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Association of serum lipase and glycated hemoglobin in type 2 diabetes mellitus

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Abstract

In diabetic patients, there is decrease in the level or the function of insulin. Diabetes mellitus patients are also found to have altered exocrine pancreatic functions. This could lead to maldigestion in these individuals with clinical features of malabsorption syndrome. This study was done to assess the association of serum lipase levels with glycated hemoglobin in Type 2 diabetes mellitus. The cross-sectional study was carried out in the Department of Biochemistry at Sri Ramachandra Institute of Higher Education and Research, Chennai involving 93 type 2 diabetic mellitus patients between the age groups of 30 to 70 years of both sexes. Analysis of fasting and postprandial plasma glucose, glycated hemoglobin and serum lipase were done by standard methods. Statistical analysis was performed utilizing SPSS software with version 16. P value less than 0.05 was considered as statistically significant. The mean HbA1c was found to be 8.35±2.30% and serum lipase level was 54.55±50.96 U/L. The cut-off of serum lipase was found to be 31.5 U/L. The exocrine pancreatic derangements can be a hall mark in type 2 diabetes mellitus. The measurement of serum lipase could help is the diagnosis and assessing prognosis of chronic exocrine pancreatic disorders especially in type 2 diabetes mellitus patients.

Keywords: Chronic pancreatic disorder, exocrine pancreatic function, insulin resistance, amylase, lipase, diabetes mellitus

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1. Introduction

Diabetes mellitus, a non-communicable disease is becoming a potential epidemic in India. The number of individuals getting affected by type 2 diabetes mellitus (T2DM) is increasing across the globe. Approximately 382 million adults had diabetes in 2013 which is projected to reach 592 million in 2035. According to International Diabetes Federation (IDF) 2013, in India, 65.1 million had diabetes in 2013 and is expected to increase to 109 million diabetics by 2035 [1]. In 2000, India, China and the United States are the top three countries having high number of diabetics compared to rest of the countries across the world. Thus, India is facing an uncertain future in relation to the rising burden of diabetes that might have major impact on the economy of the country [2].

The migrated South Asians in Europe are at four- to six-fold increased risk of developing T2DM than the native Europeans. The prevalence is almost the same across genders. As the age advances, the number of diabetics also increases in both the genders. The prevalence is the highest in the countries where the individuals started adopting Western lifestyle and the least in the rural areas of developing countries. In countries with high prevalence of T2DM also tend to have increased prevalence of obesity. There is generalized low-grade inflammation, increased oxidative stress and insulin resistance [1]. Study conducted by the Indian Council of Medical research (ICMR) revealed that there was lower proportion of diabetics in Chandigarh and Jharkhand when compared to Maharashtra and Tamil Nadu. The National Urban Survey involving metropolitan cities in India showed that Hyderabad, Chennai, Bangalore, Kolkata and New Delhi have the highest number of T2DM [2]. Obesity is a major risk factor for the onset of diabetes mellitus. Asians have lower protein to fat ratio, indicating Indians tend to develop diabetes despite their body mass index (BMI) in the normal range as per WHO guidelines. Diabetes mellitus is associated with micro-vascular and macro-vascular complications of various organs, resulting in mortality or morbidity with decreased quality of life [2].

Studies indicate that T2DM patients have 2- to 3-fold increased risk of developing pancreatic dysfunction. Pancreatic secretion has a major impact on the digestion of nutrients, especially fats. Exocrine pancreatic dysfunction (EPD) indicates the malabsorption process resulting from inadequate production or activity of exocrine pancreatic enzymes. The prevalence of exocrine pancreatic insufficiency

in healthy individuals varies from 3.8% to 18.1%. Steatorrhea, weight loss, and abdominal pain alongside bloating are observed in such patients. During the course of chronic pancreatitis, the secretory capacity of pancreas and luminal digestion by the pancreatic enzymes decreases. Studies have shown that a significant proportion of diabetic patients have EPD. It is mild to moderate in most diabetic patients. Radiological, histopathological and autopsy reports have shown that the structural and functional impairment of pancreas in diabetics. They include fibrosis, lymphocyte infiltration, calcification leading to atrophic smaller pancreas [3].

