2024, Volume 1, Issues 4 PSIJK 11 - 16

Pure Sciences International Journal of Kerbala
Journal Homepage:https://journals.uokerbala.edu.iq/index.php/psijk

Estimation of the Serum Ischemia Modified Albumin (IMA) and B-Type Natriuretic Peptide (BNP) Levels in Adult Beta-Thalassemia Major Patients in Baghdad-Iraq

Ahmed Jawad Kadhim[1*], Hedef. D. El-Yaseen[2], Ali Mohammed Jawad[3]

[1]*Department of Biochemistry, College of Medicine, University of Baghdad, Iraq.*
[2]*Department of Biochemistry, College of Medicine, University of Baghdad, Iraq.*
[3]*Department of Medicine, College of Medicine, University of Baghdad, Iraq.*

P A P E R I N F O

Received 27 May 2024
Accepted 26 June 2024
Published 31 December 2024

Keywords:
IMA, BNP, Beta-Thalassemia Major

A B S T R A C T

Background: Beta thalassemia major (β-T) is a prevalent genetic disorder worldwide that arises from a lack of globin chains. Ischemia-modified albumin (IMA) is a variant of the albumin protein that is produced in response to oxidative stress. It serves as a blood biomarker for tissue damage and myocardial ischemia. Cardiovascular disease is a widespread global health issue that results in mortality. In order to effectively prevent disease progression and administer appropriate treatment, it is crucial to diagnose the condition in its early stages by examining the extent of cardiac damage.
Objective: to quantify the levels of IMA in patients with β-thalassemia major (β-T) and compare them to those of healthy individuals. Additionally, we aim to evaluate the correlation between IMA levels and BNP.
Methods: Sixty participants were enrolled in this study in order to assess their serum IMA levels. 30 Beta-Thalassemia Major patients and 30 healthy individuals were included in this investigation, all of whom showed no signs of heart disease. The ELISA method was employed to determine the levels of serum IMA and BNP.
Results: Serum IMA and BNP increased in Beta-Thalassemia Major patients when compared with control healthy subjects ($P < 0.001$). There was no correlation between serum IMA and BNP in the patients' group.

1. INTRODUCTION

Thalassemia is a prevalent global disease characterized by the fast breakdown of red blood cells. To sustain their red blood cell count, patients must undergo regular blood transfusions. Regular blood transfusions, nevertheless, result in excessive accumulation of iron in the body, which can give rise to issues such as osteoporosis, diabetes, cardiovascular disease, and renal disease [1]. Thalassemia is mainly classified into two types: alpha-thalassemia and beta-thalassemia. Beta-Thalassemia is categorized into major, moderate, and mild forms according to clinical criteria [2].

Beta thalassemia is a condition where there are abnormalities in the production of the beta chains of hemoglobin. This can lead to a range of symptoms, from severe anemia to individuals who show no clinical symptoms. The global yearly prevalence of symptomatic persons is believed to be 1 in 100,000, while in the European Union, it is predicted to be 1 in 10,000. Three primary forms have been identified: thalassemia minor, thalassemia intermedia, and thalassemia major [3].

Beta thalassemia major patients if untreated leads to increase cardiac output that results in left ventricular hyperatrophy end with heart failure. Iron

*Corresponding Author Institutional Email:
ahmed.jawad1109f@comed.uobaghdad.edu.iq (Ahmed Jawad Kadhim)

overload will result in peroxidationand cellular injuries. Also, cardiac arrhythmia like atrial fibrillation, ventricular tachycardia and superaventricular tachycardia are increased because of increased cardiac siderosis [4]

Ischemia Modified Albumin IMA is a new marker that indicates the presence of oxidative stress and tissue ischemia. The pathophysiological events of ischemia, such as the presence of reactive oxygen species and lack of oxygen, result in a structural alteration of albumin at the N-terminus [5].

