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Original article

# Serum Lipase/Amylase Activity Ratio for Screening Insulin Resistance

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**Abstract**

Early diagnosis of insulin resistance (IR) is important to prevent the development of type 2 diabetes mellitus (DM). Type 2 DM is mainly considered as an endocrine disorder however some recent studies show that exocrine functions of the pancreas are insufficient in type 2 DM. Our aim in this study to evaluate the relation of insulin resistance with pancreatic exocrine functions. Fasting glucose, insulin, amylase, lipase, HbA1c, and demographic information of subjects were taken from the laboratory information system. Children and the diabetic subjects were excluded. Included subjects were separated according to the insulin sensitivity status determined by homeostatic model assessment. There were 335 individuals in the insulin sensitive (IS) group, 275 in the moderate IR group, and 164 in the severe IR group. The average age is 45 (34-54). Serum lipase and amylase levels were used as an indicator of pancreatic exocrine functions. Serum amylase, lipase and serum lipase/amylase activity ratio were compared between groups. Serum amylase levels were 67.8, 63 and 65.3 U/L; serum lipase levels were 31, 31 and 25.5 U / L, serum lipase/amylase ratios were 47%, 50% and 38% in the IS, moderate IR and severe IR groups, respectively. There is a significant difference in serum amylase levels between insulin- sensitive (IS) and moderate IR groups ($p=0.02$) and in serum lipase levels between IS and severe IR, and between moderate IR and severe IR ($p<0.001$, $p<0.001$ respectively). When we use serum lipase/amylase activity ratio to compare groups with each other, there is a significant difference between IS and moderate IR, IS and severe IR, and moderate IR and severe IR ($p= 0.015$, $p<0.001$, $p< 0.001$ respectively). Our results show that the exocrine functions of the pancreas are affected in insulin resistance and serum lipase/amylase activity ratio can be used as a new parameter to define and screen insulin sensitivity status of the body.

**Keywords:** Exocrine Pancreatic Function, Insulin Resistance, Amylase, Lipase, Serum Lipase/ Amylase Activity Ratio.

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## INTRODUCTION

Diabetes Mellitus (DM) is a common chronic metabolic disorder, and its prevalence is increasing worldwide. The quality of life and life expectancy decrease due to its destructive complications. The underlying pathophysiology of DM mainly bases on resistance to insulin effects and insufficient secretion of insulin. Insulin resistance (IR) is a pathological condition that occurs in the body, if left untreated, type 2 DM develops. Therefore, early diagnosis of IR is necessary to prevent the development of type 2 DM [1].

Clinical evaluation and laboratory is used for IR in practice. Homeostatic model assessment (HOMA-IR) calculated by fasting blood glucose and insulin or c-peptide levels, is a method for defining the IR and beta-cell function of the pancreas. The HOMA-IR model is correlated well with other tests showing insulin resistance, including gold standard euglycemic hyperinsulinemic clamp test. HOMA-IR is a simple test that requires only a single sample for the measurement of insulin and glucose [2]. However, insulin assays are not still standardized, making the usage of HOMA-IR difficult in clinical practice [3].

DM is mainly considered as an endocrine disorder however, it is known that exocrine pancreatic function is reduced in type 1 DM. Different authors who investigated pancreatic exocrine functions in diabetes have theories about reduced function: pancreatic fibrosis due to neuropathy and angiopathy, atrophy of pancreatic exocrine tissue due to decreased trophic action of insulin. Recent studies also show that pancreatic exocrine functions are insufficient in type 2 DM, not as much as type 1 [4].

Serum amylase and lipase activity levels are useful markers to evaluate pancreatic exocrine functions in routine clinical practice. They are mostly used for the diagnosis of acute pancreatitis and also accompany other pancreatic diseases [5, 6]. Some recent studies which prove exocrine insufficiency in DM, show that low serum amylase level is associated with pancreatic destruction due to chronic pancreatitis, [7] insulin deficiency in DM [8, 9] and insulin resistance in obese animals [10]. It is also reported that low amylase levels are associated with metabolic syndrome in Korean adults [11]. It is also shown that reduction in serum amylase levels are correlated with duration of disease in type 2 DM; whereas, reduction in lipase levels are only seen in patients with very low insulin levels [9].