The early diagnosis of EPD cases and initiation of treatment are important. It is imperative to obtain clinical clues and to apply the same in the diagnosis of mild to moderate cases. Direct or indirect EPD testing for all diabetic patients is not cost-effective. In a small number of studies, diabetic patients were followed up over several years, whereupon it was reported that mild to moderate EPD had been present since the beginning of diabetes. This study was undertaken to evaluate the exocrine pancreatic function in long-standing T2DM.

2. Materials and Methods

2.1. Study participants

The present study was conducted as a cross-sectional observation study in the Department of Biochemistry, at Sri Ramachandra Institute of Higher Education and Research (SRIHER), Porur, Chennai, from December 2019 to January 2020. Before the study was initiated, ethics approval was obtained from the Institutional Ethics Committee of SRIHER. The study consisted of 93 known cases of Type 2 diabetic mellitus. The study participants included were 30 to 70 years of age of both sexes. Patients with known pancreatic disorders, autoimmune disorders and cancer of any organ were excluded from the study. Patients who gave written informed consent were included for the study.

2.2. Analysis of samples

Fasting plasma glucose, postprandial plasma glucose, glycated hemoglobin (HbA1c) and lipase were analyzed in blood samples. The plasma glucose was estimated by the hexokinase method and HbA1c by Ion-Exchange High Performance Liquid Chromatography. Serum lipase was measured by kinetic method using the substrate, 1,2-O-Dilauryl-rac-glycerol-3-glutaricacid (6-methyl resorufin) ester.

2.3. Statistics employed

The data obtained were checked for normality of distribution using Kolmogorov-Smirnov test. The data were expressed as mean and standard deviation. Pearson Correlation was done to analyze the association between the biochemical variables. Receiver Operating Characteristic (ROC) curve was done. Youden index will be used to calculate the cut-off value of serum lipase. Statistical analysis was performed using SPSS software, Version 16.0 (SPSS Inc., Chicago IL, USA).

3. Results and discussion

3.1. Environmental and genetic factors influencing onset and progression of T2DM

The pathogenesis of type 2 diabetes mellitus (T2DM) is highly complex; interaction of environmental factors in genetically predisposed individuals. The patients either have insulin resistance or deficiency in insulin action. Polymorphisms are found to involve the genes of insulin receptor substrate-1 (IRS-1), phosphatidylinositol 3-kinase (PI-3-K), calpain 10, and transcription factor-7-like-2 (TF-7-like2). The various environmental influences on T2DM include obesity, aging, glucotoxicity and lipotoxicity. The levels of insulin can be normal or altered and most of the patients have impaired insulin action [4].

3.2. Demographic data

The present study included 93 type 2 diabetes patients in the age group of 30 to 70 years of both sexes at Sri Ramachandra Institute of Higher Education and Research. The study consisted of 93 type 2 diabetes mellitus patients with 54 males and 39 females in the average age of 54.44 ± 9.67 years (Table 1). The study group consisted of 58.1% and 40.9% male and female patients respectively (Table 2). Table 1 shows the distribution of biochemical parameters in the study participants and Table 2 shows the distribution of study participants according to gender.

3.3. Duration of diabetes mellitus in study participants

The duration of diabetes mellitus in study participants ranged from newly diagnosed cases to individuals with diabetes mellitus of more than 11 years. Most of the individuals (40.9%) had diabetes mellitus of 4 to 6 years, 25.8% had diabetes mellitus of less than three years, 19.3% had diabetes mellitus of 7 to 10 years and 14% had diabetes mellitus of more than 11 years (Fig. 1). Fig. 1 shows the distribution of study population according to the duration of diabetes mellitus.

