

Study of Isthmin-1 Levels and Serum Lipid Measurements in Patients with Metabolic Syndrome

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Abstract

Background: Metabolic syndrome (MetS) is a group of comorbidities that includes obesity, hypertension, and disturbances in carbohydrate and lipid metabolism. Isthmin-1 (ISM1) is a secreted protein that plays multiple roles in pathophysiological processes. It works either endocrine or autocrine. It was found to be upregulated in MetS patients. **Objective:** This study aimed to assess the level of ISM1 as a marker for the detection of MetS diseases and its relationship with other related biomarkers. **Materials and Methods:** An investigation into 125 individuals with metabolic diseases and 40 healthy adults aged 20–80 years was done on 165 patients at Al-Yarmouk Teaching Hospital in Baghdad, Republic of Iraq. For each patient and control, measure the levels of ISM1 using commercial ELISA kits according to the manufacturer's instructions. The body mass index (BMI), blood pressure measurements (mmHg for systolic and diastolic forms), cholesterol, triglycerides, fasting blood glucose (FBG), high-density lipoprotein, low-density lipoprotein, and very low-density lipoprotein (HDL, LDL, and VLDL) (mg/dL), were examined. **Results:** The BMI (kg/m²) in the MetS group (40) was significantly different from the control group's (20.9) value, according to the findings of the study. Systolic blood pressure, diastolic blood pressure (mmHg), and FBG (mg/dL) were significantly different ($P < 0.05$) in MetS and were measured at 15, 9, and 117.5, respectively, as opposed to the control group's 12, 8, and 98. With the exception of HDL, which was higher in the healthy group (48 mg/dL) as compared to the MetS group (29.25 mg/dL), significant differences ($P < 0.05$) were found in the cholesterol, TG, LDL, and VLDL levels in the MetS group. These values were 238, 283, 151, and 56.6 (mg/dL), respectively. ISM1 levels were considerably ($P < 0.05$) higher in the MetS group than in the healthy control group (3.22 ng/mL; 1.34 ng/mL). The receiver operating characteristic test for the ISM1 marker showed perfect cut-off values, and the area under the curve was 0.974, which indicated that ISM1 was considered a good diagnostic marker for people with MetS. **Conclusion:** We can infer from this study that people with MetS have higher blood levels of ISM1 because there is a greater need for ISM1 secretion to help lessen the severity of the metabolic problems.

Keywords: Isthmin-1, lipoprotein (LDL, cholesterol, HDL), metabolic syndrome, TG

INTRODUCTION

Obesity, hypertension (HT), and disorganized glucose and lipid metabolism are all comorbid disorders that make up the metabolic syndrome (MetS).^[1,2] The phrase “metabolic syndrome” was first used in the National Cholesterol Education Program Adult Treatment Panel III report on the detection and management of high blood cholesterol to refer to the co-existence of obesity, dyslipidemia, HT, and abnormalities in glucose metabolism.^[3] Some examples of these conditions are HT, diabetes, abdominal fat, and abnormal lipid profiles (cholesterol and triglycerides).^[4] Hyperlipidemia, also known as dyslipidemia, is a disease associated with an increase in lipids in the blood. Lipids

in the blood combine with carriers to overcome solubility problems; such carriers are called lipoproteins. The ratio of proteins to lipids determines the density of the carriers they contain.^[5] The main risk factors for MetS are being overweight and obese because these circumstances can drop “good” HDL cholesterol while raising “bad” LDL cholesterol, blood triglycerides, and high pressure. Obese

