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SHORT COMMUNICATION

GDF15 as a Marker of Ineffective Erythropoiesis and Erythroid Expansion in Thalassemia: a Clinical Perspective

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SUMMARY

Background: **Ineffective erythropoiesis is a hallmark of thalassemia syndromes. Growth differentiation factors, such as GDF15, play a crucial yet not fully understood role.**
Methods: **Serum GDF15 levels were measured by ELISA in 486 individuals (362 thalassemia patients, 53 β-trait carriers, and 71 healthy subjects) and analyzed alongside biochemical and clinical parameters.**
Results: **GDF15 levels were elevated in transfusion-dependent (TD) β-thalassemia (26-fold), non-transfusion-dependent (NTD) β-thalassemia (6-fold), and β-thalassemia carriers (2-fold) compared to healthy controls. Moreover, GDF15 levels were elevated in α-thalassemia patients (2-fold) compared to carriers. In TD β-thalassemia, GDF15 correlated inversely with hemoglobin and positively with erythropoietin. GDF15 also correlated with iron metabolism markers. Longitudinal analysis in a TD patient subgroup showed dynamic GDF15 changes post-transfusion, reflecting erythropoietic activity. Furthermore, GDF15 levels correlated with transfusion intervals, particularly in splenectomized patients.**
Conclusions: **GDF15 represents a promising biomarker for assessing thalassemia severity, monitoring treatment responses, and guiding therapies.**
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KEYWORDS

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INTRODUCTION

Ineffective erythropoiesis (IE) is a fundamental pathological mechanism of both transfusion-dependent (TD) and non-transfusion-dependent (NTD) β-thalassemia (β-thal) [1-3]. To a lesser extent, IE occurs in α-thalassemia (α-thal) and other red blood cell (RBC) disorders [4,5]. IE results from the abnormal development and expansion of erythroid precursors that fail to mature. To inhibit this process, regular RBC transfusions are required for the most severe forms of thalassemia [6]. While erythropoietin (EPO) is the master regulator of

early erythropoiesis, multiple hormones are involved in the later phases, but their reciprocal contribution is still to be unraveled. The growth differentiation factor (GDF) family, and specifically GDF11 and GDF15, has been implicated in this process. The development of luspatercept, a ligand trap that preferentially binds GDF11, first suggested the possible role of this factor in the IE observed in β-thal [7,8]. GDF11 inhibits RBC maturation through SMAD2/3-mediated downregulation of GATA1 and its drug-induced inactivation by luspatercept improves terminal erythropoiesis [7,9]. However, in a β-thal mouse model, GDF11 knockout alone was insufficient to ameliorate IE or to eliminate the therapeutic response to RAP-536, the murine analog of luspatercept [10]. These findings, though unconfirmed in patients, caution against assuming a primary role for GDF11 in promoting IE and mediating luspatercept response. Unlike GDF11, GDF15 increases throughout erythroid differentiation and promotes apoptosis by downregulating GATA1 and other transcription factors [11,12]. Elevated serum GDF15 levels have been reported in β-thal patients [13]. GDF15 alterations are also linked to disrupted iron metabolism [14-16]. Interpreting these results is challenging due to the complex interaction of erythropoiesis and iron metabolism in β-thal. A clear link between GDF15 levels and thalassemia clinical severity remains unclear. This study aimed to assess the correlation between GDF15 levels and the severity of α-thal and β-thal.

MATERIALS AND METHODS

This is a retrospective and prospective observational study, based on laboratory results and clinical records from the Thalassemia and Rare Hematological Disease Centre in Orbassano (TO), Italy. Serum GDF15 was measured by ELISA (DuoSet DY957, R&D Systems). Iron metabolism parameters were measured as per clinical practice. Demographics and clinical data were extracted from patient records. Continuous variables are presented as mean with standard deviation, or median with interquartile range (IQR), and categorical variables as frequencies and percentages. Sample number and group size were not pre-determined but were based on patient availability. Pre- and post-transfusion samples were collected within 3 hours before or after packed RBC administration, respectively. In a small subset of TD β-thal patients, GDF15 and Hb were measured at different timepoints during subsequent transfusion cycles.

