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Estimation of Tenascin-c and Thrombospondin-1 as biomarkers for cardiovascular disease in dyslipidemia patients

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Abstract

This study aimed to evaluate Tenascin-c (TN-C) and thrombospondin-1 (TSP-1) levels in patients with dyslipidemia concerning cardiovascular disease. Numerous studies have identified TN-C and TSP-1 as biomarkers of cardiovascular disease. The study included 45 dyslipidemia patients and 45 healthy controls. The results showed significantly higher levels of Tenascin-C -C and Thrombospondin-1 in patients compared to control group, with $P < 0.001$. Additionally, mean levels of serum Ca, serum ionized Ca, and vitamin D3 were significantly decreased $P < 0.001$ in patients compared to controls. Positive correlation was found between Tenascin-c and Thrombospondin -1 with cholesterol and LDL, $r = 0.532$, $r = 0.600$, respectively, with $P < 0.001$, while negative correlations were observed between both Tenascin-c and Thrombospondin -1 with HDL, Ca, ion Ca, and vitD3 with $P < 0.001$. The level of Tenascin-c was positively correlated with the level of VLDL. Finally, the study found that TSP-1 was a more sensitive and specific biomarker than TN-C for early diagnosis of cardiovascular disease.

Keywords: cardiac biomarker, cardiovascular disease, Dyslipidemia, tenascin-C, Thrombospondin-1.

تقدير تيناسين-سي وثرومبوسبوندين-1 كعلامات حيوية مبكرة لأمراض القلب والأوعية الدموية لدى مرضى اضطرابات الدهون.

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الخلاصة:

هدفت هذه الدراسة إلى تقييم مستويات التيناسين-سي (TN-C) والثرومبوسبوندين-1 (TSP-1) لدى مرضى اضطراب شحميات الدم فيما يتعلق بأمراض القلب والأوعية الدموية. لقد حددت العديد من الدراسات التيناسين-سي والثرومبوسبوندين-1 كمؤشرات حيوية لأمراض القلب والأوعية الدموية. شملت الدراسة 45 مريضاً باضطراب شحميات الدم و45 شخصاً سليماً كعينة ضابطة. أظهرت النتائج مستويات أعلى بشكل ملحوظ من التيناسين-سي والثرومبوسبوندين-1 لدى المرضى مقارنة بمجموعة الضابطة، مع قيمة دلالة إحصائية $P < 0.001$. بالإضافة إلى ذلك، كانت المستويات المتوسطة لكل من الكالسيوم في المصل، والكالسيوم المؤين في المصل، وفيتامين د3 منخفضة بشكل ملحوظ ($P < 0.001$) في المرضى مقارنة بالمجموعة الضابطة. وُجد ارتباط إيجابي بين تيناسين-سي وثرومبوسبوندين-1 مع الكوليسترول و LDL، حيث كانت قيم $r = 0.532$ و $r = 0.600$ على التوالي، مع $P < 0.001$ ، في حين لوحظت ارتباطات سلبية بين كل من تيناسين-سي وثرومبوسبوندين-1 مع HDL، والكالسيوم، والكالسيوم المؤين، وفيتامين د3 مع $P < 0.001$. وكان مستوى التيناسين-سي مرتبطاً إيجابياً بمستوى البروتين الدهني منخفض الكثافة جداً (VLDL). وأخيراً، وجدت الدراسة أن TSP-1 كان علامة حيوية أكثر حساسية وتحديداً من TN-C للتشخيص المبكر لأمراض القلب والأوعية الدموية.

