CAHIERS MAGELLANES-NS
Volume 06 Issue 1
2024

ISSN:1624-1940
DOI 10.6084/m9.figshare.2632574
http://magellanes.com/

SERUM LEVELS OF ADMA AND DYSLIPIDEMIA AS PREDICTIVE INDICATORS OF HEART DISEASE IN PA TIENTS WITH BETA-THALASSEMIA MAJOR

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Abstract

The impaired production of the β-globin chain results in β-thalassemia major (β-TM) which is a genetic disorder. The absence or defect in the β-globin chain leads to an excess of α-globin, leading to red blood cell (RBC) damage. Hemolysis causes anemia and requires continuous blood transfusions to survive. Iron overload is an indicator of β-TM. Many complications result from iron overload, such as heart disease. The objective of this study is to assess the asymmetric dimethylarginine (ADMA), lipid profile, and fatty acid binding protein 4 (FABP4) as potential indicators of cardiac disease in individuals with β-TM. Ninety children participated in this study. Sixty patients and thirty controls. All patients and controls are similar in age, and they are close in body mass index (BMI). Serum total cholesterol (TC), triglyceride (TG), and high-density lipoprotein cholesterol (HDL-c) were measured by colorimetric methods. Very low-density lipoprotein cholesterol (VLDL-c), low-density lipoprotein cholesterol (LDL-c),

Key words: Cardiac disease, anemia, Iron overload and Asymmetric dimethylarginine

1.Introduction

β-Thalassemia major (β-TM) is a prevalent hereditary condition that is seen around the globe. This condition is the result of a reduction in the formation of β-globin chains (1) . This reduction in β-globin chain leads to an increase in the formation of α-globin chains. The disparity between α and β-globin chains results in the impairment of red blood cells (RBCs). The process of hemolysis leads to the development of anemia. Continuous blood transfusion is necessary for the survival of people with β-TM. This disease is associated with numerous problems, but the main one is iron overload, which occurs as a result of blood transfusions and increased absorption of iron from the gastrointestinal system. Excessive accumulation of iron results in damage, specifically to the heart, liver, and endocrine glands.(2).

Eighty to ninety million people worldwide, or around 1.5% of the total population, are β-TM carriers (3). In 2023, the estimated total number of thalassemia cases registered in Iraq will be 13390, or approximately 3.4 per 10,000 people.(3).

Iron overload affects the cardiac organ, which is not the first target organ. This condition leads to cardiac iron overload, or iron overload cardiomyopathy (5, 6). The prevalence of cardiovascular diseases in β-TM patients is approximately 71%, and it still remains the major cause of death.(4).

Dyslipidemia has been recorded in β-TM in many studies (2). Children with β-TM are strongly

ISSN:1624-1940
DOI 10.6084/m9.figshare.2632574
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suspected of having subclinical atherosclerosis, according to recent literature.(5). Research has also shown a significant correlation between dyslipidemia and early atherosclerosis as a developing problem in these patients. Subclinical atherosclerosis initiates at an early stage in life and has the potential to progress into coronary heart disease in the future (6).

2.Methodology

-Subject

Patients: Sixty patients (31 female and 29 male) with β-TM participated in the present study. Their average ages, BMI and Hb, were 10.38±2.37 years and 15.45±2.97 kg/m2 (8.11±1.61), respectively. During the period between December 2023 and March 2024, these patients were attended to Al-Zahraa hospital (the Thalassemia and Hematology Center) in Najaf governorate, Iraq. The diagnosis of thalassemia was made based on clinical signs and symptoms as well as a biochemical test for each patient. Patients with infection and inflammation, heart and kidney conditions, diabetes, thyroid disease, and patients from non-Arabic ethnic groups were excluded from the current study.

Controls: An apparently healthy group of 30 people (13 male and 18 female) was chosen. Their ages were similar to those of the β-TM patients. The mean of BMI and Hb for the controls was 16.69±2.99 kg/m2 (14.11±1.21). Any person with cancer, anemia, chronic systemic diseases, diabetes, or thyroid disease was excluded.

