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The Relationship Between Copeptin And Cellular Oxidative Damage By Xanthine Oxidase, Heme Oxygenase-1 And Nitric Oxide Synthase In Metabolic Syndrome 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 MetS 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, Xanthine Oxidase, Heme Oxygenase-1 and Nitric Oxide synthase in addition to insulin resistance values and lipid profile among two study groups, metabolic syndrome patients and Controls group.*

Subjects: *The present study included 50 metabolic syndrome patients and 50 individuals as healthy control. Methods: current study investigated the association between Copeptin, Xanthine Oxide, Heme Oxygenase and Nitric Oxide Synthase with development risk effect of endothelial dysfunction in MetS patients by applying ELISA kit method.*

Results: *current work showed a highly significant variations among study groups, except for age.*

Key words: **MetS, Copeptin, Xanthine Oxidase, Heme Oxygenase-1, Nitric Oxide synthase, Insulin resistance.**

Article Information

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INTRODUCTION

Metabolic Syndrome (MetS) forms a cluster of metabolic dysregulations including insulin resistance, atherogenic dyslipidemia, central obesity, and hypertension [Jerry& Philipp., 2021]. The pathogenesis of MetS encompasses multiple genetic and acquired entities that fall under the umbrella of insulin resistance and chronic low-grade inflammation. If left untreated, MetS is significantly associated with an increased risk of developing diabetes and cardiovascular diseases (CVDs) [Carlos & Viveros, 2019].

Given that CVDs constitute by far the leading cause of morbidity and mortality worldwide, it has become essential to investigate the role played by MetS in this context to reduce the heavy burden of the disease [Fahed *et al.*, 2022]. The matching with the incidence of obesity and T2DM in united states leading to increase about 85% of T2DM patients who have MetS and are at higher risk of CVDs [Alberti *et al.*, 2009]. In addition to in 2017, approximately 12.2% of the USA adult population had T2DM with one-quarter of

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them were unaware of their disease, as well as the MetS prevalence was elevated three times, comprising about one-third of the American adult population [Saklayen, 2018]. Luckily, it was stated that numbers of the disease diminished to 24% in men and 22% in women according to the National Health and Nutrition Examination Survey(NHANES) data[Swarup *et al*., 2022].

Vasopressin infusion increases blood glucose in nondiabetic humans. In recent years, copeptin levels have been measured in order to assess plasma AVP concentration in relation to various conditions. AVP, copeptin, and MetS have attracted growing attention for their potential role in insulin resistance and cardiovascular disease. Copeptin levels are linked to a number of metabolic conditions, according to a number of recent studies. [Vintilă *et al*., 2016; Barchetta *et al*., 2019]. Copeptin levels were consequently linked to MetS, obesity, and high blood pressure in a number of Swedish studies involving a sizable population (4742 people). Elevated copeptin was able to predict the increased risk of type 2 diabetes independently of other significant risk factors like glucose and insulin levels, and it was also associated with diabetes at baseline [Wannamethee *et al*., 2015]. In a different study, women had a higher correlation between copeptin and the risk of developing diabetes than did men.

Xanthine Oxidoreductase (XOR) serum level is very low, in human except in case of tissue damage in pathological conditions specifically in liver [Bortolotti *et al*., 2021; Polito *et al*., 2021]. XOR derivatives like ROS and NO have role in vascular tone regulation which affect in blood pressure regulation according to endothelial activities of NADPH oxidase and NO synthase [Battelli et al., 2016]. High level of XOR activity and hyperuricemia was related with atherosclerosis development which has critical participation in pathogenesis of CVD [Battelli *et al*., 2014]. These relations are explained by XOR mediating atherosclerotic diseases by promoting inflammation and plaque formation [Kushiyama *et al*., 2016]. XOR inhibitors reduce the risk of major adverse cardiovascular events by 6.0% [Ying *et al*., 2021]. Finally, ROS and oxidative stress produced from XOR cause endothelial dysfunction which has role in the development and progression of atherosclerosis [Battelli *et al*., 2018].

Heme oxygenase-1 (HO-1) was defined as a cytoprotective enzyme, which assist in preserving vascular endothelium [Maamoun *et al*., 2019]. HO operates as a rate-limiting enzyme in heme degradation process producing carbon monoxide (CO), iron, and biliverdin [Rochette *et al*., 2018 ; Wu et al., 2019]. HO is defined also as a set of antioxidant enzymes that control intracellular levels of heme and mediating its biodegradation [Duvigneau *et al*., 2019; Rochette *et al*., 2018].

