ORIGINAL ARTICLE

Management of Alcohol Use Disorders in Patients with Chronic Pancreatitis

Margareta B Lang[1], Ralf Segersvärd[1], Måns Grundsten[1], Märta Segerdahl[2], Urban Arnelo[1], Johan Permert[1], Johan Franck[3], Matthias Löhr[1], Jon A Tsai[1]

Divisions of [1]Surgery and [2]Anesthesiology, (CLINTEC), "Karolinska Institutet" and Karolinska University Hospital; [3]Department of Clinical Neuroscience, "Karolinska Institutet". Stockholm, Sweden

ABSTRACT

Context The outcome of treatment for patients with chronic pancreatitis may be improved by multidisciplinary management. **Objective** To study patients with chronic pancreatitis, especially regarding alcohol use, within a multi disciplinary program. **Main outcome measures** Prospective assessment at baseline and follow-up of alcohol use disorders using DSM-IV criteria, AUDIT score, interview-based quantification of alcohol intake and the biomarker for alcohol use s-CDT in patients referred because of chronic pancreatitis together with retrospective classification with the M-ANNHEIM risk factor analysis and severity scoring for chronic pancreatitis. **Results** Sixty patients (95%) of 63 consecutively included patients were classified as having chronic pancreatitis. Forty-four of these (73%) were available for follow-up evaluation, which took place after a minimum of 1 year (median 3 years). Alcohol consumption decreased at follow-up and no patients had ongoing alcohol dependence (P<0.001) as compared to 10 (23%) at initial evaluation. Patients with harmful alcohol use (AUDIT score ≥8 points) and pathological s-CDT had a reduction in both parameters (P=0.004 and P=0.063, respectively). Pain score according to M-ANNHEIM was unchanged, whereas use of analgesics decreased (P=0.005). **Conclusions** This feasibility study of patients with chronic pancreatitis demonstrated that multidisciplinary management seems to give a positive and sustainable effect on alcohol abuse and may be a useful concept for optimal classification, selection and treatment of patients with chronic pancreatitis.

INTRODUCTION

Chronic pancreatitis is a heterogeneous and progressive inflammatory disease characterized by pain and failure of exocrine and endocrine function in the pancreas [1]. Previous or ongoing over-consumption of alcohol has been described as a contributing etiological factor in 55-90% of all cases [2, 3, 4]. Despite the modest reported incidence from population-based studies in selected industrialized countries (5.4-8.6/100.000 per year) [5], chronic pancreatitis is associated with decades of substantial morbidity [6, 7]. In alcoholic chronic pancreatitis there is also a risk for an enhanced progression of the disease and problems specifically related to alcohol addiction [8, 9, 10]. Management of mild forms of chronic pancreatitis consists of avoiding

triggering factors (i.e., alcohol, nicotine and high-fat diets), treatment of pain and substitution of exocrine and endocrine insufficiency [11]. In patients where conservative treatment is insufficient and/or in cases with complications in adjacent organs, e.g. duodenal or bile duct obstruction, surgical intervention may be considered [12]. In general, the long term results for surgery are superior to endoscopic treatment [13, 14], but endoscopic can be indicated in selected cases as a temporary treatment, since it does not preclude subsequent surgery, and as a definite treatment, in patients who are unfit for surgery [15]. Endoscopy may also be used to drain the commonly occurring pseudocysts in chronic pancreatitis, using transpapillary or transmural routes with complete cyst resolution in 65-92% of all cases [16].

In addition to addressing anatomical, endocrine and exocrine complications, alcohol addiction in chronic pancreatitis needs special attention. Firstly, the diagnosis of alcohol addiction is not always straightforward. Secondly, cessation of alcohol over-consumption is of benefit not only for general health and quality of life, but also after surgery, since ongoing alcohol abuse is a strong risk factor for complications and poorer ability to cope with postoperative pain [17,

18]. One month of preoperative abstinence was sufficient to reduce the postoperative morbidity in a randomized trial of patients with alcohol abuse undergoing colorectal surgery [19]. However, in clinical guidelines and routine clinical management, measures against excessive alcohol intake are often lacking [20].

