Turkish Gastroenterology Association, Pancreas Study Group, Chronic Pancreatitis Committee Consensus Report

Müjde Soytürk[1], Göksel Bengi[1], Dilek Oğuz[2], İsmail Hakkı Kalkan[3], Mehmet Yalnız[4], Mustafa Tahtacı[5], Kadir Demir[6], Elmas Kasap[7], Nevin Oruç[8], Nalan Gülşen Ünal[8], Orhan Sezgin[9], Osman Özdoğan[9], Engin Altıntaş[9], Serkan Yaraş[9], Erkan Parlak[10], Aydın Şeref Köksal[11], Murat Saruç[12], Hakan Ünal[12], Belkıs Ünsal[13], Süleyman Günay[13], Deniz Duman[14], Alper Yurçi[15], Sabite Kacar[16], Levent Filik[17]

[1]Department of Gastroenterology, Dokuz Eylül University School of Medicine, İzmir, Turkey
[2]Department of Gastroenterology, Kırıkkale University School of Medicine, Kırıkkale, Turkey
[3]Department of Gastroenterology, TOBB University of Economics and Technology School of Medicine, Ankara, Turkey
[4]Department of Gastroenterology, Fırat University School of Medicine, Elazığ, Turkey
[5]Department of Gastroenterology, Yıldırım Beyazıt University School of Medicine, Ankara, Turkey
[6]Department of Gastroenterology, İstanbul University School of Medicine, İstanbul, Turkey
[7]Department of Gastroenterology, Celal Bayar University School of Medicine, Manisa, Turkey
[8]Department of Gastroenterology, Ege University School of Medicine, İzmir, Turkey
[9]Department of Gastroenterology, Mersin University School of Medicine, Mersin, Turkey
[10]Department of Gastroenterology, Hacettepe University School of Medicine, Ankara, Turkey
[11]Department of Gastroenterology, Sakarya University School of Medicine, Sakarya, Turkey
[12]Department of Gastroenterology, Acibadem University School of Medicine, İstanbul, Turkey
[13]Health Sciences University, Katip Çelebi Training and Research Hospital, İzmir, Turkey
[14]Department of Gastroenterology, Marmara University School of Medicine, İstanbul, Turkey
[15]Department of Gastroenterology, Erciyes University School of Medicine, Kayseri, Turkey
[16]Health Sciences University, Ankara State Hospital, Ankara, Turkey
[17]Health Sciences University, Ankara Training and Research Hospital, Ankara, Turkey

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INTRODUCTION

Chronic pancreatitis (CP) is a progressive clinical picture that develops secondary to chronic inflammation of the pancreas. Endocrine and exocrine insufficiency occurs in the later stages of the disease as a result of fibrosis and atrophy of the pancreatic tissue. Its clinical course may differ from patient to patient. Abdominal pain is one of the most common symptoms in patients with CP, and it significantly affects the quality of life of patients. There may be no obvious clinical, laboratory, or imaging findings, especially in the early stage of the disease, and a difficulty may be experienced in its diagnosis. In the management of CP, diagnosis and treatment of the complications that occur during the course of the disease are of great importance, as well as abdominal pain and endocrine and exocrine insufficiency. Therefore, the patient approach needs to be individualized. Even at present, there still exist controversial points regarding the etiopathogenesis, diagnosis, and treatment of the disease.

This guideline aims to guide the clinician and the researcher about the definition, etiopathogenesis, diagnosis, treatment, and follow-up of CP in light of the current literature.

Shareholders (participants)

A substudy group consisting of 24 experts was created from the Turkish Gastroenterology Association Pancreas Study Group to prepare the CP consensus report. The group held its preliminary meeting for informative purposes in November 2018 and started meetings with the aim of creating a guideline in January 2019.

Methodology

The CP consensus report was created by following an evidence-based methodology that combined the experiences and opinions of the experts with the evidence obtained by systematic literature review to answer questions related to the definition, etiology, diagnosis, treatment, monitorization, and prognosis of CP that were previously determined by gastroenterologists who are experts in CP (1). The level of scientific evidence was based on the ratings given by the Oxford Centre for Evidence-Based Medicine (2).

As a first step in the preparation of the report, a study group consisting of physicians with expertise in CP was created. Using the Delphi method, the members of the study group

Corresponding Author: ***Dilek Oğuz; ddkoguz@yahoo.com***
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were asked to identify research questions on important topics related to the definition, etiology, diagnosis, treatment, monitoring, and prognosis of CP. Thereafter, these questions were combined and discussed in a 1-day face-to-face meeting, and the questions were finalized. In the same meeting, the questions were prepared for systematic literature review using the Patient–Intervention–Comparator–Outcome framework for each. As a result, a total of 56 questions were identified, eight of which were main questions with their subtitles. For each question, the keywords to be used in the literature review were determined. On the basis of the literature review, decisions were taken regarding which articles with which features would be analyzed, which evaluation criteria would be used during the analysis, and what method would be used to analyze.

The members of the study group who were responsible for the systematic literature review received a training on systematic literature review methodology, including the selection of studies, the extraction of data from studies, and the statistical methods by which the obtained data would be combined and analyzed.

Each of the study group members responsible for the literature review conducted the systematic literature review related to their questions as stated above and presented the results to the group in the second meeting. During the second meeting, which lasted 2 days, the selected studies and the analysis of the data obtained from these studies were presented to the group and discussed, and draft recommendations were formulated for the questions for which sufficient data were available through literature review. The data were considered insufficient for some of the questions. For these questions, the additional analyses that were required were determined by the group. Two questions considered to be related to acute pancreatitis rather than CP were excluded from this project, to be evaluated in the acute pancreatitis project.

Missing analyses were completed between the second and the third meeting. In the third meeting, which lasted 2 days, these analyses were presented to the study group by each member. A recommendation was formulated for each research question by combining the evidence from the literature and the opinions of the expert group. The recommendations were prepared for voting by a larger group of gastroenterologists with special interest in CP.

A total of 24 gastroenterologists working in University hospitals, state hospitals, and private practice in different cities of Turkey who are interested in CP attended the last meeting. In this meeting, the results of the systematic literature review for each question and the recommendation that was developed based on these results were presented. Each recommendation was discussed by the group, and when deemed necessary, minor changes were made and voted. Recommendations approved by at least 70% of the participants were accepted. The recommendations that did not reach this rate were discussed, modified, and voted again. The members of the CP consensus study group decided to evaluate the grade of the power of each suggestion according to the level of agreement of each statement, with strong consensus attributed to a level of agreement of 80% or above and weak consensus to a level of agreement less than 80%.

Questions and suggestions

Question A: What is CP?

Suggestion A: CP is an irreversible, progressive, and fibroinflammatory disease of the pancreas that can lead to functional disorders and/or morphological changes. (Level of evidence: 5; Power of suggestion: Strong consensus)

Comment: CP is a chronic irreversible injury of the pancreas owing to progressive inflammation and fibrosis that might cause loss of endocrine and exocrine function. It is a complex disease with multiple etiologic factors, and its clinical course may vary. Therefore, the diagnosis of CP is challenging.

The definition of CP was based on morphological, functional, and clinical criteria in the initial consensus reports (3-5). Major morphological changes seen in CP include increased pancreatic parenchymal density, gland atrophy, calcification, pseudocyst, and irregularity in the main pancreatic duct and lateral branches. However, it has been reported that morphological changes associated with CP may also be seen years after the first episode of acute pancreatitis. The differentiation of acute pancreatitis from CP by histological features has not been widely accepted because of difficulties in obtaining pancreatic tissue (6, 7).

In recent years, a new definition covering the mechanism and typical features of the disease has been proposed. Accordingly, CP is a fibroinflammatory syndrome that is caused by various etiologies in people with environmental, genetic, and/or other risk factors. In the later stages of the disease, pancreatic atrophy, fibrosis, pain, duct distortion, strictures, calcifications, pancreatic exocrine/endocrine dysfunction, and dysplasia may develop (3, 8).

Question B1-a: What is CP etiology?

Suggestion B1-a: The etiology of CP is multifactorial. The most common causative agent known in its etiology is alcohol. Genetic, autoimmune, obstructive, and environmental causes are other factors that play a role. (Level of evidence: 2A; Power of suggestion: Strong consensus)

Comment: Although the incidence of CP varies from country to country, CP has an incidence of 4-23 per 100,000 and a prevalence of 17-42 per 100,000 (9-14). Its incidence in men is 1.5 to 3 times higher than in women. Different etiological factors play a role in CP. Although it is generally multifactorial, the most common cause of CP is alcohol consumption (39%-68%) across the world, with the exception of a few countries (15-23).

Patients with alcohol-related CP are typically young to middle-aged (30-50 years old) men who experience recurrent acute pancreatitis attacks and have a history of regular alcohol consumption (24). The prevalence of pancreatitis is 3-6 times higher in alcoholics than in non-alcoholics. The absolute risk of pancreatitis among those with heavy alcohol use is 2.5% to 3%. Interestingly, less than 5% of alcoholic individuals develop CP. This observation means that other factors also contribute to the development of CP. Although there is a parallel relationship between the amount of consumed alcohol and the incidence of the development of CP, its relationship with the type of alcohol and the type of drinking is uncertain (25, 26). In a meta-analysis, a linear relationship was found between mean alcohol consumption and CP in both sexes (relative risk [RR] 25 g/day, 1.58, 95% confidence interval [CI], 1.32-1.90; RR 50 g/day, 2.51, 95% CI, 1.74-3.61; RR 75 g/day, 3.97, 95% CI, 2.30-6.85; RR 100 g/day, 6.29, 95% CI, 3.04-13.02) (27). In a person who consumes at least 60 g alcohol per day, alcohol should first be considered in the etiology of CP (28, 29). However, drinking a smaller amount of alcohol can also cause damage to the pancreas and affect the course of the disease (30, 31). Pain, acute or recurrent pancreatitis attacks, exocrine insufficiency, complications, and hospitalization are more common in patients with alcohol-induced CP (32-34).

Smoking is an important risk factor for the development of CP and also a dose-dependent cofactor (35, 36). Smokers have 2.8 times (95% CI, 1.7-4.8) higher risk of developing CP than non-smokers. According to a meta-analysis, the risk of developing CP in individuals who smoke less than one pack per day is 2.4 (95% CI, 0.9-6.6), whereas this risk increases to 3.3 in those who smoke more than one pack per day (95% CI, 1.4-7.9). It has also been shown that quitting smoking reduces the risk of CP and the risk of developing calcification in patients with CP (37).

Obstructive causes, autoimmunity, and genetic and hereditary factors also play a role in the etiology of CP. No reason can be identified in 13% to 40% of patients with CP (15-21).

Hereditary CP is a rare form characterized by recurrent episodes of severe epigastric pain, usually seen at an early age. Genetic variations associated with pancreatitis have been reported in the genes for serine protease 1 (*PRSS1*), serine protease inhibitor kazal type 1 (*SPINK1*), cystic fibrosis transmembrane conductance regulator (*CFTR*), chymotrypsin C (*CTRC*), and carboxypeptidase A1 (*CPA1*) (38-40). All these genes make trypsins more active than they should be or keep them active for a longer duration. Mutations in *CPA1* and *CTRC* are less common than those in other genes.

The pancreatic duct can be partially or completely blocked because of some reasons such as pancreatic divisum (PD), annular pancreas, trauma, pseudocyst, sphincter of Oddi dysfunction, calcific stones, or stenoses secondary to tumors. Pancreatic pressure increases with any obstruction. In case of an obstruction becoming chronic, it causes dilatation of the duct, loss of acinar cells, and fibrosis, followed by the development of CP. In CP etiology, obstructive factors other than PD are rare. Various reports have shown that PD incidence is higher in patients with acute pancreatitis or CP than in the control group (41, 42). However, PD was found at a rate of 7% to 9% in patients who underwent endoscopic retrograde cholangiopancreatography (ERCP) and in autopsy examination of individuals (43). Therefore, it is still a matter of debate whether PD increases the risk of CP (44, 45). With additional risk factors, PD can lead to the development of CP. Genetic screening may be recommended for predisposing variants if no etiological factor is identified.

Autoimmune pancreatitis (AIP) is a special type of pancreatitis with chronic course that arises with autoimmune mechanisms (46). In a study involving 73 patients with type 1 AIP in Japan regarding whether or not AIP caused CP, it was found that CP developed in 16% of cases in an average of 88 months (47). In a study conducted in France, it was shown that atrophy, calcification, and/or duct irregularities and functional impairment developed in pancreas imaging within 3 years after the diagnosis of more than one-third of patients with AIP (48).

Metabolic and toxic causes such as hyperlipidemia, hypercalcemia, medications, and chronic kidney failure are among the rare causes thought to play a role in the etiology of CP (15-21).

Question B1-b: What are the scoring systems that can be used to classify CP etiologically?

Suggestion B1-b: The toxic-metabolic, idiopathic, genetic, autoimmune, recurrent and severe acute pancreatitis and obstructive (TIGAR-O) classification can be used in etiological classification. (Level of evidence: 5; Power of suggestion: Weak consensus)

Comment: One classification for etiology is the TIGAR-O classification, which includes toxic-metabolic, idiopathic, genetic, autoimmune, recurrent, and obstructive causes (49). This classification system has been developed with the assumption that the development of CP may depend on one or more risk factors. A new version of this classification, both updated in content and containing a checklist for healthcare workers, has been published, and it can therefore be recommended for use in daily practice (50). In the M-ANNHEIM classification, the stage, severity, and clinical findings of the disease are evaluated. The scoring system is also included in this classification (51).

Question B2: How should CP etiology be investigated?

Suggestion B2-a: To determine the etiology, alcohol, tobacco use, disease, medicine, and family history should be questioned first. (Level of evidence: 5; Power of suggestion: Strong consensus)

Suggestion B2-b: Basic biochemical laboratory tests, lipid profile, and metabolic tests including calcium level should be performed. (Level of evidence: 5; Power of suggestion: Strong consensus)

Suggestion B2-c: Diagnostic imaging methods can help determine the etiology. (Level of evidence: 1A; Power of suggestion: Strong consensus)

Suggestion B2-d: Immunoglobulin G4 (IgG4) and autoantibody levels, imaging methods, and, if necessary, biopsy are used in those who are considered to have AIP or when etiology is not detected. (Level of evidence: 1A; Power of suggestion: Strong consensus)

Suggestion B2-e: Considering hereditary pancreatitis, family examination, and genetic testing help. (Level of evidence: 4; Power of suggestion: Strong consensus)

Suggestion B2-f: Cystic fibrosis should be investigated in young patients and in those with unknown etiology (Level of evidence: 4; Power of suggestion: Strong consensus)

Comment: It is important to identify the underlying etiology, as the natural course of the disease, the development of exocrine and endocrine insufficiency, the appropriate treatment approach, and the risk of pancreatic cancer differ significantly depending on the etiology of CP (52, 53). Different etiological factors play a role in CP. Alcohol is the most responsible factor, but the disease is usually multifactorial. In some cases, etiology cannot be determined, and this group is classified as idiopathic CP.

