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Exocrine Pancreatic Function (Serum Immunoreactive Trypsin, Fecal Chymotrypsin, and Pancreatic Isoamylase) in Indian Diabetics

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Summary: Forty-nine patients with tropical calcific pancreatitis (TCP), 51 insulin-dependent diabetics (IDDMs), 87 non-insulin-dependent diabetics (NIDDMs), and 66 nondiabetic controls were studied to evaluate their exocrine pancreatic function by measurement of serum immunoreactive trypsin (IRT, normal for white caucasians from the U.K. of 140–414 μg/L), pancreatic isoamylase (PIA, normal of 35–125 U/L), and fecal chymotrypsin (FCT, normal of >6.6 u/g). The majority of patients were studied within 1 year of diagnosis. TCP subjects included 7 nondiabetics, 6 with impaired glucose tolerance (IGT-TCP), and 36 diabetics [fibrocalculous pancreatic diabetes (FCPD)]. There was evidence of active pancreatitis (IRT >800 μg/L) and partial preservation of function in nondiabetic TCP subjects [median IRT of 220 μg/L (range of 102–1,360 μg/L), FCT of 2.2 u/g (range 0.7–12.8 u/g)] and also in IGT-TCP subjects [IRT of 370 μg/L (range of 30–1,360 μg/L), FCT of 4.2 u/g (range of 1–38 u/g)]. FCPDs showed severely diminished exocrine function [IRT of 50 μg/L (range of 0–184 μg/L), FCT of 0.23 u/g (range of 0–10.4 u/g)]; none showed IRT > 800 μg/L. IDDMs and NIDDMs also showed diminished exocrine pancreatic function in ~30 and ~10%, respectively. Controls showed a wide range of IRT and FCT concentrations; IRT concentrations tended to be higher than those reported in white Caucasians from the U.K. Three controls, one IDDM, and two NIDDMs showed "pancreatitic" IRT concentrations in the absence of symptoms. PIA concentrations were diminished in FCPD but were similar in IDDM and NIDDM subjects compared to controls. Simultaneous measurements showed that IRT concentrations were reduced when PIA concentrations were still normal. Our results suggest that TCP and FCPD (diagnosed by radiographically demonstrable pancreatic calculi) represent advanced disease and that a subclinical "pancreatopathy" appears to be common in tropical subjects (diabetic as well as nondiabetic). Endocrine impairment (hyperglycemia) in TCP parallels exocrine damage. **Key Words:** Exocrine pancreatic function—Indian diabetics—Tropical calcific pancreatitis—Fibrocalculous pancreatic diabetes—Immunoreactive trypsin—Fecal chymotrypsin—Pancreatic isoamylase.

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Exocrine pancreatic involvement is the major feature of fibrocalculous pancreatic diabetes (FCPD) (1). FCPD is secondary to tropical calcific pancreatitis (TCP) (2). In a preliminary study, we have shown (3) that serum immunoreactive trypsin

(IRT), a simple marker for exocrine pancreatic function, is subnormal in over 90% of FCPD subjects, in one-third of patients with insulin-dependent diabetes mellitus (IDDM), and also in some with non-insulin-dependent diabetes mellitus (NIDDM). Such diminished exocrine pancreatic function has also been demonstrated in western diabetics (4–10). It is thought that diminished exocrine function in IDDM and NIDDM results from loss of the local trophic effect of insulin on adjacent exocrine acini (11). In tropical areas, however, there might be another explanation, i.e., subclinical pancreatopathy of the type seen in FCPD may be more common and may possibly be a result of some environmental "toxin" (2,12).

We have studied three markers of exocrine pancreatic function—IRT, serum pancreatic isoamylase (PIA), and fecal chymotrypsin (FCT)—in our diabetic and control subjects to determine whether IRT—a serum enzyme—compares well with FCT, based on the release of the pancreatic enzyme into the intestinal lumen. In a smaller number of subjects, we have compared IRT and PIA results to obtain more information on "selectivity" and the possible "sequence" of pancreatic enzyme loss.

