ULTRASONOGRAPHIC SCREENING FOR PREMATURE ATHEROSCLEROSIS IN TRANSFUSION-DEPENDENT THALASSEMIA PATIENTS BY MEASURING CAROTID INTIMA-MEDIAL THICKNESS (CIMT)

BY
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B.L.D.E (DEEMED TO BE UNIVERSITY)

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In partial fulfilment of requirements for

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RADIO DIAGNOSIS

Under the guidance of

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I hereby declare that this dissertation entitled **"ULTRASONOGRAPHIC SCREENING FOR PREMATURE ATHEROSCLEROSIS IN TRANSFUSION DEPENDENT THALASSEMIA PATIENTS BY MEASURING CAROTID INTIMA-MEDIAL THICKNESS CIMT"** is a genuine research work carried out by me under the support and guidance of **Dr RAJASEKHAR MUCHCHANDI**, M.D, Radiodiagnosis, Professor and Head of the Department, Department of Radiology, B.L.D.E (Deemed to be University) Shri. B.M. Patil Medical College and Research Centre, Vijayapura.

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ABBREVIATIONS

Beta TM	-	Beta Thalassemia Major
CIMT	-	Carotid Intima Medial Thickness
Hb	-	Hemoglobin
TDT	-	Transfusion Dependent Thalassemia

ABSTRACT

INTRODUCTION:

Patients with thalassemia major, a chronic hemoglobinopathy that need lifelong transfusions, are at risk for early atherosclerosis and other complications. The usefulness of carotid intima-media thickness ultrasonographic assessment as a noninvasive screening method for early atherosclerotic changes in patients with transfusion-dependent thalassemia was investigated in the dissertation due to the urgency and significance of early detection.

METHODOLOGY:

In the cross-sectional investigation, we tried to compare a cohort of transfusion-dependent thalassemia patients to age- and sex-matched healthy controls. CIMT was measured using standardized ultrasonographic procedures, and the results were compared to biochemical indicators such as lipid profiles, serum ferritin, and inflammatory indices. The association between iron burden and vascular changes was evaluated using sophisticated statistical techniques, such as regression analysis and correlation research.

The results of our study are significant, showing that CIMT values were considerably more significant in thalassemia patients than in controls, with a strong link between increased CIMT and blood ferritin levels. These results imply that one of the leading causes of early atherosclerosis in this population may be iron-induced endothelial dysfunction. The study emphasizes how early intervention techniques to reduce cardiovascular risk may be made possible by routinely integrating CIMT screening into

clinical practice, enlightening us on the potential for improved patient outcomes.

CONCLUSION:

The dissertation demonstrates that CIMT evaluation by ultrasonography is practical, noninvasive method for the early identification of subclinical atherosclerosis in patients of transfusion-dependent thalassemia. This early diagnosis can guide prompt treatment decisions and potentially improve long-term cardiovascular outcomes. However, further longitudinal research is needed to investigate the causative pathways and assess how targeted therapies affect disease progression, enhancing our understanding and treatment of thalassemia-related atherosclerosis.

Keywords: Cardiovascular Risk, Iron Overload, Ultrasonography, Atherosclerosis, Carotid Intima-Media Thickness, and Thalassemia.

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1. INTRODUCTION

The lack or absence of Z1 chains in adult hemoglobin (Hb) defines the group of diseases known as thalassemia (1). A kind of hereditary blood disease, thalassemia lowers hemoglobin, the oxygen-carrying protein found in red blood cells.

β-TM is the most often occurring hereditary blood disorder worldwide. Iran belongs to the thalassemic belt; the northern and southern areas along the Persian Gulf and Caspian Sea have higher prevalences (about 10%) (2–5).

Many hematological conditions, such as sickle cell disease, spherocytosis, aplastic anemia, myelodysplastic syndrome, glucose-6-phosphate dehydrogenase (G6PD) deficiency, and various types of beta-thalassemia, have been linked to lipid abnormalities (6–10). Although the precise cause of these abnormalities is still unknown, a number of theories have been put forth, including hormonal imbalances, anemia-induced liver dysfunction, accelerated erythropoiesis, which causes the reticuloendothelial system's macrophages and histiocytes to absorb more cholesterol, and anemia-induced plasma dilution (8, 11–16).

Regular blood transfusions and higher gastrointestinal iron absorption expose thalassemic individuals to iron overload and injury to parenchymal

organs [17, 18]. Among patients with β TM, the severe transfusion-dependent phenotype of this condition, cardiovascular problems are still somewhat common even with chelation therapy improving survival. A hypercoagulable state and vascular endothelial activation have both been implicated in the higher-than-average frequency of vascular complications.[17–21].

Usually occurring in the 3rd decade of life [20] in 1 % of individuals with beta-TM [19, 20], these thromboembolic events account for 4% of mortality [19].

Iron overload and thalassemia major may have a pro-atherothrombotic impact, according to earlier research. Increased nitric oxide destruction, LDL oxidation, stimulation of macrophage activity, and enhanced platelet activation are some potential mechanisms in oxidative stress and hemolysis [21–25]. Although endothelial function, circulating cholesterol oxidation products, and perhaps vascular diseases have been linked to iron overload [27–32], thalassemia may accelerate atherogenesis by creating a procoagulant environment [26, 28–35].

Coronary artery disease will undoubtedly become one of the new CV problems when β-TM patients live longer (36). Atherosclerosis in β-TM patients is primarily preceded by vascular diseases characterized by increased arterial stiffness and endothelial dysfunction. Iron overload and

atherosclerosis susceptibility have been linked in a number of studies. Chronic blood transfusions caused oxidative tissue damage in b-TM patients, which led to endothelial dysfunction, the unavoidable precursor of atherosclerosis (37). Beta-thalassemia major has been associated with vascular dysfunction, such as arterial stiffness and endothelial dysfunction (38). Atherosclerosis has endothelial dysfunction as a principal predecessor, whereas arterial stiffness is a marker of increased risk for development (39). (40). In addition, various studies have established an association with iron burden and risk for atherosclerosis (41). Thus, beta-thalassemia major patients with the above-discussed potential risk factors will be susceptible to early-onset atherosclerosis.

Reduced flow-mediated dilatation of the brachial artery is regarded as an indicator of early atherosclerosis because of its correlation with atherosclerotic risk factors and prognostic prognosis [42]. Similarly, carotid artery intima-media thickness (IMT), a widely recognized indicator of subclinical atherosclerosis [43] and linked to incident and prevalent cardiovascular disease [46–51], is linked to cardiovascular risk factors such as fibrinogen, blood viscosity, and iron-related oxidative stress [42–45].

Immune dysregulation in β-TM patients is thought to be caused by a number of causes, including as iron overload, cytokine composition in

allogenic blood, antigenic stimulation from infections and transfusions, and stroma cells of hyperplastic bone marrow [52–61]. Additionally, β-TM patients' peripheral blood contains activated leukocytes [35], and their bone marrow erythroid precursors show enhanced apoptosis, which is thought to be linked to the development of carotid plaque [42, 43]. Therefore, given the distinctive, comparatively protective lipid profile, it makes sense—based on the information presented—that the proatherogenic state in beta-TM could be linked to the interaction of iron overload, increased oxidative stress, hemostatic disorder, endothelial activation, proinflammatory status, and thalassemia.