3.4. Pathogenesis of exocrine pancreas in diabetes mellitus

Pancreatic islet cells are distributed as clumps in between exocrine pancreas. Nearly 84% of pancreas consists of exocrine component with endocrine part consisting of 2% and they are in close proximity to each other. Rest 14% is made up of extracellular matrix, ductal cells and blood vessels [5]. Diet

poor in essential amino acids especially leucine inhibits pancreatic synthetic capacity bydecreasing entry of amino acids into pancreas. This results in decreased synthesis of pancreatic digestive enzymes leading to pancreatic insufficiency, malnutrition and various gastrointestinal complications. Studies have shown that long-standing diabetes mellitus results in decreased pancreatic mass with less secretion of exocrine digestive enzymes. There is diffuse intra-acinar pancreatic fibrosis. These are the consequences of loss of acinar cells, loss of trophic action of insulin or alteration in neural control. Thus, the pancreatic dysfunction found in diabetic individuals is termed as diabetic exocrine pancreatopathy. When pancreas is exposed to high insulin concentrations from islet-acinar portal circulation, there is decreased expression of insulin receptors. Even though the exocrine and endocrine portions of the pancreas are anatomically and functionally distinct from each other, studies show that one portion influences the other portion. This is seen by the effect of insulin on the growth of acinar cells adjacent to the pancreatic islet cells. Hyperglycemia seen in diabetes mellitus is found to affect the synthesis and secretion of enzymes from the exocrine pancreas [6].

Yadav, et al., have demonstrated that the diabetic individuals with higher blood glucose had lower serum amylase levels. This is due to the derangement in endocrine-exocrine axis of the pancreas, showing that diabetic individuals had associated anatomical and functional dysfunction of the exocrine pancreas. When the pancreatic derangement is long standing, the exocrine pancreas loses its function by becoming fibrosed and insensitive to hormonal stimuli [7, 8, 9]. Even though many animal and cellular studies have demonstrated exocrine-endocrine relationship in the pancreas, very little research is being done on pancreatic exocrine functions especially in diabetic patients. Hence the present study has been aimed to study the correlation between serum lipase and glycated hemoglobin levels in type 2 diabetes mellitus patients.

Animal studies have documented that the pre-existing diabetes may increase the risk of severe pancreatitis which could increase mortality in diabetic individuals. This could be due to impaired protective role of insulin role during conditions such as acute or chronic pancreatitis. Type 2 diabetics have an approximately three-fold increased risk of developing acute pancreatitis, due to insulin resistance. Hyperglycemic individuals who present with acute pancreatitis have high chances of developing organ failure in the future [6].

3.5. Analysis of biochemical variables

In the present study, the mean plasma fasting and postprandial plasma glucose were 169.96±65.68 mg/dL and 245.06±88.98 mg/dL respectively; while the mean HbA1c was 8.35±2.30 % (Table 1). The plasma fasting and postprandial glucose were positively correlated with HbA1c (r=0.635, *P*=0.0001 and r=0.578, *P*=0.0001) respectively (Fig. 2a & 2b). In a study by Bing Wang et al., it was found that there were positive correlations between fasting and postprandial plasma glucose with HbA1c (r = 0.83, *P* = 0.000, and r = 0.795, *P* = 0.000) respectively [10]. Sunday Chinenye et al., had demonstrated that fasting and postprandial plasma glucose levels were 7.5 ± 3.3 mmol/L and 11.0 ± 4.0 mmol/L respectively. HbA1c was 9.0 ± 2.5%, with statistical significant correlation between postprandial plasma glucose and HbA1c (*P* = 0.000) [11]. Fig. 2a & 2b shows correlation between HbA1c and fasting and postprandial plasma glucose.

