Russian Consensus on Exo- and Endocrine Pancreatic Insufficiency After Surgical Treatment

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ABSTRACT

The Russian consensus on exo- and endocrine pancreatic insufficiency after surgical treatment was prepared on the initiative of the Russian Pancreatic Club using the Delphi method. Its goal was to consolidate the opinions of national experts on the most relevant issues of diagnosis and treatment of exo- and endocrine insufficiency after surgical interventions on the pancreas. An interdisciplinary approach is ensured by the participation of leading gastroenterologists and surgeons.

Keywords: *Consensus, exocrine pancreatic insufficiency, endocrine pancreatic insufficiency, pancreatic surgery, Pancreatic Club*

INTRODUCTION

Any condition that damages the pancreas can result in exo- and/or endocrine insufficiency.[1] Chronic pancreatitis (CP) is the leading among other potential causes that eventuate in pancreatic insufficiency, as CP leads to irreversible structural parenchymal and ductal changes with subsequent replacement of these with the connective (fibrous) tissue.[2] Exocrine insufficiency leads to malabsorption, impaired nutritional status, vitamin deficiency, and osteoporosis; while endocrine

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pancreatic insufficiency results in type 3C diabetes mellitus (DM).[3]

The increasing number and extent of pancreatic surgeries urge for the comprehensive investigation of exo- and endocrine pancreatic insufficiency (PI) after surgery. The first step was made after publication of the international evidence-based guidelines for the diagnosis and treatment of exocrine PI after surgery in 2016.[4] The guidelines state that the severity of exocrine PI depends on the underlying disease, the type of surgery, the extent of pancreatic resection, and the type of anatomical reconstruction. However, the endocrine PI was not covered in these guidelines.

Therefore, in order to fill this gap in existing guidelines the Russian public organization Professional Medical Society "Pancreatic Club" (www.pancreaticclub.ru) has launched an initiative to create a consensus on standards of care based on scientific information and medical expertise, and therefore to consolidate framework of reference provided by the leading national experts (gastroenterologists and surgeons) on the most topical issues of exo- and endocrine PI after surgical treatment.

Panel selection: Totally 35 experts (gastroenterologists and surgeons) from 13 cities of Russia representing 25 institutions were invited to implement this task.

MAIN POINTS

- *Under the auspices of professional medical society Pancreatic Club Russia (www.pancreaticclub.ru), 35 leading Russian gastroenterologists and surgeons according to the Delphi system developed consensus on the most relevant issues of exo- and endocrine pancreatic insufficiencies after surgical treatment.*
- *We assessed the epidemiology of exo- and endocrine pancreatic insufficiencies after various surgical procedures depending on the procedure type, underlying etiology (acute or chronic pancreatitis, benign or malignant pancreatic tumors), morphological features (non-calcifying or calcifying pancreatitis), and location of the process.*
- *We evaluated the prognostic influence of main pancreatic duct dilation on the risk of pancreatic insufficiency development.*
- *We estimated the diagnostic approaches of exo- and endocrine pancreatic insufficiencies and nutritional status impairment prior and after surgical treatment and surgical tactics modification depending on the results.*
- *We reviewed key principles of post-surgical pancreatic insufficiency treatment, strategies of treatment success evaluation, diabetes mellitus type 3c diagnostic criteria, and basic approaches to hypoglycemic therapy.*

Systematic review of the literature: The list of topics for discussion was developed by the action group of Pancreatic Club and sent to the experts. The experts were supposed to validate their choices by literature references on the relevant topics. They studied the corresponding statements of foreign consensuses, analyzed available publications, evaluated the evidence and current opinion on the topic in Russia, and proposed theses for voting.

Provided literature references were compiled into one prefinal document which was sent again to all participating members of the panel in order to substantiate their positions for the final online e-voting. The polling was based on the Delphi technique using the following six-point in the Likert scale: "1": "strongly agree" (A+), "2": "agree with mild comments" (A), "3": "agree with major comments" (A–), "4", "disagree with major comments" (D–), "5": "disagree with mild comments" (D), "6": "strongly disagree" (D+). The consensus would be reached if more than ⅔ experts (≥67%) agree with the statements (A+, A, A–).[5]

The progress and results were presented at the Consensus conference on exo- and endocrine PI after surgical treatment organized by the Pancreatic Club for the 43rd Session of the Central Research Institute of Gastroenterology (CRIG; Moscow, 2 March 2017). The Russian Consensus on exo- and endocrine PI after surgical treatment consists of 30 statements grouped into 5 chapters.

CHAPTER 1. EXO- AND ENDOCRINE PANCREATIC INSUFFICIENCY, NOSOLOGY

1. *What is the incidence of exo- and endocrine pancreatic insufficiency in patients operated for necrotizing pancreatitis?*

   In patients operated for necrotizing pancreatitis, the incidence of exocrine pancreatic insufficiency ranges from 25 to 50%, and the incidence of endocrine pancreatic insufficiency is more than 30%.

   Level of evidence 1c. Grade of recommendation: B.

   The achieved level of consensus—A+: 70.6%; A: 23.5%; A–: 5.9%; D–: 0%; D: 0%; D+: 0%.

   The incidence of exo- and endocrine PI after acute pancreatitis (AP), according to various authors, ranges from 11 to 85% (after severe pancreatitis) and from 13 to 55% (after mild pancreatitis).[6,7] There is a proneness to a more severe course of exocrine and endocrine PI in patients who were operated for infected necrotizing

pancreatitis, compared to patients with sterile pancreonecrosis. Patients with segmental dilation of the main pancreatic duct and with pseudocysts are also likely to develop exo- and endocrine PI.[7,8] A prospective study of 23 patients with AP showed that exocrine pancreatic insufficiency was common in patients who had experienced severe AP, and exocrine PI correlated with the severity of pancreatic necrosis and concomitant endocrine PI.[9] In the 2013 prospective study[10] of 109 patients with a history of AP, endocrine PI was detected in 34.7% of patients.