1. Introduction:

Dyslipidemia refers to an of lipids, including triglycerides, cholesterol, low density lipoprotein (LDL) and high-density lipoprotein (HDL).. It is a well-established risk factor for cardiovascular disease [1-5]. Cardiovascular disease is a group of diseases that affect the blood vessels and heart. Dyslipidemia is the most common danger factor for cardiovascular disease, causation more than four million deaths each year worldwide[6-9]. Matricellular proteins are non-structural components of the extracellular matrix proteins that regulate cellular activity, hibernation, and cardiac inflammation. Examples include thrombospondins, osteopontin, tenascins, periostin, and osteonectin. These proteins are typically acidic, rich in cysteine, as well as the presence of CCN proteins (the initial three members' names, CYR61, CTGF, and NOV, inspired the abbreviation CCN). Each of the six CCN family members has four cysteine-rich modular domains. Thrombospondins are categorized into two subgroups: the pentameric subgroup B, which includes Thrombospondin -3, -4, and -5, and the trimeric subgroup A, comprising TSPs -1 and -2. TSPs family, encompassing TSPs -1 through 5, consists of multimeric glycoproteins that bind calcium ions Ca^{2+} , interact with other extracellular matrix components, and facilitate the connection between cells and the extracellular matrix. TSPs have a complex, multidomain structure that includes type III repeats, a C-terminal domain, and epidermal growth factor-like repeats across all members of the family[10, 11]. TSPs are multifunctional and can engage in various partner interactions. Thrombospondins are widely dispersed throughout the body's tissues and organs, including the heart. Though it is little in a steady state, TSP expression can rise in response to injury. Thrombospondins may aid in tissue remodeling and healing following damage. As the most studied TSPs, TSP -1 was identified initially. Due to its ability to release Transforming growth factor beta ($TGF-\beta$) from its latent state and increase its bioavailability, it is acknowledged for its efficient role in regulating angiogenesis and thrombosis [3,12]. Tenascin-C is usually expressed in early-stage embryos, plays significant roles in the growth of the coronary vessels, myocardium, valves and wound healing, and cancer diffusion, and participates in the guideline of cell actions during tissue remodeling of various tissues [2,13]. In the heart, TN-C is re-expressed under diseased environments such as acute myocardial infarction closely related to tissue damage [2]. Tenascin-C, tenascin-X, and tenascin-R are the three members of TN-C, which are particularly prevalent in developed embryonic tissues such as cartilage, tendon, bone, and the nervous system. These proteins promote the

migration, differentiation, and proliferation of stem and lineage-specific progenitor cells in these tissues [14,15]. This study aims to quantify the plasma concentrations of TSP-1 and TN-C in individuals with dyslipidemia.

2. Materials and Methods

2.1 Design of the study

This case-control study involved attending to the National Center for Teaching Laboratories (NCFTL) and Baghdad Teaching Hospital in Iraq, who were randomly selected casually between January to September 2023. The study was conducted under the supervision of the hospital's professional and ethics committee and with the permission of the participating patients and controls. Subjects with autoimmune diseases, chronic diseases, emergency conditions, and pregnant women were excluded.

2.2 Subjects and Sample Size

A total of ninety (90) participants were screened in a case-control study, comprising 45 dyslipidemia patients (32 males and 13 females) aged 30 to 72 years. Additionally, 45 apparently healthy subjects (30 males and 15 females) were selected as the control group.

2.3 Blood Samples

Eight milliliters of venous blood were drawn from the antecubital fossa of each participant using a 10 ml plastic disposable syringe. The blood was then transferred into gel-separated tubes and centrifuged for 20 minutes at 3000 rpm using a Hettich EBA 200 centrifuge. The tubes were labeled accordingly, with a portion of the sera utilized for various biochemical tests, while the other portion was stored at -20°C for later ELISA analysis to quantitatively measure serum TN-C and TSP-1.

2.4 Methods

All subjects underwent testing for lipid profile. Serum calcium, and serum magnesium levels were measured by an automated (Roche Cobas C111-Germany). Serum potassium and sodium were measured by an automated (Beckman Colter Olympus AU480- Germany). Serum-ionized calcium (iCa) was measured by an automated (Roche 9180 electrolyte analyzer- Germany). Serum vitamin D₃ was measured by an automated (Roche Cobas E411-Germany). While using the (ELISA) technique for TN-C was done by a human Tenascin-c ELISA kit from (Cat. No MBS2024375, USA), and TSP-1 was done by a human Thrombospondin-1 ELISA kit from (Cat. No.MBS701627, USA) using an ELISA reader device (Human Reader HS).