Patients with T2DM are found to have chronic pancreatitis, which could be symptomatic as diagnosed by severe abdominal pain and altered pancreatic enzymes. But in most of the patients it could be asymptomatic, diagnosed during examination of abdomen due to various other problems of abdomen. Other than diabetes mellitus, chronic pancreatitis is also caused by excessive consumption of alcohol, nutritional excesses or deficiencies, metabolic abnormalities, autoimmune disorders, hereditary (enzyme defects, cystic fibrosis), trauma, hypercalcemia, or it could be idiopathic [12]. Chronic pancreatitis is defined as an inflammatory disorder of the pancreas, which could cause irreversible pancreatic parenchymal injury [13]. This is a progressive disease resulting in complete destruction of exocrine pancreas. With progression, exocrine and endocrine pancreatic functions start failing [14]. The ongoing inflammation of the pancreas leads to progressive loss of pancreatic tissue, atrophy of the pancreas or replacement with fibrous tissue [15].

The pancreas is the major tissue which has the capacity to synthesize and secrete most of the hormones involved in the digestion of macromolecules when they reach small intestine. During inflammatory conditions of the pancreas, amylase and lipase get leaked out of pancreas which is measured in the circulation. On the contrary, in chronic conditions the functioning parenchyma of the pancreas decreases, such that the serum levels of amylase and lipase values decrease which is proportionate to the remaining function of the pancreas [16].

Human pancreatic lipase has a molecular weight of 48KDa; it is a monomeric glycoprotein; the gene for lipase resides on the chromosome 10. The lipase concentration is much higher in pancreas than in other tissues such as adipose tissue or skeletal muscle. For full catalytic activity and greatest specificity, bile salts and colipase are needed. The half-life of lipase in serum is 12 hours. Lipases are defined as enzymes that hydrolyze triacylglycerol contained in food. It hydrolyzes the ester bonds at carbons 1 and 3 of triacylglycerol. This releases two moles of fatty acids and one mole of 2- monoacylglycerol which are absorbed into small intestinal cell [17].

3.6. Serum lipase levels in diabetes mellitus

In this present study, the mean serum lipase level was found to be 54.55±50.96 U/L (Table 1). According to the kit insert the biological reference interval is less than 60 U/L. This study confirms that serum lipase value tends to decrease substantially with the progression of chronic pancreatitis. In pancreatic disorders, there are structural and functional impairment in both exocrine and endocrine parts of the pancreas. Studies have shown that individuals with all types of diabetic mellitus are predisposed to exocrine pancreatic dysfunction. Exocrine pancreatic dysfunction is either mild or moderate degree in most diabetic patients. Therefore, complaints related to malabsorption of lipids may be present in diabetic individuals [3].

Pancreatic islet cells and exocrine acinar cells show infiltrates of immune cells and autoantibodies. In addition, there is found to be increased collagen deposition leading to fibrosis and loss of functioning pancreas. Also, they are found to have ectopic fat deposition as well as compensatory expansion pancreatic ductular cells [18]. Various theories explain the exocrine pancreatic insufficiency in diabetic patients. Endocrine hormones of pancreas have regulatory effect on exocrine pancreatic functions and this is not regulated in diabetic patients. Insulin has trophic effect on pancreatic acinar cells. Autonomic neuropathy and gastroparesis as seen in diabetes interfere with entero-pancreatic reflex and subsequently on exocrine functions. Antibodies found in endocrine pancreas in diabetics, also react with exocrine pancreatic tissue. Diabetic microvascular complications cause decreased blood supply to pancreas resulting in fibrosis and atrophy of pancreas [3, 18] (Fig. 3). Fibrosis is found in exocrine portion of pancreatic acinar cells which is carried out by proinflammatory cytokines and hyperglycemia resulting in increased collagen production. Besides fibrosis, diabetes mellitus is also associated with lipogenesis of the pancreas. But, pathogenesis behind the fat deposition is not clear [18]. Fig. 3 shows the factors involved in exocrine pancreatic dysfunction in diabetic patients [18].