Elevated levels of ischemia-modified albumin (IMA) can be an early sign of permanent necrosis in cardiomyocytes. When comparing the biochemicals associated with myocardial injury in patients with acute coronary syndrome, specific markers can be detected at an earlier stage and with higher sensitivity than other compounds. IMA levels also increase during myocardial ischemia-reperfusion injury, which is associated with oxidative stress resulting from both cardiac and non-cardiac events [6].

B-type natriuretic peptide (BNP) is a cardiac hormone secreted by the myocardium of the left ventricle in response to increased pressure or volume in the heart. BNP stimulates sodium excretion and causes the narrowing of blood vessels to control the amount of blood and the pressure within it. Elevated BNP levels are observed as the left ventricular function worsens [7].

2. MATERIALS AND METHODS

2.1 Patients and Control

The samples collected at the beginning of the study were 60 subjects selected with an age range (18-30 years) living in Baghdad; each patient completed a questionnaire sheet that included the following information: code number, name, age, gender, date, address, ethnicity, family history of thalassemia, weight, length, and medical history. In this cross sectional study was performed in the Ibn Albaladi Center of Blood Diseases (during the period from 1st of March 2023 to the end of August 2023). These subjects were divided into two groups: 30 Beta-Thalassemia Major patients without any symptoms of heart dysfunction, and 30 normal subjects. Patients with cardiovascular disease were excluded in this study. Consent has been acquired from all patients and healthy volunteers, or their parents, for this study, and it was publically acknowledged.

2.2 Statistics

Continuous data were described as mean± SD (Standard Deviation). The student's t-test has been used to examine and compare the means of the markers and variables between the patients and control group. A Pearson correlation analysis was conducted to determine if there was a significant association between the parameters. The alpha level for statistical significance was set to $p < 0.05$. Statistical analysis was measured using the program MedCalc version 19.6.1

2.3 Blood Sampling

Blood samples collected from subjects before the blood transfusion in the morning at 8:00 a.m- 11:00 a.m. The sample was obtained by collecting blood from the vein using a 10 ml disposable syringe. The collected sample was then placed in tubes that contained a gel, which aids in the separation of serum. Blood kept in gel tubes was allowed to clot at 37°C approximately at 10 min and then centrifuged at 2000 Xg for 15 min then the serum was divided and stored at (-20°C) by using sterilized eppendrof tubes, 0.5ml of serum used until analysis Serum IMA and Serum BNP. Determination of Serum IMA and BNP by enzyme - linked immunosorbent assay (ELISA) kits which are sandwich enzyme immunoassay for in vitro quantitative measurement [Ischemia-Modified- Albumin-(IMA)-CEA825Hu and Brain Natriuretic Peptide (BNP)-CEA541Hu Cloud-Clone Corp (USA).

3. RESULTS

Demographic characteristics of the β-Thalassemia major Group (n = 30) and control subjects (n =30) enrolled in the present study are shown in Table (1). There was no significant difference in the frequency distribution of individuals according to sex between beta thalassemia major and control group, with 17 (57.0 %) and 13 (43.0 %) males and females in each group.

In **Table 1** and **Figure 1**, the Mean±SD for age across the groups was statistically similar, as indicated by the p-value of 0.987.

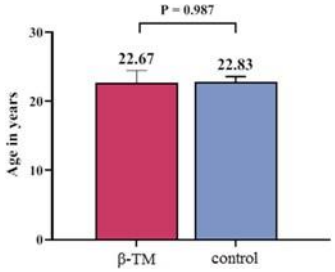

Figure 1. Means of age by Groups with 95.00% CI Error Bars

TABLE 1. Demographic and laboratory data among β-thalassemia major (β-TM) and controls groups

parameter	Controls (n = 30)	β-Thalassemia Major (β-TM) (n = 30)	P value
Male	17/30	17/30	1
Female	13/30	13/30	1
Age (Years)	22.83± 2.03	22.67± 4.78	0.987
IMA ng/mL	2310.63± 1490.97	7834.33± 993.00	<0.001
BNP (pg/mL)	96.63± 16.13	361.63± 74.72	<0.001

Note: Each parameter's mean and standard deviation (Mean± SD) are provided, along with the p-value indicating the significance of the differences between the groups.

