

## Association of serum amylase with insufficient insulin action in Type I and Type II Diabetes Mellitus and Metabolic syndrome

Chandana G<sup>1</sup>, Nina M. Veigas<sup>2,\*</sup>, Raghavendra DS<sup>3</sup>

<sup>1</sup>Assistant Professor, PES Institute of Medical Sciences & Research, Kuppam, Andhra Pradesh, <sup>2</sup>Assistant Professor, <sup>3</sup>Professor & Head, Dept. of Biochemistry, Vydehi Institute of Medical Sciences & Research Centre, Bengaluru, Karnataka

**\*Corresponding Author:**

Email: prabhunina@gmail.com

### Abstract

**Background:** Metabolic syndrome (MetS) and Diabetes mellitus (type I and type II) are emerging as epidemics among non-communicable diseases. A lot of research has been done on hyperglycemia in Diabetes mellitus and Metabolic syndrome, but very few studies on pancreatic exocrine function have been conducted in these conditions. Therefore, the present study is an attempt to link endocrine and exocrine parts of the pancreas by investigating the association of serum amylase with insufficient insulin action in clinical settings.

**Objectives:** To estimate and compare serum amylase and insulin levels in Metabolic syndrome and in type I Diabetes mellitus and type II Diabetes mellitus

**Materials and Methods:** The subjects included in this study were divided into 3 groups. Group I consisted of 30 Diabetes mellitus Type I patients aged  $\leq 25$  yrs. Group II consisted of 30 patients of Diabetes mellitus Type II aged  $\geq 40$  yrs and Group III consisted of 30 Metabolic syndrome patients aged  $\geq 40$  yrs. Serum insulin, Serum amylase, Fasting blood sugar (FBS) and lipid profile were measured using autoanalyser. Statistical package for social science software version 15 was used for statistical analysis.

**Results:** Serum amylase was significantly less in DM Type I ( $40.53 \pm 16.58$ ) compared to both DM Type II ( $75.13 \pm 44.81$ ) and Metabolic syndrome ( $58.77 \pm 17.45$ ). The insulin levels were lowest in DM Type I compared to both DM Type II and MetS. In DM Type I, there was a positive correlation between insulin & amylase levels. In DM Type II and MetS there was a positive correlation between insulin & amylase levels at low insulin levels of  $\leq 10$   $\mu$ IU/ml and negative correlation with insulin resistance i.e. the serum amylase was lower with higher insulin resistance than with moderate insulin resistance.

**Conclusion:** Our results suggest a significant association between serum amylase levels and insufficient insulin action either due to inadequate insulin secretion and/or insulin resistance in Type I DM, Type II DM and MetS. This indicates a possible exocrine-endocrine relationship in these clinical conditions. Low serum amylase is associated with decreased basal insulin levels and insulin secretion, as well as high insulin resistance than with moderate resistance. Low serum amylase suggests exocrine pancreatic insufficiency and if pancreatic amylase replacement therapy is given to these patients it may improve the nutritional status and also analysis of serum amylase could provide valuable information regarding prognosis of the illness.

**Keywords:** Metabolic Syndrome, Amylase, Insulin, Diabetes mellitus Type I, Diabetes mellitus Type II

### Introduction

Diabetes mellitus (DM) and Metabolic syndrome (MetS) are among the most challenging health problems in the 21st century. Diabetes mellitus (DM) is a metabolic disease in which there is high blood sugar due to the body's failure to produce enough insulin (Type I DM) or insulin resistance (Type II DM). Metabolic syndrome (MetS) is a collection of cardiometabolic risk factors that includes obesity, insulin resistance, hypertension and dyslipidemia. This clustering of risk factors predisposes to an increased risk of developing Type II diabetes and cardiovascular disease.

Several pathogenic processes are involved in the development of diabetes. These range from autoimmune destruction of the beta cells of the pancreas (Type-I DM) with consequent insulin deficiency to abnormalities that result in resistance to insulin action (Type- II DM). Deficient action of insulin on target tissues affects carbohydrate, fat, and protein metabolism in diabetes. Deficient insulin action results from inadequate insulin secretion and/or diminished

tissue responses to insulin at one or more points in the complex pathways of hormone action<sup>1</sup>. Type- II DM is characterized by insulin resistance where there is impaired ability of hormone to suppress hepatic glucose output and to promote peripheral glucose utilization and compromised function of pancreatic  $\beta$ -cells such that insulin secretion is insufficient to match the degree of insulin resistance<sup>13</sup>.