For a prenatally diagnosed patient, serum GDF15 was measured prior to scheduled transfusion events. Statistical differences were analyzed using Student's *t*-test or the Wilcoxon matched-pairs test, while correlations were assessed using Pearson's R or Spearman's r. Statistical analysis was performed with Statistica 10 (StatSoft). The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. Informed consent was obtained from all patients.

RESULTS

GDF15 levels were measured in β-thal (47 carriers and 342 patients), in α-thal (6 carriers and 20 patients), and in 71 healthy subjects (Table 1). Median (IQR) GDF15 levels differed significantly among groups, being highest in affected individuals for both diagnoses ($p < 0.0001$). Specifically, GDF15 serum levels were 0.23 (0.16 - 0.34) ng/mL in healthy controls, 0.48 (0.28 - 0.96) ng/mL in β-thal carriers, 1.35 (0.42 - 5.76) ng/mL in NTD β-thal, and 5.93 (3.19 - 10.34) ng/mL in TD β-thal (Figure 1A).

In TD β-thal patients, GDF15 showed a negative correlation with Hb, both at the time of sampling ($r = -0.29$, $p < 0.001$) and when considering the mean Hb over the prior year ($r = -0.35$, $p < 0.001$). GDF15 correlated positively with EPO ($r = 0.48$, $p < 0.001$) and transferrin saturation (TSat) ($r = 0.25$, $p < 0.001$) (Supplementary Figure 1). Additionally, GDF15 levels correlated with the duration of transfusion intervals in splenectomized patients over subsequent transfusion cycles ($r = 0.66$, $p < 0.001$, $n = 25$ measured in 6 patients (transfusion interval range: 17 - 34 days). In this subset, GDF15 serum levels (± SD) were 1.58 (± 0.90) ng/mL, 2.52 (± 1.54) ng/mL, 3.78 (± 0.78) ng/mL, and 3.98 (± 0.06) ng/mL at 0 (± 0), 7 (± 3), 14 (± 3), 21 (± 3), and 28 (± 3) days post transfusion. An opposite trend for Hb levels was observed during the same time frames (Figure 1B).

No significant changes in GDF15 levels were observed immediately before and after transfusion in a larger subgroup of 28 TD β-thal patients. In a patient with a prenatal diagnosis of severe TD β-thal (homozygous for HBB c.93-21G>A), GDF15 levels were high at 5 months of age and progressively declined after initiation of regular transfusion therapy. After reaching a pre-transfusion Hb threshold above 10 g/dL, GDF15 levels were approximately halved compared to those ones observed at 5 months of age (6.2 vs. 2.7 ng/mL) (Supplementary Figure 2).

In NTD β-thal patients, GDF15 positively correlated with TSat ($r = 0.52$, $p < 0.001$), serum iron ($r = 0.47$, $p < 0.001$) and ferritin (Ftn) ($r = 0.28$, $p = 0.02$) (Supplementary Figure 3). Among TD and NTD β-thal patients, 45 and 19 were in the 0 - 18 age range, respectively, with no significant differences observed when compared to adults. In β-thal carriers, GDF15 negatively correlated with Hb levels ($r = -0.41$, $p = 0.001$) and positively with EPO ($r = 0.78$, $p = 0.02$), TSat ($r = 0.65$, $p < 0.001$), serum iron ($r = 0.53$, $p = 0.001$) and Ftn ($r = 0.45$, $p = 0.003$) (Supplementary Figure 4).

In α-thal patients, GDF15 levels were 0.22 (0.15 - 0.41) ng/mL in carriers and 0.48 (0.31 - 0.86) ng/mL in patients ($p = 0.01$) (Figure 1C). A mild positive correlation between GDF15 and age was observed in both

Table 1. Demographics and baseline hemoglobin (Hb) of enrolled patients, divided by diagnosis.

		n	F/M (%)	Age (median [IQR])	Single-point Hb (median [IQR])
Healthy		71	40/31 (56/44)	32.0 (14.7)	11.9 (1.4)
α-thal	carriers	6	4/2 (67/33)	21.6 (30.8)	13.7 (3.3)
	affected	20	13/7 (65/32)	30.6 (21.6)	9.2 (1.7)
β-thal	carriers	46	24/22 (52/48)	38.7 (52.1)	10.4 (2.8)
	NTD β-thal	76	42/34 (55/45)	33.3 (25.4)	9.4 (1.9)
	TDT β-thal	266	133/133 (50/50)	30.9 (15.1)	10.3 (1.4)