Biochemical Studies

According to the Genetic and Rare Diseases Information Center (GARD) criteria, thalassemia was identified and diagnosed based on either current medication use, medical history, or both. Colorimetric methods were used to Evaluate the levels of triglyceride (TG) , total cholesterol (TC) , and high-density lipoprotein cholesterol (HDL-c) in the blood. The equations were used to compute the levels of very low-density lipoprotein cholesterol (VLDL-c), low-density lipoprotein cholesterol (LDL-c), atherogenic index of plasma (AIP), Castelli's Risk Index (CRI-I), Castelli's Risk Index (CRI-II), and atherogenic coefficient (AC). Fatty acid binding protein 4 (FABP4) and Asymmetric dimethylarginine (ADMA) were measured by the ELISA technique.

All patients and controls are fasting. A disposable needle and plastic syringes were used to draw 5 ml of venous blood from each patient and control subject. Two anticoagulant tubes and gel tubes were used to separate the blood. The blood in the gel tube was left at room temperature for 15 minutes to clot. The serum was separated from the blood in disposable tubes and centrifuged at 3000 x g for 5 minutes.

-Statistical analysis

The statistical analysis was presented in the form of the mean ± standard deviation. The comparison between the patients and control groups in the assessed parameters was conducted using a pooled t-test. The statistical analyses were conducted using the SPSS program, with a significance level set at $P< 0.05$.

ISSN:1624-1940
DOI 10.6084/m9.figshare.2632574
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3.Results and Discussion

Comparison between Patients and Control

-Lipid profile

Parameters	Patients (60) Mean ±SD	Controls (30) Mean ±SD	p-value
TC mg/dl	90.54±15.34	108.55±12.97	<0.001
TG mg/dl	144.49±43.07	100.5±37.38	<0.001
HDL-c mg/dl	28.13±9.39	36.97±9.85	0.0001
VLDL-c mg/dl	28.89±6.10	20.82±8.47	<0.001
LDL-c md/dl	30.48±18.71	50.74±15.17	<0.0001
AIP	0.69±0.23	0.42±0.23	0.0001
CRI-I	3.33±0.94	2.97±0.66	0.0375
CRI-II	1.36±0.480	1.32±0.42	0.675
AC	2.33±0.94	1.86±0.66	0.0374

The results in Table 1 of lipid profile variables in healthy controls and patients with β-TM are presented. All lipid profiles were significantly decreased except TG and VLDL-c significantly increased in patients than controls. The atherogenic index of plasma (AIP), Castelli's risk index (CRI-II), and atherogenic coefficient (AC) were significantly higher in β-TM patients as compared to the healthy group. Castelli's Risk Index (CRI-I) is not significant between the two groups. The patients with B-TM have shown abnormal lipid activity or dyslipidemia.

Table (1): Comparison between lipid profile levels in patients and control.

Abbreviations: total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-c), very-low-density lipoprotein cholesterol (VLDL-c), low-density lipoprotein cholesterol (LDL-c), atherogenic index of plasma (AIP), Castelli's Risk Index (CRI-I), Castelli's Risk Index (CRI-II), and atherogenic coefficient (AC).

The lower levels of TC, HDL-c, and LDL-c in individuals with β-TM may be attributed to increased erythropoietic synthesis, which leads to higher cholesterol demands, as well as liver damage caused by excessive iron accumulation. Furthermore, the primary factor that determines low levels of cholesterol in the blood plasma of patients with β-TM is the enhanced absorption of LDL by macrophages and histiocytes of the reticuloendothelial system.**(7)**. Other reasons for dyslipidemia in BTM are less activity, different pathophysiologic pathways, defects in cytokine release, hormonal disturbances, and oxidative stress. These results correspond with other research by Jabbar et al. in Iraq (10), Daswani et al. in India (6). Arica et al. in Turkey (11). and in Egypt, Sherief et al. **(8)**.