The pancreas has dual functions. It acts as a digestive organ by secreting digestive enzymes such as amylase and as an endocrine organ secreting insulin<sup>24</sup>. The acinar tissue in the pancreas is in the close vicinity of the islets. Because of this close morphological relationship, functional interactions are likely to occur between the exocrine and endocrine pancreas in any diseases affecting the pancreas<sup>20</sup>. The pancreatic endocrine hormones influence pancreatic exocrine function. Insulin has a trophic effect on the exocrine pancreas. Insulin binds to its own receptor on the acinar cell<sup>14</sup>, leading to stimulation and potentiation of amylase secretion by various mechanisms including regulation of amylase gene transcription<sup>11</sup>; stimulation

of DNA, RNA, and acinar protein synthesis<sup>15</sup>; and increase in glucose uptake.

In DM Type I, the pancreatic acinar cells become fibrosed and show a reduced response to the hormonal stimulation<sup>5</sup>. The autoimmune mediated damage of islet cells leads to reduction of insulin levels resulting in a decreased trophic action on the amylase secreting exocrine cells<sup>19</sup>. In DM Type II and MetS, autonomic neuropathy and microvascular damage may play a key role in inducing pancreatic atrophy and fibrosis. In these conditions, the increased oxidative stress activates islet-exocrine-interface (IEI) matrix degrading proteases such as matrix metalloproteinases (MMPs) resulting in enzymatic degradation of the desmosomes and adherens junctions between the islet and acinar cells. Thus, communication between the exocrine and endocrine cell types is lost. Loss of cellular paracrine communication and fibrosis of the IEI, the endoacinar and the interlobular periacinar interstitium results in a dysfunctional insulin-acinar hormone axis<sup>9</sup>. As a result, action of islet hormone -insulin's trophic effects on acinar cells may be impaired or lost leading to decreased serum amylase. Besides these mechanisms, there are multiple defects in insulin secretion and signaling in Type II DM<sup>2</sup>, which might be associated with the low amylase secretion from the pancreas.

Elevation of serum amylase levels is seen in acute pancreatitis. Decreased serum amylase has been observed in diffuse pancreatic destruction due to advanced chronic pancreatitis or alcoholic disease<sup>7,12</sup>. A recent study by Zhao Y et al<sup>25</sup> observed an association between low serum amylase levels and an increased prevalence of metabolic syndrome and diabetes in Chinese asymptomatic population. Rakhee Yadav et al<sup>23</sup> found a significantly low amylase activity in the Type II DM patients compared to that in healthy subjects. Nakajima et al<sup>17</sup> has shown an increased risk for Metabolic Syndrome and Diabetes in Japanese population with low serum amylase levels.

However there is a lack of studies on serum amylase and insulin levels in the clinical settings of MetS, Type I DM and Type II DM in Indian population. In Type I DM there is insulin deficiency. In Type II DM and MetS there is impaired insulin action. Hence this study was conducted to put an insight into the possible endocrine-exocrine relationship of the pancreas in patients of MetS, Type I DM and Type II DM by investigating the association of serum amylase with insufficient insulin action.

## Materials and Methods

This study was conducted on 30 patients of DM Type I (Group I) aged  $\leq 25$  yrs, 30 patients of DM Type II (Group II) aged  $\geq 40$  yrs and 30 patients of MetS (Group III) aged  $\geq 40$  yrs, both males and females visiting Departments of Medicine and Endocrinology at Vydehi Institute of Medical Sciences & Research Centre, Bengaluru. The study was approved by the

