Role of N-Terminal Pro-Brain Natriuretic Peptide (NT-proBNP) and Lipid Profile Parameters in Assessing the Severity of Coronary Artery Occlusion

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ABSTRACT

Background: Coronary artery disease is an extremely common heart ailment affecting millions of individuals around the globe and is one amongst the most common causes of morbidity and mortality. Several biomarkers are currently used for the diagnosis and management of cardiovascular diseases. Among them, N-terminal Pro-Brain Natriuretic Peptide (NT-ProBNP), is a true cardiac hormone exerting pleiotropic systemic effects.

Aim of the study: To identify the role of plasma NT-ProBNP and atherogenic index (TG/HDL-C) in the prediction of the number of occluded coronary arteries and distinguish between them (single versus multiple vessels).

Subjects and methods: This study was carried out at Mosul Center for Cardiology and Cardiac Surgery. It involved 90 patients (age ≥ 20 years) classified into three groups based on the findings of coronary angiography, each group consisted of 30 patients. Group I: included patients with no coronary artery occlusion and served as the control group, group II: CAD patients with single vessel occlusion, and group III: involved patients with CAD having multi-vessels occlusion (2 vessels or more).

Plasma NT-proBNP, total cholesterol (TC), triglyceride (TG), low density lipoprotein-cholesterol (LDL-C), and high density lipoprotein- cholesterol (HDL-C) were measured for all patients and atherogenic index of plasma (AIP) was calculated (as TG/HDL-C).

Results: The study revealed that the mean (±SD) value of plasma NT-proBNP was significantly higher in group III compared with group I and group II ($P < 0.0001$). In addition, the mean value of plasma NT Pro-BNP of group II was significantly increased in comparison with group I ($p < 0.001$). The mean values of AIP of group III and group II were significantly higher when compared to group I ($p< 0.001$ and 0.023 respectively), but with non-significant differences between group II and group III.

Receiver operator characteristic (ROC) curve analysis showed that the optimal cutoff point for plasma NT-proBNP was 72.50 pg/ml for diagnosing CAD with the sensitivity of (81.7%) and the specificity of (80%) and that for AIP was 0.55 with the sensitivity of (70%) and the specificity of (70%) as well.

Conclusion: Plasma levels of NT-ProBNP and /or atherogenic index of plasma can significantly predict the severity of coronary artery disease and differentiate between single and multi-vessels occlusion.

Keywords: coronary artery disease, N-terminal Pro-Brain Natriuretic Peptide, lipid profile.

دور الببتيد الدماغي المدر للصوديوم ومعلمات الدهون في تقييم شدة إنسداد الشريان التاجي

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الخلاصة

الخلفية : مرض الشريان التاجي هو من اكثر الامراض القلبية شيوعاً والتي تؤثرعلى ملايين الاشخاص في جميع انحاء العالم وهو احد الاسباب الشائعة والمهمة للمراضة والوفيات. يتم استخدام العديد من المؤشرات الحيوية حاليا لتشخيص امراض القلب والاوعية الدموية وعلاجها, إن من ضمن هذه المؤشرات هو الببتيد الدماغي المدر للصوديوم (NT-proBNP) والذي يعد هرمون قلبي حقيقي له العديد من التاثيرات الجهازية متعددة المظاهر.