According to Russian sources, in the long-term exocrine PI developed in 35% of patients after severe AP, and in 59% of patients—after pancreatic necrosis. After surgery for necrotizing pancreatitis exocrine PI developed in the long term in 66.7% of patients, endocrine PI was documented in 40.5% of patients operated for infected necrosis.[11]

2. *Is there any difference in the incidence of exo- and endocrine pancreatic insufficiency between calculous and non-calculous pancreatitis?*

   Calculous pancreatitis is a risk factor for exocrine and endocrine PI.

   Level of evidence 3c. Grade of recommendation: C.

   The achieved level of consensus—A+: 70.6%; A: 20.6%; A–: 5.9%; D–: 2.9%; D: 0%; D+: 0%.

   Exocrine and endocrine PI is found in 20% of CP patients.[12] CP is associated with gradual loss of functioning parenchyma, its' replacement with the fibrous tissue, reduced exocrine secretion of enzymes and bicarbonates, eventually leading to exocrine PI.[13,14] Endocrine PI in CP is caused by secondary damage to the islet apparatus of the pancreas.[15-17] Calcification reflects the severity of structural changes in the pancreas and increases the risk of pancreatic insufficiency, especially after pancreatic surgeries.

3. *Is it possible to predict the development of exocrine pancreatic insufficiency, taking into account the localization and extent of the tumor?*

   Localization of the tumor in the pancreatic head and its malignant nature are predictors of exocrine pancreatic insufficiency.

   Level of evidence 5. Grade of recommendation: D.

   The achieved level of consensus—A+: 58.8%; A: 29.4%; A–: 8.8%; D–: 0%; D: 2.9%; D+: 0%.

   In malignant pancreatic tumors, the preoperative elastase levels are lower than in benign, that is, abnormal levels are documented in every second patient with a malignant tumor and in every fifth patient with a benign tumor.[18] In the group of patients with the lowest levels of elastase, the tumor was statistically significantly more often localized in the head of the pancreas.[19] Tumor localization in the head of the pancreas and obstruction of the main pancreatic duct are the predictors of exocrine pancreatic insufficiency.[20] The malignant tumor was reported to cause malabsorption syndrome when it replaces at least 65% of the acinar tissue.[21,22]

   Localization of the tumor in the distal pancreas with or without the involvement of isthmus, regardless of its nature, is not a predictor of exocrine pancreatic insufficiency.

   Level of evidence 5. Grade of recommendation: D.

   The achieved level of consensus—A+: 41.2%; A: 47.1%; A–: 5.9%; D–: 5.9%; D: 0%; D+: 0%.

   A study by Speicher and Traverso[23] involving 115 patients with distal pancreatectomy did not show any significant influence on the plane—on right or on the left of the portal vein—of transection on exocrine function.

   Data confirming the effect of tumor size on the severity of exocrine insufficiency are currently limited.

   Level of evidence 5. Grade of recommendation: D.

   The achieved level of consensus—A+: 79.4%; A: 14.7%; A–: 5.9%; D–: 0%; D: 0%; D+: 0%.

   The literature review from the United States published in 2015 analyzes two groups of patients: patients with resectable and unresectable pancreatic cancer.[24] However, various diagnostic modalities to evaluate exocrine PI failed to produce reliable results. It was stated that disease progression leads to the progression of exocrine pancreatic insufficiency.

4. *What are the incidence rates of exo- and endocrine pancreatic insufficiency in patients with pancreaticoduodenal tumors?*

   Exocrine pancreatic insufficiency is diagnosed in 46-100% of patients with pancreaticoduodenal tumors, endocrine pancreatic insufficiency—in 45-65% of cases.

   Level of evidence 2c. Grade of recommendation: C.

The achieved level of consensus—A+: 64.7%; A: 26.5%; A–: 8.8%; D–: 0%; D: 0%; D+: 0%.

Different authors report varying data on incidence rates of exocrine PI in patients with pancreaticoduodenal tumors. The Dutch authors reported exocrine PI in 66% of patients at the moment of "pancreatic tumor" diagnosis, however, PI continued to increase up to 92% at a median follow-up of 2 months.[20] The high incidence rate of exocrine PI is also stated in the literature review by the Italian group in 2013, although in most cases it was moderately severe. Fat malabsorption was documented in 65% of patients with pancreatic cancer.[25]

The above-mentioned literature review from the USA (2015) stated varying 46-100% incidence rates of exocrine PI in patients with resectable pancreatic cancer depending on the tumor extent.[24] Following surgical removal, the incidence of exocrine PI remained high and increased up to 70-100% in most cases regardless of the type of surgical procedure.

Endocrine PI was detected in 45-65% of patients with pancreaticoduodenal tumors. The majority of authors report a newly diagnosed DM is highly predictive of a subsequent diagnosis of pancreatic cancer.[26,27]

5. *Does pancreatic hypertension caused by obstructive tumor aggravate the risk of exo- and endocrine pancreatic insufficiency?*

Pancreatic hypertension should not be considered as an independent factor with the potential to impair glucose metabolism in patients with pancreatic cancer.

Level of evidence 3c. Grade of recommendation: C.

The achieved level of consensus—A+: 58.8%; A: 41.2%; A–: 0%; D–: 0%; D: 0%; D+: 0%.