3.7. Correlation studies

In the present study, there was no significant correlation between lipase and HbA1c (r=0.031, *P*=0.766). This could probably be due to small sample size of the study. Various observational studies have indicated that people with T2DM may have increased risk of acute pancreatitis which in the long run leads to chronic pancreatitis. During the course of chronic pancreatitis, the number of the functioning pancreatic cells decreases leading to impaired digestion of food. Pancreatic enzymes of protein digestion such as chymotrypsin, trypsin and elastase-1 were also found to be decreased as indicated in certain studies. Fecal elastase-1 was measured to indicate pancreatic insufficiency. Larger E et al., have stated that the elastase-1 and chymotrypsin activities were lower in type 1 diabetics compared to type 2 diabetics. Also, the individuals experiencing diabetes mellitus was longer in patients with type 1 than with type 2 diabetes mellitus; the duration being 16.1 years for T1DM whereas it was only 8.7 years for T2DM. In very advanced chronic pancreatic pathologies, enzymes involved in protein digestion were found to be very low that it is difficult to detect their levels in serum [19]. Table 3 shows the correlation between lipase and glycemic indicators.

3.8. Cut-off levels of HbA1c and serum lipase

In the present study, the serum lipase level was not compared with the duration of T2DM, since the sample size of the individual groups was very small. When serum lipase levels were correlated with fasting plasma glucose, postprandial plasma glucose and HbA1c, there was no statistical significant correlation between them (Table 3). In the present study, optimal cut off levels were arrived at to diagnose individuals who are in the process of developing pancreatic dysfunction. The cut-off value for HbA1c was found to be 7.15%, with sensitivity of 62.5% and specificity of 31.9% and the cut-off level for serum lipase was found to be 31.5 U/L with sensitivity of 66.7% and specificity of 33.3% (Table 4). Both HbA1c and lipase had low sensitivities and specificities. But between the two markers, serum lipase showed a better sensitivity and specificity than HbA1c; thus, serum lipase could have more diagnostic potential in identifying chronic pancreatitis in asymptomatic diabetic patients. Lipase has a longer half-life of 12 hours compared to amylase which has a half-life of 10 hours; thus, lipase is a better diagnostic and prognostic marker of asymptomatic progressive chronic pancreatitis. Table 4 shows the cut off levels of HbA1c and lipase.

3.9. Serum amylase in T2DM

Aughsteen A et al., had shown statistically significant lower levels of serum amylase and lipase levels in both the types of diabetes mellitus. The reduction in serum amylase was more significant in type 1 diabetics when compared to type 2 diabetics. The magnitude of decrease positively correlated with the duration of the disease especially in T1DM. In T2DM the enzyme levels were correlated with the duration of T2DM as well as with insulin levels [20]. Oh HC, et al., found that low enzyme levels correlated with non-calcific or calcific chronic pancreatitis. The cut off values obtained for serum amylase and lipase were found to be 40 U/L and 20 U/L in healthy controls and non-calcific chronic pancreatitis. Serum lipase had a higher diagnostic potential compared to serum amylase [21]. Serum lipase level was lower probably due to destruction of acinar cells [22]. In Kawamori R et al., study, analysis of secretions obtained from pancreatic duct showed decreased amylase level in diabetic patients [23].

3.10. Alterations of exocrine pancreatic function in diabetes mellitus

Madole MB, et al., demonstrated that increase in fasting blood glucose was associated with decrease in exocrine pancreatic enzymes. Insulin enhances, while glucagon decreases sensitivity of the exocrine pancreas to secretagogues. Also, decreased volume of the pancreas also contributes to decreased secretion of enzymes of exocrine pancreas [5]. In diabetes mellitus, hyperglycemia could damage exocrine pancreas with decreased synthesis and secretion of pancreatic digestive enzymes. Increased blood glucose in diabetics might interfere with intracellular signaling involved in transcription and translation in pancreas leading to pancreatic exocrine insufficiency in diabetes mellitus [9]. Andriulli et al., states that in 66% of chronic pancreatitis patients, there was remarkable impairment of pancreatic secretion in patients with diabetes and steatorrhea. Diabetes and steatorrhea were present in 74% and 79% of study participants respectively; however, serum trypsin level below the cut-off limit in all the individuals. When diabetes mellitus and steatorrhea were combined pancreatic insufficiency increased to as high as 94% [24].

