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ORIGINAL ARTICLE

Impact of HbF inducers use on anti-cardiolipin and anti-beta2-glycoprotein I antibody levels in beta-thalassemia patients: a pilot study

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ABSTRACT

Objective: To determine the levels of anti-cardiolipin (aCL) IgM/IgG and anti-β2-glycoprotein I (anti-β2-GPI) IgM/IgG antibodies in β-thalassemia patients receiving fetal hemoglobin (HbF) inducers.

Methods: This cross-sectional study was conducted from June-2024 to November-2025 at Peshawar General Hospital, Peshawar. Ethical approval was obtained from Institute of Pathology and Diagnostic Medicine, Khyber Medical University (Ref# KMU/IPDM/IEC/2024/21). Forty-two diagnosed β-thalassemia patients aged ≥ 1 year receiving HbF inducers (hydroxyurea 10-20 mg/kg and/or thalidomide 2-3 mg/kg) for at least six months were enrolled using convenient sampling. Patients with prior thromboembolic events, bleeding disorders, or acute illness were excluded. Serum aCL (IgM, IgG) and anti-β2-GPI (IgM, IgG) antibodies were measured using chemiluminescence immunoassay. Appropriate statistical analysis was performed using GraphPad Prism 10.2.3, with $p \leq 0.05$ considered statistically significant.

Results: Out of 42 β-thalassemia patients, 66.7% were males with a median age of 4.0 years (range 1.3-25). Majority (n=34) received combination HbF-inducing therapy, while four received thalidomide monotherapy and four received hydroxyurea monotherapy. Median antibody levels were as follows: anti-cardiolipin (aCL) IgM 2.22 U/mL and IgG 2.49 U/mL; anti-β2-GPI IgM 2.23 U/mL and IgG 1.11 U/mL. All measured values were below the established positivity cut-off (≥20 AU/mL). No statistically significant differences were observed between males and females, and no correlation was found between antibody levels and age ($p > 0.05$).

Conclusion: In β-thalassemia patients receiving HbF inducers, no detectable aCL or anti-β2-GPI antibodies were identified, and no association with age or gender was observed, suggesting no antibody elevation with hydroxyurea or thalidomide therapy.

Keywords: beta-Thalassemia (MeSH); Fetal Hemoglobin (MeSH); HbF inducers (Non-MeSH); Thalidomide (MeSH); Hydroxyurea (MeSH); Glycoproteins (MeSH); Antibodies (MeSH); beta 2-Glycoprotein I (MeSH); anti-beta2-glycoprotein I antibodies (Non-MeSH); Antibodies, Antiphospholipid (MeSH); Antibodies, Anticardiolipin (MeSH).

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INTRODUCTION

Beta (β) thalassemia is one of the most common hereditary blood disorders due to defective β-globin chains resulting in severe anemia.[1] Regardless of clinical manifestation as transfusion-dependent (TDT) or non-transfusion-dependent thalassemia (NTDT), the common complications include severe anemia, hepatosplenomegaly, skeletal deformities and endocrine problems.[2] Apart from the aforementioned complications, the hypercoagulability in β-thalassemia has been associated with fatal thromboembolic events.[3]

In addition to low anticoagulant proteins, mainly proteins C and S, erythrocyte membrane damage due to chronic hemolysis exposes the phospholipids on the cell membrane, which contributes to pro-coagulant tendency.[4,5] Apart from insufficiency in the coagulation pathway, anti-cardiolipin (aCL) and anti-beta2-glycoprotein I (anti-β2-GPI) antibodies, commonly encountered in autoimmune disorders, are also increased in β-thalassemia.[6,7] These antibodies are commonly seen in autoimmune disorders such as antiphospholipid antibody syndrome and are associated with thromboembolic events.[4,8,9] β-thalassemia related hypercoagulability and exposure to treatments with increased risk of thromboembolism; the presence of these antibodies might increase the risk of complications.[10] Treatment options include regular blood transfusions, fetal hemoglobin (HbF) inducers, drugs targeting ineffective erythropoiesis such as Luspatercept, hematopoietic stem cell transplantation and recently approved gene therapy.[11] Due to the high cost and non-availability of newer treatment options, the majority of patients in Pakistan and other endemic countries are treated with blood transfusions. However, due to the risk of transfusion-transmissible infections, iron overload and costly iron chelation, HbF inducers are now increasingly used.[12] Commonly used HbF inducers include hydroxyurea (HU) and thalidomide, with promising results, reducing the transfusion needs and improving overall well-being.[13]

