Section A-Research paper

The Comparison of Copeptin levels and Endothelial dysfunction properteis of E-Selectin and Thrombomodulin in Metabolic syndrome and T2DM Patients

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ABSTRACT

Background: Metabolic syndrome (Mets) is the medical term for a cluster of metabolic abnormalities that increases in individuals risk of T2DM and CVD. The component of MS are glucose intolerance, obesity, hypertension and dyslipidemia. An insulin resistance is the key phase of metabolic syndrome constitutes the major risk factor for the development of diabetes mellitus.

Objectives: The present study aimed to comprise Copeptin, E-Selectin and Thrombomodulin in addition to insulin resistance values among two study groups, metabolic syndrome patients and diabetes mellitus type2 patients .

Subjects: The present study included 50 metabolic syndrome patients, 50 cases who suffered T2DM as pathological control, finally 50 individuals as healthy control. **Methods:** current study investigated the association between Copeptin, E-Selectin, and Thrombomodoluin with development risk effect of endothelial dysfunction in MS and T2DM patients by applying ELISA kit method.

Results: current work showed a highly significant variations among study groups, no significant differences were shown when the comparison was carried out between two genders of the same subgroups.

Keywords: MetS, Vasopressin, Copeptin, E-Selectin, Thrombomodulin, T2DM, Insulin resistance.

INTRODUCTION

Since the NCEP: ATPIII's inception in 2001, the term Metabolic Syndrome(Mets) has become widely used. For decades, scientists have discussed the idea of "clustering" metabolic disorders and CVD risk factors (1). Indeed, according to recent reviews, independent scientists published reports of the link between diabetes mellitus and hypertension as early as the 1920s, when Kylin documented a link between hypertension, hyperglycemia, and gout(2). Visceral obesity was fully appreciated as a component of the insulin resistance syndrome by the early 1990s, despite the fact that the primer for understanding visceral adiposity did not appear until nearly 30 years later. Margaret Albrink's seminal work on the relationship between obesity, hypertriglyceridemia, and hypertension was published in 1980 (3). Obesity and insulin resistance was hypothesized as the cause of metabolic syndrome(6). Interestingly, elevated visceral fat mentioned to be highly associated with the metabolic syndrome(7). Also, upper-body subcutaneous fat is associated with greater risk for metabolic syndrome the excessive nutrition takes priority more than excess adipose tissue in causing metabolic syndrome(8). Arginine vasopressin (AVP) is released from the pituitary gland in conditions of high plasma osmolality, low plasma volume, and low blood pressure. AVP is involved in diverse physiological functions, including

vasoconstriction, platelet aggregation, stimulation of liver glycogenolysis, inhibition of diuresis, modulation of ACTH secretion from the pituitary, and insulin and glucagon secretion from the pancreas. These effects are mediated through three different receptors (V1aR, V1bR, and V2R). The V1aR is widely expressed (9), whereas V1bR is more specifically expressed in the pituitary gland, white adipose tissue, and pancreas and V2R in the renal collecting ducts (10, 11). The antidiuretic effect of AVP is mediated through V2R, whereas the prothrombotic and vasoconstrictor effects of AVP are primarily mediated through the V1aR (12, 13).

Recently we showed that high copeptin is independently associated with hyperinsulinemia and that it predicts future development of diabetes mellitus (DM) (15). Previous findings indicate several links between the AVP system and components of the MetS. A cross-sectional association was found between plasma copeptin and MetS, high waist circumference (waist), systolic blood pressure (BP), DM and triglycerides (TG) after adjustment for body mass index (BMI), sex, and age in a hypertensive population (16). Furthermore, data from humans and animals have suggested involvement of the AVP system in fat metabolism; AVP stimulate production of triglycerides in rat hepatocytes (17) and accordingly, V1aR-deficient mice have low triglycerides compared to wild type (10). AVP exerts diverse actions on BP, including vasoconstriction, volume control, and direct cardiac effects (18).

E-selectin is an endothelial adhesion molecule which promotes leukocytes adhesion to the endothelial wall and cascades atherosclerotic plaque(19). The markers of endothelial dysfunction, including soluble E-selectin (sE-selectin), are related to insulin resistance, which is associated with metabolic inflexibility, i.e., impaired stimulation of carbohydrate oxidation and impaired inhibition of lipid oxidation by insulin. Obesity mainly visceral adiposity and enhanced levels of markers of TNF-α activation increase levels of E-selectin (20, 21). Several studies have evaluated E-selectin in association with diabetes and hypertension(22), and with malignancies (23).

