Long-term outcome of patients with chronic pancreatitis treated with micronutrient antioxidant therapy

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BACKGROUND: Micronutrient antioxidant therapy did not relieve pain in a European randomized trial of patients with chronic pancreatitis without malnutrition. However, intervention was undertaken only for 6 months leaving unanswered the question of whether long-term antioxidant therapy may modulate chronic pancreatitis. The aim of this study is to assess the outcome of long-term use of micronutrient antioxidant therapy in patients with chronic pancreatitis.

METHODS: This is a single center clinical cohort report of patients with chronic pancreatitis prescribed micronutrient antioxidant therapy and followed for up to 10 years. Data were collected on demographic detail, clinic pain assessment, insulin requirements, interventions and outcome.

RESULTS: A group of 30 patients with a diagnosis of chronic pancreatitis constitute the study population. Median age at time of diagnosis was 40 years (range 14-66); 19 (63%) were male and the median duration of symptoms was 2 years (range 0-18). Alcohol was the dominant cause in 22 (73%) patients and 16 (53%) patients were Cambridge stage 1. Twenty-four (80%) patients had pain at presentation. During antioxidant treatment of 4 years (range 1-10), pain decreased but the proportion with abdominal pain compared to those who were pain-free remained constant (*P*=0.16; two-way ANOVA with Bonferroni correction). There was a significant increase in requirement for insulin (*P*=0.028) with time together with use of both endoscopic and surgical interventions.

CONCLUSIONS: This is the first study to report long-term disease-specific outcome in patients with chronic pancreatitis prescribed micronutrient antioxidant therapy. There appears to be no effect of intervention on outcome.

(*Hepatobiliary Pancreat Dis Int 2017;16:209-214*)

KEY WORDS: chronic pancreatitis; antioxidant therapy; micronutrient; Antox; outcomes

Introduction

The micronutrient antioxidant-deficiency hypothesis of cellular injury in chronic pancreatitis proposes that acinar damage is mediated by short-lived oxygen free radicals.[1] Deficient intracellular free radical quenching pathways combined with excess free radical production leads to cellular injury.[2] Specifically, deficiencies in key co-factors of endogenous protective free-radical quenching mechanisms such as the glutathione peroxidase pathway are proposed to be causally linked to injury and it was postulated that these deficiencies could be addressed by exogenous micronutrient antioxidant supplementation.[3] Selenium, vitamin C (ascorbic acid) and methionine were proposed as key antioxidants.[3]

After two small randomized trials of selenium, β-carotene, vitamins C & E and methionine-based antioxidant therapy reported a reduction in severity and frequency of episodes of pain in patients with recurrent and chronic pancreatitis, a commercially available formulation, Antox (Pharma Nord, Morpeth, UK) was developed comprising vitamin C, vitamin E, β-carotene, selenium and methionine.[4-6] Despite the obvious attraction of a pharmacologic intervention for this difficult disease, antioxidant therapy for chronic pancreatitis never became accepted as standard therapy. The small, heterogeneous

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doi: 10.1016/S1499-3872(16)60128-5
Published online October 17, 2016.

clinical trial base was thought to be a main reason for the lack of acceptance.

The 2009 publication of a report from Delhi in which 147 patients were randomized to antioxidant therapy or placebo and which reported as main outcome measure a reduction in "painful days" appeared to alter the position of equipoise.[7] However, the Delhi study population comprised mainly young patients (aged 31.3±11.4 years in the antioxidant group) with a high proportion of individuals with malnutrition [median study population BMI (body mass index) 19.7±3.5] and 28 of 71 patients in the antioxidant arm having a BMI of <18.5.

The ANTICIPATE study was a similarly designed, contemporary randomized controlled trial evaluating the effect of micronutrient antioxidant therapy (Antox, Pharma Nord) undertaken in a European population of older patients with a predominantly alcohol-related etiology and a disease phenotype featuring mass-forming chronic pancreatitis.[8] The principal finding of this study was that 6 months intervention with Antox did not reduce clinical pain scores compared to placebo despite demonstrating a significant elevation in blood antioxidant levels.[8,9]

In both modern studies, the duration of intervention was six months. However, in a chronic disease such as chronic pancreatitis the effect of long-term treatment is not known and the question of whether long-term intervention is required to modulate the course of this chronic disease is unanswered. Thus the aim of this study is to assess the long-term outcome in patients with chronic pancreatitis prescribed micronutrient antioxidant therapy with specific reference to effects on pain and the natural history of the disease.

Methods

Study design

This is a clinical cohort study based on retrospective analysis of case notes.

Ethics committee approval

The study was approved by the United Kingdom Health Research Authority (NRES Committee North East, 14/NE/1117). Site-specific approval was also obtained from Central Manchester University Hospitals NHS Foundation Trust's Research board.

