Iron overload and chelation therapy in myelodysplastic syndromes

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Accepted 14 January 2014

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Abstract

Iron overload remains a concern in MDS patients especially those requiring recurrent blood transfusions. The consequence of iron overload may be more relevant in patients with low and intermediate-1 risk MDS who may survive long enough to experience such manifestations. It is a matter of debate whether this overload has time to yield organ damage, but it is quite evident that cellular damage and DNA genotoxic effect are induced. Iron overload may play a critical role in exacerbating pre-existing morbidity or even unmask silent ones. Under these circumstances, iron chelation therapy could play an integral role in the management of these patients. This review entails an in depth analysis of iron overload in MDS patients; its pathophysiology, effect on survival, associated risks and diagnostic options. It also discusses management options in relation to chelation therapy used in MDS patients and the impact it has on survival, hematologic response and organ function.

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Keywords: MDS; Myelodysplastic syndrome; Iron chelation; Iron overload; Transfusion-dependent; Deferasirox; Deferoxamine; Deferiprone

1. Introduction

Myelodysplastic syndromes (MDS) represent a group of hematologic disorders characterized by dysplastic and ineffective hematopoiesis. Approximately 80% of patients present with anemia and a substantial percentage of them...
will become transfusion-dependent during the course of their disease [1].

Chronic transfusions lead to secondary iron overload (IO). The relatively longer survival of low and intermediate-1 risk MDS groups classified by the International Prognostic Scoring System (IPSS) [2,3] places them at an increased risk of damage by IO from prolonged red cell transfusions compared to high risk patients who have a markedly reduced survival [1]. MDS population consists mainly of elderly with co-morbid conditions and a propensity to have cardiac failure, infection, hemorrhage and hepatic cirrhosis IO may rapidly exacerbate these pre-existing conditions [4].

In this review, we provide an overview of IO in MDS patients, its pathophysiology, associated risks and management options as recent and more systematic data on chelation therapy in MDS patients has become available in the past few years.

2. Iron overload

2.1. Pathophysiology

The pathophysiology of IO in MDS patients is related to that observed in thalassemia syndromes and consists of ineffective erythropoiesis and hepcidin dysregulation in some subtypes of MDS (primary IO) as well as transfusional siderosis (secondary IO). There are however some differences. Hepcidin is a key hormone mediating iron homeostasis. Hepcidin has a role in the down-regulation of ferroportin, the membrane transporter delivering duodenal iron from enterocytes to transferrin, thus resulting in decreased duodenal iron absorption [5,6]. In disease states of ineffective erythropoiesis, serum hepcidin levels are low that result in unrestrained duodenal iron absorption and subsequent IO [7]. Recently, we measured serum hepcidin by mass-spectrometry in 113 MDS patients, and found the lowest levels in refractory anemia with ring sideroblasts (RARS, 1.43 nM) and the highest in refractory anemia with excess blasts (RAEB 11.3 nM) [8]. RARS patients are particularly refractory to therapy with erythropoietic stimulating factors, and thus are frequently transfusion dependent, have a particularly expanded erythropoiesis, with an extremely frequent presence of acquired mutations in SF3B1, a gene encoding a core component of the RNA splicing machinery in MDS patients with ring sideroblasts [8,9]. A genetic study has confirmed our findings, correlating SF3B1 with ring sideroblasts and low hepcidin levels [10]. The growth differentiation factor 15 (GDF15), which has been shown to suppress the activity of hepcidin in thalassemia [11], did not seem to regulate hepcidin in our work and that of our authors. Therefore, low levels of hepcidin further predispose patients with RARS subtype of MDS to the risk of IO.