The current research examined the hypothesis that the CIMT of β-TM patients is higher.

Atherosclerosis (62), which is associated with systemic arterial stiffness.

The typical risk factors for atherosclerosis do not accurately predict major cardiovascular events (MACE). For diagnostic reasons, clinical trials look for non-invasive ways to link native coronary artery disease to cardiac risk. One of the often used surrogates for the prediction of cardiovascular event rates is carotid intimal-medial thickness (CIMT) by B-mode ultrasonography, a method that was established and validated in the middle of the 1980s. Recently, CIMT has been used as a diagnostic tool in clinical trials to assess how well medications like statins lower cardiovascular risk

and slow the progression of vascular disease. Age-related thickening CIMT of common carotid arteries, as demonstrated in human and animal models, can also occur without overt atherosclerosis, which reduces the validity of CIMT (75). It is important to remember that pathological alterations like medial hypertrophy or intimal thickening that do not occur in the presence of atherosclerosis are not the same as atherosclerosis. Because the two conditions share underlying mechanisms for the development and progression of the disease, the pathologist believes that CIMT is a more accurate measure of the overall risk of coronary heart disease than a precise assessment of atherosclerosis per se, as demonstrated by multiple trials. It is well recognized that non-inflammatory, smooth muscle-rich intimal thickening plaques and atherosclerosis have different distributions. Usually found in low-shear areas, carotid atherosclerosis is mainly restricted to the bulb region and is invisible on B-mode ultrasound. Conversely, intimal thickening occurs in more proximal parts of the common carotid artery at the bifurcation as a result of excessive shear, or hypertension, and aging. Compared to atherosclerosis, intimal thickening is easier to detect by B-mode ultrasonography as CIMT since it is dependent on its location in the common carotid (75).

Carotid Plaque Morphology

Despite these variations, there are many morphologic parallels between the development of coronary and carotid atherosclerosis. Adaptive intimal thickening, or early flow-dependent neointima, usually appears in all arterial beds soon after birth. A proteoglycan/collagen matrix, a few inflammatory cells, and smooth muscle cells produce the lesions. According to the majority of researchers, adaptive intimal thickening is not a mechanism associated with atherosclerotic disease. The fatty streak, also known as intimal xanthoma, is the first recognized atherosclerotic lesion. It manifests as yellow, non-raised streaks made up of intracellular and extracellular lipids, as well as foam cells from smooth muscle cells and/or macrophages (75).

Intimal xanthomas are nonprogressive and typically regress, according to observational evidence. It was observed that the onset of atherosclerosis is caused by aberrant thickening of the intima (65). In the lower intima areas that are high in proteoglycan, lipid will build up; these lesions are characterized by speckled calcification and loss of smooth muscle cells.

When a basal lamina that is apparent around vesicle clusters is consistent with a smooth muscle cell origin and is in charge of SMC loss within lipid pools, apoptotic cell death can be more easily identified ultrastructurally (66). Macrophage invasion in PIT is not uniform and is primarily restricted

to the plaque's luminal surface, which is not part of the lipid pool. Advanced atheromatous plaques with necrotic cores are believed to develop as a result of macrophage invasion of lipid pools. It is believed that the release of active proteolytic enzymes, such as matrix metalloproteinases (MMPs), and other chemicals that break down nearby tissue and cause necrotic core development in conjunction with macrophage death, facilitates this crucial stage. It is believed that the acceleration of plaque rupture and acute thrombosis is mostly caused by the enlargement of the necrotic core and the decrease of the fibrous cap (67). Delineating the necrotic core using any imaging modality, such as MRI, multidetector CT (MDCT), or B-mode ultrasonography, may therefore be the most effective method of identifying rupture-prone susceptible plaques (75).

Normal Range

Normal CIMT in healthy middle-aged people is usually 0.6-0.7 millimeters. CIMT has been used in the majority of studies to establish the risk of atherosclerosis in children and adults. There have been very few such studies in children with TDT, however. Since there is a rise in life expectancy in such children, it is the responsibility of researchers to offer an early diagnosis of premature atherosclerosis.

2. HISTORICAL BACKGROUND

The word 'thalassemia,' which has Greek origins in 'Thalassa' (meaning 'the sea' in the Mediterranean Sea) and 'Emma' (having something to do with blood), holds an important historical and cultural significance. It is among the most common monogenic disorders due to defects in the globin gene. The genetics and molecular biology of thalassemia disorders have discovered more than 200 mutations in Southeast Asian and African populations. Thalassemia carrier rates in North Indians vary from 3% to 17% based on the ethnic group. About 90% of children older than one year have the main hemoglobin, HbA, and 23% have the minor hemoglobin, HbA2. HbF is the primary hemoglobin during fetal life, and barely traces of it remain after a year (68).

Structure of hemoglobin

Hemoglobin consists of four protein chains, consisting of two alpha and two beta globin chains. Deficiency or missing genes in the chain lead to thalassemia because defective hemoglobin formation occurs. The severity of the genetic defect in the alpha or the beta chain will indicate the level of thalassemia.

Pathophysiology:

A change in globin chain production results in thalassemia, a genetic disorder affecting haemoglobin synthesis.

Decreases in alpha, beta, gamma, and delta globin production rates cause haemoglobin synthesis to be delayed and disrupt the equilibrium of normally formed globin chains. Because both chains (alpha and non-alpha) mix in almost equal amounts to generate normal haemoglobin, there is an excess of the normally produced form of haemoglobin. Because it is an unstable product, it builds up inside the cell and prematurely breaks down the red cell. It is common to refer to the kind of thalassemia by the chain or chains that are either absent or underproduced. The decline may be minimal, or it may be non-existent (68).

β- TM refers to a decreased rate of beta chain synthesis, whereas β-TM denotes a complete lack of beta chain synthesis from the afflicted allele. The illness is inherited in a Mendelian recessive manner. With the development of molecular genetics, significant progress has been made in the treatment of thalassemia. Carriers are quite simple to find and filter. Because of prenatal diagnosis and genetic counselling programs, the number of newborns born with thalassemia major has drastically decreased in the majority of countries (68).

Clinical presentation:

It is important to test for thalassemia in children who have hypochromic, microcytic anemia that does not improve with iron therapy. Children with thalassemia major are often asymptomatic until they are a few months old, at which point chaining is required to join up with chains to create HbA. After chain synthesis is stopped, however, symptoms typically do not appear.

Because HbF production occasionally does not stop until a kid is three to five years old, the issue could go unnoticed.

Almost always, there is hepatosplenomegaly and noticeable pallor. Icterus would be uncommon, although mild to moderate jaundice might be observed as a result of iron overload-induced liver failure and chronic hepatitis. A variety of symptoms, including heart failure symptoms, irritability, murmurs, and intolerance to movement, might be indicative of severe anemia of thalassemia major. There are typically bony abnormalities of frontal bossing, prominent facial bones, and dental malocclusion. A hypermetabolic condition brought on by inefficient erythropoiesis is linked to tith fever and failure to thrive. Additionally, hyperuricemia may coexist, providing a full picture of the illness (68).