Setting and study population

Patients with a final discharge diagnosis of chronic pancreatitis were identified from the clinical coding department of the Manchester Royal Infirmary. The International Classification of Disease (ICD) version 9 code 577.1 was used together with the ICD version 10 codes K86.0 (alcoholic chronic pancreatitis) and K86.1 (chronic pancreatitis other).[10]

Data retrieval and collection

The case notes or microfilmed records of these patients were retrieved. The notes were reviewed by two researchers and information extracted to populate a predefined case report form. Data were collected on the following: gender, age at enrolment into this study, disease duration in years at time of enrolment, body mass index (BMI), cigarette smoking status, alcohol use, diabetes mellitus at first presentation, insulin treatment at first presentation and use of opiate analgesia.

Data reporting and categories

Inclusion period

The inclusion period is the eight years from 1st January 1990 to 1st January 1998. During this period, all patients were managed by a specialist multi-disciplinary pancreatobiliary service (including medical and surgical pancreatology) with micronutrient antioxidant therapy being used as first-line treatment. After 1998 the policy of regular use of micronutrient antioxidant therapy was discontinued for new diagnoses of chronic pancreatitis but those who were already taking this therapy were continued on it. Patients enrolled during the 8-year period were eligible for follow-up for up to 10 years.

Inclusion/exclusion criteria

Patients were included in this study if they had a discharge diagnosis of chronic pancreatitis within the study time frame and were prescribed micronutrient antioxidant therapy and had at least 12 months of follow-up. Patients were excluded if they did not meet these criteria or if they were in contemporaneous trials of antioxidant therapy.

Diagnosis of chronic pancreatitis

The diagnosis of chronic pancreatitis was by the Cambridge classification of chronic pancreatitis (class 1 to 5).[11] For the purposes of the present study, case notes and the reports of radiological and endoscopic imaging were systematically reviewed for all patients in order to allocate category.

Allocation of etiology

The etiology allocated by the treating clinician was noted and divided into alcoholic chronic pancreatitis and non-alcoholic chronic pancreatitis. Non-alcoholic

chronic pancreatitis was further subdivided into idiopathic and other causes.[12]

Intervention

Patients were prescribed Antox (Pharma Nord). There were minor modifications of Antox over the study period, Antox version 1.2 contained the following: 38.5 mg selenium yeast, of which 50 g was L-selenomethionine; 113.4 mg d/L tocopherol acetate; 126.3 mg ascorbic acid; and 480 mg L-methionine, together with the following secondary ingredients: 285.6 mg microcrystalline cellulose, 14.0 mg croscarmellose sodium, 7.0 mg colloidal anhydrous silica, and 3.0 mg magnesium stearate.

The coating included 4.2 mg carotene. In addition to oral micronutrient antioxidant therapy, patients admitted with exacerbations of pain were prescribed intravenous antioxidant therapy based on methionine, selenium and vitamin C. It is specifically disclosed that antioxidant therapy should be regarded as an investigational use of a product not yet approved by the United States Food and Drug Administration (USFDA) for any purpose.

Definition of baseline

The first out-patient consultation or hospital admission where a decision was made by a member of the pancreatobiliary team to commence antioxidant therapy team and recorded in the case notes was taken as the baseline.

Assessment of symptoms at baseline

Presence or absence of pain was recorded from case notes. Specifically, if the case note entry mentioned the presence of pain, this was recorded. Similarly, analgesic use was captured from case notes. Analgesic use was obtained either from the out-patient clinic letter or the in-patient record. Other symptoms such as vomiting, jaundice or steatorrhoea were recorded as described in the notes.

Assessment of symptoms on follow-up

The out-patient clinic appointment or in-patient admission closest to 12 months from baseline was used as the first anniversary. At this consultation a record was made of the presence or absence of pain, opiate use (yes/no), insulin dependent diabetes mellitus (yes/no), continued alcohol use (yes/no), hospital admissions in the previous year (number of admissions from review of case notes), days in hospital in the preceding year, need for intervention and type of intervention (radiological, endoscopic, surgical). Interventions were further categorized as urgent or elective. This process was repeated annually for the 10-year follow-up period or until loss from follow-up. For each anniversary, the appointment or hospital admission closest to the anniversary marker date was selected for sampling. The interval between the actual anniversary and the appointment was recorded in weeks and noted as either earlier or later.

Antioxidant levels

Antioxidant levels were obtained from the specialist in-house pancreatic laboratory. Antioxidant levels were recorded at baseline-prior to starting treatment and at the end of follow-up. Antioxidant levels included selenium, methionine and vitamin C.

