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Assessment of Serum Netrin-1 Levels in Patients with Acute Coronary Syndrome with and without Type 2 Diabetes Mellitus

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ABSTRACT

Although the role of netrin-1 in cardiovascular disease and inflammation is an emerging area of study, current literature on the subject remains limited, highlighting a considerable knowledge gap. Therefore, this study aimed to evaluate serum netrin-1 levels in patients with acute coronary syndrome (ACS), with and without type 2 diabetes mellitus (T2DM). The study included 60 patients diagnosed with ACS, subdivided into two groups: 30 patients with ACS and T2DM and 30 patients with ACS but without T2DM. A control group comprising 30 healthy individuals, matched for age and sex, was also included. Serum netrin-1 level, lipid profile, fasting blood glucose, hemoglobin A1c, cardiac troponin I, and routine hematological parameters were assessed. Serum netrin-1 levels were significantly higher in patients with ACS, with or without T2DM, than in healthy individuals (53.38, 45.57, and 32.37 pg/mL, respectively; $P < 0.001$). In the ACS with T2DM group, serum netrin-1 levels demonstrated a significant positive correlation with body mass index ($r = 0.498$; $P = 0.005$). In the ACS without T2DM group, a significant positive correlation was observed between serum netrin-1 level and troponin I level ($r = 0.436$; $P = 0.02$). Receiver operating characteristic curve analysis of netrin-1 yielded clear cut-off values for patients with ACS, with and without T2DM (39.99 and 37.91, respectively).

Conclusion: Serum netrin-1 levels are higher in patients with ACS, irrespective of T2DM status, than in healthy individuals.

Introduction

Acute coronary syndrome (ACS) comprises a spectrum of clinical conditions associated with atherosclerosis in the coronary arteries: unstable angina, non-ST-elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI) [1]. Diabetes mellitus considerably accelerates the progression of atherosclerosis and it is associated with increased risk of developing ACS. Approximately 25%–30% of patients hospitalized with ACS have diabetes [2]. In patients with type 2 diabetes mellitus (T2DM), coronary atherosclerosis arises from a complex interplay of pathophysiological mechanisms, including dysregulation of lipid and lipoprotein metabolism, inflammation, oxidative stress, glycation, and vascular damage [3].

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Diabetic patients with ACS exhibit higher mortality rates and an increased risk of recurrent cardiovascular events than those without diabetes [4]. This elevated risk is partially attributed to comorbid conditions, including obesity, hypertension, hypercholesterolemia, and chronic renal disease, which dramatically enhance susceptibility to cardiovascular diseases. Moreover, diabetes promotes a pro-inflammatory and pro-thrombotic state characterized by heightened platelet reactivity and increased clot formation [5]. The netrin family, comprising laminin-like proteins, was originally discovered in the early 1990s as a group of axonal guidance molecules involved in embryogenesis. In humans, four types of netrins have been identified: netrin-1, -3, -4, and -5 [6]. Netrin-1 is by far the most studied. The *NTN1* gene, which is located on chromosome 17, encodes netrin-1 and another protein consisting of 604 amino acids. This gene is highly conserved across species. Netrin-1 is

synthesized by various cells and is present in most tissues. On the basis of relative mRNA expression levels, netrin-1 is the most abundantly expressed in the brain, heart, lungs, and kidney, whereas its expression is comparatively lower in the intestine, spleen, and liver [6, 7]. Apart from its role in axonal guidance during neuronal development, netrin-1 has been implicated in several additional physiological and pathological processes, including organogenesis of the mammary glands, pancreas, and lungs, angiogenesis, and tumor development [6]. Moreover, netrin-1 has been shown that netrin-1 to contribute to tissue regeneration, leukocyte transmigration in peripheral organs, and the modulation of inflammatory-related responses [8]. Owing to its immunomodulatory properties and tissue regeneration functions, netrin-1 is hypothesized to play a considerable role in the pathogenesis of inflammation and progression of T2DM [9].