SUBJECTS AND METHODS

A total of 253 subjects were studied. Forty-nine subjects were diagnosed as having TCP by history of abdominal pain suggestive of pancreatitis and plain abdominal radiograph that showed pancreatic calculi. Ultrasonography confirmed pancreatic calculi in all. Alcoholism was excluded by history and hepatobiliary disease by ultrasound. Classification as nondiabetic (n = 7), impaired glucose tolerance (IGT-TCP, n = 6), and diabetic (FCPD, n = 36) was based on a 75 g (1.75 g/kg in children below 15 years) oral glucose tolerance test (OGTT) and WHO criteria (1). IDDM subjects (n = 51) were young and ketosis-prone diabetics; NIDDM subjects (n = 87) were treated by diet with or without oral hypoglycemic agents. Nondiabetic controls (n = 66) were without a first-degree family history of diabetes. Clinical characteristics of all subjects are shown in Table 1. IDDMs and NIDDMs were studied within 1 year of the diagnosis of diabetes; 20 FCPDs were studied within 1 year of diagnosis, and the remainder were studied between 1 to 3 years after diagnosis. In subjects taking oral pancreatic enzyme supplements (one FCPD and two IGT-TCP), these were stopped 5 days before blood and stool samples were collected.

TABLE 1. *Basic information on subjects*

	TCP (n = 49)	IDDM (n = 51)	NIDDM (n = 87)	Controls (n = 66)
Age (years)	22 (7–55)	22 (5–38)	40 (23–72)	33 (18–70)
Sex	24M	34M	58M	38M
BMI (kg/m^2)	15.2 (10–24)	16.7 (11–21)	22.5 (17–35)	21.8 (15–33)
Fasting plasma glucose (mmol/L)	6.7 (1.7–26.8)	13.8 (2.7–31.9)	6.4 (3.6–20.7)	4.6 (3.8–7.1)
HbA_1 (μmol/L)	63 (28–160)	88 (41–222)	57 (33–155)	42 (36–54)

Values are median (range).
TCP = tropical calcific pancreatitis; IDDM = insulin-dependent diabetes mellitus; NIDDM = non-insulin-dependent diabetes mellitus; BMI = body mass index; HbA_1 units refer to fructose standards.
TCP patients include 7 nondiabetic, 6 with impaired glucose tolerance, and 36 diabetic [fibrocalculous pancreatic diabetes (FCPD)] subjects.

Fasting serum samples, stored at −20°C, were transported on dry ice to the Royal Free Hospital, London, where IRT was assayed by a specific radioimmunoassay (Hoechst) as described before (6). The normal range of serum IRT for white Caucasians in that study was 140–414 μg/L.

PIA was measured by electrophoretic separation as described (13). The normal range of PIA for white caucasians is 35–125 U/L.

FCT was assayed using "Chymotrypsin-C-System" kit (Boehringer Mannheim GmbH Diagnostica). The assay was adapted to the Abbott VP-Super System and is linear at least between 1 and 100 u/g. Values below 6.6 u/g are thought to be pathologically low.

IRT results were available in a total of 222 subjects, FCT in 115 subjects, and PIA in 42 subjects. In 76 subjects, IRT and FCT were estimated in samples collected within 1 week of each other, and in 42 subjects IRT and PIA results were available on the same sample. Two IRT and FCT tests (up to 1 month apart) were performed in 20 subjects each to test the reproducibility.

Statistical analysis was by the χ^2 test and the Mann–Whitney U test. Correlations were tested using Spearman's rank correlation coefficient.

RESULTS

Serum immunoreactive trypsin (IRT)

Thirty-one of 32 FCPD subjects (97%) had subnormal IRT (<140 μg/L), and 21 (65%) showed se-

verely diminished (<50 μg/L) IRT (Fig. 1). The only FCPD subject to have a normal IRT was shown to have focal pancreatitis on ultrasonography and computed tomography (CT) scan. In the IGT-TCP group, one showed very diminished IRT (<50 μg/L), two were normal, and two were >800 μg/L. In nondiabetic TCP subjects, one had subnormal, three normal, and one >800 μg/L levels of IRT. Twelve of 42 IDDM subjects (26%) had subnormal IRT ($p < 0.02$ compared to controls), and only one had a level <50 μg/L. In NIDDM subjects, there was a wide scatter: 7/77 (9%) showed subnormal IRT (not significant compared to controls), and none < 50 μg/L.

