Pancreatology 20 (2020) 579–585

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

International Consensus Guidelines for Risk Factors in Chronic Pancreatitis. Recommendations from the working group for the international consensus guidelines for chronic pancreatitis in collaboration with the International Association of Pancreatology, the American Pancreatic Association, the Japan Pancreas Society, and European Pancreatic Club

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ARTICLE INFO

Article history:
Received 20 December 2019
Received in revised form

ABSTRACT

Background: Chronic pancreatitis (CP) is a complex inflammatory disease with remarkably impaired quality of life and permanent damage of the pancreas. This paper is part of the international consensus guidelines on CP and presents the consensus on factors elevating the risk for CP.

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https://doi.org/10.1016/j.pan.2020.03.014

10 March 2020
Accepted 22 March 2020
Available online 8 April 2020

Keywords:
Definition
Classification
Risk factors
Genetics
Treatment

Methods: An international working group with 20 experts on CP from the major pancreas societies (IAP, APA, JPS, and EPC) evaluated 14 statements generated from evidence on four questions deemed to be the most clinically relevant in CP. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was used to evaluate the level of evidence available per statement. To determine the level of agreement, the working group voted on the 14 statements for strength of agreement, using a nine-point Likert scale in order to calculate Cronbach's alpha reliability coefficient.
Results: Strong consensus and agreement were obtained for the following statements: Alcohol, smoking, and certain genetic alterations are risk factors for CP. Past history, family history, onset of symptoms, and life-style factors including alcohol intake and smoking history should be determined. Alcohol consumption dose-dependently elevates the risk of CP up to 4-fold. Ever smokers, even smoking less than a pack of cigarettes per day, have an increased risk for CP, as compared to never smokers.
Conclusions: Both genetic and environmental factors can markedly elevate the risk for CP. Therefore, health-promoting lifestyle education and in certain cases genetic counselling should be employed to reduce the incidence of CP.

Introduction

Chronic pancreatitis (CP) is a heterogeneous inflammatory disease, which can develop via multiple pathological mechanisms and can have diverse clinical presentations. Frequently, recurrent acute attacks precede CP and pain is the most disabling symptom [1]. Quality of life is remarkably impaired in CP, one third of the patients are unable to work. For these patients, the main goal of treatment is pain reduction since pain is the most important factor that influences the quality of life in CP [2–6]. However, in a number of cases, CP develops silently without acute episodes and/or significant pain, and clinical care is focused primarily at the management of the endocrine and exocrine insufficiency [7]. CP patients without prior acute pancreatitis appear to be significantly older and may have distinct risk factors such as a so far unknown genetic variants. For etiologic classification of CP, the TIGAR-O system has been most commonly used, with etiologies categorized as toxic-metabolic, idiopathic, genetic, autoimmune, recurrent and/or severe acute pancreatitis-associated, and obstructive [8]. Toxic-metabolic causes include alcohol [9–12], smoking [13,14], hypercalcemia [15–17], hyperlipidemia [18,19], chronic renal failure [20,21], medications, and toxins [22]. While smoking is considered an independent risk factor for CP, a large population study indicated that alcohol can have a bidirectional effect. Thus, moderate alcohol consumption (less than 2 drinks per day in men) was found to be protective, whereas heavy drinking (more than 4 drinks per day in men) was shown to be a risk factor for CP [10,23]. These data suggest that recording an accurate medical history is important for the identification of the correct etiology. An incorrectly applied diagnosis of alcoholic CP may stigmatize the patient and delay the recognition of the true disease cause [10,23]. Idiopathic cases include those with early onset, late onset, or tropical [24]. Genetic etiology includes clinically significant, pathogenic mutations or other alterations in risk genes [25,26] (in alphabetical order) *CEL* [27], *CFTR* [28,29], *CPA1* [30,31], *CTRC* [32], *PRSS1* [33,34] and *SPINK1* [35–37]. Autoimmune processes include both isolated and syndromic occurrences. Cases complicating recurrent or severe acute pancreatitis-associated CP may have post-necrotic, vascular/ischemic, or post-irradiation etiologies. Obstructive causes include divisum, sphincter of Oddi disorders, duct obstruction, and posttraumatic pancreatic duct scars. The M-ANNHEIM system classified risk factors for CP into 7 categories, specifically alcohol consumption (excessive >80 g/d; increased, 20–80 g/d; and moderate, <20 g/d; nicotine consumption; nutritional factors such as calorie derived from fat and protein, and hyperlipidemia; hereditary factors responsible for some familial, idiopathic, and tropical cases; efferent duct factors including pancreas divisum, annular pancreas, other congenital abnormalities of the pancreas predisposing to pancreatic duct obstruction, posttraumatic pancreatic duct scars, and sphincter of Oddi dysfunction; autoimmune pancreatitis; miscellaneous metabolic and toxic disorders including hypercalcemia, hyperparathyroidism, chronic renal failure, and drugs, or toxins [38].