DM is diagnosed simultaneously with pancreatic ductal adenocarcinoma in about 45-65%, while the rate of newly diagnosed hyperglycemia following an established cancer diagnosis is as high as 80%.[26,27] The cause of hyperglycemia in pancreatic cancer patients remains unclear.[28] Impaired glucose metabolism can arise from altered proinsulin-to-insulin conversion since patients with ductal adenocarcinoma demonstrate increased proinsulin levels alongside with reduced C-peptide concentrations. Impaired glucose tolerance is also explained by insulin resistance.[26] There is a certain contribution of insulin resistance to impaired glucose metabolism which is confirmed by elevated serum insulin levels in patients with ductal adenocarcinoma and impaired glucose tolerance. The effect of pancreatic hypertension on glucose metabolism comes from upregulated insulin production due to induced pancreatic beta-cell proliferation, contrary to the expected atrophy of pancreatic islets caused by the sclerotic transformation of glandular tissue and subsequent drop of insulin levels. The involvement of this mechanism was proved experimentally in pancreatic duct-ligated mice with resulting beta-cell hyperplasia mediated by the upregulated synthesis of survivin (encoded by the gene *Birc5*), which is a typical mechanism of beta-cell hyperplasia during embryogenesis and in the postnatal period.[29] There are no available publications analyzing the relationship between pancreatic hypertension and ductal adenocarcinoma in humans. Nevertheless, the proven increase of insulin levels in patients with ductal adenocarcinoma and experimental data on upregulated beta-cell proliferation in response to main pancreatic duct ligation does not contradict the hypothesis on the leading role of peripheral insulin resistance within the mechanism of glucose tolerance and DM in patients with ductal adenocarcinoma.

Tumor obstruction of the main pancreatic duct induces the development and progression of exocrine PI.

Level of evidence 3c. Grade of recommendation: C.

The achieved level of consensus—A+: 85.3%; A: 14.7%; A–: 0%; D–: 0%; D: 0%; D+: 0%.

Summary data from different (mostly retrospective) studies show that incidence rates of exocrine PI in patients with pancreatic cancer vary within 50-100%.[20,30] According to the recent systematic review and meta-analysis by Tseng et al.[31] about half of the patients with pancreatic ductal adenocarcinoma have exocrine PI which is worsened after pancreatic resection. Acinar tissue atrophy resulting from impaired drainage of pancreatic secretions is commonly believed to be the main causative mechanism of exocrine PI development and progression.[32]

CHAPTER 2. POSTSURGICAL INCIDENCE (SEVERITY) OF EXO- AND ENDOCRINE PANCREATIC INSUFFICIENCY WITH REGARDS TO THE TYPE OF SURGICAL PROCEDURE AND AMOUNT OF PANCREATIC TISSUE REMOVED

1. *Is there any difference in the severity of exo- and endocrine pancreatic insufficiency in patients after surgical*

resection of similar amounts of pancreatic tissue for the tumor or chronic pancreatitis?

Higher incidence of more severe exo- and endocrine pancreatic insufficiency is commonly documented after surgical interventions for CP, than for pancreatic tumors, given the procedures were identical.

Level of evidence 1c. Grade of recommendation: C.

The achieved level of consensus—A+: 61.8%; A: 35.3%; A–: 0%; D–: 0%; D: 2.9%; D+: 0%.

It is rather difficult to compare the long-term results in these two groups, because the median life expectancy after surgeries for malignant pancreatic tumors is 20-24 months (given the best standard of care is provided), and there is not much published data available. Nevertheless, the amount of pancreatic tissue affected by the tumor usually remains functionally active, while in CP it becomes functionally deficient. Therefore, after surgeries for CP exo- and endocrine PI is more severe and develops in 90-94% of cases, requiring pancreatic enzyme replacement therapy (PERT) which is usually initiated without diagnostic verification.[33,34]

2. *What is the incidence of exo- and endocrine pancreatic insufficiency in patients after drainage surgeries?*

   The incidence of exo- and endocrine PI after BPD surgeries is usually determined by the baseline status of the pancreas.

   Level of evidence 2c. Grade of recommendation: C.

   The achieved level of consensus—A+: 79.4%; A: 17.6%; A–: 0%; D–: 0%; D: 2.9%; D+: 0%.

   Published evidence does not provide a definite answer to the question whether drainage surgeries have an altering effect on the exo- and endocrine pancreatic function. Some authors believe that the severity of pancreatic dysfunction after surgery for CP depends on the baseline—prior to surgery—status of the pancreas, resected tissue amount, adequate drainage of pancreatic secretions, and the type of anastomosis between pancreatic ducts and the GI lumen.[35]

   Some authors report that early surgery for CP reduces the risk of PI and re-interventions in the future.[36] As the majority believe that almost all CP patients have endo- and exocrine PI at baseline, it is really difficult to evaluate the impact of surgical procedure on pancreatic functional status, since postsurgical disorders can be caused by both—surgery per se and natural CP progression.[37,38] In long-term follow-up of CP patients after drainage procedures, DM is diagnosed in ½ of them, while exocrine PI with steatorrhea develops in ⅔ resulting rather from the natural course of the disease than being a sequela of surgery.[12]

3. *What is the incidence of exo- and endocrine pancreatic insufficiency in patients after proximal pancreatic resections altering normal anatomy (pancreaticoduodenectomy)?*

   The incidence of endocrine pancreatic insufficiency after pancreaticoduodenectomy (PDE) is 8-49%, and the incidence of exocrine pancreatic insufficiency after PDE is 53-88%.

   Level of evidence 2c. Grade of recommendation: C.

   The achieved level of consensus—A+: 64.7%; A: 23.5%; A–: 11.8%; D–: 0%; D: 0%; D+: 0%.