A decrease in extrahepatic lipolytic activity leads to an increase in TG and VLDL-c, which may explain the elevated levels of circulating TG in thalassemic individuals (9). Iron overload, steatosis, and persistent viral infections resulting from recurrent hemotransfusions can trigger a hepatic acute-phase response, which is linked to increased VLDL secretion.(7). Increased TG, VLDL-c, and HDL-c levels increase the risk of vascular complications due to iron overload and a pro-inflammatory environment (9). Endothelial dysfunction increases arterial thickness and is noted as a significant risk factor for

ISSN:1624-1940
DOI 10.6084/m9.figshare.2632574
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atherosclerosis (10). This result is in agreement with the Egypt study (7), but different from the Iran study, which found no significant difference between patients and controls in TG and VLDL-c. (9).
There is a significant increase in AIP, CRI-I, and AC in children compared to controls, while there is no significant difference in CRI-II. This results in agreement with Sanghamitra et al.(10). Serum TG and HDL, both independent risk factors for coronary artery disease form the basis for the calculation of AIP (11). The few other clinically significant indexes that predict risk factors for CAD include CRI-I, CRI-II and the AC (12). Recent studies have indicated that AIP not only reflects the relationship between protective and atherogenic lipoproteins but is also a strong predictor of atherosclerosis and coronary heart disease (13). Further research found that an increase in AIP was associated with a 43% higher risk of cardiovascular events, whereas the per-unit increment of the TG/HDL-C ratio was associated with an 8% higher risk of cardiovascular complications, and it was concluded that the TG/HDL-C ratio may be useful in the prediction and prevention of cardiovascular disease (11).
There are few studies analyzing lipid indexes in children with thalassemia-dependent blood transfusions. A recent study performed on children with thalassemia-dependent blood transfusions found elevated levels of AIP and CRI-1 similar to those in our study (12). A separate study, published in 2018, shown a strong correlation between the indexes of atherogenicity, specifically the AIP, and nutritional status, abdominal obesity, and measures of insulin resistance in children with beta thalassemia (13). lipid profile abnormality, which is significantly correlated with increased ferritin level due to iron overload complication in β-TM patients with multiple blood transfusion(14)

-Asymmetric dimethylarginine (ADMA)

The result of ADMA appears in Table 2. There is a significant increase (P = 0.039) in levels of ADMA in patients as compared with the healthy group.

Parameters	**Patients (60) Mean ±SD**	**Controls (30) Mean ±SD**	**p-value**
ADMA (ng/l)	0.204± 0.027	0.188±0.034	0.027