Endothelial nitric oxide synthase (eNOS) uncoupling, known by the transition of eNOS from catalysing NO production to generating superoxide anion (O2•2) where “electron leak” to molecular oxygen, is major cause of endothelial dysfunction [Karbach *et al*., 2014]. Additionally, the superoxide anion may react with NO to form peroxynitrite anion (ONOO2), which consumes NO, decreases its bioavailability, and worsens endothelial dysfunction [Xu *et al*., 2016; Daiber & Chlopicki, 2020]. oxidative stress is worsened by eNOS uncoupling. eNOS uncoupling is a common in numerous CVDs and conditions like atherosclerosis, diabetes, stroke, cardiac hypertrophy, and pulmonary hypertension [Daiber and Chlopicki, 2020; Wu *et al*., 2021].

MATERIAL AND METHODS.

The period of the study is from February. 2022 to August. 2022, (During seven months

period) 100 cases were collected to participate in the work. These cases were divided into two groups, the first group included 50 patients suffered metabolic syndrome their age ranged from 40 to 77 the second group involved 50 persons their age ranged from 34 to 68, to be control group. blood spacemen were drawn from avein for the evaluation of Copeptin, Xanthine Oxidase, Heme Oxygenase-1, Nitric Oxaide, fasting plasma lipids and Insulin Resistance in case and control groups. Biochemical assays. Serum samples were obtained after an overnight fast. The analyses of BP systolic, BP diastolic, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, insulin resistance. For copeptin, Xanthine Oxidase, Heme Oxygenase-1 and Nitric Oxide synthase, serum samples were collected and stored at -2-8ºC until measurement. It was measured using a competitive enzyme immunoassay. The SPSS program was used for all statistical analysis was used to compare categorical variables between groups, continuous variables with normally distributed data, and variables with non-normal distributions. To find any correlations between continuous variables, pearson correlation analysis were used. to assess the prognosis accuracy, receiver operating characteristic (ROC) curves were used.

RESULT

Showed in Tables (1, 2 and 3). Our results showed statistically significant values, except for age between the groups. The measurements were considered significant when they were (p- value ≤o.o1). In Mets group, when compared to controls, patients with had significantly greater levels of copeptin, Xanthine Oxidase and Heme Oxygenase-1, except nitric oxide synthase showed low values in the group of patients (p < 0.001). this result indicates that these markers really differ between Mets and control groups that show in the Table 1.

Table 1: Comparison of clinical biochemical markers for Two groups.

PARAMETERS	MetS group	Control group	p. value
	Mean±SD	Mean ±SD	
Age (years)	57.46 ±9.389	57.52± 9.472	0.974
BMI	36.70± 6.338	24.233± 3.003	0.000
Copeptin	258.4± 106.60	90.64 ±36.356	0.000
Xanthine Oxidase	2.847 ±1.117	0.574 ±0.365	0.000
Heme Oxygenase-1	4.893 ±2.154	0.904± 0.470	0.000
Nitric Oxide synthase	0.636 ±0.562	3.417 ±1.195	0.000
BP systolic	146.68 ±6.594	120.74 ±5.263	0.000
BP diastolic	93.48± 4.866	82.68± 7.568	0.000
HOMA IR	10.647± 1.560	1.103 ±0.371	0.000
TG(mg/dL)	316.24 ±94.688	88.3± 18.701	0.000
TC(mg/d/L)	304.94± 18.405	179.392± 17.348	0.000
LDL-C(mg/dL)	213.18 ±76.966	90.28 ±11.481	0.000
HDL-C(mg/dL)	29.16 ±7.017	54.82 ±10.147	0.000

BMI. Body mass index, Data represented as **Mean±SD**, **SD.**Stander deviation, **SBP**: Systolic blood pressure, **DBP**: Diastolic blood pressure, **HOMA IR**. Insulin resistanse, **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 leve

Table 2: Correlation between biomarkers Copeptin, Xanthine Oxidase, Heme Oxygenase-1 and Nitric Oxide synthase levels in MetS