As a group, FCPDs had significantly lower IRT concentrations [median of 50 μg/L (range of 0–253 μg/L)] compared to all other groups ($p < 0.001$ vs. all); IDDMs [median of 175 μg/L (range of 0–1,260 μg/L)] had significantly lower concentrations than NIDDMs [median of 294 μg/L (range of 51–1,260 μg/L)] and controls [median of 371 μg/L (range of 133–1,117 μg/L)], ($p < 0.001$ both). NIDDMs showed significantly lower concentrations than controls ($p < 0.03$).

Controls showed a wider scatter than that reported for the white Caucasian subjects. Seventeen of 53 controls (32%) showed IRT > 414 μg/L, the upper limit reported for the white Caucasian population in U.K.; so did 18/77 NIDDMs (23%). One IDDM, two NIDDM, and three controls showed IRT > 800 μg/L, although none had any clinical evidence of pancreatitis. Remarkably, the mean –

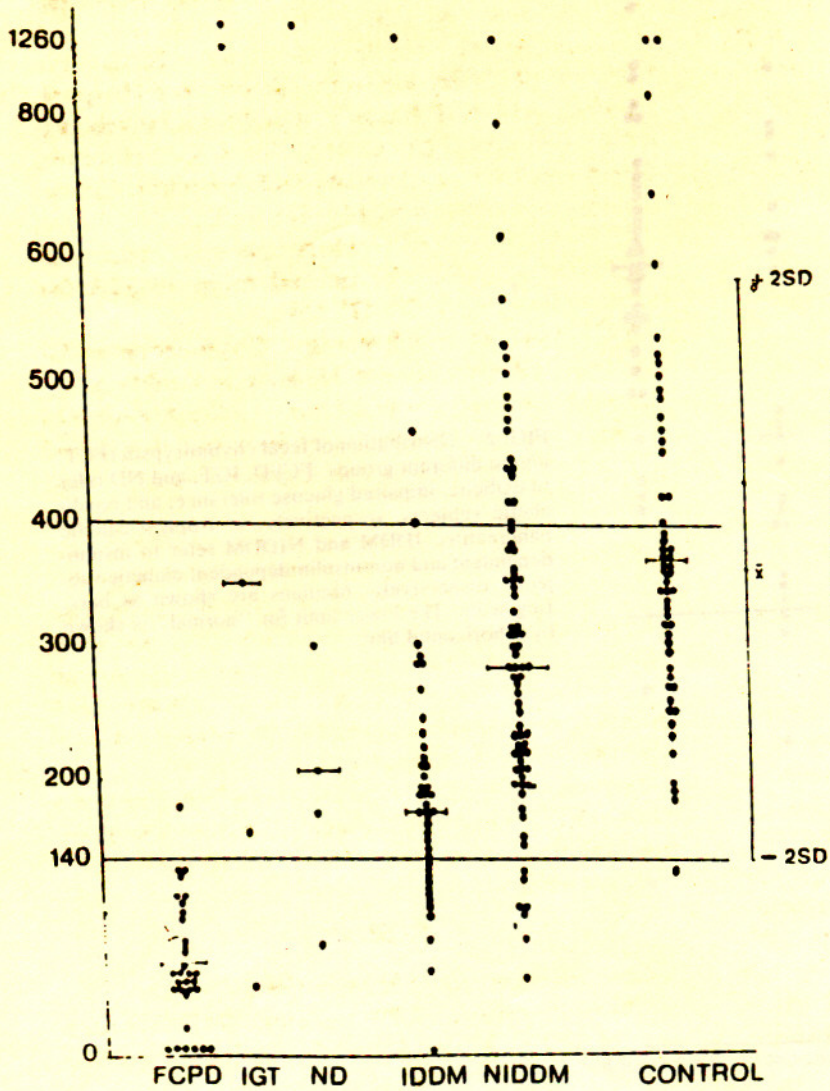

FIG. 1. Distribution of immunoreactive trypsin (IRT, μg/L) in different groups. FCPD, IGT, and ND refer to diabetic, impaired glucose tolerance, and nondiabetic subjects, respectively, of tropical calcific pancreatitis. IDDM and NIDDM refer to insulin-dependent and non-insulin-dependent diabetic subjects, respectively. Medians are shown as bars. "Normal" range for Caucasians is shown by horizontal lines. Mean ± 2SD for nondiabetic controls is shown.

2SD for controls was 142 μg/L, very similar to that in white Caucasians (140 μg/L).