ethical committee of the institution. Cases of DM Type I and DM Type II according to the American Diabetes Association diagnostic criteria<sup>2</sup>, defined as Fasting Plasma Glucose  $\geq 126$  mg/dl or HbA1c  $\geq 6.5\%$ , or being treated with oral hypoglycemic drugs or insulin were included in the study. The diagnosis of MetS was based on the Adult Treatment Panel (ATP) III criteria<sup>8</sup> with the following cutoff limits: 1) systolic blood pressure  $\geq 130$  mmHg or diastolic blood pressure  $\geq 85$  mmHg 2) triglyceride (TG)  $\geq 150$  mg/dl 3) high-density lipoprotein cholesterol (HDL-C)  $< 40$  mg/dl for men and  $< 50$  mg/dl for women 4) fasting plasma glucose  $\geq 100$  mg/dl 5) waist circumference  $\geq 90$  cm for men and  $\geq 80$  cm for women. Subjects meeting three or more of these criteria were included in MetS group. If subjects were treated for any of these components, they were determined to meet that criterion. Patients with confirmed or suspected cases of pancreatic pathology, diabetic ketoacidosis and renal dysfunction were excluded from the study. An informed written consent was taken from all patients  $\geq 18$  yrs and parent or guardian of patients  $\leq 18$  yrs. After detailed clinical history and physical examination fasting blood samples were collected from these patients. Height, weight, waist circumference, hip circumference, blood pressure were measured as per standard procedures. Body mass index (BMI) was calculated by formula [weight (Kg) / height (m<sup>2</sup>)]. Serum insulin level was measured by one-step immunoenzymatic ("sandwich") assay and Serum amylase levels by an enzymatic rate method. The estimation of Fasting blood sugar (FBS) was done by Hexokinase method. The serum triglycerides were measured by the enzymatic (GPO) method. Total cholesterol, LDL and HDL were estimated by enzymatic methods.

**Statistical Methods:** Results are presented as Mean $\pm$ SD. Analysis of variance (ANOVA) was used for the comparison of the three groups. Pearson's correlation coefficient was used for the correlation. Statistical analysis was performed using the statistical package of social sciences (SPSS-15). P values of  $< 0.05$  were considered as statistically significant.

## Results

The age distribution of patients is shown in Table 1. There were 17 males and 13 females in DM type I, 18 females and 12 males in DM type II and 17 females and 13 males in MetS. Waist circumference and hip circumference were compared between the groups which showed both waist and hip circumference were significantly higher ( $p < 0.01$ ) in DM type II than DM type I (Table 2). The subjects with MetS had significantly higher ( $p < 0.001$ ) waist and hip circumference compared to both DM type I and DM type II. The systolic BP & diastolic BP was significantly higher in MetS ( $p < 0.001$ ) and DM type II ( $p < 0.01$ ) compared to DM type I. BMI was significantly increased ( $p < 0.001$ ) in MetS compared to

both the groups and in DM type II ( $p < 0.01$ ) compared to DM type I. There was no significant difference in FBS between DM type I and DM type II (Table 3). However the FBS was significantly increased ( $p < 0.01$ ) in MetS compared to both DM type I and DM type II. The lipid profile parameters-Total cholesterol ( $p < 0.05$ ), Triglycerides ( $p < 0.001$ ) and VLDL ( $p < 0.001$ ) were significantly higher in MetS as compared to DM Type I and DM Type II. HDL was significantly lower in MetS as compared to DM Type I ( $p < 0.001$ ) and DM Type II ( $p < 0.05$ ). When compared to DM Type I, DM Type II patients had lower HDL ( $p < 0.05$ ). LDL was significantly higher in MetS ( $P < 0.001$ ) and DM Type II ( $P < 0.05$ ) as compared to DM Type I. Serum amylase was significantly less in DM Type I

( $40.53 \pm 16.58$ ) compared to DM Type II ( $75.13 \pm 44.81$ ) with  $P < 0.01$  and MetS ( $58.77 \pm 17.46$ ) with  $P < 0.001$  (Table 3). The insulin levels in DM Type I ( $6.94 \pm 1.39$ ) is low ( $P < 0.05$ ) due to insulin deficiency and in DM type II the insulin levels is high ( $16.01 \pm 3.25$ ) due to insulin resistance. In MetS ( $9.38 \pm 1.60$ ) the levels are lower than DM type II offering less insulin resistance. In DM Type I, there was a positive correlation between insulin & amylase levels (Table 4). In DM Type II and MetS there was a positive correlation between insulin & amylase levels at insulin levels  $\leq 10$   $\mu\text{IU/ml}$  and negative correlation with insulin resistance i.e. the serum amylase is lower with higher insulin resistance than with moderate insulin resistance (Table 4).

