Fibrocalculous Pancreatic Diabetes

Long-term survival analysis

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OBJECTIVE — To determine the long-term survival and causes of death in fibrocalculous pancreatic diabetes, a form of diabetes secondary to tropical chronic pancreatitis.

RESEARCH DESIGN AND METHODS — A cohort of 370 patients with fibrocalculous pancreatic diabetes were analyzed with respect to survival time from the date of occurrence of the first symptom of the disease as well as after the onset of diabetes. The cause of death was analyzed in the patients who died. Cumulative survival rates were calculated by the actuarial method, and life table graphs were plotted by mathematical calculations.

RESULTS — Long-term survival of patients with fibrocalculous pancreatic diabetes is much better today than that described 30 years ago. About 80% of patients were alive 35 years after the first episode of abdominal pain. The median survival time after the diagnosis of diabetes was 25 years. These figures, however, are still considerably lower than the life expectancy of the age- and sex-matched general population. Diabetic nephropathy was the main cause of death. Pancreatic cancer and other chronic pancreatitis-related causes as well as malnutrition and infections were also important contributors to mortality.

CONCLUSIONS — The overall prognosis for patients with fibrocalculous pancreatic diabetes appears to have improved possibly because of earlier diagnosis, better management of diabetes, and improved nutrition.

Fibrocalculous pancreatic diabetes is a unique form of diabetes secondary to tropical nonalcoholic chronic pancreatitis (1–3). Tropical chronic pancreatitis differs from temperate-zone chronic pancreatitis in several respects: the disease is seen in endemic proportions in certain areas of the world, e.g., southern India; the onset of the disease is at a younger age and alcoholism is absent. We (4–7) and others (8–11) have reported on the clinical profile of fibrocalculous pancreatic diabetes. The first symptom of the disease is usually severe recurrent abdominal pain, which invariably starts in childhood. Pain is present in 80–90% of patients in most series (2,3,8–11). Pancreatic calculi are usually detected a decade after the first episode of abdominal pain, and diabetes invariably sets in soon thereafter (2,3,8–11). The prevalence of diabetes in tropical chronic pancreatitis is considerably higher (>90%) than in temperate-zone pancreatitis (40–50%) (2,3). There are several reports on the course and survival of temperate-zone chronic pancreatitis (12–16), but there is virtually no such data on fibrocalculous pancreatic diabetes. We report here on a large cohort of fibrocalculous pancreatic diabetes patients in whom a survival analysis was done.

RESEARCH DESIGN AND METHODS

A total of 421 patients with fibrocalculous pancreatic diabetes was seen by the senior author (V.M.) over a period of 15 years, i.e., from 1981. Cases were studied initially at the Diabetes Research Center (DRC) and later at the M.V. Diabetes Specialties Center (MVDSC). Both the DRC and MVDSC are private diabetes centers at Madras in the southern state of Tamil Nadu, with several thousand diabetic patients. Fibrocalculous pancreatic diabetes constitutes ~1% of all diabetic patients registered at these centers (3). Out of the 421 patients, 51 had incomplete case records (e.g., there were no details of pain and other vital statistics), and patients were lost to follow-up and, hence, these were excluded. The remaining 370 patients, in whom reliable data with respect to two specific events, namely abdominal pain and diabetes, were available, were included in the study.

Diagnosis of fibrocalculous pancreatic diabetes was made based on our previously published criteria (3). All patients had diabetes according to criteria of the World Health Organization (WHO) study group on diabetes (1). All had chronic pancreatitis, evidence for which was based on presence of pancreatic calculi on a plain abdominal X-ray and/or ultrasound or endoscopic retrograde cholangio-pancreatographic (ERCP) evidence of dilated pancreatic ducts with intraductal stones and low fecal chymotrypsin levels according to criteria established earlier (17).

All patients were recalled for a final review before completion of the study in June of 1995. If the patient was unable to come back for review, contact was made with the patient's family by telephone or letter to inquire about the present vital status of the patient, if alive, or the cause of death. In 278 patients, the vital status could be determined in 1995. In the remaining 92 patients, the vital status was unknown in 1995. However, data with respect to the last known date of survival was included in the actuarial survival analysis. For example, if a patient was known to be alive up to 1991 and thereafter lost to follow-up, the survival up to 1991 was included in the analysis.