Management:

Avoiding further cases of thalassemia major in a family requires genetic counselling. Genetic counselling must be provided to the spouse and family so they are informed of the dangers and options. Prenatal testing highlights proactive measures that may be performed to combat thalassemia major by determining if the second kid in a household with this issue has the condition or not. Major thalassemia may be treated with hematopoietic stem cell transplantation. Families and patients might feel more at ease knowing that there are contemporary therapeutic options accessible. Additionally, it informs healthcare providers on the latest developments in thalassemia treatment (68).

Thalassemia major patients need medical follow-up to avoid complications.

For promoting growth and avoiding abnormalities, blood transfusions need to be initiated as early as the infant is asymptomatic, and attempts should be made to keep the pretransfusion hemoglobin at 9–10 g/dL.

To prevent organ failure, chelation treatment for the stored iron overload must be undertaken.

A normal diet must be adopted, and supplements of folic acid, alpha-tocopherol (vitamin E), and small doses of ascorbic acid (vitamin C) must be consumed.

The administration of iron preparations as hematinic or dietary supplements is not advisable. Intake of tea with meals has been shown to inhibit the absorption capacity of the gut for iron. Infections and Blood Transfusions Transfusion reactions or alloimmunization of red cell antigens are common symptoms in patients who undergo many transfusions. Leukocyte filters at the time of transfusion or leuko-poor-packed red blood cells processed by the blood banks can minimize such issues. Acetaminophen and diphenhydramine hydrochloride are given before transfusions to minimize the risk of allergic or febrile reactions. The most significant concerns are those regarding blood-borne viral transmission (68).

Routine management involves hepatitis B immunization and routine testing of HIV and hepatitis C status.

Ferritin levels are utilized to monitor iron overload, and folate supplements are required. A ubiquitous constituent of polymorphonuclear leukocyte granules, lactoferrin possesses bacteriostatic activity against many infections. In iron-overloaded patients, very high transferrin saturation undermines the protein's bacteriostatic activity, enhancing the risk of Y. enterocolitica infections presenting as fever and diarrhea. Iron Overload Iron overload ranks among the major causes of morbidity. High gastrointestinal iron absorption and repeated transfusions are responsible

for the excessive iron load. Besides decreased growth and sexual immaturity, patients have signs of endocrinopathy of the thyroid, parathyroid, and pancreatic glands. The simplest method to monitor iron status is to take serum ferritin. Liver biopsy, liver MRI, and echocardiogram are other tests (68).

One of the advanced and non-invasive techniques for assessing the heart's iron status is cardiac T2* magnetic resonance (CMR) (68).

Identification and early detection of atherosclerotic changes in people with transfusion-dependent thalassemia (TDT).

3. AIM AND OBJECTIVES

Identification and early detection of atherosclerotic changes in people with transfusion-dependent thalassemia (TDT).

4. SOURCE OF DATA

Patients at B.L.D.E (Deemed to Be University) Shri B.M. Patil Medical College Hospital and Research Centre.

Study setup - Tertiary care hospital

Type of study - Prospective cross-sectional study

Study Period - April 2022 - February 2025

5. INCLUSION CRITERIA

All patients with Thalassemia who are admitted to the pediatric department requiring blood transfusion at Shri B.M. Patil Medical College and Hospital.

Age: 2-16 years

Regular transfusion regimen for more than 6 months

6. EXCLUSION CRITERIA

Age groups less than 2 years and more than 16 years

Irregular transfusion

Nephrotic syndrome

Familial hyper cholesterolemia.

7. SAMPLE SIZE

Means: Disparity between two independent means (two groups) in t tests

Evaluation: From the outset: Determine the necessary sample size.

Enter: Tail(s) = 2.

Size of effect d = 0.6290981

α err probability = 0.05

1-β err prob power = 0.87

N2/N1 allocation ratio = 1.

Results: δ = 3.1454905 is the noncentrality parameter.

Df = 98, critical t = 1.9844675

Group 1 sample size = 50

Group 2 sample size = 50

The entire sample size is 100.

Real power is equal to 0.8758641.

To achieve a power of 87% for detecting a difference in Means: Inequality, two independent means (two groups) (t test) with a 5% level of significance, the BMI Study Group (Mean=17.34, SD=3.03) and Control Group (Mean=19.59, SD=4.05)5 uses G*Power software to calculate

sample size. This study requires a total sample size of 100 (for each group, 50, assuming equal group sizes).

8. STATISTICAL ANALYSIS

A Microsoft Excel sheet is used to enter the collected data, and a statistical package for the social sciences (SPSS) (Version 20) is used to do statistical analyses.

Means, SD, counts, percentages, and graphs are used to display the results.

An independent sample t-test will be used to compare the two groups' continuous variables that are normally distributed.

The Mann-Whitney U test is applied to variables that are not regularly distributed. The Chi-square test, often known as Fisher's exact test, is used to compare categorical variables between the two groups. A p-value of less than 0.05 is deemed statistically significant.

All statistics are performed two-tailed.

9. METHODOLOGY

It is a Prospective Cross-Sectional study.

All the patients who fulfilled the inclusion criteria were included in the study. Consents of the patients were taken once they were admitted.

Group 1: cases

Group 2: controls (patients of same age with no comorbidities)

Outcomes: The outcome measures recorded were:

This study involved physicians from the Department of Radiology in coordination with the Department of Pediatrics, ranging in rank from professors to junior residents. The approval of the Institutional Ethical Committee (IEC/75/2023-24) was acquired before the study started.

Machine: GE VOLUSON S8 BT 18; GE VERSANA PREMIER

Methods: ULTRASONOGRAPHY CAROTID DOPPLER

The common carotid arteries' intima-media thickness will be measured at a 1 cm segment near its bifurcation using electronic calipers, and the result will be reported in millimeters. The CIMT is the separation between the lumen and intima and the media and adventitia junctions.

The CIMT measurements will be carried out using the GE VOLUSON S8 BT 18 and GE VERSANA PREMIER duplex ultrasound systems, which have a linear array high-frequency transducer at 7.5 MHz scanning frequency in B mode USG.