   Reconstruction after PDE for pancreatic neoplasms and periampullary tumors leads to major changes in the anatomy and physiology of the upper gastrointestinal tract and the pancreas, which contributes to the development of exo- and/or endocrine PI and adversely affects patients' quality of life.[39-41] According to summarized data, the incidence of endocrine PI after PDE varies within 8-49%, and the incidence of exocrine PI after PDE is 53-88%.[42-45]

4. *What is the incidence of exo- and endocrine pancreatic insufficiency in patients after proximal pancreatic resection not altering normal anatomy (Frey's (*pancreatojejunostomy*), Beger (*duodenum-preserving pancreatic head resection—DPPHR) *procedures)?*

   The incidence of endocrine and exocrine pancreatic insufficiency after proximal pancreatic resections not altering normal anatomy (Frey's, Beger procedures) ranges from 44 to 88% and from 39 to 83%, respectively, and depends on the degree of functioning pancreatic tissue loss due to CP.

   The achieved level of consensus—A+: 82.4%; A: 14.7%; A–: 2.9%; D–: 0%; D: 0%; D+: 0%.

   Altered exo- and/or endocrine pancreatic function is usually found before the surgery in the majority of CP patients.[16,46,47] Proximal pancreatic resection without significant modifications of GI anatomy has a favorable effect on patients' quality of life in the postop

period, as the duodenum and physiological passage of chymus are preserved.

The incidence rate of endocrine and exocrine PI after proximal pancreatic resections without major changes in GI anatomy ranges from 44 to 88% and from 38.7 to 83%, respectively. When comparing the long-term results (5, 7, and 16 years) of various surgical procedures, there is a comparable relief of pancreatic pain and quite similar incidence rates of exo- and endocrine PI,[48-50] mostly due to the progression of underlying disease than to the type/extent of surgical procedure.

5. *What is the incidence of exo- and endocrine pancreatic insufficiency in patients after organ-sparing operations for benign pancreatic tumors?*

   The incidence of exo- and endocrine PI in patients after organ-sparing operations for benign pancreatic tumors depends on the extent of surgery and looks as follows: 1.1-5% and 2.4-7%, respectively after tumor enucleation; 5 and 4%, respectively after median pancreatectomy. After radical antegrade modular pancreatosplenectomy (RAMPS) procedure, 8-15.6% of patients will develop exocrine PI, and 13-38%—endocrine PI.

   Level of evidence 1b. Grade of recommendation: B.

   The achieved level of consensus—A+: 82.4%; A: 11.8%; A–: 5.9%; D–: 0%; D: 0%; D+: 0%.

   In 2016, Y. Zhou et al.[51] analyzed 27 clinical studies published between 1990 and 2016 and totally involving 1316 patients after pancreatic tumors enucleation. In the long-term exocrine and endocrine PI was documented in 1.1% and 2.4% of cases, respectively. A.P. Jilesen et al.[52] analysis of long-term results after enucleation or standard resections of neuroendocrine pancreatic tumors demonstrates that exocrine/endocrine PI developed in 55/19% of cases after PDE, in 8/13%—after distal pancreatectomy and in 5/7% of cases after enucleation. Crippa et al.[53] report endocrine PI developing in 4% of patients after median pancreatectomy and in 38%—after RAMPS procedure. Exocrine pancreatic insufficiency was observed in 5 and 15.6% of patients, respectively.

6. What is the incidence of exo- and endocrine pancreatic insufficiency in patients after distal pancreatectomy with the removal of > 50% of the pancreatic tissue?

   After resection of >50% of pancreas, exocrine pancreatic insufficiency will develop in 20-40% of patients. After resection of ≥50% of pancreatic tissue undergoing fibrotic transformation exocrine PI will develop in ≤ 90% of patients. The incidence of endocrine pancreatic insufficiency reaches 73.3%.

   Level of evidence 2b. Grade of recommendation: B.

   The achieved level of consensus—A+: 76.5%; A: 17.6%; A–: 5.9%; D–: 0%; D: 0%; D+: 0%.

   Distal pancreatectomy is the standard surgical procedure for neoplastic and non-neoplastic lesions in the body and tail of the pancreas. The incidence of exocrine PI correlates with the baseline—prior to surgery—pancreatic fibrosis: it will be 10-15% after resection of unaffected parenchyma and can reach up to 80% in patients with severe fibrosis. There is a positive correlation between the duration of postoperative period and progression of exocrine PI (within 10 years postoperative PI will develop in 25% of patients, while after more than 25 years postoperatively—in over 80%).[54]

   The risk for postoperative endocrine complications depends on the patient's preoperative glucose tolerance status. Such conditions will develop in 9.1% of patients with normal glucose tolerance. In patients with preoperatively impaired glucose tolerance the risk for DM in the postoperative period is much higher—29.9%. In this study, 20-40% of patients will develop exocrine PI after resection of > 50% of pancreas. After resection of ≥50% of pancreatic tissue undergoing fibrotic transformation exocrine PI will develop in≤90% of patients. After distal pancreatectomy with the removal of >50% of the pancreatic tissue, the incidence of endocrine PI reaches 73.3%.[55]

CHAPTER 3. DIAGNOSIS OF EXOCRINE AND ENDOCRINE PANCREATIC INSUFFICIENCY

1. *What parameters can adequately assess the functional status of the pancreas prior to elective surgery for chronic pancreatitis?*

   In the context of current practice, costs and sensitivity of enzyme immunoassay for fecal elastase-1 would be optimal for evaluation of exocrine function, and fasting plasma glucose (FPG) concentration and glycosylated hemoglobin (HbA1c) are recommended for assessment of endocrine function.

   Level of evidence 2c. Grade of recommendation: B.

The achieved level of consensus—A+: 73.5%; A: 20.6%; A–: 5.9%; D–: 0%; D: 0%; D+: 0%.

Coefficient of fat absorption based on 72 h quantitative fecal fat measurement[12] has really become impractical in the clinical setting and is not used any longer as "gold standard" for verification of exocrine PI. The breath test with ^{13}C-labeled triglycerides (sensitivity 91%, specificity 91%)[56] has very limited use, mostly for clinical research purposes, because of its' specific requirements and complexities.

