Duodenal total and ionised calcium secretion in normal subjects, chronic alcoholics, and patients with various stages of chronic alcoholic pancreatitis

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SUMMARY Previous studies have shown increased secretion of total calcium in the duodenal juice of patients with chronic alcoholic pancreatitis compared with healthy subjects. In order to get more detailed information on calcium secretion and pancreatic stone formation in chronic alcoholic pancreatitis, ionised and total calcium concentrations were determined in the duodenal juice of normal subjects, chronic alcoholics, and patients with various stages of chronic alcoholic pancreatitis. Total calcium secretion was in agreement with previously published data. Chronic alcoholics presented a significant increase of ionised calcium. In the course of pancreatitis all calcium fractions increased progressively revealing highest concentrations in patients with severe exocrine insufficiency. In non-calcified and calcified pancreatitis all calcium fractions were identical. It is suggested that the increase of ionised calcium originates from serum ionised calcium passing by diffusion into the damaged pancreatic duct system.

Several authors have observed an increase of calcium secretion in the secretin stimulated duodenal juice of patients with chronic pancreatitis¹⁻⁹ which has been interpreted to be not only due to a decreased secretion independent of exocrine pancreatic enzymes.¹⁰ Highest concentrations for calcium were found in the duodenal juice of patients with chronic calcified pancreatitis after secretin¹ and under exogenous CCK administration. Basal and secretin/CCK stimulated calcium outputs in these patients were significantly enhanced as compared with controls.¹ It was suggested that enhanced calcium secretion in the duodenal juice of patients with alcoholic pancreatitis is a precondition for calcium carbonate precipitation and subsequent stone formation in the pancreatic ductal system.⁹ Warwick *et al*⁷ postulated an increased intra-pancreatic calcium pool to be responsible for high concentrations of calcium in the duodenal juice, whereas Goebell *et al*¹ suggested that ionised plasma calcium enters the pancreatic duct system by diffusion from serum through damaged duct epithelia characterised by an increased permeability as described by Nakamura *et al*¹¹ in pancreatic tissues of patients with chronic alcoholic

pancreatitis.

The aim of this study was to investigate the secretion of the different calcium fractions in the course of chronic alcoholic pancreatitis.

Methods

PATIENTS

Seventy patients entered the study and were classified into three groups according to their history and the results of the secretin/CCK test.

Group 1

Twenty healthy subjects, 11 women and nine men with a mean age of 44 years (range 24-68 years), served as normals (N). They had no history or any clinical signs of alcoholism, gastrointestinal disease, of hyperparathyroidism.

Group 2

Fifteen chronic alcoholics (A), eight women and seven men with a mean age of 41 years (range 27-71 years), had an alcohol index of more than 100 g/day for at least five years. They were characterised by a fatty liver, but had no history or biochemical signs of pancreatic affection.

Group 3

Thirty five patients suffered from chronic alcoholic

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Received for publication 17 October 1983.

pancreatitis of different stages. They were classified according to the results of the secretin/CCK test into four subgroups: (a) Eight patients (CP), three women and five men with a mean age of 37 years (range 29–47 years), had chronic alcoholic pancreatitis with a typical history of chronic relapsing hyperamylasaemia, hyperlipasaemia accompanied by painful abdominal attacks. They presented a normal secretin/CCK test and were classified as 'early stage' of chronic pancreatitis. (b) Eight patients (NCP_{mod}), one woman and seven men with a mean age of 43 years (range 31–67 years), had chronic alcoholic pancreatitis accompanied by moderate exocrine pancreatic insufficiency characterised by a decrease of two parameters as determined in the secretin/CCK test. (c) Nine patients (NCP_{sev}), one woman and eight men with a mean age of 41 years (range 34–49 years), had advanced alcoholic pancreatitis with severe exocrine insufficiency of all parameters. (d) The remaining 10 patients (CCP), two women and eight men with a mean age of 43 years (range 32–49 years), presented distinct exocrine insufficiency and radiologically visible calcifications in the pancreatic area.