The reported effects of netrin-1 in atherosclerosis have been inconsistent. Some studies has demonstrated that it has pro- and anti-inflammatory functions in the progression of the disease. This discrepancy may be attributed to spatial and temporal variability netrin-1 expression. Specifically, netrin-1 secreted by the endothelium into the bloodstream exerts a protective effect on the cardiovascular system by reducing monocyte adhesion and migration. By contrast, netrin-1 produced by macrophages within atherosclerotic plaques has been shown to contribute to atherosclerosis by inhibiting macrophage egress from lesion sites [10–12]. Many of the biological effects of netrin-1 are mediated through its interactions with uncoordinated (UNC)5 family of receptors. Specifically, its chemorepulsive activity in the nervous system is primarily modulated by the UNC5 homolog b (UNC5b) receptor [13].

Netrin-1 and UNC5b have been identified within atherosclerotic plaques in mice and humans, predominantly localized in macrophage-derived foam cells. Their expression is upregulated by hypoxic conditions and the accumulation of oxidized low-density lipoprotein (LDL) [14]. Furthermore, plaque regions enriched with macrophages contain elevated levels of extracellular netrin-1 [12]. The interaction between netrin-1 and UNC5b contributes to the persistence and progression of atherosclerotic lesions by inhibiting the migration of monocytes and macrophages, promoting cell retention through autocrine or paracrine mechanism or both [12].

Although the role of netrin-1 in cardiovascular disease and inflammation is an emerging area of study, existing literature remains limited, and a considerable knowledge gap persists. Accordingly, the present study aimed to evaluate serum netrin-1 levels in patients with ACS, with and without T2DM. In addition, the study sought to investigate potential correlations between serum netrin-1 concentrations and clinical and biochemical parameters.

Patients and Methods

Study population

The study was conducted from November 2023 to February 2024 at AL-Ramadi Teaching Hospital (Al-Anbar, Iraq), specifically in the emergency and coronary care unit. A total of 60 patients diagnosed with ACS, aged 35–65 years, were enrolled. These patients were divided into two cohorts: 30 patients with ACS and T2DM and 30 patients with ACS but without T2DM. A control group comprising 30 healthy individuals matched to the patient groups by age and sex, was also included. None of the control group had a prior history of cardiovascular diseases, encompassing all forms of coronary heart disease and stroke.

The exclusion criteria included heart failure, valvular heart disease, renal or hepatic dysfunction, chronic inflammatory disorders (such as inflammatory bowel disease, osteoarthritis, and rheumatoid arthritis), evidence of active infectious or neoplastic conditions, and major surgery or trauma. Demographic data, body mass index (BMI), seated blood pressure, history of risk factors, smoking status, and family history of cardiovascular disease in first-degree relatives were documented. BMI was calculated by dividing body weight in kilograms by the square of height in meters. Standard clinical examinations were conducted on all study participants. This study was approved by the ethics committee of the University of Anbar, under reference number 72, dated April 4, 2024.

Sampling

After informed consent was obtained from all participants and according to stringent aseptic procedures, 7 mL of fasting venous blood was collected from each participant within 24 h of symptom onset. Control subjects were sampled under similar fasting conditions. Two milliliters of venous blood was carefully placed in a tube containing ethylenediaminetetraacetic acid for the analysis of hemoglobin A1c (HbA1c) analysis. The remaining venous blood was gradually transferred to a gel tube and allowed to clot for 15 min at room temperature. The samples were then centrifuged at 4000 rpm for 10 min. The resulting serum was aliquoted and stored at −20 °C until further analysis.

Measurement

Fasting serum netrin-1 levels were quantified using commercially available enzyme-linked immunosorbent assay kits (Sunlong Biotech, China). Fasting blood glucose (FBG), total cholesterol, triglyceride (TG), high-density lipoprotein (HDL), LDL, calcium (Ca^{+2}), and routine blood tests were performed using colorimetric and turbidimetric methods and commercial kits (Abbott, USA). Cardiac troponin I (cTnI) and HbA1c were assessed using electro-chemiluminescence immunoassay and HPLC, respectively, with commercial kits (Nipigon, Canada).