The onset of the disease was defined by the date of the first symptom clearly related to chronic pancreatitis. In the majority of patients (n = 299), this was the first episode of typical abdominal pain. In some patients, there was no history of pain, and pancreatic

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ACP, alcoholic chronic pancreatitis; DRC, Diabetes Research Center; ERCP, endoscopic retrograde cholangio-pancreatographic; MVDSC, M.V. Diabetes Specialties Center; NACP, nonalcoholic chronic pancreatitis.

Table 1—*Clinical details of patients with fibrocalculous pancreatic diabetes*

Sex	
Male	260 (70)
Female	110 (30)
Age at onset of abdominal pain (years) (range 2–68 years)	21 ± 14
Age at onset of diabetes (years)	29 ± 11
BMI (kg/m^2)	18.6 ± 3.2
Abdominal pain	299 (81)
Pancreatic calculi	364 (98)
Smoking	53 (14)
Fasting plasma glucose (mmol/l)	10 ± 1
HbA_{1c} (%)	10.3 ± 2.0
Fecal chymotrypsin (U/g)	3.8 ± 4.0
Normal	>5.8

Data are means ± SD or *n* (%). *n* = 370.

calculi and diabetes were the initial manifestations of the disease (*n* = 71).

For each patient, the following data was recorded: sex, age at first occurrence of abdominal pain, age at diagnosis of pancreatic calculi and/or ductal dilatation and diabetes, the date and cause of death, or the date of last follow-up available.

Statistical analysis

Cumulative survival rates were calculated by the actuarial method (18). Briefly, the life table estimate of the survivor function, which is also known as the actuarial estimate, is obtained by first dividing the period of observation into a series of time intervals. This method is suitable where the survival times are frequently censored. The survival time of an individual is said to be censored when the endpoint of interest (e.g., death) has not been observed for that individual. This may be because the data from a study are analyzed at a point in time when some individuals are still alive. Alternatively, the survival status of an individual at the time of the analysis might not be known because that individual has been lost to follow-up. Using mathematical calculations, the cumulative survival can then be derived and presented in graphic form. The survival in the patients with fibrocalculous pancreatic diabetes was compared with the life expectancy of the age- and sex-matched normal population of Tamil Nadu based on the life tables provided by the Registrar General of India (19).

RESULTS — Table 1 lists the clinical data of the study population. There were 260 men and 110 women (sex ratio M:F, 7:3). The mean age at the time of study was 41 ± 13 years (range 7–77). History of abdominal pain was present in 299 patients, while the remaining 71 patients denied any history of pain. Pancreatic calculi were present in 364 patients. In the remaining 6 patients, ductal dilatation was demonstrated by ERCP, and ultrasonography and fecal chymotrypsin tests were also abnormal according to criteria established earlier (17).

Table 2 shows the prevalence and causes of death in the 27 patients who died. The two leading causes of death were diabetic renal failure (41%) and pancreatic cancer (22%). Malnutrition and severe infections (e.g., tuberculosis, meningitis) and chronic pancreatitis–related complications were other important causes of death. The mean age at the time of death was 39 ± 10 years, and the mean survival time after onset of abdominal pain and diabetes was 15 ± 10 and 10 ± 5 years, respectively.

On analyzing the 299 patients who had abdominal pain, the average length of follow-up after the onset of abdominal pain was 23.2 years, i.e., 6,937 patient-years.

Table 2—*Causes of death in fibrocalculous pancreatic diabetes*

Diabetes-related deaths	14 (51.9)
Renal failure	11 (40.7)
Ketoacidosis	1 (3.7)
Myocardial infarction	1 (3.7)
Cerebrovascular accident	1 (3.7)
Pancreatic cancer	6 (22.2)
Malnutrition and infections	3 (11.1)
Related to chronic pancreatitis (e.g., pseudocysts, acute pancreatitis)	2 (7.4)
Postoperative complications	1 (3.7)
Unknown causes	1 (3.7)

Data are *n* (%). *n* =27.

There were 22 deaths in this cohort. Thus, the mortality rate after abdominal pain is 22 in 6,937 or 317 in 100,000 patient-years.

The average length of follow-up after the onset of diabetes in the whole cohort of 370 patients was 7.7 years, i.e., a total of 2,849 patient-years. The mortality rate after the onset of diabetes is therefore 27 in 2,849 or 948 in 100,000 patient-years.

