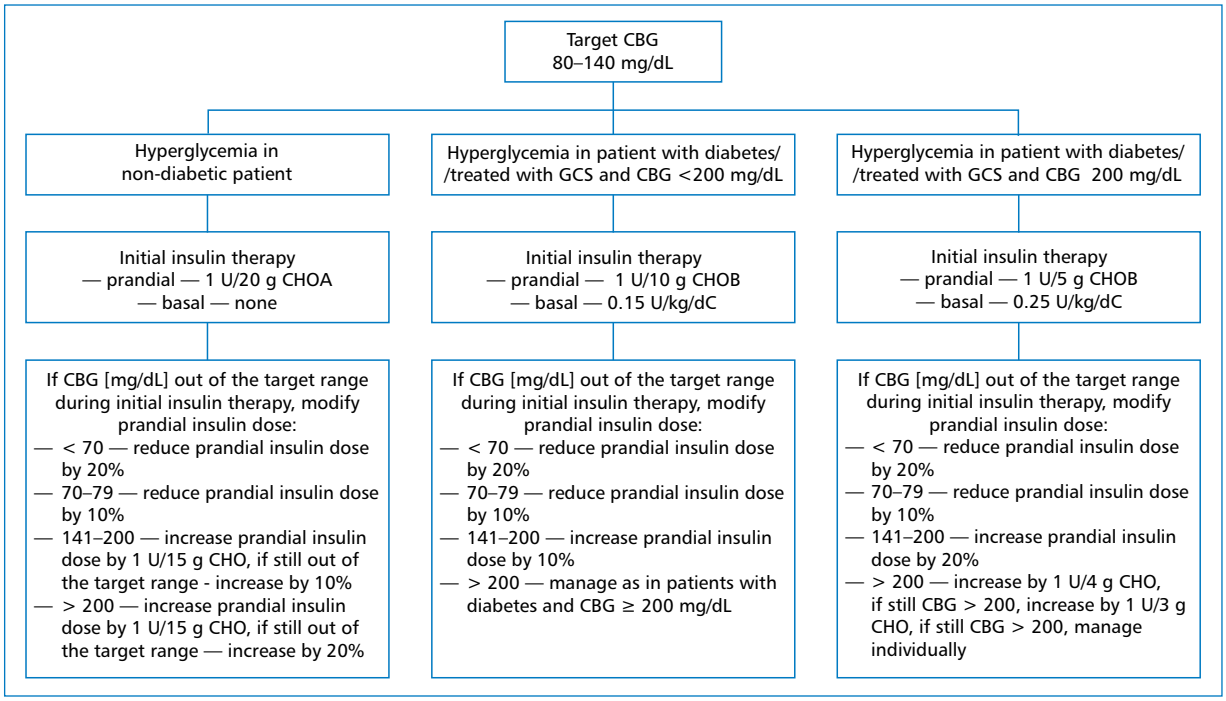

Figure 3. Suggested insulin therapy regimen. Modified from [7]. CBG — capillary blood glucose. CHO — carbohydrates (total content in the parenteral nutrition bag). GCS — glucocorticosteroids. [A]The calculated insulin dose should be divided by 3 and administered as follows: two thirds as human insulin added to the parenteral nutrition bag, one third subcutaneously as NPH insulin in 4 equally divided doses. If the calculated prandial insulin dose was <14 U/d, it was given only as NPH insulin in 4 equally divided doses 6 hours apart. [B]Two thirds given as human insulin added to the parenteral nutrition bag, one third as NPH insulin in 4 equally divided doses 6 hours apart. [C]The calculated dose should be divided by 4 and given as NPH insulin every 6 hours. Hypoglycaemia should be managed according to the usual standards of care

restoration of intestinal absorption is possible with appropriate management and treatment of SBS, which potentially allows a return to oral antidiabetic drugs [9]. It should be noted that a glucagon-like peptide 2 (GLP-2) analogue, teduglutide (Revesive®), which is a naturally occurring human peptide secreted by intestinal L cells, has been approved for the management of patients with SBS. It increases intestinal and portal blood flow, stimulates gastric acid secretion, and reduces intestinal motility. This drug enhances intestinal mucosal integrity and increases nutrient absorption in patients with SBS [10].

Due to incretin axis disruption following intestinal resection, initiation of incretin-based treatment should be considered, including with glucagon-like peptide 1 (GLP-1) [11]. Patients with SBS and concomitant diabetes may potentially gain more benefits from the use of GLP-1 analogues or dipeptidylpeptidase-4 (DPP-4) inhibitors [12]. Available data indicate that disruption of incretin secretion is partially responsible for the symptoms of SBS. However, this treatment may only be of benefit in patients with preserved beta cell secretory function. Ultimately, the autoimmune aetiology of diabetes was not confirmed in the reported patient and GLP-1 analogue was not initiated. Other drugs that might be beneficial are sodium-glucose cotransporter 2 (SGLT2) inhibitors due to their additional diuretic effect in patients with volume overload induced by parenteral nutrition. Currently, SGLT2 inhibitors may also be used in patients with diabetes type 1 in some clinical settings, and even in patients with heart failure without concomitant diabetes [13, 14]. For these reasons, a proper diagnosis of diabetes is the basis for selecting appropriate treatment in patients after intestinal resection.