Statistical analysis

Statistical analysis was conducted utilizing IBM SPSS Statistics software version 22 (IBM Corp., Armonk, NY, USA). Descriptive statistics were employed to summarize numerical variables, including the calculation of means, standard deviations, and standard errors. Categorical variables were presented as frequencies and percentages. To assess the significance of mean differences among the three groups (ACS with T2DM, ACS without T2DM, and a control group), a one-way analysis of variance (ANOVA) was performed. Statistically significant differences in numerical parameters across the groups were further examined using ANOVA tables and Fisher's least significant difference test. Statistically significant differences among the three groups for the numerical parameters were identified. To evaluate the strength and direction of linear relationships between pairs of numerical variables within each group, Pearson's correlation coefficients (r) were calculated. The degree of association between two variables is quantified through correlation analysis, which employs coefficients ranging from −1 (indicating perfect negative correlation) to 1 (indicating perfect positive correlation). Two-tailed tests were employed to ascertain the significance of the correlation coefficients. These tests evaluate were used to determine the statistical significance of the observed correlation, testing the null hypothesis that no correlation exists between variables. A significance level of 0.05 was adopted for all statistical analyses.

Results

Baseline clinical and laboratory characteristics

The clinical and laboratory characteristics of the study are summarized in Table 1. Within the ACS with T2DM group, 10 patients (33%) were diagnosed STEMI, 16 (54%) with NSTEMI, and 4 (13%) with UA. In the ACS without T2DM group, 9 patients (30%) were diagnosed with STEMI, 14 (47%) with NSTEMI, and 7 (23%) with UA. No statistically significant differences were observed among the three groups with respect to age, sex, BMI, total cholesterol, and LDL-C. The ACS with T2DM group exhibited significantly higher levels of FBG, HbA1c, TG, and VLDL-C than the control group or the ACS without T2DM group ($P < 0.01$). Compared with the control group, the ACS with T2DM group exhibited significantly higher levels of SBP, DBP, urea, creatinine, and troponin I but lower levels of HDL-C and Ca^{+2} ($P < 0.05$), whereas the ACS without T2DM group exhibited significantly higher levels of SBP, TG, VLDL, urea, creatinine, uric acid, and troponin I but lower levels of Ca^{+2} ($P < 0.05$).

Table 1. Research population's clinical and biochemical characteristics.

Variables	Control (n = 30)	ACS with T2DM (n = 30)	ACS without T2DM (n = 30)
	Mean ± SD	Mean ± SD	Mean ± SD
Age (years)	54.23 ± 8.56	55.67 ± 8.15	55.87 ± 7.73
Male/Female, n	21/9	22/8	20/10
Smoking, n (%)	3 (10%)	8 (27%) [a, c]	17 (57%) [b]
BMI (kg/m^2)	28.22 ± 2.02	28.93 ± 1.62	27.87 ± 2.38
SBP (mmHg)	119.83 ± 5.82	139.73 ± 23.16 [a]	136.66 ± 22.35 [b]
DBP (mmHg)	75.43 ± 4.09	83.66 ± 14.55 [a]	81.33 ± 17.01
FBG (mg/mL)	91.40 ± 9.72	245.67 ± 60 [a, c]	100.37 ± 17.94