Fecal chymotrypsin (FCT)

Sixteen of 17 FCPD subjects (94%) showed a level of <1 u/g of chymotrypsin activity in the stool (Fig. 2). Although IGT-TCP and nondiabetic TCP subjects showed lower FCT concentrations than controls, they showed better preservation of FCT than FCPD subjects. There was a wide scatter of FCT in IDDM, NIDDM, and control subjects. Nine of 27 IDDM (33%, $p < 0.01$ compared to controls) and 3 of 24 NIDDM subjects (12.5%, not significant) showed subnormal FCT. Thirty-four of 36 control subjects (95%) showed normal concentrations.

As a group, FCPD subjects had significantly lower FCT [median of 0.23 u/g (range of 0–10.4 u/g)] than all other groups ($p < 0.001$ vs. all). IDDM subjects [median of 20 u/g (range of 0.84–81.0 u/g)] were similar to NIDDM subjects [median of 14 u/g (range of 3.7–71.0 u/g)] and controls [median of 29.5 u/g (range of 2.1–106 u/g)]. NIDDM subjects showed significantly lower concentrations than controls ($p < 0.02$).

Repeated IRT and FCT

Two separate tests were performed in 20 subjects (Fig. 3). Both IRT and FCT appear to be fairly reproducible over a period of at least 1 month. The effect of a high-protein diet (>80 g/day for 3 days) on FCT was investigated in eight subjects. In two

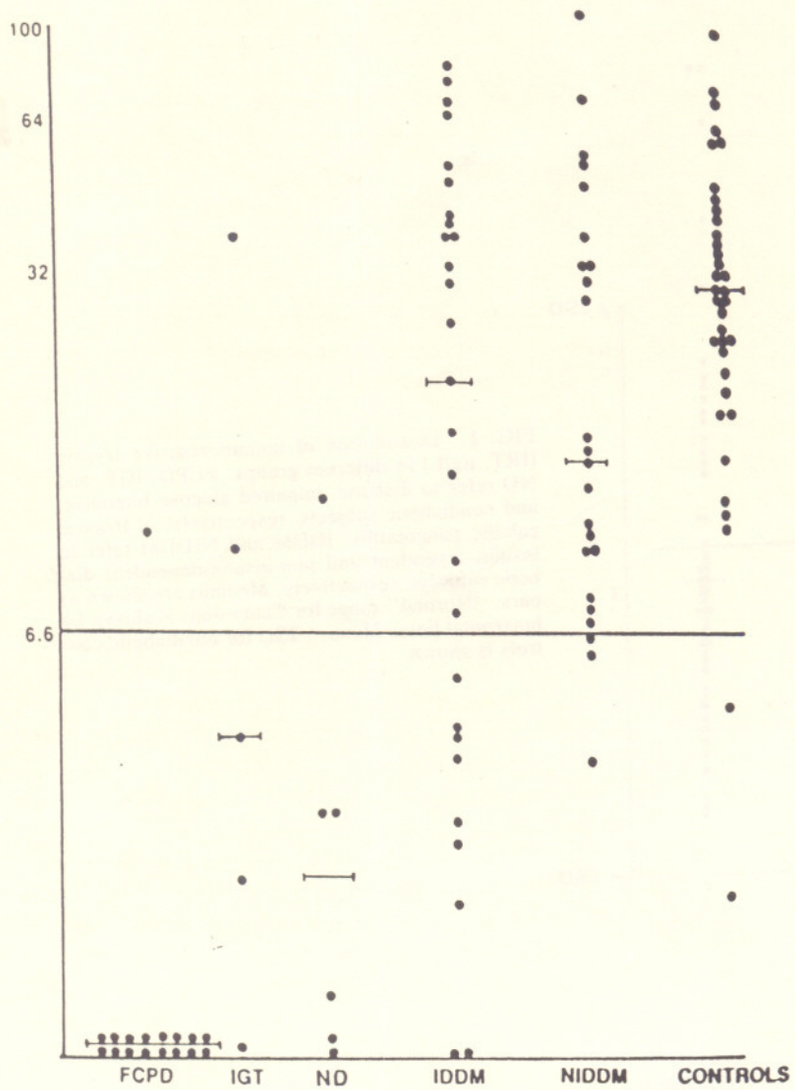

FIG. 2. Distribution of fecal chymotrypsin (FCT, u/g) in different groups. FCPD, IGT, and ND refer to diabetic, impaired glucose tolerance, and nondiabetic subjects, respectively, of tropical calcific pancreatitis. IDDM and NIDDM refer to insulin-dependent and non-insulin-dependent diabetic subjects, respectively. Medians are shown as bars. Log scale. The lower limit for "normal" is shown by a horizontal line.