Therefore, the enzyme immunoassay for fecal elastase-1 is considered as an optimal test for evaluating pancreatic exocrine function.[57] Levels <200 μg/g indicate mild exocrine PI, and levels <50 μg/g indicate severe PI.[34,58,59]

The pancreatic endocrine function should regularly be checked by measuring the HbA1c and FBG levels, or carb load glucose tolerance test. The optimal screening option remains controversial.[60] As recommended by the international expert committee, normal HbA1c levels are ≥6.5%.[12]

2. *What are the clinical manifestations of exocrine pancreatic insufficiency?*

   Exocrine pancreatic insufficiency after surgical interventions is manifested by symptoms of impaired intestinal digestion (steatorrhea, flatulence, and dyspepsia) and/or signs of malnutrition (weight loss, deficiency of fat-soluble vitamins, etc.).

   Level of evidence 1b. Grade of recommendation: B.

   The achieved level of consensus—A+: 79.4%; A: 20.6%; A–: 0%; D–: 0%; D: 0%; D+: 0%.

   Exocrine PI becomes clinically obvious when pancreatic lipase levels are very low, and manifests with symptoms of fat maldigestion and intestinal disorders (diarrhea, steatorrhea, polyfecalia) low,[14,61] but also with multiple clinical markers of malnutrition, that is, body weight loss, slow recovery and healing, signs of vitamin deficiencies, electrolyte disbalance, osteoporosis, and osteomalacia leading to bone fractures.[4,62]

3. *What method is optimal for diagnosing exocrine pancreatic insufficiency?*

   In current clinical practice, fecal elastase-1 test is the most accessible and widely used to diagnose exocrine PI, being most sensitive in cases with severe PI.

   Level of evidence 5. Grade of recommendation: D.

   The achieved level of consensus—A+: 70.6%; A: 29.4%; A–: 0%; D–: 0%; D: 0%; D+: 0%.

   Elastase-1 enzyme is specific for humans, its level is relatively stable in GIT and is not affected by enzyme replacement therapy.[4,57]

4. *What are the characteristic features of pancreatogenic diabetes?*

   DM due to pancreatic diseases is classified as type IIIc diabetes mellitus. It should be called pancreatogenic DM. Type IIIc DM is characterized by labile course, rapid transition from a hyperglycemic state to hypoglycemia, and low incidence of ketoacidosis and hyperosmolarity.

   Level of evidence 1a. Grade of recommendation: B.

   The achieved level of consensus—A+: 82.4%; A: 11.8%; A–: 0%; D–: 2.9%; D: 2.9%; D+: 0%.

   All patients with pancreatic diseases and especially after pancreatic surgery should be evaluated for pancreatogenic DM.

   Level of evidence 1a. Grade of recommendation: B.

   The achieved level of consensus—A+: 97.1%; A: 2.9%; A–: 0%; D–: 0%; D: 0%; D+: 0%.

   DM and impaired glucose tolerance are quite common in pancreatic diseases and especially after pancreatic surgery.[63] According to the current classification, this is the third type (type IIIc) of diabetes, or pancreatogenic DM.[3,16] The risk for DM increases two- to threefold in patients with long-standing CP, especially with early onset of calcification, and in the postop period after partial pancreas resection,[64] following either damage or loss of the islets of Langerhans.[60] All types of cells in the islet apparatus are affected, their mass is decreased, and functional activity is impaired. Damage to beta-cells results in insulin deficiency, whereas alpha-cell dysfunction leads to impaired synthesis of contra-insulin hormones, primarily glucagon. Therefore, type IIIc DM is characterized by labile course, rapid transition from a hyperglycemic state to hypoglycemia, and low incidence of ketoacidosis and hyperosmolarity.[65] The incidence of hypoglycemic episodes is as high as 79%, and the rate of severe hypoglycemia, associated with an increased risk of death, reaches up to 41%.[57]

5. *What methods should be used to diagnose pancreatogenic diabetes?*

Endocrine PI should be diagnosed timely by regular measurements of HbA1c and FBG levels.

Level of evidence 3b. Grade of recommendation: B.

The achieved level of consensus—A+: 76.5%; A: 17.6%; A–: 5.9%; D–: 0%; D: 0%; D+: 0%.

As HbA1c level is less variable than the blood glucose, the International Expert Committee recommends using HbA1c (threshold level ≥ 6.5%) test rather than blood glucose for diagnosing DM.[66]

CHAPTER 4. THE NUTRITIONAL STATUS OF PATIENTS

1. *Should the NRS-2002 scale be used to assess the nutritional risks?*

   The NRS-2002 scale is recommended to assess the nutritional risks in patients with exocrine PI.

   Level of evidence 2a. Grade of recommendation: B.

   The achieved level of consensus—A+: 55.9%; A: 38.2%; A–: 5.9%; D–: 0%; D: 0%; D+: 0%.

   The European Society of Parenteral and Enteral Nutrition (ESPEN) recommended yet in 2002 to use the Nutritional Risk Screening (NRS) for assessment of the nutritional status of adult hospitalized patients. This is a screening test to assess the adequacy of nutritional support in acutely ill patients. The initial assessment includes three parameters: body mass index (BMI), the rate of weight loss over the last 3 months and during the last week, and patient's clinical status based on the severity of illness.[67] Further rating implies the assessment of nutritional status depending on the BMI reduction, patient's age, and disease severity. A European prospective cohort study of 5051 patients from 26 European hospitals based on the use of NRS-2002 rating scale has demonstrated that patients at risk ("risk group," 32.6%) had a higher incidence of clinical complications (30.6% vs. 11.3%), higher mortality rates (12% vs. 1%), and longer hospital stay (9 vs. 6 days) versus patients who were not at risk.[68,69]

2. *Should the initial assessment of nutritional status include lab parameters: the absolute lymphocyte count, blood total protein, and albumin levels?*

   The initial assessment of nutritional status should include laboratory data: absolute lymphocyte count, blood levels of total protein, and albumins.