Drop-out from study

Patients ceased to be in the study if they stopped attending out-patients, if they discontinued antioxidant therapy (for a period of more than 6 months) or if they developed another serious illness such as cancer. Patients who discontinued attendance but returned later (after a gap of more than 6 months) were not re-included.

Statistical analysis

Data were analyzed using the StatsDirect software package (StatsDirect, Altrincham, Cheshire, UK). Non-parametric tests were used as appropriate and significance was accepted at the $P<0.05$ level.

Results

A total of 30 patients coded by the hospital records department as having a diagnosis of chronic pancreatitis were identified for the study period 1st January 1990 to 1st January 1998.

Demographic profile

The demographic profile of the study population is seen in Table 1. Categorization of chronic pancreatitis by the Cambridge criteria is shown. In terms of etiology, alcohol was the dominant cause. The two patients categorized as "metabolic" had recurrent acute pancreatitis with a background of probable chronic pancreatitis. Although autoimmune pancreatitis was not universally recognized during the time of the study (and thus may not have been recorded), on retrospective analysis no patient in this study had features of autoimmune pancreatitis.[13]

Clinical course on follow-up and long-term antioxidant use

Details on follow-up are shown in Table 2. Trends in reporting of abdominal pain are seen in Fig. Of the

Table 1. Demographic details of the cohort of 30 patients with chronic pancreatitis

Characteristics	Data
Age at time of diagnosis (yr, median, range)	40 (14-66)
Gender (male/female)	19/11
Duration of symptoms (yr, median, range)	2 (0-18)
BMI (kg/m^2, median, range)	23 (13-35)
Cigarette smokers at time of diagnosis (data available for 28) (*n*, %)	21 (75)
Etiology (*n*, %)	
Alcoholic	22 (73)
Idiopathic	6 (20)
Metabolic	2 (7)
Cambridge classification of chronic pancreatitis	
Stage 1	16
Stage 2	3
Stage 3	0
Stage 4	6
Stage 5	5
Diabetes mellitus at first presentation (*n*, %)	2 (7)
Insulin use at first presentation (*n*, %)	1 (3)
Baseline symptoms	
Abdominal pain	24
Isolated steatorrhoea	1
Recurrent pancreatitis	2
No recorded symptoms	0
Diabetes mellitus as index presentation	1

BMI: body mass index.

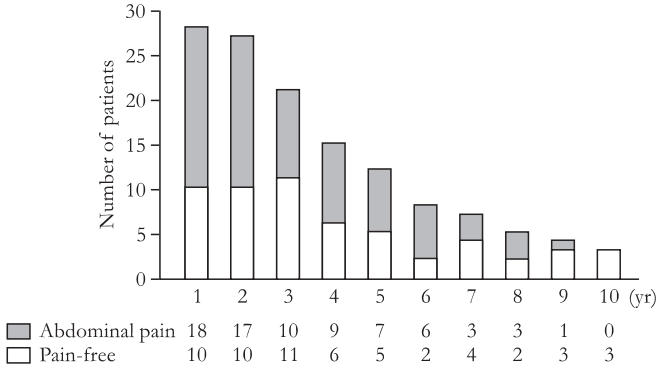

Fig. Trends in reporting of abdominal pain in patients with chronic pancreatitis on Antox over 10-year follow-up. Twenty-four patients reported abdominal pain as a presenting symptom. The numbers reporting pain over the subsequent 10 years are seen in the red component of the block. *P*=0.16, abdominal pain vs pain free (two-way ANOVA with Bonferroni correction; 95% CI: -4.47-0.87).

original cohort, patients were followed up for a median period of 3.5 years (range 1-10) with 3 patients being followed for 10 years (Fig.). Four patients who were on opiate analgesia at baseline became opiate-independent whilst taking antioxidant therapy on follow-up with one individual sustaining this for 10 years. Three of these individuals had minimal diagnostic criteria for chronic pancreatitis at baseline (Cambridge 1) and all four ceased consumption of alcohol. There was no significant difference in recorded opiate use at last follow-up compared to baseline (*P*=1.0; Fisher's exact). There was a significant increase in insulin use at follow-up compared to baseline (*P*=0.028; Fisher's exact). Although there were more endoscopic interventions for chronic pancreatitis during antioxidant therapy than in the 12 months prior to commencement, this difference was not statistically significant. Similarly, three elective chronic pancreatitis-directed surgical interventions were undertaken during follow-up with no significant difference.