It seems that the role of endothelial dysfunction is important in MetS (24, 25). Endothelial dysfunction is related to the insulin resistance state. It could be an early stage in the atherosclerosis process, and leads to many diseases, such as cardiovascular events (26) and type 2 diabetes (27).

Thrombomodulin (TM), a transmembrane proteoglycan receptor, exhibits potent anti-thrombogenic properties. At the surface of the vascular endothelium. Its soluble extracellular component is broken down into fragments with various molecular weights that circulate in the blood and are excreted in the urine(28). Elevated levels of thrombomodulin have also been reported in participants with chronic diseases such as T2DM caused by inflammation and endothelial dysfunction (29).

SUBJECTS AND DESIGN

The period of the study is from February. 2022 to August. 2022, (During seven months period) 150 cases were collected to participate in the work. These cases were divided into three groups, the first group included 50 patients suffered metabolic syndrome their age ranged from 40 to 77 the second group involved 50 patients with diabetes mellitus with the age ranged from 36 to 70 the third group included 50 persons their age ranged from 34 to 68, to be control group. Groups of the present research were classified in to two groups according to their gender.

Initial diagnosis was performed by specialist physicians who depended on definition of metabolic syndrome requiring the presence of five criteria elevated fasting glucose (≥ 100mg/dL), elevated blood pressure (systolic ≥130 mmHg and/ or diastolic ≥ 85 mmHg), reduced HDL-cholesterol (<40mg/dL), elevated triglycerides (≥ 150 mg/dL) and elevated body mass index (BMI) > 3022 and through several of clinical and laboratory tests specialist for metabolic syndrome. The individuals as pathological controls suffered from T2DM. More than, control group might at approximate age range with the patients group, no smoking, no alcohol drinking with similar food style to patients group.

Samples Collection

Five milliliters of venous blood samples were collected from the patients and healthy individuals, after fasting period more than eight hours. Samples were allowed to clot at lab temperature, centrifuged at 5000xg for 5 minutes. Sera were collected and stored at -18^{o}C until used.

METHODS

Fasting insulin was measured using Sandwich-ELISA kit of Calbiotech company, USA. Determination of hemoglobin A_{1C} (HbA_{1C}) values by using kits of Stan biolaboratory company, USA. Colorimetric method was applied for estimating fasting blood glucose using a kit of Spinract, Spain. The lipid profile included total cholesterol TC, triglyceride TG and high density lipoprotein cholesterol HDL- and low density lipoprotein cholesterol LDL-C concentrations were determined using a commercial available kits of Bilbao company, France. Copeptin, thrombomodulin and E-Selectin measured using a Sandwich enzyme immunoassay kit from SunLong company, China.

Statistical Analysis

The statistical analysis of the result obtained in the present study was carried out using the 26th edition of the statistical package for the social science (SPSS). The result were expressed in terms of Mean ± Standard Deviation (Mean±S.D.). The analysis of variance (ANOVA) was used to compare the results of the three groups included in the study, as well the subgroups based on gender differences. Comparison between among studied parameters were done using persons correlation test. In addition to the receiver operating characteristic (ROC) curves used to assess the prognosis accuracy. The result were statistically significant at 5% probability ($p<0.05$).

RESULT AND DISCUSSION

The current study aims for comparison the changes of insulin resistance values in patients with metabolic syndrome, pathological and healthy control taking into account differences in age, gender, and body mass index (BMI), as well as the relationship between insulin resistance values and other metabolic disorders in metabolic syndrome. Additionally, to assess the current state of knowledge about the potential role of copeptin as a novel biomarker of cardiometabolic syndrome and to analyze the association of E-selectin and thrombomodulin with insulin sensitivity and metabolic syndrome disorders which related to endothelial dysfunction. In order to investigate the most age–matched cases of metabolic syndrome in both genders, the study samples were classified based on their gender.