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adults have lower insulin sensitivity (insulin resistance [IR]). Adipokines are a class of bioactive chemicals that play a role in insulin sensitivity and secretion, inflammation, appetite, energy expenditure, and cardiovascular function. Because adipocyte and adipose tissue dysfunction are important abnormalities in obesity. Obesity is associated with type 2 diabetes, IR, high blood pressure, fatty liver, airway disease, dyslipidemia, dementia, atherosclerosis, and certain cancers.^[6] If you are overweight or obese while pregnant, your unborn child may be more likely to have MetS.^[7] Isthmin-1 (ISM1), a unique chordate-specific secreted protein that is strongly expressed in the thyroid, placenta, and adipose tissue, was discovered in the developing brain of the frog *Xenopus laevis* in 2002.^[8] Notably, ISM1 was identified in 2021 as an adipokine with significant roles in glucose absorption and lipid metabolism by combining bioinformatic analysis and expression data of adult brown and white adipocytes.^[9] ISM1 has an endogenous role in glucose control, as shown by the effects of ISM1 ablation on impaired glucose tolerance, decreased adipose glucose absorption, and decreased insulin sensitivity. ISM1 operates independently of insulin and insulin-like growth factor receptors to activate a PI3K-AKT signaling pathway.^[10] ISM1 is a member of the isthmin gene family, which also includes ISM1 and ISM2 (also known as Tail1). The human isthmian genes (ISM1 on chromosome 20 and ISM2 on chromosome 14q24.3) both encode secreted proteins with TSR1 and AMOP domains.^[11,12] ISM1 causes hepatocytes to switch from a lipogenesis state to a protein synthesis state to prevent fat accumulation in the liver. It produces a 60 kDa protein with 499 amino acids, 3 helices, and 2 folded layers.^[13] In addition to its role as an adipokine in metabolism, ISM1 is an important component of many pathological processes, such as cancer, immunity, cell proliferation, endothelial cell permeability, and physiogenesis.^[14] More and more studies have shown that ISM1 is involved in the process of tumorigenesis and, at the same time, controls the migration and invasion of cancerous cells, particularly in solid tumors like breast, colorectal (CRC), hepatocellular carcinoma, and melanoma. It is known to be angiogenesis-dependent.^[15,16] This study aimed to investigate the association between serum ISM1 levels and MetS in MetS patients in comparison to healthy individuals.

MATERIALS AND METHODS

Subjects: case-control study

We opted for 125 participants clinically presented with MetS and 40 healthy participants aged 20 to 80 years during December 2022 to May 2023 from Al-Yarmouk Teaching Hospital, Baghdad-Republic of Iraq.

Blood sample collection: 40 healthy volunteers and 125 patients with metabolic disorders each had 10 mL of blood drawn. Blood samples were collected in gel tubes

under sterile circumstances and centrifuged at 1000×g for 15 min. Small aliquots of the acquired serum were then separated into and stored at 20°C until a portion of it was used for lipid profile measurement.

Analysis

The height and weight of each subject were calculated in kg/m². By dividing the weight (in kg) by the square of the height (in m²), the body mass index, or BMI, was determined. Each patient had their systolic and diastolic blood pressure, fasting blood glucose (FBG), TG, HDL, LDL, and VLDL tested in mg/dL. According to the advice of the manufacturer Linear, Spain, the level of ISM1 was measured using a commercial ELISA kit in the USA.

Statistical analysis

The median for numerical variables with an irregular distribution (the 25th and 75th percentiles). Numerical variables that were not regularly distributed were described using the Mann-Whitney *U* tests. Using receiver operating characteristic (ROC) curve analysis, the significance level was selected at a *P* value of 0.05, and the ISM1 cut-off value was determined.

Ethical approval

On December 5 2022, the local ethics committee approved this study, which adheres to the ten ethical principles outlined in the Declaration of Helsinki. The Scientific Committee supported this study at the Department of Chemistry/College of Sciences for Women, University of Baghdad.

RESULTS

Table 1 lists the median (25th and 75th percentiles) values for age and BMI for MetS patients and healthy subjects.

The collected data were analyzed by median (25th and 75th percentiles) via the Mann-Whitney *U* test at the 0.05 level.

The study's findings demonstrated a substantial difference in BMI (kg/m²) between the MetS group (40) and the controls (20.9) but not between the two groups' ages (53.5 and 49, respectively) because such differences were not statistically significant when the median (25th and 75th percentiles) of the collected data were analyzed using the Mann-Whitney test at the 0.05 threshold.