To determine the etiology, alcohol, tobacco use, family history, previous and current diseases, and drug history should be questioned first, and general laboratory tests should be performed. Careful anamnesis should be taken from all patients for alcohol. The likelihood of alcohol to play a role in the etiology of CP has increased in patients with a history of high alcohol intake (an average of ≥60 g per day for at least 6 years) (29, 30). Its relationship with alcohol type and drinking style is uncertain (26, 27). The Alcohol Use Disorders Identification Test questionnaire can be used to assess alcohol addiction. Information can be obtained from relatives in case of patients who deny alcohol use. In addition, gamma-glutamyltransferase level, aspartate transaminase/alanine transaminase ratio, ferritin level, and mean corpuscular volume increase in those who consume excessive alcohol. Smoking must be questioned because alcohol and tobacco use have a clear relationship with the development of CP.

Laboratory tests should be ordered to evaluate other potential etiologies such as hypercalcemia and hyperlipidemia. It is useful to perform transabdominal ultrasonography (USG) at the initial stage to assess the etiologies affecting the canal, such as PD, annular pancreas, and pancreatic duct obstruction (e.g., tumors). PD is the most common congenital variant of the pancreas. It has clinical significance in only a small percentage of patients with recurrent acute pancreatitis and CP. Magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasonography (EUS) can be used in the investigation of the etiology for obstructive pathologies such as PD. If possible, secretin-enhanced MRCP (s-MRCP) may be preferred in the first place (54, 55). Because ERCP is a procedure with morbidity and mortality, it should not be used for diagnostic purposes if not necessary.

Hereditary pancreatitis should be considered, especially in patients with early age onset and family history and when other causes are excluded. In these patients, it is necessary to evaluate genetic abnormalities (mutations in *CFTR*, *PRSS1*, *SPINK1*, and *CTRC*) (56). Cystic fibrosis should be considered especially in pediatric patients whose etiology has not been determined. Sweat test is useful in the diagnosis of cystic fibrosis (57).

CP is a disease with complex pathogenesis that can have a genetic basis. It was first found in 1996 that the *PRSS1* gene plays a role in cases of hereditary pancreatitis (58). In the following years, *PRSS1*, *SPINK1*, *CFTR*, *CTRC*, *CPA1*, and calcium-sensing receptor (*CaSR*) mutations have been reported as the genes most associated with CP. In an international multicenter study, patients were divided into groups according to the age at which the diagnosis of pancreatitis was established, and *PRSS1*, *SPINK1*, *CFTR*, and *CTRC*, the most commonly known gene mutations, were investigated in each group. The rate of the detection of at least one genetic mutation was reported to be 71% in patients who had the first pancreatitis attack under the age of 6 years, and it was found that *PRSS1* gene mutations were significantly higher in this group. However, if the family has a history of acute pancreatitis or CP, pancreatitis can occur because of mutations at any age and mutations are most commonly encountered in the *PRSS1* gene (59). Therefore, if the family has at least one or two patients with pancreatitis, screening should be started by mutation analysis of the *PRSS1* gene. The same gene screening and genetic counseling should be offered to first-degree relatives of a patient with a *PRSS1* mutation.

In a meta-analysis investigating the role of *PRSS1* gene mutations in CP, it was found that the *R122H* mutation was detected most commonly in 1,733 cases and the risk of hereditary CP increased (odds ratio [OR], 4.78) (60). If there is no *R122H* mutation in patients diagnosed as having hereditary pancreatitis, the full sequence of the *PRSS1* gene should be recommended and other rare mutations should also be investigated.

The investigation of genetic mutations at an older age is necessary only in cases of idiopathic CP or recurrent acute pancreatitis. Similarly, in a community-based study conducted in the United States of America, the probability of detection of a gene associated with pancreatitis was reported to be 20% in the older age group. However, the presence of these mutations does not affect prognosis at an advanced age and does not change the treatment. Therefore, requesting genetic tests should be discussed with the patient, except for familial pancreatitis cases. If the result is positive, genetic counseling should be given (16).

Another gene considered as a risk factor in hereditary pancreatitis is *SPINK1*. In a meta-analysis including CP cases associated with all etiologies, genetic risk factors were investigated in 2,981 patients with CP and 5,819 controls. As a result, *SPINK1* mutation was found to increase the risk of CP (OR, 9.6) (61). The *SPINK1* mutation rate was found to be 8% in idiopathic pancreatitis cases, whereas this rate was reported to be 3% in the healthy population. A similar rate of *SPINK1* mutations was found in the healthy population in Turkish society (62). The most reported mutation in the *SPINK1* gene is the N34S mutation. Accompaniment of *SPINK1* mutations with other gene mutations such as *CFTR* has been shown to be more common in recurrent pancreatitis (63).

CFTR gene mutations are also important in the development of CP. *CFTR* is a large gene, and it has more than 1,000 mutations defined to date. Rapid gene analysis methods can be preferred in the detection of mutations because the full sequence method is expensive and difficult to interpret. The F508 mutation in the *CFTR* gene is an important risk factor that facilitates CP (OR, 3.59). *CFTR* should be investigated in patients who developed CP before the age of 20 years and in idiopathic CP cases. *CFTR* mutations can be the cause of idiopathic CP without any lung involvement (64). However, *PRSS1*, *SPINK1*, and *CFTR* mutations were not encountered in genetic research conducted in 38 idiopathic CP cases in Turkish society (65). In the Turkish population, the variants of these genes may be different or rare.

The relationship between *CTRC* mutations and CP was first reported in 2008 (66). *CTRC* mutations are a rarer risk factor for idiopathic CP, and mutation in this gene has been reported in 3.3% of patients with CP. *CTRC* variants have been associated with alcoholic and hereditary CP (67). CaSR is a receptor that regulates the amount of intracellular calcium. Variants in this gene have been found to be of importance, particularly in alcohol-related and hyperparathyroidism-related CP (68). The carboxyl ester lipase (*CEL*) gene is highly polymorphic and difficult to analyze. Variants in the *CEL* gene can lead to the development of maturity-onset diabetes of the young and exocrine pancreatic insufficiency (EPI) (69). *CPA1* was similarly detected in 3% of CP cases that occur at an early age (70). CP is associated with many molecules

in inflammatory pathways. However, in practice, it is not necessary to investigate mutations in the genes of molecules involved in these pathways as a risk and prognosis factor (71).

SPINK1 mutations were detected more in patients who received a diagnosis of alcoholic CP. Similarly, alcohol dehydrogenase gene mutations, which play a role in alcohol metabolism, increase the risk of CP in Far East races, but they are rarely observed in Turkish society (72, 73). There is no need for further genetic tests in patients diagnosed as having alcoholic CP because the treatment and prognosis do not change.

If another CP etiology cannot be identified or if there are findings suggesting AIP in imaging methods, research should be conducted accordingly. The most common clinical findings of AIP are obstructive jaundice, abdominal symptoms, and weight loss. The most frequent findings in imaging are delay in contrast enhancement in the pancreas, rim-like contrast enhancement around the pancreas, and stenosis in the pancreatic duct (74). The most sensitive and specific serum marker for type 1 AIP is serum IgG4 (≥135 mg/dL; sensitivity, 86%; specificity, 96%) (75). In addition, various antibodies such as anti-lactoferrin antibody, anti–carbonic anhydrase II antibody, antinuclear antibody, and rheumatoid factor are seen at the rates of 75%, 55%, 60%, and 20% to 30%, respectively (76). Extrapancreatic involvement is also seen in patients with AIP. The most common is the involvement of the common bile duct distal. Sjogren's syndrome, interstitial nephritis, and retroperitoneal fibrosis rarely coexist (75). In type 2 AIP, IgG4 level is generally normal and extrapancreatic involvement is rarely seen (77). In patients with obstructive jaundice and/or mass images but without type 1 AIP serology findings and extrapancreatic involvement, type 2 AIP and pancreatic cancer should be excluded. The response rate to steroid in both type 1 and type 2 AIP is 97% to 98% (78, 79). In AIP cases, EUS both helps in imaging and provides cytopathological diagnosis if necessary (80).

Question C1-a: What are the types of pain in CP?

Suggestion C1-a: The pain may be intermittent and/or chronic. Some patients with CP may not have pain. (Level of evidence: 1A; Power of suggestion: Strong consensus)

Comment: More than half of patients with CP have intermittent or continuous pain. In CP, the mechanism of pain is basically of the inflammatory type. In animal models, inflammatory pain in CP has been shown to be generally similar to other chronic inflammatory conditions (81). Inflammatory mediators, neuropeptides, and a number of neurotropic factors increase in CP and can contribute to the pathogenesis of pain. Neuropathic pain is proposed as a second pain mechanism. The perineurium of the intrapancreatic nerves is often infiltrated by immune cells (82, 83). Pain may occur because of pancreatic duct obstruction, strictures, peripancreatic fibrosis, or ischemia (84, 85). Nociceptive pathways are also thought to be effective on pain in CP, and it has been shown that there are changes at the cortical level in the central nervous system (86). Pain may also occur in CP because of complications. There may be abdominal pain in association with defective digestion or maldigestion in CP. In a randomized clinical study conducted on this issue, a marked improvement in dyspeptic complaints and abdominal pain was shown with pancreatic enzyme replacement (87). Consequently, to investigate the etiology of pain, appropriate imaging methods should be used in terms of obstructive pathologies and complications. If these causes are excluded, the pain is considered to be of inflammatory or neuropathic origin.

Question C1-b: How do we score pain in CP?

Suggestion C1-b: The pattern of the pain, along with its severity, should be evaluated. Although there is not a standard method for assessing pain, the visual analog scale (VAS) can be used because of its ease of use to score the severity of pain in daily practice. (Level of evidence: 1A; Power of suggestion: Strong consensus)

Comment: The pain pattern in CP may be characterized by one or more different pain periods separated from each other by painless periods, or it may be in a different pattern accompanied by exacerbations of persistent pain in some patients (88). In a prospective cohort study involving a total of 540 patients with CP, patients with continuous pain patterns were demonstrated to have a lower quality of life than those with intermittent pain patterns (89).

There are many scoring systems to score pain in CP. Among these, VAS, which is used most frequently in studies, consists of numbers from 0 to 10 on a 10-cm line and shows the severity of pain increasing between 0 and 10. Although scoring with VAS is simple, this method is not very successful in scoring pain, because the quality of life cannot be evaluated and it focuses only on the pain at that moment and does not show the course of pain (90).

The McGill Pain Score, which was first used in 1971, consists of four subsections, and the location, duration,

severity, and feature of the pain (throbbing pain, breakthrough pain, etc.) and change in its severity over time are questioned in this scoring system. However, there is no question about quality of life in this scoring system (91).

In the Brief Pain Inventory, which is another scoring system, there are 4 VASs related to the lightest, most severe, and moderate pain and pain currently felt in the last 24 hours. There is also a diagram in this inventory in which the patient will mark the areas where he feels pain (92). The Short Form 36 (SF-36) scoring system consists of 36 questions in total, including physical functionality (10 items), body pain (2 items), role restrictions because of physical health problems (4 items), role restrictions because of personal or emotional problems (4 items), emotional well-being (5 items), social functionality (2 items), energy/fatigue (4 items), and role restrictions because of general health perceptions (5 items) (93). Scores for each area range from 0 to 100; a higher score defines a more positive health condition. In this system, the quality of life can be questioned. Quality of life and pain are questioned together in the Short Form 12 (SF-12) scoring system, which is a summary derived from SF-36. In a study involving 141 patients with CP and healthy controls, SF-12 was shown to be a good alternative to SF-36 in terms of questioning the quality of life (94).

In the İzbicki Pain Score, the average of the scores given between 0 and 100 for the four subquestions, including VAS, the frequency of pain attacks, the use of pain killers, and the inability to work, are taken. This scoring partially includes the quality of life, but it has not been validated (95).

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 scoring system, which is the most comprehensive system among these systems, is a multidimensional scoring system in which pain and quality of life are questioned in detail (96).

Recently, a new scoring system called Pancreatitis Quality of Life Instrument, which is specific to CP and allows for the evaluation of the quality of life, has been developed (97). Among these numerous tests, scoring systems that particularly include quality of life criteria and pain questioning at the same time should be preferred to scoring systems that only question pain (90).

Question C2-a: What is EPI?

Suggestion C2-a: EPI is a condition characterized by the insufficiency of pancreatic exocrine secretion (enzyme and bicarbonate), resulting in impaired digestive function and nutrient malabsorption. It can appear through several mechanisms, including failure to secrete, activate, and synthesize the enzymes and impaired transport of enzymes to the duodenum of the pancreatic duct. Consequently, nutrients do not encounter the pancreatic exocrine secretions in duodenum. (Level of evidence: 1A; Power of suggestion: Strong consensus)

Comment: EPI is a condition characterized by insufficient pancreatic exocrine enzymes and/or insufficient secretion of sodium bicarbonate, resulting in the inability of digestion of fats, carbohydrates, and proteins (98-100).

EPI usually occurs when the digestive enzymes cannot be synthesized as a result of damage to the functional parenchyma of the pancreas or to the vagal innervation that stimulates enzyme secretion. It may also occur because of failure in the activation of the synthesized enzymes in the duodenum, an increase in their inactivation, or failure in encountering nutrients in the duodenum as a result of gastrointestinal (GI) bypass surgeries (101, 102).

Question C2-b: When should EPI be investigated?

Suggestion C2-b: Every patient who has received a diagnosis of CP should be investigated in terms of EPI. (Level of evidence: 1B; Power of suggestion: Strong consensus)

Comment: The prevalence of EPI in the general population is not fully known because of the lack of an appropriate screening test. In CP, EPI develops after the destruction of more than 90% of functional pancreatic parenchyma. Stricture in the pancreatic duct or obstruction resulting from stones causes the picture to develop earlier or worsen. The development of exocrine insufficiency increases in parallel with the duration of the disease in CP. The time from the onset of symptoms to the development of EPI is an average of 26.3 years for early-onset CP, 16.9 years for late-onset idiopathic CP, and 13.1 years in alcoholic pancreatitis (33).

EPI occurs in 80% of patients with AIP. Its prevalence was detected to be 85% in advanced CP, 50% in inoperable pancreatic cancer, 56% after pancreaticoduodenectomy, 85% in cystic fibrosis, 30% in celiac disease, and 40% in diabetes (33, 100, 103, 104).