In the case of S.IMA, β-Thalassemia Major (β-TM) Group demonstrates the highest Mean±SD value 7834.33±181.30 (ng/mL), against the control Group with 2310.63±272.21(ng/mL). The p-value< 0.001, indicating significant differences between the groups, Figure 2.

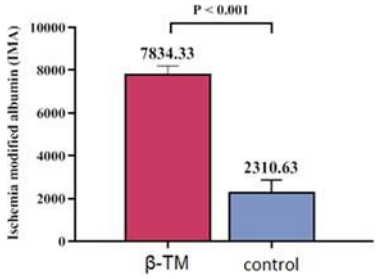

Figure 2. Means of IMA by groups with 95.00% CI error bars

In this study, it was shown that BNP levels were elevated in the β-TM group had Mean±SD (361.63±74.72 pg/mL) compared with the healthy control group had Mean±SD (96.63±16.13 pg/mL). exhibit significant differences with p-value < 0.001, Figure 3.

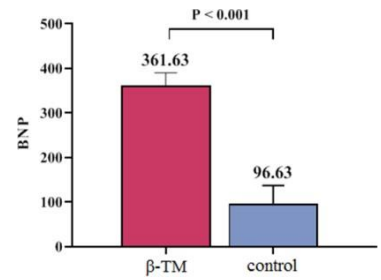

Figure 3. Means of BNP by Groups with 95.00% CI Error Bars

No correlation exists between Age, IMA and BNP as shown in **TABLE 2**

TABLE 2. Correlation matrix (Pearson) / Group Group B:

Variables	Age	BNP	IMA
Age	**1**	0.08	0.1
BNP	0.08	**1**	-0.23
IMA	0.1	-0.23	**1**

4. DISCUSSION

This study showed no significant difference in distribution between male (57.0 %), female (43.0 %) patient and control groups. Brain (B-type) natriuretic peptide (BNP) is a neurohormone that is produced and released by the heart ventricles when there is an increase in wall tension. The level of this factor is elevated in patients suffering from heart failure, myocardial infarction, and unstable angina. The extent of the increase is directly related to the severity of left ventricular (LV) dysfunction. However, other illnesses can cause elevated BNP levels, either cardiac, such as acute coronary syndromes, pulmonary embolism, tachyarrhythmias, and cardioversion, or non-cardiac, such as anemia [8].

This study demonstrated that thalassemia patients in the Group had higher BNP levels than the healthy control group. The results are comparable to those reported by(Mohammed et al 2019) [9].

The most important complications in patients with beta thalassemia major are cardiomyopathy and various types of arrhythmias.in patients with beta thalassemia major anemia leads to increase cardiac output that results in left ventricular hyperatrophy end with heart failure. Iron overload will result in peroxidationand cellular injuries. As results of iron overload that cause left ventricular cardiomyopathy. Also, cardiac arrhythmia like atrial fibrillation ventricular tachycardia and superaventricular tachycardia are increased according to increased cardiac siderosis [4].

The main causes of cardiomyopathy in patients with thalassemia are increasing intestinal absorption of iron, hemolysis, and lifelong blood transfusions. When intracellular iron increases, it is metabolized, releasing reactive oxidative species, which damage the cell membrane, and interfere with the respiratory chain in the mitochondria resulting in cardiotoxicity [10].

Serum IMA of β-TM patients Group was significantly higher than that of control group. Previous studies had shown that children with β-Thalassemia had significantly greater levels of IMA compared to healthy controls [11].

Albumin is a highly prevalent protein found in the bodies of mammals. Its characteristics undergo alterations during ischemia events that are linked to oxidative stress, acidosis, and the generation of reactive oxygen species. Under these circumstances, the presence of ischemia leads to the production of IMA, which has a diminished ability to bind to metals, particularly transition metals [12].