Method of collection of data

- Informed written consent
- Detailed history
- Brief physical examination
- Imaging of the participant
- Histopathological examination

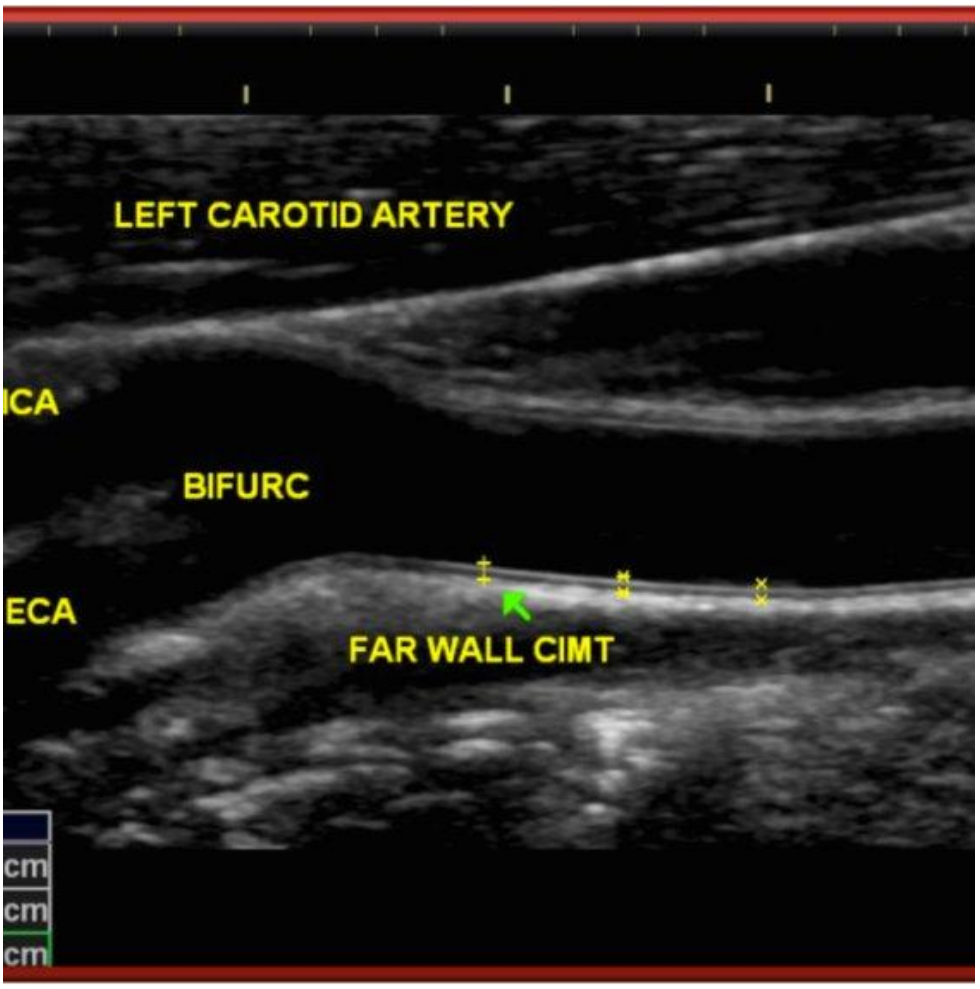

Figure 1 : demonstrate the ideal anatomical and radiological location to measure CIMT.

10. REVIEW OF LITERATURE :

1. KS Kumaravel et al. (2022) performed this case-control study to quantify "carotid intima-media thickness (CIMT) and examine its correlation with clinical and biochemical markers to evaluate the risk of premature atherosclerosis in children with transfusion-dependent thalassemia (TDT) compared to healthy controls. Children aged 2 to 15 years were included. In all age groups, children with TDT had significantly elevated CIMT levels. The 2–5 years, 6–10 years, and 11–15 years age groups had mean (SD) CIMT measurements of 0.27 (0.07) mm, 0.39 (0.03) mm, and 0.46 (0.05) mm, respectively, in the control group. The corresponding CIMT measurements for the TDT cases were 0.43 (0.08) mm, 0.55 (0.07) mm, and 0.63 (0.08) mm ($P<0.001$)". The liver enzymes and triglycerides also had significantly increased mean values in children with TDT. Through logistic regression analysis, it was determined that while dyslipidemia was not significantly related to elevated CIMT, increased serum ferritin levels and older age were. Overall, children with TDT are likely to have premature atherosclerosis, which underscores the need for early vascular health surveillance and treatment (69).

2. Ramy El Jalbout et al (2022)., "The carotid artery is typically employed to measure intima-media thickness (IMT), a recognized subclinical radiological marker of early atherosclerosis changes. It represents the vessel wall thickness and is assessed by radiofrequency ultrasound and conventional ultrasound, either automatically or manually. To improve the validity and comparability of results across studies, several guidelines have been established in light of the heterogeneity in IMT assessments, especially in youngsters". To avoid misinterpretation, quality control is crucial, and mistakes should be avoided. The latest studies on the clinical application of IMT measurement in children with risk factors such as obesity, liver steatosis, hypercholesterolemia, diabetes, hypertension, systemic inflammatory disorders, cancer survivors, kidney and liver transplant recipients, sickle cell disease, and β-thalassemia major are discussed in this paper. Outcomes need to be considered in combination with other markers, even though most potential uses of IMT remain in the realm of research. The onset of a multidisciplinary treatment process to prevent further development of the disease and its long-term consequences in adulthood is the goal of diagnosing increased IMT (70).

3. Seif El-Din Abaza et al (2017)., In a case-control study, 36 age- and sex-matched healthy controls and 42 β-TM patients (twenty-eight males and eighteen females) between the ages of three and thirty were included. All subjects' CIMT was measured using carotid duplex ultrasonography. Results: Nineteen percent of patients had abnormal CIMT. For the right anterior, right posterior, and right lateral, the mean CIMT measured 0.8 ± 0.16mm, 0.8 ± 0.17mm, 0.81 ± 0.17mm, 0.80 ± 0.17mm, and 0.81 ± 0.18mm, respectively. There were no differences detectable based on chelation status, splenectomy, or gender ($P > 0.05$). Disease duration was related to the CIMT of the right lateral wall ($r = 0.3$, $P = 0.04$). Conclusion: Despite iron overload status, carotid ultrasonography can measure subclinical atherosclerosis in patients with β-thalassemia major (71).

4. Hoda A Abdelsamei et al. (2015)., a study included 62 children with BTM and 30 age- and sex-matched controls. Both cohorts underwent carotid Doppler ultrasonography to assess CIMT, ferritin, serum cholesterol, and complete blood count, determined BTM patients to have a much higher CIMT compared to controls ($p=0.001$). Age, time elapsed since the 1st blood transfusion, s. cholesterol, and fe2+ overload markers (serum ferritin, number of transfusions, and iron chelation) were all directly related to CIMT. Inefficient iron chelation was another risk factor,

and the duration of the transfusion was the largest. CIMT was not significantly related to height, weight, BMI centiles, or hemoglobin values, although it did reflect a negative correlation with hematocrit (72).

5. Laila M Sherief et al (2014)., performed a cross-sectional study from March 2014 to March 2015 at the Pediatric Hematology Unit of Zagazig University Children's Hospital, Egypt, in 115 children. Sixty-five beta-thalassemia major (B-TM) patients between the ages of 5 and 18 years on regular transfusion regimens comprised the patient group, whereas 50 age- and gender-matched healthy children were the controls. All the subjects had clinical history assessment, physical examination, and laboratory examinations. The CIMT was also measured through a duplex ultrasound. Results: In comparison to controls, transfusion-dependent B-TM patients for 8.5 ± 3.8 years had significantly elevated levels of liver enzymes, bilirubin, CRP, and serum ferritin (2490 ± 1579 vs. 83 ± 32 ng/dL) (5.7 ± 5.7 vs. 0.9 ± 0.9). "They also presented lower concentrations of HDL-C (39 ± 2 vs. 61 ± 5, $p < 0.001$), LDL - C (44 ± 9 vs. 73 ± 6, $p < 0.001$), and cholesterol (116 ± 16 vs. 143 ± 5 p- value < 0.001), but higher concentrations of triglycerides (128 ± 20 vs. 101 ± 7 mg/dL, p - value = 0.009) and atherogenic index of plasma (0.45 ± 0.12 vs. 0.22 ± 0.04, p = 0.001)". In CAIMT, B-TM patients were significantly higher (Rt 0.62 ±

0.2 vs. 0.29 ± 0.07 mm; Lt 0.66 ± 0.17 vs. 0.29 ± 0.05 mm, p-value = 0.001) and positively correlated with OPG, triglycerides, and the atherogenic index. Concluded that Patients with beta-thalassemia appear to develop subclinical atherosclerosis at an earlier age than other individuals. Serum OPG and CAIMT, an easy non-invasive measurement, can be helpful early markers of atherosclerosis in this group (73).