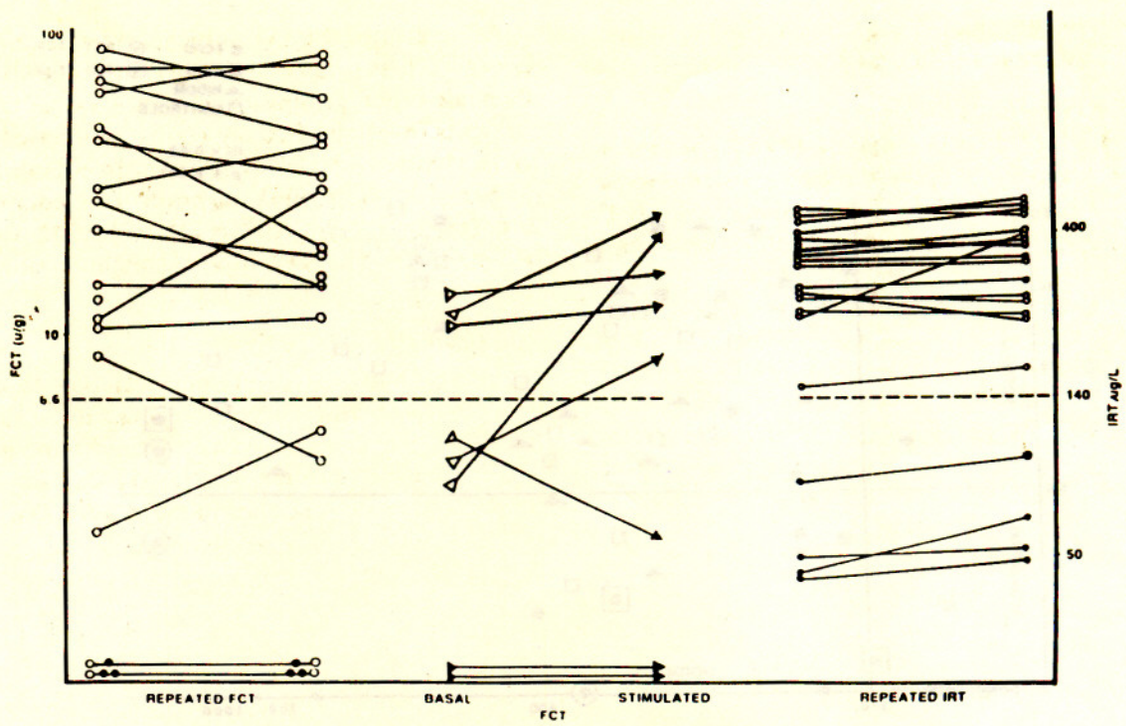

FIG. 3. Two measurements of fecal chymotrypsin (FCT) and immunoreactive trypsin (IRT), up to 1 month apart. In eight subjects, FCT was measured on a normal diet and after 3 days of a high-protein diet (middle panel). Log scale. FCPDs are shown by solid circles or triangles. Broken horizontal lines show the lower limits of normal.

IDDM subjects, there was a rise in FCT significant enough to make a difference in their classification. In the rest, there was no difference.

Pancreatic isoamylase (PIA)

PIA results were available in a total of 42 subjects (6 FCPD, 11 IDDM, 17 NIDDM, and 8 controls). Concentrations in FCPD patients [median of 26 U/L (range of 0–101 U/L)] were significantly lower than those in control subjects [median of 59 U/L (range of 41–99 U/L)] ($p < 0.05$) but not from those in IDDM [median of 43 U/L (range of 15–76 U/L)] and NIDDM subjects [median of 49 U/L (range of 23–116 U/L)].

Correlation between IRT, FCT, and PIA

There was a highly significant correlation between IRT and FCT ($r_s = 0.68$, $p < 0.001$), and between IRT and PIA ($r_s = 0.61$, $p < 0.001$) (Figs. 4 and 5). There were 13 subjects with subnormal FCT but normal or elevated IRT, and 10 with subnormal IRT but normal PIA.