HbA1c (%)	**5.04 ± 0.351**	**9.18 ± 2.14** [a, c]	**5.38 ± 0.223**
T.C. (mg/dL)	**166.87 ± 25.01**	**179.47 ± 47.79**	**180.27 ± 48.64**
TG (mg/dL)	**117.07 ± 32.62**	**186 ± 39.14** [a, c]	**144.53 ± 42.65** [b]
HDL (mg/dL)	**46.63 ± 10.79**	**37.57 ± 11.80** [a]	**42.07 ± 11.58**
LDL (mg/dL)	**96.82 ± 23.38**	**102.92 ± 39.59**	**109.29 ± 34.12**
VLDL (mg/dL)	**23.41 ± 6.52**	**38.97 ± 21.98** [a, c]	**28.90 ± 20.40** [b]
Urea (mg/dL)	**28.80 ± 6.88**	**34.33 ± 11.41** [a]	**34.47 ± 12.06** [b]
Creat. (mg/dL)	**0.793 ± 0.154**	**0.948 ± 0.231** [a]	**0.917 ± 0.215** [b]
U.A. (mg/dL)	**4.67 ± 1.11**	**5.39 ± 1.87**	**5.84 ± 1.71** [b]
Ca^{+2} (mg/dL)	**9.30 ± 0.362**	**8.81 ± 0.395** [a]	**8.77 ± 0.465** [b]
cTnI (ng/mL) median (range)	**0.013 (0.009–0.024)**	**0.950** [a] **(0.021–42)**	**0.231** [b] **(0.016–29.79)**

[a] P < 0.05, ACS with T2DM compared to the control group.
[b] P < 0.05, ACS without T2DM compared with the control group.
[c] P < 0.05, ACS with T2DM compared with ACS without T2DM.

Fasting serum netrin-1 levels

Fasting serum netrin-1 concentrations in healthy individuals and patients with ACS with and without T2DM are shown in Fig. 1. The serum netrin-1 levels were significantly higher in the ACS with T2DM or ACS without T2DM groups compared with healthy individuals (53.38, 45.57, and 32.37 pg/mL, respectively; P < 0.001). Although median fasting serum netrin-1 levels were higher in the ACS with T2DM group than in the ACS without T2DM group, but the difference between the groups was nonsignificant (P = 0.940).

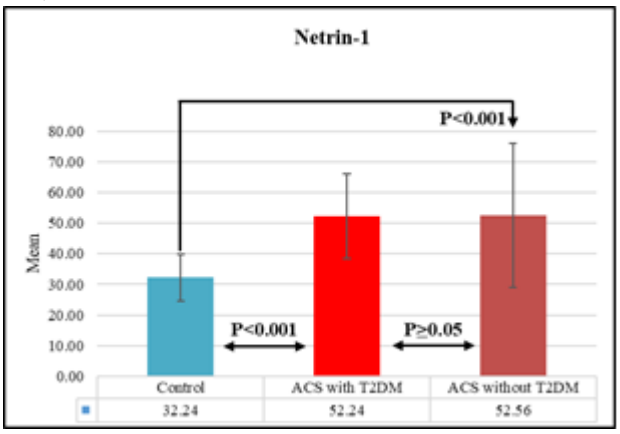

Figure 1. Mean, Standard Deviation, and Comparison of Netrin-1 Levels (pg/ml) in Patients with ACS with and without T2DM and Healthy Control Group. Statistical Significance is Indicated as Significant at P < 0.05; Non-Significant, P ≥ 0.05. Sample Sizes: ACS with T2DM, n = 30; ACS without T2DM, n = 30; Healthy Controls, n = 30.

Correlation of serum netrin-1 levels and other variables

Data analysis revealed a significant positive correlation between serum netrin-1 levels and BMI in the ACS with T2DM group (r = 0.498; P = 0.005) and a significant positive correlation between serum netrin-1 levels and troponin I level in the ACS without T2DM group (r = 0.436; P = 0.02). No significant correlations were observed between serum netrin-1 levels and other variables, including age, sex, FSG, total cholesterol, TG, HDL, LDL, VLDL, HbA1c, urea, creatinine, uric acid, and Ca^{+2} (Table 2).