6. Orhan Gursel et al. (2012)., A control group of 36 healthy children matched for age and a study group of 31 children (age range 4–16) who had β-thalassemia major were assessed. Apart from electrocardiographic, echocardiographic, and carotid IMT examination, ferritin, homocysteine, calcium, chitotriosidase, lipid profile, complete blood count, serum glucose, and nitrater/nitrite concentrations were also measured, determined that Serum VLDL cholesterol levels were higher in the study group, however, serum total cholesterol, LDL, and HDL concentrations were decreased significantly. The activity of chitotriosidase was increased, carotid IMT was increased, and plasma nitrater/nitrite concentration was lowered. The only variable that was significantly correlated with carotid IMT was nitrate/nitrite levels, and it was concluded that children with β-thalassemia are at major risk because subclinical atherosclerosis begins early (74).

7. Mustafa Dogan et al (2011)., The study included 30 healthy age- and gender-matched controls (18 boys and 12 girls, median age: 8 years) and 33 thalassemic children (22 boys and 11 girls, median age: 8 years). All patients underwent CIMT measurement with high-resolution ultrasonography. Concluded that The median time of diagnosis was 0.6 months, and the patients were diagnosed at 0.25 to 2 years of age. The median duration of their disease was 6.5 years, ranging from 4 to 13.75 years. Patients with thalassemia had a significantly higher median CIMT (0.87 mm compared with 0.74 mm, $p < 0.005$) than controls. Furthermore, there was also a strong correlation between the mean CIMT and blood ferritin concentration and duration of disease. Atherosclerosis and early vascular changes are more probable in beta-thalassemia major patients. As an early, non-invasive, diagnostic procedure for detecting vascular changes in this group of patients, common carotid artery CIMT measurement is recommended.

8. Sezaneh Haghpanah et al. (2010). This research study consisted of 130 age- and sex-matched healthy subjects, 55 BTM and 50 BTI patients. Hemoglobin (Hb) and ferritin levels and serum lipid profiles were studied in all of these groups. The significance level was set at $P < 0.05$.

There was no significant difference between BTM and BTI groups for age or sex.

Mean triglycerides in patients and controls were equal to each other.

Compared to the control group, patients with BTM and BTI had significantly lower levels of total cholesterol and LDL cholesterol ($P < 0.001$).

BTI patients also had significantly lower HDL cholesterol compared to controls ($P < 0.03$). Compared with healthy controls established that, BTM and BTI patients both had reduced levels of LDL and total cholesterol. Iron overload and oxidative stress in BTM patients and increased erythropoiesis and cholesterol utilization in BTI patients can be related to these lipid disturbances.

9. Azza A.G. Tantawy et al (2009.)., The current research compared patients with young beta-thalassemia major (β-TM) with patients with type 1 diabetes and healthy subjects to evaluate subclinical atherosclerosis and the relevant risk factors, including dyslipidemia. The ninety subjects were divided into three groups: thirty β-TM patients "(mean age 18.4 ± 6.18 years), 30 type 1 diabetes patients (mean age 19.23 ± 4.25 years), and 30 healthy controls comprised Group I. Hemoglobin (Hb) electrophoresis, serum ferritin, fasting lipid profiles, and high-resolution ultrasound

assessments of carotid artery intima-media thickness (CIMT) were assessed". It was found that both diabetic and thalassemic patients significantly possessed higher amounts of apoprotein A (ApoA), total cholesterol, and serum triglycerides along with higher CIMT in comparison to the controls. Contrarily, they possessed much less high-density lipoproteins (HDL). CIMT was found to have positive correlation with age, ferritin, cholesterol, and Hb F in thalassemia patients. These findings underscore the importance of high CIMT and atherogenic lipid profiles as key prognostic indicators of vascular risk stratification in young β-TM patients.

10. Cheung et al.'s 2006 research work on 20 beta-thalassemia major patients compared with healthy controls.

The authors compared 20 beta-thalassemia major patients with healthy controls. Key findings include, Elevated carotid IMT in patients compared to controls, with an odds ratio of 39 for increased IMT. Twenty patients with beta-thalassaemia major had their augmentation index and Young's elastic modulus (YEM) measured. In contrast to controls, patients exhibited higher. There were significant differences in the CIMT, stiffness and augmentation indices. In patients with high CIMT, the odds ratio was 39. These associations of carotid IMT with arterial stiffness indexes such

as Young's Elastic Modulus, stiffness index, and augmentation index. Beta-thalassemia status was recognized as an important determinant of raised IMT by multivariate analysis. These findings indicate that beta-thalassemia major patients may be more susceptible to premature atherosclerosis, moderated by arterial stiffness and vascular dysfunction.

11. RESULTS

In our study, of all 100 admissions, 50 pediatric cases have received blood transfusion for thalassemia and are classified under group 1. 50 controls are classified under group 2. The results of the study are described below

Age (Years)	Group 1	Group 2	Total	Chi square test	Significant value
< 5	6	0	6	6.542	0.088
%	12.0%	0.0%	6.0%		
5 – 9	15	16	31		
%	30.0%	32.0%	31.0%		
10 – 14	24	27	51		
%	48.0%	54.0%	51.0%		
15+	5	7	12		
%	10.0%	14.0%	12.0%		
Total	50	50	100		
%	100.0 %	100.0%	100.0%		
Statistically Insignificant					

Table 1: Mean Age of cases and controls.

This table indicates the allocation of participants into two groups (Group 1 and Group 2) among four age groups.

Six participants (6% of the total) were aged below five years, 12% in Group 1 and 0% in Group 2. 31 persons (31% of the total) were aged between 5 to 9; 30% were in Group 1 and 32% in Group 2.

51 of the participants (51% of the total) were aged 10 to 14; 48% were in

Group 1 and 54% were in Group 2. 12 participants (12% of the total) were aged 15 and above, with 10% being in Group 1 and 14% being in Group 2.