Variables		CPP	ES	TM	XOD	HO-1	eNOS
CPP	Pearson Correlation (r)	1	0.020	0.474*	0.095	0.375*	-0.285
	Sig. (2-tailed)		0.675	0.027	0.473	0.039	0.484
XOD	PearsonCorrelation (r)	0.095	0.462**	0.575**	1	0.054	-0.091
	Sig. (2-tailed)	0.473	0.002	0.001		0.754	0.654
HO-1	Pearson Correlation(r)	0.375*	0.264	0.148	0.054	1	-0.468**
	Sig. (2-tailed)	0.039	0.036	0.264	0.754		0.002
eNOS	Pearson Correlation(r)	-0.285	-0.053	-0.005	-0.091	-0.468**	1
	Sig. (2-tailed)	0.484	0.648	0.864	0.654	0.002	

*. Correlation is significant at the 0.05 level (2-tailed).
**. Correlation is significant at the 0.01 level (2-tailed).

Table 3: Diagnostic test of between Metabolic syndrome and controls group.

Markar	Area under the curve	Cut of value	Sensitivity	Specificity
Copeptin	0.989	124.5000	96%	96%
Xanthine Oxidase	0.953	1.4550	94%	86%
Heme Oxygenase 1	0.838	1.2100	86%	50%
Nitric Oxaide synthase	0.954	1.3350	88%	14%

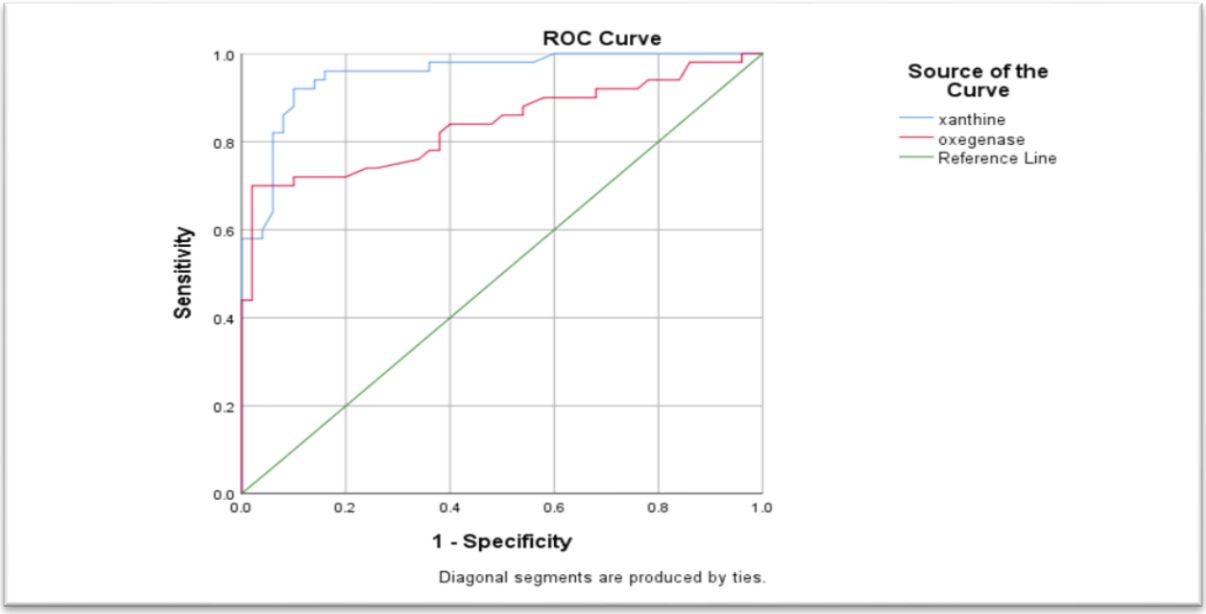

Figure 1: Reciver Operating Characteristic (ROC) Curve of XOD and HO-1 in MetS.