Although HbF inducers effectively improve anemia and its associated complications, their impact on coagulation profile and thrombo-embolic risk remains underexplored. While no studies have reported increased thromboembolic events with HU, thalidomide has been linked to such complications in other diseases and, in rare cases, β-thalassemia.[13,14]

Given the hypercoagulable background of β-thalassemia, it is important to determine whether HbF-inducing therapy modulates antiphospholipid antibody levels and thereby alters thromboembolic susceptibility. This pilot study was planned to assess the levels of aCL (IgM and IgG) and anti-β2-GPI (IgM and IgG) antibodies in β-thalassemia patients receiving HbF inducers. The findings may contribute to improved risk stratification and inform safer therapeutic decision-making in this high-risk population.

METHODS

This cross-sectional study was conducted from June 2024 to November 2025 at the Pathology Laboratory, Peshawar General Hospital, Peshawar. The ethical approval was obtained from the Institutional Ethical Committee of the Institute of Pathology and Diagnostic Medicine, Khyber Medical University, Peshawar (Reference #: KMU/IPDM/IEC/2024/21, dated: October 05, 2024) prior to starting this study. A sample of 42 β-thalassemia patients was selected, in line with recommended pilot study sample sizes to assess feasibility and generate preliminary estimates.[15-17] Diagnosed β-thalassemia patients fulfilling the inclusion criteria of age ≥1 years and taking HbF inducers (HU 10-20 mg/kg, thalidomide 2-3 mg/kg) for at least 6 months were included using simple convenient sampling technique. Patients with a history of thromboembolic events, bleeding disorder or acute illness were excluded. Drug history of patients including prophylactic anticoagulant therapy (a combination pill containing Aspirin 75mg+ Clopidogrel 75mg) with thalidomide or iron chelation therapy was taken into account.

After informed consent and clinical details, blood samples were collected in gel tubes for estimation of aCL (IgM & IgG) and anti-β2-GPI (IgM & IgG) antibodies (CLIA-based MAGLUMI® Snibe Diagnostic, China). As per the manufacturer guidelines, the cut-off values were interpreted as <20 AU/ml =negative and ≥20 AU/ml = positive.

Statistical analysis was performed using GraphPad Prism software (Version 10.2.3). Frequency (n) and percentages (%) were calculated for categorical variables and median with minimum to maximum range for numerical variables. Based on the non-parametric data distribution, the Mann-Whitney test was applied with a p-value of ≤0.05 regarded as statistically significant. Pearson's correlation and simple linear regression analysis were done to determine an association of antibody levels with age and gender.

RESULTS

The majority of the study participants were males (66.66%, n=28) with a median age of 4.0 years (range 1.3-25 years). Based on the drug history, the majority of the patients were taking HU and thalidomide in combination (n=34, 81%), while a small number of participants were taking either thalidomide or HU alone (n=04 on thalidomide only and n=04 on HU only). All participants taking thalidomide were also on Aspirin 75mg+ Clopidogrel 75mg combination pill, once daily, the last dose taken at least 12 hours prior to sample collection. The majority of these patients were transfusion free on HbF inducers therefore, only 16 (38.1%) were on oral iron chelation (Deferasirox). Data summarized in Table I. Overall, the median aCL IgM antibodies were 2.22 U/mL (range 0.50-19.5) and IgG antibodies were 2.49 U/mL (range 0.78-15.10) in β-thalassemia patients. On the other hand, the median anti-β2-GPI IgM antibodies were 2.23 U/mL (range 0.50-17.50), and IgG were 1.11 U/mL (range 0.50-5.28). Based on the cut-off range, all samples were negative for aCL (IgM & IgG) or anti-β2-GPI (IgM & IgG) antibodies.