Table 2 Correlation between serum netrin-1 levels and other variables

Variables	ACS with T2DM		ACS without T2DM	
	Netrin-1		Netrin-1	
	r	P value	*r*	P value
Age (years)	**−0.041**	**0.757**	**−0.033**	**0.801**
BMI (kg/m2)	**0.498***	**0.005**	**0.10**	**0.59**
SBP (mmHg)	**−0.32**	**0.08**	**0.01**	**0.95**
DBP (mmHg)	**−0.16**	**0.41**	**0.06**	**0.77**
FBG (mg/mL)	**−0.13**	**0.48**	**−0.05**	**0.80**
HbA1c (%)	**−0.26**	**0.17**	**−0.14**	**0.45**
T.C. (mg/dL)	**−0.07**	**0.71**	**0.03**	**0.89**
TG (mg/dL)	**0.11**	**0.57**	**−0.07**	**0.73**
HDL (mg/dL)	**−0.17**	**0.38**	**0.06**	**0.74**
LDL (mg/dL)	**−0.07**	**0.71**	**0.08**	**0.67**
VLDL (mg/dL)	**0.19**	**0.32**	**-0.26**	**0.16**
Urea (mg/dL)	**−0.08**	**0.68**	**0.05**	**0.78**
Creat. (mg/dL)	**−0.20**	**0.29**	**0.02**	**0.91**
U.A. (mg/dL)	**−0.27**	**0.15**	**0.08**	**0.69**
Ca^{+2} (mg/dL)	**−0.25**	**0.19**	**−0.09**	**0.64**
cTnI (ng/mL)	**0.13**	**0.50**	**0.436***	**0.02**

* Significant.

Receiver operating characteristic (ROC) analysis of serum netrin-1 levels

ROC curve analysis was employed to evaluate the effectiveness of serum netrin-1 level as a marker for discriminating between the ACS groups and healthy control group. The area under the curve (AUC) illustrates how serum netrin-1 levels can serve as a prognostic indicator of ACS. Every point on the ROC curve additionally demonstrates the specificity and sensitivity of this parameter in the prediction of ACS. ROC analysis produces two major outcomes, the optimal cut-off point (maximum specificity and sensitivity) value for the test and the test's diagnostic role. The test values are dichotomized using cut-off points, which serve to classify individuals as either diseased or non-diseased. Determining the cut-off point value

necessitates a concurrent evaluation of specificity and sensitivity [15].

ROC analysis for the ACS with T2DM group demonstrated that a serum netrin-1 level exceeding 39.99 pg/mL was associated with a higher likelihood of ACS (AUC = 0.903, sensitivity = 76.67%, specificity = 76.67%, likelihood ratio = 3.286, Fig. 2). By contrast, ROC analysis in the ACS without T2DM group showed a serum netrin-1 level exceeding 37.91 pg/mL was associated with an elevated incidence of ACS (AUC = 0.805, sensitivity = 66.67%, specificity = 66.67%, likelihood ratio = 2, Fig. 2).

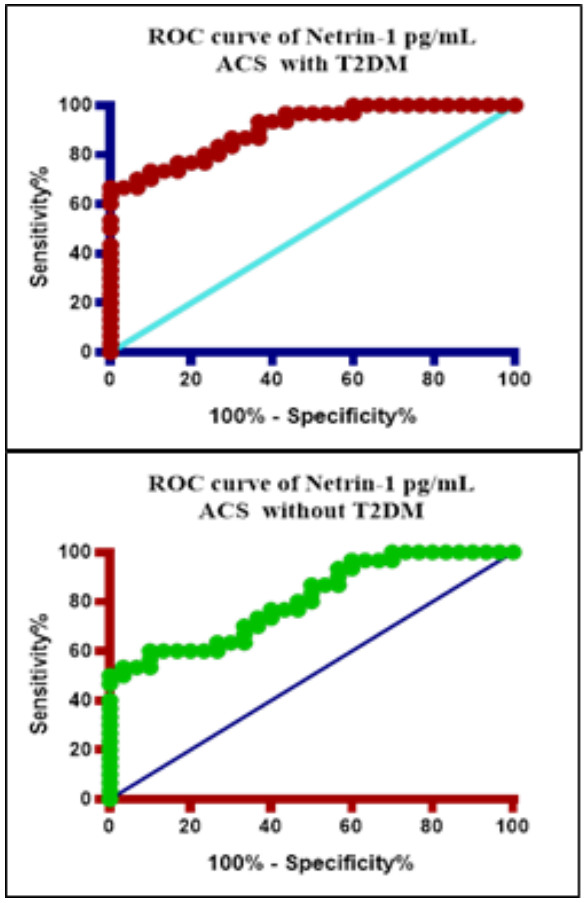

Figure 2. ROC Curve of Serum Netrin-1 (ng/mL) for Predicting Patients with ACS with and without T2DM