Specificity and sensitivity of IRT and FCT

The specificity and sensitivity of subnormal IRT and subnormal FCT were calculated for the diagnosis of TCP (clinical history and pancreatic calculi seen on abdominal radiograph, confirmed by ultrasonography) and FCPD (diabetic by WHO criteria) (Table 2). The results show a good specificity and sensitivity for both tests.

DISCUSSION

These results confirm on a larger number of subjects our previous observations of IRT in Indian diabetics, and extend it to IGT-TCP and nondiabetic TCP subjects. The results of FCT and PIA are complementary to those of IRT and confirm severe exocrine pancreatic loss in FCPD, with some preservation in IGT and nondiabetic TCP subjects. Similarly, we found diminished exocrine function in about one-third of our IDDM and about one-tenth of NIDDM subjects.

Pancreatic exocrine–endocrine interactions have been recognized for many years (11,14–16). Thus, endocrine deficiency (IGT and diabetes mellitus) is common in subjects with chronic pancreatitis, and endocrine loss parallels exocrine loss (17). On the other hand, exocrine pancreatic deficiency has been demonstrated in IDDM and NIDDM subjects without any history of exocrine pancreatic disease. Exo-

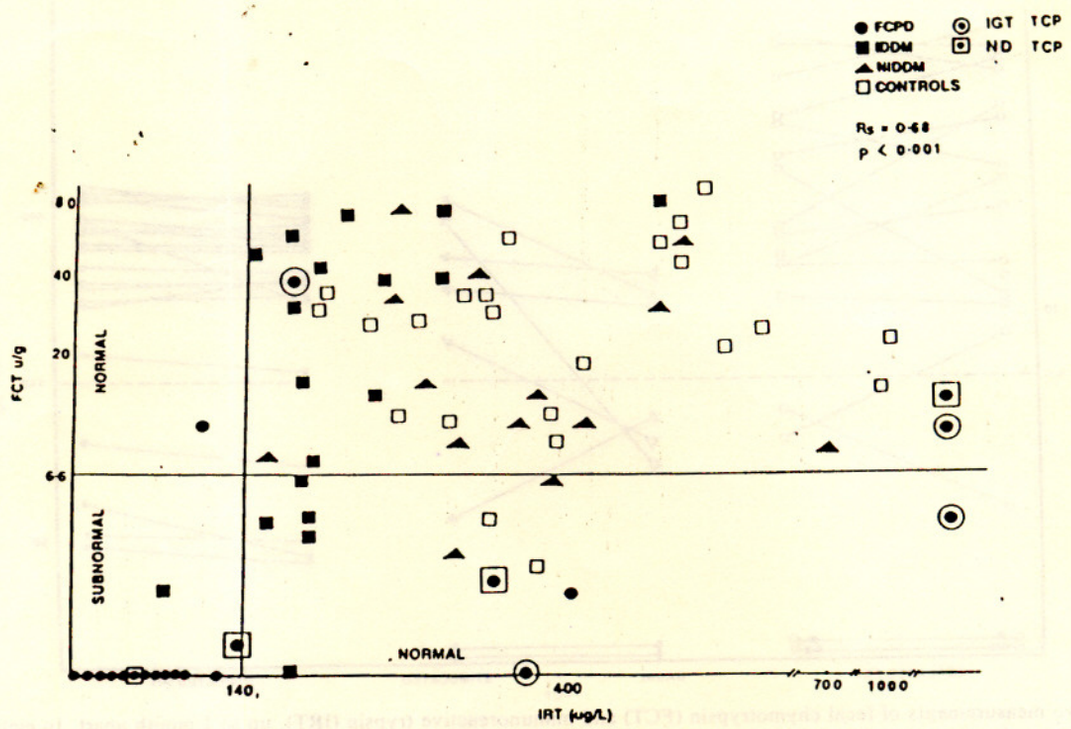

FIG. 4. Correlation between immunoreactive trypsin (IRT) and fecal chymotrypsin (FCT). The lower limits of normal for both are shown.