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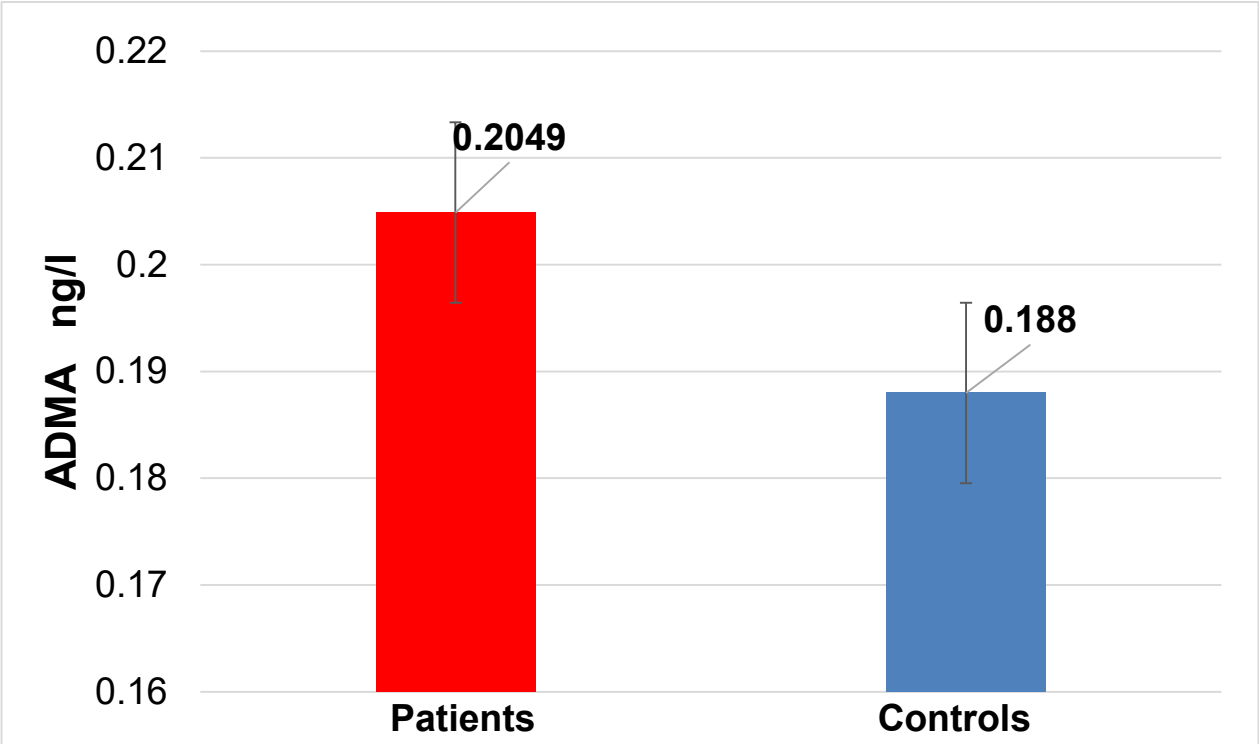

Figure 1: ADMA level in patients and control.

In the present study, similar to Gursel et al.'s study, it was found that there was an there was an increase in ADMA in β-TM in healthy children. Elevated plasma levels of ADMA in children diagnosed with β-TM could potentially serve as an early indicator of impaired endothelial function and contribute to the progression of premature atherosclerosis in patients with β-TM (15).ADMA plasma concentrations are elevated in patients with nearly all risk factors for atherosclerosis, including dyslipidemia(16).

Asymmetric dimethylarginine (ADMA) plays a detrimental role in cardiovascular health. It acts as a roadblock for the enzyme endogenous nitric oxide synthase (NOS) that produces nitric oxide (NO) and increases oxidative stress. NO is a molecule essential for maintaining healthy blood vessels and heart function (17). The ADMA is inhibited synthesis NO molecules in in macrophages (18) and in endothelial cells(19).

In addition to its function in facilitating endothelial dysfunction, ADMA also has the capacity to trigger oxidative stress by encouraging the dissociation of NOS (20).

Increased amounts of ADMA hinder the action of NOS and encourage the separation of NOS, which leads to the production of reactive oxygen species (ROS) and peroxynitrite ions (ONOO). These substances are responsible for causing oxidative stress within cells, which ultimately results in cellular damage (21). Therefore, high levels of ADMA in the bloodstream are linked to more severe coronary artery disease (CAD), worse outcomes after heart attacks (ischemia/reperfusion injury), and a buildup of fatty deposits in the coronary arteries (atherosclerosis). Elevated concentrations of ADMA stimulate inflammation and fibrosis in endothelial cells, potentially playing a role in the initiation and progression of microangiopathy (22). This makes

ISSN:1624-1940
DOI 10.6084/m9.figshare.2632574
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ADMA a significant risk factor for heart attacks and other cardiovascular problems(23, 24). Elevated levels of ADMA are associated with common cardiovascular risk factors like diabetes, hypertension, and hypertriglyceridemia, contributing to endothelial dysfunction and major adverse cardiovascular events (25, 26). Elevated ADMA levels revealed higher levels of lipid content in the plaques. This suggests a potential link between ADMA and lipid accumulation within the plaques, indicating a possible role of ADMA in plaque vulnerability and long-term outcomes in coronary artery disease patients (27).