2.5 Statistical analysis:

The SPSS version (28) was utilized for data analysis. To compare the results between the groups, t-tests, mean, standard deviation, and chi-square were employed. Furthermore, the Calc program utilized the receiver operating curve (ROC) to estimate sensitivity and Med specificity with positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (+LR), and negative likelihood ratio (-LR). Results were deemed significant when the P-value was less than 0.05.

3. Results and Discussion

This study analyzed lipid profiles and other markers in patients with dyslipidemia and apparently healthy individuals, as presented in Table 1. The study included 45 dyslipidemia cases aged from 30 to 72 years, with a mean± SD (56.93±11.56, compared to younger of 70 years for controls and mean± SD (49.89±9.56 with no significant differences.

Table 1: Demographic features of the studied groups

Variables		Patients (n=45)	Control (n=45)	P-value
Age (years)	Range	30-72	30-71	P=0.452*
	Mean $\pm$ SD	56.93 $\pm$ 11.56	49.89 $\pm$ 9.56	
Total No.		45	45	
*Non-significant difference between studied groups using t-test for quality of means at 0.05				

Numerous studies have identified various factors linked to cardiovascular disease, including age and physical inactivity, etc.[16-21]. These findings align with a recent cross-sectional study in Bangladesh, which reported a 13.17% prevalence of dyslipidemia with a high prevalence at 60-69 years old [22]. That maybe due to increased exposure to risk factors such as smoking, hypertension, and alcohol drinking. Another study concluded closely associated chronological age with the risk of dyslipidemia [20,21].

Table 2 illustrates that serum levels of lipid parameters, including cholesterol, triglyceride, LDL, and VLDL, were significantly increased in dyslipidemia patients compared to controls (P<0.001), while HDL levels were significantly lower in patients than controls. According to TN-c and TSP-1, there were noticeably raised levels in patients than in controls with P<0.001. The mean serum levels of Ca, ionized Ca, and vitamin D3 were significantly decreased (p<0.001) in patients which were observed by decreasing mean values compared to controls. There were no discernible variations between the serum levels of K, Na, and Mg (p=0.382, 0.239, and 0.287, respectively).

Table 2: Comparisons between the serum levels of some biochemical markers among dyslipidemia patients and healthy controls.

Biochemical markers	Dyslipidaemia group(n=45) Mean $\pm$ SD	Control group(n=45) Mean $\pm$ SD	t-test for Equality of Means (Sig.(2-tailed))
cholesterol(mg/dl)	252.89 $\pm$ 54.605	163.27 $\pm$ 37.954	<0.001*
TG(mg/dl)	171.04 $\pm$ 88.725	95.29 $\pm$ 20.445	<0.001*
HDL(mg/dl)	36.47 $\pm$ 10.159	48.56 $\pm$ 7.276	<0.001*
LDL(mg/dl)	162.32 $\pm$ 41.215	86.03 $\pm$ 25.205	<0.001*
VLDL (mg/dl)	34.21 $\pm$ 17.745	19.06 $\pm$ 4.089	<0.001*
Thrombospondin-1(ng/ml)	123.46 $\pm$ 8.71	74.71 $\pm$ 24.23	<0.001*
Tenascin-c(ng/ml)	15.53 $\pm$ 4.53	7.26 $\pm$ 2.45	<0.001*
Ca(mg/dl)	6.31 $\pm$ 1.26	9.20 $\pm$ 0.59	<0.001*
Ionize Ca(mmol/L)	1.04 $\pm$ 0.11	1.29 $\pm$ 0.09	<0.001*
Vitamin D(ng/mL)	18.51 $\pm$ 10.03	36.76 $\pm$ 5.47	<0.001*
K(mmol/l)	4.22 $\pm$ 1.49	3.96 $\pm$ 1.38	0.382
Na (mmol/l)	135.40 $\pm$ 16.56	131.51 $\pm$ 14.50	0.239
Mg(mg/dL)	2.59 $\pm$ 0.11	2.61 $\pm$ 0.05	0.287