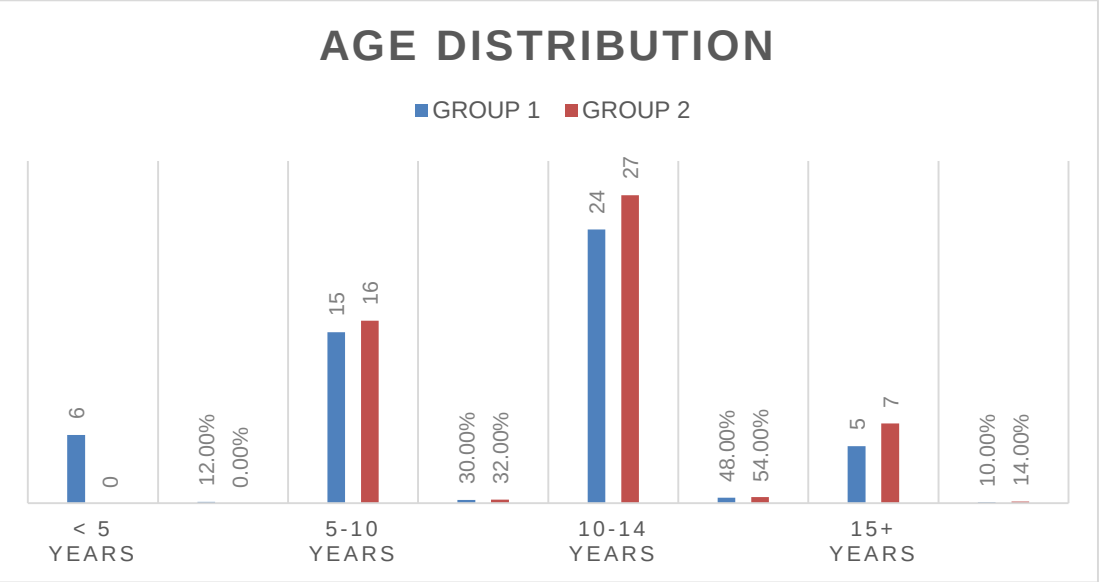

Figure 2: Mean Age of cases and controls.

The bar chart illustrates two groups' ages and shows the following trends: Group 1 consists of representatives of all age groups, but the under-5 age group has a special high representation. Group 2 has a slightly higher representation in higher age groups but no person below the age of five. The 10–14 age group is the largest age group, with the highest proportion in both groups. In age groups 5–10 & 15+, group distribution is fairly level with Group 2 enjoying a slight lead in the second case.

Gender	Group 1	Group 2	Total	Chi square test	Significant value
Female	24	28	52	0.641	0.423
%	48.0%	56.0%	52.0%		
Male	26	22	48		
%	52.0%	44.0%	48.0%		
Total	50	50	100		
%	100.0%	100.0%	100.0%		
Statistically Insignificant					

Table 2: Gender Distribution among cases and controls.

The gender distribution of participants in Groups 1 and 2 is shown in this table, along with a Chi-square test to see if gender and group membership are significantly correlated.

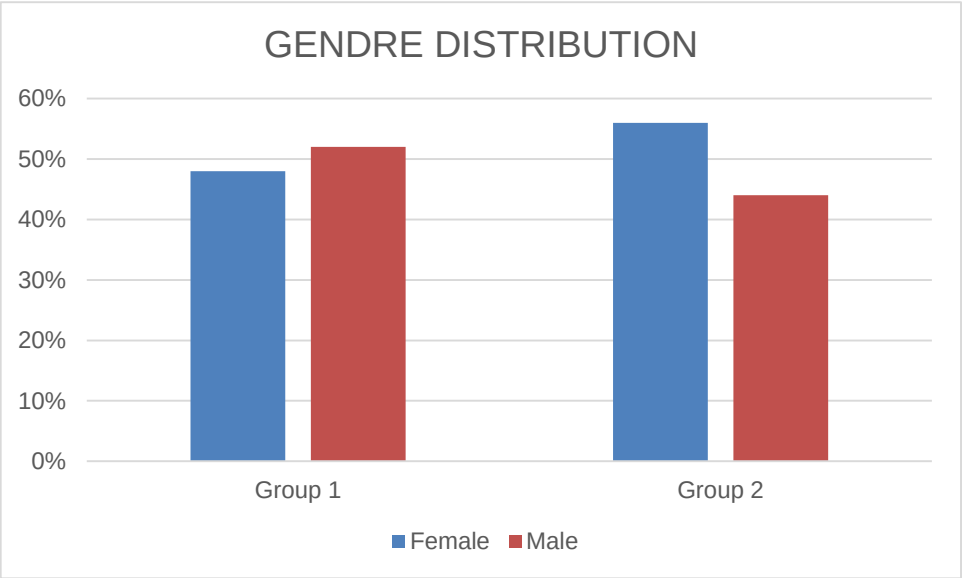

Figure 3: Gender Distribution among cases and controls.

The gender distribution statistics for the two groups shows:

Group 1 has a slightly higher ratio of males than females but a roughly equal gender balance.

With a slightly higher ratio of females to males, Group 2 is slightly skewed toward females.

With few exceptions, the gender ratio within both groups tends to be close to equal.

S. ferritin	Group 1	Group 2	Total	Chi square test	Significant value
Normal	4	50	54	88.679	.000
%	8.0%	100%	54.0%		
Raised	46	0	46		
%	92.0%	0.0%	46.0%		
Total	50	50	100		
%	100.0%	100.0%	100.0%		
Statistically Insignificant					

Table 3: Distribution of serum ferritin among cases and controls.

The comparison of serum ferritin (S. ferritin) levels between Group 1 and Group 2 is presented in this table, along with the results of a Chi-square test to identify whether group membership and ferritin status are significantly related. There is a significant difference between the two groups' serum ferritin levels. Ferritin levels in Group 2 are mostly normal, whereas those in Group 1

are mostly elevated.

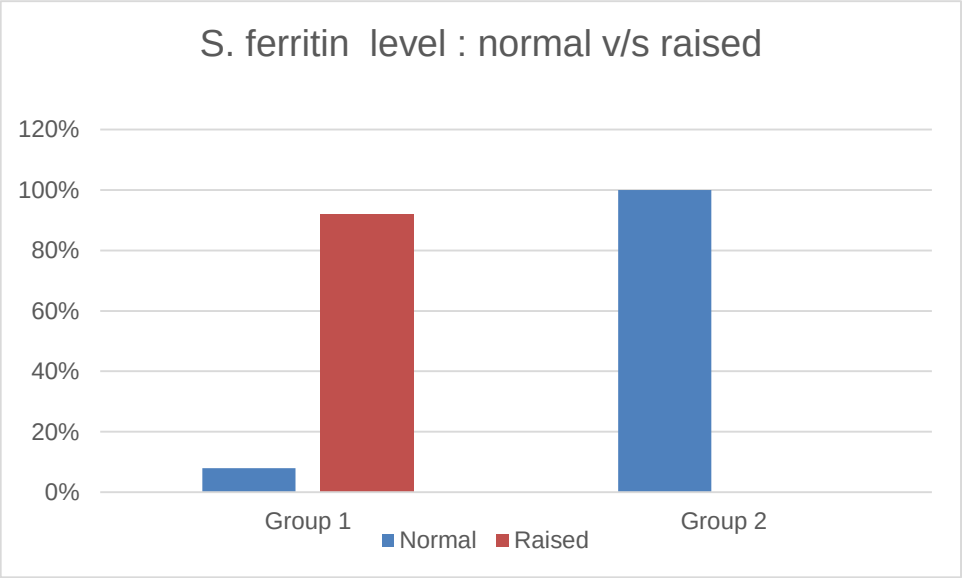

Image 4: Distribution of serum ferritin among cases and controls.