Iron overload in thalassemia leads to elevated levels of reactive oxygen species (ROS), which significantly contribute to the formation of intramolecular aggregates (IMA). Recently, it has been discovered that IMA is a final result of oxidative stress. Higher concentrations of IMA may indicate a state of oxidative stress that affects the entire body rather than being limited to a specific organ. Studies have shown that persons with thalassemia have a reduced ability to counteract the harmful effects of oxidants. Thus, it is imperative to utilize efficient iron chelators in order to eliminate the harmful iron ions and prevent oxidative harm to the essential organs [11].

In addition, recent laboratory studies have shown that the production of hydroxyl radicals (•OH) through the Fenton reaction is linked to a sudden increase in the concentration of IMA. Based on these data and considering the presence of oxidative stress, increased formation of reactive oxygen species (ROS), reduced antioxidant defense systems, hypoxia, and anemia in thalassemia patients, it is reasonable to expect higher levels of ischemia-modified albumin (IMA) in these individuals. The primary factors that are most likely responsible for the alteration of the N-terminus of serum albumin and the subsequent increase in levels of IMA in thalassemia patients are iron-induced oxidative stressors in conjunction with chronic anemia and hypoxia [13]. The increase in B-type natriuretic peptide (BNP) and ischemia-modified albumin (IMA) in thalassemia patients without cardiac dysfunction could be due to a higher degree of cardiac strain and injury,which leading to elevated levels of these biomarkers without any symptoms of heart dysfunction [14]. This could stem from factors such as chronic anemia, increased iron deposition, or other complications [15].

non-cardiac factors such as inflammation, oxidative stress, and endothelial dysfunction may play a more prominent role in elevating these biomarkers in patients without cardiac dysfunction. These factors can contribute to myocardial injury and dysfunction [16].

5. CONCLUSION

Iron overload and oxidative stress pathways in β-TM patients led to higher levels of IMA. Elevated levels of IMA (ischemia-modified albumin) and BNP (B-type natriuretic peptide) in β-thalassemia major (β-TM) individuals who show no signs of cardiac failure could be a significant signal. This abnormality may arise during the early stages of heart disease.

6. REFERENCES

1. Talib NH, Al-yaseen HD, Jwad AM. Serum Preptin Level in Iraqi Beta Major Thalassemic Patients. Indian J Forensic Med Toxicol. 2022;16(1):913–9.
2. Faraj SA. Hemostatic parameters in Thalassemia patients; a single institute experience. J Fac Med Baghdad. 2016 Jul 3;58(2):132–5.
3. Makis A, Voskaridou E, Papassotiriou I, Hatzimichael E. Novel therapeutic advances in β-thalassemia. Biology (Basel). 2021;10(6).
4. Khaleel KJ. Thalassemia in Iraq Review Article. 2020;13(1):13–6.
5. Abed BA, Al-AAraji SB, Salman IN. Estimation of Galanin Hormone in Patients with Newly thyroid Dysfunction in Type 2 Diabetes Mellitus. Biochem Cell Arch. 2021;21(1):1317–21.
6. Chen X, Lin Y, Tian L, Wang Z. Correlation between ischemia-modified albumin level and coronary collateral circulation. BMC Cardiovasc Disord. 2020 Jul 8 ;20(1):1–7.
7. Nasser TH, El-Yassin HD, Yakoob S. B-Natriuretic Peptide Level as a Predictor for the Severity of LV Dysfunction. J Fac Med Baghdad. 2008;49(4):438–48.
8. DUTT A, KARIYAPPA M, RANGEGOWDA RK. Correlation of N-Terminal Pro-Brain Natriuretic Peptide (Nt Pro Bnp) With Serum Ferritin and Number of Blood Transfusions in Thalassemia Patients-a Cross-Sectional Study. Int J Curr Pharm Res. 2023;15(5):115–8.
9. Mohammed AG, Elmalah AA, Abdel R, Mohammad A. Biomarkers of Myocardial Dysfunction in Children with B-Thalassemia Major: Controlled Study. Saudi J Biomed Res. 2019;4(3):81–7.
10. Fan X, Li A, Yan Z, Geng X, Lian L, Lv H, et al. From Iron Metabolism to Ferroptosis: Pathologic Changes in Coronary Heart Disease. Oxid Med Cell Longev. 2022;2022.
11. Jagadish Kumar K, Jagadish Kumar K, Bhagiratha S, Vishwanath P. Evaluation of Ischaemia Modified Albumin as a Marker of Oxidative Stress in Beta Thalassemia Major Children.researchgate.net. 2021;41.
12. Shevtsova A, Gordiienko I, Tkachenko V, Ushakova G. Ischemia Modified Albumin: Origins and Clinical Implications. Dis Markers. 2021;2021.
13. Awadallah S. Protein Antioxidants in Thalassemia [Internet]. 1st ed. Vol. 60, Advances in Clinical Chemistry. Elsevier Inc.; 2013. 85– 128 p. Available from: http://dx.doi.org/10.1016/B978-0-12-407681- 5.00003-9
14. Patanè S, Marte F. Abnormal troponin I levels in a thalassemia major patient with high ferritin concentration, permanent atrial fibrillation and without acute coronary syndrome. Int J Cardiol . 2010;138(2):e24–7.
15. Akiki N, Hodroj MH, Bou-Fakhredin R, Matli K, Taher AT. Cardiovascular Complications in β-Thalassemia: Getting to the Heart of It. Thalass Reports 2023, Vol 13, Pages 38-50. 2023 Jan 30;13(1):38–50.
16. Higashi Y. Roles of Oxidative Stress and Inflammation in Vascular Endothelial Dysfunction-Related Disease. Antioxidants. 2022;11(10)