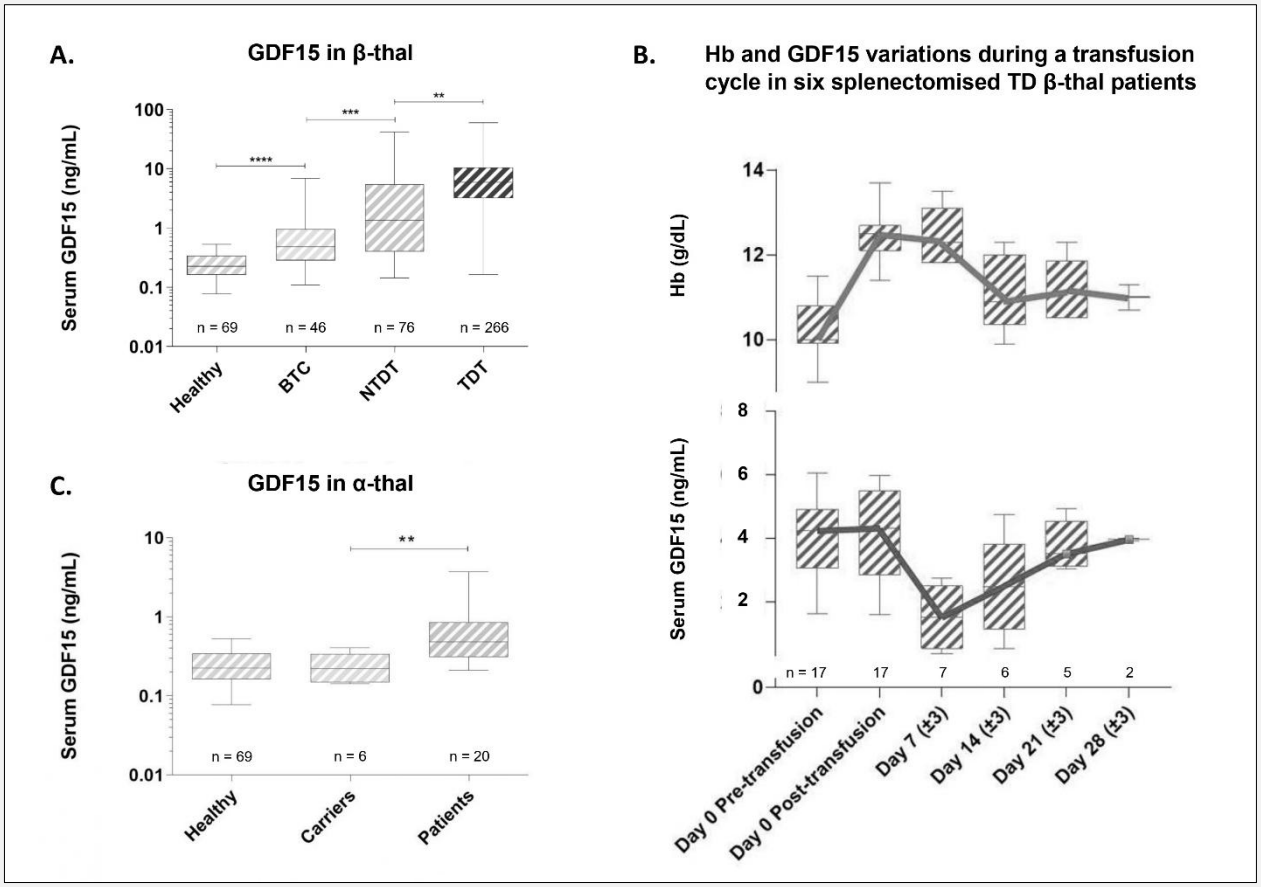

Figure 1. A) Serum levels of GDF15 measured in healthy, β-thal carriers (BTC) and β-thal patients, clinically divided by transfusion requirement in non-transfusion dependent (NTD) and transfusion-dependent (TD) β-thal. B) GDF15 and Hb variations during a transfusion cycle in a subset of six splenectomized TD β-thal patients. C) Serum levels of GDF15 measured in healthy, α-thal carriers and α-thal patients, considered regardless of their transfusion requirement.
Box plots include values from first to third quartile (IQR), the line across box indicates the median value, bottom and top line-sextend from minimum to maximum values, n indicates the number of samples analyzed.

healthy subjects ($r = 0.30$, $p = 0.01$) and α-thal patients ($r = 0.51$, $p = 0.02$), but not in carriers.