*H.S. highly significant

The lipid profiles of the study groups showed increases in all lipid parameters except for HDL, which was decreased. This finding is consistent with previous studies, highlighting

that reduced HDL-C is the most common form of dyslipidemia [22,23]. The HDL-C levels decreased linearly through age, perhaps due to physiological variations in the levels of sexual hormones throughout puberty and ageing [24,25]. Several studies have examined TN-C expression in biopsies from patients with cardiovascular diseases, with less research on the association of serum TN-C concentrations with cardiovascular problems [14-16]. The findings of this study showed an increased in serum level of TN-C, which agrees with other studies that reported TN-C increment in patients with a range of cardiac problems like acute myocardial infarction and pulmonary-artery-hypertension [26, 27]. The TN-C is up-modulating at high levels in many physiological and pathological conditions and is associated with major pathways of biological signaling. Different growth factors, cytokines, inflammatory processes, stress, and cardiac affecting factors, like endothelin I, angiotensin II, and hypoxia, affected the expression and production of TN-C [28]. While Hwang *et al* showed no associations were found with TN-C and TSP-2 levels [29]. The TN-C's physiological role is yet to be clarified, but the possibility remains that it plays a role in tissue organization and cell differentiation during the embryonic stage. It's TN-C expression appears to be a sensitive marker for tissue injury in cardiovascular and non-cardiovascular diseases like cancer [2]. These findings suggest that serum TN-C is most likely valuable when measured alongside other clinical and biomarker analyses to be of clinical value. As shown in Table 2, patients had significantly higher mean levels of TSP-1 compared to controls, consistent with the results of Jana *et al.*'s study [28]. TSP-1 increment in adults with dilated cardiomyopathy, and the study of Huang *et al.* showed elevated TSP-1 in cardiovascular disease[29].

Table 3 illustrates the correlation findings for TSP-1 and TN-C in relation to other parameters, indicating a positive, highly significant correlation between TSP-1 and TN-C with cholesterol and LDL, with $p < 0.001$. Conversely, there was a negative, highly significant correlation observed for both TSP-1 and TN-C with HDL, Ca, ionized Ca, and vitamin D3, with $p < 0.001$. Additionally, the results indicate that the level of Tenascin-C is positively correlated with the level of TG and VLDL, $p < 0.001$.

Table 3: Pearson Correlation between the levels of Thrombospondin -1 and Tenascin-c with some biochemical markers among the studied groups.

Parameter	Thrombospondin-1(ng/ml) N=(90)		Tenascin-c(ng/ml) N=(90)	
	r	p	r	p
cholesterol	0.600**	0.000	0.532**	0.000
TG	0.274**	0.009	0.456**	0.000
HDL	-0.564**	0.000	-0.539**	0.000
LDL	0.658**	0.000	0.590**	0.000
VLDL	0.274*	0.009	0.456**	0.000
Ca	-0.693**	0.000	-0.672**	0.000
Ionize Ca	-0.597**	0.000	-0.556**	0.000
Vitamin D	-0.584**	0.000	-0.609**	0.000
K	0.024	0.824	0.096	0.370
Na	0.294	0.006	-0.005	0.964
Mg	-0.173	0.103	-0.081	0.446
Thrombospondin-1	-	-	0.564	0.000
Tenascin-c	0.564	0.000	-	-

r, Pearson Correlation ** highly significant correlation

Table 4 shows the correlation for TSP-1 and TN-C with other parameters, showing a positive significant correlation between TN-C and ionized ca ($P<0.05$), while no correlation between TN-C with other parameters. Conversely, there was a positive and significant correlation observed for TN-C with HDL ($P<0.05$) and a positive, highly significant correlation with Na ($P<0.001$). Additionally, the results indicate that the level of TN-C is not correlated with other parameters.

Table 4 :Pearson Correlation between the levels of Thrombospondin -1 and Tenascin-c with some biochemical markers in the patients.