The cumulative survival rates for fibrocalculous pancreatic diabetes after the onset of abdominal pain are shown in Table 3 and Fig. 1. It can be seen that ~80% of patients were alive 35 years after the first episode of abdominal pain.

The cumulative survival rates after the onset of diabetes are shown in Table 4 and Fig. 2. The median survival time was estimated to be 25 years after the onset of diabetes.

Table 5 shows a breakdown of the median survival of the 299 patients with abdominal pain according to the age at onset of pain. The data is compared with the expected life expectancy of the age- and sex-matched general population of Tamil Nadu (9).

Table 3—*Cumulative survival after first episode of abdominal pain*

Survival time (years)	No. of patients at start of interval (n_i)	Death (d_i)	Censored (c_i)	No. exposed to risk $n'_i = n_i - c_i/2$	Proportion surviving $(n_i - d_i)/n$	Proportion surviving to end of interval $S(t)$	SE of $S(t)$	95% CI for $S(t)$
0–4	299	6	74	262	0.9771	0.9771	0.009	(0.9595–0.9947)
5–9	219	3	44	197	0.9848	0.9622	0.012	(0.9387–0.9857)
10–14	172	3	33	155	0.9807	0.9436	0.016	(0.9122–0.9750)
15–19	136	3	25	123	0.9757	0.9207	0.021	(0.8795–0.9619)
20–24	108	2	34	91	0.9780	0.9005	0.025	(0.8515–0.9495)
25–29	72	3	20	62	0.9516	0.8569	0.034	(0.7903–0.9235)
30–34	49	1	22	38	0.9737	0.8344	0.040	(0.7560–0.9128)
35+	26	1	25	13	0.9259	0.7726	0.056	(0.6628–0.8824)

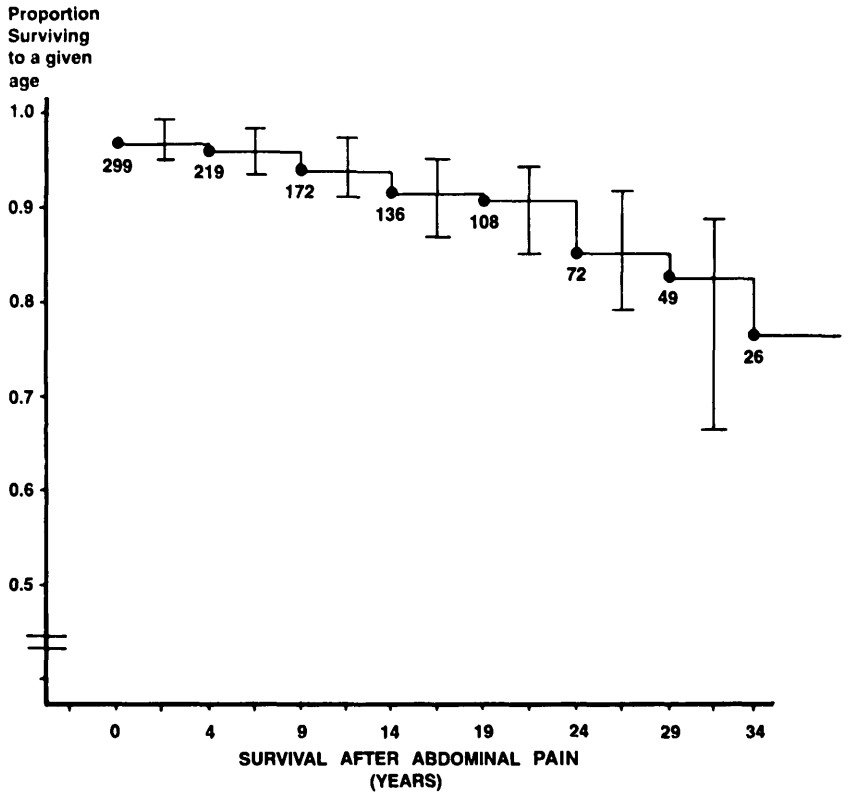

Figure 1—*Cumulative survival in fibrocalculous pancreatic diabetes patients after onset of abdominal pain. Numbers represent number of patients surviving at the beginning of each interval. The vertical lines represent 95% CI.*

For this analysis, the median of the known period of survival of each patient in the various class intervals was calculated. The survival time of the study cohort is considerably lower than the general population at all age intervals, in both sexes.