Arabic Abstract

خلفية البحث: بيتا ثلاسيميا الكبرى هو اضطراب وراثي منتشر في جميع أنحاء العالم ينشأ من نقص سلاسل الجلوبين. الألبومين المعدل الإقفاري هو أحد أنواع بروتين الزلال الذييتم إنتاجه استجابةً للإجهاد التأكسدي. إنه بمثابة علامة حيوية للدم لتلف الأنسجة ونقص تروية عضلة القلب. أمراض القلب والأوعية الدموية هي مشكلة صحية عالمية واسعة النطاق تؤدي إلى الوفيات. من أجل منع تطور المرض بشكل فعال وإدارة العلاج المناسب، من الضروري تشخيص الحالة في مراحلها المبكرة من خلال فحص مدى الضرر الذي يصيب القلب.

الاهداف: قياس مستويات الألبومين المعدل الإقفاري في المرضى الذين يعانون من الثلاسيميا الكبرى ومقارنتها بمستويات الأفراد الأصحاء. بالإضافة إلى ذلك، نحن نهدف إلى تقييم العلاقة بين مستويات الألبومين المعدل الإقفاري وببتيد مدر الصوديوم الدماغي نوع ب .

المرضى وطرق العمل/ المواد وطرق العمل: تم تسجيل ستين مشاركا في هذه الدراسة من أجل تقييم مستويات الألبومين المعدل الإقفاري في مصلهم. تم تضمين 30 مريضًا من مرضى بيتا الثلاسيميا الكبرى و30 شخصًا سليمًا في هذا البحث، ولم تظهر عليهم جميعًا أي علامات لأمراض القلب. تم استخدام طريقة الالايزا لتحديد مستويات الألبومين المعدل الإقفاري وببتيد مدر الصوديوم الدماغي نوع ب في الدم .

النتائج: مصل الألبومين المعدل الإقفاري وببتيد مدر الصوديوم الدماغي نوع ب زاد في مرضى بيتا ثلاسيميا الكبرى بالمقارنة مع الأشخاص الأصحاء. لم يكن هناك ارتباط بين مصل الألبومين المعدل الإقفاري وببتيد مدر الصوديوم الدماغي نوع ب في مجموعة المرضى .