Researchers have shown that ADMA drives lipid accumulation via a novel NO-independent pathway involving the calcium-sensing receptor (CaSR). In adipocytes and liver cells, ADMA activates the mammalian target of rapamycin (mTOR) signaling and upregulates lipogenic genes, resulting in increased triglyceride content. This lipid accumulation can be inhibited by blocking CaSR, indicating that ADMA potentiates CaSR signaling through G alpha protein subunit (Gq) and , G protein subtypes (Gi/o) pathways (28).

A symmetric dimethylarginine (ADMA) is a molecule that can increase the amount of fat stored in cells by activating a specific receptor called the calcium-sensing receptor (CaSR) in a way that does not involve nitric oxide (NO) synthase. When ADMA interacts with CaSR, it triggers a signaling pathway known as the mammalian target of rapamycin (mTOR), which is crucial for cell growth and fat production. This activation leads to an increase in the expression of genes that are responsible for making fats, resulting in higher triglyceride levels in cells (29).

Iron overload could potentially be another cause for increased ADMA levels, since it can decrease the bioactivity of endothelium -derived NO and lead to higher ADMA levels. (30). Iron overload leads to increased levels of ADMA in the serum, while decreasing nitric oxide (NO) levels. The reason for this is that dimethylarginine dimethylaminohydrolase II (DDAHII) expression and activity are stopped, and endothelial nitric oxide synthase (eNOS) is phosphorylated in aortic tissue. ROS are made by the extra iron ions in the cytoplasm. These ROS start the ADMA/eNOS/DDAHII/NO pathway. This pathway, along with the ROS-induced ROS release (RIRR) mechanism, creates a vicious cycle leading to mitochondrial dysfunction and damage in vascular endothelial cells (31). Excess free iron within cells, known as the "labile iron pool", can lead to the overproduction of ROS (32, 33). ROS can decrease the activity of the enzyme dimethylarginine dimethylaminohydrolase (DDAH), which is responsible for metabolizing ADMA. This leads to ADMA accumulation (34), ROS inhibit DDAH activity, thereby reducing ADMA degradation(35).

-Fatty acid binding protein 4 (FABP4)

There is a significant decrease ($P < 0.001$) in patients with beta thalassemia major compared to controls. This result is shown in Table 3.

ISSN:1624-1940
DOI 10.6084/m9.figshare.2632574
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Table 3: FABP4 in patients and control.

Parameters	Patients (60) Mean ±SD	Controls (30) Mean ±SD	p-value
FABP4 (ng/l)	21.31±9.45	34.08±9.8	<0.001

The result of FABP4 appearance in Table 2 indicates a decrease in levels of FABP4 in patients as compared with the healthy group.