In addition, no statistically significant difference (p>0.05) was observed between females and males for any of the tested antibodies (Figure 1: A-D). The association between age and antibodies was determined using linear regression analysis and Pearson correlation, which showed no correlation (p>0.05) (Figure 2: A-D).

DISCUSSION

In this pilot study, we evaluated antiphospholipid antibody profiles, specifically aCL (IgM, IgG) and anti-β2-GPI (IgM, IgG), in β-thalassemia patients receiving HbF inducers, to explore their potential influence on hypercoagulability and thromboembolic susceptibility. Given the established prothrombotic milieu in β-thalassemia, driven by chronic hemolysis, endothelial dysfunction, and coagulation pathway abnormalities, our findings provide preliminary insight into the immuno-coagulative interplay associated with these therapeutic agents. These results contribute to the limited evidence regarding the safety of HbF inducers in this population and offer a basis for risk stratification and future large-scale

Table I: Characteristics of the study participants

Variables	Characteristics	Patients (n=42)
Gender	Males; n (%)	28 (66.66)
	Females; n (%)	14 (33.34)
Drug History	Fetal hemoglobin (HbF) inducers; n (%)	Hydroxyurea+Thalidomide: 34 (81%), Thalidomide alone: 04 (9.5%), Hydroxyurea alone: 04 (9.5%)
	Anticoagulant (Aspirin 75mg +Clopidogrel 75mg); n (%)	Yes: 38 (90.5%), No: 04 (9.5%)
	Deferosirox; n (%)	Yes: 16 (38.1%), No: 26 (61.9%)