Several different treatment guidelines on CP exist [39–46], however, there is a clear lack of consensus on the risk factors elevating the incidence of CP. Our aim was to create a consensus guideline that is international and multidisciplinary, from development and early diagnosis to progression and treatment of CP. During the EPC2016 conference the four major pancreatic societies, namely the International Association of Pancreatology (IAP), American Pancreatic Association (APA), Japan Pancreas Society (JPS) and the European Pancreatic Club (EPC) have decided to develop an evidence based management guideline on CP. International experts were identified to have a multidisciplinary representation within subgroups focusing on 16 key topics of CP. The first major step was the agreement on a new mechanistic definition of CP [1].

Thereon several parts of the consensus guidelines have been published, covering the early diagnosis of CP [1], imaging of CP [47] and understanding and management of pain [2]. This manuscript is another part of the international consensus guidelines, covering the topic on risk factors in CP and is meant to guide the clinical practitioners and surgeons in the treatment and education of patients with CP.

Methods

Twenty experts on CP were appointed. PH and MST were chosen as chairs of the group. Based on a review of data from the relevant literature all experts presented their perspectives on risk for CP. The method of the systematic literature review has been previously described [10]. The international experts evaluated fourteen statements generated from evidence of the relevant literature.

Grading

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was used to evaluate the level of evidence per statement (see http://www.uptodate.com/home/gradingtutorial). Quality assessment of evidence was graded as 'high' if there was (very) low probability of further research substantially changing the conclusions, 'moderate' if further research

might completely change the conclusions, and 'low' if further research was likely to completely change the conclusions. The strengths of the recommendation were graded as 'strong' if it was very certain that benefits outweigh risks and burdens, 'weak' if risks and burdens appear to be finely balanced, or when benefits, risks, and burdens are closely balanced or uncertain, or 'conditional' if it was in between strong and weak recommendation.

Consensus

After grading, the working group of international experts voted on the 14 statements for strength of agreement, using a nine-point Likert scale. Out of the results, a Cronbach's alpha reliability coefficient was calculated per statement (http://hdl.handle.net/1805/344). The voting results were classified for agreement as either; 'strong' if 80% of votes were 7 or above, 'conditional' if 65% of votes were 7 or above, and 'weak' less than 65% of votes were 7 or above. In addition, comments to each question and statements were compiled to explain the surrounding issues, supported by key references. All statements and comments were reviewed by all authors to ensure the general relevance and applicability of the conclusions. Eventually a final draft of the document was generated and circulated to all authors for final editing and approval.

Results

Q-1. What are the risk factors for CP?

Statement-1: Alcohol, smoking, and certain genetic alterations are risk factors for CP.

Quality assessment: high; Recommendation: strong; Agreement: strong ($\alpha = 100\%$)