The outcomes showed a statistically significant variation ($p<0.05$) was observed when both genders in Mets group were compared with their peers of healthy and pathological controls (T2DM group). Body mass index (BMI) and waist circumference (WC) measurements can evaluate obesity as a marker of body fat, which can be used to predict the risk of Mets(31, 32). Not just for the development of Mets, but also for other cardiovascular risk factors(33), obesity appears to be the main underlying risk factor. A roughly 2-fold increase in the 10-year risk of coronary artery disease in subjects with a BMI of 30 kg/m2 or more compared to those with a BMI less than 21 kg/m2 after adjusting for age(34) has not been reported, despite findings from numerous studies showing an association between increasing body weight and BMI and the elevation of ischemic heart disease in several populations(32, 35, 36). On the other hand, the outcomes of the prospective cardiovascular study showed that, according to multiple logistic regression analysis(37), BMI did not independently influence cardiovascular risk.

Results of the present study showed significantly ($p<0.05$) different when the patients groups compared with the healthy control using ANOVA test. The study created a set of individual observations, included: A significant increase in fasting blood glucose, Fasting insulin level, HbA1c,

(vLDL-C)levels, (TGs), and low density lipoproteins binding cholesterol (LDL-C) in the sera of patients with metabolic syndrome and pathological control subjects comparison to healthy individuals group. As well as **Table 1** shows highly significant decrease in the levels high density lipoprotein binding cholesterol(HDL-C) in the sera of Mets patients and T2DM subjects comparison to healthy control group. Metabolic syndrome is characterized by a low HDL in association with an elevated triglyceride concentration. This is believed to be a result of an increased triglyceride load in the HDL particle that is acted on by hepatic lipase, which hydrolyzes the triglyceride. The loss of the triglyceride results in a small HDL particle that is filtered by the kidney, resulting in a decrease in apolipoprotein (Apo) A and HDL concentrations. Apart from an increase in the loss of apoA, there are data demonstrating that insulin may promote apoA gene transcription33. Therefore, insulin resistance states may be associated with diminished apoA biosynthesis34.

The current investigation demonstrated that there were no differences between the healthy, pathological control, and Mets study groups. The development of visceral adiposity, insulin resistance, dyslipidemias, high blood pressure, and poor glucose metabolism are all directly related to the presence of overweight and obesity. Additionally, the development of insulin resistance, other hormonal changes, and an increase in visceral adipose tissue are all linked to aging and play significant roles in the pathogenesis of the metabolic syndrome(30).

Independent ANOVA test results showed that IR in the Mets group was higher than those in T2DM group and healthy control group, and the differences were statistically significant($p<0.05$) demonstrated in **Table 1.**

Table 1: Comparison of clinical biochemical markers forThree groups

Parameters	MetS Patients Group G1 Mean±S.D. Min-Max	T2DM Patients Group G2 Mean±S.D. Min-Max	Healthy Control Group G3 Mean±S.D. Min-Max	P-value
No.	50	50	50	-
Age(years)	57.46±9.389 40-77	57.14±11.574 36-70	57.52±9.472 34-68	a=0.879 b=0.974 c=0.857
BMI(Kg/m^2)	36.70±6.338 30.13-40.87	24.142±2.474 26.76-20.56	24.233±3.003 25.92-20.04	a=0.000 b=0.000 c=0.060
WC	96.24±7.240 88-108	79.26±9.868 70-90	81.530±8.772 72-88	a=0.000 b=0.000 c=0.194
SBP(mmHg)	146.68±6.594 130-160	120.46±4.870 120-135	120.74±5.263 120-130	a=0.000 b=0.000 c=0.479
DBP(mmHg)	93.48±4.866 85-100	82±6.060 60-90	82.68±7.568 60-90	a=0.000 b=0.000 c=0.000
Glucose(mg/dl)	318.66±89.811 156-512	275.9±75.950 146-421	94.26±8.105 83-117	a=0.000 b=0.000 c=0.000
Insulin(pmol/l)	18.61±1.672	15.76±2.224	4.748±1.599	a=0.000

	15-22	10.8-20	2.5-8	b=0.000 c=0.000
HOMA IR	10.647±1.560 6.597-20.765	8.369±1.345 4.861-17.892	1.103±0.371 0.561-1.797	a=0.000 b=0.000 c=0.000
HbA1c	9.218±1.639 7.7-10	7.378±1.010 7.1-9	4.864±0.289 4.5-5.7	a=0.000 b=0.000 c=0.000
TG(mg/dl)	316.24±94.688 187-358	100±20.054 84-115	88.3±18.701 83-100	a=0.000 b=0.000 c=0.487
TC(mg/dl)	304.94±81.405 242-398	190.152±18.354 173-201	179.392±17.348 158-195	a=0.000 b=0.000 c=0.491
LDL-C(mg/dl)	213.18±76.966 150-226	98.76±13.643 90-100	90.28±11.481 84-99	a=0.000 b=0.000 c=0.075
VLDL-C(mg/dl)	63.802±18.953 50-73	18.2±4.010 15-21	17.664±3.747 14-26	a=0.000 b=0.000 c=0.491
HDL-C(mg/dl)	29.16±7.017 15-36	45.36±9.471 37-60	54.82±10.147 44-73	a=0.000 b=0.000 c=0.006