EPI may develop because of diabetic exocrine pancreatic pathology, and sometimes the underlying CP may be missed in patients diagnosed as having diabetes mellitus (DM). In a study in which 1,868 newly diagnosed patients with diabetes were evaluated retrospectively, it was re-

ported that 9.2% of cases were pancreatogenic diabetes (78.5% CP), and half of them were treated as type 2 DM (105). In a meta-analysis on this subject, 1,178 patients with type 1 DM were compared with 1,566 controls, and 1,938 patients with type 2 DM were compared with 1,928 controls, for the presence of EPI. It was observed that the frequency of EPI (39% and 28%, respectively) was significantly higher in both patient groups than the controls (106).

Steatorrhea and weight loss are late symptoms, and they appear when pancreatic lipase secretion decreases below 10% of normal value. Swelling, abdominal pain, and diarrhea are frequent symptoms (100). Osteomalacia, osteoporosis, and kidney failure occur because of impaired absorption of fat-soluble vitamins when EPI is mild or moderate (100, 107). Therefore, EPI should be considered in patients with the above-mentioned risk factors, even in the presence of non-specific symptoms.

Question C2-c: Which laboratory methods are used in the diagnosis of EPI?

Suggestion C2-c1: The pancreatic exocrine function can be tested either directly or indirectly. The direct tests are more valuable tests; however, they are less accessible and difficult to implement. Regarding indirect tests, quantitative fat measurement in the stool sample, ^{13}C-mixed triglyceride (^{13}C-MTG) breath test, and fecal elastase-1 (FE-1) levels are alternative tests. The FE-1 test is recommended for daily use because of its easy accessibility and applicability. (Level of evidence: 1B; Power of suggestion: Strong consensus)

Suggestion C2-c2: When the tests are inaccessible, diagnosis can be made from treatment by evaluating the patient's response to pancreatic enzyme replacement therapy (PERT). (Level of evidence: 5; Power of suggestion: Strong consensus)

Comment: Direct and indirect tests are used in the diagnosis of EPI (100, 107). The gold standard in EPI diagnosis is direct pancreatic function tests. These tests are based on collecting and measuring pancreatic secretions from the duodenum or pancreatic duct after the administration of a secretagogue (107). They are invasive and technically difficult to apply in daily practice. Therefore, they are not preferred apart from clinical studies.

Quantitative fecal fat measurement (72-hour quantitative fat test and steatocrit test), which is one of the indirect tests, is accepted as the gold standard in the diagnosis of EPI and in the evaluation of the effectiveness and adequacy of PERT. However, this test is not preferred in daily practice as it is difficult to apply in terms of both patient and laboratory (107).

Pancreatic elastase is highly stable throughout the GI transition, and the fecal concentration of this enzyme is greater than the pancreatic duct concentration. Therefore, it is significantly associated with exocrine pancreatic functions (107-109). The FE-1 test is performed with specific enzyme immunoassay on a small amount of stool sample. It offers an important advantage in that it is not affected by PERT. Because this test is easy to apply and to attain in daily practice, it can be used as a first step test for EPI research. Although FE-1 measurement is not sensitive enough to detect patients with mild CP, its sensitivity reaches 100% in moderate and severe disease states (110, 111). In another study comparing the FE-1 test with the secretin-cerulein test, fecal fat analysis, and FC test, a similar result was reached. The FE-1 test has been shown to be a sensitive test in the diagnosis of moderate and severe EPI (112). In a meta-analysis on this subject, it was found that a level of FE-1 <200 μg/g was significant for the diagnosis of EPI. The sensitivity and specificity of the FE-1 test in EPI diagnosis were found to be 0.77 (95% CI, 0.58-0.89) and 0.88 (95% CI, 0.78-0.93), respectively. In subgroup analysis, the sensitivity of the FE-1 test for the diagnosis of mild, moderate, and severe EPI was found to be 0.47 (95% CI, 0.29-0.70), 0.67 (95% CI, 0.25-0.92), and 0.97 (95% CI, 0.86-0.99), respectively (113).

The ^{13}C-MTG breath test is a simple, non-invasive method for the diagnosis of EPI. This test can be easily performed in the clinical routine and can be repeated if necessary. The test can be used not only in the diagnosis of EPI but also in monitoring PERT activity. Therefore, the ^{13}C-MTG breath test can be used in the diagnosis of EPI developing after CP, cystic fibrosis, pancreatic cancer, acute necrotizing pancreatitis, and stomach or duodenum surgery (107, 114, 115). In a prospective randomized controlled study, the results of the ^{13}C-MTG breath test in 78 patients with CP with EPI were significantly lower than in those without EPI. The sensitivity of ^{13}C-MTG breath test in the diagnosis of EPI was 92.9%, its specificity was 92.9%, and its accuracy was 92.3%. It has been concluded that the test is easy, accurate, and safe for the diagnosis of EPI (116). In a study involving 54 patients with CP, the ^{13}C-MTG breath test and the FE-1 test were found to have similar efficacy in the diagnosis of EPI (117). In another study comparing the ^{13}C-MTG test with FE-1 and chymotrypsin tests, the FE-1 test was found to

be more sensitive in patients with severe EPI, but it was concluded that the ^{13}C-MTG test could also be used in these cases (118).

Question C2-d: Which imaging methods are used in the diagnosis of EPI?

Suggestion C2-d: In the diagnosis of EPI, s-MRCP is a new and safe test. (Level of evidence: 3B; Power of suggestion: Strong consensus)

Comment: s-MRCP is a non-invasive direct pancreatic function test that allows the structure and function of the pancreas to be evaluated together. It does not help to reveal the cause of EPI, but it has an important role in its diagnosis (119) Studies on s-MRCP are limited to small patient groups, and there is not sufficient evidence to recommend its use alone in the diagnosis of EPI yet.

In a study involving 41 patients with CP, the sensitivity of the s-MRCP test in the diagnosis of EPI was 72% and specificity was 87% (120). In another study, magnetic resonance (MR) and s-MRCP findings of 36 patients with suspected CP were compared with the findings of an endoscopic pancreatic function test, and it was found that s-MRCP had 100% sensitivity and specificity (121). According to the results of a study comparing MR, MRCP, s-MRCP, and diffusion-weighted imaging methods, it was concluded that only the last two methods were suitable for use in the diagnosis of EPI (122). In 36 CP cases with mild, moderate, and severe EPI, FE-1 test, MRCP, and s-MRCP were compared, and it was found that s-MRCP was a new, safe, and adequate test to evaluate EPI (123).

Question C3a: How is endocrine insufficiency diagnosed?

Suggestion C3a: Diabetes may develop in patients with CP. The diagnosis of diabetes is made according to the American Diabetes Association (ADA) criteria. (Level of evidence: 3B; Power of suggestion: Strong consensus)

Comment: DM is a metabolic disease with insulin deficiency and/or insulin resistance. According to the International Diabetes Federation 2017 data, the prevalence of diabetes in adults is reported as 8.8% worldwide. The diagnosis of DM is made according to ADA guidelines, which define the following diagnostic criteria: (a) fasting (longer than 8 hours) blood glucose above 126 mg/dL, (b) second hour blood glucose level of ≥200 mg/dL in the oral glucose tolerance test with 75 g glucose, (c) plasma glucose level of ≥200 mg/dL measured at a random time and in the presence of diabetes symptoms, and (d) glycated hemoglobin (HbA1c) level of ≥6.5%. If one of these four criteria is met by measurements made preferably on 2 different days, DM can be diagnosed. According to the ADA 2018 guide review report, DM is divided into four categories, type 1 DM, type 2 DM, gestational DM, and specific type DM owing to other causes (such as drug-induced DM, monogenic diabetic syndrome, and EPI-associated DM) (124).

Question C3b: Is diabetes associated with CP different from other types of diabetes?

Suggestion C3b: Pancreatogenic diabetes can be considered in patients with DM having islet cell antibody negativity and an FE-1 level under 200 µg/g. (Level of evidence: 3B; Power of suggestion: Strong consensus)

Comment: Pancreatogenic DM accounts for approximately 10% (the range varies from 1.75% to 35.2%) of all diabetes cases (106, 125, 126). However, because of a lack of standardized criteria, the exact prevalence is not known. The most sensitive diagnostic method for pancreatogenic DM is low levels of pancreatic polypeptide (PP) in serum after a mixed meal in islet cell antibody–negative patients with diabetes. However, this method is not used in clinical practice.

The definition of pancreatogenic diabetes varies among studies. In most studies, it is defined as a FE-1 level below 200 µ/g with the presence of imaging findings suggesting CP in patients with diabetes who are islet cell antibody–negative (106, 125-127). However, in some studies, it is also accepted as diabetes developing after an acute pancreatitis attack and/or in patients with a history of CP (23, 128, 129). In a retrospective study, the diagnoses of 1,868 patients diagnosed with DM were reviewed, and 172 of these patients were found to have pancreatogenic DM. It was reported that 11 of these 172 patients were previously followed up for type 1 DM and 69 for type 2 DM, and the initial diagnosis of only 88 was reported as pancreatogenic DM (106).

Approximately 80% of DM cases accompanying EPI are caused by CP (106). The frequency of DM in patients with CP is reported between 20% and 70% (23, 106, 125-129). This rate increases with increasing disease age and increases up to 85% in 25 years, especially in patients with alcohol-related CP. For this reason, diabetes screening with annual fasting blood glucose and HbA1c is recommended in patients with CP (130). In the study by Wang et al. (129), 347 patients with CP were evaluated, and

51% of patients developed diabetes in 20 years. Considering the characteristics of patients who developed DM in the same study, it has been reported that diabetes occurs more frequently in smokers, those with pancreatic calcification, those diagnosed as having CP at a young age, and those who develop alcohol-related CP (129).

The mechanism of the occurrence of pancreatogenic DM is different from that of type 1 and type 2 DM. Severe fibrosis in the pancreatic parenchyma and associated ischemia damage the insulin-secreting beta cells, glucagon-secreting alpha cells, and PP-secreting PP cells. Damage of alpha cells results in inadequate glucagon response in case of hypoglycemia. Reduced PP release from PP cells in patients with pancreatogenic DM decreases the sensitivity of hepatocytes to insulin. Although these patients have insulin resistance in the liver because of PP deficiency, peripheral insulin sensitivity is increased or normal. Another factor contributing to hepatic insulin resistance in patients with CP is inflammation. Insulin controls gluconeogenesis in the liver through insulin receptors and glucose transporter type 2 (GLUT2) protein. Inflammation in CP stimulates hepatocyte I-kappa beta kinase beta and nuclear factor κB receptors, reducing the number of insulin receptors on hepatocytes and decreasing the effect of insulin on hepatocytes by causing GLUT2 proteins to be internalized. As a result, insulin stimulation of hepatic gluconeogenesis does not decrease as required and creates a tendency to hyperglycemia. Moreover, because of increased/normal peripheral insulin sensitivity, the contribution of glucagon deficiency also creates a predisposition to hypoglycemia, especially in patients using insulin. As a net result of these events, brittle DM may emerge (131-134).

The interaction between diabetes and pancreas is not unidirectional. Studies evaluating the effect of DM on pancreatic parenchyma recently show that interacinar and acinar fibrosis can develop in type 1 and type 2 DM before the development of pancreatic duct damage and marked parenchymal inflammation. Although pancreatic exocrine secretions decrease in this picture, EPI does not develop clinically. This effect of diabetes on the pancreatic parenchyma is defined as diabetic exocrine pancreatopathy (107).

Although it is not always possible to differentiate clinically from diabetes types, pancreatogenic DM can be seen in all age groups, hyperglycemia is usually mild, and the risk of ketoacidosis is low in these patients (135). There are insufficient data on the risk and duration of complications associated with pancreatogenic diabetes. In the 15-year follow-up of patients with diabetes, there was no difference between other diabetes types in terms of the development of retinopathy (136).

Question D1-a: Are biochemical laboratory tests useful in the diagnosis of CP?

Suggestion D1-a: The sensitivity and specificity of biochemical tests in the diagnosis of CP are low. (Level of evidence: 3B; Power of suggestion: Strong consensus)

Comment: Routine laboratory tests are not generally useful in CP. Complete blood count, electrolytes, and liver function tests are often normal in these patients. Tests may reveal malabsorption-related anemia, and apolipoprotein, total cholesterol, magnesium, fat-soluble vitamins (A, D, E, and K), vitamin B_{12}, calcium, zinc, selenium, and prealbumin levels may be decreased (98, 137). If alkaline phosphatase (ALP), transaminases, and bilirubin levels are high, edema, fibrosis, or choledochal stenosis because of pancreatic cancer should be considered (138, 139). Investigation of lipid panel and serum calcium levels in these patients is important for determining the etiology of CP. Hyperparathyroidism should also be investigated in the presence of high calcium levels (140).

Serum amylase and lipase levels are mostly normal or slightly increased because CP is a patch-style focal disease and parenchyma has fibrosis. However, during acute pancreatitis attacks, pancreatic enzyme levels typically increase more than 3 times the normal levels. As a result, amylase and lipase do not have diagnostic or prognostic significance in CP (139). In the literature, the only study on the adequacy of amylase and lipase in the diagnosis of CP reported the sensitivity of the tests as 56% and 54%, respectively, in CP patients who received a diagnosis of ERCP (140).

The diagnosis of CP can be made easily in advanced disease with the help of typical clinical findings and imaging methods. In early-stage disease, diagnosis is difficult, especially in patients without classical clinical findings, and there is no single diagnostic test. In this case, those that can be reached among pancreatic exocrine function tests can be applied for helping the diagnosis by calculating profit and loss (138, 139). Tests used to determine exocrine pancreatic functions are the FE-1, fecal chymotrypsin (FC), and pancreolauryl serum (PLS) tests. Apart from these biochemical tests, the cholecystokinin (CCK)-secretin stimulation test, which is an endoscopic test, is the most sensitive test in determining exocrine pancre-

atic function, but it has no place in daily clinical practice because it is uncomfortable for the patient and it is not easily accessible (141, 142).

In the literature, there are no satisfactory data regarding the use of non-invasive biochemical tests in the diagnosis of CP. The test that has been examined in terms of diagnostic adequacy the most and has relatively higher sensitivity than other tests is the FE-1 test. In a study involving 131 patients with CP, the sensitivity of the FE-1, FC, and PLS tests in diagnosing CP was found to be 79%, 48%, and 71%, respectively (143). In the study by Dominguez-Munoz et al. (109), the sensitivity of FE-1, FC, and PLS was reported to be 0% in diagnosing early CP.