Comments

Many authors have reported alcohol to be a particularly important risk factor. Evidence also suggests a positive association of cigarette smoking with development of pancreatitis, independently of alcohol. A systematic review and meta-analysis based on 6 studies of a total population of 146,517 including 1,671 persons with pancreatitis showed a smooth curve representing as approximately exponential dose-response relationship between average amount of alcohol consumed and occurrence of pancreatitis [9]. Individuals consuming 36 g of alcohol per day had a relative risk (RR) of 1.2 (95% confidence interval or CI, 1.2–1.3) compared with non-drinkers, while those consuming 96 g per day had a four-fold increased risk of pancreatitis (relative risk 4.2, 95% CI, 3.1–5.7) [9]. A case-control study in Japan showed that long-term alcohol consumption for over 35 years was associated with increased risk (odds ratio or OR = 4.0) [48]. A recent meta-analysis showed that dose-response relationships between alcohol consumption and risk of pancreatitis were curvilinear for CP and acute pancreatitis in men but non-linear for acute pancreatitis in women [10]. In addition, a large population-based prospective study in the USA showed that moderate alcohol consumption (<24 ethanol g/day or <2 drinks/day) is associated with a lower risk of RAP/CP (hazard ratio 0.57, 95% CI 0.41–0.79), whereas heavy drinking (>48 ethanol g/day or >4 drinks/day) results in elevated risk of RAP/CP (hazard ratio 1.50, 95% CI 0.94–2.39) in men.

A meta-analysis concerning smoking assessed 10 case-control studies and 2 cohort studies concluding that tobacco smoking may increase risk of developing CP [13]. Compared to lifelong nonsmoker, pooled risk estimates for current smokers were 2.8 (95% CI, 1.8–4.2) overall and 2.5 (95% CI, 1.3–4.6) when data were adjusted for alcohol consumption. In a recent systematic review and meta-analysis examining 22 studies [49], summary relative risks and 95% CI for CP for all subjects who ever smoked, current smokers and former smokers respectively were 3.00 (1.46–6.17), 2.72 (1.74–4.24), and 1.27 (1.00–1.62), respectively. In a case-control study including 241 patients, smoking was associated with pancreatic exocrine insufficiency, (odds ratio and 95% CI, 2.4 and 1.17–5.16), calcifications (2.33 and 1.10–4.95), and major morphologic changes (3.41 and 1.31–8.85) [50].

In a prospective long-term study of 227 patients with alcoholic CP followed over 18 years, 54.2% were overweight before disease onset and 15.0% were obese, compared with 37.7% (3.1%) in a contemporary male control population. The authors concluded that obesity may be an additional risk factor for alcoholic CP [51].

Mutations or other alterations in susceptibility genes increase risk for both alcoholic and non-alcoholic disease [52–54]. Highly penetrant, strong genetic variants (e.g. *PRSS1* and *CPA1* mutations) may cause autosomal dominant hereditary pancreatitis, while the majority of variants are associated with sporadic disease with no family history. The effect size tends to be smaller for alcoholic CP. Genetic testing should target risk genes with relatively strong effects; which currently include *CEL, CFTR, CPA1, CTRC, PRSS1* and *SPINK1*. Although common variants in *CLDN2*, an inversion at the *CTRB1-CTRB2* locus, and a variant in the *PRSS1* promoter modify risk in alcoholic and non-alcoholic disease, the small effect size and the high frequency of these genetic changes limit their utility in determining genetic etiology. Similarly, testing for a protective variant in *PRSS2* is not helpful clinically. A summary table of risk genes and alleles in CP can be found in Table 1.

Frequency of progression from acute pancreatitis to CP was reported in a meta-analysis where 10% of patients with a first episode of acute pancreatitis and 36% of patients with recurrent acute pancreatitis developed CP [55]. In a cohort study including 352 patients with acute pancreatitis, progression of pancreatitis occurred in 85 patients during follow-up (24.1%); 48.2% of cases becoming chronic originated as alcoholic acute pancreatitis, 47.0% as idiopathic acute pancreatitis, and 4.8% as acute pancreatitis with another cause. Smoking plus drinking over 20 g of alcohol was the strongest risk factor for progression (hazard ratio, 3.18; 95% CI, 1.06–9.55) [56]. Notably, in a number of patients CP develops without a preceding acute pancreatitis attack [7].

Autoimmune pancreatitis has been considered a risk factor for CP. However, high-level evidence such as meta-analysis data is not available. In a case-control study including 69 patients with autoimmune pancreatitis, multivariate analysis identified Wirsung and Santorini duct narrowing at diagnosis as a significant independent risk factor for pancreatic stone formation (odds ratio, 4.4; P = 0.019) [57]. Autoimmune pancreatitis indeed may progress to CP.