EXPERIMENTAL DESIGN

After overnight fasting all subjects were intubated with a double luminal Lagerlöf tube under radiological control to localise its exact position in the stomach and duodenum. Pancreatic stimulation was performed by simultaneous intravenous administration of 1 U/kg/h secretin (Kabi Diagnostica, Studsvik, Sweden, batch no 69200901) and CCK (Kabi Diagnostica, batch no 169901) respectively (secretin/CCK test). Duodenal and gastric juices were collected separately. The continuously aspirated gastric juice was discarded. Duodenal juice was collected on ice in three 20 minute samples (fraction I–III) for one hour and directly submitted to analysis.

ANALYTICAL DETERMINATIONS

The volumes of all samples were read to the nearest 0.1 ml. Each sample was then analysed for total and ionised calcium concentrations. Finally, in each sample the pH was determined. pH values were monitored by a pH electrode (Radiometer, Copenhagen, Denmark). Total calcium concentrations were determined by flame photometry (Eppendorf, Hamburg, West Germany). The concentration of ionised calcium was determined by means of a calcium selective ion exchange electrode (type IS 561-Ca⁺⁺, Philips, Netherlands). The characteristics of ion selective electrodes and techniques of measurements have been described in detail else-

where.^{12–17}

All measurements were performed at 25°C. Calcium values are given in concentration terms. The electrode was calibrated with solutions containing different concentrations of CaCl₂ (10⁻³–10⁻² mM) but constant concentrations of NaCl (141 mM), KCl (7.5 mM) and MgCl₂ (0.25 mM), corresponding to the values obtained in human duodenal juice.^{18, 19} Standard solutions were adjusted to pH 7.8–8.2 and pH 8.3–8.7 by triethanolamine respectively²⁰ according to the pH determined in the sample solution. The electrode response was linear over the 0.05–100.00 mM range (Fig. 1). Neglecting the possible effects of other cations within this range the potential difference ΔE between unknown and standard solution is given by:

$$[Ca^{++}_{unk}] = [Ca^{++}_{std}] \times 10^{\Delta E/S}$$

S is the slope of the plot of log [Ca⁺⁺] against millivolt potential obtained from measurements in standard solutions. The measuring accuracy of 59 samples of ionised calcium standard solutions presented a variation coefficient of 4.08%. Outputs for ionized and total calcium were calculated as

$$\frac{\text{conc} \times \text{vol}}{\text{kg body weight}}$$

STATISTICAL ANALYSIS

Values are given as means ± SEM. Statistical analysis was carried out using the Student's *t* test for unpaired values.

Fig. 1 Calibration line of standard solutions with pH 7.8–8.2.

Results

CALCIUM CONCENTRATIONS

Total and ionised calcium concentrations are shown in Figures 2 and 3. Chronic alcoholism leads to a significant increase in total calcium concentration in fractions II and III and of ionised calcium in all three fractions when compared with normal subjects.

In the early stage of chronic alcoholic pancreatitis (CP), total calcium concentrations are not statistically different from those of normal subjects, whereas ionised calcium values are significantly enhanced in fraction I and II. Comparing alcoholics (A) to CP patients, no difference can be seen for total as well as for ionised calcium concentrations.

In later stages of the disease, (NCP_{mod}) total calcium is raised in fraction II and III and ionised calcium concentrations are increased in all three fractions as compared to normal. Comparing A to NCP_{mod} and CP to NCP_{mod} respectively, a significant increase was only found for ionised calcium concentrations in fraction I and II of NCP_{mod} patients ($p < 0.05$).

For total calcium significant differences are found comparing advanced stages of chronic alcoholic pancreatitis (NCP_{sev}, CCP) with normal subjects. When comparing these two groups with alcoholics, significant higher calcium concentrations are

observed ($p < 0.001$ in I, $p < 0.05$ in II, and $p < 0.005$ in III). Statistical differences are also found for fraction I and II of CP patients ($p < 0.005$) and for NCP_{mod} in fraction I ($p < 0.05$).