No. Number of subject, BMI. Body mass index, Data represented as Mean±SD, SD.Stander deviation, WC:Waist* Circumference*, SBP: Systolic blood pressure, DBP: Diastolic blood pressure,HOMA IR:Insulin resistance, TG: triglyceride, HDL-L: High-lipoprotein-cholesterol, TC: total cholesterol, LDL-C: low density lipoprotein-cholesterol, VLDL-C: Very Low-Density Lipoprotein-cholesterol. a=G1×G2, b=G1×G3, c=G2×G3. the mean difference is significant at 0.05 level.

In the present study there were significant increasing of copeptin levels in Mets patients compared to T2DM group and healthy controls, same results were noted when the healthy and T2DM compared together, as shown in **Table 2.**

Table 2: Levels (Mean±S.D.) of Copeptin (pg/mL) in The Sera of The Study Individuals

Subjects(n)	CPP (pg/mL) Mean±S.D.	CPP (pg/mL) Min-Max	p –value
MetS PatientsG1 50	258.4±106.6	88-398	a=0.021
T2DM G2 50	208.28±106.4	81-288	b=0.000
Healthy Control G3 50	90.64±36.356	14-107	c=0.000

a=G1×G2, b=G1×G3, c=G2×G3. The mean difference is significant at 0.05 level.

No significant differences were observed when females and males compared in the same group (p=0.116, p=0.053and p=0.066)for the healthy control, pathological control and MetS subgroups, respectively). A statistically significant ($p < 0.05$) increase of copeptin concentration was recorded in the male MetS patient subgroup comparison to those in healthy and T2DM. On the other hand, copeptin showed significant differences when male Mets patients compared to healthy male (p=0.004), and pathological male (p=0.000) as demonstrated in **Table 3.**

Table 3: Levels (Mean±S.D.) of Copeptin (pg/mL) in Sera of The Different Study Groups

Study Groups(n)	Gender(n)	CPP (pg/mL) Mean ± S.D.	CPP (pg/mL) Min.-Max.	p-value
MetS Patients 50	Male G1 26	230.884±123.900	88-398	a=0.116
	Female G2 24	184.041±79.578	99-356	b=0.004
T2DM 50	Male G3 23	210±102.76	81-288	c=0.000
	Female G4 27	222.93±105.55	90-224	d=0.000
Healthy Control 50	Male G5 30	81.633±28.063	14-107	e=0.000
	Female G6 20	76.65±21.156	18-79	f=0.053
				g=0.000
				h=0.000
				i=0.066

a=G1×G2, b=G1×G3, c=G1×G5, d=G2×G4, e=G2×G6, f=G3×G4, g=G3×G5, h=G4×G6, i=G5×G6. The mean difference is significant at 0.05 level.

According to these findings, higher copeptin levels were associated with higher odds of Mets, due to the T2DM subjects have lower levels of copeptin than individuals who have all components of Mets definitions.

Arginine vasopressin (AVP), which is also called antidiuretic hormone (ADH), is a neurohormone synthetized from a pre-pro-hormone precursor in the supraoptic and paraventricular nuclei of the hypothalamus in response to increased plasma osmolality and decreased blood volume. AVP binds to the V1aR, V1bR, and V2R receptors to exert a variety of actions(41). Recently, it has been proposed that elevated plasma concentrations of AVP may influence glucose homeostasis and lipid metabolism through a variety of potential mechanisms involving V1aR and V1bR, resulting in the development of type 2 diabetes, the metabolic syndrome, renal dysfunction, and cardiovascular disease. Hepatic glycogenolysis and gluconeogenesis are regulated by the liver's V1aR. Adrenocorticotrophic hormone (ACTH), insulin, and glucagon are secreted by the action of the V1bR protein, which is present in the pituitary and pancreas(42).