crine pancreatopathy of "primary" diabetes mellitus is thought to arise from the loss of local trophic effects of insulin on adjacent exocrine pancreatic acini (11). Both of these phenomena are reflected in our results. Subjects with chronic pancreatitis showed the most severe exocrine deficiency, and there was a gradient of exocrine–endocrine loss in this group. Thus, those with relatively better exocrine preservation showed a normal or impaired glucose tolerance, and the group with the most severe exocrine loss showed diabetes mellitus (FCPD). This has not been shown previously in TCP, and strengthens the view that diabetes in TCP is secondary to pancreatitis. Our results also indicate that active pancreatitis (elevated IRT) is frequent in TCP subjects in the earlier stages before diabetes develops. By the time the latter sets in, the exocrine pancreatic mass is severely diminished and active pancreatitis has subsided. In the "primary" varieties of diabetes, IDDM subjects showed a more severe exocrine loss than NIDDM subjects, who in turn showed diminished exocrine function compared to control subjects.

"Environmental factors" (dietary deficiencies and/or toxins, other nondietary factors) damaging the pancreas may be more prevalent in tropical countries (12). Our finding that NIDDM and control subjects in tropics tend to have higher concentrations of IRT than those reported in white caucasians assumes special significance since such elevated concentrations of serum enzymes have not been reported to precede diminished concentrations in western diabetics. While an abnormal circulating "trypsin" (indistinguishable on radioimmunoassay) or a genetically different blood–acinar barrier cannot be ruled out, it is probable that "pancreatopathy" is more common in tropical countries. A comparative study (18) has demonstrated higher concentrations of calcium and lactoferrin in the pancreatic juice of Indian subjects (controls as well as TCP patients) compared to French subjects (controls and alcoholic pancreatitis patients). Calcium is a nonspecific marker for pancreatic damage while lactoferrin is a natural antioxidant. These findings support the hypothesis that subclinical pancreatopathy is common in a tropical country like India. A total of six non-TCP subjects (one IDDM, two NIDDM, and three controls) showed very elevated IRT (>800 µg/L), indicating active pancreatitis in asymptomatic subjects. Thus, FCPD as diagnosed