In 2005, a new concept for management of chronic pancreatitis was introduced at our department. The patients undergo separate and a joint assessment by pancreatologists together with specialists in addiction medicine and pain management. The objectives of this concept were to identify the etiology of the disease, to deliver optimal conservative, endoscopic or surgical treatment and to specifically address issues related to alcohol. The aim of the current study was to evaluate the feasibility of such multidisciplinary management for chronic pancreatitis, aimed at assessment of and intervention for alcohol use disorders, using a combination of M-ANNHEIM classification of chronic pancreatitis [21], together with the fourth version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) addiction criteria.

MATERIALS AND METHODS

Patients

Sixty-three consecutive patients referred between October 2005 and May 2009 with suspected chronic pancreatitis (i.e. no suspicion of pancreatic malignancy and signs of chronic pancreatitis in the pancreatic parenchyma or pancreatic ducts according to CT or MRT) and a clinical history of recurrent pancreatitis or abdominal pain. Patients unable to comply with the concept of interviews and questionnaires were excluded. After individual assessment by pancreatologists, addiction and pain specialists, a treatment plan was set up.

Study Enrolment (Figure 1)

Of the 63 patients, the diagnosis of chronic pancreatitis were confirmed in 60 cases (95.2%), and of these 44 were available for a follow-up evaluation, which took place after a median time of 3 (range: 2-4) years. Four patients had died, one had emigrated, two refused to
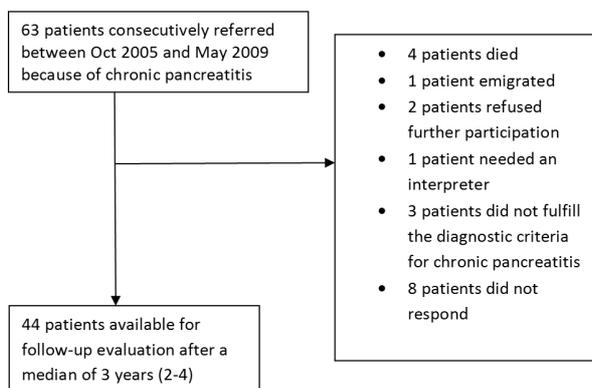
participate further in the study, and one needed an interpreter who was not available. Three patients did not fulfill the diagnostic criteria for chronic pancreatitis at the initial evaluation and additional eight patients did not respond. The follow-up frequency was thus 73.3% of those who had chronic pancreatitis.

Pancreatological Evaluation and Management

Pancreatological parameters were classified according to the M-ANNHEIM system [21]. M-ANNHEIM was first introduced at our clinic in 2008 and the initial evaluation of the patients was therefore done retrospectively with this modality. Each letter in M-ANNHEIM represents a risk factor: (M=multiple, A=alcohol, N=nicotine, N=nutrition, H=hereditary, E=efferent duct factors, I=immunological, M=miscellaneous). The severity of chronic pancreatitis was classified with the M-ANNHEIM scoring system, which consists of 0-4 points for reported pain, pain control usage, endoscopic and surgical intervention, endocrine insufficiency, exocrine insufficiency, morphological status according to pancreatic imaging and severe organ complications. Scores for the different symptoms and interventions were analyzed separately as well as combined in a total score. In addition, age, sex and body mass index (BMI) were registered [22]. Surgical (n=13) or endoscopic intervention (n=19) was done when indicated and the remaining patients were managed conservatively.

Addiction Evaluation and Management

Prior to the appointment, the patients were asked to fill out the Alcohol Use Disorder Identification Test (AUDIT), which estimates drinking habits over the last twelve months. The ten questions in AUDIT result in a total score of 0-40 points. To receive an acceptable sensitivity and specificity in this selected group of patients, we used the recommended cut-off value of ≥ 8 points as an indicator for problematic drinking [23]. The interview instrument "Timeline follow-back" was used to obtain the past 90 days data on the quantity and frequency of the patient's alcohol consumption to average daily drinking in grams of alcohol per day [24]. Serum carbohydrate-deficient transferrin (s-CDT) is a biological marker for alcohol over-consumption. s-CDT detects the effect of regular alcohol consumption of at least 60 grams per day over a period of two weeks and is a marker with high specificity for alcohol over-consumption. The half-life for s-CDT is around two weeks provided no further alcohol consumption and the reference value is less than 2% [25, 26]. AUDIT, alcohol consumption and s-CDT was used to help determine if the patient has an alcohol addiction diagnosis according to DSM-IV, but the diagnosis is set by the clinician that interviewed the patient. The patients in this study were divided into four groups regarding alcohol addiction and alcohol consumption as follows:

A) neither history of alcohol addiction nor alcohol over-consumption, defined as never having fulfilled ≥ 3

Figure 1. Study enrollment: summary of patient inclusion.

Content of the figure:
63 patients consecutively referred between Oct 2005 and May 2009 because of chronic pancreatitis

- 4 patients died
- 1 patient emigrated
- 2 patients refused further participation
- 1 patient needed an interpreter
- 3 patients did not fulfill the diagnostic criteria for chronic pancreatitis
- 8 patients did not respond

44 patients available for follow-up evaluation after a median of 3 years (2-4)

DSM-IV criteria and no alcohol-induced chronic pancreatitis according to patient records (n=18);

B) previous alcohol-induced acute pancreatitis, but no addiction to alcohol, defined as no history of a DSM-IV addiction diagnosis, more than 12 months not fulfilling any of DSM-IV criteria for addiction, but a history of alcohol-induced acute pancreatitis (n=5);

C) alcohol addiction in remission, defined as a history of a DSM-IV addiction diagnosis and more than 12 months having passed without fulfilling ≥3 of DSM-IV criteria (n=11);

D) ongoing alcohol addiction, defined as ≥3 DSM-IV criteria fulfilled within the last 12 months (n=10).

All patients met with an addiction specialist at the time of initial evaluation and got a thorough assessment of their current alcohol consumption and general information about alcohol addiction. The ten patients classified as having an ongoing alcohol addiction were offered further appointments. Six of these patients agreed upon participation and were offered validated therapies consisting of medication (disulfiram, acamprosat, naltrexon) [27, 28] in combination with the validated treatment methods of "Motivational Interviewing" [29], or "Relapse Prevention" [30, 31, 32]. "Motivational Interviewing" is a set of techniques and a counseling style focused to identifying and mobilizing the patient's intrinsic values and goals to stimulate behavioral change and "Relapse Prevention" consists of both a conceptual model of relapse and cognitive and behavioral strategies to prevent or limit relapse episodes. No specific intervention was performed against smoking.

Follow-up Evaluation

After a minimum time period of twelve months, all data collection was repeated at a follow-up visit.

ETHICS

The Regional Ethics Committee reviewed this project and classified it as being a quality control and thus outside the scope of the Committee; therefore, the informed consent was not needed. The patients were treated according to the ethical guidelines of the "World Medical Association (WMA) Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects" adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the 59th WMA General Assembly, Seoul, South Korea, October 2008.

STATISTICS

The data is presented as median and interquartile range (IQR). The Wilcoxon signed rank test for comparison of paired data was used for comparing changes between initial evaluation and follow-up. Comparisons of addiction and alcohol over-consumption were done by the McNemar test. Two tailed P values less than 0.05 were considered as statistically significant. Sigma Stat software (Jandel, San José, CA, USA) was used for all calculations.

RESULTS

Study Demographics and M-ANNHEIM Risk Factor Analysis (Table 1)

A risk factor analysis according to the M-ANNHEIM classification system and basic demographic data was available for all 44 subjects. A majority of the study population had more than one risk factor (32 subjects, 72.7%). The most common risk factor was smoking (39 subjects, 88.6%) and 29 (74.4%) of the smokers had ≥20 pack years. Twenty-six of the 44 patients (59.1%) were classified as having alcohol consumption as the most likely contributing cause to their chronic pancreatitis. For the remainder of the M-ANNHEIM risk factor analysis the results were as follows: one patient (2.3%) had "Immunology" as a risk factor due to Crohn's disease. Three cases (6.8%) had "Nutrition" as a risk factor, all had hyperlipidemia. Six patients (13.6%) had partial (n=1) or complete (n=5) pancreas divisum, who were classified as having "Efferent duct factor" as a risk factor, and the 6 patients (13.6%) with "Hereditary" as risk factor had either familial chronic pancreatitis or early/late-onset idiopathic chronic pancreatitis. Two patients (4.5%) were classified with "Miscellaneous" risk factor; prior to the first episode of acute pancreatitis, 1 (2.3%) had chronic renal failure and 1 (2.3%) was diagnosed with hypercalcemia.