Pancreas divisum causing drainage impairment can be

Table 1
Risk genes and alleles in chronic pancreatitis. Allele frequency and effect size are shown for European non-alcoholic patient populations. Risk size estimates are given for heterozygous variants unless indicated otherwise. Common haplotypes associated with chronic pancreatitis at the *CLDN2, CTRB1-CTRB2* and *PRSS1-PRSS2* loci are not listed.

Gene symbol	Typical variants	Frequency	Risk effect
PRSS1	p.N29I, p.R122H	4%	>300-fold
CPA1	p.V251 M, p.N256K	3%	25-fold
SPINK1	p.N34S, c.194+2T>C	10%	15-fold
CTRC	c.180C>T (p.G60 =) homozygous	4%	10-fold
	p.R254W, p.K247_R254del	2%	5-fold
CEL	*CEL-HYB1* hybrid allele	4%	5-fold
CFTR	p.F508del, p.R117H	10%	3-fold

considered a risk factor for CP [57,58]. In a cohort study, multivariate analysis identified pancreas divisum as an independent risk factor for recurrent acute pancreatitis (odds ratio, 11.5; 95% CI, 1.6–83.3) [59].

Q-2. What should be done to determine the risk factors/etiology for CP at the time of diagnosis?

Statement-2. Past history, family history, onset of symptoms, and life-style factors including alcohol intake and smoking history should be determined.

Quality assessment: high; Recommendation: strong; Agreement: strong ($\alpha = 100\%$)

Statement-3. Laboratory data including serum triglycerides, calcium, IgG4, and possible morphologic abnormalities of the pancreas including pancreas divisum might be assessed.

Quality assessment: low; Recommendation: weak; Agreement: strong ($\alpha = 89.5\%$)

Statement-4. In idiopathic disease, full sequence analysis of the *CFTR, CPA1, CTRC*, *PRSS1* and *SPINK1* gene exons and exon-intron boundaries and testing for the *CEL* gene pathogenic hybrid allele is recommended in order to explore the genetic background.

Quality assessment: low; Recommendation: conditional; Agreement: conditional ($\alpha = 73.7\%$)

Comments

The etiology of CP has been considered by meta-analyses and, alternatively, by reviews of population-based epidemiologic data; risk of CP is multifactorial with strong likelihood of interaction among the various factors [8,13,38]. Determination of risk factors and etiology for CP at the time of diagnosis is important for treatment and prevention of recurrence, because continuing alcohol abuse and smoking are associated with disease progression. However, individual risk factors can be difficult to isolate, because the factors are influenced by associations and interactions.

Alcohol has been identified as a definitive risk factor of CP [60]. Persons who drink 80 g or more of alcohol per day over 6–12 years are at risk of developing CP [9]. Obtaining as accurate alcohol intake history is extremely important. As smoking is another important risk factor for CP [13], a detailed smoking history should be obtained.

Laboratory data including serum triglycerides, calcium, and IgG4 might be assessed at the time of diagnosis [57,61]. Morphology of the pancreas might be examined by imaging to diagnose pancreas divisum [59].

CP can be a genetic disease and the yield of genetic testing is high, particularly in pediatric and early-onset cases. Genetic testing can help with the determination of etiology and may guide therapeutic choices such as total pancreatectomy, which is more likely to be performed if underlying genetic risk has been demonstrated. As carriers of *SPINK1* variants often exhibit more rapid progression; genetic testing also has prognostic value. Patients with *CFTR* variants may benefit from the novel CFTR-modifying drugs once these become available for the treatment of CP. Robust development of sequencing technology continuously decreases costs of testing, which should not be a limiting factor any more.

Q-3. How much alcohol consumption can be considered as risk factor/etiology for CP?

Statement-5. Alcohol consumption dose-dependently elevates the risk of CP. Heavy drinkers have some 5 times more chances to develop CP than non-alcohol consumers.

Quality assessment: moderate; Recommendation: strong; Agreement: strong ($\alpha = 100\%$)

Statement-6. Alcohol consumption of less than 60 g/day increases the risk and promotes the progression of CP in susceptible individuals.

Quality assessment: low; Recommendation: conditional; Agreement: weak ($\alpha = 63.2\%$)

Statement-7. Alcohol consumption of equal to or more than 60 g/day increases the risk of CP.