Copeptin is strongly and favorably linked with insulin resistance, obesity, metabolic abnormalities, and key risk factors for the onset of diabetes, according to a number of cross-sectional population studies (43, 44). Although the current study revealed that the link is apparent with other Mets components, copeptin has been demonstrated to be elevated in people with diabetes. However, there are few and mixed findings from prospective trials on the relationship between copeptin with the incidence of incident Mets components, particularly T2DM(45). The Malmö Diet and Cancer (MDC) Study revealed an association independent of fasting insulin and blood glucose (44), whereas the FINRISK97 Study did not find an independent association between copeptin and diabetes after adjusting for metabolic risk factors (45). These findings come from three prospective studies that looked at the

relationship between copeptin and the risk of incident T2DM. Tissue plasminogen antigen (tPA) and von Willebrand factor (vWF)(46, 47), markers of endothelial dysfunction and systemic inflammation, are connected to insulin resistance and have been linked to the development of Mets and T2DM (47, 48).

previous Study in Sweden showed a significant positive association between copeptin and T2DM even after adjustment for fasting insulin and fasting blood glucose. Contrarily, some studies show a strong correlation between copeptin and the risk of T2DM, which was eliminated when the metabolic syndrome's contributing factors—including WC, blood lipids, blood glucose, and hypertension—were taken into account(49).

current research in line with other studies that have found significant cross-sectional relationships between copeptin and liver enzymes, insulin resistance, and a group of cardiometabolic risk factors like hypertension, abdominal obesity, and the dyslipidemia typical of insulin resistance (high triglycerides and low HDL-C) (43, 50). a sign of endothelial dysfunction, all of which have been linked to T2DM(47, 48) and insulin resistance(46). Specifically in the diabetic patients with high blood glucose level, copeptin could expect heart disease and death therefore it could be potential target for predicting diabetic heart disease and death (51). Plasma copeptin level is elevated in not only type 2 diabetes mellitus patients but also in type 1 diabetes mellitus patients(52). Copeptin did, however, only moderately link with HbA1c and glucose levels. Even after adjusting for HOMA-IR and fasting plasma glucose, there was still a significant independent connection between copeptin and diabetes, which was largely explained by insulin resistance. This is consistent with the findings that copeptin correlated significantly with inflammation and with E-selectin and thrombomodulin (markers of endothelial dysfunction) independently of insulin resistance. Up-regulation of proinflammatory cytokines leads to disturbances in the normal function of the vascular endothelium reflected by increased secretion of endothelium-derived products such as E-selectin and thrombomodulin, which have been shown to be predictive of T2DM and Mets (47, 48, 55).

Table 4: Levels (Mean±S.D.) of E-Selectin (pg/mL) in The Sera of The Study Individuals

Subjects(n)	ES(pg/mL) Mean ± S.D.	ES(pg/mL) Min-Max	p – value
MetS Patients G1 50	65.58±6.14	55-79.3	a=0.000
T2DM G2 50	51.15±2.59	47.2-56.1	b=0.000
Healthy Control G3 50	41.45±1.74	38.6-45	c=0.000

a=G1×G2, b=G1×G3, c=G2×G3. The mean difference is significant at 0.05 level.

Results of the present work agreed with the study of Lee and his team, which indicated an increase in E-Selectin in patients (female) with metabolic symdrome (67). Associations between MetS and biomarkers of inflammation and endothelial dysfunction have been previously established. Measuring the serum concentration of these markers in patients could potentially stratify the risk of individuals for possessing the characteristic MetS components and associated diseases such as cardiovascular disease and diabetes. Inflammatory cytokines, tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) are all recognized

as components of the inflammatory mechanisms accompanying the status of obesity and MetS (68, 69). Adhesion molecules such as selectins, intercellular vascular adhesion molecule-1 (ICAM-1) and vascular cell adhesion moloecule-1 (VCAM-1) are expressed both in the endothelium and certain types of leukocytes, allowing them to recruit circulating leukocytes into the endothelium to initiate atherogenesis (70). As such, E-selectin is an endothelial adhesion molecule known to be integrally involved in the development of atherosclerotic plaque by promoting the adhesion of leukocytes to the endothelial wall (71). E-selectin levels are also elevated in obesity, particularly in connection with elevated indicators of TNF- activation and elevated visceral adiposity (72).