Table 1: Shows the demographics of MetS for patients and controls

<i>P</i> -value	Control	MetS	Variables
0.014	49.00 (61.50–36.00)	53.50 (68.50–42.00)	Age (year)
0.0001	20.90 (22.25–19.50)	40 (44.50–35.42)	BMI (kg/m ²)

Table 2: The MetS' and the controls' diastolic and systolic blood pressure

Variables	MetS	Control	P value
Systolic blood pressure (mmHg)	15.00 (16.00–15.00)	12.00 (12.00–12.00)	0.0001
Diastolic blood pressure (mmHg)	9.00 (9.50–9.00)	8.00 (8.00–8.00)	0.0001

Table 3: The cholesterol, TG, HDL, LDL, and VLDL of MetS and controls

P value	Control	MetS	Variables
0.0001	150.00 (158.50–134.50)	238.00 (257.00–229.00)	Cholesterol (mg/dL)
0.0001	112.00 (145.00–97.00)	283.00 (304.00–265.50)	TG (mg/dL)
0.0001	48.00 (49.00–46.95)	29.25 (31.00–28.00)	HDL (mg/dL)
0.0001	73.00 (87.00–64.65)	151.00 (168.60–142.45)	LDL (mg/dL)
0.0001	24.00 (31.55–20.70)	56.60 (60.20–53.00)	VLDL (mg/dL)

The Mann–Whitney test was used to assess the data at the 0.05 level by median (25th and 75th percentiles)

TG, triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, volatile low-density lipoprotein

Table 4: The isthmin 1 level and FBG of MetS and controls

P-value	Control	MetS	Variables
0.0001	98.00 (105.00–95.00)	117.50 (136.50–102.00)	FBG (mg/dL)
0.0001	1.34 (1.43–1.27)	3.22 (3.93–2.49)	Isthmin-1 (ng/mL)

The Mann–Whitney test was used to assess the data at the 0.05 level by median (25th and 75th percentiles).

Table 2's findings revealed significant differences ($P < 0.05$) between the MetS' systolic and diastolic, which were 15, 9, and the control's 12, 8.

Results from Table 3 illustrated significant differences ($P < 0.05$) between the MetS group and the controls in terms of cholesterol, total triglyceride index, LDL, and VLDL, with the exception of HDL, which was higher in the healthy group (48 mg/dL) than in the MetS group (29.25 mg/dL).

Table 4 shows the ISM1 level and FBG for patients with MetS and controls. According to Table 4's findings, FBG readings, which were 117.5 for patients and the control's 98. The level of ISM1 in the MetS group (3.22 ng/mL) was significantly ($P < 0.001$) higher than that in the healthy controls (1.34 ng/mL) [Figure 1].

The ROC test for the ISM1 marker showed perfect cutoff values with a sensitivity of 100% and a specificity of 95.1%,

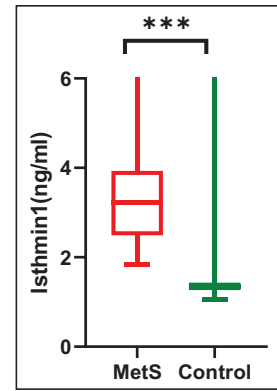


Figure 1: Median of isthmin-1 in MetS and controls

and the area under the curve is 0.974 [Figure 2], which indicated that ISM1 was considered a good diagnostic marker with a cutoff value of >1.757 , below which the level tested are considered patients.

DISCUSSION

Characteristics of MetS include obesity and IR, whereby the body develops a supernormal insulin response to a glucose load.^[17] BMI serves as a health indicator for people and is frequently linked to metabolic diseases.^[18] As shown in Table 1. This finding is consistent with that of Amini *et al.*,^[19] who found a patient group with a 27.5 BMI (kg/m²) compared to a 22.6 BMI (kg/m²) for the control group while noting a nonsignificant difference in age (year) between the two groups.

Table 2 shows the diastolic blood pressure and systolic blood pressure of the MetS and control groups. With a comparatively higher incidence in developing countries, HT is a significant health risk factor that contributes to a rise in worldwide mortality in both developed and developing nations.^[20] This finding is consistent with that of Wong *et al.*^[21] who found that there was a link between MetS and HT.