Conclusions

Small intestine resection, which may be a consequence of mesenteric embolism, leads in some patients to the development of SBS which may require parenteral nutrition and preclude oral antidiabetic therapy. For these reasons, diabetes in such patients should be managed in specialized centres experienced in the choice of appropriate therapy to provide adequate metabolic control. The mainstay of the treatment is insulin therapy, the regimen of which often requires modification. Currently, there are no clear guidelines regarding the mode of insulin

administration in patients receiving parenteral nutrition (injected subcutaneously or added directly to the nutritional formula). In patients with diabetes type 1, use of personal insulin pump should be considered for patient convenience. In patients with SBS, early treatment including GLP-2 analogues should be initiated as these drugs may restore normal intestinal absorption which allows partial return to oral food intake and administration of oral medications. In patients with diabetes type 2, GLP-1 analogues may also be considered. With growing literature data and changes in licensing of antidiabetic drugs it may be hoped that in the near future, achieving adequate metabolic control in patients with diabetes and SBS will be easier and more effective.

Conflict of interests

The authors declare no conflicts of interest.

REFERENCES

1. Kaur R, Kaur M, Singh J. Endothelial dysfunction and platelet hyperactivity in type 2 diabetes mellitus: molecular insights and therapeutic strategies. Cardiovasc Diabetol. 2018;17(1):121. Epub 2018/09/02. doi: 10.1186/s12933-018-0763-3. PubMed PMID: 30170601; PubMed Central PMCID: PMCPMC6117983.
2. Bala M, Kashuk J, Moore EE, Kluger Y, Biffl W, Gomes CA, et al. Acute mesenteric ischemia: guidelines of the World Society of Emergency Surgery. World J Emerg Surg. 2017;12:38. Epub 2017/08/11. doi: 10.1186/s13017-017-0150-5. PubMed PMID: 28794797; PubMed Central PMCID: PMCPMC5545843.
3. Karam BS, Chavez-Moreno A, Koh W, Akar JG, Akar FG. Oxidative stress and inflammation as central mediators of atrial fibrillation in obesity and diabetes. Cardiovasc Diabetol. 2017;16(1):120. Epub 2017/10/01. doi: 10.1186/s12933-017-0604-9. PubMed PMID: 28962617; PubMed Central PMCID: PMCPMC5622555.
4. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). European Heart Journal. 2020. doi: 10.1093/eurheartj/ehaa612.
5. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41(1):111-88. Epub 2019/09/11. doi: 10.1093/eurheartj/ehz455. PubMed PMID: 31504418.
6. McCulloch A, Bansiya V, Woodward JM. Addition of Insulin to Parenteral Nutrition for Control of Hyperglycemia. JPEN J Parenter Enteral Nutr. 2018;42(5):846-54. Epub 2017/08/10. doi: 10.1177/0148607117722750. PubMed PMID: 28792863.
7. Jakoby MG, Nannapaneni N. An insulin protocol for management of hyperglycemia in patients receiving parenteral nutrition is superior to ad hoc management. JPEN J Parenter Enteral Nutr. 2012;36(2):183-8. Epub 2011/08/10. doi: 10.1177/0148607111415628. PubMed PMID: 21825091.
8. Stawny M, Olijarczyk R, Jaroszkiewicz E, Jelinska A. Pharmaceutical point of view on parenteral nutrition. ScientificWorldJournal. 2013;2013:415310. Epub 2014/01/24. doi: 10.1155/2013/415310. PubMed PMID: 24453847; PubMed Central PMCID: PMCPMC3885274.
9. Billiauws L, Joly F. Emerging treatments for short bowel syndrome in adult patients. Expert Rev Gastroenterol Hepatol. 2019;13(3):241-6. Epub 2019/02/23. doi: 10.1080/17474124.2019.1569514. PubMed PMID: 30791759.
10. Pironi L. Translation of Evidence Into Practice With Teduglutide in the Management of Adults With Intestinal Failure due to Short-Bowel Syndrome: A Review of Recent Literature. JPEN J Parenter Enteral Nutr. 2019. Epub 2019/12/06. doi: 10.1002/jpen.1757. PubMed PMID: 31802516.
11. Nauck MA, Holst JJ, Willms B, Schmiegel W. Glucagon-like peptide 1 (GLP-1) as a new therapeutic approach for type 2-diabetes. Exp Clin Endocrinol Diabetes. 1997;105(4):187-95. Epub 1997/01/01. doi: 10.1055/s-0029-1211750. PubMed PMID: 9285204.
12. Holst JJ. From the Incretin Concept and the Discovery of GLP-1 to Today's Diabetes Therapy. Front Endocrinol (Lausanne). 2019;10:260. Epub 2019/05/14. doi: 10.3389/fendo.2019.00260. PubMed PMID: 31080438; PubMed Central PMCID: PMCPMC6497767.
13. Maj-Podsiadło A, Cichocka E, Gumprecht J. SGLT-2 inhibitors as adjunctive to insulin therapy in type 1 diabetes. Clinical Diabetology. 2020;9(3):189-92. doi: 10.5603/dk.2020.0013.
14. Stelmaszyk A, Dworacka M. The impact of dapagliflozin on cardiovascular system in the course of type 2 diabetes mellitus. Clinical Diabetology. 2017;6(4):142-6. doi: 10.5603/dk.2017.0024.