Table 5: Levels (Mean±S.D.) of E-Selectin (pg/mL) in Sera of The Different Study Groups

Study Groups(n)	Gender(n)	ES(pg/mL) Mean ± S.D.	ES(pg/mL) Min.-Max.	p-value
MetS Patients 50	Male G1 26	64.492±6.016	55-76.5	a=0.194
	FemaleG2 24	66.766±6.369	56.9-79.3	b=0.000
T2DM 50	Male G2 23	52.117±2.432	48-56.1	c=0.000
	Female G4 27	53.33±2.474	47.2-55.3	d=0.000
Healthy Control 50	Male G5 30	41.45±1.678	38.6-44.5	e=0.000
	Female G6 20	41.46±1.888	38.9-45	f=0.013
				g=0.000
				h=0.000
				i=0.984

a=G1×G2, b=G1×G3, c=G1×G5, d=G2×G4, e=G2×G6, f=G3×G4, g=G3×G5, h=G4×G6, i=G5×G6. The mean difference is significant at 0.05 level.

Present study could explain this gender-specificity by hormonal interactions. Selectins have a well-established involvement in female reproduction because they regulate ovarian function, menopause, and the pathophysiology of preeclampsia (74). Cominacini et al. (1995) found that E-selectin plasma concentration was positively correlated with the levels of glycated hemoglobin in diabetic patients, suggesting that the soluble adhesion molecules, especially E-selectin, may be related to metabolic control in diabetic patients. Previous studies have examined E-selectin in association with diabetes and hypertension (81, 82, 83), as well as with malignancies (84). Additionally, compared to healthy controls, patients with hyperlipoproteinemia had higher E-selectin concentrations, which suggests that the activation of endothelial cells may have had some role in the rise in cholesterol levels (82). According to a recent study, patients with hypertriglyceridemia had higher blood levels of soluble E-selectin, soluble ICAM-1, and soluble VCAM-1, and multivariable analysis indicated that this increase was unrelated to other risk factors (83). According to Calabresi et al., large levels of soluble E-selectin were found in participants with low HDL concentrations in both hyper and normolipidemic patients. These findings

confirm earlier in vitro research that suggests triglyceride and HDL metabolism issues may influence CAMs and E-selectin to influence vascular cell activation and atherogenesis. insulin resistance syndrome's anomalies of high triglyceride/low HDL and improper glucose metabolism may work together to promote the expression of E-selectin and CAMs.

Table 6: Levels (Mean±S.D.) of Thrombomodulin (pg/mL) in The Sera of The Study Individuals

Subjects(n)	TM (pg/mL) Mean ± S.D.	TM (pg/mL) Min-Max	p – value
MetS Patients G1 50	64.86±19.779	32-87	a=0.002
T2DM G2 50	55.24±13.548	25-99	b=0.000
Healthy Control G3 50	38.38±9.864	23-62	c=0.000

a=G1×G2, b=G1×G3, c=G2×G3. The mean difference is significant at 0.05 level.

Thrombomodulin plays an important role in activation and control of protein C. protein C levels is a significant cardiovascular disease risk factor. glycoprotein called thrombomodulin, TM can be present in the plasma a soluble form as well as membrane-bound in the vascular endothelium. In conditions involving vascular injury, such as infections, sepsis, and inflammation, the membrane-bound TM is released from the endothelium, likely by neutrophil-delivered enzymes, and becomes soluble in the bloodstream(86). When viewed together, soluble TM is recognized as a marker of endothelium injury and has been noted as such in a number of studies(87, 88). Additionally, the involvement of TM in inflammation has been documented, and studies have shown that thrombomodulin production in monocytes initiates a lipopolysaccharide-induced inflammatory response that raises IL-6 levels in the blood. Another study shown that endothelial injury may be a mediator of nuclear-B signaling, resulting in increased production of the pro-inflammatory cytokine IL-6 in the vascular endothelial cells (88).

Table 7: Levels (Mean±S.D.) of Thrombomodulin (pg/mL) in Sera of The Different Study Groups

Study Groups(n)	Gender(n)	TM (pg/mL) Mean ± S.D.	TM (pg/mL) Min.-Max.	p-value
MetS Patients 50	Male G1 26	64.115±14.199	32-86	a=0.892
	FemaleG2 24	66.583±13.609	33-87	b=0.074
T2DM 50	Male G3 23	56±19.014	25-91	c=0.000
	FemaleG4 27	58.296±20.291	36-99	d=0.018
Healthy Control 50	Male G5 30	40.333±10.443	23-62	e=0.000
	FemaleG6 20	35.45±9.864	24-56	f=0.681 g=0.000 h=0.000 i=0.073

a=G1×G2, b=G1×G3, c=G1×G5, d=G2×G4, e=G2×G6, f=G3×G4, g=G3×G5, h=G4×G6, i=G5×G6. The mean difference is significant at 0.05 level.