CONCLUSIONS — This study reports for the first time to our knowledge on survival rates for fibrocalculous pancreatic diabetes. Our data suggests that long-term prognosis for fibrocalculous pancreatic diabetes is quite good, with a mean survival of 35 years after the first episode of abdominal pain and 25 years after the onset of diabetes. Thus, this report is in contrast to the observation made 30 years ago by Geevarghese, when the disease was originally described, that fibrocalculous pancreatic diabetes is a disease where "abdominal pain occurs in early adulthood, diabetes sets in during adolescence and death occurs in early adulthood" (2). An overall improvement in nutrition and dietary habits, early diagnosis of the disease, and better management of diabetes and its complications are the possible factors for the better prognosis noted now. It must be admitted, however, that despite improved survival, the quality of life still remains poor for many patients because of repeated episodes of abdominal pain, steatorrhea, and diabetes-related complications.

The data shown in Table 5 suggests that the median survival of the patients with fibrocalculous pancreatic diabetes is considerably shorter than that of the age- and sex-matched general population. Although we do not have survival data for NIDDM and IDDM in India, it is possible that even in these more common types of diabetes, the survival rate is less than that for the general population. However, it should be pointed out that the survival figures in Table 5 are probably an underestimate. This is because while the period of survival is accurate in the death cases and in those who are definitely known to be alive, in those lost to follow-up, the survival has been calculated only up to the last follow-up date available. It is therefore likely that the actual survival rates are higher because many of those lost to follow-up may be alive.

Comparison of our data with reports on temperate-zone pancreatitis is difficult because of different methodologies used in different studies. Levy et al. (13) reported that in the French population studied, the cumulative survival rate was 64.2% after 20 years of the disease. However, the age at onset of the pancreatitis was considerably later in their series (41.5 ± 6.1 years) compared with our series (21 ± 14 years). Layer et al. (16) reported a mean life expectancy of 80 years in late onset idiopathic chronic pancreatitis and 71.9 years in alcoholic chronic pancreatitis. Lankisch et al. (15) reported a 10-year survival rate of 80% for nonalcoholic pancreatitis and 65% for alcoholic pancreatitis. After 20

Table 4—*Cumulative survival after diagnosis of diabetes*

Survival time (years)	No. of patients at start of interval (n_i)	Death (d_i)	Censored (c_i)	No. exposed to risk $n'_i = n_i - c_i/2$	Proportion surviving $(n_i - d_i)/n$	Proportion surviving to end of interval $S(t)$	SE of $S(t)$	95% CI for $S(t)$
0–4	370	2	139	300	0.9933	0.9933	0.005	(0.9835–1.000)
5–9	229	9	99	179	0.9499	0.9435	0.017	(0.9102–0.9768)
10–14	121	10	58	92	0.8913	0.8410	0.034	(0.7744–0.9076)
15–19	53	4	33	36	0.8904	0.7488	0.053	(0.6449–0.8527)
20–24	16	1	8	12	0.9167	0.6864	0.077	(0.5355–0.8373)
25+	7	1	6	4	0.7500	0.5148	0.129	(0.2620–0.7676)

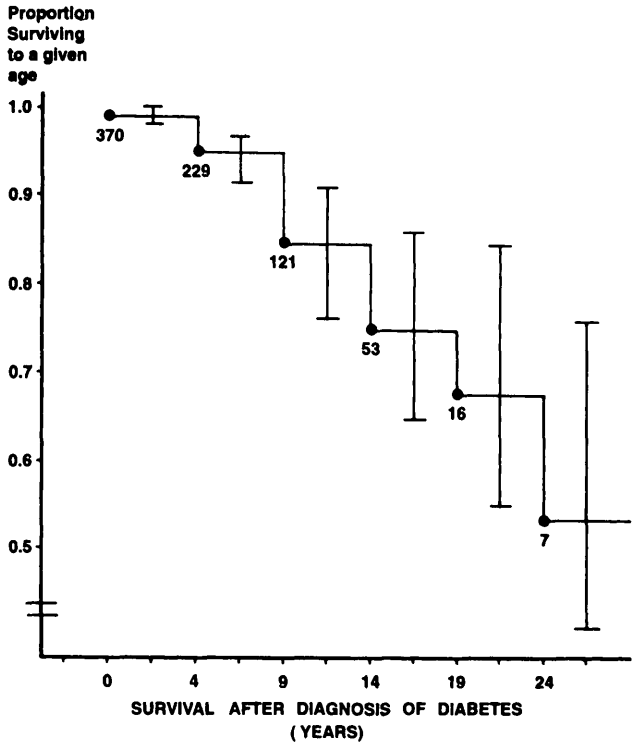

Figure 2—*Cumulative survival in patients with fibrocalculous pancreatic diabetes after diagnosis of diabetes. Numbers represent number of patients surviving at the beginning of each interval. The vertical lines represent 95% CI.*

years, these figures decreased to 46 and 12%, respectively, and after 30 years, to 15 and 4%, respectively.