الهدف من الدراسة : صممت هذه الدراسة للتعرف على دور الببتيد الدماغي المدر للصوديوم ومؤشر تصلب الشرايين (TG/HDL-C) في التنبؤ بعدد الشرايين التاجية المسدودة والتفريق بينها.
الاشخاص والطرق : اجريت هده الدراسة المقطعية في مركز الموصل لامراض وجراحة القلب خلال الفترة من نيسان إلى تموز ٢٠٢٣, وقد شملت ٩٠ مريضاً يشتبه باصابتهم بمرض الشريان التاجي وخضعوا لتصوير الاوعية الدموية التاجية في وحدة القسطرة القلبية من قبل إستشاريي امراض القلب وتم تقسيمهم الى ثلاث مجموعات بناءً على نتائج تصوير الاوعية التاجية:
المجموعة الاولى: شملت المرضى الذين ليس لديهم انسداد في الشرايين التاجية وتعد مجموعة مراقبة وعددهم ٣٠ شخصاً.
المجموعة الثانية: تالفت من مرضى الشريان التاجي المصابون بانسداد وعاء واحد وعددهم ٣٠ مريضاً.
المجموعة الثالثة: تضمنت مرضى الشريان التاجي ممن لديهم انسداد بشريانين او اكثر وعددهم ٣٠ مريضاً.
تم قياس مستوى الببتيد الدماغي المدر للصوديوم في البلازما ومستويات الكوليسترول الكلي (TC), الدهون الثلاثية (TG), الكوليسترول الدهني منخفض الكثافة (LDL-C) والبروتين الدهني عالي الكثافة (HDL-C) في مصل الدم بالاضافة الى مؤشر تصلب الشرايين (TG/HDL-C) لجميع المجموعات.
النتائج : كشفت الدراسة ان متوسط مستوى الببتيد الدماغي المدر للصوديوم كان أعلى بشكل ملحوظ لدى مرضى المجموعة الثالثة عند مقارنتهم بالمجموعة الاولى والثانية بالاضافة الى ارتفاع ملحوظ بمتوسط مستواه لدى مرضى المجموعة الثانية عند مقارنتهم بالمجموعة الاولى. كما اظهرت الدراسة ارتفاع مؤشر تصلب الشرايين (TG/HDL-C) بشكل ملحوظ في مرضى المجموعة الثالثة والمجموعة الثانية مقارنة بالمجموعة الاولى. تم اجراء منحنى خاصية تشغيل الخزان (ROC) للتنبؤ بمرض الشريان التاجي وانسداد الاوعية المفردة والمتعددة, واظهر ان نقطة العتبة المثالية للببتيد الدماغي المدر للصوديوم كانت ٧٢.٥٠pg/ml بحساسية ٨١.٧% ونوعية ٨٠%. أما بالنسبة الى مؤشر تصلب الشرايين, فأن نقطة القطع كانت ٠.٥٥ بحساسية ٧٠% ونوعية ٧٠%.
الاستنتاج : يمكن لمستوى الببتيد الدماغي المدر للصوديوم و/ أو مؤشر تصلب الشرايين التنبؤ بشكل كبير بوجود مرض الشريان التاجي والتمييز بين هؤلاء المرضى الذين يعانون من انسداد الاوعية الدموية المفردة والمتعددة.

الكلمات المفتاحية : مرض الشريان التاجي, الببتيد الدماغي المدر للصوديوم, معلمات الدهون.

INTRODUCTION

Coronary artery disease (CAD) is a condition in which there is an inadequate supply of blood and oxygen to the myocardium which results from occlusion of the coronary arteries causing a demand-supply mismatch of oxygen[1].

The diagnostic work-up of patients with chest pain suggestive of CAD at presentation is typically oriented toward the detection of a relevant obstructive stenosis, which serves as the basis for further treatment decisions[2].

Atherogenic dyslipidemia is a clinical condition characterized by elevated levels of serum triglycerides (TG) and small-dense low-density lipoprotein (sdLDL) particles with low levels of high-density lipoprotein cholesterol (HDL-C). It is often observed in patients with metabolic syndrome, obesity, insulin resistance and type 2 diabetes mellitus and regarded as an important risk factor for CAD in these patients[3].

Several biomarkers are currently used for the diagnosis, risk stratification, and management of cardiovascular disease. Among them, NT-ProBNP can help to diagnose heart failure and acute coronary syndrome as well as to determine the prognosis of such patients[4]. Human BNP is a 32 amino acid polypeptide containing a 17 amino acid ring structure with a disulfide bond connecting two cysteine residues[5]. It is synthesized from BNP precursor (pre-proBNP) and cleaved inside the cells by furin, an intracellular endoprotease that is enriched in the Golgi apparatus, into the biologically active (BNP 32-amino acids), and the inactive (76-amino acid NT-proBNP)[6]. Various causes, such as tissue hypoxia, transmural pressure or volume overload induce BNP synthesis in cardiomyocytes[7]. BNP is a true cardiac hormone exerting pleiotropic systemic effects that range from blood pressure regulation to both glucose and lipid metabolism, with a wide spectrum of cardio-metabolic properties, including vasodilation, diuresis, natriuresis and inhibition of the renin–angiotensin– aldosterone system (RAAS), which enable this hormone to play key roles in regulating blood pressure and fluid volume[8]. Also BNP acts locally on the heart, exerting both paracrine and autocrine activities, mainly preventing hypertrophy, fibrosis, arrhythmias and cardiomyopathies, counteracting the development and progression of heart failure[9].

AIM OF THE STUDY

To identify the possible role of NT-ProBNP and atherogenic index of plasma (AIP) (TG/HDL-C) in the prediction of the severity of coronary arteries occlusion based on their number (single versus multiple vessels).