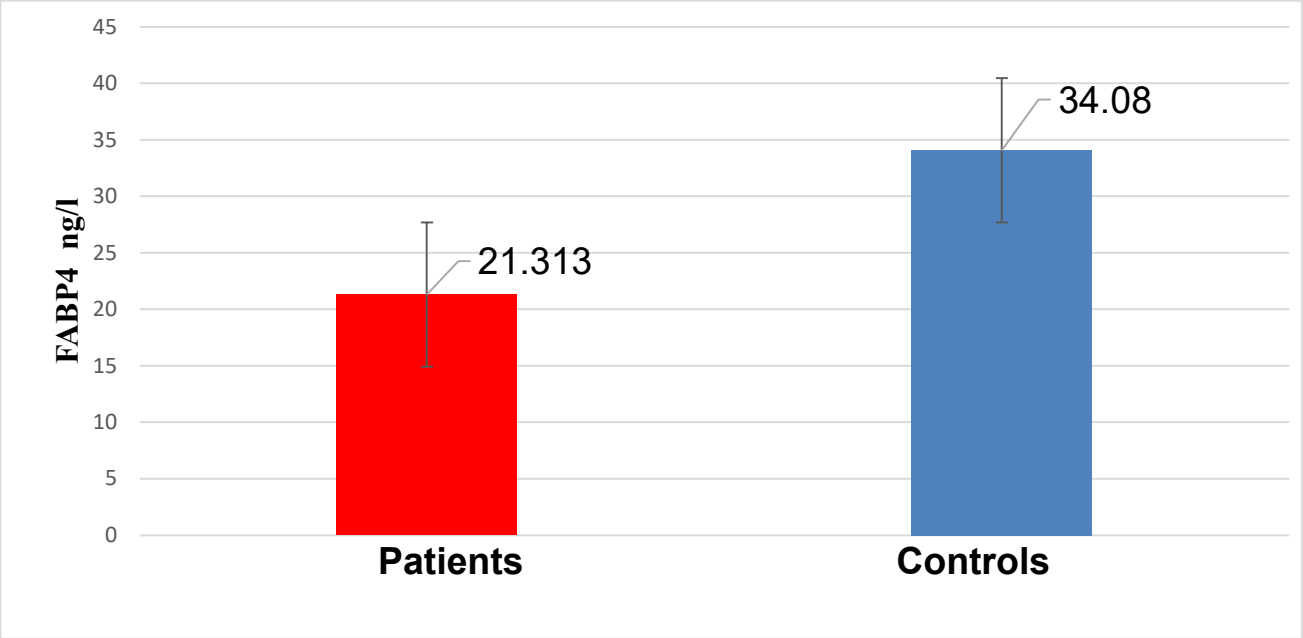

Figure 2: FABP4 level in patients and control.

This result differs from others, where Fianza et al (36) . and Eman et al (37) found that FABP4 increased in patients with β-TM. This decrease is due to increased ferritin levels in β-TM patients. According to an Egypt study, the correlation between ferritin and FABP4 is opposite (37). Another reason to decline FABP4 may be a decrease BMI in these patients, where FABP4 is secreted from adipose tissue.(38) (39). A high-protein diet significantly reduces circulating FABP4 levels compared to a high-carbohydrate diet, suggesting dietary modifications as a potential strategy to lower FABP4 and improve metabolic health(40).

Several investigations have discovered that the level of FABP4 is higher. This rise is associated with the metabolic and inflammatory pathways that are influenced by the accumulation of iron and its harmful effects in individuals with thalassemia major (41).

ISSN:1624-1940
DOI 10.6084/m9.figshare.2632574
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Other studies have also found FABP4 may play a role in the development of complications in thalassemia, as it connects various aspects of metabolic and inflammatory processes(41). FABP4 levels are linked to myocardial lipid storage and insulin resistance in type 2 diabetes, suggesting its role in diabetic cardiomyopathy. Inhibition of FABP4 can improve cardiac lipid metabolism and insulin signaling(42).

Increased circulating FABP4 levels have been linked to insulin resistance and obesity, according to reports, as well as heart failure, atherosclerosis, hypertension, and type 2 diabetes(38). Circulating FABP4 levels have been positively associated with triglyceride levels in multiple studies (43)

Conclusion

Patients with beta thalassemia had dyslipidemia, elevated ADMA, and decreased FABP4. High levels of ADMA and atherogenic index have been shown to be risk predictors of cardiovascular events and all-cause cardiovascular mortality in children with β-TM. Low levels of FABP4 may be because of increased ferritin levels and decreased BMI.

Ethical approval:

Ethical approval and consent to participate

The research was approved by the University of Kufa's institutional ethics board (8298/2024). All controls and patients as well as their guardians (parents or other close family members) gave written informed consent prior to participation in this study.

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