Question D1-b: Which imaging method is used for the diagnosis of CP?

Suggestion D1-b: Transabdominal USG, EUS, MR/MRCP, and computed tomography (CT) can be used in the diagnosis of CP. EUS, MR/MRCP, CT, and ERCP are more sensitive and specific than conventional USG. Considering the safety and cost, transabdominal USG can be accepted as the first-line diagnostic method. Because of its invasiveness, the use of ERCP for diagnostic purposes should be avoided. (Level of evidence: 2A; Power of suggestion: Strong consensus)

Comment: Imaging methods play a key role in the diagnosis of CP. The main imaging methods used in diagnosis are transabdominal USG, EUS, MR/MRCP, CT, and ERCP. In a meta-analysis on this subject, imaging methods were compared with each other, and the sensitivity and specificity of ERCP was found to be numerically superior to that of transabdominal USG, CT, and EUS, but it was not found to be statistically significant (144). In a study by Pungpapong et al. (145), the sensitivities of EUS and MRCP in the diagnosis of CP were found to be 93% and 80%, respectively, and both tests were demonstrated to be an alternative imaging method to ERCP. In another conducted study, USG, EUS, CT, and ERCP methods were compared for the diagnosis of CP, and the lowest sensitivity and specificity values were determined in transabdominal USG (58% and 75%, respectively). According to the study, the sensitivity and specificity of CT were found to be 75%; the sensitivity of EUS and ERCP was 88% and 74%, respectively; and the specificity was 100% in both (146).

Although EUS elastography is used primarily in the differential diagnosis of solid pancreatic masses, there are recent data showing that it is also useful in the diagnosis of CP (147). In studies investigating the effectiveness of EUS elastography in the diagnosis of CP (although different elastography parameters and threshold values are used), its sensitivity was found as 71% to 77% and its specificity as 72% to 92% (147-149).

Question E1-a: When should biliary stenosis be investigated in CP?

Suggestion E1-a: Asymptomatic biliary stenosis may occur in patients with CP. Patients with increased persistent ALP and/or increased bilirubin should be evaluated for biliary stenosis. (Level of evidence: 2A; Power of suggestion: Strong consensus)

Comment: Before the choledoch opens to the duodenum, it proceeds in an average of 3 cm (1.5-6 cm) of the pancreatic parenchyma. In CP, which is a fibroinflammatory process, inflammation and fibrosis occurring in the pancreatic parenchyma can affect the intrapancreatic part of the choledoch and cause biliary obstruction, which is one of its important complications. The frequency of biliary stenosis has been reported in between 5% and 64% of patients who underwent ERCP or percutaneous transhepatic cholangiography (PTC) (127, 150-153). Patients with CP with biliary stenosis can be asymptomatic. The earliest finding detected is high persistent ALP values. In a meta-analysis on this subject, ALP was found to be more than two times higher in 63% to 100% of patients, whereas 38% to 100% of patients had higher bilirubin values (150). Littenberg et al. (154) reported that the persistent elevation of ALP in CP was associated with biliary stenosis because of fibrosis, whereas transient elevations were caused by acute attacks developing in the background of CP.

Question E1-b: What imaging methods are used to diagnose biliary stenosis in CP?

Suggestion E1-b: Transabdominal USG, MR/MRCP, and EUS can be used to assess stenosis. (Level of evidence: 2A; Power of suggestion: Strong consensus)

Comment: The accuracy of transabdominal USG, which can be reached rapidly and easily, in diagnosing extrahepatic biliary obstruction is quite high (96%) (155). However, the accuracy of USG in detecting the cause of biliary obstruction is 71%. If the cause of stenosis is CP, this rate decreases to 59%. ERCP and PTC are accepted as the gold standard in evaluating the diagnosis, level, and etiology of biliary obstruction. However, because of their invasiveness and the risk of complications, their use for diagnostic purposes has gradually decreased, and MRCP

and EUS have replaced them. In the study by Materne et al. (156), the sensitivity of MR and EUS in the diagnosis of biliary stenosis was 91% and 97%, respectively, and the specificity was 94% and 88%, respectively. In another study investigating the role of EUS in evaluating distal choledoch stenoses, EUS was found to be 91% sensitive and 100% specific, and it was reported that its sensitivity was 94% and its specificity was 82% in the distinction of malignant and benign (157).

Question E1-c: How is gastric outlet obstruction recognized?

Suggestion E1-c: It should be considered in patients with persistent nausea and vomiting. For diagnosis, barium x-ray, oral contrast-enhanced CT, and upper GI endoscopy can be used. (Level of evidence: 3A; Power of suggestion: Strong consensus)

Comment: Gastric outlet obstruction because of CP is a rare complication seen in 5% (0.5%-13%) of patients (127, 158-161). In patients with CP, it should be considered in the presence of clinically early saturation, nausea/vomiting, and weight loss. Vomiting usually occurs shortly after eating, and if stenosis is in the distal papilla, there may be bile. Symptoms usually last less than 2 weeks if they occur because of inflammation occurring in acute pancreatitis attacks developing in the background of CP and inflammation-triggered duodenal spasm. Longer symptoms are considered as irreversible because of fibrosis (160, 162-164). In addition to the mechanical compression caused by the fibroinflammatory process occurring in the pancreas, arteriolar narrowing and thrombosis, ischemia in the wall of the duodenum, and fibrosis and related narrowing over time can develop (160, 162).

In the literature, barium x-rays and upper GI system endoscopy were used in the diagnostic approach in patients suspected to have gastric outlet obstruction. Barium x-rays provide information about the level, severity, and length of the stenosis. Oral contrast-enhanced upper abdominal CT provides additional benefits in detecting other causes of stenosis (e.g., tumor infiltration, pseudocyst pressure, or hematoma in the duodenum wall). In upper GI system endoscopy, malignancies infiltrating the duodenum wall can be eliminated by biopsies collected from the region of stenosis (158, 159, 161).

Question E2-a: How is splanchnic venous thrombosis (SVT) diagnosed?

Suggestion E2-a: Doppler USG should be the preferred method in the diagnosis of SVT. As a second option, contrast-enhanced CT should be chosen because of its easy applicability and advantage it offers in evaluating complications related to CP. (Level of evidence: 4; Power of suggestion: Strong consensus)

Comment: In CP, SVT can affect one or more vessels. SVT involves hepatic vein, portal vein, mesenteric vein, and splenic vein thrombosis. Although splenic vein thrombosis is more common in patients with CP than in those with acute pancreatitis, portal vein thrombosis and mesenteric vein thrombosis are less common. In CP, the prevalence of SVT, portal vein, splenic vein, and mesenteric vein thrombosis are reported as 11.6%, 3.5%, 12.8%, and 1.2%, respectively (165).

The sensitivity and specificity of the D-dimer and P-selectin combination, which are among the serum markers, in the diagnosis of splenic vein thrombosis are 82% and 97.6%, respectively (166). However, there is no study evaluating these markers in patients with CP. In addition to serum markers, Doppler USG, contrast-enhanced CT, and contrast-enhanced MR imaging methods can be used in the diagnosis of SVT. In the literature, there is no randomized controlled study comparing non-invasive methods to diagnose SVT in CP. Doppler USG is a low-cost method that allows real-time evaluation of the flow direction and flow rate of the portal venous system. Therefore, it can be considered as the first method to be preferred in the diagnosis of SVT. In patients with pancreatitis, contrast-enhanced CT has the advantage of showing extravascular pancreatic pathologies as well as evaluating the splanchnic venous system (167). However, it should be preferred in selected cases because of the nephrotoxic effect of the contrast agent. Contrast-enhanced MR is more sensitive than USG in displaying the portal venous system and portosystemic collaterals, but it is not a cost-effective method (168).

Question E2-b: How is a pseudoaneurysm diagnosed?

Suggestion E2-b: The sensitivity and specificity of contrast-enhanced cross-sectional examinations are high in the diagnosis of pseudoaneurysm. It can be preferred in cases with suspected bleeding. Conventional angiography is the most effective method, and in addition to diagnosis, it can provide therapeutic contribution. (Level of evidence: 4; Power of suggestion: Strong consensus)

Comment: Pseudoaneurysm is a rare, life-threatening vascular complication of CP. It often develops in CP because of the damage of proteolytic enzymes on the vessel wall (169). Pseudoaneurysms can rupture into the GI

tract, peritoneal cavity, pseudocyst, retroperitoneum, and pancreatic and biliary ducts (170). Non-invasive and invasive imaging methods are used to diagnose pseudoaneurysm. Transabdominal USG is an easy-to-apply, repeatable, and cost-effective non-invasive method that provides real-time imaging. However, in the diagnosis of pseudoaneurysm, its sensitivity is low compared with contrast-enhanced CT (171). Although it has been reported that methods such as USG-based contrast-enhanced examination and super microvascular imaging may be useful in the diagnosis of pseudoaneurysm, these methods are not yet widely clinically used (172, 173). Contrast-enhanced CT and MR are non-invasive cross-sectional examination methods that can provide an advantage in evaluating other complications of CP other than vascular pathologies (171, 174). It is reported in a few case reports that EUS, which is one of the invasive imaging methods, can play an active role in the diagnosis and treatment of pseudoaneurysm (175-177). Conventional angiography, which is an invasive method in the diagnosis of pseudoaneurysm, is a highly sensitive method and provides a therapeutic contribution (178, 179).

Question F1-a: Does ceasing alcohol and smoking affect the course of CP?

Suggestion F1-a: It is useful to cease alcohol (Level of evidence: 2A; Power of suggestion: Strong consensus) and smoking (Level of evidence: 1A; Power of suggestion: Strong consensus) in patients with CP.

Comment: There are only a few studies investigating the effects of ceasing alcohol on the natural course of CP. In alcohol-related CP, even though alcohol intake is stopped, the progression of the disease continues, but this process is slower and the course of the disease is less severe (180). Because those who consume large amounts of alcohol are generally heavy smokers, it makes it difficult to determine the pathogenic role of these two factors in the tissue damage of the pancreas (37).

A significant number of patients with CP describing pain consist of those who smoke. There is no clear evidence about the positive effect of quitting smoking on pain. In retrospective cohort studies, tobacco use has been shown to accelerate the development of calcification and DM in chronic alcoholic pancreatitis, independent of alcohol consumption (28, 181, 182). It was demonstrated in a prospective cohort study that smoking cessation in the first years since the onset of clinical signs of CP reduced the risk of developing calcification in the pancreas (183). Considering that patients with CP who smoke have a worse quality of life, ceasing smoking may be thought to be beneficial (28, 37, 181-184).

Question F1-b: How should micronutrient and vitamin therapy be?

Suggestion F1-b: In terms of fat-soluble vitamin (A, D, E, and K), vitamin B_{12}, zinc, and magnesium deficiency, patients should be screened and replaced if necessary. (Level of evidence: 2A; Power of suggestion: Strong consensus)

Comment: In patients with CP, hemoglobin, serum albumin, prealbumin, retinol binding protein, and magnesium levels may decrease in parallel with EPI (185). In a study, vitamin A, D, E, and K deficiencies in patients with CP were found to be 3%, 53%, 10%, and 63%, respectively (186). In a prospective cohort study, serum vitamin A level in 14.5% of patients with CP and vitamin E level in 24.2% were lower than healthy controls, whereas in another controlled study, plasma level in 16% of patients and vitamin E level in 75% of patients were found to be low (187, 188). Although there are differences between the results of the studies, a significant number of patients with CP have vitamin deficiencies. Therefore, supportive treatment should be applied in terms of fat-soluble vitamins (vitamins A, D, E, and K) and other micronutrients in patients requiring them (189).

In patients with CP, the prevalence of vitamin D deficiency is high, and a decrease in bone mineral density can be detected accordingly (190, 191). Osteoporosis is found in approximately one-fourth of patients and osteoporosis or osteopenia in approximately two-thirds of patients (192, 193). Consequently, osteoporosis and osteopenia should be kept in mind and treated in patients with CP.

Question F1-c: How should a diet be in the treatment of CP?

Suggestion F1-c: Every patient diagnosed as having CP should be evaluated in terms of malnutrition and sarcopenia. Nutritional support must be applied simultaneously with PERT. Dietary fat restriction should be avoided. If oral nutrition is insufficient, enteral nutrition support can be applied. (Level of evidence: 2A; Power of suggestion: Strong consensus)

Comment: Nutritional disorders may occur in CP because of abdominal pain, nausea, vomiting, and DM, and malnutrition is quite common. Patients with CP generally tend to have low body weight (194, 195). Malnutrition is manifested by a decrease in muscle mass (sarcopenia). Sar-

copenia has negative effects in terms of disease course, risk of complications, and quality of life. While evaluating the nutritional status of patients with CP, the amount of nutrients that the patient receives, body composition, daily activities, quality of life, and inflammatory processes should be taken into consideration (196). In these patients, anthropometric measurements and the Nutritional Risk Screening 2002 scoring system can be used for nutritional evaluation (197).

PERT taken with meals with normal fat content (30%-35% of total energy intake) forms the basis of EPI treatment. In these patients, daily calorie intake should be 25-30 kcal/kg, protein amount should be 1.2-1.5 g/kg/day, and fat amount should constitute 30% to 35% of total energy (196, 198). In patients with CP, dietary fat restriction and very-high-fiber diets should be avoided (199, 200). In CP, more than 80% of patients can be fed with normal foods supported with pancreatic enzymes. Nutritional supplements are needed in 10% to 15% of all patients, and tube feeding may be required in approximately 5% (196). In a randomized controlled study conducted on 60 patients with CP with undernutrition, balanced nutrition with home-cooked food with the guidance of dietary counseling has been shown to be as effective as commercial food supplements in improving malnutrition (201).

Question F2-a: How should analgesic treatment be?

Suggestion F2-a: In the medical treatment of pain associated with CP, the step therapy recommended by the World Health Organization (WHO) for chronic pain treatment should be applied. Opioid drugs should be attempted to be discontinued as quickly as possible, and combined therapies should be considered to reduce the dose of opioid drugs and thus the risk of side effects. (Level of evidence: 1B; Power of suggestion: Strong consensus)

Comment: Approximately 85% to 97% of patients with CP experience pain throughout their illness. Pain is more likely to occur in patients who develop the disease at an early age and for whose etiology alcohol is responsible. Pain in CP also negatively affects the quality of life of the patient (81). The mechanisms of pain in CP have not been fully clarified yet. It is thought to occur because of multifactorial causes such as inflammation, duct obstruction, high pancreatic tissue pressure (compartment syndrome), fibrotic changes in sensory nerves, and neuropathy (202).