   Level of evidence 3a. Grade of recommendation: B.

   The achieved level of consensus—A+: 61.8%; A: 29.4%; A–: 8.8%; D–: 0%; D: 0%; D+: 0%.

   According to Domingues-Munoz,[34] exocrine PI is associated with the following markers in the nutritional status: decreased levels of hemoglobin, albumin, prealbumin, retinol-binding protein, transferrin, vitamin D, magnesium, and absolute lymphocyte count. According to the Russian Gastroenterological Association (RGA) guidelines for the diagnosis and treatment of chronic pancreatitis (2014), the laboratory assessment of the nutritional status is generally available and effective in most Russian clinics even when a combination of simple tests is used, that is, total protein, albumin, peripheral blood absolute lymphocyte count, and hemoglobin. It has been demonstrated that when the altered nutritional status was timely diagnosed and corrected, treatment prognosis improved significantly, and length of hospital stay, as well as the direct costs of treatment, were reduced.[57]

3. *When nutritional status should be assessed in patients undergoing pancreatic surgery?*

   It is recommended to evaluate the nutritional status of patients undergoing pancreatic surgery (resection of the pancreas head or pancreatectomy) before surgery, 6 months after surgery, and every 6-12 months thereafter as clinically indicated.

   Level of evidence 5. Grade of recommendation: D.

   The achieved level of consensus—A+: 64.7%; A: 23.5%; A–: 11.8%; D–: 0%; D: 0%; D+: 0%.

   The nutritional status of patients after pancreatic surgery depends on their status prior to surgery, the severity of baseline pancreatic parenchyma atrophy and of exocrine PI, the volume of the resected parenchyma, and the degree of underlying disease progression after surgery.[70] Therefore, it is critically important to have a clear idea of the patient's nutritional status prior to surgical intervention.

   The important factors related to the nutritional status and adversely affecting the long-term survival of patients include progressive weight loss after surgery,[71] senile asthenia or preasthenia,[72] and sarcopenia (loss of skeletal muscles).[73] All patients should be followed up and regularly, that is, each 6- to 12-month—re-assessed by specialists (gastroenterologist/dietitian).[74]

4. *Is it necessary to use bioelectrical impedance analysis for expert assessment of a patient's nutritional status after pancreatic surgery?*

   Bioelectrical impedance analysis (BIA) of body composition is recommended for expert assessment of the nutritional status of patients after pancreatic surgery.

   Level of evidence 2b. Grade of recommendation: B.

   The achieved level of consensus—A+: 52.9%; A: 20.6%; A–: 14.7%; D–: 5.9%; D: 2.9%; D+: 2.9%.

   Bioelectrical impedance analysis is a non-invasive technique allowing to calculate the absolute and relative values of fat, lean, musculoskeletal, and active cell mass, as well as volume and distribution of fluid in the body. BIA was recommended by the European Society for Clinical Nutrition and Metabolism for assessment of the nutritional status of patients.[75,76]

5. *What laboratory parameters should be used for expert assessment of a patient's nutritional status after pancreatic surgery?*

   Expert assessment of the nutritional status of patients with exocrine PI should include the following parameters: fat-soluble vitamins (vitamin E), prealbumin, retinol-binding protein, zinc, and magnesium.

   Level of evidence 1b. Grade of recommendation: B.

   The achieved level of consensus—A+: 58.8%; A: 29.4%; A–: 8.8%; D–: 2.9%; D: 0%; D+: 0%.

   There is a lot of published evidence stating the deficiency of vitamins A, D, E, and K, as well trace elements such as zinc, selenium, and iron in CP patients and after surgery for pancreatic cancer.[77,78] These markers, however, are not specific for the nutritional deficiency related to exocrine PI, and all mentioned deficiencies can originate from other causes. Based on available evidence and published data vitamin E should be considered the most reliable marker of exocrine PI among fat-soluble vitamins,[79] while the high prevalence of vitamin D deficiency in the general population, especially in northern countries, means that this vitamin cannot be used as exocrine PI marker.[80]

   The list of potential markers that are commonly used for assessment of the nutritional status in patients with exocrine PI may include fat-soluble vitamins (preferably vitamin E), prealbumin, retinol-binding protein, zinc, and magnesium.[81] This approach was documented in the guidelines of the Spanish Pancreatic Club[16] and RGA.[57]

6. *Is it necessary to calculate the body mass index for the detection of malnutrition in patients after pancreatic surgery?*

   Evaluation of nutritional deficiency in patients after pancreatic surgery envisages calculation of BMI and assessment of nutritional risks.

   Level of evidence 1b. Grade of recommendation: B.

   The achieved level of consensus—A+: 78.3%; A: 12.4%; A–: 3.1%; D–: 3.1%; D: 0%; D+: 3.1%.

   In patients undergoing pancreatic surgery, body mass is measured along with common laboratory parameters,[82] and body weight loss should be thoroughly monitored.[83] There are no specific RGA guidelines for monitoring BMI in patients after pancreatic surgery. It has been noted, however, that CP is often associated with malnutrition even in patients who are of normal weight or even overweight, while body weight loss is the most significant predictor of the risk to be malnourished.[57,84]

7. *Is densitometry necessary for patients with nutritional deficiency symptoms after pancreatic surgery?*

   In patients with signs of nutritional deficiency, it is clinically appropriate and feasible to undergo once a bone density scan after pancreatic surgery so that to undertake timely and adequate therapeutic and preventive measures.

   Level of evidence 4. Grade of recommendation: C.

   The achieved level of consensus—A+: 46.9%; A: 37.5%; A–: 0%; D–: 0%; D: 12.5%; D+: 3.1%.