**Table 1: Age distribution of patients studied**

Age in years	DM type I		DM type II		Metabolic Syndrome	
	No	%	No	%	No	%
13-20	19	63.3	0	0.0	0	0.0
21-30	10	33.3	0	0.0	0	0.0
31-40	1	3.3	3	10.0	4	13.3
41-50	0	0.0	8	26.7	9	30.0
51-60	0	0.0	9	30.0	9	30.0
61-70	0	0.0	9	30.0	5	16.7
>70	0	0.0	1	3.3	3	10.0
Total	30	100.0	30	100.0	30	100.0

**Table 2: Comparison of Anthropometric characteristics of Group I (Diabetes Mellitus type 1), Group II (Diabetes Mellitus type 2), Group III (Metabolic syndrome)**

Parameter	Group I (DM type I)	p-value (I vs II)	Group II (DM type II)	p-value (II vs III)	Group III (Met S)	p-value (I vs III)
BMI	15.47 $\pm$ 4.0	<0.01	21.67 $\pm$ 2.9	<0.001	24.37 $\pm$ 3.2	<0.001
BP Systolic (mm of Hg)	104.93 $\pm$ 14.2	<0.01	127.53 $\pm$ 16.9	-	127.57 $\pm$ 15.3	<0.001
BP Diastolic (mm of Hg)	64.43 $\pm$ 9.8	<0.01	77.33 $\pm$ 6.4	-	81.47 $\pm$ 10.13	<0.001
Waist Circumference (cm)	29.23 $\pm$ 2.8	<0.01	32.11 $\pm$ 3.29	<0.001	37.35 $\pm$ 4.13	<0.001
Hip circumference (cm)	31.48 $\pm$ 3.0	<0.01	33.78 $\pm$ 3.16	<0.001	39.84 $\pm$ 4.41	<0.001

Statistically significant P values < 0.05 are indicated

**Table 3: Comparison of Biochemical parameters of Groups I, II, III (Mean  $\pm$  SD)**

Parameter	Group I (DM type 1)	p-value (I vs II)	Group II (DM type II)	p-value (II vs III)	Group III (Metabolic syndrome)	p-value (I vs III)
FBS (mg/dl)	158.27 $\pm$ 43.9	-	151.73 $\pm$ 55.23	<0.01	212.43 $\pm$ 98.68	<0.01
Total cholesterol (mg/dl)	164.7 $\pm$ 16.49	-	156.33 $\pm$ 22.68	<0.01	187.82 $\pm$ 48.96	<0.05
TG(mg/dl)	142.53 $\pm$ 18.53	-	137.33 $\pm$ 30.23	<0.001	211.83 $\pm$ 87.27	<0.001
HDL(mg/dl)	45.83 $\pm$ 16.48	<0.05	39.25 $\pm$ 7.86	<0.05	34.21 $\pm$ 9.05	<0.001
VLDL(mg/dl)	28.51 $\pm$ 3.71	-	27.47 $\pm$ 6.05	<0.001	42.03 $\pm$ 17.55	<0.001

LDL(mg/dl)	94.32±14.63	<0.05	106.28±25.57	-	121.49±42.45	0.001
Insulin(μIU/ml)	6.94±1.39	<0.05	16.01±3.25	-	9.38±1.60	<0.05
Amylase(U/L)	40.53±16.58	<0.01	75.13±44.81	-	58.77±17.46	<0.001

Statistically significant P values < 0.05 are indicated

**Table 4: Correlation between serum amylase and serum insulin ± SD**

		Insulin (μIU/ ml)		
		≤10	10-20	≥20
Amylase (U/L)	DM type I	38.5±16.74	47.5±0.70*	60±1.41
	DM type II	59.21±35.27	117.25±41.8	74.13±41.67
	MetS	59.95±18.57	72.6±8.44	55.5±14.67

SD- standard deviation, \*statistically significant at p<0.01

## Discussion

The cardiometabolic conditions such as MetS and type 2 diabetes are increasing in incidence worldwide. A lot of research has been done on normalization of abnormal lipid profile and hyperglycemia but very little attention has been paid to pancreatic exocrine function. The endocrine and exocrine pancreas has a complex anatomical and functional interaction<sup>21</sup>. For the normal functioning of exocrine pancreas, intact islets of Langerhans is necessary<sup>15,18</sup>. The exocrine pancreas is influenced both systemically by the islet hormones and directly through a islet-acinar portal system<sup>10</sup>.

In this study, we investigated the levels of serum amylase in association with insulin in DM Type I, DM Type II and MetS patients. It revealed that the amylase activity was lowest in DM Type I compared to DM Type II and MetS. In DM Type I, the autoimmune mediated damage of islet cells leads to reduction of insulin levels<sup>19</sup>. Insulin affects basal and stimulatory secretion of amylase via the islet-acinar axis<sup>22,4</sup>. Insulin binds to its receptor on acinar cells and stimulates amylase secretion. Hence insulin deficiency results in a decreased trophic action on the exocrine cells leading to low serum amylase levels. Dandona et al.<sup>6</sup> proposed that exocrine pancreatic deficit in diabetes closely parallels the endocrine β cell deficit in DM Type I and a common process is involved in the pathogenesis of impaired functioning of endocrine and exocrine pancreas.