When arranging pain treatment, the possible causes of pain should be considered first. GI complications such as peptic ulcer can develop in CP. In patients with peptic ulcer or thought to be at a high risk for developing peptic ulcer, proton pump inhibitor (PPI) therapy can be started. In patients with stenosis or stones in the pancreatic duct, further interventional treatments should be taken into account to provide pain palliation (203). The causes, type, and severity of pain and comorbid conditions or symptoms may differ in patients with CP. Therefore, pain treatment needs to be individualized. When starting pain treatment in patients with CP, the first step is to stop smoking and alcohol use because these agents are known to negatively affect the prognosis of the disease (180, 184).

In the medical treatment of pain, the pain ladder approach, which was proposed by WHO in 1986 but remains valid, is applied (204). This treatment approach was developed for patients with cancer but later became widely used in the treatment of chronic pain. According to this treatment approach, if the pain response cannot be obtained with the drugs in one step, it is passed to the next step. When applying step therapy, patients should be monitored in terms of whether drugs are used in the appropriate dose and range and for side effects.

According to this approach, it is recommended to use non-opioid analgesics (acetylsalicylic acid, acetaminophen, and selective or non-selective non-steroidal anti-inflammatory drugs [NSAIDs]) in the first step. However, there is no study evaluating the effectiveness of acetaminophen, acetylsalicylic acid, or NSAIDs in pain management in CP. According to step treatment, pain treatment can be started with acetaminophen in patients with CP, but NSAIDs should be avoided because of the risk of GI complications.

If pain palliation cannot be achieved with the first-line drugs, the second step is used. In this step, weak opioids (codeine, hydrocodone, and tramadol) can be used alone or in combination with non-opioid or adjuvant treatments. In the third step, strong opioids (morphine, oxycodone, methadone, hydromorphone, and fentanyl) are used alone or in combination with non-opioid or adjuvant treatments. Both tramadol and morphine are highly effective in the treatment of pain in CP. In a randomized controlled study comparing these two opioids, tramadol was found to be more successful in the treatment of pain in CP, and it was shown to have fewer GI side effects (205). Considering that the risk of addiction is lower than morphine, tramadol may be preferred in patients with CP.

Transdermal fentanyl may be an option for pain management in patients with limited oral intake. In a study conducted by Niemann et al. (206), the effectiveness of transdermal fentanyl in pain management in CP was found to be similar to that of morphine. However, attention should be paid to dermal side effects.

Neuropathic pain has become prominent in recent years as one of the formation mechanisms of pain in CP. In the treatment of neuropathic pain, tricyclic antidepressants, selective serotonin reuptake inhibitors, and anticonvulsants are used. Although there are no data on the effectiveness of antidepressants in CP, they can be used as adjuvant therapy from the early stages based on indirect evidence. By adding them, it may be possible to reduce the opioid dose, and they can also help patients to cope with pain. In a study conducted by Olesen et al. (207), the effect of pregabalin, which is an anticonvulsant, was investigated in the treatment of pain in patients with CP. It has been shown that pregabalin used in addition to analgesic treatments is superior to placebo and helps to reduce opioid dose. Drug-related side effects were observed in 91% of patients, but most of these side effects were mild or moderate and well tolerated by patients.

Successful results have not been achieved with leukotriene receptor antagonists (208) and tetrahydrocannabinol (209) in the treatment of pain in CP. Similarly, short-term inhibition of pancreatic secretion with octreotide was not effective in pain palliation (210).

Question F2-b: Is PERT used in pain treatment?

Suggestion F2-b: PERT has no effect on pain. In patients with EPI, PERT may have a beneficial effect on bloating. (Level of evidence: 1A; Power of suggestion: Strong consensus)

Comment: CCK and pancreatic secretions are also thought to play a role in the occurrence of pain in CP. Active proteases can be effective in pain palliation by reducing the level of CCK and pancreatic secretion in the duodenum. Activated serine protease can reach the duodenum only with uncoated tablets. According to a meta-analysis involving five studies, PERT treatment has no effect on pain in CP (211). The longest use of PERT in these studies is 4 months. In the study performed by Isaksson et al. (212), uncoated PERT was used, and it was reported to be effective on pain. In patients with EPI, the complaints (such as bloating, gas, or cramping) because of malabsorption can be reduced with PERT treatment.

Question F2-c: Where can antioxidant therapy be used?

Suggestion F2-c: Antioxidants can be tried in patients whose pain is difficult to be treated. (Level of evidence: 1A; Power of suggestion: Strong consensus)

Comment: Antioxidants seem to be beneficial in the treatment of pain in CP according to numerous studies and five meta-analyses (213-217). However, there is heterogeneity between both patient populations included in the studies and formulations of the antioxidants used. In addition, side effects such as allergy, headache, nausea, vomiting, rash, dyspepsia, and abdominal pain because of antioxidants have been reported. The longest period of use of antioxidants in the studies is 6 months, and there are no data on their reliability in longer use. Therefore, routine use of antioxidants in CP pain is not recommended. However, they can be added to the existing treatment in patients who have difficulty in pain management.

Question F3-a: What are the indications of endoscopic treatment in CP?

Suggestion F3-a: Endoscopic treatment is indicated for the treatment of pain and complications. If the main pancreatic duct is dilated because of stricture and/or obstruction by a stone, endoscopic treatment should be the first choice. (Level of evidence: 5; Power of suggestion: Strong consensus)

Comment: Pain and complications are the indications of endoscopic treatment in CP. Pseudocyst, walled-off necrosis, ascites, pleural effusion owing to pancreatic duct leakage, and biliary and duodenal obstruction because of inflammatory compression are among the complications that can be treated using various endoscopic methods. In patients with uncomplicated pain, endoscopic treatment should be the first choice if the main pancreatic duct is dilated because of stricture and/or obstruction by a stone located in the head and/or body of the pancreas (81, 218).

Question F3-b: How is endoscopic treatment of main pancreatic duct stones performed?

Suggestion F3-b: Most of the stones obstructing the main pancreatic duct can be extracted by ERCP alone using the standard stone removal equipment after pancreatic sphincterotomy if they are small in size (<5 mm), low in number, and located at the head or body of the pancreas, and if there is no associated downstream stricture. (Level of evidence: 4; Power of suggestion: Strong consensus)

Comment: Main pancreatic duct stones can be extracted using ERCP, extracorporeal shock wave lithotripsy

(ESWL), or both. After pancreatic sphincterotomy, attempts to extract stones using the standard stone removal equipment, such as balloon and baskets, will fail in up to 90% of patients (219-222). A retrospective study revealed that mechanical lithotripsy for pancreatic stones was associated with three times higher complications than biliary stones (11.6% and 3.6%, respectively) (223). Endoscopic treatment success rate increases when the stones are low (≤3) in number, ≤10 mm in diameter, not impacted, and located at the head and/or body of the pancreas without an associated downstream stricture (224). On the basis of these results, ERCP alone is recommended for the extraction of stones small in size (≤5 mm in diameter), low in number, and located at the head or body of the pancreas.

Question F3-b1: When should ESWL be used?

Suggestion F3-b1: ESWL alone is an effective method for the treatment of main pancreatic duct stones in experienced centers. Radiopaque obstructive stones ≥5 mm are first fragmented with ESWL and then extracted using endoscopy. (Level of evidence: 2; Power of suggestion: Strong consensus)

Comment: ESWL fragments pancreatic stones and facilitates their endoscopic removal. A meta-analysis of 11 studies, published in 2010, revealed an 89% success rate of ESWL for fragmenting main pancreatic duct stones (225). A recent meta-analysis of 27 studies showed that ESWL alone or combined with ERCP achieved complete clearance of pancreatic ducts in 70% of patients, and 52% remained pain free within 2 years of follow-up (226).

In patients with uncomplicated painful CP with ≥5 mm radiopaque stones obstructing the main pancreatic duct, it is recommended to start treatment with ESWL and extract the remaining stone fragments by ERCP if spontaneous clearance does not occur (222). A comprehensive literature review of studies reporting the outcomes of ESWL treatment showed that ESWL was an effective method of treatment and fragmented 58% to 100% of the stones. When combined with ERCP, 41% to 89% of the main pancreatic duct stones can be completely extracted, and during a follow-up longer than 24 months, pain relief could be achieved in 38% to 93% of patients, whereas 34% to 79% remained pain free (93, 221, 227-263). Factors favoring complete clearance of stones by endoscopy after ESWL were the presence of a single and low-density stone(s) (<820 Hounsfield units), absence of main pancreatic duct stricture, insertion of a pancreatic stent before the procedure, and use of secretin during the first ESWL session (225, 236, 237, 239, 243, 252, 253, 255, 261). Long-term pain response after treatment was higher in patients who had a short disease duration and low frequency of attacks before treatment, stone(s) located at the head of the pancreas, complete clearance of the main pancreatic duct after the procedures, no stricture or stricture resolved after treatment, steatorrhea, and never smoked or quit smoking (220, 227-229, 233, 235-237, 243, 247, 249). Pain relapse after ESWL alone or combined therapy was usually observed within the first 2 years after treatment (230, 237, 238).

Three retrospective studies revealed that 49% to 75% of pancreatic duct stones can be completely removed with ESWL alone (245, 255, 256). There is only one prospective randomized study (n=55) comparing the efficacy of ESWL and ESWL plus ERCP. Although there was no significant difference in pain recurrence (42% and 45%, respectively) during the 52-month follow-up period, duration of hospitalization and cost were higher in the combined group (238). Another retrospective study (n=146) compared patients who underwent ESWL alone with those who received combined treatment and found no difference in terms of pain relief at the end of 6-month follow-up (250). When ESWL is performed in well-established centers, approximately 70% of the fragmented stones spontaneously pass through the pancreatic orifice to the duodenum (256). On the basis of these results, ESWL alone may be reasonable for the treatment of main pancreatic duct stones in experienced centers, and this approach was found to be more cost-effective than systematically performing ERCP after ESWL in all patients to extract possible residual, small, main pancreatic duct stone fragments (222).

The contraindications of ESWL include uncorrected coagulation disorders; pregnancy; and presence of bone, calcified aneurysm, or lung tissue on the path of shockwave. It is not indicated in patients with extensive stones located throughout the main pancreatic duct, isolated stones at the tail of the pancreas, mass in the head of the pancreas, moderate or massive amount of ascites, and in those who had more than one main pancreatic duct stricture (222, 257). ESWL is a relatively safe procedure. When used alone or in combination with ERCP, the most common complication is acute pancreatitis. A recently published prospective study including 1,470 ESWL plus ERCP procedures reported a 6.7% total rate of complications, namely pancreatitis, hemorrhage, infection, steinstrasse, and perforation. Out of these, 1.1% were moderate or severe. In addition, 21% of the patients had transient side

effects such as hematuria, asymptomatic hyperamylasemia, and GI mucosal damage (248).

Question F3-b2: Does intraductal laser or electrohydraulic lithotripsy have a role in the treatment of main pancreatic duct stones?

Suggestion F3-b2: Intraductal laser or electrohydraulic lithotripsy is a treatment choice that can be used alone or after failure of ESWL. (Level of evidence: 4; Power of suggestion: Strong consensus)

Comment: There are a limited number of studies about the efficacy of intraductal laser or electrohydraulic lithotripsy for the treatment of main pancreatic duct stones. Most of these studies are small case series and reported that complete clearance of the main pancreatic duct can be achieved in 43% to 100% by using different methods and equipment for lithotripsy (258-268). Depending on the experience of the clinic, intraductal laser or electrohydraulic lithotripsy can be used before ESWL or after failure of ESWL. A multicenter study reported that the only factor associated with technical failure was the presence of a main pancreatic duct stricture (266). Randomized, prospective studies are needed to compare their efficacy with ESWL.

Question F3-c: How should main pancreatic duct strictures be treated?

Suggestion F3-c: After dilating the dominant stricture with a balloon, bougie, or Soehendra stent retriever, it is recommended to insert a 10 French (F) plastic stent to the main pancreatic duct, if technically possible. (Level of evidence: 3; Power of suggestion: Strong consensus)

Comment: A multicenter retrospective study reported that main pancreatic duct stricture was observed in 79% of 1,000 patients with CP who underwent endoscopic treatment (269). Dominant stricture is defined when at least one of the following criteria is present: upstream main pancreatic duct diameter ≥6 mm, inability of contrast medium delivered from a 6F catheter advanced to the upstream main pancreatic duct to flow into the distal pancreatic duct, and pain during the infusion of saline through a nasopancreatic drain inserted to the upstream main pancreatic duct (270).

Dominant stricture of the main pancreatic duct is dilated by inserting single or multiple plastic stents. Malignancy should be excluded by imaging methods and brush cytology before the dilatation treatment. During the ERCP procedure, the main pancreatic duct is cannulated first, and afterward, pancreatography is obtained to identify the length and location of the stricture. Pancreatic sphincterotomy is performed later. Biliary sphincterotomy can be performed for the treatment of concomitant biliary pathology or to facilitate pancreatic duct cannulation (271). Tight strictures are dilated by a balloon, bougie, or Soehendra stent retriever before stenting. Finally, a 10F plastic stent is inserted across the stricture, if technically possible, with its tip extending to the upstream dilatation. A retrospective study revealed that patients who received stents ≤8.5F were more likely to require hospitalization because of abdominal pain than those who received a 10F stent (272). The clinical response is evaluated 6-8 weeks after the procedure.

A comprehensive review of studies reporting the outcomes of stent dilatation treatment for main pancreatic duct strictures showed that 5-12F stents were used, and technical success varied between 81% and 100%. Of 25 studies, stents were exchanged at regular intervals (2-5 months) in 14, whereas they were exchanged on demand in five studies. In nine studies, the average stenting duration was 1 year or longer. Early pain response was observed in 70% to 100% of patients after a single plastic stent insertion (218, 242, 273-294). In the long term (14 months-7.1 years), pain recurred in most patients, and complete or partial permanent pain relief could be achieved in 32% to 90% of them. In patients who had a minimum stenting duration of 1 year, permanent pain reduction was observed in 51% to 80% of those with an average follow-up period of less than 5 years and in 62% to 80% of those with an average follow-up period of at least 5 years. In the same group, the need for surgery was 14% to 31% in patients with an average follow-up of less than 5 years, whereas it was 0% to 7.5% in those with a minimum average follow-up of 5 years (218, 274, 277, 280, 289, 291, 294). Factors favoring long-term pain response were absence of continuous pain before treatment, absence of daily narcotics use, short disease duration before treatment, absence of PD, absence of pain just before the procedure, no smoking, quitting alcohol, insertion of a 12F stent during treatment, resolution of the stricture after treatment, and improvement in the main duct diameter after treatment (275, 277, 278, 284, 285, 291, 293). Complications such as pancreatitis (6.3%), sphincterotomy bleeding (0.9%), sepsis (0.6%), cholangitis (0.4%), abscess (0.2%), stent migration (3.1%), and changes in the pancreatic duct (0.8%) may be observed during stenting treatment.