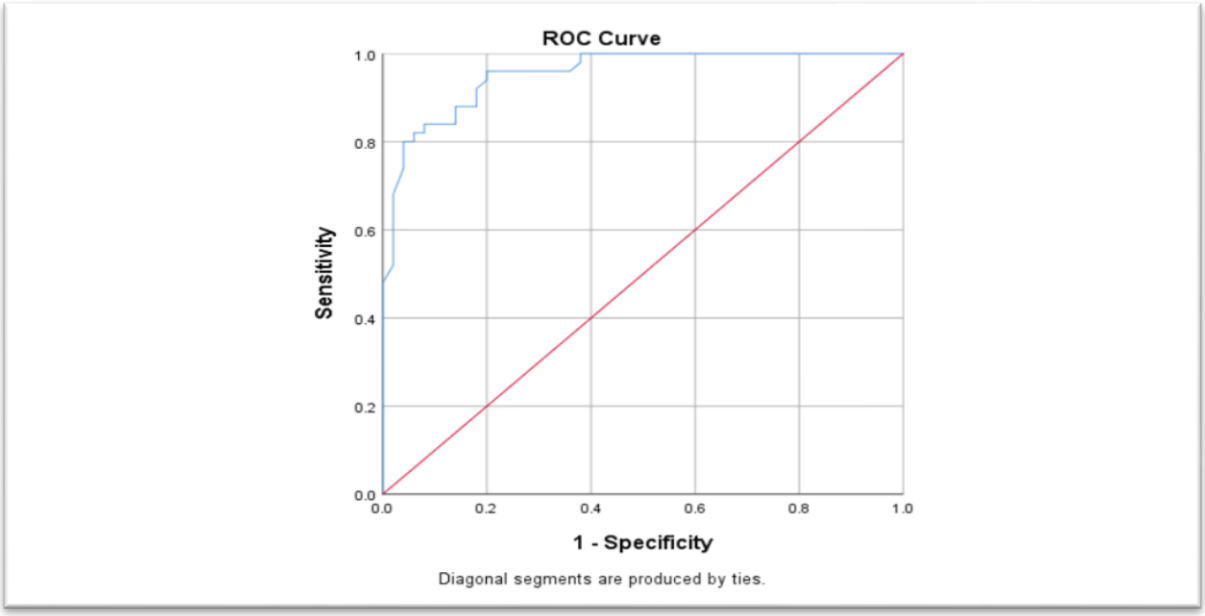

Figure 2 : Reciver Operating Characteristic (ROC) Curve of Nitric Oxide Synthase in MetS.

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DISCUSSION

MetS has been associated with type 2 diabetes due to its high prevalence worldwide since it is both related to the increase in obesity and a sedentary lifestyle. Several studies suggest that individuals with MetS are 5 times more likely to develop type 2 diabetes. Type 2 diabetes is a rising global health problem [Mills *et al*., 2016]**.** Metabolic syndrome is characterized by a term (atherogenic dyslipidemia) which described by low HDL and elevated triglyceride concentration. In the liver of insulin-resistant patients, FFA flux is high, TG synthesis and storage are increased, and excess TG is secreted as VLDL[Hirano 2018]. Thus believed that dyslipidemia associated with insulin resistance is a direct consequence of increased VLDL secretion by the liver**[**Choi& Ginsberg 2011]. Copeptin has been pointed as a substitute marker of AVP because of its long-term stability and measurable on blood easily [Christ-Crain, 2019]. It appears in several cardiometabolic diseases like as heart failure, T2DM, and renal disease [Balling & Gustafsson, 2014 ; Bellos *et al*., 2020]. Plasma copeptin independently associated microalbuminuria incidence, abdominal obesity, and hypertension in a 15.8-year follow-up study [Enhörning *et al*., 2013]. 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 [Enhörning *et al*., 2015].

Plasma copeptin level is elevated in not only type 2 diabetes mellitus patients but also in type 1 diabetes mellitus patients [Velho *et al*., 2016]. Moreover, there were direct link between copeptin plasma level on β-cell function and leptin plasma levels only in the subjects with bipolar disorders [Mansur *et al*., 2017]. There was Stronger relation in women than in men between steady state copeptin plasma level and the occurrence of type 2 diabetes mellitus [Abbasi *et al*., 2012]. Even though, copeptin plasma level was correlated with type 2 diabetes mellitus in men but not in women [Then *et al*., 2015]. Copeptin plasma level was also meaningfully correlated with a high risk of developing type 2 diabetes mellitus in older men, which was somewhat facilitated through diminished insulin sensitivity [Wannamethee *et al*., 2015]. The current study recorded an increase in the levels of copeptin in the group subjected to Mets and diabetic compared to the control group, this rise in copeptin levels in the patients of the current study may be due to hyperinsulinemia and that it predicts future development of diabetes mellitus (T2DM).