There are many studies about serum amylase activity in both types of DM and IR; however, the literature is limited about serum lipase activity, especially in IR. Our aim in this data mining study is to explore how the serum amylase and lipase activity levels change in insulin resistance, which assessed by HOMA-IR. We also investigated the serum lipase/ amylase activity ratio (Serum L/A activity ratio) between the groups. The results of this study may contribute to the evaluation of patients, who are at risk in the development of IR and metabolic syndrome using serum amylase and lipase activity which are tested by standardized, simple and economic assays in clinical laboratories.

## MATERIALS and METHODS

### Acquisition of the Data

The laboratory test results (fasting plasma glucose, fasting plasma insulin, fasting serum amylase activity, fasting serum lipase activity and HbA1c) and demographic information of subjects who applied to Ankara Ataturk Education and Training Hospital between January and April in 2017 were taken from laboratory information system (LIS). A total of 774 subjects were included in this study (351 male and 432 female). The median of the age of the participants is 45 (IQR 34-54). There is no difference in gender (p= 0.49). The research was performed according to the Declaration of Helsinki principles and was approved by the local ethics committee. The subjects who have DM (fasting plasma glucose levels ≥126 mg/dL and HbA1c ≥ %6.5) and children (age <18) were excluded from this study. The participants who have amylase and lipase activity levels above the upper limit of reference range were excluded because high values indicate different disorders like acute pancreatitis.

### Laboratory Procedures

Fasting plasma glucose, amylase, and lipase analysis with spectrophotometric method and HbA1c analysis with immunoturbidimetric method were performed on the Cobas 8000 (Roche Diagnostic) and insulin tests were analyzed by ElectroChemiLuminescence (ECLIA) method on the Cobas 6000 e601 (Roche Diagnostic).

### Calculation of the HOMA-IR

HOMA-IR was calculated with this formula: [fasting plasma glucose(mg/dL) × insulin (UI/L)] / 405. The subjects were separated into three groups according to the HOMA-IR scores (<3: insulin-sensitive (IS), 3-5: moderate IR, >5: severe IR) [12].

### Calculation of the Serum Lipase/ Amylase Activity

Serum Lipase/ Amylase Activity was calculated with this formula: [fasting serum lipase (U/L)/ fasting serum amylase (U/L)] *100.

### Statistical Analysis

Categorical data are demonstrated as numbers, and continuous data are shown as median values with interquartile ranges. To evaluate the distribution of continuous data, we use a Shapiro- Wilk test. Comparisons of the continuous data were performed using a Kruskal-Wallis rank sum and Man Whitney U test.

## RESULTS and DISCUSSION

A total of 774 subjects were included in this study (351 male and 432 female). The median of the age of the participants is 45 (IQR 34-54). There is no difference in gender (p= 0.49). The data of these

subjects were separated according to the insulin sensitivity status. The characteristics and laboratory test results of the subjects among the groups are shown in Table 1. Three hundred thirty-five (%43.2) subjects are insulin sensitive, 275 (%35.5) of them have moderate IR and 164 (%21,1) of them have severe IR. The serum amylase and lipase levels between groups are significantly different (p=0.067 and p<0.001, respectively).

Table 1. The characteristics and laboratory test results of the enrolled subjects according to insulin sensitivity status.

| | **Overall** | **Insulin-Sensitive (IS)** | **Moderate IR** | **Severe IR** | ***p* value** |
|---|---|---|---|---|---|
| | *n*=774 (%100) | *n*=335 (%43.2) | *n*=275 (%35.5) | *n*=164 (%21.1) | |
| Age (year) | 45 (19) | 46 (22) | 46 (18) | 45 (21) | 0,69 |
| Gender (F-M) | 432-351 | 193-142 | 151-131 | 88-78 | 0,49 |
| Fasting glycemia (mg/dL) | 94 (14) | 91 (12) | 96 (13) | 98 (17) | <0.001* |
| Fasting insulin (μU/mL) | 13,4 (10,79) | 7,4 (3,58) | 15,1 (3,57) | 27,6 (27,26) | <0.001* |
| Amylase (U/L) | 65,0 (26,86) | 67,8 (27,37) | 63,0 (24,63) | 65,3 (27) | 0.067 |
| Lipase (U/L) | 30,0 (14) | 31,0 (14) | 31,0 (15) | 25,5 (19,63) | <0.001* |
| HbA1c (%) | 5,4 (0,46) | 5,3 (0,39) | 5,5 (0,44) | 5,5 (0,47) | <0.001* |
| HOMA-IR | 3,2 (2,68) | 1,7 (0,94) | 3,6 (0,92) | 6,5 (5,62) | <0.001* |