Question F3-c1: How are patients followed up with after stent insertion?

Suggestion F3-c1: In patients with clinical response, it is recommended to exchange the stent when symptoms develop or findings of stent dysfunction are noticed in imaging methods, which should be performed no later than 6 months. Total duration of stenting should be at least 1 year. Stent exchange interval should not exceed 1 year. (Level of evidence: 4; Power of suggestion: Strong consensus)

Comment: There are different opinions in the literature about the exchange interval of pancreatic stents. Most of the studies recommend to exchange stents within 3 months because most of them are occluded within this time (242, 275, 276, 280, 282, 285, 286, 288-290, 292, 295). However, some studies suggest to exchange stents on demand, when pain recurs or recurrent dilatation in the main pancreatic duct develops (274, 277, 282, 284, 287). In the latter, it is recommended to follow-up with patients every 1-6 months with abdominal USG, abdominal X-ray, s-MRCP, and blood and urine amylase for the detection of signs of stent dysfunction, as stent dysfunction is not always correlated with pain. Infectious complications such as pancreatic juice infection, abscess, and pancreatic sepsis can develop in 6.7% of patients during on-demand stent exchange strategy (274, 277, 279, 284, 287, 292).

In patients with clinical response, stenting duration should be at least 1 year. If a 6F catheter can be easily advanced through the stricture and the contrast medium injected to the upstream from the stricture can adequately flow into the duodenum within 1-2 minutes, treatment can be terminated. Patients with symptomatic persistent or recurrent dominant strictures after 1 year of treatment should be evaluated for treatment with multiple plastic stents, metallic stents, or surgery. Absence of pain during the year following stent removal can be considered as long-term clinical success (284).

Question F3-c2: In which situations are multiple plastic stents or self-expandable metallic stents (SEMSs) used?

Suggestion F3-c2: Symptomatic patients whose stenosis continues or recurs at the end of treatment are evaluated for multiple plastic stents or full covered SEMSs (FC-SEMSs). (Level of evidence: 3B; Power of suggestion: Strong consensus)

Comment: The recommended method for endoscopic treatment of CP is the placement of a plastic stent (222). Plastic stents, however, become clogged, so they require replacement from time to time. Recurrence is common when they are left stent-free because they provide a remodeling just as much as their diameter (296). Two methods can be applied to overcome these problems. One method is to increase the number of plastic stents and to enlarge the opening to be formed in this way. There is one study on multiple plastic stent application in the treatment of CP-related stenosis (297). In this study, to treat pancreatic duct stenosis in 19 patients, an average of three 8.5-11.5F stents were inserted, and they were removed after 6-12 months. Symptomatic stricture recurrence was reported as 10.5% at a mean follow-up of 38 months. The second method is to use FC-SEMSs. Because these stents have large diameters, their openings are greater. Uncoated metal stents were used in the pancreatic duct, and despite the immediate improvement in pain, recurrent stricture developed because of epithelial hyperplasia (298). For this reason, it is preferred that the stent used is completely covered.

The fastest development in the endoscopic treatment of CP has been related to FC-SEMS, and many studies have been published recently on this subject (299-309). Most of these studies are retrospective case series, and some are pilot studies to find the ideal stent design. All of the patients included in the studies were patients refractory to plastic stent treatment. Stents in various lengths (3-10 cm), diameters (6-10 mm), and designs have been used with 100% technical success from major or minor papillae. Generally, they are planned to be removed in 2-6 months, but patients whose stents were kept for 10 months have also been reported. The stent was successfully removed in all patients. The main side effect in the early period is temporary pain, which can usually last for days. There may also be cholestasis because of pancreatitis and metal stent compression. To prevent cholestasis, either a biliary sphincterotomy or insertion of a stent in the biliary system is recommended. It is doubtful that the pancreatitis attack is associated with the stent; it is thought to be related to the bougie or balloon dilatation performed before the procedure. It is known that most of them have a mild course. The long-term problem is the development of new (de novo) stenosis caused by migration and stent. It is observed that the migration rate has decreased with the new stent designs. De novo stenosis development could be reduced by choosing thinner stents such as 6-8 mm, suitable for pancreatic duct diameter. It is reported that these stenoses are short segments and easily respond to dilatation and plastic stent treatment. The rates of pain reduction, stricture reso-

lution, and regression in upstream dilation are high with FC-SEMS. It is reported that it facilitates the removal of stones in the pancreatic duct, as the stenosis improves significantly (310). The frequency of pain owing to recurrent stenosis does not appear to be very high after leaving stent-free (299-309).

According to these results, the use of pancreatic FC-SEMS seems very promising. There is a need for studies that are used as primary treatment methods compared with multiple plastic stents. Metal stents should be developed to prevent migration and de novo stricture development. Until then, FC-SEMSs can be used in patients refractory to plastic stent.

Question F3-d: Under what guidance can EUS-pancreatic duct drainage (EUS-PDD) be used?

Suggestion F3-d: It can be applied in patients in whom ERCP has failed and who are not suitable for surgery. (Level of evidence: 4; Power of suggestion: Strong consensus)

Comment: Although ERCP is successful in most of the patients whose pancreatic ducts will be intervened, the pancreatic duct cannot be entered for various reasons in 3% to 10% of patients (257). EUS-PDD has been described as a rescue technique in patients whose papilla cannot be reached and in whom the pancreas duct cannot be cannulated despite reaching or passed because of the stenosis. EUS-PDD includes pancreatography and pancreatic duct drainage. Drainage can be applied transgastrically, transenterically, or transpapillary (anastomotic) by antegrade or retrograde route. It is also possible to remove stones in the pancreatic duct with this method. The stones can be removed from the newly created path, pushed from the papilla or anastomosis, or broken in the pancreatic duct. EUS-PDD is an alternative to surgery because the morbidity of surgical treatment methods is higher than that of endoscopic ones (311, 312). Studies comparing the method with surgical treatment are needed.

Most studies on EUS-PDD are case series and are retrospective. These studies focused on the technique of the procedure, its early effectiveness, and complications (313-338). Patient groups do not include patients with CP alone. Therefore, no special comment can be made for CP. However, it is observed that technique and accessories have improved, and technical success and effectiveness are increasing. Side effects reported in the early period include pain requiring hospitalization, pancreatitis, abscess, perforation, and bleeding. Stent migration or dysfunction may occur. In this case, the stent can be placed from the same place, and repetition of the procedure may be required (311, 312). Complications are comparable to those in surgery.

EUS-PDD seems to be an effective and safe procedure in pancreatic diseases. It requires both ERCP and EUS experience. There are also some difficulties; the pancreatic duct is thin, it is necessary to pass through the hard pancreatic tissue, the guide wire is inserted relatively shortly into the pancreatic duct, and there are no accessories produced for this aim (312).

Question F4: Which method should be applied for celiac plexus blockade (CB)/neurolysis (CN)?

Suggestion F4: CB/CN can be applied under EUS, fluoroscopy, or CT guidance. However, EUS-guided CB (EUS-CB) provides longer pain palliation than CT- or fluoroscopy-guided procedures. (Level of evidence: 4; Power of suggestion: Moderate consensus)

Comment: Because opiates used in pain control in CP have side effects such as sedation, Oddi sphincter spasm, and constipation, different methods have been developed for pain management. The process to block the sympathetic nerve ganglia, which carry the pain sensation from the pancreas (nociception) to the brain with afferent nerves and located in the celiac plexus region using local anesthetics or corticosteroids, is called CB. The same process performed by injecting alcohol in the same region is named CN (339).

Both CB and CN decrease the pain of pancreatic origin. Although pain control is temporary in CB, theoretically the function of the celiac plexus is permanently terminated by chemical ablation in CN (340). Although performing CN in CP may potentially interfere with future pancreatic operation by inducing fibrosis, CB does not have such an adverse effect. Therefore, CB is preferred in patients with CP and CN is preferred in patients with inoperable pancreatic cancer.

Depending on the expertise of the practicing physician and the facilities of the center, CB/CN can be performed under the guidance of EUS, fluoroscopy, or CT (341, 342). Although it was initially started to be performed under fluoroscopy, EUS-CB is increasingly used because of the better view of the celiac region with EUS. In a prospective randomized study comparing EUS- and CT-guided CB (CT-CB), EUS-CB provided more effective and prolonged pain palliation than CT-CB, along with fewer numbers of

process-related discomfort (343). In a study comparing fluoroscopy-guided CB with EUS-CB, EUS-CB decreased pain in 70% of patients, whereas fluoroscopic percutaneous CB decreased pain only in 30% of patients. As a result, EUS in pain control in CP was found to be superior to the method performed under fluoroscopy (341). Gress et al. (344) reported a reduction in pain scores in 55% of patients who underwent EUS-CB. In these patients, it was shown that the mean pain scores (when evaluated over a scale of 10 points) decreased from 8 to 2 both at the fourth and eighth weeks after EUS-CB. Pain loss lasting more than 12 weeks was observed in 26% of all patients (344).

Although EUS-CB has been used for the treatment of pain in patients with CP for many years, there are only a few articles on this subject, with no placebo-controlled studies, and the number of cases included in the studies is relatively low (345). When two published meta-analyses were considered, it was noteworthy that almost half of the patient data they included came from abstracts and both studies used a mostly shared patient pool. A total of 376 and 221 patients, respectively, were included in these two meta-analyses conducted by Puli et al. (346) and Kaufman et al. (347) and the CB procedure was shown to be effective at 59% and 51%, respectively. In another recent study, 76% of 248 patients with CP who underwent EUS-CB were provided sustained pain control for 10 (range, 1-54) weeks (348).

Instead of making a general injection into the celiac region, it was thought that finding celiac ganglia by EUS and applying CB directly to the ganglia would be more successful. In this way, 64 patients with ganglion injection were evaluated 1 week after the procedure, and it was observed that pain palliation was achieved in 50% of the patients (349). However, it is not always possible to identify the ganglia lined up with hypoechoic, small rosary beads with EUS. According to the experience obtained from the CN study conducted later in cadavers, it has been concluded that injection of both sides of the celiac region and with high volume is more effective than trying to visualize the ganglia, because alcohol will spread to the celiac region anyway (350, 351).

However, it is still unclear whether the injection will be made bilaterally or centrally, because another study reported that the success of both methods was indistinguishable (352). LeBlanc et al. (352) compared the effectiveness of injection into one or two different sites of the celiac trunk level in the same procedure. In the study in which 50 patients with CP were included, 60% of patients reported an average of 51 days of pain reduction, and no difference was found between the time and duration of pain palliation between the two techniques (352). A similar study was performed in patients with pancreatic cancer for the procedure of CN under the guidance of EUS, and no difference was found between the two methods (353).

The effectiveness of repetitive EUS-CB in CP for pain relief was investigated in a retrospective study. In this study, EUS-CB was performed an average of 3.1 times, and it was stated that it was safe to repeat the procedure. Criteria for good prognosis to EUS-CB procedures after the first procedure were advanced age at the first EUS-CB and a positive response to the first EUS-CB (348). In this study, mild side effects were generally described after the EUS-CB procedure. These are usually self-healing complications owing to the blocking of sympathetic efferent nerves such as hypoxia, hypotension, orthostatic hypotension, and diarrhea during or immediately after the procedure. The procedure should be performed under antibiotic prophylaxis, as local infection may develop rarely at the injection site. Serious complications, although rare, can be seen with CB. These are usually infectious complications such as retroperitoneal abscess and empyema. *Serious complications such as ischemic or vascular injuries, retroperitoneal bleeding, paraplegia, and spinal cord injuries have been reported with CN. Fatal complications in the form of case reports have also been described in the literature (354). Performing CB or CN under the guidance of EUS results in much less complication development than other percutaneous methods. The complication rate was 1.8% in a series where 189 EUS-CBs and 31 EUS-CNs were applied to patients with CP and pancreatic cancer, and it was concluded that EUS-CB and EUS-CN were safe (355).*

Question F5: Which patients should be directed to surgery?

Suggestion F5: Patients who have failed endoscopic treatment for pain or are not candidates for endoscopic treatment and do not respond to medical treatment for pain are candidates for surgical treatment. (Evidence level: 4; Power of suggestion: Strong consensus)

Comment: Recurrent and persistent pain is the leading indication for endoscopic and surgical intervention in CP (356). The idea of reducing parenchymal hypertension because of pancreatic duct obstruction, which is included in the pathophysiology of pain, is the rationale

of endoscopic and surgical treatments. If the endoscopic treatments that provide channel decompression such as sphincterotomy, stone removal, narrow segment dilation, or stent placement provide only temporary relief or fail, a surgical approach for decompression will be appropriate (357). In two prospective randomized controlled trials comparing surgical and endoscopic treatments, and in the Cochrane review examining them, surgical treatments were found to be more successful in mid- and long-term pain control than endoscopic treatments. A surgical approach may be preferred primarily in the presence of an inflammatory mass at the head of the pancreas, in the presence of stenosis in the biliary tract and/or duodenum, or when malignancy cannot be excluded (242, 280, 358). Early surgery has been shown to be superior to surgery at an advanced stage of the disease in ensuring long-term pain control (359-361). Pain duration being shorter than 3 years, not using opioid in the preoperative period, and the number of endoscopic interventions being fewer than five are factors that positively affect pain control (359). Yang et al. (360) found that surgical treatment was more successful in patients having a duration between the diagnosis of CP and surgery shorter than 26.5 months than the longer ones. In a recent study, it was revealed that early surgery (no more than 3 years since diagnosis) provides better pain control, and exocrine and endocrine functions are better preserved in these patients (361). The results of the first randomized controlled prospective study (ESCAPE) comparing early surgery with step therapy in pain control in CP are expected (362).

Types of operations applied in pain treatment in CP can be defined as decompression purpose drainage operations and resection operations. Puestow longitudinal pancreatojejunostomy and Frey operation (distal and proximal longitudinal pancreatojejunostomy) are drainage operations, and Whipple operation (pancreaticoduodenectomy), duodenum-sparing Beger and Berne operations (pancreatic head resection), and distal pancreatectomy are surgical methods aimed at resection (363, 364).

Question F6-a: When is PERT applied?