Quality assessment: moderate; Recommendation: strong; Agreement: strong ($\alpha = 100\%$)

Statement-8. The effects of alcohol seems to be independent of smoking.

Quality assessment: low; Recommendation: conditional; Agreement: conditional ($\alpha = 73.7\%$)

Statement-9. Alcohol abuse increases the risk of progression from acute pancreatitis to CP. After an acute attack of pancreatitis almost half of alcohol abusers develop CP. Figures rise to 80% after recurrent pancreatitis.

Quality assessment: moderate; Recommendation: strong; Agreement: strong ($\alpha = 89.5\%$)

Comments

Alcohol misuse is the most common single cause of CP and accounts for approximately 45%–70% of CP cases in industrialized nations worldwide [62]. The Zurich conference defined alcoholic CP which developed following a daily intake of alcohol >80 g/day for several years [63]. Only 2–5% of heavy drinkers develop pancreatitis [62,64]. The increased risk of CP in individuals who consume equal to or more than 5 drinks/day has been consistently demonstrated. The North American Pancreatitis Study-2 [65] revealed a significant association between alcohol and CP only in subjects who consumed $\geq$5 drinks/day (odds ratio: 3.1). A population-based cohort study in Denmark [66] showed alcohol intake of 35–48 drinks/week increased the risk of CP (Hazard ratio: 3.2). In Japanese case-control studies [48,67], the risk of CP was higher even with a smaller amount of alcohol. The odds ratio was 5.7 for alcohol consumption of 50–99 g/day [6]. In another Japanese case-control study [67], alcohol consumption of even 20$\leq$~<40 g/day increased the risk of CP compared with nondrinkers; the odds ratios for alcohol consumption of 20$\leq$~<40 g/day, 40$\leq$~<60 g/day, 60$\leq$~<80 g/day, 80$\leq$~<100 g/day, and $\geq$100 g/day were 2.6, 3.2, 9.2, 13.0, and 19.6, respectively. A systematic review and meta-analysis of these 4 studies [48,65–67] showed that the risk of CP increased monotonically according to the average alcohol consumption with no identifiable threshold (relative risks at 25 g/day = 1.58, 50 g/day = 2.51, 75 g/day = 3.97, and 100 g/day = 6.29) [10]. One unit of alcohol equals 10 ml or 8 g of pure (100%) ethanol. In USA, 1 drink equals 14 g of pure (100%) ethanol or 1.75 units [65].

Although associations were similar for men and women [66,67], susceptible women might develop alcoholic CP after a shorter duration of alcohol consumption and lower cumulative amounts of alcohol consumption than men [68]. Alcohol intake, even less than 50 g/day, induced earlier disease characterized by more frequent severe pain, calcification, and complications [69].

Q4. How much smoking can be considered as risk factor/etiology for CP?

Statement-10. Ever smokers (even smoking less than 1 pack of cigarettes per day) have an increased risk for CP, as compared to never smokers.

Quality assessment: moderate; Recommendation: strong; Agreement: strong ($\alpha = 89.5\%$)

Statement-11. There seems to be a dose-response effect for the amount of daily consumption on the risk to develop CP.

Quality assessment: low; Recommendation: conditional;

Table 2
Summary of the statements.