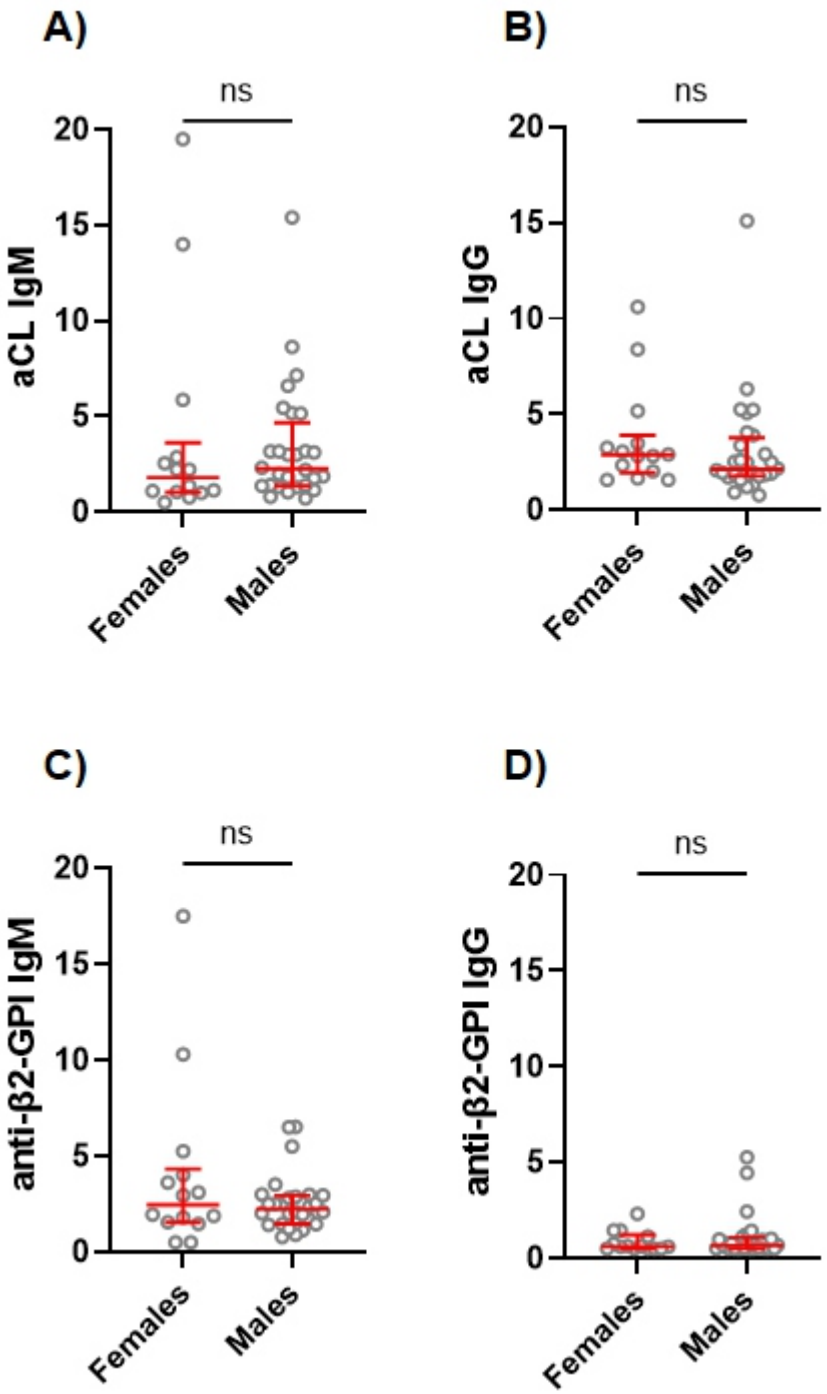

Figure 1: Comparison of antibody levels between females and males. The levels of **A)** anti-Cardiolipin (aCL) IgM antibodies, **B)** anti-cardiolipin (aCL) IgG antibodies, **C)** anti-Beta 2 Glycoprotein I (anti-β2-GPI) IgM antibodies and **D)** anti-Beta 2 Glycoprotein I (anti-β2-GPI) IgG antibodies were compared between female (n=14) and male (n=28) patients. Data represented as median and interquartile range, compared between two groups using Mann-Whitney test with p>0.05 considered as non-significant (ns).

prospective investigations. The hypercoagulable state in β-thalassemia is multifactorial, encompassing platelet activation, endothelial injury, red cell membrane phospholipid exposure, and dysregulation of natural anticoagulant pathways.[3,4,10] The risk of thromboembolic events further increases with advancing age, splenectomy status, transfusion burden, and clinical phenotype.[18]

The use of HbF-inducing agents to augment fetal hemoglobin production in β-thalassemia has expanded considerably in recent years.[19–21] Although these agents demonstrate encouraging efficacy and overall safety, thrombotic complications-particularly with thalidomide-have been reported in isolated cases, warranting careful evaluation of their prothrombotic potential.[14,22]

In this study, 42 β-thalassemia patients taking HbF inducers: HU and thalidomide in combination or alone were included. None of the patients had reported any major adverse effects on treatment or any significant comorbidities. The concomitant use of Aspirin/Clopidogrel combination pill to minimize the risk of thrombosis in patients taking thalidomide has been well documented.[13] The age of the study participants ranged from 1.3 to 25 years, with the majority of them were males (66.66%). Previous studies have reported an increased risk of thrombosis with advancing age, splenectomy, iron overload, clinical phenotype and previous history of thromboembolic events.[18,23-25] Though our study had more male participation due to random selection of patients, no association between gender and thrombosis risk has been found in previous studies. Previous studies have reported thrombosis risk in β-thalassemia patients on blood transfusions.[6,7] Owing to the limited number of patients receiving thalidomide or HU as monotherapy, a meaningful comparison between patients treated on thalidomide and HU combination therapy, and those receiving either agent alone could not be done. Nevertheless, previous studies have not shown an increased risk of thrombosis associated with HU alone, whereas an elevated thrombotic risk has been reported with thalidomide, either as a single agent or in combination with other therapies. Although thromboembolic events are reported in β-thalassemia patients using thalidomide, none of the studies have attempted to evaluate the coagulation profiles.[14] The risk of thrombosis