Our study showed that the amylase levels are significantly higher in DM Type II (75.13±44.81) compared to DM Type I (40.53±16.58). Insulin influences the enzyme synthesis and release in the exocrine pancreas. The insulin levels in DM Type II (16.01±3.25) was significantly higher than DM type I (6.94±1.39). This explains the higher levels of serum amylase in DM Type II compared to DM Type I. Similar to our finding Aughsteen et al<sup>3</sup> demonstrated that serum amylase activity in type II diabetics was higher than in type I diabetics. Rakhee Yadav et al<sup>23</sup> found a significantly low amylase activity in the DM type II patients as compared to that in the healthy subjects. Nakajima et al<sup>17</sup> demonstrated that low serum amylase was independently associated with MetS and

diabetes. They suggested that low serum amylase levels preceded the overt metabolic abnormalities and may be inversely related with many cardiometabolic risk factors. As they did not measure blood insulin levels, whether low serum amylase levels were truly associated with hypoinsulinemia or hyperinsulinemia was unclear in their study.

Our study shows that the serum amylase levels are positively correlating with insulin levels in DM type I, being lowest (38.5±16.74) with serum insulin levels of <10 μIU/ml. In DM Type II, the serum amylase (74.13±41.67) is lower with higher insulin levels of ≥20 μIU/ml than with moderate insulin resistance of 10-20 μIU/ml. Finally in MetS also the amylase levels (55.5±14.67) are low with high insulin resistance. This suggests a nonlinear association between serum amylase and insulin resistance in cardiometabolic diseases- MetS and DM Type II. Thus measurement of insulin levels in this study helped us to come to a probable conclusion that low serum amylase is associated with decreased basal insulin levels and insulin secretion as seen in DM type I and is associated with high insulin resistance than with moderate resistance in MetS and DM Type II. This is because the high insulin secretion in severe insulin resistance state downregulates insulin receptor expression in pancreatic acinar cells<sup>14</sup>. This leads to reduced insulinotropic action on the acinar cells ultimately resulting in low serum amylase<sup>22</sup>. On the other hand, in light to moderate insulin resistance the insulin secretion is increased, leading to increased insulinotropic action on the acinar cells resulting in increased serum amylase<sup>16</sup>.

## Limitations of the study

Analysis of additional parameters to link the exocrine and endocrine function of the pancreas would have added weight to the study. Sample size is small. Further studies with larger sample size are required to establish association of serum amylase with insufficient insulin action in Type I and Type II DM and MetS.

## Conclusion

Our results suggest a significant association between serum amylase levels and insufficient insulin

action either due to inadequate insulin secretion and/or insulin resistance in Type I DM, Type II DM and MetS. These findings indicate a relationship between the endocrine and the exocrine pancreas and show that insulin affects amylase secretion via the islet-acinar axis. Insulin plays a major role in the control of pancreatic amylase biosynthesis and insulin resistance has an impact on the function of the exocrine pancreas. In DM Type I due to deficient insulin activity, stimulatory effect by insulin in secreting amylase from exocrine part of pancreas is less resulting in low serum amylase. In Type II DM and MetS, the serum amylase is significantly low with higher insulin resistance than with moderate insulin resistance. Low serum amylase suggests exocrine pancreatic insufficiency and if pancreatic amylase replacement therapy is given to these patients it may improve the nutritional status and also analysis of serum amylase could provide valuable information regarding prognosis of the illness.