Results are given as median (IQR); Abbreviations: HbA1c, glycated hemoglobin A1c; HOMA-IR, homeostasis model assessment; IQR, interquartile range; *$p$<0.05 were considered significant, Kruskal Wallis statistic was used.

There is a significant difference in serum amylase levels between IS and moderate IR groups ($p$=0.02). There is no significant difference ($p$=0.2, $p$=0.4 respectively) between IS and severe IR and between moderate IR and severe IR (Figure 1).

When we compare the serum lipase levels between IS and moderate IR groups, there is no significant difference (p=0.8). However, between IS and severe IR, and between moderate IR and severe IR, there is a significant difference (p<0.001, p<0.001 respectively) (Figure 2).

When we use Serum L/A ratio to compare groups with each other, there is a significant difference between IS and moderate IR, IS and severe IR, and moderate IR and severe IR ($p$= 0.015, $p$<0.001, $p$<0.001, respectively) (Figure 3).

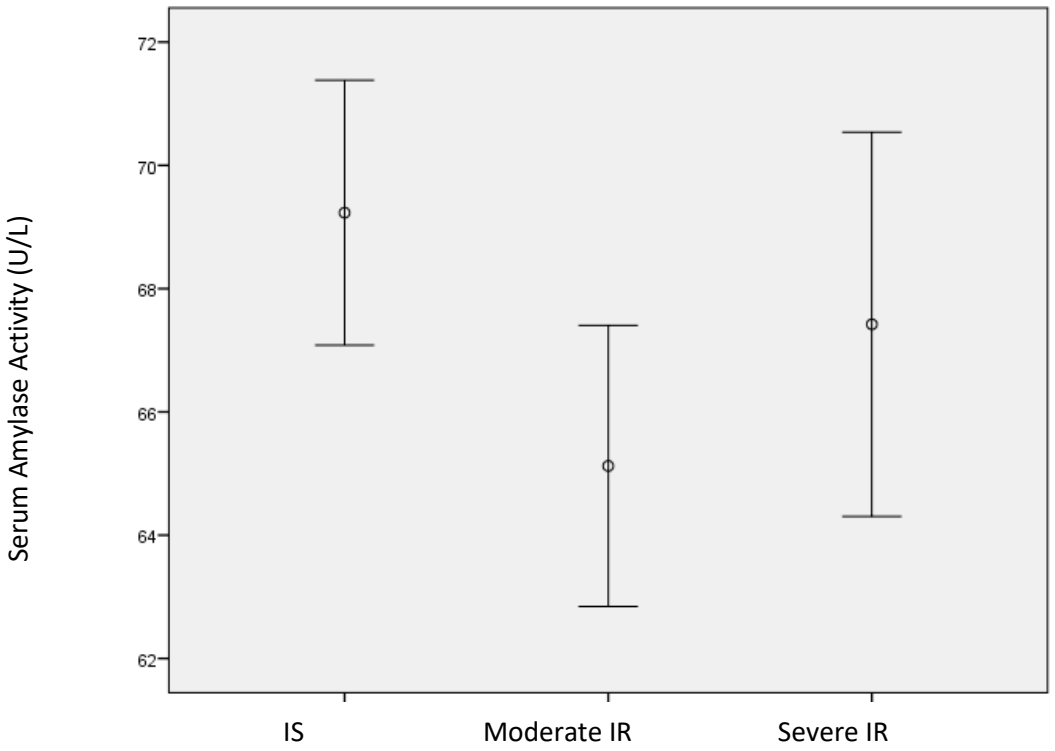


**Figure 1.** Serum Amylase activities according to insulin sensitivity status.

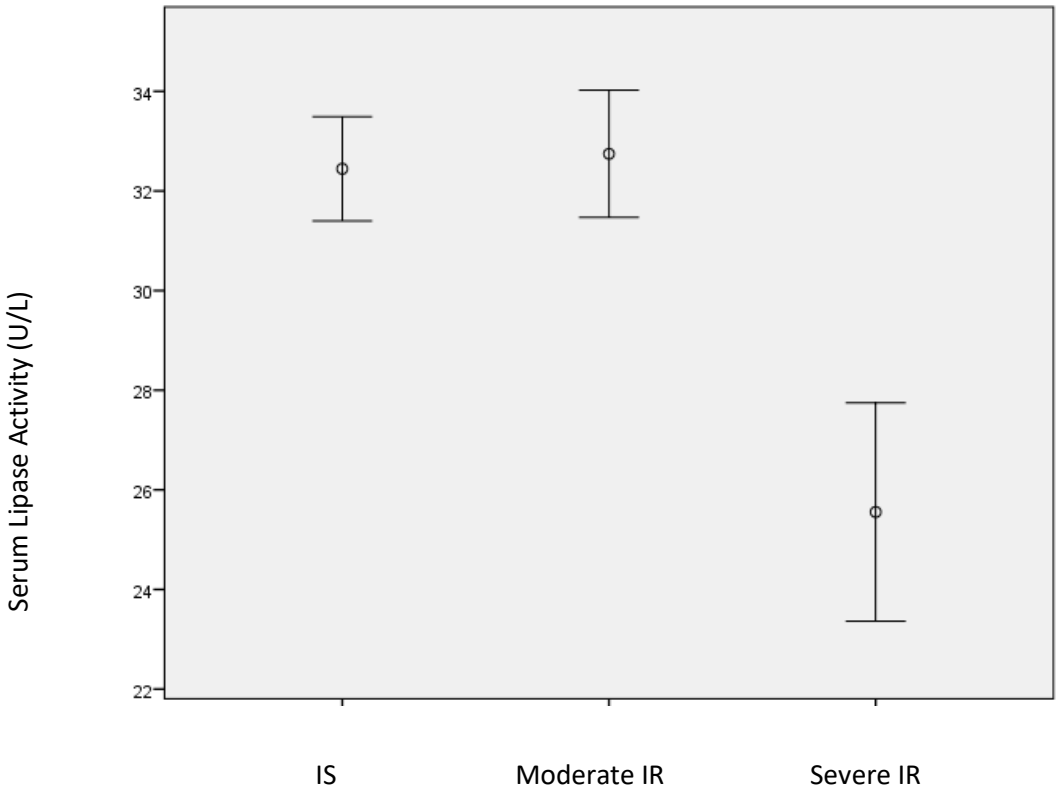


**Figure 2.** Serum Lipase activities according to insulin sensitivity status.

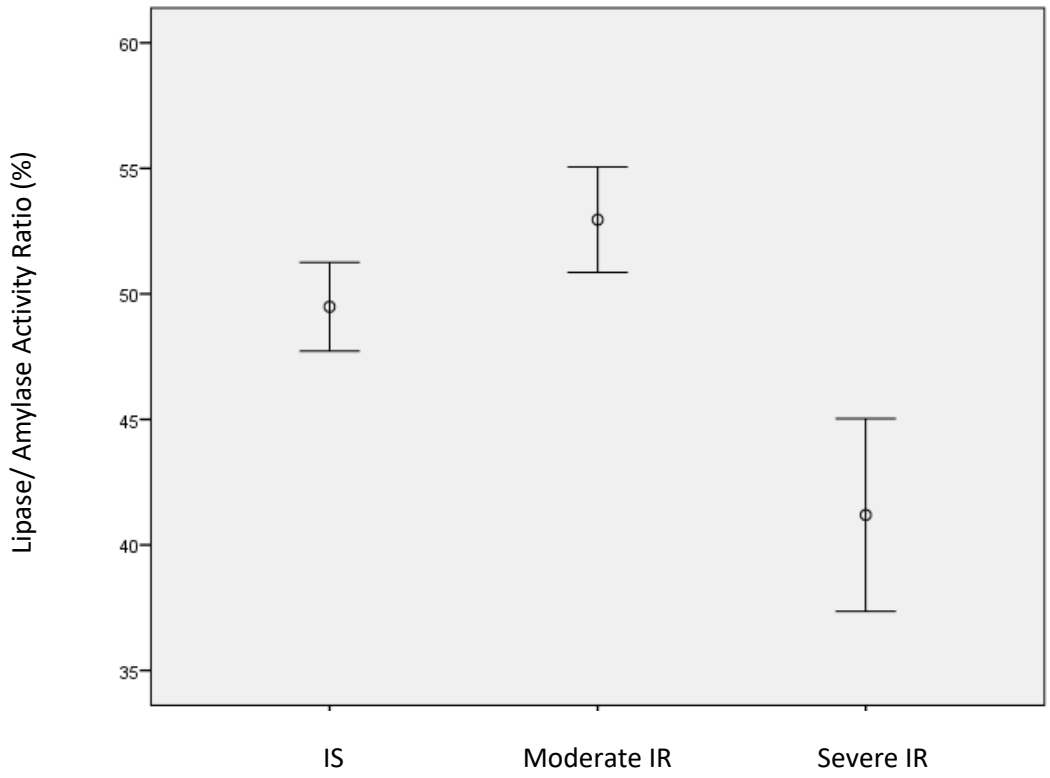


