Exocrine Dysfunction Correlates with Endocrinal Impairment of Pancreas in Type 2 Diabetes Mellitus

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Abstract

Background: Diabetes mellitus (DM) is a chronic abnormal metabolic condition, which manifests elevated blood sugar level over a prolonged period. The pancreatic endocrine system generally gets affected during diabetes, but often abnormal exocrine functions are also manifested due to its proximity to the endocrine system. Fecal elastase-1 (FE-1) is found to be an ideal biomarker to reflect the exocrine insufficiency of the pancreas. **Aim:** The aim of this study was conducted to assess exocrine dysfunction of the pancreas in patients with type-2 DM (T2DM) by measuring FE levels and to associate the level of hyperglycemia with exocrine pancreatic dysfunction. **Methodology:** A prospective, cross-sectional comparative study was conducted on both T2DM patients and healthy nondiabetic volunteers. FE-1 levels were measured using a commercial kit (Human Pancreatic Elastase ELISA BS 86-01 from Bioserv Diagnostics). Data analysis was performed based on the important statistical parameters such as mean, standard deviation, standard error, t-test-independent samples, and Chi-square test/cross tabulation using SPSS for Windows version 20.0. **Results:** Statistically nonsignificant ($P = 0.5051$) relationship between FE-1 deficiency and age was obtained, which implied age as a noncontributing factor toward exocrine pancreatic insufficiency among diabetic patients. Statistically significant correlation ($P = 0.003$) between glycated hemoglobin and FE-1 levels was also noted. The association between retinopathy ($P = 0.001$) and peripheral pulses ($P = 0.001$) with FE-1 levels were found to be statistically significant. **Conclusion:** This study validates the benefit of FE-1 estimation, as a surrogate marker of exocrine pancreatic insufficiency, which remains unmanifest and subclinical.

Keywords: Exocrine pancreatic insufficiency, fecal elastase-1, glycated hemoglobin, type 2 diabetes mellitus

INTRODUCTION

Diabetes mellitus (DM) is a chronic, lifelong metabolic disorder characterized by high blood sugar level (hyperglycemia) over a prolonged period. Uncontrolled hyperglycemic condition for an extended period can induce tissue damage, which subsequently causes end-organ damage due to micro and macrovascular complexities.[1,2] The endocrine system is found to be majorly affected in a diabetic patient, but a significant impact of this disease is also expected in exocrine functions due to its adjacency to the endocrine system.[3,4] Therefore, a proper exocrine function is essential for digestion and absorption of food in the gastrointestinal (GI) tract.[1,3,5] During the last two decades of 20th century, indirect pancreatic function tests became accessible; specifically, the fecal elastase-1 (FE-1) concentration measurement. This study was conducted to assess the exocrine dysfunction of the pancreas in type-2 diabetes mellitus (T2DM) patients by measuring FE-1 levels and to correlate the degree of hyperglycemia with exocrine pancreatic dysfunction.[4,6]

METHODOLOGY

The comparative cross-sectional study was conducted on both inpatients and outpatients who attended a multi-specialty hospital based in India, with clinical symptoms of diabetes, without any other comorbid diseases. The study was approved by the Institutional Ethical Committee, and informed consent was obtained from all the patients. The inclusion criteria of the study were patients with T2DM who were on treatment and within the age range >18 years to <60 years. Nondiabetic healthy individuals served as controls. Patients with alcohol

Access this article online

Quick Response Code:

Website:
www.ijem.in

DOI:
10.4103/ijem.IJEM_139_17

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intake > 40 g/day, intake of Orlistat or Acarbose and Gliptins, history of chronic diarrhea and known pancreatic disorders, GI surgery, immunodeficiency, cancer, critical illness, or acute infective disorders were excluded from the study. The patient's demographic data, glycemic parameters, glycated hemoglobin (HbA1c), peripheral neuropathy (PN), retinopathy, peripheral pulses, proteinuria, electrocardiogram (ECG) abnormality, and hemoglobin were used across the level of pancreatic insufficiency (level of FE-1), and statistical significance was estimated. Routine blood investigations such as fasting blood sugar (FBS), postprandial blood sugar (PPBS) by glucose oxidase method using calorimeter, and HbA1c by high-performance liquid chromatography were carried out. FE-1 levels were measured using commercial kit (Human Pancreatic Elastase ELISA BS 86-01 from Bioserv Diagnostics). As per the validated cutoffs, levels of <100 μg/g, 100–200 μg/g and >200 μg/g were considered as severe pancreatic insufficiency, moderate pancreatic insufficiency, and normal pancreatic function, respectively. In addition, possible correlations between FE-1 levels and patients' characteristics such as gender, the duration of diabetes, and the blood glucose levels were also analyzed. Data analysis was performed based on the important statistical parameters such as mean, standard deviation, standard error, *t*-test-independent samples, and Chi-square test/cross tabulation using SPSS for windows version 20.0 (IBM statistical software).