	STATEMENT	QUALITY ASSESSMENT	RECOMMENDATION	AGREEMENT (alfa%)
1.	Alcohol, smoking, and certain genetic alterations are risk factors for chronic pancreatitis.	high	strong	strong (100%)
2.	Past history, family history, onset of symptoms, and life-style factors including alcohol intake and smoking history should be determined.	high	strong	strong (100%)
3.	Laboratory data including serum triglycerides, calcium, IgG4, and possible morphologic abnormalities of the pancreas including pancreas divisum might be assessed.	low	weak	strong (89.5%)
4.	In idiopathic disease, full sequence analysis of the *CFTR, CPA1, CTRC*, *PRSS1* and *SPINK1* gene exons and exon-intron boundaries and testing for the *CEL* gene pathogenic hybrid allele is recommended in order to explore the etiological background.	low	conditional	conditional (73.7%)
5.	Alcohol consumption dose-dependently elevates the risk of CP. Heavy drinkers have some 5 times more chances to develop chronic pancreatitis than non-alcohol consumers.	moderate	strong	strong (100%)
6.	Alcohol consumption of less than 60 g/day increases the risk and promotes the progression of CP in susceptible individuals.	low	conditional	weak (63.2%)
7.	Alcohol consumption of equal to or more than 60 g/day increases the risk of CP.	moderate	strong	strong (100%)
8.	The effects of alcohol seems to be independent of smoking.	low	conditional	conditional (73.7%)
9.	Alcohol abuse increases the risk of progression from acute to chronic pancreatitis. After an acute attack of pancreatitis almost half of alcohol abusers develop CP. Figures rise to 80% after recurrent pancreatitis.	moderate	strong	strong (89.5%)
10.	Ever smokers (even smoking less than 1 pack of cigarettes per day) have an increased risk for CP, as compared to never smokers.	moderate	strong	strong (89.5%)
11.	There seems to be a dose-response effect for the amount of daily consumption on the risk to develop CP.	low	conditional	strong (94.7%)
12.	Risk increases with time of exposure.	low	conditional	strong (89.5%)
13.	Risk tends to diminish with abstinence (former smokers).	low	conditional	strong (94.7%)
14.	Risk seems to be independent of alcohol abuse.	low	conditional	conditional (78.9%)

Agreement: strong ($\alpha = 94.7\%$)

Statement-12. Risk increases with time of exposure.

Quality assessment: low; Recommendation: conditional; Agreement: strong ($\alpha = 89.5\%$)

Statement-13. Risk tends to diminish with abstinence (former smokers).

Quality assessment: low; Recommendation: conditional; Agreement: strong ($\alpha = 94.7\%$)

Statement-14. Risk seems to be independent of alcohol abuse.

Quality assessment: low; Recommendation: conditional; Agreement: conditional ($\alpha = 78.9\%$)

Comments

Accumulating and convincing evidence suggests that tobacco smoking is independently and dose-dependently associated with increased risk of CP [23,65,67,70–76]. The relative risk for CP in ever smokers is 3.0 (95% CI: 1.48–6.17), in current smokers is 2.72 (95% CI: 1.74–4.24) and in former smokers is 1.27 (95% CI: 1.00–1.62) as compared to never smokers [49]. The number of studies investigating detailed tobacco use (instead of only stating the numbers of ever, current and former smokers), including pack-years or daily quantity (mostly restricted to more or less than 1 pack per day), and CP risk are limited [23,75]. However, it seems that increasing smoking dose and duration elevate the risk for CP development. A meta-analysis of five studies (some of which also included the data of acute pancreatitis and/or recurrent acute pancreatitis patients) by Andriulli et al. [13] revealed that the relative risk of CP in current smokers smoking less than 1 pack per day was 2.4 (95% CI, 0.9–6.6) which increased to 3.3 (95% CI, 1.4–7.9) in those smoking 1 or more packs per day. Another recent meta-analysis [49] of CP patients and a large multiethnic prospective cohort of recurrent acute pancreatitis/CP patients [23] reported somewhat lower risk values. The increased risk of CP due to smoking is present in both genders, but it is more pronounced in males [75].

The detrimental effect of tobacco use in CP patients is highlighted by the fact that smoking is associated with earlier diagnosis of the disease and with the appearance of calcifications and diabetes, independent of alcohol consumption [77,78]. Furthermore, cessation of smoking was shown to reduce the progression of CP [74]. Therefore, the importance of smoking cessation should be stressed in patients with CP.

Summary

The authors have reviewed, summarized and discussed the available evidences on the risk factors for CP. Importantly, both genetic and environmental factors were found to play crucial roles in the development of CP. Therefore, health-promoting lifestyle education and in certain cases genetic counselling should be applied to reduce the incidence of CP. These evidence-based guidelines provide the current state of the art of the risk factors in CP. An overview of the statements is presented in Table 2.

Acknowledgement

EM is a consultant for Takeda Pharmaceutical Company, Abbott and Mylan. MML is a consultant for Abbott, Mylan, Nordmark, Centogene, Fractyl, KMG Kliniken and Akcea, PH is a consultant for CalciMedica and Samsung Bioepis. JPN has received grants from NUCANA and Pharma Nord.

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