Table 8: Person Correlation between Copeptin and other Parameters in Three Studied Groups

Parameters	Control		Mets Patients Groups		T2DM Patients Group	
	r	P-value	r	P-value	r	P-value
BMI	0.258	0.068	0.586**	0.000	0.497**	0.001
FBG(mg/dl)	0.089	0.487	0.678**	0.000	0.467**	0.002
Insulin(pmol/L)	0.005	0.846	0.687**	0.000	0.587**	0.000
HbA1C	-0.275	0.587	0.763**	0.000	0.578**	0.000
HOMA-IR	-0.046	0.078	0.586**	0.000	0.468**	0.000
Cholesterol	-0.006	0.867	0.865**	0.000	0.245	0.097
LDL	0.003	0.678	0.576**	0.000	0.134	0.476
vLDL	-0.244	0.081	0.045	0.578	0.213	0.078
HDL	-0.002	0.967	-0.861	0.000	-0.378	0.654
TG	0.003	0.686	0.579**	0.000	0.176	0.365

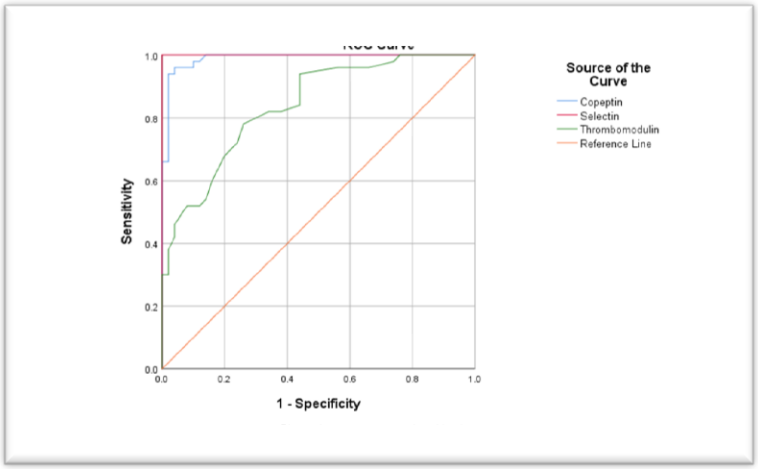

Figure 1: ROC Curve between MetS and Control group

Table 11: Coordinates of the Curve between MetS and Control group

Test Result Variable	Area	Cut of value	Sensitivity	Specificity
Copeptin	0.989	124.5000	0.960	0.96
E-Selectin	1.000	50.0000	1.000	1
Thrombomodulin	0.839	44.5000	0.800	0.7

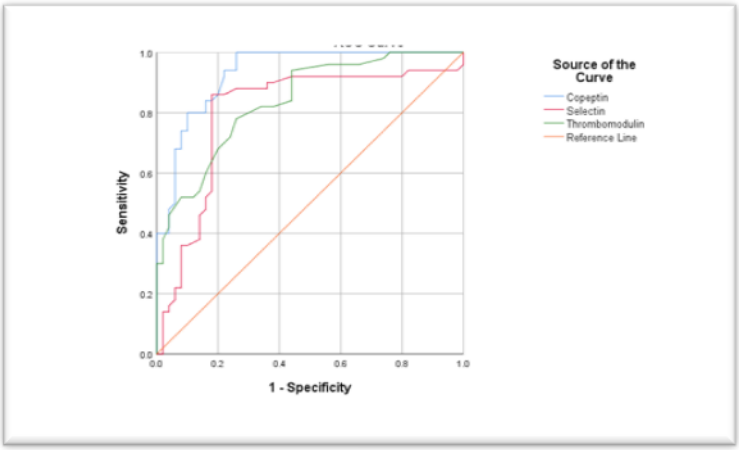

Figure 2: ROC Curve between T2DM and Control group.

Table 12: Coordinates of the Curve between T2DM and Control group

Test Result Variable	Area	Cut of value	Sensitivity	Specificity
Copeptin	0.931	98.5000	0.940	0.78
E-Selectin	0.802	46.1000	0.860	0.180
Thrombomodulin	0.839	44.5000	0.800	0.300

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