In the brain and peripheral nervous system, particularly, excessive lipid storage leads to persistent cellular and tissue damage, which results in metabolic diseases such as Gaucher's disease, Tay-Sachs disease, Niemann–Pick disease, etc.^[22] Numerous elements are interconnected. A sedentary lifestyle and obesity increase the risk of MetS. Excessive blood pressure, IR, and excessive cholesterol are a few of them. Cardiovascular disease (CVD) and type 2 diabetes may result from these risk factors.^[23] The main component of MetS is dyslipidemia, which is defined by elevated levels of free fatty acids, TG, and low-density lipoprotein cholesterol (LDL-C) but low levels of HDL cholesterol.^[24]

As shown in Table 3. This result is comparable to that of Kosmas *et al.*,^[25] which discovered an increase in cholesterol, total lipids, LDL, and VLDL in the MetS

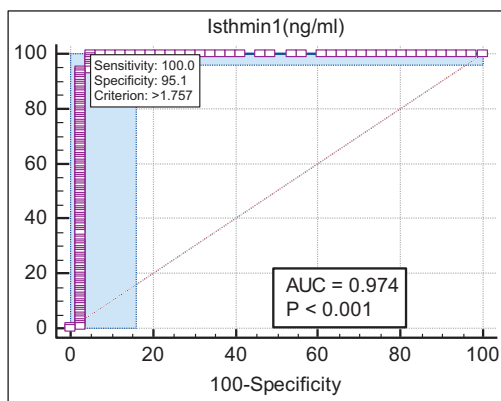


Figure 2: ROC curve of isthmin-1

group compared to healthy controls while also discovering a decrease in HDL levels in the MetS group compared to healthy controls. In addition to having elevated LDL-C, people with MetS, a group that is at a high risk of developing CVDs, also have elevated triglyceride levels and low levels of HDL and LDL (sd-LDL) particles.^[26]

ISM1 is a novel adipokine that affects glucose homeostasis and lipid metabolism.^[8] The protein ISM1 is released by mature adipocytes and has been defined as a unique adipokine that acts through an unidentified receptor tyrosine kinase. It triggers a signaling cascade similar to that of insulin.^[27,28] ISM1 improves metabolic abnormalities linked to T2D, such as hyperglycemia and hepatic steatosis, when administered pharmacologically to mice.

According to Table 4's findings, these results obtained in this study are consistent with the researchers' findings, as the researchers noted in the results that high-FBG and high WC are the most common MetS components of young Saudi Arabia.^[29] Various factors, including diet, can lead to high blood sugar levels. The consumption of excess sugar and carbohydrates increases blood sugar levels after meals because the food is decomposed into glucose molecules into the blood.^[30] The level of ISM1 in the MetS group is consistent with Ruiz-Ojeda *et al.*,^[31] who hypothesized that obese individuals had higher serum ISM1 levels than normal-weight individuals and that these levels were positively correlated with BMI.

ISM1 is a secreted protein that is expressed in the brain, lung, vasculature, skin, and immune cells. It was first identified during fetal brain development. ISM1, which controls glucose uptake while inhibiting hepatic lipid production, has recently been discovered in mouse and human adipocytes.^[32] This improves hyperglycemia and lowers lipid buildup in mice models. ISM1 levels are positively correlated with fat mass in children, according to Anguita-Ruiz *et al.*'s^[33] study. This finding suggests that adipose cells may secrete more ISM1 than is typically seen, which could have endocrine implications on other tissues.

The ROC analysis, short for the receiver operating characteristic curve, is a graph showing the discriminative power of a dual classifier as a function of the discriminative threshold.^[34] This indicated that ISM1 was considered a good diagnostic marker with a cutoff value below which the level tested is considered patients.

CONCLUSIONS

Due to the increased need for ISM1 secretion to lessen the severity of metabolic abnormalities, patients with MetS have higher levels of ISM1 in their blood. ISM1, a recently characterized adipokine, is transported throughout several bodily compartments and is essential to numerous biological activities. Results obtained from ROC suggest that ISM1 is considered a good diagnostic marker for MetS, and finally, it's still unclear whether the secretory factor ISM1 may be found in bodily fluids like blood or function as a biological marker for different disorders.

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Conflicts of interest

There are no conflicts of interest.

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