**Conflict of Interest:** None

**Source of Support:** Nil

## References

- American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2007;30:42-7.
- American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2010;33:62-9.
- Aughsteeen AA, Abu-Umair MS, Mahmoud SA. Biochemical analysis of serum pancreatic amylase and lipase enzymes in patients with type 1 and type 2 diabetes mellitus. *Saudi Med J* 2005;26(1):73-7.
- Barreto SG, Carati CJ, Toouli J, Saccone GT. The islet-acinar axis of the pancreas: more than just insulin. *Am J Physiol Gastrointest Liver Physiol* 2010;299:G10-22.
- Bertelli E, Bendayan M. Association between endocrine pancreas and ductal system. More than an epiphenomenon of endocrine differentiation and development? *J Histochem Cytochem* 2005;53(9):1071-86.
- Dandona P, Freedman DB, Foo Y, Perkins J, Katrak A, Mikhailidis DP, et al. Exocrine pancreatic function in diabetes mellitus. *J Clin Pathol* 1984;37:302-6.
- Domínguez-Muñoz JE, Pieramico O, Büchler M, Malfertheiner P. Ratios of different serum pancreatic enzymes in the diagnosis and staging of chronic pancreatitis. *Digestion* 1993;54:231-6.
- Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. American Heart Association; National Heart, Lung, and Blood Institute: Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation* 2005;112(17):2735-52.
- Hayden MR, Patel K, Habibi J, Gupta D, Tekwani SS, Whaley-Connell A, et al. Attenuation of endocrine-exocrine pancreatic communication in type 2 diabetes: pancreatic extracellular matrix ultrastructural abnormalities. *J Cardiometab Syndr* 2008;3(4):234-43.
- Iwabe C, Shiratori K, Shimizu K, Hayashi N. Role of endogenous insulin in pancreatic secretion in rats. *Pancreatology* 2001;1(4):300-5.
- Korc M, Owerbach D, Quinto C, Rutter WJ. Pancreatic islet-acinar cell interaction: amylase messenger RNA levels are determined by insulin. *Science* 1981;213:351-3.
- Maruyama K, Takahashi H, Okuyama K, Yokoyama A, Nakamura Y, Kobayashi Y, et al. Low serum amylase levels in drinking alcoholics. *Alcohol Clin Exp Res* 2003;27:16S-21S.
- McGarry JD. Dysregulation of Fatty Acid Metabolism in the etiology of Type 2 Diabetes. *Diabetes* 2002;51:7-18.
- Mössner J, Logsdon CD, Goldfine ID, Williams JA. Regulation of pancreatic acinar cell insulin receptors by insulin. *Am J Physiol* 1984;247(2):G155-G160.
- Moessner J, Logsdon CD, Williams JA, Goldfine ID. Insulin, via its own receptor, regulates growth and amylase synthesis in pancreatic acinar AR42J cells. *Diabetes* 1985;34:891-97.
- Muneyuki T, Nakajima K, Aoki A, Yoshida M, Fuchigami H, Munakata H, et al. Latent associations of low serum amylase with decreased plasma insulin levels and insulin resistance in asymptomatic middle-aged adults. *Cardiovascular Diabetology* 2012;11:80.
- Nakajima K, Nemoto T, Muneyuki T, Kakei M, Fuchigami H, Munakata H. Low serum amylase in association with metabolic syndrome and diabetes: A community-based study. *Cardiovascular Diabetology* 2011;10:34.
- Okabayashi Y, Moessner J, Logsdon CD. Insulin and other stimulants have nonparallel translational effects on protein synthesis. *Diabetes* 1987;36:1054-60.
- Piciocchi M, Capurso G, Archibugi L, Delle Fave MM, Capasso M, Delle Fave G. Exocrine Pancreatic Insufficiency in Diabetic Patients: Prevalence, Mechanisms, and Treatment. *Int J Endocrinol* 2015;595-649.
- Singh J, Yago MD, Adeghate E. The role of insulin, glucagon, somatostatin, cholecystokinin, acetylcholine and nerve stimulation in the interactions between the endocrine and exocrine pancreas in normal and diabetic conditions in rats. *Int J Diabetes* 1999;7(1):114-19.
- Williams JA, Goldfine ID. The insulin-acinar relationship. In: *The Exocrine Pancreas: Biology, Pathobiology and Diseases*. In: Go VLW et al. (eds) Raven Press, New York, 1993;789-802.
- Williams JA, Goldfine ID. The insulin-pancreatic acinar axis. *Diabetes* 1985;34:980-98.
- Yadav R, Bhartiya JP, Verma SK, Nandkeoliar MK. The Evaluation of Serum Amylase in the Patients of Type 2 Diabetes Mellitus, with a Possible Correlation with the Pancreatic Functions. *JCDR* 2013;7(7):1291-4.
- Yegneswaran B, Pitchumoni CS. When should serum amylase and lipase levels be repeated in a patient with acute pancreatitis? *Cleve Clin J Med* 2010;77:230-1.
- Zhao Y, Zhang J, Zhang J, Wu J, Chen Y. Metabolic syndrome and diabetes are associated with low serum amylase in a Chinese asymptomatic population. *Scand J Clin Lab Invest* 2014;74(3):235-9.