PATIENTS AND METHODS

This cross sectional study was carried out at Mosul Center for Cardiology and Cardiac Surgery during the period from April to July 2023. It included ninety patients (age ≥ 20 years) with suspected CAD who underwent coronary angiography at the catheterization unit by consultant cardiologists and were classified into three groups based on the findings of their coronary angiography:

1. Group I: included those patients with no coronary artery occlusion, served as control group (n=30),
2. Group II: consisted of patients with CAD who had single vessel occlusion (n=30),
3. Group III: involved patients with CAD having multi-vessels occlusion (2 vessels or more; n=30).

Inclusion Criteria

The included patients were defined to have or haven't CAD upon vessels narrowing by 50% or more that reflect 50% reduction in the luminal diameter as revealed by angiography.

Exclusion Criteria

1. Patients with heart failure and left ventricular (LV) dysfunction
2. Recent myocardial infarction (MI)
3. Valvular heart diseases and cardiomyopathies, and
4. Those with renal impairment

Ethical Consideration

The study was approved by the Council of the Iraqi Board of Medical Specialization and Nineveh Health Directorate and a verbal consent was obtained from each included patient.

Blood Samples Collection

Five milliliters (ml) of peripheral venous blood was collected from each patient after 10-12 hour overnight fasting and just before undergoing angiography, and the sample was divided into two parts, each of them was treated in different way as follows:

1. For lipid profile parameters measurement, 3ml of blood was transferred into serum separating gel tube, left for half an hour at room temperature and then centrifuged at 3000 rpm for 10 minute to obtain serum.
2. For NT-proBNP measurement, 2 ml of blood was transferred into ethylene diamine tetra acetic acid (EDTA) test tube, with gentle shaking for proper mixing with anticoagulant material, to obtain plasma that was separated and stored frozen at -20 o C for subsequent measurement of NT-proBNP in batches.

Laboratory Methods

Electrochemiluminescence immunoassay (ECLIA) was used for quantitative determination of NT-proBNP in human plasma, using a kit supplied from Nipigon Health corp (Canada). NT-proBNP was measured by a fully automated “sandwich” ECLIA method using a Nipigon Health corp Robot-R1 automated ECL analyzer.

Reference Range:
adults under 75 years old: ≤ 125 pg/ml
adults older than 75 years old: ≤ 521 pg/ml [10]

Total cholesterol (TC), HDL-c and triglycerides (TG) were measured in the serum manually using the spectrophotometric enzymatic method with the kits supplied from BIOLABO (France). Friedewald equation was used to estimate LDL-C [11], as follows:

LDL-C=Total cholesterol–[HDL-C+triglycerides (TG)/5]

Where TG/5 is an approximate estimation of VLDL-c. The reference values of TC, HDL-C, LDL-C,TG and VLDL-C [12] are demonstrated in Table(1).

Table (1): Reference values of lipid profile parameters

Parameter	Recommended values	Low risk	High risk
TC (mg/dl)	< 200	200-239	≥ 240
LDL-C (mg/dl)	**<** 100	100 – 129	≥ 130
HDL-C (mg/dl)	≥ 60	< 40 is at risk	
TG (mg/dl)	< 150		
VLDL-C (mg/dl)	2 to 30		

Atherogenic index of plasma (AIP) was calculated as a logarithm of the ratio of the concentration of triglyceride (TG) to HDL-C. It is used as an optimal indicator of dyslipidemia and associated cardiovascular diseases [13], as follows:

AIP = $\log_{10}$ (TG/HDL-C)

Reference range[14] : Low risk AI < 0.11
Intermediate risk 0.11 to 0.21
High risk > 0.21

Statistical Analysis

The data obtained in the current study were analyzed using Statistical Package for Social Sciences (IBM SPSS-29), Chicago, IL, USA. The data were presented as mean± standard deviation (SD), number and percentage. Students-t-test (unpaired) was used to reveal differences between two independent means or Paired-t-test for differences of two dependent means. Analysis Of Variance (ANOVA) test was used to compare the results of various biochemical parameters among the three studied groups. Statistical significance was considered whenever the p-value was < 0.05.

Receiver Operator Characteristic “ROC” curve was constructed in order to determine whether NT-proBNP and AIP can be used as diagnostic (or screening) tools for CAD and to determine the “cut-off value” of optimum sensitivity and specificity.

RESULTS

Table (2) shows the basic characteristics of the study groups including age, body mass index (BMI) and gender distribution. The differences in the mean age values of group I or the control group (53.9 ± 8.6 year), groups II (56.3 ± 9.3 year) and group III (58.9 ± 8.9 year) were statistically non-significant (p=0.097). The number of males was higher in the three studied groups, with non-significant differences in sex distribution among these groups (p=0.079).