Parameter	Thrombospondin-1(ng/ml) N=(45)		Tenascin-c(ng/ml) N=(45)	
	r	p	r	p
cholesterol	0.194	0.201	-0.106	0.487
TG	-0.247	0.102	0.140	0.358
HDL	-0.310*	0.038	-0.204	0.179
LDL	0.250	0.097	-0.068	0.658
VLDL	-0.247	0.102	0.140	0.358
Ca	-0.180	0.237	-0.185	0.223
Ionize Ca	0.035	0.817	0.314*	0.036
Vitamin D	-0.044	0.776	-0.186	0.221
K	-0.097	0.528	0.048	0.752
Na	0.430**	0.003	-0.171	0.262
Mg	-0.167	0.273	-0.031	0.839
Thrombospondin-1	-	-	-0.040	0.793
Tenascin-c	-0.040	0.793	-	-

r, Pearson Correlation * significant correlation ** highly significant correlation

Many cardiovascular diseases are associated with remodeling of the extracellular matrix and cell dysfunction, in which TSP-1 may have a regulatory role in different mechanisms [30-32]. Due to the multi-domain structure of TSP-1, it can interact and activate many ligands[33]. In inflammatory cardiac conditions, hypoxia-inducible factor-1 alpha (HIF1 α) affects the release of many mediators, including TSP1, which acts as a pro-fibrotic factor, causing alteration in vascular homeostasis[34,35]. The influence of TSP1 on VCDs is more complicated and multi-factorial due to the diversity in activation and function of endothelial receptors and co-receptors. Deficiency of Vitamin D is considered to be a global problem of public health that occurs in sun-poor countries, which is associated with an increased development of cardio-metabolic disorders[34,35]. These investigations supported our findings, and an explanation for these findings could stem from the hypothesized mechanisms for the effects of low vitamin D on the cardiovascular system, which include increased blood clotting, increased arterial stiffness, and activation of the renin-angiotensin-aldosterone system[35]. The low calcium levels that the study showed contradicted those stated in previous studies [36,37], which made clear the existence of a positive association between serum-ionized calcium and the odds of dyslipidemia. The Na, K, and Mg states that there were no appreciable variations between the control and patient groups in the study.

The results of TN-C and lipid parameters, including cholesterol and LDL, were incompatible with the study in China[38]. That represented levels of cholesterol and LDL

were significantly decreased as TN-C levels increased in cardiovascular disease related to diabetes mellitus. This study appears to be the first to investigate the relationship between TSP-1 and the lipid profile in dyslipidemia. We found a significant correlation between TSP-1 levels and cholesterol, LDL, and HDL. While TSP-1 has been studied in cardiovascular disease [31], its specific link to dyslipidemia remains unexplored. McGillicuddy *et al.* demonstrated that TSP-1 declines as a result of the fluvastatin action, which eliminates TGF- β 1's capacity to stimulate TSP-1 expression[12]. In contrast to Yaldis *et al.* work, which indicated a substantial positive association between serum TN-C level and calcium score, this study found an inverse correlation between TN-C and calcium (Ca and iCa)[39]. Many factors can induce TN-C expression, like oxidative stress, inflammatory cytokines, and mechanical stress, which both act as mediators in the advancement of cardiovascular disease[2,11,14]. According to a study by Huang *et al.*, TSP-1 deficiency enhances myocardial MMP-3 and MMP-9 activation under pressure overload, leading to early cardiac hypertrophy and late dilatation [29].

ROC analysis was conducted to estimate the strength of serum analyses to reveal TSP-1 and TN-C, as presented in Table 5 and Figure 1A. Figure 1 shows TSP-1 (AUC: 0.950, p-value <0.001, 95% CI: 0.890 - 0.988, cut off >97.65 (ng/ml), sensitivity:100%, specificity 95.56%, ppv95.7%, NPV100%, + LR:22.5%, -LR0.00%), while the same Table with Figure 1B observed TN-C (AUC:0.940, p-value <0.001, CI: 0.869 - 0.979, cut off >8.94 (ng/ml), sensitivity: 93.33%, specificity 91.11%, PPV 91.3%, NPV 93.2 %, + LR:10.5% and -LR: 0.073%)respectively.