From the graph, Group 1 TDT patients predominantly have elevated serum ferritin levels (approximately 90%), reflecting a significant iron overload which is likely a consequence of chronic transfusions. All Group 2 members present with normal ferritin levels, reflecting effective iron control—likely through chelation therapy compliance or other intervention. These findings emphasize the importance of ensuring TDT patients with personalized iron-overload management and regular follow-up in a bid to prevent adverse outcomes.

Age(Years)	**Group 1**		**Group 2**		**Mann-Whitney Test**	**Significant value**
	Mean	Std. Deviation	Mean	Std. Deviation		
Age(Years	9.78	3.940	11.06	3.060	1044.500	**0.155**
Statistically Insignificant						

Table 4: Distribution of age (years) among cases and controls.

The age distribution (in years) of Groups 1 and 2 is illustrated in this table, together with the results of the Mann-Whitney test, a non-parametric technique for testing whether the distributions of two independent groups are the same. Age Distribution: Group 1 participants are, on average, 9.78 years old, while Group 2 participants are 11.06 years old. The standard deviations (3.94 and 3.06, respectively) indicate that the age distributions of the two groups are relatively identical.

The Mann-Whitney Test The p-value of 0.155 shows that the differences in age between the two groups are not statistically significant.

Height (cm)	**Group 1**		**Group 2**		**Mann-Whitney Test**	**Significant value**
	Mean	Std. Deviation	Mean	Std. Deviation		
Height (cm)	87.20	34.215	122.76	37.375	675.500	.000
Statistically Insignificant						

Table 5: Distribution of height (cm) among cases and controls.

As compared to Group 2, which also has a higher mean height of 122.76 cm and a standard deviation of 37.375 cm, the mean height of Group 1 is 87.20 cm with a standard deviation of 34.215 cm. This can be interpreted that the two groups' height distributions are different. The Mann-Whitney Test The 0.000 p-value

The height distributions of Groups 1 and 2 are statistically significantly different from each other. On average, Group 2 members are significantly taller than Group 1 members.

weight (kg)	**Group 1**		**Group 2**		**Mann-Whitney Test**	**Significant value**
	Mean	Std. Deviation	Mean	Std. Deviation		
weight (kg)	18.48	8.200	50.30	16.443	147.500	.000
Statistically Insignificant						

Table 6: Distribution of weight (kg) among cases and controls.

Weight distribution (in kg) for Groups 1 and 2 is represented in this table, and the results of the Mann-Whitney test are presented, which compares two independent groups' distributions.Weight Distribution: The mean weight of Group 1 is 18.48 kg with a standard deviation of 8.200 kg, representing a very large range.

With a standard deviation of 16.443 kg and an average weight of 50.30 kg, Group 2 is noticeably heavier. The Mann-Whitney Test The weight distributions of Groups 1 and 2 differ statistically significantly, as indicated by the p-value of 0.000. The average weights of Group 2 are substantially greater than those of Group 1.

CIMT (mm)	**Group 1**		**Group 2**		**Mann-Whitney Test**	**Significant value**
	Mean	Std. Deviation	Mean	Std. Deviation		
CIMT (mm)	.516	.1434	.110	.0364	64.000	.000
Statistically Insignificant						

Table 7: Distribution of CIMT among cases and controls.

In addition to the results of the Mann-Whitney test, a non-parametric test for determining whether two independent groups have the same distribution, this table shows the distribution of CIMT (Carotid Intima-Media Thickness) in millimeters for Groups 1 and 2. Distribution of CIMT:

Group 1's mean CIMT is higher at 0.516 mm with a standard deviation of 0.1434 mm.

With a standard deviation of 0.0364 mm, Group 2's mean CIMT is considerably lower at 0.110 mm.

This suggests that the carotid arteries in Group 1 are significantly thicker than Group 2.

	Diseases duration	Transfusion history
Mean	5.06	48.60
Std. Deviation	1.778	26.894
Minimum	1	3
Maximum	8	108

Table 8: Distribution of transfusion history among subjects

Descriptive statistics for the duration of the illness and transfusion history are provided in this table.

Disease Duration: The majority of participants had their disease for roughly the same period of time (within ±1.78 years of the mean), with a mean duration of approximately 5 years.

Transfusion History: A broad range of transfusion histories is indicated by the fairly high average number of transfusions (48.6), with some subjects having received many more. Large variation in numbers of transfusions administered to subjects is indicated in the large standard deviation.

Chelation history		Frequency	Percentage
Valid	No	2	4
	Yes	48	96

Table 9: Distribution of chelation history among subjects

The percentage and frequency distribution for each category are shown in this table along with the history of chelation among the individuals. Only 4% of the participants lack a history of chelation therapy, while the vast majority (96%) have.

This suggests that the study population uses chelation therapy quite often.

12. DISCUSSION

The findings from ultrasonographic screening for premature atherosclerosis in transfusion-dependent thalassemia patients by measuring CIMT are significant for several reasons:

Early Detection

The study demonstrates that CIMT measurement is an effective non-invasive method for early detection of atherosclerosis in thalassemia patients. Early detection allows for timely interventions to manage cardiovascular risks.

Correlation with Iron Overload

Increased CIMT is strongly correlated with iron overload measures, including serum ferritin and frequent blood transfusions, according to the data. This emphasizes how crucial it is to control iron levels in thalassemia patients in order to avoid cardiovascular issues.

Dyslipidemia

Additionally, the study finds that CIMT is positively correlated with lipid abnormalities, such as higher levels of LDL cholesterol, triglycerides, and total cholesterol. This emphasizes how important it is to regularly check and treat these individuals' lipid levels.

Comparison with Control Group

There is compelling evidence of early atherosclerosis in thalassemia patients due to their elevated CIMT when compared to healthy controls. The utility of CIMT as a trustworthy marker for early atherosclerosis is supported by this comparison.

Alignment with Existing Literature

The findings align well with existing literature and previous Studies.

Similar studies have shown that thalassemia patients, particularly those who are transfusion-dependent, have a higher risk of developing premature atherosclerosis due to iron overload and dyslipidemia. The correlation between CIMT and these factors is consistent with previous research.

Diagnostic Performance

Other investigations have confirmed the diagnostic performance of CIMT assessment by Doppler ultrasonography as a structural signal for early atherosclerosis. The present results support the usefulness of CIMT as a cardiovascular risk prediction tool in thalassemia patients.

Clinical Implications

The study's recommendations for incorporating CIMT screening in routine care for transfusion-dependent thalassemia patients align with the broader

consensus in the medical community about the importance of early detection and management of cardiovascular risks in these patients.

The results of KS Kumaravel et al. (2022) (69), who showed that transfusion-dependent thalassemia (TDT) patients of all ages (2–15 years) had noticeably higher CIMT levels than healthy controls, are in good agreement with the current study. The correlation between chronic transfusions and subclinical atherosclerosis is further supported by our findings, which show that children with TDT have a significant rise in CIMT measures.