**Figure 3.** Serum Lipase /Amylase Activity Ratio according to insulin sensitivity status.

In this study, we investigated pancreatic exocrine functions in insulin resistance using serum amylase, serum lipase activity and Serum L/A activity ratio levels. Our results show that Serum L/A activity ratio can be used as a new parameter to define the insulin sensitivity status of the body.

According to our findings, serum amylase activity levels are significantly decreased in moderate IR; however, serum lipase activity levels are not changed until severe IR. So that, Serum L/A activity ratio is increased in moderate IR. In severe IR, serum lipase activity levels are severely decreased compared to amylase activity. So that, serum L/A activity ratio is decreased in severe IR. Consequently, when insulin resistance develops in the body serum L/A activity ratio is increased firstly. After that serum L/A activity ratio is decreased with the progression of IR. According to our results we can assume that any disturbance in serum L/A activity ratio indicates a disturbance in insulin sensitivity.

Evidence of a possible linkage between serum amylase activity and IR comes from the study by Jeong Gyu Lee et al. These authors showed that the prevalence of metabolic syndrome increased with decreasing amylase concentration. The pathophysiology of metabolic syndrome is still unknown; however, as far as we know, IR and abdominal obesity are the most important underlying mechanisms (1).

A study by Kondo et al. shows that serum amylase activity, but not lipase activity was significantly decreased in obese subjects, compared to lean subjects. A secondary finding in their study, an initial low serum activity amylase increased in obese adults and children by weight reduction (2). It is also shown that serum amylase activity is reduced in streptozotocin-diabetic rats, as well as patients with both types of diabetes (1, 3). Tanaka et al. found a positive correlation between serum amylase activity and serum ghrelin levels. Recently we know that ghrelin concentration is decreased in metabolic syndrome, type 2 diabetes, and obesity (4-6).

Aughsteen et al. investigated pancreatic exocrine insufficiency using serum amylase and serum lipase activity in patients with type 1 and type 2 DM. They found a reduction in serum amylase activity levels in both types of DM; however, reduction in serum lipase activity levels was only recorded in type 1 DM. They clearly illustrated pancreatic exocrine insufficiency in both types of DM, and they suggest the analysis of these parameters to follow illness and response to therapy (7). The results of the study by Hardt et al who investigate pancreatic exocrine functions in type 1 and type 2 DM with an indirect test (fecal elastase-1 concentration), support that exocrine pancreatic function is impaired in both types of DM (8). According to the findings in the study by Madole MB et al. increase in fasting blood glucose with decrease in serum lipase and amylase activity indicates the imbalance in exocrine- endocrine axis of the pancreas (9).