The enzyme needed to break down purine nucleotides into uric acid is called xanthine oxidase. The organism may suffer negative effects from both the uric acid itself and the reactive oxygen species that are generated during the enzymatic activity. This pathway leads to increased uric acid production, which is a common cause of gout [Chen&Yao., 2016]. As a result, various medications have been developed to treat gout by preventing the action of the xanthine oxidase enzyme. Moreover, controlling this enzyme has been shown to be successful in the fight against cancer [Pacher *et al*., 2006]. Xanthine oxidase (XOD) could contribute to the pathogenesis of metabolic syndrome through the oxi-dative stress and the inflammatory response induced by XOR-derived reactive oxygen species and uric acid. Hyperuricemia is strongly linked to hypertension, insulin resistance, inflammation, endothelial dysfunction, obesity and hypertriglyceridemia. This investigation corroborated the findings of other studies that showed elevated xanthine levels in those with metabolic syndrome and diabetes [Battelli *et al*., 2018, Battelli *et al*., 2019, Hasan *et al*., 2022].

Heme oxygenase plays an increasingly important role in understanding t e effects of chronic inflammation caused by obesity. Upregulation of heme oxygenase increases adiponectin, improves glucose tolerance and

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insulin sensitivity, and reduces multiple inflammatory markers[Peterson et al., 2019]. Since Insulinresistance is required to make a diagnosis of the metabolic syndrome, reducing insulin resistance must be a critical part of any future therapy. Heme oxygenase-1 expression in endothelial cells could also play a role in the protection against atherosclerosis induced by environmental factors such as smoking and exposure to air pollution[Araujo *et al.*, 2012]. Obesity is a critical risk factor for endothelial dysfunction and the subsequent development of diabetes mellitus and vascular diseases including hypertension. Abdominal obesity is associated with insulin resistance and the pathogenesis of T2DM and hypertension, contributes to high serum levels of LDL and triglycerides but low serum levels of HDL, and leads to the development of atherosclerotic CVD [Kajikawa *et al*., 2022]. HO-1, the inducible isoform of the heme-degrading enzyme HO-1, is activated in response to oxidative and inflammatory stimuli in an attempt to counteract tissue insults. The explanation for the rise in Heme oxygenase-1 in patients with the metabolic syndrome and patients with type 2 diabetes may be due to its protective role as an anti-inflammatory and antioxidant.

Nitric oxide (NO), which is generated from the endothelium, has been known to be critical for the preservation of cardiovascular homeostasis since the early 1980s. Eventually, it became clear that various cardiovascular illnesses, including atherosclerosis and hypertension, were influenced by a decrease in the bioavailability of NO [Mudau *et al*., 2012]. Patients with cardiovascular risk factors (such as hypertension, hypercholesterolaemia, diabetes mellitus, cigarette smoking, etc.) and patients with vascular disease show endothelial dysfunction, i.e. the inability of the endothelium to generate adequate amounts of bioactive NO (and to produce NO-mediated vasodilation). Endothelial dysfunction , such as impaired NO production , is considered an early stage in the development of insulin resistance , atherosclerosis and T2DM [Dhananjayan *et al*., 2016]. Studies assessing the relationship between ischemic heart disease (CHD) and endothelial dysfunction have clearly shown that reduced NO - dependent endothelial vasodilatation is an early functional disorder in the development of atherosclerotic lesions [Matsuzawa & Lerman, 2014; Medina-Leyte *et al*., 2021]. Moreover, among the many effects of NO, its ability to modulate peripheral and hepatic glucose metabolism and insulin secretion has also been demonstrated. It has also been suggested that changes in NO play an important role in the development of insulin resistance and T2DM [Tessari *et al*., 2010] . Insulin resistance strongly associates with decreased nitric oxide (NO) bioavailability and endothelial dysfunction. In the vasculature, NO mediates multiple processes that affect insulin delivery, including dilating both resistance and terminal arterioles in skeletal muscle in vivo[Muniyappa *et al*., 2008]. In the current study, the eNOS levels in patients with MetS and T2DM were significantly reduced when compared to the controls, which was similar to the majority of the studies [Tuppad *et al*., 2022;]. The possible reason is endothelial dysfunction, which is a common sequel of diabetes, leading to impaired endothelial nitric oxide synthase (eNOS) activity, causing decreased NO production. Hyperglycemia impairs endothelial function through increased oxidative stress which is a hallmark of diabetics. Hyperglycemia accelerates the formation of advanced glycosylated end products, boosts the polyol pathway, and activates protein kinase C, resulting in oxidative stress**.**

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