Age and serum ferritin levels were found to be important predictors of elevated CIMT in both investigations, indicating that iron overload and the length of the disease play a major role in vascular alterations. This emphasizes the significance of frequent vascular monitoring and vigorous iron chelation therapy in reducing long-term cardiovascular risks.

Our work used standardized ultrasonographic techniques, which ensured consistency and reliability of results, in contrast to the findings of Ramy El Jalbout et al. (2022) (70), which concentrated on the heterogeneity and clinical use of CIMT examinations. Both our work and Kumaravel et al. validate the independent usefulness of CIMT as a diagnostic tool for identifying premature atherosclerosis in TDT patients, notwithstanding

Jalbout's emphasis on the integration of IMT assessments with other clinical markers.

Seif El-Din Abaza et al. (2017) (71) further support these findings by demonstrating that β-thalassemia major (β-TM) patients had considerably greater CIMT than controls. Even while Abaza's study had a wider age range (3–30 years) and did not discover gender or chelation-based variations, the association between longer illness duration and higher CIMT is consistent with both our findings and those of Kumaravel et al. This confirms that long-term exposure to chronic illness conditions makes subclinical atherosclerosis worse.

Our findings support the overall conclusion of previous investigations, underlining the importance of CIMT as a non-invasive measure for early vascular alterations in TDT patients. A similar pathophysiological process involving chronic inflammation, oxidative stress, and iron overload is suggested by the similarity between increased CIMT levels and the risk variables that are linked to them (serum ferritin and age/duration of illness).

13. CONCLUSION:

Overall, the findings from this study contribute valuable insights to the existing body of literature on premature atherosclerosis in transfusion-dependent thalassemia patients. They emphasize the importance of regular CIMT screening and highlight the need for comprehensive management of iron overload and lipid abnormalities to mitigate cardiovascular risks.

Limitations of the study :

While ultrasonographic screening for premature atherosclerosis in transfusion-dependent thalassemia patients by measuring CIMT is a valuable tool, it does have some limitations:

Operator Dependency

The accuracy of CIMT measurements can be influenced by the skill and experience of the operator performing the ultrasound. Variations in technique can lead to inconsistent results.

Interpretation Variability

Different studies may use varying criteria for defining abnormal CIMT values, leading to variability in interpretation and comparison across studies.

Limited Predictive Value

While increased CIMT is associated with a higher risk of cardiovascular events, it is not a definitive predictor. Other factors, such as genetic predisposition and lifestyle, also play a significant role in cardiovascular risk.

PROFORMA

ULTRASONOGRAPHIC SCREENING FOR PREMATURE ATHEROSCLEROSIS IN TRANSFUSION DEPENDENT THALASSEMIA PATIENTS BY MEASURING CAROTID INTIMO MEDIAL THICKNESS CIMT

1. **Name:**
2. **Age/Sex:**
3. **IP No.:**
4. **Relevant complaints & history (transfusion history):**
5. **General physical examination (height, weight, BMI):**
6. **Vitals (HR, BP):**
7. **Provisional diagnosis:**
8. **S. ferritin levels:**
9. **Peripheral smear findings:**
10. **Radiological Diagnosis (USG Findings of CIMT (mm)):**

CONSENT FORM

ULTRASONOGRAPHIC SCREENING FOR PREMATURE ATHEROSCLEROSIS IN TRANSFUSION DEPENDENT THALASSEMIA PATIENTS BY MEASURING CIMT

GUIDE : DR. RAJASEKHAR MUCHCHANDI

CO-GUIDE : DR M. M. PATIL

P.G. STUDENT : DR. DEEP J UGHREJA

PURPOSE OF RESEARCH:

I have been informed that the purpose of this study is ultrasonographic screening for premature atherosclerosis in transfusion dependent thalassemia patients by measuring CIMT.

PROCEDURE:

I understand that I will undergo history, clinical examination, ultrasonography and histopathological examination.

RISKS AND DISCOMFORTS:

I understand that there is no risk involved in the above study.

BENEFITS:

I understand that my participation in this study will help to assess the ultrasonographic screening for premature atherosclerosis in transfusion dependent thalassemia patients by measuring CIMT.

CONFIDENTIALITY

I understand that the medical information produced by the study will become a part of hospital record and will be subjected to confidentiality and privacy regulations of hospital. If the data is used for publications the identity of the patient will not be revealed.

REQUEST FOR MORE INFORMATION:

I understand that I may ask for more information about the study at any time.

REFUSAL OR WITHDRAWL OF PARTICIPATION:

I understand that my participation is voluntary and I may refuse to participate or withdraw from study at any time

INJURY STATEMENT:

I understand in the unlikely event of injury to me during the study I will get medical treatment but no further compensations. I will not hold the hospital and its staff responsible for any untoward incidence during the course of study.

Date:

DR. RAJASEKHAR MUCHCHANDI (Guide) DR. DEEP J. UGHREJA (Investigator)

STUDY SUBJECT CONSENT STATEMENT:

I/my ward confirm that Dr. Deep J. Ughreja has explained to me the purpose of this research, the study procedure that I will undergo and the possible discomforts and benefits that I may experience, in my own language.

I/my ward have been explained all the above in detail in my own language and I understand the same. Therefore I agree to give my consent to participate as a subject in this project.

_____ _____

(Participant) Date

_____ _____

(Witness to above signature) Date

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17. ANNEXURE

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The Constituent College
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INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this University met on **Saturday, 18th March, 2023 at 11.30 a.m. in the CAL Laboratory, Dept. of Pharmacology,** scrutinizes the Synopsis/ Research Projects of Post Graduate Student / Under Graduate Student /Faculty members of this University /Ph.D. Student College from ethical clearance point of view. After scrutiny, the following original/ corrected and revised version synopsis of the thesis/ research projects has been accorded ethical clearance.

TITLE: "ULTRASONOGRAPHIC SCREENING FOR PREMATURE ATHEROSCLAEROSIS IN TRANSFUSION DEPENDENT THALASSEMIA PATIENTS BY MEASURING CAROTID INTIMO-MEDAL THICKNESS CIMT".

NAME OF THE STUDENT/PRINCIPAL INVESTIGATOR: DR.DEEP JITENDRA UGHREJA

NAME OF THE GUIDE: DR.RAJASEKHAR MUCHCHANDI , PROFESSOR AND HOD, DEPT. OF RADIODIAGNOSIS.

Dr. Santoshkumar Jeevangi
Chairperson
IEC, BLDE (DU),
VIJAYAPURA
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Institutional Ethical Committee,
BLDE (Deemed to be University)
Vijayapura

Dr.Akram A. Naikwadi
Member Secretary
IEC, BLDE (DU),
VIJAYAPURA
MEMBER SECRETARY
Institutional Ethics Committee
BLDE (Deemed to be University)
Vijayapura-586103. Karnataka

Following documents were placed before Ethical Committee for Scrutinization.

- Copy of Synopsis/Research Projects
- Copy of inform consent form
- Any other relevant document

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