   Bone mineral density loss is quite common in CP patients.[85–87] The risk is yet higher in patients with exocrine PI and patients undergoing pancreatic surgery. CP patients are recommended to have a single assessment of bone mineral density (DEXA-scan) as osteoporosis is a proven complication of CP resulting from pancreatogenic malabsorption.[12,54]

8. *What CT-based measurements should be used for expert assessment of nutritional status in patients undergoing pancreatic surgery?*

   CT-imaging provides data for quantitative analysis of skeletal muscle and calculation of mean

musculoskeletal index (MSI) as the ratio of skeletal muscles area (cm^2) at the L_3-level (CT data) to the square of the patient's height. It is recommended for expert assessment of nutritional status in patients undergoing pancreatic surgery, along with the assessment of other above-discussed parameters.

Level of evidence 3a. Grade of recommendation: C.

The achieved level of consensus—A+: 52.9%; A: 35.3%; A–: 11.8%; D–: 0%; D: 0%; D+: 0%.

Quantitative analysis of skeletal muscle allows identifying the degree of sarcopenia, which reflects the severity of metabolic disorders related to pancreatic pathology. Musculoskeletal index (MSI) is a criterion of sarcopenia, which is calculated as the ratio of skeletal muscles area (cm^2) at the L_3-level to the square of the patient's height.[88] The area of skeletal muscles is measured using CT-imaging data (arithmetic mean from two consecutive axial slices at the L_3-vertebral body level). MSI is easy to calculate, it is widely used for the diagnosis of various diseases as a tool for quantification of skeletal muscle, and therefore it has great practical significance.[89] CT images provide data for analysis of body composition and estimation of visceral fat.[90] CT images-based calculation of MSI is widely used in scientific research and medical practice all over the world, being particularly important in oncology research,[91] DM, obesity, etc.[92] However, no multicenter studies evaluating MSI in a comprehensive assessment of the nutritional status in patients undergoing pancreatic surgery were conducted.

CHAPTER 5. TREATMENT OF EXOCRINE AND ENDOCRINE PANCREATIC INSUFFICIENCY

1. *When therapy of exocrine pancreatic insufficiency should be initiated?*

   Treatment of exocrine PI should be initiated with emerging clinical (loss of ≥10% body weight, severe steatorrhea, and flatulence), and/or laboratory evidence (reduced fecal elastase or laboratory markers of the nutritional status) of the condition.

   Level of evidence 1b. Grade of recommendation: A.

   The achieved level of consensus—A+: 73.5%; A: 17.6%; A–: 8.8%; D–: 0%; D: 0%; D+: 0%.

   Pancreatic enzyme replacement therapy (PERT) is indicated in CP patients or after pancreatic surgery when known signs of maldigestion appear, such as loss of body weight, muscle and bone mass, steatorrhea. Clinically evident malabsorption develops with the loss of >90% of the pancreatic parenchyma, and steatorrhea, which precedes the protein deficiency, is its earliest symptom. However, the sensitivity of steatorrhea for the diagnosis of exocrine PI is ≤ 38%,[93] which should be taken into consideration.

   The majority of consensuses stipulate the following indications for PERT in CP patients: weight loss >10%, daily fat excretion 15 g, dyspeptic symptoms accompanied by diarrhea and flatulence, or changes in the nutritional status (magnesium <2.05 mg/dL, decreased levels of prealbumin, albumin, retinol-binding protein, ferritin, and hemoglobin).[14,57,94]

2. *What are the principles of exocrine pancreatic insufficiency treatment?*

   Therapy of exocrine PI should include pancreatin-based products in enterosoluble coating with a particle size <2 mm and containing sufficient amount of lipase units.

   Level of evidence 1b. Grade of recommendation: A.

   The achieved level of consensus—A+: 94.1%; A: 5.9%; A–: 0%; D–: 0%; D: 0%; D+: 0%.

   PERT should be initiated at a minimum dose of 25 000-40 000 lipase units per main meal and 10 000-25 000 units per snack.

   Level of evidence 2b. Grade of recommendation: B.

   The achieved level of consensus—A+: 91.2%; A: 8.8%; A–: 0%; D–: 0%; D: 0%; D+: 0%.

   When therapy is ineffective, the dose is doubled and/or proton pump inhibitors are administered.

   Level of evidence 3b. Grade of recommendation: B.

   The achieved level of consensus—A+: 76.5%; A: 23.5%; A–: 0%; D–: 0%; D: 0%; D+: 0%.

   Cases of severe exocrine pancreatic insufficiency and patients after pancreatic surgery require higher doses, that is, 50 000-75 000 lipase units per main meal and 25 000-50 000 lipase units per snack. PERT as any other type of replacement therapy lasts lifelong.

   Level of evidence 1a. Grade of recommendation: A.

   The achieved level of consensus—A+: 91.2%; A: 5.9%; A–: 0%; D–: 2.9%; D: 0%; D+: 0%.

   The basic principles of therapy are not determined by exocrine PI etiology and do not differ in most

consensuses.[4,16,57,74,95] The Cochrane review[96] demonstrated higher effectiveness of pancreatin in the form of enteric-coated microspheres (ECM) in the treatment of PI due to cystic fibrosis. Pancreatin products to treat exocrine PI should contain a sufficient amount of lipase units in the starting dose, that is, 25 000–40 000 units per main meal and 10 000–25 000 units per snack. If these doses are ineffective, they should be doubled or tripled and/or proton pump inhibitors should be initiated.[16,74,93,97]

After pancreatic surgery, PERT for exocrine PI should include pancreatin in the form of ECM. Effective doses are 72 000-75 000 lipase units per main meal and 36 000-50 000 lipase units per snack.[4]

3. *What are the treatment effectiveness criteria in patients with exocrine pancreatic insufficiency?*

   The main criteria of exocrine PI therapy effectiveness should include positive dynamics of clinical symptoms (improved control of diarrhea and bloating, weight gain) and of laboratory parameters (improved steatorrhea, normal serum levels of fat-soluble vitamins, vitamin B12, calcium, and zinc).