M-ANNHEIM Severity Scores (Table 2)

Forty-three patients (97.7%) were available at follow-up. Between initial evaluation and follow-up, the total median M-ANNHEIM score increased from 11 to 12 (P=0.001), but the reported use of analgesics decreased from 2 to 1 (P=0.005). Exocrine insufficiency and thus also enzyme supplementation, which is included in the definition of exocrine insufficiency according to M-ANNHEIM, increased between the initial evaluation and follow-up (P=0.027), even though the median values were the same. There was a borderline significant increase in number of patients with diabetes

Table 1. Demographics and risk factor profile.

Age (years) [a]	
- Initial evaluation	58 (51-63)
- Follow-up	62 (53-65)
Male gender [b]	33 (75.0%)
BMI (m/kg^2) [a]	
- Initial evaluation	21.7 (19.4-25.0)
- Follow-up	23.6 (20.3-26.4)
M-ANNHEIM risk factors [b]	
- Multiple	32 (72.7%)
- Alcohol	26 (59.1%)
- Nicotine	39 (88.6%)
- Nutrition	3 (6.8%)
- Hereditary	6 (13.6%)
- Efferent duct	6 (13.6%)
- Immunology	1 (2.3%)
- Miscellaneous	2 (4.5%)

[a] median and interquartile range
[b] frequencies

Table 2. M-ANNHEIM: separate dimensions and total score.

Score	Initial evaluation (n=44)						Follow-up (n=43 [a])						P value [b]
	0	1	2	3	4	median (IQR)	0	1	2	3	4	median (IQR)	
Patient report of pain	3	12	8	13	8	2 (1-3)	13	4	6	7	13	2 (0-4)	0.640
Use of analgesics	6	11	27			2 (1-2)	16	9	18			1 (0-2)	0.005
Endocrine insufficiency	37				7	0 (0-0)	31				12	0 (0-4)	0.063
Exocrine insufficiency	16	2	26			2 (0-2)	8	5	30			2 (1-2)	0.027
Organ complications	28		12		4	0 (0-2)	20		15		8	1 (0-2)	0.016
Endoscopic intervention	30		14			0 (0-2)	25		19			0 (0-2)	0.063
Surgical intervention	42				2	0 (0-0)	29				15	0 (0-4)	<0.001
Total	**162**	**26**	**89**	**16**	**25**	**11 (9-12)**	**142**	**19**	**90**	**10**	**52**	**12 (9.5-16)**	**0.001**

IQR: interquartile range
[a] Information about surgical intervention was available for all 44 patients.
[b] Wilcoxon matched-pairs test

Table 3. Alcohol use and addiction.

Alcohol use and drinking habits	Initial evaluation (n=44)	Follow-up (n=44)	P value
A. Neither any history of alcohol addiction nor alcohol overconsumption	18 (40.9%)	18 (40.9%)	-
B. Alcohol over-consumption in remission	5 (11.4%)	5 (11.4%)	-
C. Alcohol addiction in remission	11 (25.0%)	21 (47.7%)	0.002 [a]
D. Ongoing alcohol addiction	10 (22.7%)	0	0.002 [a]

[a] McNemar test calculated by taking into account groups C and D only because there were no changes in the other two groups.

mellitus at follow-up compared to the initial evaluation (12 *vs*. 7 patients, P=0.063). The number of patients that had a potentially reversible organ complication increased from 12 to 15 and the number of cases with irreversible splenic or portal vein thrombosis increased from 4 to 8 (P=0.016 for all organ complications combined).