DISCUSSION

To our knowledge, this is the largest published study evaluating GDF15 levels in patients with α- and β-thalassemia syndromes. While a portion of the findings was previously presented in a conference abstract [17], the present study provides a more comprehensive and detailed analysis, including novel data such as the evaluation of GDF15 levels in α-thalassemia patients. The results are consistent with previously published smaller-scale studies evaluating GDF15 in β-thalassemia across different clinical contexts [13-16,18,19].

GDF15 levels were altered in all patients affected β-thalassemia, with levels of GDF15 correlated with the clinical severity: a 26-fold increase in TD β-thal, a 6-fold increase in NTD β-thal, and a 2-fold increase in carriers compared to controls. Additionally, GDF15 levels were also 2-fold higher in α-thal patients compared to healthy carriers. In TD β-thal patients, we observed an inverse correlation between GDF15 and Hb and a positive correlation with EPO. Low levels of Hb are typically associated with high levels of EPO in the context of the IE in thalassemia. Additionally, GDF15 correlated with altered iron metabolism markers, such as TSat and serum iron. These results, which confirm on a larger scale what has been previously reported in both carriers and patients, suggest that a single GDF15 measurement could help quantify erythropoietic stress and serve as a potential marker of IE [13-19]. Recent studies also suggest GDF15 may play a neuroendocrine role, potentially explaining some metabolic alterations in thalassemia patients that are not captured by standard biochemical parameters alone [15,16].

However, most previous studies have focused on steady-state conditions, which only partially reflect the clinical realities of chronically transfused thalassemia patients. In these patients, not only Hb levels but also numerous hormones and cytokines undergo chronic fluctuations in a dynamic biological environment. Our study includes a longitudinal evaluation to assess how GDF15 changes in the context of regular RBC transfusions.

We hypothesized that transfusions, by inhibiting IE, would suppress thalassemic bone marrow activity, with erythropoiesis becoming more active closer to the end of each transfusion cycle. To test this, we measured GDF15 levels at multiple time points between transfusions in a small subset of TD β-thal patients, assessing whether GDF15 could reflect bone marrow activity. We observed a significant drop in GDF15 levels shortly after RBC transfusions, followed by a clear increase in the following weeks, which inversely correlated with Hb levels. These findings suggest that RBC transfusions transiently inhibit, together with IE, GDF15 release, with levels progressively increasing as bone marrow activity and erythropoiesis resume.

Interestingly, we found a significant correlation between GDF15 levels and the duration of transfusion intervals, but only in splenectomized patients. A possible explanation is that in the absence of the spleen, the degradation of IE products, both mature RBCs and early erythroid precursors, is impaired, allowing serum GDF15 levels to provide a more accurate estimate of erythropoietic expansion. However, further data is needed to confirm this hypothesis.

A limitation of this study is the lack of data on other iron metabolism regulators, such as hepcidin and erythroferrone. Previous research suggests that GDF15 levels decrease as hepcidin increases, but the precise biological interactions between these factors remain unclear. Future studies should address this, particularly considering emerging therapies like luspatercept, which likely targets GDFs but whose effects on bone marrow remain to be fully understood. Interestingly, treatment with luspatercept in TD β-thal is associated with elevated levels of GDF15, possibly reflecting an increased erythropoietic pressure upon luspatercept treatment [20].

In conclusion, our study supports GDF15 as a clinically relevant biomarker in thalassemia. It is the first to show GDF15 variations associated with erythropoietic expansion in the dynamic context of TD β-thal treatment. While further studies are needed, GDF15 holds promise for assessing disease severity, monitoring treatment responses, and potentially guiding the use of novel therapies, including luspatercept and other agents targeting IE.

Declaration of Interest:

GBF reports consultancy fees from Bristol Myers Squibb, Vertex and Pfizer. AP received research grants from Acceleron, Celgene (Bristol Myers Squibb), Novartis, Apopharma and Chiesi and consultancy fees from Celgene (Bristol Myers Squibb). The other authors declare that there are no financial interests or personal relationships that could be perceived to influence the work reported in this study. No specific funding was received for conducting this research.

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Additional material can be found online at:
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