Table 2. Clinical course during the follow-up

Characteristics	Data
Follow-up (yr, median, range)	3.5 (1-10)
Duration of antioxidant treatment (yr, median, range)	4.0 (1-10)
Insulin use at index presentation vs at last follow-up	1 vs 7 (*P*=0.028; Fisher's exact)
Opiate use at index presentation vs at last follow-up	10 vs 11 (*P*=1.0; Fisher's exact)
Endoscopic intervention in 12 months prior to antioxidant therapy vs during follow-up	2 vs 6 (*P*=0.25; Fisher's exact)
Pancreatic surgical intervention in 12 months prior to antioxidant therapy vs during follow-up	0 vs 3 (*P*=0.23; Fisher's exact)

Table 3. Blood levels of antioxidants at baseline and at the end of follow-up

Antioxidant values (laboratory reference range in parentheses)	Baseline median (95% CI)	End of follow-up (median, 95% CI)	*P* value*
Vitamin C (4-20 μg/mL)	7.15 (3.8-10.9)	17.3 (14-19.8)	**<0.001**
Selenium (83-152 μg/L)	66.5 (54-88)	138.0 (108-149)	**<0.001**
Glutathione (7.49-12.21 μmol/g)	8.45 (7.72-9.79)	10.19 (9.34-11.14)	**<0.05**

*: Mann-Whitney *U* test.

Antioxidant levels

Median baseline levels of selenium and glutathione were below those of the laboratory reference range. There was a significant increase in antioxidant levels when last follow-up was compared to baseline (Table 3).

Discussion

This study reports long-term outcome in patients taking micronutrient antioxidant therapy for chronic pancreatitis. As with other similar cohorts referred to specialist centers for chronic pancreatitis,[14] patients had a relatively prolonged median duration of symptoms prior to

seeking specialist advice.

Pain is the predominant symptom for which patients with chronic pancreatitis seek medical assistance and was a baseline symptom in this series. The overall dominance of pain as a symptom of chronic pancreatitis decreased with time such that only 7 of 12 patients followed for 5 years continued to complain of this symptom.

The major finding of the study is that antioxidant therapy does not appear to influence the natural history of pain in chronic pancreatitis as the proportion of patients with abdominal pain compared to those who were pain-free is not significantly different. Four patients who were taking opiates at baseline did become opiate-free whilst taking antioxidant therapy on long-term follow-up. However, in all four an important confounding factor was that they ceased consumption of alcohol and had early stage disease at the time of their index presentation.[15] With a small population, further subgroup analysis by etiology is inappropriate. The natural history of pain in chronic pancreatitis can feature "burn-out".[16, 17] This phenomenon possibly accounts for the long-term changes in pain in chronic pancreatitis seen in this study.

Overall, during a median duration of antioxidant therapy, there was a significant increase in the number of patients requiring insulin and no significant change in opiate use. Although more patients underwent endoscopic intervention or pancreatic surgical intervention during follow-up than in the 12 months prior to antioxidant therapy neither of these differences were significant and are likely to simply reflect ongoing treatment in chronic pancreatitis.[18, 19]

Current concepts of the pathophysiology of chronic pancreatitis are that oxygen-derived free radicals are indeed thought to be involved in the mediation of acinar injury. However, a modern view is that this is but one of a range of mechanisms involved in chronic pancreatitis with ductal hypertension, aberrant nociceptive pain signaling and altered central nervous system pain perception also being involved.[20] The role of exogenous supplementation of oxygen free radical quenching pathways is now questioned with no substantive proof that exogenous antioxidant therapy alters antioxidant levels within the injured human pancreas. In keeping with this, although small clinical trials (with their inherent bias) found a benefit from antioxidant therapy, the large ANTICIPATE trial showed no benefit and thus questions the role of antioxidant therapy in chronic pancreatitis.[9]

Important potential sources of error in this study could include the small sample size-as this study predates the creation of large specialist centers and the retrospective nature of collection of information.

In conclusion, although this is a small study, it is thought to represent a unique long-term systematic assessment of patients with chronic pancreatitis treated with micronutrient antioxidant therapy. Although the results of the ongoing EUROPAC study of antioxidant therapy in hereditary and idiopathic chronic pancreatitis are required for a final resolution to the question of whether antioxidant therapy has a role in chronic pancreatitis[21] the current evidence suggests that long-term antioxidant therapy does not appear to have any impact on either the symptoms or the natural history of this disease.

Acknowledgements: We acknowledge the assistance of David Schofield and the Pancreatic Laboratory at the Manchester Royal Infirmary.

Contributors: SAK proposed the study. RSN and SAK co-wrote the protocol and ethics application. RSN collected the data. RSN and SAK jointly analysed and wrote the manuscript. SAK is the guarantor.

Funding: None.

Ethical approval: The study was approved by the United Kingdom Health Research Authority (NRES Committee North East, 14/NE/1117).

Competing interest: No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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Received December 1, 2015
Accepted after revision May 22, 2016