Use of Alcohol and Alcohol Addiction (Table 3)

At follow-up, no patients had an ongoing alcohol addiction (group D) and all these patients instead

fulfilled criteria for group C, i.e. alcohol addiction in remission (P<0.001). There were no changes in the other groups.

**Alcohol Use Disorder Identification Test (AUDIT; Figure 2)**

Forty-two patients were available at follow-up. The median score of the patients with a total AUDIT score of ≥8 points at the initial evaluation (median, IQR: 14, 9-22; n=10) had significantly (P=0.004) decreased at follow-up (median, IQR: 0, 0-1; n=9). No significant change was found in the other 32 patients with AUDIT score less than 8 (data not shown).

Serum carbohydrate-deficient transferrin (s-CDT; Figure 3)

Follow-up samples were available in 36 patients. Among the patients with pathological s-CDT levels (≥2%, n=6) at initial evaluation a trend toward a significantly lower value at follow-up was observed (median, IQR: 4.3%, 2.5-6.6% *vs*. 1.6%, 0.7-2.7%; P=0.063). No significant change was found in the other 30 patients with normal s-CDT basal values (data not shown).
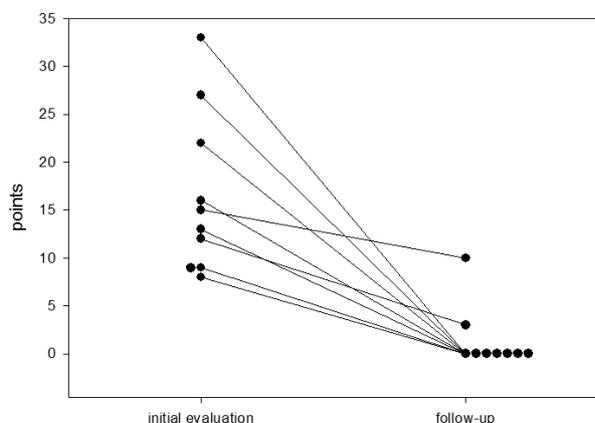
Figure 2. Alcohol Use Disorder Identification Test (AUDIT) at initial evaluation and follow-up among the 10 subjects with problematic drinking (≥8 points) at initial evaluation (data of one subject was not available at follow-up).
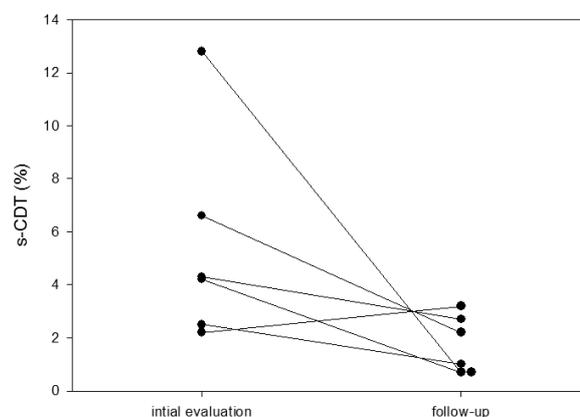

Figure 3. Serum carbohydrate deficient transferring (s-CDT) at initial evaluation and follow-up among the 6 subjects with pathological value (≥2.0%) at initial evaluation.

Quantification of Alcohol Consumption (Figure 4)

Among the 10 patients classified as having an ongoing addiction (group D) at initial evaluation alcohol consumption had significantly decreased at follow-up (median, IQR: 4.4, 2.1-28 g/day *vs*. 0, 0-0 g/day; P=0.018).