3.11. Practical applications

Diabetes mellitus alters exocrine pancreatic function in addition to endocrine pancreatopathy. Diabetic patients manifesting with symptoms of impaired digestion and absorption should be investigated for alterations in pancreatic function.

3.12. Limitations of the study

The study could have been done on a large sample size consisting of both type I DM and type 2 DM. The study samples could have included samples with very high plasma glucose levels. Duration of diabetes as well as the level of HbA1c could be compared with serum lipase. Serum amylase, trypsin and fecal elastase can be included in further studies.

Table 1: Distribution of biochemical parameters in study participants

	Age (years)	**Fasting plasma glucose (mg/dL)**	**Postprandial plasma glucose (mg/dL)**	**HbA1c (%)**	**Lipase (U/L)**
Mean	54.44	169.96	245.06	8.35	54.55
Standard Deviation	9.67	65.68	88.98	2.30	50.96

Table 2: Distribution of study participants according to gender

Sex	**n (93)**	**Percentage (%)**
Male	54	58.10
Female	39	41.90

Table 3: Correlation between lipase and glycemic indicators

Parameters	**r value**	***P* value**	**Statistical Significance**
Correlation between lipase & HbA1c	-0.031	0.766	Not Significant
Correlation between lipase & fasting plasma glucose	0.090	0.390	Not Significant
Correlation between lipase & post plasma Prandial glucose	-0.005	0.962	Not Significant

Table 4: The cut off levels of HbA1c & Lipase

Variables	Cut off values	Sensitivity	Specificity
HbA1c	7.15	62.5	31.9
Lipase	31.5	66.7	33.3

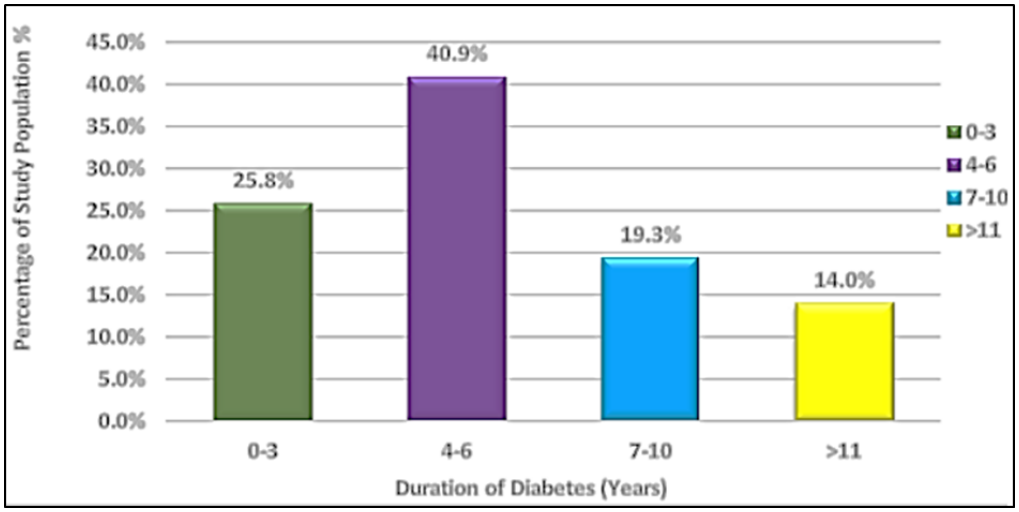
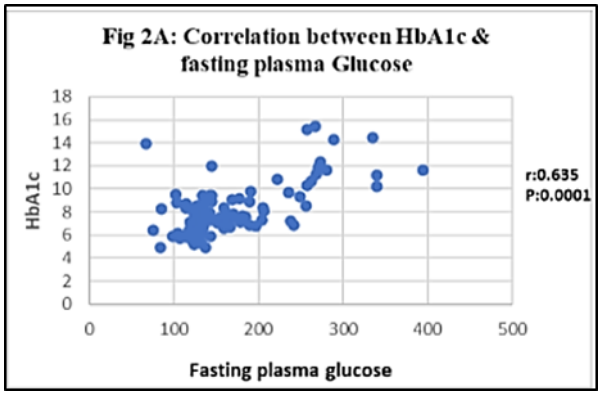
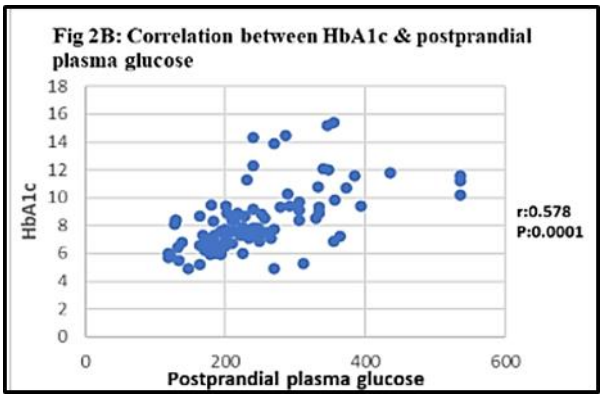