The mean (±SD) values of BMI of the studied groups did not differ significantly (29.63 ± 4.05, 27.76 ± 4.13, and 29.43 ± 4.28 Kg/m^2, respectively, p=0.166).

Table (2): Comparison of basic characteristics (age, body mass index and gender distribution) of the studied groups. Data are Expressed as mean (±SD) or n(%) as appropriate

Parameter		Group I (n=30)	Group II (n=30)	Group III (n=30)	p-value
Age (year)		53.9 ± 8.6	56.3 ± 9.3	58.9 ± 8.9	0.097
Gender	**Male**	17 (56.7%)	25 (83.3%)	21 (70.0%)	0.079
	Female	13 (43.3%)	5 (16.7%)	9 (30.0%)	
BMI (kg/m^2)		29.63 ± 4.05	27.76 ± 4.13	29.43 ± 4.28	0.166

Table (3) shows the mean (±SD) values of the measured lipid profile parameters of the three studied groups. The mean values of serum triglyceride and VLDL of group III were significantly higher than those of group I (p= 0.003 and 0.002 respectively). Also, the mean values of serum triglyceride and VLDL of group II were significantly higher than those of group I (p= 0.026), (p= 0.018), respectively. However, there were no significant differences in mean serum triglyceride and VLDL values upon comparing group II and group III. The mean values of total cholesterol, LDL-cholesterol and HDL-cholesterol did not differ significantly among and between the three studied groups.

Table (3): Comparison of the mean values of total cholesterol, triglyceride, HDL-C, LDL-C and VLDL-C of the studied groups

Parameters	Group I n=30	Group II n=30	Group III n=30	p-value
Total Cholesterol (mg/dl)	152.23 ± 37.22	152.97 ± 43.94	171.97 ± 47.77	NS
Triglyceride (mg/dl)	130.00 ± 50.01	160.77 ± 57.30♠	177.23 ± 50.69●	0.003● 0.026♠
HDL-C (mg/dl)	38.63 ± 7.06	35.98 ± 4.74	35.43 ± 5.79	NS
LDL-C (mg/dl)	84.37 ± 29.64	84.70 ± 36.49	100.33 ± 44.35	NS
VLDL-C (mg/dl)	25.67 ± 9.45	32.15 ± 11.46♠	35.43 ± 10.12●	0.002● 0.018♠

● Significant increase in triglycerides& VLDL-c in group III compared to group I, ♠ significant increase in triglycerides& VLDL-c in group II compared to group I, NS non-significant.

Table (4) demonstrates that the mean (±SD) values of plasma NT-proBNP was significantly higher in group III (188.44 ± 86.07 pg/ml) compared with those of group I (51.64 ± 23.72 pg/ml) and group II (109.88 ± 61.57 pg/ml), p= 0.0001. Also it depicts that the mean (±SD) values of (AIP) of group III (0.683 ± 0.165) and group II (0.625 ± 0.166) were significantly higher than that of group I (0.518 ± 0.199), p=0.002.

Table (4): Comparison of the mean (±SD) values of plasma NT-proBNP levels & AIP of the three studied groups

Parameter	Group I	Group II	Group III	p-value
NT-proBNP (pg/ml)	51.64 ± 23.72	109.88 ± 61.57	188.44±86 .07	0.0001
AIP	0.518 ±0.199	0.625 ± 0.166	0.683 ± 0.165	0.002

Using ANOVA test

Receiver Operator characteristic (ROC) curve was constructed to evaluate the ability of NT-proBNP and AIP to predict CAD. The AUC for plasma NT-proBNP was 88% and for AIP was 70%. The optimal cutoff point for NT-proBNP was found to be 72.5 pg/ml for diagnosing CAD with a sensitivity value of 81.7% and specificity of 80%, while that of AIP was 0.55 with both sensitivity and specificity of 70%, Figure (1) and Table (5).

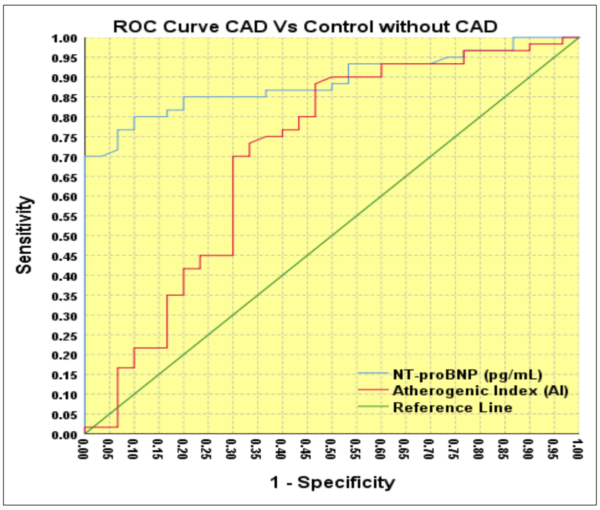

Figure (1): ROC curve for plasma NT-proBNP and AIP in the prediction of CAD.