DISCUSSION

Previous or ongoing over-consumption of alcohol is an important factor in the pathogenesis of both acute and chronic pancreatitis and addiction to alcohol is also common among these patients [2, 3, 4]. Despite this, studies on interventions for alcohol abuse in this population are scarce [20]. In a recent trial specific interventions against harmful alcohol use resulted in a reduction of episodes with alcoholic acute pancreatitis [33]. By introducing a multidisciplinary group consisting of pancreatologists, addiction and pain specialists, we aimed to improve the outcome of both interventional and conservative treatment for the complex group of patients with chronic pancreatitis. There was an obvious selection of patients given that all were referrals. However, all patients complied with the initial evaluation and the follow-up frequency was also reasonably high (73%), only 2 patients (3%) actually refused to participate in follow-up and 8 (13%) did not respond. In this patient cohort, we found that all who had an ongoing alcohol use disorder according to DSM-IV at the initial evaluation were in remission at follow-up. Furthermore, self-reported data implying problem drinking (AUDIT) and quantification of alcohol intake decreased, and there was also a trend towards lower levels of s-CDT, a biomarker for alcohol use. Alcohol addiction has scarcely been investigated in earlier studies of chronic pancreatitis. Addiction was generally managed successfully herein, based on the different modalities for evaluation that we applied. The special circumstances in patients with chronic pancreatitis and an alcohol use disorder, i.e. somatic symptoms such as recurrent or chronic pain as well as gastrointestinal and metabolic manifestations, may have facilitated the successful cessation of alcohol
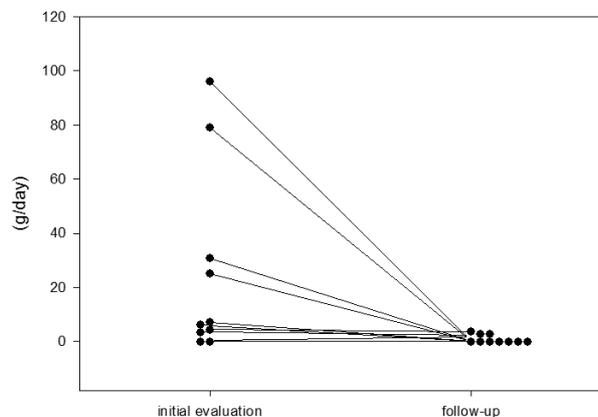
Figure 4. Alcohol consumption among the 10 patients of group D at initial evaluation and follow-up, estimated with the time-line follow back instrument.

abuse, possibly as a result of the multidisciplinary management.

The M-ANNHEIM multiple risk factor classification and scoring system was applied for clinical classification of the patients according to the etiology and the severity of chronic pancreatitis [3]. M-ANNHEIM also includes rare risk factors and the treatment options and prognosis may therefore be better evaluated. The current study demonstrates that the etiology of chronic pancreatitis often is multifactorial. Historically, alcohol addiction has been recognized as the major risk factor for chronic pancreatitis. In contrast, several recent studies [5, 34], including the present, show that alcohol abuse might be less frequent than previously reported and that smoking may be an independent risk factor for chronic pancreatitis. Although selection bias might contribute to the relatively low number of patients with a history of harmful alcohol use in the present sample, due to reluctance to referral or follow-up, the systematic assessment of alcohol use disorders suggests that the incidence of alcohol abuse was in the same range as reported in other cohorts [34].

The M-ANNHEIM scoring system also estimates the severity of chronic pancreatitis and due to the progressive character of the disease, the total score increases over time [21]. The M-ANNHEIM assessment presented here should be interpreted with some caution as scoring was made retrospectively and in most cases no new imaging was indicated from a clinical perspective, leaving the scoring of the pancreas morphological status arbitrarily unchanged. Furthermore, exocrine and endocrine insufficiency was assessed only by clinical presentation and not by laboratory testing, which may have underestimated these parameters. Nevertheless, when comparing the separate dimensions of the M-ANNHEIM scoring initially and at follow-up, we observed an increase in the use of enzyme supplementation and a decrease in the use of analgesics. The decreased need for analgesics and particularly the combination of a stable degree of pain and decreased consumption of analgesics indicates that the total pain burden may have decreased. Increased enzyme substitution as well as endoscopic and/or surgical intervention or psychological factor (e. g. attention from a pain specialist) could all have contributed to the reduced need for analgesics.

In conclusion, the multidisciplinary management model presented here, which includes thorough evaluation and intervention jointly by pancreatologists, addiction and pain specialists, is feasible and seems to have potential for providing a sustainable effect on alcohol use disorders among patients with chronic pancreatitis.

Conflict of interest The authors declare no conflict of interest

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