Morphological studies demonstrate that the endocrine islet cells of pancreas are scattered within the exocrine tissue. Blood supplied to endocrine islet cells flow into the exocrine acinar tissue to establish islet-acinar portal system. As blood flows into the acinar capillaries from the islets, acinar cells are exposed to high levels of the islet hormones (such as glucagon, insulin, pancreatic polypeptide, and somatostatin). These hormones regulate the synthesis and secretion of pancreatic exocrine enzymes. This interaction is called the ‘insulo-acinar axis. It is known that insulin has a trophic effect on the exocrine acinar tissue. High level of insulin causes larger peri-insular acini which contain more zymogen granules. Several studies demonstrate that insulin promotes uptake of amino acids by exocrine cells and control the response to hyperglycemia of them. It is believed that other islet hormones have a negative effect on the exocrine pancreas (10, 11).

The secretion of major digestive enzymes of pancreas; proteases, amylase, and lipase, is regulated at both transcriptional and translational levels according to the need for the body. Some of the signals that regulate enzyme secretion are vagal nerve and gastrointestinal hormones. Nutrients, particularly amino acids, and islet hormones, especially insulin also influence the regulation. The level of the carbohydrates in the diet affects pancreatic amylase content and mRNA levels. It is believed that this effect is mediated by insulin. (12) Because of the insulin resistance or deficiency in DM, pancreatic amylase content and mRNA levels fall dramatically, whereas lipase increases moderately. CCK and insulin stimulate translational initiation through the P13K-PKB-MTORc1 pathway which leads to an

increase in protein synthesis of digestive enzymes in pancreas. So that insulin affects both transcriptional and translational levels of pancreatic amylase and lipase (12).

Aughsteen et al. also investigated the effects of insulin on lipase and amylase activity in the pancreas of streptozotocin-diabetic rats. The serum and pancreatic insulin levels were decreased by 85% and 37% in untreated diabetic rats. Their pancreatic lipase and amylase were also decreased by 43% and 66%. Approximately 25% and 47% increase in the pancreatic lipase and amylase in insulin-treated diabetic rats. These results show that insulin has a stimulant effect on lipase and amylase activity in the pancreas of diabetic rats. These results also show that amylase activity is more vulnerable to insulin effects compared to lipase. These findings reported by Aughsteen et al. support the decrease in serum amylase in moderate IR, however, no significant change in serum lipase levels were detected until severe IR in our study (13).

The results of this study show that the exocrine function of the pancreas reduced when IR develops. However, serum amylase and lipase levels are affected differently according to the stage of IR; despite, both show pancreatic exocrine functions. This can be explained by the different effects of insulin on the regulation of the secretion of major digestive enzymes. This is the first study to evaluate serum L/A activity ratio in IR. The only clinical situation in which serum L/A activity ratio was investigated previously, is alcoholic-non alcoholic acute pancreatitis (14).

**Conclusion**

In summary, our study shows that serum L/A activity ratio can be used to follow the insulin sensitivity status of subjects. The advantage of this, serum amylase and lipase assays are simple, easy, inexpensive, and accessible in most of the laboratories and hospitals.

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**Ek Beyan:**Yazar katkı oranları

"1. yazar %50 oranında, diğer yazarlar %10 oranında katkı sağlamıştır."

“Araştırma ve yayın etiği ilkelerine uygun hareket edildiğine dair metin "Makalenin tüm süreçlerinde JIAM'ın araştırma ve yayın etiği ilkelerine uygun olarak hareket edilmiştir."

**Çıkar çatışması bildirimi**

Bu çalışmada herhangi bir potansiyel çıkar çatışması bulunmamaktadır.

**Etik kurul izin bilgileri**

"Ankara Yıldırım Beyazıt Üniversitesi Tıp Fakültesi Etik Kurulu tarafından 21.02.2018 tarihinde 48 sayılı etik kurul onayı alınmıştır."

**Biyografik Not**

**Emine Feyza Yurt:** Tıbbi Biyokimya uzmanlığı eğitimini Ankara Yıldırım Beyazıt Üniversitesi Tıp Fakültesi’nde tamamlamıştır. Şu anda Beypazarı Devlet Hastanesi’nde uzman doktor olarak görev yapmaktadır.

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**Özcan Erel:** Ankara Yıldırım Beyazıt Üniversitesi Tıp Fakültesi Tıbbi Biyokimya Anabilim Dalında profesör doktor olarak görev yapmaktadır. Ankara Şehir Hastanesi Tıbbi Biyokimya Kliniği klinik şefidir.