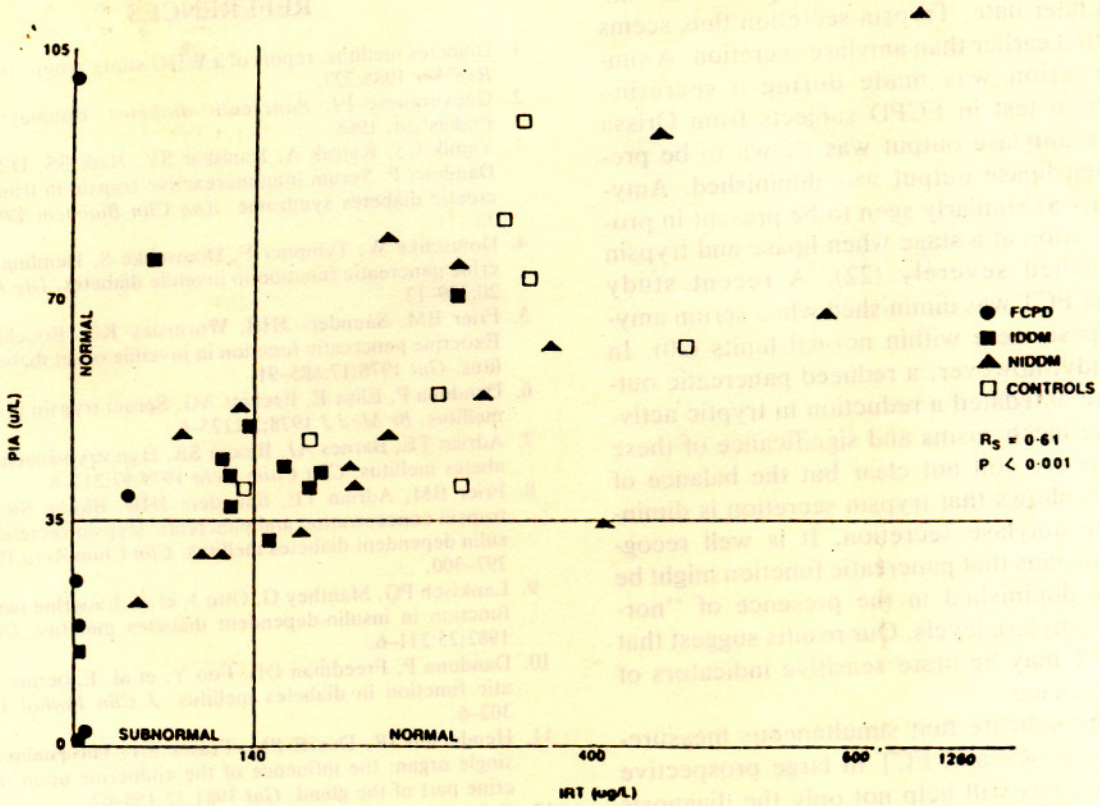

FIG. 5. Correlation between immunoreactive trypsin (IRT) and pancreatic isoamylase (PIA). The lower limits of normal for both are shown.

by demonstrable pancreatic calculi may only represent the extreme end of the spectrum in TCP. Some of the subjects of the "classical" IDDM and NIDDM varieties may represent "precalcific"/"noncalcific" milder variants of TCP or have a concomitant exocrine damage due to unknown factors. Prospective follow-up of such subjects and study of specific markers (genetic or other) may help resolve this issue in the future. FCPD subjects from South India share genetic markers of both IDDM (HLA DQ-B) and NIDDM (class 3 allele of insulin gene) (19). This raises the possibility of an overlap between these conditions.

TABLE 2. *Specificity and sensitivity of IRT and FCT assays*

		Sensitivity		Specificity	
		TCP	FCPD	TCP	FCPD
IRT (μg/L)	<140	79	97	89	89
FCT (u/g)	<6.6	86	94	84	78

Figures represent percentages.
IRT = immunoreactive trypsin; FCT = fecal chymotrypsin; TCP = tropical calcific pancreatitis; FCPD = fibrocalculous pancreatic diabetes.

FCT results in our subjects are broadly similar to those reported from South India (20). However, many of our FCPD subjects seem to have a more severe exocrine pancreatic loss (FCT < 1 u/g). IGT-TCP and nondiabetic TCP subjects are not discussed in that paper. The proportion of IDDM and NIDDM subjects with subnormal FCT appears to be similar in these two studies.

Comparison of IRT, FCT, and PIA allows us to construct a possible sequence of events. FCT (a test of "luminal" secretion) indicates the pancreatic mass, and only reduced concentrations are significant. IRT (a blood test dependent on breakdown of the acinar–blood barrier) is elevated due to active pancreatic damage but actual concentrations will depend on pancreatic mass. Our results would then indicate that elevated serum IRT is the earliest manifestation of TCP, with FCT showing progressive diminution when serum IRT may still be "normal." By the time diabetes has set in, both of the tests are

severely affected. PIA seems to be "preserved" until a much later date. Trypsin secretion thus seems to be affected earlier than amylase secretion. A similar observation was made during a secretin–pancreozymin test in FCPD subjects from Orissa (21), where amylase output was shown to be preserved when lipase output was diminished. Amylase output was similarly seen to be present in protein malnutrition at a stage when lipase and trypsin had diminished severely (22). A recent study showed that FCT was diminished when serum amylase and lipase were within normal limits (20). In another study, however, a reduced pancreatic output of lipase antedated a reduction in tryptic activity (23). The mechanisms and significance of these observations are still not clear but the balance of observations shows that trypsin secretion is diminished before amylase secretion. It is well recognized by clinicians that pancreatic function might be significantly diminished in the presence of "normal" serum amylase levels. Our results suggest that IRT and FCT may be more sensitive indicators of pancreatic damage.

Our results indicate that simultaneous measurement of serum IRT and FCT in large prospective population studies will help not only the diagnosis but also improve our understanding of the natural history of TCP. Use of sensitive cutoff points (140 μg/L for IRT, and 6.6 u/g for FCT) (Table 2) would be helpful in screening individuals requiring further imaging investigations.

In conclusion, we have demonstrated a graded loss of exocrine pancreatic function in TCP that reflects a parallel endocrine loss (hyperglycemia). Exocrine pancreatic involvement in "primary" varieties of diabetes in the tropics seems to pass through a "pancreatitic" phase before exocrine deficiency sets in. In addition to the well-known effects of the loss of local trophic effects of insulin, "toxic" environmental factors could be responsible for such an observation. Serum IRT and FCT provide simple and useful markers for investigation of exocrine pancreatic involvement in diabetes.

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