RESULTS

The study was conducted on a total of 123 patients, out of which 88 were T2DM patients, and 35 were nondiabetic healthy volunteers (control group) [Table 1]. Among 88 diabetics, 52 (59.1%) were male, and 36 (40.9%) were female [Table 1]. In control group, 18 (51.4%) subjects had normal FE-1 levels, 13 (37.1%) had moderate, and 4 (11.4%) had severe FE-1 deficiency whereas in the study group (diabetics), only 16 (18.2%) patients had normal FE-1 levels, 42 (47.7%) had moderate, and 30 (34.1%) had severe deficiency of FE-1. Statistically nonsignificant ($P = 0.5051$) relationship between FE-1 deficiency and age was observed, suggesting that the exocrine pancreatic insufficiency is noncorrelated with age among diabetic patients [Table 2]. The results also implied a statistically nonsignificant relationship of gender with FE-1 levels. There were nondiabetic controls with some degree of exocrine pancreatic dysfunction; however, the FE-1 deficiency was found to be more among diabetics. Statistically nonsignificant relationship ($P = 0.641$) was observed between the use of antidiabetic medications and FE-1 levels. There was no significant correlation between FE-1 levels and duration of diabetes. A significant linear correlation of FE-1 deficiency among diabetics with the degree of dysglycemia was observed. Statistically significant *P* values were achieved between glycemic parameters such as FBS ($P = 0.001$), PPBS ($P = 0.012$), HbA1c (0.001) [Table 3], and FE-1 levels in diabetic patients whereas the association between glycemic parameters and FE-1 level was found to be nonsignificant in

nondiabetic patients. The association between FE-1 levels and PN ($P = 0.2$) was not found to be statistically significant. The association between retinopathy (*P* 0.001) and peripheral pulses (*P* 0.001) with FE-1 levels was found to be statistically significant [Table 2]. As per the results, there was statistically nonsignificant relationship between proteinuria (0.3), ECG abnormality ($P = 0.90$), and hemoglobin levels with FE-1 level. The mean age of study subjects (diabetics) was 47.53 ± 8.9 years and control group (nondiabetic) was 47.77 ± 9.0 years. The mean FE-1 levels were found to be higher, i.e., 179.85 ± 48.91 μg/g of stool among nondiabetics compared to diabetics (137.38 ± 60.53 μg/g of stool). This difference was found to be statistically significant ($P < 0.0001$) [Table 4].

DISCUSSION

The current study validated a significant correlation between pancreatic exocrine dysfunction with endocrine impairment by involving FE-1 as a consistent biomarker. Elevated FE-1 level was detected in both healthy volunteers and T2DM patients. The study also emphasized a correlation between several parameters such as gender, level of hyperglycemia, and duration of diabetes with exocrine pancreatic dysfunction.

Exocrine dysfunction of pancreas is amongst the newer arena of studies in the field of diabetes, preventive gastroenterology and other fields of medicine. For example, disorders of the pancreas such as acute or chronic pancreatitis, cystic fibrosis, hemochromatosis, and pancreatic carcinomas. primarily affect the functioning of the exocrine system, but in some cases, the endocrine system was also found to be impacted and resulted in diabetes although the reported percentage was minimal (0.5%–1.15%).[7] The previous research validates that the size of the pancreas in diabetic patients is smaller than the healthy individuals.[8] Moreover, exocrine pancreatic insufficiency interrupts the food absorption process, which in turn, causes deregulation of the blood glucose level.[8,9] FE-1 can be utilized as a biomarker for analyzing exocrine pancreatic dysfunction, and a quantitative test can be easily performed using sandwich ELISA to achieve a highly specific report.[10-14] FE-1 is found to possess stability for an extended period and remains unaffected even after medications, gastric surgery, dysmotility, or small intestine diseases.[15,16] FE-1 was reported to be superior to both fecal lipase and fecal chymotrypsin tests in the assessment of exocrine pancreatic function.[17-22] However, there is a lack of a single, comparative study focusing only on the intricate relationship between FE-1 measurement and levels of hyperglycemia in T2DM in India. In our study, FE levels were measured and correlated between diabetics and nondiabetics. In 88 diabetics, 30 (34.1%) had severe deficiency, 42 (47.7%) had moderate FE deficiency, and only 16 (18.2%) had normal FE-1 levels. There was a statistically significant association between diabetes and FE-1 levels. The observations, in our current study, were found to be comparable to the results obtained from the study conducted by Andriulli *et al.* among 556 patients with T2DM where mild/moderate and severe FE-1 were reported in 275 and 281 patients, respectively.[23] After pooling the data,