Suggestion F6-a: PERT should be initiated immediately upon diagnosis of any patient with EPI. (Level of evidence: 1B; Power of suggestion: Strong consensus)

Comment: The overall goal of EPI therapy is to normalize digestion to improve survival and quality of life. PERT is recommended to patients with the diagnosis of CP who developed EPI and in the presence of clinical symptoms (weight loss, fatty stool, diarrhea, and dyspepsia) and/or laboratory findings (level of fat-soluble vitamins [vitamins A, D, E, and K], prealbumin, magnesium, etc.) associated with malabsorption (185). It is aimed to correct the signs and symptoms of malabsorption detected by treatment, to decrease the mortality and morbidity associated with this, and to improve survival and quality of life (137). If symptoms are certain, the patient can benefit from 4-6 weeks of PERT (365). Therefore, PERT should be applied to every patient with CP with EPI (185, 189, 366, 367).

Question F6-b: How is PERT performed?

Suggestion F6-b: PERT is recommended to be taken with enteric-coated, micro- or mini-microspheres in <2 mm size, initiated with the first bite of food at a dose of 40,000-50,000 European Pharmacopoeia (Ph Eur) units and taken in half the dose for snacks. (Level of evidence: 1B; Power of suggestion: Strong consensus)

Comment: For the ideal PERT, pancreatic enzymes should be met at a sufficient level, when and where necessary. Dose adjustment is based on lipase activity. When lipase released from the pancreas into the duodenum after a standard meal in physiological conditions is less than 10% of normal, fat digestion is impaired and steatorrhea observed (368). The minimum amount of lipase required for normal digestion is at least 30,000 international units (IU) (365, 368, 369, 370). Enzyme activity is evaluated in different units by different institutions. These units are Ph Eur, Fédération Internationale Pharmaceutique (FIP), and United States Pharmacopeia (USP). The amylase and protease units of these three units differ among themselves. Whereas 1 FIP unit for amylase equals 1 Ph Eur unit or 4.15 USP units, for protease, 1 FIP unit equals 62.5 USP units or 1 Ph Eur unit. However, this does not differ for lipase. In other words, 1 FIP unit for lipase, 1 Ph Eur unit, and 1 USP unit are equal. The efficiency of the preparations can be evaluated by assuming that 1 IU lipase is equal to 3 Ph Eur (371).

In ideal PERT, >30,000 Ph Eur units of lipase is intended to be <2 mm particle size considering the gastric motility and pyloric channel kinetics for homogeneous meeting with nutrients in the duodenum after meal. For this, pancreatic enzyme preparations are in the form of enteric-coated mini-microspheres (1-1.2 mm) or microspheres (1.8-2.0 mm). There are insufficient data on micro or mini tablets >2 mm. Although there are studies showing that the transition of mini-microspheres with nutrients to the duodenum is better than microspheres, there are not enough data to show its superiority (372).

Enzymes are inactivated at a pH of <5.5. Therefore, preparations should be enteric-coated to protect enzymes from stomach acid (373). Preparations that are not enteric-coated are less effective (374). Different enteric-coated microspheres are not bioequivalent in vitro, and there are not enough clinical studies describing in vivo bioavailability. In in vitro studies, the dissolution time of the preparations (49-71 minutes half-life) and their optimum pH (pH 5.0-5.8) vary (375, 376). In a double-blind, randomized, multicenter study, 10,000 Ph Eur unit microsphere and 10,000 Ph Eur unit mini-microsphere preparations were found to be equally effective in improving the coefficient of fat absorption (CFA) in patients with EPI because of CP. It was found that both preparations were well tolerated, and mild side effects (abdominal pain, headache, diarrhea, and infection) were similar in both treatment groups (377). In another randomized placebo-controlled study, the efficacy of Kreon 40,000 mini-microsphere tablets in EPI was investigated, and CFA, coefficient of nitrogen absorption, and daily stool amounts were compared in the patients receiving treatment and the placebo group. The drug was found to be more effective than placebo and was well tolerated. In the drug group, complaints of abdominal pain and bloating decreased (378). In recent randomized controlled trials, enteric-coated mini-microspheres are recommended to be taken at a dose of 40,000-80,000 Ph Eur units at main meals and half-dose in snacks (377, 379, 380-382).

PERT has characteristics in terms of dosage and frequency of application. It is recommended to be taken with the first bite at a meal. PERT is more effective when half of the dose is taken at the beginning and half of the dose at the middle of the meal. (380, 383).

Question F6-c: How should the response be evaluated?

Suggestion F6-c: The effectiveness of treatment is evaluated by improvement in clinical findings, in laboratory parameters, and in the level of fecal fat excretion. (Level of evidence: 1B; Grade of recommendation: A)

Comment: PERT is the corner stone of patient management with EPI. PERT provides a decrease in fecal fat excretion, weight gain, improvement in abdominal pain, and improvement in clinical symptoms and laboratory findings owing to malabsorption without significant side effects in the patient (384, 385). Significant improvement in maldigestion and nutritional status was achieved with PERT at a dose of 24,000 IU administered in EPI developed because of CP and/or pancreatic surgery. Patients who received treatment improved clinical symptoms, increased body weight, and decreased stool frequency (386). In a study with microbial lipase in liquid formulation applied in patients who need to be fed with a nasogastric tube, an increase in stool consistency was achieved while bloating and a decrease in the amount of fecal fat (387). Although its effect on long-term survival in CP has not been studied, PERT is known to increase survival rates in patients with irreversible pancreatic cancer and after pancreatic surgery (368, 388).

In patients who do not respond to treatment, pancreatic function tests (CFA or ^{13}C-MTG breath test) should evaluate the efficacy of the treatment and adequacy of the dose used (115, 366, 389). If fatty defecation continues with other clinical signs and laboratory findings related to malabsorption, the dose should be increased and PPI should be added if necessary.

Suggestion F6-d: PPI may be recommended in addition to treatment for those who do not respond adequately to enzyme replacement therapy. (Level of evidence: 2B; Power of suggestion: Weak consensus)

Comment: Pancreatic enzymes show their effects at maximum with a pH of >6. Their activities are significantly reduced at low pH. In duodenal acidification (gastric hyperacidity with or without diminished bicarbonate secretion), enzyme release from enzyme preparations decreases and activation of released enzymes decreases. With the use of drugs that inhibit the synthesis of stomach acid, gastric pH rises and the improvement of EPI symptoms can be increased by reducing the duodenal acidification and ensuring the effectiveness of PERT. In patients with CP with resistant steatorrhea, the addition of gastric acid blockers to PERT (373, 390) can be recommended. In one study, the effects of two different (10,000-20,000 IU) enteric-coated pancreatic enzyme preparations on fecal fat excretion and abdominal symptoms were investigated in patients with CP-induced EPI with omeprazole gastric acid inhibition. As a result, it was found that the abdominal well-being score of PPI users increased, and there was a significant decrease in fecal fat excretion (391). In another study, it was found that PPIs especially increase fat absorption and decrease fatty stool (392). In another study comparing the H2 receptor blocker and PPI, no difference was found between the drugs in terms of fat excretion (393). In a study in which the use of PERT alone or together with the PPI/H2 receptor blocker in patients with EPI was analyzed retrospectively in terms of efficacy and safety, no difference was found between the groups in terms of CFA levels. As a result, it has been shown that concomitant use of PERT

and PPI/H2 receptor blocker drugs does not increase PERT efficacy in the population of patients with EPI, and therefore, it is recommended that acid inhibitors should not be routinely co-administered with PERT (394).

Question F7: What should be considered in the treatment of pancreatogenic diabetes?

Suggestion F7: In patients with mild hyperglycemia (HbA1c < 8), metformin should be added to the treatment in addition to lifestyle change and pancreatic enzyme support. Insulin should be added for patients with severe hyperglycemia (HbA1c ≥ 8) or inadequate response to basal metformin therapy. In particular, one should be careful in terms of hypoglycemia when using insulin. (Level of evidence: 5; Power of suggestion: Weak consensus)

Comment: CP can include glucose intolerance, DM, and metabolic disorders. DM developing secondary to CP is called pancreatogenic DM (130). The purpose of pancreatogenic DM therapy is to prevent malnutrition, control the steator, and reduce meal-induced hyperglycemia. With PERT, an increase in insulin secretion and postprandial glycemia secondary to an increase in hormone incretin can be achieved. In addition, loss of fat-soluble vitamins can be prevented with enzyme support (28, 130, 395).

There are no studies showing the long-term efficacy and safety of hypoglycemic agents in CP. The main problem in pancreatogenic DM is insulin deficiency. Therefore, in most patients, insulin is the preferred treatment, but in patients with mild hyperglycemia (HbA1c < 8), hyperglycemia can be brought under control with oral agents (especially metformin). In patients with advanced hyperglycemia (HbA1c ≥ 8), it is recommended to use insulin and for the insulin dose to be similar to type 1 DM guidelines (130, 396, 397).

In a recent review, less and frequent feeding was recommended without skipping meals for pancreatogenic DM treatment. It has been found appropriate to give up alcohol and smoking and to avoid liquid drinks with a high glycemic index. After physical activity in patients who receive insulin and in patients with malnutrition and hypoglycemic symptoms, glucose measurement should be done frequently. PERT treatment should also be given at the appropriate dose (135).

Question F8: How should the approach to peripancreatic fluid collections be?

Suggestion F8: Peripancreatic fluid collections occurring during the course of CP are approached as in acute pancreatitis. Patients with pseudocysts can be monitored if they are not symptomatic, regardless of the size of the cyst. (Level of evidence: 5; Power of suggestion: Strong consensus)

Comment: Pancreatic pseudocyst (PPC) develops in approximately 13% to 30% of patients during the course of CP (398, 399). Classification of peripancreatic collections is made according to the revised Atlanta criteria, which were last adopted in 2011 (400). PPCs can regress spontaneously or disappear. Spontaneous regression rate differs from study to study and varies from 20% to 70% (401, 402). Although PPC size and patient complaints are correlated, they can be monitored for spontaneous regression if they are not symptomatic (403). If the cyst formation is before 4-6 weeks and is asymptomatic, it can be said that a consensus has been reached about not intervening with the cysts (404). It is important to differentiate small pancreatic cysts from malignant pancreatic cysts. If the PPCs are complicated (compression to abdominal vessels, gastric outlet or duodenal obstruction, jaundice because of cholesterol compression, PPC infection, development of hemorrhage in PPC, or pancreaticopleural fistula) and symptomatic (abdominal distension, nausea, vomiting, and pain), an intervention is required.

PPCs can be treated by percutaneous, endoscopic, or surgical (open, laparoscopic, or robotic) means. Endoscopic treatment options have lower morbidity and mortality than other treatment options and are cost-effective (405-410).

Question F9-a: What are the treatment indications for biliary stenosis in CP?

Suggestion F9-a: Endoscopic treatment is recommended in the presence of cholangitis and jaundice. In asymptomatic cases, if the ALP is ≥2 times normal and/or continues for ≥1 month, endoscopic treatment is recommended. (Level of evidence: 5; Power of suggestion: Strong consensus)

Comment: Benign biliary stenosis may develop because of the anatomical relationship of the main bile duct with the pancreatic head during the course of CP (411). The length of the intrapancreatic part of the choledoch varies from 1.5 to 6 cm, which can cause stenosis of varying lengths (412). The frequency of biliary obstruction has been reported to be 3% to 46% in the course of CP (413). Symptoms of biliary obstruction can be clinically faint or symptomatic (cholangitis, jaundice, and choledocholithiasis). In approximately 7.3%, secondary biliary

cirrhosis may develop. In asymptomatic patients, biliary drainage is recommended if ALP is detected for more than 1 month because of biliary stenosis and is ≥2 times higher than normal (414).

Question F9-b: What should be the stent preference?

Suggestion F9-b: Use of multiple plastic stents or FC-SEMS is recommended. The use of a single plastic stent is not recommended because of treatment failure and a high risk of complication. (Level of evidence: 5; Power of suggestion: Moderate consensus)

Comment: The use of a single plastic stent for endoscopic biliary drainage in patients with CP-related biliary obstruction is not recommended because of low success, high recurrence, and complication rates in previous studies (415-421). In studies conducted, biliary strictures are first dilated with a biliary bougie or balloon, and then multiple plastic stents (mostly 5-6) are attached to the stenosis area (245, 421-423). It is recommended in the literature to replace stents every 3 months (421, 424, 425).

In a randomized controlled study, long-term success rates (92% and 90%, respectively) of FC-SEMS and multiple plastic stents were found to be similar (423). FC-SEMS reintervention rate is lower, but stent migration can be encountered (426).

In a meta-analysis performed by Khan et al. (420), FC-SEMS was compared with multiple plastic stents in terms of improvement of stenosis, recurrence, and side effects. With FC-SEMS, the cumulative stenosis improvement rate was 83%, and the stenosis recurrence rate was between 15% and 17%. FC-SEMS is cost-effective and rework rates are lower. It has been observed that the recurrence rate decreases as stenting time increases, and keeping the stent for less than 6 months is associated with a high recurrence rate. In those with short biliary stenosis (<20 mm), stenting may be more successful than in long ones (246).

Question F9-c: When is the patient directed to surgery in the treatment of biliary stenosis?

Suggestion F9-c: Surgery may be recommended in patients who cannot respond after 1 year of stenting. (Level of evidence: 5; Power of suggestion: Strong consensus)

Comment: Patients who have relapsed biliary obstruction after 1 year of endoscopic biliary drainage may be offered surgical treatment, or it may be decided to continue endoscopic biliary drainage (427). However, there are insufficient data in the literature on this subject, and it has been seen in current studies that surgical indication and the selected surgical method vary from center to center.

In a retrospective study comparing surgery with endoscopic biliary drainage treatment, multiple plastic stents or metal stents were used for endoscopic biliary drainage. Patients who had multiple plastic stents were given an endoscopic control every 3 months, and stent replacement was achieved; the metal stents of the patients were replaced every 6 months. Surgical treatment was recommended for patients who developed recurrence after 12 months of follow-up, and endoscopic biliary drainage treatment was continued in patients who did not accept surgical treatment or had contraindications for surgery. At the end of the 2-year follow-up, the rate of patients still having good biliary drainage was 15% in the endoscopic biliary drainage group, whereas this rate was 66% in those with surgical biliary drainage (422).

Question F10: How should thrombotic complications be followed and treated?