NCP_{sev} and CCP show significantly enhanced concentrations of ionised calcium compared with normal subjects, chronic alcoholics ($p < 0.001$), CP ($p < 0.001$), and NCP_{mod} ($p < 0.005$) in all fractions. Between severe non-calcified (NCP_{sev}) and calcified pancreatitis (CCP) no statistical difference can be observed in respect to their total and ionised calcium concentrations.

Values of bound calcium are shown in Table 1. Bound calcium concentrations in A, CP, and NCP_{mod} were similar to those of normal subjects, except for fraction III of A and NCP_{mod}, which presented higher concentrations of bound calcium. In severe exocrine insufficiency (NCP_{sev}, CCP) bound calcium concentrations were distinctly raised as compared with normal subjects, chronic alcoholics ($p < 0.005$) in I, $p < 0.05$ in II and III, respectively), to CP in fraction I ($p < 0.01$) and II ($p < 0.05$) and to NCP_{mod} in fraction I ($p < 0.05$). These significances are similar to those of total calcium concentrations in the duodenal juices. No statistical difference was observed for bound calcium concentrations in the duodenal juice between A and CP as well as between NCP_{sev} and

Fig. 2 Total calcium concentrations in duodenal juice of normals (N), chronic alcoholics (A), and patients with different stages of chronic alcoholic pancreatitis (CP, NCP_{mod}, NCP_{sev}, CCP). A, CP, NCP_{mod}, NCP_{sev}, CCP vs N: * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.005$, † = $p < 0.001$; NS = not significant.

Fig. 3 Ionised calcium concentrations in duodenal juice of normals (N), chronic alcoholics (A), and patients with different stages of chronic alcoholic pancreatitis (CP, NCP_{mod}, NCP_{sev}, CCP). A, CP, NCP_{mod}, NCP_{sev}, CCP vs N: * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.005$, † = $p < 0.001$; NS = not significant.

CCP respectively.

CALCIUM OUTPUTS

Total, ionised, and bound calcium outputs are shown in Table 2. Patients with severe exocrine insufficiency (NCP_{sev}, CCP) present significantly raised values of total, ionised, and bound calcium in fraction I; in fraction II and III only total and ionised calcium outputs are significantly enhanced compared with those of normals, except bound calcium outputs of NCP patients in fraction II. NCP_{sev} and CCP are not statistically different from each other with exception of ionised calcium output in fraction I ($p < 0.05$). Comparing A with CP and A with NCP_{mod} respectively, no significant differences of calcium outputs in these groups were found. The comparison of calcium outputs of alcoholics with those of normal subjects, however, reveal significantly higher outputs for all calcium fractions in alcoholics except total and bound calcium outputs in fraction I.

Table 3 shows the percentage difference of

ionised and bound calcium to total calcium outputs. No major differences in the proportionate calcium binding was observed in A, CP and NCP_{mod}. In fraction III of patients with severe non-calcified pancreatitis (NCP_{sev}) ionised calcium was significantly increased ($p < 0.05$) and the bound calcium fraction was decreased. In CCP patients all fractions showed a significant difference in the proportionate calcium binding showing a significant increase of the ionised calcium fraction.

Discussion

The applied method of ionised calcium determination in the duodenal juice presented reliable and reproducible results after calibration with appropriate standard solutions. Simultaneous determination of total and ionised calcium concentrations in the same sample allowed calculation of the bound calcium fraction. The application of Ca^{++} selective electrodes is an appropriate method to study in detail calcium secretion in the duodenal juice.