Fig. 1: Distribution of study population according to duration of diabetes mellitus





HbA1c: Glycated hemoglobin; P < 0.0001: highly significant

Fig. 2a & 2b: Correlation between HbA1c & Fasting plasma glucose, Postprandial plasma Glucose

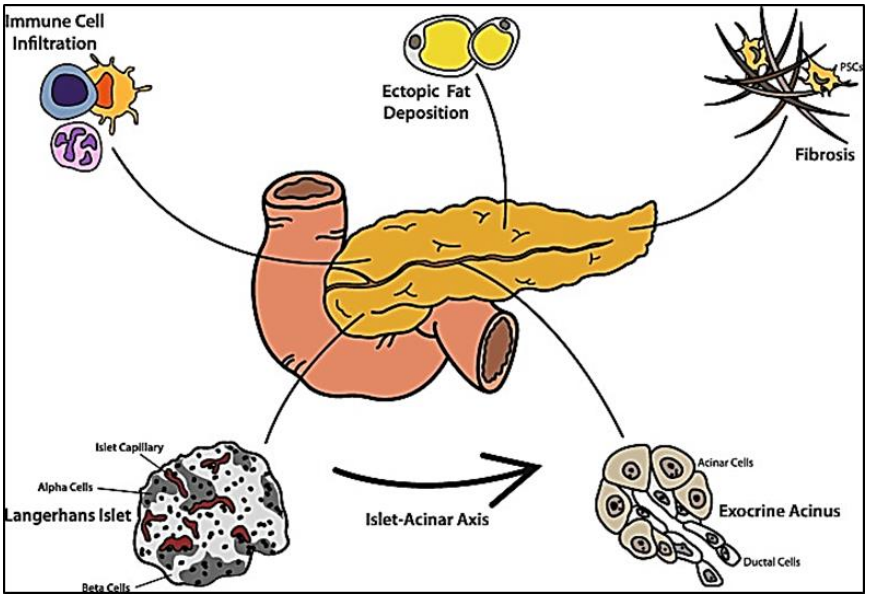


Fig. 3: Factors involved in exocrine pancreatic dysfunction in diabetic patients [18]

Conclusion

Serum HbA1c with a cut off value of 7.15 % provided a high diagnostic potential with sensitivity and specificity of 62.5% and 31.9% respectively. Serum lipase value with a cut off value of 31.5 U/L provided the diagnostic accuracy with sensitivity and specificity of 66.7% and 33.3% respectively. Optimal cut off values of 7.15% for serum HbA1c and 31.5 U/L for serum lipase is useful in diagnosis and prognosis of chronic pancreatitis in type 2 DM patients.

Authors' contributions

Both authors have contributed equally in all the stages of the research as well as bringing out this article.

Conflict of interest

No conflict of interest was encountered during the research as well as in the publication of the article.

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