   Level of evidence 2b. Grade of recommendation: B.

   The achieved level of consensus—A+: 76.5%; A: 23.5%; A–: 0%; D–: 0%; D: 0%; D+: 0%.

   In current practice, the effectiveness of EPI treatment is mainly assessed based on the dynamics of clinical symptoms (better control of steatorrhea and abdominal symptoms, weight gain) and laboratory markers (fecal fat, ^{13}C-mixed triglyceride breath test, normalized serum levels of fat-soluble vitamins, vitamin B12, calcium, and zinc).[16,93]

   The German consensus outlines that clinical characteristics (weight gain, normalization of nutritional status, resolution of abdominal symptoms) would suffice to assess the effectiveness of PERT, while lab parameters should be used only when clinical symptoms persist.[93] Meanwhile the majority of consensus documents recommend mandatory concomitant monitoring of clinical and laboratory parameters,[16,98,99] and surgical consensus strongly relies on laboratory tests.[4]

4. *What are the special considerations for the management of patients with pancreatogenic diabetes?*

   Similar regimens and doses of insulin as in type 1 DM is the recommended treatment for pancreatogenic DM. Higher risk for hypoglycemia requires constant monitoring of blood glucose levels.

   Level of evidence 2. Grade of recommendation: B.

   The achieved level of consensus—A+: 79.4%; A: 20.6%; A–: 0%; D–: 0%; D: 0%; D+: 0%.

   PERT is an important component in the management of pancreatogenic DM.

   Level of evidence 4. Grade of recommendation: C.

   The achieved level of consensus—A+: 76.5%; A: 17.6%; A–: 5.9%; D–: 0%; D: 0%; D+: 0%.

   Hypoglycemic therapy is prescribed depending on the severity of hyperglycemia, it should be preferably insulin at doses and regimens recommended for type 1 DM.[100] Insulin therapy is indicated when HbA1c > 9.5%. Management of pancreatogenic DM should envisage correction of exocrine PI with PERT,[3] which improves carbohydrate metabolism and glycemic control, stabilizes glycosylated hemoglobin, and reduces the risk of DM-associated complications. Therefore, in pancreatogenic DM adjuvant PERT should always be considered.[16]

5. *What are the specific considerations for management of post-operative apancreatic state after total pancreatectomy?*

   After total pancreatectomy, patients need permanent PERT using high doses of pancreatin, permanent insulin therapy, and continuous monitoring of glycemia because of the potential risk for hypoglycemia caused by glucagon deficiency.

   Level of evidence 5. Grade of recommendation: D.

   The achieved level of consensus—A+: 100%; A: 0%; A–: 0%; D–: 0%; D: 0%; D+: 0%.

   The majority of experts agree that the post-surgical management of exocrine PI is based on the same principles as management of EPI in CP patients.[34,101] Exocrine PI is corrected by high doses of enzymes in the form of ECMs starting from 40 000 to 50 000 lipase units per main meal and half the dose per snack; if necessary, these doses can be increased up to 90 000 lipase units and even more,[34,102] individually up to a maximum dose of 10 000 lipase units/kg body weight/day.[100]

   Complete lack of insulin and glucagon after total pancreatectomy means 100% permanent and severely

liable DM with a high frequency of postprandial hypoglycemia.[103,104] Insulin therapy should be prescribed as lifelong replacement therapy.

6. *Are there any differences in the correction of exocrine and endocrine pancreatic insufficiency in patients undergoing similar extent of surgery for pancreatic tumors or chronic pancreatitis?*

   The principles of exocrine and endocrine PI correction in patients undergoing similar extent of surgery for pancreatic tumors or CP do not differ.

   Level of evidence 5. Grade of recommendation: D.

   The achieved level of consensus—A+: 70.6%; A: 20.6%; A–: 5.9%; D–: 0%; D: 2.9%; D+: 0%.

   The presence and severity of exocrine and endocrine PI are determined by the following factors:

- the volume of the removed pancreatic parenchyma;
- structural changes in the residual pancreas (severity of fibrosis in CP or parenchyma substitution by the tumor tissue after non-radical surgeries);
- functional adaptation determined by the impact of surgical procedure and method for the reconstruction after stomach, duodenum, and/or pancreas resection;
- variety of involved secondary mechanisms of maldigestion (impaired natural passage, vagotomy, impaired release of cholecystokinin, small intestine bacterial overgrowth (SIBO), etc.).[105-107]

   Underlying pancreatic pathology requiring surgery may also contribute to PI severity,[105] but there is still no convincing evidence from comparative randomized studies.

CONCLUSION

The article presents the Russian consensus on diagnosis and management of exo- and endocrine PI after surgical treatment. The consensus was developed and adopted with the support and approval of the Russian Pancreatic Club using the Delphi method. The consensus reflects the current state of scientific knowledge and clinical practice and is characterized by the interdisciplinary approach as the leading Russian experts in pancreatic pathology (gastroenterologists, surgeons) were involved in the process.

With a growing number of various surgical interventions on the pancreas, the proportion of patients with exocrine and endocrine PI is also increasing, and the severity of this condition is determined both by the underlying disease and the type and extent of surgery performed. In this paper, we tried to highlight all aspects of this problem, including the prevalence of exocrine and endocrine PI in patients with CP and pre- and postoperative patients with pancreatoduodenal tumors; optimal methods of exocrine and endocrine PI diagnosing; methods and timelines for adequate assessment of postsurgical nutritional status; principles of exocrine and endocrine PI therapy, which is critically important for improving patients' condition, quality of life, and socialization of this group of patients.

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