The study by Miyake et al. (12) also confirms that the prognosis is worse in alcoholic chronic pancreatitis (ACP) compared with nonalcoholic chronic pancreatitis (NACP). In their series, the cumulative survival in ACP was 60% after 12 years' duration, while it was 65% in NACP.

There is virtually no data available on long-term survival in patients with fibrocalculous pancreatic diabetes. A recent report by Yajnik and Shelgikar (20) reported on causes of death in 11 patients with fibrocalculous pancreatic diabetes, but no lifetime survival data was presented, obviously because of the small number of patients studied.

Diabetes-related complications appear to be the most frequent cause of death in our patients with fibrocalculous pancreatic diabetes, and renal failure contributes to 40% of all deaths. Malnutrition, probably secondary to both chronic pancreatitis (due to steatorrhea and malabsorption) and uncontrolled diabetes in association with chronic infections, is another important cause of death. Similar findings have been reported earlier (20). The occurrence of pancreatic cancer in fibrocalculous pancreatic diabetes has been previously reported by us (21) and others (22). Indeed, the risk of developing pancreatic cancer appears to be higher in tropical pancreatitis compared with temperate-zone chronic pancreatitis (21–25).

The low frequency of deaths due to myocardial infarction (n = 1) in this series is of interest. In temperate-zone pancreatitis, higher prevalence of ischemic heart disease has been reported, and between 9 and 25% of deaths have been reported to be due to cardiac causes (12,14,16). This is probably related to the older age group

Table 5—*Median survival of study group with abdominal pain compared with age- and sex-matched life expectancy of the general population of Tamil Nadu*

	Males (n = 205)		Females (n = 94)	
Age at onset of pain (years)	Known median survival time of study cohort (years)	Life expectancy of general population in Tamil Nadu (years)	Known median survival time of study cohort (years)	Life expectancy of general population in Tamil Nadu (years)
1–5	26.0 (12)	63.7	8.0 (4)	64.8
6–10	27.0 (57)	61.2	19.0 (23)	62.8
11–15	19.0 (22)	56.8	14.0 (13)	58.4
16–20	17.0 (18)	52.1	15.0 (10)	53.8
21–25	18.0 (9)	47.6	4.0 (13)	49.4
26–30	8.0 (21)	43.2	3.0 (6)	45.0
31–35	7.0 (16)	38.8	7.0 (8)	40.6
36–40	5.0 (18)	34.5	2.0 (5)	36.1
41–45	4.5(14)	30.2	1.0 (1)	31.8
46–50	2.0 (8)	26.0	6.0 (6)	27.3
51–55	3.0 (4)	22.0	5.0 (2)	23.1
56–60	1.0 (2)	18.5	—	19.1
61–65	5.0 (2)	15.2	2.0 (2)	15.3
66–70	1.0 (1)	12.3	1.0 (1)	12.1
>70	1.0 (1)	9.9	—	9.4

For known median survival time of study cohort, data are median (n) and survival is rounded off to the nearest whole number.

of the patients. It is well known that the prevalence of ischemic heart disease is high in Indian NIDDM patients, both in India and abroad (26,27). The low prevalence of ischemic heart disease in fibrocalculous pancreatic diabetes has been reported by us earlier (4). In the report by Yajnik and Shelgikar, out of the 11 deaths, none were due to myocardial infarction. The possible factors responsible for lower rates of ischemic heart disease in fibrocalculous pancreatic diabetes are the younger age of the patients, leanness, and the low serum cholesterol levels (4). The latter could be due to poverty and/or malabsorption secondary to chronic pancreatitis.

In summary, we present survival and mortality data on patients with fibrocalculous pancreatic diabetes and conclude that while long-term survival is more favorable than that reported 30 years ago, it is still considerably less than the survival rate of the general population. The causes of death are usually due to complications related to diabetes and/or chronic pancreatitis.

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