Table 5 : The ROC analysis for Thrombospondin-1 and Tenascin-C in study groups.

Biochemical markers	AUC	P-value	95% CI	Cut-off value	Sensitivity (%)	Specificity (%)	PPV	NPV	+ve LR	-ve LR
Thrombospondin-1(ng/ml)	0.950	<0.001	0.890 - 0.988	>97.65	100	95.56	95.7	100	22.50	0.00
Tenascin-c(ng/ml)	0.940	<0.001	0.869 - 0.979	>8.94	93.33	91.11	91.3	93.2	10.50	0.073

AUC(The area under the curve), NPV is the negative predictive value, LR is the likelihood ratio, and PPV is the positive predictive value.

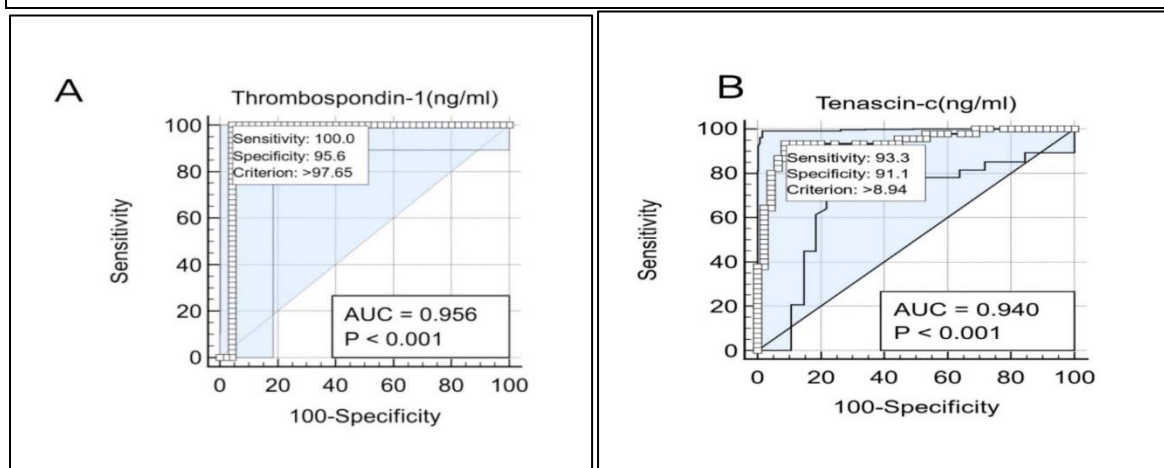


Figure 1: The ROC curves for (A) Thrombospondin-1 and (B) Tenascin-C.

The other studies found that the cut-off value for TSP-1 (1840 ng/mL) is higher than the result of the present study, with low (sensitivity 0.667, specificity 0.742) [12] may be differences in the studied groups, in which this study on acute coronary syndrome, while

present study on the early cardiovascular disease diagnosis as a result of dyslipidemia. These differences in results between studies may be differences in the manufacture of the kit used and the country of study.

Tenascin-C glycoprotein is deposited in the myocardium, but soluble forms are released into the blood. Stress, Hypoxia, and elevated pro-inflammatory cytokine levels can stimulate interstitial fibroblasts to produce TN-C. The TN-C influences metalloproteinases' activity, which results in connective tissue degradation[40-44]. The resulting AUC for this study gives significantly lower AUC but higher sensitivity and specificity than other study results done by Gao. *et al* found that AUC for TN-c (cut off value:100.91 ng/mL, sensitivity and specificity were 82.7% and 79% respectively), which recommended using TNC as a possible biomarker for severity of atherosclerosis[45]. This difference was mostly due to differences in the regional areas or the equipment of the test procedure.

Conclusion

For the early detection of patients with cardiovascular disease, TSP-1 demonstrated greater specificity and a high positive likelihood ratio. On the other hand, TN-C was recognized as a beneficial marker for detecting cardiovascular disease patients, characterized by a high positive probability value but with lower specificity.

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