Total calcium concentrations in the duodenal juice were in agreement with those reported previously by Goebell *et al*¹ and Warwick *et al*,⁷ who found similar values in normal subjects and patients with chronic calcified pancreatitis. Enhanced levels of total calcium concentrations in patients with moderate and severe non-calcifying pancreatitis as shown in the present study, are in accordance with preceding results^{4,5,7} but are in contrast with observations of reduced total calcium concentrations in non-calcifying pancreatitis.¹

The increase of total calcium outputs in the duodenal juice of patients suffering from chronic alcoholic pancreatitis are similar to those reported earlier^{8,9} indicating that raised duodenal calcium secretion is not merely a reflexion of reduced

Table 1 Concentration of bound calcium (=calculated difference of total and ionised calcium) in the duodenal juice under simultaneous stimulation with 1 U/kg/h secretion and CCK respectively

Patients	Fraction I	Fraction II	Fraction III
N (n=20)	0.65±0.11	0.41±0.06	0.27±0.03
A (n=15)	0.61±0.07‡	0.58±0.10‡	0.37±0.04*
CP (n=8)	0.67±0.15‡	0.48±0.08‡	0.42±0.12‡
NCP _{mod} (n=8)	0.91±0.25‡	0.66±0.16‡	0.47±0.05†
NCP _{sev} (n=9)	1.85±0.46**	1.04±0.26**	0.60±0.11***
ccp (n=10)	1.82±0.44***	0.97±0.17†	0.59±0.14*

A, CP, NCP_{mod}, NCP_{sev}, CCP vs N: * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.005$, † = $p < 0.001$; ‡ = not significant. Values in mmol/l.

Table 2 Outputs of total (Ca_{tot}), ionised (Ca_{ion}), and bound (Ca_{bound}) calcium in duodenal juice under simultaneous stimulation with 1 U/kg/h secretin and CCK respectively

Patients	Fraction I			Fraction II			Fraction III		
	Ca_{tot}	Ca_{ion}	Ca_{bound}	Ca_{tot}	Ca_{ion}	Ca_{bound}	Ca_{tot}	Ca_{ion}	Ca_{bound}
N (n=20)	1.06±0.18	0.16±0.02	0.90±0.17	1.04±0.13	0.22±0.03	0.82±0.12	0.84±0.09	0.22±0.03	0.63±0.08
A (n=15)	1.28±0.25‡	0.22±0.07*	0.96±0.18‡	1.63±0.21*	0.39±0.07**	1.24±0.17*	1.30±0.07**	0.34±0.07*	0.97±0.12**
CP (n=8)	1.18±0.22‡	0.25±0.03*	0.94±0.20‡	1.28±0.21‡	0.30±0.04*	0.98±0.19‡	1.08±0.25‡	0.25±0.07‡	0.83±0.19‡
NCP _{mod} (n=8)	1.18±0.20‡	0.30±0.03*	0.89±0.18‡	1.30±0.28‡	0.42±0.14‡	0.89±0.18‡	1.11±0.20‡	0.36±0.13‡	0.76±0.09‡
NCP _{sev} (n=9)	2.17±0.43**	0.49±0.08‡	1.68±0.42*	1.70±0.25**	0.52±0.09‡	1.18±0.24‡	1.22±0.20*	0.48±0.10**	0.75±0.12‡
CCP (n=10)	3.03±0.53‡	0.73±0.08‡	2.31±0.50***	1.89±0.34**	0.53±0.07‡	1.36±0.30***	1.23±0.23	0.37±0.05‡	0.80±0.20‡

*A, CP, NCP_{mod}, NCP_{sev}, CCP vs N; **10<0>0.05, ***10<0>0.005, †0.001<0>0.01; ‡Values in µmol/20 min/kg. Values in µmol/20 min/kg.

Table 3 Percentage difference of ionised and bound to total calcium within each group

Patients	Fraction I		Fraction II		Fraction III	
	Ca _{ion}	Ca _{bound}	Ca _{ion}	Ca _{bound}	Ca _{ion}	Ca _{bound}
N (n=20)	18.9±2.1	81.1±2.1	21.9±2.6	78.1±2.6	26.2±2.3	73.8±2.3
A (n=15)	24.7±2.1‡	75.3±2.0	25.5±3.3‡	74.5±3.3	25.2±2.0‡	74.8±2.0
CP (n=8)	26.8±6.4‡	73.2±6.4	25.4±3.0‡	74.6±3.0	22.9±1.9‡	77.1±1.9
NCP _{mod} (n=8)	28.3±5.7‡	71.7±5.7	31.4±5.3‡	68.6±5.3	27.4±4.3‡	72.6±4.3
NCP _{sev} (n=9)	29.6±6.8‡	70.4±6.8	32.4±5.2‡	67.6±5.2	38.4±4.7*	61.6±4.7
CCP (n=9)	29.4±4.0*	70.6±4.0	32.5±4.4*	67.5±4.4	38.6±2.0***	61.4±2.0