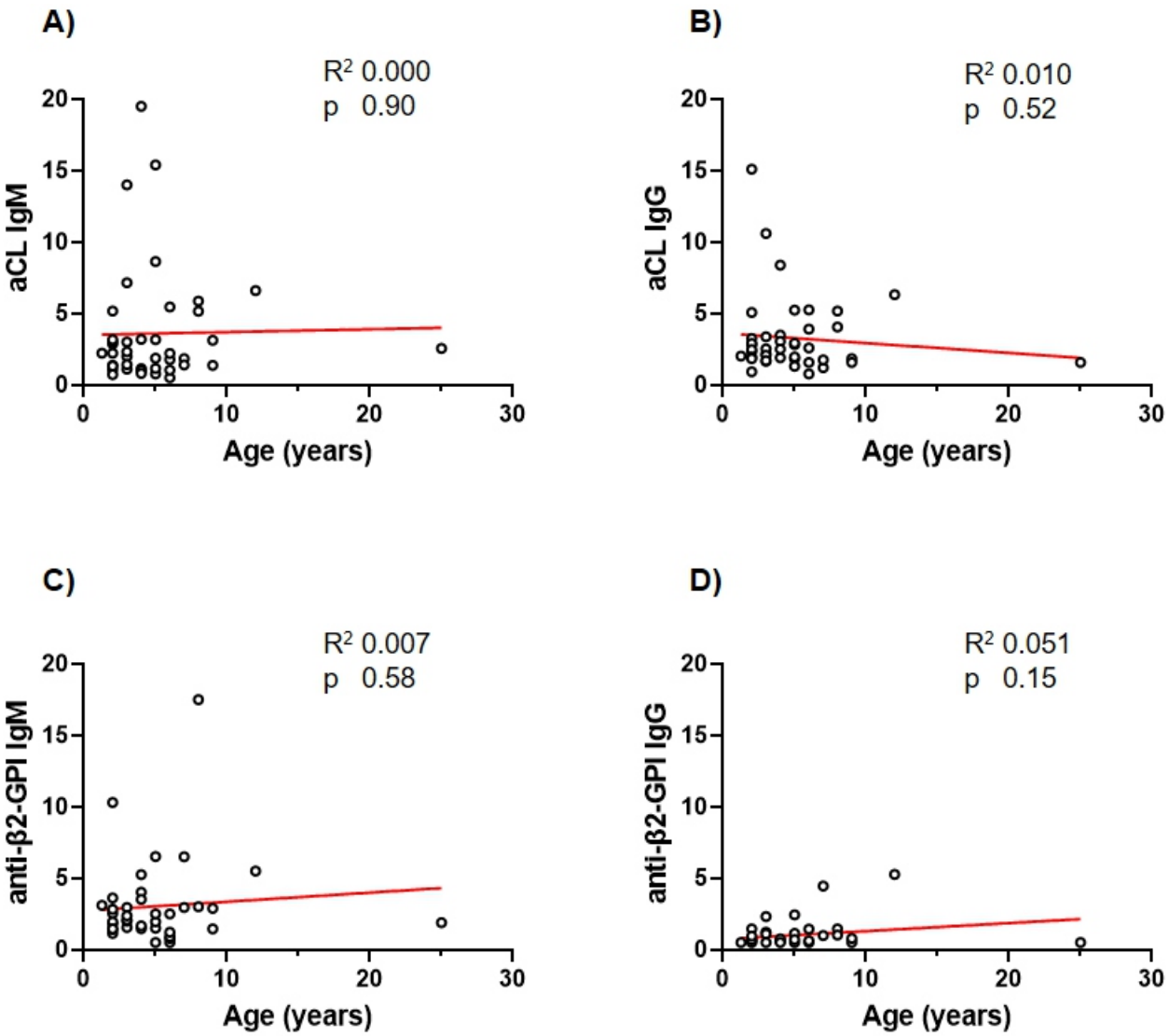

Figure 2: Association between age and antibody levels. The association between age (years) and the levels of **A)** anti-Cardiolipin (aCL) IgM antibodies, B) anti-cardiolipin (aCL) IgG antibodies, **C)** anti-Beta 2 Glycoprotein I (anti-β2-GPI) IgM antibodies and **D)** anti-Beta 2 Glycoprotein I (anti-β2-GPI) IgG antibodies was determined using simple linear regression. R2 denotes coefficient of determination with p value calculated using Pearson correlation.