weighted estimates of mild/moderate or severe FE-1 were 49.7% and 50.3%, respectively, (*P* = 0.023). As per Löser *et al.*, based on FE-1 level measurement, significantly higher proportion of diabetics possessed pancreatic insufficiency.[24] These literature findings substantiate the usefulness of FE-1 levels in assessing pancreatic exocrine insufficiency in T2DM. Various international studies have observed the relationship between T2DM and its relation to exocrine dysfunction of pancreas and various levels of hyperglycemia.[5,16,25,26] In our current study, no correlation between FE-1 levels and duration of diabetes was observed. Study conducted by Hardt and Ewald on 1021 patients (334 females, 687 males; mean age 50 years; mean diabetes duration 11 years; mean age at onset

Table 1: Age and Gender distribution of study subjects

Age (Years)	Diabetic (Subjects)			Non-Diabetic (Subjects)		
	Male	Female	Total	Male	Female	Total
<30	2 (66.7)	1 (33.3)	3 (3.4)	2 (66.7)	1 (33.3)	3 (8.6)
31-40	15 (65.2)	8 (34.8)	23 (26.1)	8 (88.9)	1 (11.1)	9 (25.7)
41-50	15 (51.7)	14 (48.3)	29 (33.0)	6 (50.0)	6 (50.0)	12 (34.3)
51-60	20 (60.6)	13 (39.4)	33 (37.5)	7 (63.6)	4 (36.4)	11 (31.4)
Total	52 (59.1)	36 (40.9)	88 (100)	23 (65.7)	12 (34.3)	35 (100.0)

Table 2: Relationship of various parameters with fecal elastase-1 activity

Parameters/ factors/variables	FE-1 level			Total	*P*
	Normal	Moderate	Severe		
Age					
<30	1 (16.7)	4 (66.6)	1 (16.7)	6 (4.9)	0.5051
31-40	8 (25.0)	18 (56.2)	6 (18.8)	32 (26)	
41-50	14 (34.1)	15 (36.6)	12 (29.3)	41 (33.3)	
51-60	11 (25.0)	18 (40.9)	15 (34.1)	44 (35.8)	
Total	34 (27.6)	55 (44.7)	34 (27.7)	123 (100.1)	
Retinopathy					
Absent	15 (20.8)	39 (54.1)	18 (25.0)	72 (81.8)	0.001
Present	1 (6.2)	3 (18.7)	12 (75.0)	16 (18.1)	
Total	16 (18.2)	42 (47.7)	30 (34.1)	88 (100.0)	
Neuropathy					
Absent	13 (17.1)	39 (51.3)	24 (31.6)	76 (86.3)	0.2
Present	3 (25.0)	3 (25.0)	6 (50.0)	12 (13.7)	
Total	16 (18.2)	42 (47.7)	30 (34.1)	88 (100)	
Peripheral pulses					
Abnormal	2 (10.0)	4 (20.0)	14 (70.0)	20 (22.7)	0.001
Normal	14 (20.6)	38 (55.9)	16 (23.5)	68 (77.3)	
Total	16 (18.2)	42 (47.7)	30 (34.1)	88 (100.0)	

FE: Fecal elastase-1

of diabetes 39 years) attained similar outcome.[27] FE-1 was found to be normal (>200 µg/g) in 59.3% and severely reduced (<100 µg/g) in 22.9% which further verified weak associations between FE-1 and diabetes duration. As per Rathmann *et al.*, no significant association was found between diabetes duration and FE-1 levels which was based on a study conducted on 544 T2DM patients, in which FE-1 concentrations were significantly lower in study subjects compared to controls (median: cases 308 µg/g; controls 418 µg/g; *P* < 0.01).[28] Whereas, contradictory results were obtained from a study conducted by Ewald *et al.*[27] The study conducted among 307 subjects with 167 diabetics demonstrated a significant (*P* < 0.004) positive correlation between duration of diabetes and pancreatic exocrine insufficiency. Observations from our study implied no significant correlation between the use of antidiabetic medication and FE-1 level. Similar observation was also evidential from a prospective study conducted by Nunes *et al.*, where 80 patients were enrolled, of which 42 patients with DM, diagnosed for 11.5 ± 8 years, with structural changes of the pancreas detected on ultrasound in three cases and calcifications in one case.[29] There was no relationship between FE-1 determination <200 µg/g and the duration or the type of therapy for DM. Amann *et al.* validated normal (>200, µg/g) FE-1 concentration in four out of seven patients with mild-to-moderate exocrine pancreatic insufficiency.[30] This low sensitivity might be due to the different subclassification criteria. As per our study, the association between FE-1 levels and PN was not found to be statistically significant function. Moreover, identical outcome was evidential from a study conducted by Rathmann *et al.* studied where, FE-1 concentrations were significantly lower in experimental group than control (*P* < 0.01), and therefore, no significant association was found in-between FE-1 level and diabetic PN.[28]