*=p<0.05, ***=p<0.005 vs N; ‡=not significant.

volume secretion by the diseased pancreas, but represents an increase in the absolute amount of calcium flux into the duodenum. The distinctly raised total calcium outputs in chronic alcoholics, which are similar to those of severe non-calcified and calcified pancreatitis may be explained by the increased volume secretion as compared with normal subjects.

The decrease of all calcium fractions (concentrations and outputs) with time after stimulation may be interpreted as a 'washout' phenomenon.

Gall bladder bile with its high calcium concentration^{1 18} (and unpublished results) may be excluded as the predominant source of enhanced calcium concentrations in the duodenum of patients with reduced volume secretion, since Regan *et al*⁸ showed that the rise of duodenal calcium concentration in chronic alcoholic pancreatitis is independent of the presence or absence of the gall bladder.

The increase of duodenal total calcium concentrations in chronic alcoholics and the progressive increase in the course of chronic alcoholic pancreatitis is the result of an increased secretion of ionised as well as of bound calcium. As no major differences were found in the proportionate calcium binding for A, CP, and NCP_{mod} it is suggested that all three calcium fractions rise in parallel. Modifications of the proportionate calcium binding were observed in fraction III of NCP_{sev} and in all fractions of CCP in favour of the ionised calcium fraction. The fact that about 38% of total calcium was ionised in fraction III of NCP_{sev} and CCP patients, which is near to that of ionised serum calcium (40–45%),^{14 21} suggests a direct flux of calcium from serum into the pancreatic juice. It is possible that this serum calcium passes through ductal lesions by diffusion into the ductal system. Those lesions have been shown by Nakamura *et al*.¹¹ Another source of raised ionised calcium concentrations could be a decrease of pancreatic enzyme bound calcium in exocrine insufficiency and a decreased citrate secretion²² which has been shown in chronic

calcified pancreatitis. As enzyme concentrations in chronic alcoholics and patients with early stages of alcoholic pancreatitis are in the range of normals, raised ionised calcium concentrations in these groups cannot originate from a decrease of enzyme bound calcium. As no linear relationship was found between pH and ionised calcium concentrations in all groups it is suggested that moderate pH variations in the duodenal juice do not affect ionised calcium concentrations.

The increase of bound calcium in the course of chronic alcoholic pancreatitis, which is accompanied by a progressive decrease of enzyme secretion, may suggest that other substances than pancreatic enzymes are responsible for calcium binding in the duodenal juice. Those substances could be serum proteins (albumin, immunoglobulins) which occur in higher concentrations in the duodenal juice of patients with chronic alcoholic pancreatitis.^{23 24} Therefore we assume that not only ionised serum calcium but also serum proteins could pass through ductal lesions in the pancreatic ducts.

Increased calcium concentrations in the pancreatic juice are considered to be a major cause of pancreatic lithogenicity. As increased calcium concentrations are already present in the duodenal juice of chronic alcoholics and patients with early stages of alcoholic pancreatitis, we suggest that additional factors must be involved in pancreatic stone formation. This assumption is based on the observation that no difference in calcium secretion was found between severe non-calcified and calcified pancreatitis. We have recently isolated a so far unknown secretory protein from human pancreatic stones ('stone protein')^{25 26} with high calcium binding affinity²⁷ which was shown to inhibit specifically the precipitation and nucleation of calcium carbonate *in vitro*.²⁸ Its concentration in pure pancreatic juice of patients with advanced alcoholic pancreatitis is distinctly decreased²⁹ and may therefore favour calcium carbonate precipitation and pancreatic stone formation in the supersaturated pancreatic juice.

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