secondary to thalidomide use has been reported with advice for appropriate thromboprophylaxis.[26,27]

In this study, as per the defined cut-offs, none of the patients were positive for any of the tested antibodies. Both IgM and IgG aCL antibodies had been reported in TDT and NTDT.[6,7,9,28,29] Similarly, previous studies have also confirmed the presence of anti-β2-GPI IgM and IgG in β-thalassemia patients.[6,9] Hemoglobinopathies other than β-thalassemia, such as sickle cell disease, are associated with thrombotic events have also shown increased antibody levels, though the underlying mechanisms remain different.[30] These antibodies are commonly reported and are used for the diagnosis of autoimmune conditions, particularly antiphospholipid syndrome, associated with high risk of thrombosis.[31] Apart from diseases with risk of thrombosis, aCL antibodies have been reported in 10-15% of healthy individuals after infections, autoimmune disorders and malignancies.[32,33]

In this study, no statistically significant difference in antibody levels was observed between female and male patients. Although disorders associated with these antibodies, such as antiphospholipid syndrome, are reported more frequently in females, no sex-based differences were detected among patients with β-thalassemia.[34] Immune-related complications are well documented in β-thalassemia and are attributed to immune system dysregulation, chronic transfusion exposure, and iron overload, all of which predispose patients to increased antibody formation and immune complications.[35-37] Despite evidence suggesting that advancing age is

associated with a higher risk of disease-related immune complications, our analysis did not demonstrate a significant correlation between age and antibody levels.

Previous studies, which have confirmed the presence of aCL and anti-β2-GPI antibodies in β-thalassemia patients, have tested patients treated with blood transfusions. Though the risk of thrombosis has been associated with the use of thalidomide, none of the studies have tested thalidomide treated β-thalassemia patients for the presence of these antibodies. In conclusion, despite the presence of thrombotic risk in thalidomide treated β-thalassemia patients, positive antibody levels were not detected suggesting mechanisms other than antibody-mediated thrombosis.

Strengths and Limitations of the study

One of the major strengths of this study is that it is the first study to determine the levels of aCL and anti-β2-GPI antibodies in β-thalassemia patients treated using HbF inducers.

The limitations of this pilot study included the absence of control groups (β-thalassemia patients receiving transfusions and healthy controls), a small sample size and the lack of pre-treatment antibody levels and complete coagulation profiles. In addition, the concomitant use of anticoagulant therapy in thalidomide-treated patients may have influenced antibody levels. Future large-scale longitudinal studies should assess subtle changes in coagulation profiles, the balance between pro- and anticoagulant proteins and the roles of platelets and erythrocytes in both TDT and NTDT β-thalassemia patients using HbF inducers to better understand thrombotic risk.

CONCLUSION

The findings of this pilot study concludes that the levels of aCL and anti-β2-GPI antibodies in β-thalassemia patients treated using HbF inducers particularly thalidomide were negative. Furthermore, no association was observed in aCL and anti-β2-GPI antibody levels with gender or age. These results suggest the possibility of alternate mechanisms responsible for thromboembolic events reported in patients using thalidomide.

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AUTHORS' CONTRIBUTION

The following authors have made substantial contributions to the manuscript as under:

GFR: Conception and study design, acquisition, analysis and interpretation of data, drafting the manuscript, critical review, approval of the final version to be published

HB, KK: Study design, acquisition, analysis of data, drafting the manuscript, approval of the final version to be published

AAII: Acquisition, analysis and interpretation of data, drafting the manuscript, critical review, approval of the final version to be published

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST

Authors declared no conflict of interest, whether financial or otherwise, that could influence the integrity, objectivity, or validity of their research work.

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DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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