In this current study, statistically significant correlation (*P* = 0.001) between HbA1c and FE-1 levels was evidential. A similar outcome was also acquired by Ewald *et al.* where statistically significant (*P* < 0.031) HbA1c levels were obtained with pancreatic exocrine insufficiency as mild/moderate and severe in 307 subjects with 167 diabetics as study group.[31] Diabetic angiopathy has been proposed to cause arterial lesions and leads to pancreatic fibrosis and exocrine atrophy. The hypothesis that exocrine pancreatic pathology is a diabetes-associated complication mediated by angiopathy implicates that it may be correlated with diabetes duration. In our current study, out of 88 diabetic patients, 20 (22.7%) had abnormality in peripheral pulses (macroangiopathy) among which 2 (10.0%) had normal, 4 (20.0%) had moderate, and

Table 3: Relationship of glycemic parameters with FE-1 activity

Glycemic Parameters	Non-Diabetic			*P*	Diabetic			*P*
	Normal	Moderate	Severe		Normal	Moderate	Severe	
FBS	87.1±12.4	83.76±9.2	90.00±6.3	0.53	123.56±29.9	130.9±30.8	174.10±58.2	0.001
PPBS	125.1±15.4	122.6±16.2	120.2±25.8	0.84	146.31±55.6	185.1±65.2	226.20±51.4	0.012
HbA1C	5.05±0.79	5.3±0.71	5.4±0.51	0.84	8.1±1.64	8.3±1.5	10.1±1.47	0.001

Table 4: Distribution of FE-1 levels between diabetic and non- diabetic controls

Fecal elastase Levels	Non-Diabetic	Diabetic	Total
Normal	18 (51.4)	16 (18.2)	34 (27.6)
Moderate	13 (37.1)	42 (47.7)	55 (44.7)
Severe	4 (11.4)	30 (34.1)	34 (27.6)
Total	35 (100.0)	88 (100)	123

P value<0.0001, chi- square test

14 (70.0%) had severe elastase insufficiency. Statistically significant relationship was found to be associated between peripheral pulses and FE-1 levels. A compatible outcome was obtained in a study conducted by Larger *et al.* in 2012 where FE-1 concentration was <200 μg/g in 23% of the patients.[32] In patients with T2DM, association of decreased pancreatic exocrine function with vascular disease suggests a role of pancreatic arteriopathy. Hence, this proves that, diabetic angiopathy is associated with low FE levels and pancreatic exocrine insufficiency. In our study, 73 (82.9%) diabetics had HbA1c ≥7%, of which 30 (41.09%) had severe, 33 (45.20%) had moderate deficiency, and only 10 (13.6%) had normal FE-1 levels with statistically significant correlation ($P = 0.003$) between HbA1c and FE-1 levels. A similar outcome was analyzed in research conducted by Terzin *et al.* which included a total of 101 diabetic subjects who were divided into, HbA1c 7% ($n = 59$) and HbA1c <7% ($n = 42$) followed by FE-1 level were assessment.[33] It was found that FE-1 levels were significantly higher in group HbA1c <7% (454.6 ± 147.3 μg/g) compared with HbA1c 7% (385.9 ± 171.1 μg/g) with significant *P* value (0.038).[33] A study conducted by Ewald *et al.* also exhibited a significant ($P < 0.031$) positive association between the levels of hyperglycemia by measuring HbA1c levels with pancreatic exocrine insufficiency as mild/moderate and severe in 307 subjects with 167 diabetics as a study group.[31] Research conducted by Yilmaztepe *et al.* had validated that the exocrine function declined in 28% of T2DM patients while there was no decrease in the control subjects.[34,35] However, there were no significant correlations between pancreatic elastase levels and the duration of diabetes. Hence, this study has revealed that the FE-1 estimated by ELISA can help us to prove exocrine pancreatic function and found to be associated with the levels of hyperglycemia in T2DM concurring with similar studies supporting this finding. A more intense research involving a large sample size and a diverse age group is warranted to substantiate the association.

Conclusion

This study demonstrates the benefit of FE-1 estimation as a surrogate marker of exocrine pancreatic insufficiency during T2DM, which remains unmanifest and subclinical. The results obtained indicated significant deficiency of pancreatic FE- 1 level among diabetics as well as some nondiabetic individuals. The severity of exocrine pancreatic insufficiency was found to possess statistically significant association with degree of dysglycemia, retinopathy, and peripheral vascular disease based on the level of FE-1 deficiency. Early identification and treatment with pancreatic enzyme supplementation of may help to improve the quality of life in patients with severe pancreatic insufficiency.

Conflicts of interest
There are no conflicts of interest.

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