Table (5): Area under curve (AUC) and cutoff values for plasma NT-proBNP and AIP for diagnosis of CAD

Parameters	(AUC)	p-value	Cutoff value	Sensitivity %	Specificity %	95% Confidence Interval	
						Lower Bound	Upper Bound
NT-proBNP (pg/mL)	0.88	0.0001	72.50	81.7	80	0.822	0.955
AIP	0.70	0.002	0.55	70	70	0.580	0.830

DISCUSSION

Natriuretic peptides are well-established markers for diagnosis and prognosis of heart failure and it has been found that they become elevated in ischemic heart diseases independent of ventricular wall stress[15]. In patients with stable CAD, BNP levels have been correlated linearly with number of coronary artery involvement[16].

In this study, the mean value of NT-proBNP in patients with multi-vessels disease was significantly higher than the control group and those with single vessel disease.

A significantly higher level of NT-proBNP was also noticed in patients with single vessel disease when compared to the control group. These findings are consistent with that reported by Marchenko et al. (2021) who studied 131 Ukrainian patients whose complaints were highly suggestive for CAD. They found that NT-proBNP levels were highest in patients with multi-vessel coronary artery disease[17]. Several other studies have also confirmed that NT-ProBNP is a useful marker in the prediction and assessment of the severity of CAD. A study on stable angina patients, Caselli et al. stated that the presence and severity of CAD based on the computed tomographic angiography score was significantly associated with the serum level of NT-ProBNP[18]. Saha and Mandal's (2019) showed that highest level of NT-proBNP was noticed in patients with triple vessel disease and concluded that in presence of normal systolic and diastolic function NT-proBNP is useful to predict the angiographic severity of CAD[19].

Several possible mechanisms can explain the diagnostic value of circulating NT-proBNP levels. First, higher NT-proBNP concentrations may reflect the presence of structural heart disease or cardiac remodeling resulting from increased cardiac stretch[20]. Second, elevated NT-proBNP levels may be linked with the degree of systemic atherosclerosis[21]. Apart from increased ventricular stretch and wall tension, natriuretic peptides synthesis has been observed in atherosclerotic coronary plaques as well and NT-proBNP levels might reveal the severity of coronary stenosis[22].

At a cut-off point of 72.5 pg/ml, NT-proBNP could predict the presence of CAD in the present study. Such value was nearly similar to that reported by Rahmani et al. (2019). Their cutoff point was 69.5 pg/ml in predicting CAD[23], while Ribiero et al. (2014) showed that NT-ProBNP levels above 250 pg/ml could independently predict CAD[24]. Belle et al. (2018) found an optimal cut-off for serum NT-proBNP for predicting CAD to be 120.8 pg/mL in their study[25]. Such discrepancy may be attributed to technical assay used and population studied.

Regarding AIP, a new comprehensive lipid index, the present study revealed significantly higher values in single and multi-vessel disease groups compared to controls, suggesting that AIP could be used as a biomarker for the evaluation of CAD severity. Li et al. (2023), Mangalesh et al. (2022), Wang et al. (2021), and Cai et al. (2017), have demonstrated that AIP was associated with the development and severity of CAD potentially making it a strong and independent predictor for CAD[26-29]. Elevated TGs and low HDL-c levels are strong markers of CAD. Therefore, the AIP combines these two lipid parameters into a single biomarker to boost its predictive capabilities[30].

An increase in AIP indicates a reduction in the LDL particle diameter and a rise in the proportion of small-dense LDL (sdLDL) which is more prone to oxidation promoting the formation of foam cells, the initial stages of atherogenesis[31].

All the currently available methods to detect sdLDL have limitations and suffer from the problem of high cost, which is difficult to popularize in clinical practices. Nevertheless, the calculation of AIP is easy and effectively reflects the sdLDL level. Therefore, the use of AIP to evaluate the risk of developing atherosclerosis is feasible for the prevention and control of cardiovascular diseases in a community population[32].

Conclusions

NT-proBNP and / or AIP are associated with the severity of CAD based on the number of occluded vessels and can significantly predict the presence of CAD and differentiate between those patients with single and multi-vessels obstruction. AIP was a significant and independent predictor for CAD risk and might be better than traditional lipid parameters and other lipid ratios.

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