Discussion

In the present study, we found that the serum levels of netrin-1 were significantly higher in the ACS with T2DM or ACS without T2DM group compared with healthy individuals. This finding may be attributed to three factors. First, hypoxia, a condition strongly associated with atherosclerosis and acute coronary syndrome, stimulates the production of netrin-1 [16]. In addition, Van Gils et al. found that the molecule's expression was elevated in cholesterol-loaded macrophages, leading to the retention of these cells in vitro. This cellular retention potentially accelerates the development of atherosclerotic plaque and increases the likelihood of thrombus formation and occurrence of heart attack [12].

Second, plasma netrin-1 is produced mainly by the endothelium. Macrophages demonstrate expresses and secretes netrin-1, and elevated netrin-1 levels have been observed in macrophage-derived foam cells within atherosclerotic plaques examined in humans and mice. Furthermore, macrophages with plaques have elevated levels of the UNC5b receptor, which is the sole receptor expressed by leukocytes and is responsible for the inhibitory impact of netrin-1 on cell migration. Accordingly, the netrin-1/UNC5b signaling pathway prevents macrophage egress, thereby contributing to the progression of ACS [17].

Third, Nguyen and Cai demonstrated that netrin-1 stimulate angiogenesis by activating endothelial cell growth and migration and triggering NO release [18]. Durrani et al. conducted an animal investigation, demonstrating that synthesized netrin-1 reduced apoptosis in endothelial cells and increased vascular density, hence reducing ischemia–reperfusion injury [19]. These studies indicated that patients with ACS have elevated netrin-1 levels [20]. Furthermore, Mutlu et al. hypothesized that the netrin-1 level of a patient with ACS is already elevated at the time of hospital admission and subsequently declines following the restoration of coronary blood flow through angiography. Considerably reduced netrin-1 levels were observed in the patient group with TIMI 3 flow after angiography, suggesting that netrin-1 is a potential reperfusion marker in ACS [21]. Leocadio et al. hypothesized that the severity of ACS is positively correlated with the level of netrin-1. This hypothesis is based from evidence indicating that the expression of netrin-1 occurs following cellular injury and can serve as a biomarker for organ damage or disease, as demonstrated in the context of heart surgery [22].

Data regarding the levels of netrin-1 in the circulation of individuals with diabetes is concerning.

Five published studies have shown that patients with T2DM have considerably higher netrin-1 levels than control groups [8, 23–26]. However, Nedeva et al. [9] and Liu et al. [27] reported considerably lower levels of netrin-1 in T2DM. In the present study, although median fasting serum netrin-1 levels were higher in the ACS with T2DM group than in the ACS without T2DM group, the difference between the groups was nonsignificant. One potential explanation for this finding is the involvement of netrin-1 in inflammation, which has been shown to have detrimental effects on insulin secretion and contribute to β-cell dysfunction [28].

We determined the cut-off point for netrin-1 as a prognostic factor for ACS. We exhibited that netrin-1 in serum at 39.99 pg/mL concentration resulted in specificity and sensitivity of 76.67% and 76.67%, respectively, in the prediction of incidence of ACS with T2DM. The accuracy (AUC) for netrin-1 was 0.903. Although we exhibited that netrin-1 in serum at the cut-off of 37.91 pg/mL resulted in specificity and sensitivity of 66.67% and 66.67%, respectively, in the prediction of incidence of ACS without T2DM. The accuracy (AUC) for netrin-1 was 0.805. The presented data showed that netrin-1 is a suitable biomarker for predicting ACS with and without T2DM.