Suggestion F10: Follow-up is recommended in asymptomatic patients who develop SVT on CP background. In acute thrombosis, anticoagulation may be considered in patients where collaterals do not develop and if they are not contraindicated. (Level of evidence: 4; Power of suggestion: Strong consensus)

Comment: SVT is relatively common in CP cases. In these cases, the most important reasons leading to the decision of treatment are potential gastroesophageal variceal bleeding risk and, to a lesser extent, issues because of hypersplenism such as anemia, fatigue, and abdominal mass (splenomegaly). In times when endovascular interventions haven't been established in clinical practice yet, splenectomy could be applied even in asymptomatic patients. However, in the natural course of these patients, the need for splenectomy decreases with the relatively low incidence of GI system bleeding (4%) and effective treatment of gastroesophageal variceal bleeding with endoscopic hemostatic techniques. Therefore, follow-up is recommended in asymptomatic patients (428, 429). Sclerosanes and cyanoacrylate are used in the treatment of gastric varices that have a lower bleeding risk but have more severe bleeding and higher mortality rates than esophageal varices (430, 431). Cyanoacrylate injection and coil applications, accompanied by EUS, which facilitate access to mediastinal and abdominal vessels, are increasingly used with high success and low complication rates, alone or in combination (432-437).

In patients who underwent pancreatic surgery without splenectomy, the resolution rate in thrombus is low (<40%), and the rate of development of variceal bleeding (29%) is higher than the risk of bleeding in the natural course (15%) (438). Moreover, the addition of splenectomy to surgery does not cause a significant increase in morbidity and mortality and prevents variceal bleeding in patients with CP who will undergo pancreatic surgery and have splenic venous thrombosis (439, 440). For this reason, adding splenectomy for patients who will undergo surgery for other reasons, those who have gastroesophageal variceal bleeding, or patients who have an increased risk of bleeding will benefit the patient.

There are insufficient data on the use of anticoagulant therapy in thrombosis accompanied by pancreatitis. Gastric variceal bleeding has been reported, especially in cases of aggressive anticoagulation therapies. However, it should be kept in mind that thrombosis is a life-threatening and more dangerous complication than bleeding (439). In one study, thrombophilia was detected in 18% of patients with recurrent acute pancreatitis (73% CP) with extrahepatic portal venous thrombosis. In this study, recanalization was observed only in 19% of patients (8/41 patients) with recent thrombosis, and 62.5% (5/8 patients) of them were reported to use anticoagulant therapy (441). In other studies, it was concluded that the use of anticoagulants in patients with acute pancreatitis in the treatment of splanchnic and non-splanchnic venous thrombosis in the acute thrombotic episode does not increase bleeding risk and mortality compared with those who do not use anticoagulants; however, it was concluded that it had no significant effect on recanalization rates (442-444). Anticoagulant therapy is not recommended in these patients, because there is not enough study on the efficacy and risk of anticoagulant therapy in patients with CP accompanied by thrombosis. However, based on the results of studies involving patients with acute pancreatitis and previous experience, anticoagulant therapy can be decided based on the duration of thrombosis and the general health of the patient. Anticoagulant therapy can be applied in patients with acute venous thrombosis who do not have collaterals and have no contraindications for anticoagulant use, paying attention to the risk of bleeding (especially in the presence of a pseudocyst).

Question F11: How should a pseudoaneurysm be treated?

Suggestion F11: Angiography and arterial embolization should be performed to stop pseudoaneurysm bleeding. Surgery is recommended for unstable patients and cases where arterial embolization fails. (Level of evidence: 4; Power of suggestion: Strong consensus)

Comment: In patients who develop a pseudoaneurysm because of CP, timely and proper treatment is important because of the risk of life-threatening bleeding. There are no randomized, controlled, and prospective studies in the literature. There is a systematic review on this subject between 1995 and 2012, which generally includes retrospective studies, mostly single-center and observational studies (445).

In the years with low embolization experience, surgical treatment was recommended as the first-line treatment because the success rate was lower (20% versus 88.9%, respectively) and mortality was the same (33% versus 33%, respectively) (170, 446). However, except for early studies, outcomes in surgical and non-surgical interventions were similar, and mortality was found to be higher in surgical groups (50%-100%) than embolization treatments (13%-50%). In recent studies, it is seen that embolization is the first-line treatment (46%-92%) with modern minimally invasive interventional methods, and surgical treatment is applied in unsuccessful embolizations or hemodynamically unstable patients (445). The success rate with angioembolization varies according to the bleeding location (80% in pancreatic head circumference bleedings and 50% in the splenic artery), an average of 67%, but the success rate increased to 95% between 2000 and 2005. The recommended treatment method in hemodynamically stable patients with CP with bleeding pseudoaneurysm is immediately performing an angiography to detect the bleeding site and, if possible, embolization. Angioembolization and then endoscopic drainage with ERCP have a high chance of success in patients with CP with pseudoaneurysm in the presence of a pseudocyst (447). Endovascular metallic coil and stents are used frequently and with high success in the treatment of pseudoaneurysm. In the absence of treatment, mortality approaches 90% (448).

As another method, direct thrombin injection into the pseudoaneurysm by entering from the femoral artery reaches a success rate of 97%. There are few case reports or series where EUS-guided glue injection and coil embolization were applied alone or in combination in the treatment of CP-associated pseudoaneurysm bleeding (176, 449-451). Although data are limited, it is a promising technique. It can be used safely as a first-line treatment option with high technical and clinical success rates, especially in cases that cannot be reached endovascularly and in patients with high surgical risk (452).

In patients with surgical indications, embolization can be applied as a bridge therapy in the interim period until appropriate conditions are established. In hemodynamically unstable cases, surgery is indicated if embolization is not possible or fails, but perioperative morbidity (bleeding) is high. Emergency hemostatic surgery is performed in patients who undergo surgery because of hemodynamic disorder, according to the general condition and anatomical condition of the patient (vascular ligation in the head of the pancreas, distal resection if there is bleeding in the splenic artery or its branches). Partial pancreatic resection is more reliable only in preventing recurrence of hemorrhage compared with surgical intervention control of the bleeding vessel. Whether embolized or operated, recurrent embolization can be performed for recurrent bleeding (178, 447, 453).

Question G1-a: What are the risk factors for pancreatic cancer development with a background of CP?

Suggestion G1-a: Advanced age, smoking, alcohol use over 80 g/day, and hereditary and tropical pancreatitis are risk factors for cancer development in these patients. (Level of evidence: 4; Power of suggestion: Strong consensus)

Comment: The etiology of pancreatic cancer is not defined clearly yet. Hereditary pancreatitis is strongly linked to pancreatic cancer. Tobacco or alcohol use and high body mass index are other risk factors for pancreatic cancer in the general population (454). Zhang et al. (455) first reported the relationship between CP and pancreatic cancer. There are scanty amount of studies to define risk factors of those patients with CP to develop pancreatic cancer (456-461). These studies showed advanced age, tobacco use, and alcohol consumption (>80 g/day) as significant risk factors (454). In fact, all causes of CP may also be considered as risk factors for pancreatic cancer in the long term, as well. The relationship of chronic inflammation with organ-specific cancers may also be relevant for CP and pancreatic cancer. In a recent meta-analysis, it was stated that cancer risk in CP increased significantly. This risk is 16 times higher in the first 2 years and 8 times higher in 5 years. Although the risk rate slows within years, it still four times higher in the 10th year (462-464).

Question G1-b: Should patients be screened for pancreatic cancer?

Suggestion G1-b: Although the risk of pancreatic cancer is known to increase in CP, there is no ideal cost-effective method and time for screening. Patients with hereditary pancreatitis should be screened for high risk. (Level of evidence: 4; Power of suggestion: Strong consensus)

Comment: Although there is a strong relationship between CP and pancreatic cancer, less than 5% of patients with CP develop pancreatic cancer during 20 years of follow-up. This risk is more apparent in hereditary forms. In addition, the risk attributed to society is 1.34% (465). Because this rate is less than 5%, screening and prevention programs are not recommended by the International Pancreatic Cancer Consortium. One reason for this is the lack of adequate, reliable, cost-effective early detection and screening methods (456). Therefore, screening is recommended only in patients with hereditary pancreatitis or for clinical research purposes. Among the methods to be used for screening, EUS and MR are primarily preferred; less frequently, CT and ERCP can only be used in selected cases (456, 466).

Question G1-c: Should metformin be recommended to prevent pancreatic cancer development?

Suggestion G1-c: Metformin should be preferred in patients with diabetes with a background of CP, as it reduces the risk of developing pancreatic cancer. (Level of evidence: 2D; Power of suggestion: Strong consensus)

Comment: Pancreatic cancer ranks fifth among the causes of death worldwide and fourth among cancer-related deaths, and its 5-year survival is below 5%. The main risk factors for the development of pancreatic cancer are smoking, heavy alcohol consumption, DM, CP, family history, diet, and endocrine factors. The relationship between pancreatic cancer and DM is complex and bidirectional. Although long-term DM is a risk factor for pancreatic cancer, newly diagnosed DM can be a result of pancreatic cancer. Pancreatic cancer can cause DM by destroying islet cells or by causing peripheral insulin resistance through increased islet amyloid polypeptide (455-458, 461).

The relationship between CP, DM, and pancreatic cancer is multifactorial. In the course of CP, DM develops in at least 20% of cases. Pancreatogenic DM accounts for 5% to 10% of the diabetic population in Western societies (135, 460). Metformin is one of the most commonly used oral antidiabetic drugs in the treatment of type 2 DM. One of the mechanisms explaining its possible antitumor effect is that it reduces insulin resistance and hyperinsulinemia by affecting insulin-like growth factor 1 path. Another mechanism is that it can inhibit the growth of cancer cells by affecting the signal path of the liver kinase B1–AMP-activated protein kinase–mammalian target of rapamycin pathway, which regulates the energy metabolism and protein synthesis of cells. In addition, its ability

to suppress tyrosine kinase receptors (human epidermal growth factor receptor [HER]1 and HER2), its having antioxidant and anti-inflammatory effects, and the fact that it can kill cancer stem cells are among the mechanisms that explain the possible antitumor effect of metformin (454-456).

According to the results of the meta-analysis conducted by Wang et al. (466), it has been shown that the use of metformin in patients with type 2 DM significantly decreased the risk of pancreatic cancer (RR, 0.63; 95% CI, 0.46-0.86, p=0.003). In another meta-analysis involving 37 studies involving individuals with type 2 DM, it has been shown that the use of metformin does not make a difference in terms of prostate cancer, but it reduces the risk of liver, pancreas, colorectal, and breast cancer at the rates of 78%, 46%, 23%, and 6%, respectively, and has a positive effect on mortality (454). In a cohort study conducted to investigate the effects of these drugs on cancer risk in patients using metformin and sulfonylurea, the risk of pancreatic cancer decreased in the metformin group, but no such effect was observed in the sulfonylurea group (467). In another meta-analysis evaluating the effects of metformin on cancer risk in patients with diabetes, it has been shown to reduce the risk of all cancers, including pancreatic cancer, by 31% (468).

In another meta-analysis evaluating the effect of metformin, sulfonylureas, insulin, and thiazolidinediones on the risk of pancreatic cancer, it was concluded that the sulfonylurea group increased the risk of pancreatic cancer, whereas others did not have an effect on the development of pancreatic cancer (469). Apart from these, although there are many studies showing that metformin increases survival in patients with pancreatic cancer, there are no studies evaluating the effect of metformin in patients with CP (457, 462-465).

Considering the relationship between CP, DM, and pancreatic cancer, the use of metformin can be recommended in patients with diabetic CP based on the above studies.

Question H: What are the factors affecting prognosis?

Suggestion: Factors affecting prognosis in CP are age, continued alcohol use, smoking, malignancy, and male sex. (Level of evidence: 2D; Power of suggestion: Strong consensus)

Comment: CP is known to significantly reduce the quality of life and life expectancy. Treatment and monitoring of symptoms and complications that may occur throughout life are required.

When the studies determining the prognosis were examined, patients were followed up for 6 years with the Chronic Pancreatitis Prognosis Score developed and validated in a cohort study in the literature. According to the results of this study, although the rate of hospitalization has increased (30%), it has been observed that the mortality rate has increased from 12.8% to 19.8% within the 6.3-9.8 year observation period (470, 471). In another community-based study examining the natural course of CP, patients were followed up for 10 years and it was found that only 20% of patients needed invasive therapeutic procedures. One of the most important results of this study is pain in CP because of alcohol, recurrent acute pancreatitis attacks, pseudocyst development, and higher frequency of EPI. Accordingly, the profile of the disease was found to be more serious in alcoholic CP. However, in this study, the total life span of both groups was not found to be different (32). In another study showing that the average life expectancy in CP is 8 years shorter than the general population, 11,972 patients with alcoholic and non-alcoholic CP were examined, and it was shown that mortality increased with age. Mortality is higher in patients who receive the diagnosis of CP at an early age such as hereditary pancreatitis than in those diagnosed as having CP at an advanced age. It is more possible for the elderly to achieve lifestyle change better than young people, to adapt to the diabetes diet, to leave negative habits such as alcohol and smoking, and to modify the prognosis in this way. In this study, the mortality rate was reported to be 46% in patients with alcoholic CP (471). In another study investigating the effect of age on prognosis, various age groups were studied in terms of death risk and life span. Accordingly, compared with patients diagnosed before the age of 40 years, it has been shown that the risk of death increases between 2.3 and 6.3 times in patients of middle and advanced age. When simultaneous alcohol consumption and tobacco use were added to this group, the risk was shown to increase even more (472). In another study investigating the risk factors affecting CP prognosis, the natural courses of 2,037 patients were followed and it was found that alcoholic CP showed a more serious course. This study is important for emphasizing the differences between alcoholic CP and non-alcoholic CP. In this study, it has been showed that male sex and cigarette smoking rates are higher in patients with alcoholic CP and these patients are younger than those with non-alcoholic CP (153). Average life expectancy in alcoholics has been reported to be 20-24 years after diagnosis in other studies (473-475).

Because smoking and alcohol consumption are common behaviors, together they can also contribute to the development of CP. In a study of 108 patients with alcoholic CP who smoke, smoking has been shown to increase the progression of the disease in a dose-dependent manner, regardless of the level of alcohol consumed (476). In a meta-analysis, smoking has been shown to increase the risk of CP in a dose-dependent manner (37). In another study in which risk factors were evaluated and 3 million individuals were included in the analysis, active smoking was shown to increase the risk of CP by 1.87 times (RR, 1.87; 95% CI, 1.54-2.27) (477).

CONCLUSION

Chronic pancreatitis is a chronic fibroinflammatory disease of the pancreas. Although its etiology is multifactorial, the most common factor is alcohol. Abdominal pain is common, and it reduces the quality of life of patients. Weight loss and malnutrition are other important clinical findings noted during the course of the disease. Early diagnosis can be especially difficult. It is important to diagnose CP and EPI and to start the appropriate treatment on time to protect the patient from long-term morbidities such as malnutrition, pancreatogenic DM, and pancreatic cancer and to improve the quality of life. Multidisciplinary approach is essential in its diagnosis and treatment.

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