An intriguing result from our study is that serum netrin-1 levels exhibited a significant positive correlation with BMI in the ACS with T2DM and a significant positive correlation with troponin I in the ACS without T2DM group. However, in these two groups, we found no significant correlation between serum netrin-1 levels and other variables, that is, age, sex, FSG, total cholesterol, TG, HDL, LDL, VLDL, HbA1c, urea, creatinine, uric acid, and Ca^{+2}.

The current study has some limitations. First, the study population was relatively small and merely showed some correlations (small sample size causes statistical power to be lacking). Thus, we recommend the conduct of comparable studies with larger sample sizes to obtain more precise findings. Second, methods of ACS therapy were not considered, and characteristics associated with obesity, including body fat distribution and composition were not investigated. Third, only Iraqi participants were included in this study. Therefore, the results may not apply to participants of other ethnicities.

Conclusions

Netrin-1 levels were significantly higher in the ACS with T2DM or ACS without T2DM groups compared with the healthy control. The serum levels of netrin-1 in the present study demonstrated a positive correlation with troponin I level in the ACS without T2DM group. Therefore, netrin-1 levels in patients with ACS may serve as a marker of myocardial ischemia. In addition, a significant positive correlation was found between netrin-1 levels and BMI in the ACS with T2DM group. These findings suggests that netrin-1 is a potential indicator for predicting and diagnosing ACS in patients with and without T2DM.

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تقييم مستويات النيترين-1 في المصل لدى مرضى متلازمة الشريان التاجي الحادة المصابين أو غير المصابين بداء السكري من النوع الثاني

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الخلاصة:

الخلفية: على الرغم من أن دور النترين-1 في أمراض القلب والأوعية الدموية والالتهابات يعد مجالًا ناشئًا للدراسة، إلا أن هناك كمية محدودة من بيانات الأدبيات المتاحة وتوجد فجوة معرفية حول هذا الموضوع. لذلك، هدف بحثنا إلى تقييم مستويات النيترين-1 في مصل الدم لدى مرضى متلازمة الشريان التاجي الحادة المصابين بداء السكري من النوع الثاني وغير المصابين به.

الطرق: شملت هذه الدراسة مجموعة من 60 مريضا تم تشخيص إصابتهم بمتلازمة الشريان التاجي الحادة. تم تصنيف المشاركين إلى مجموعتين: 30 مريضًا يعانون من كل من متلازمة الشريان التاجي الحادة وداء السكري من النوع الثاني و30 مريضًا يعانون من متلازمة الشريان التاجي الحادة ولكن بدون داء السكري من النوع الثاني. تتألف المجموعة الضابطة من 30 فردًا يتمتعون بصحة جيدة والذين يتطابقون مع مجموعات المرضى من حيث الجنس والعمر. تم تقدير مستويات مصل النترين-1، والدهون، وجلوكوز الدم الصائم، والهيموجلوبين السكري، والتروبونين، واختبارات الدم الروتينية.

النتائج: كانت مستويات النترين-1 في المصل أعلى بكثير في مرضى متلازمة الشريان التاجي الحادة سواء المصابين او غير المصابين بداء السكري من النوع الثاني. مقارنة بالأفراد الأصحاء (53.38 بيكوغرام / مل و45.57 بيكوغرام / مل مقابل 32.37 بيكوغرام / مل، على التوالي). أظهر تحليل البيانات وجود علاقة إيجابية كبيرة بين مستويات النترين-1 ومؤشر كتلة الجسم وكذلك التروبونين. كانت قيمة القطع للنترين-1 (39.99، 91.37) عند حسابها في مرضى متلازمة الشريان التاجي الحادة المصابين مع وبدون داء السكري من النوع الثاني على التوالي .

الاستنتاج: تكون مستويات النترين-1 أعلى في المرضى الذين يعانون من متلازمة الشريان التاجي الحادة، سواء مع أو بدون داء السكري من النوع الثاني، مقارنة بالأفراد الأصحاء .

الكلمات المفتاحية: متلازمة الشريان التاجي الحادة، تصلب الشرايين، داء السكري من النوع الثاني، نيترين-1، التروبونين.