Anemia affects 80% of MDS patients and in their disease course many of them will receive transfusions. Red blood cell transfusions, while alleviating anemia may improve quality of life and prolong survival, but expose to several risks [12]. Patients with MDS may have an extremely high frequency of transfusions and may accumulate excess iron in a short time lapse. The rapidity and intensity of transfusions accounts for IO more than the total number [13]. In this state of iron repletion, ferritin production is increased to permit adequate storage of iron and transferrin receptor production is decreased to prevent further entry of iron into the cell [14,15]. When the binding capacity of transferrin in the blood is exceeded, iron is found in the plasma as non-transferrin bound iron (NTBI) [16]. Since iron cannot be actively excreted out of the body, it initially accumulates in the reticuloendothelial macrophages and is later deposited in the parenchymal cells of liver, heart and endocrine organs [17]. Intracellular iron can be found in endocytotic vesicles following entry of iron into the cell through the transferrin receptor-1, in ferritin where each ferritin molecule can hold up to 4500 atoms of iron or in association with proteins that form prosthetic groups involved in biological reactions [18]. In this IO state, NTBI changes to its redox active form termed labile plasma iron (LPI). Patients with low risk MDS have the higher NTBI levels compared to high risk MDS; highest levels are seen in RARS followed by 5 q-syndromes and CMML, respectively [8]. Entry of LPI into cells is mediated via several transporters; DMT1 in enterocytes [19], Zrt-Icon-like protein in hepatocytes [20] and L-type voltage dependent calcium channels in cardiac myocytes [21]. LPI is a toxic compound that enters the cell forming the labile cell iron (LCI) [22]. LPI in MDS is high and correlates with ferritin levels quite well. LCI results in the formation of reactive oxygen species (ROS) that can suppress renewal and number of hematopoietic stem cells [23] and can induce DNA damage and genomic instability [24]. This results in tissue damage and subsequent fibrosis which could result in complications as cardiomyopathy, cirrhosis and diabetes [25,26].

2.2. Impact of IO on survival

Several retrospective studies suggest a negative association between transfusion dependency in MDS and overall survival (OS) [27–29]. Whether this is due to the transfusions themselves or to the fact that more severe diseases require more frequent transfusions is a matter of debate. Furthermore, the impact of IO on OS in MDS patients has also been demonstrated. In a retrospective nationwide survey of Japanese patients, Takatoku et al. found that in 37 of 38 patients who died of hepatic or cardiac failure had ferritin levels >1000 μg/L suggesting that IO resulted in increased mortality [30]. On the other hand, in a retrospective analysis of a US database, complications potentially attributable to IO in MDS such as cardiac events, diabetes and liver disease occurred at a higher frequency in MDS patients receiving blood transfusions [31]. Also, Sanz et al. confirmed these results in a large series of 2994 patients where they showed that IO is an independent prognostic variable of OS and also AML transformation [32]. However, the results have never
been published in definitive form. Transfusion dependency coupled by increases in serum ferritin levels further exacerbates OS [29].

2.3. Impact of IO on cardiac, hepatic and endocrine function

The risk of cardiac events is increased in MDS patients, particularly in those who are transfusion-dependent [33]. Chronic anemia remains a co-factor in the development of cardiac failure because it necessitates increased cardiac output in order to compensate for impaired tissue oxygenation thereby leading to heart complications. MDS patients are reported to be at higher risk of cardiac events compared to the general population (73.2% versus 54.5%; \(P < 0.01\)) with transfused MDS patients having a higher risk than non-transfused ones (82.4% versus 67.1%; \(P < 0.001\)) [33]. Once again, this maybe attributable to cardiac remodeling correlated to anemia [34], which is there even in transfused patients who suffer from fluctuating hemoglobin levels, and to subsequent myocardial hypoxia, as well as to IO. Some inconsistency in fact exists in results from studies employing cardiac magnetic resonance imaging T2* (MRI) as measure of IO in MDS. These studies suggest that cardiac iron accumulation is not frequent in MDS patients [35–37].

Although the majority of MDS patients do not live long enough to manifest conditions of liver cirrhosis, hepatic complication nevertheless have been implicated in IO. In one retrospective study of 4546 patients with MDS and other hematopoietic disorders, transfusion dependency was significantly associated with risk of potential complications of IO (liver disease \(P = 0.0008\) and diabetes \(P = 0.0025\)) [38]. Moreover, in another Japanese retrospective study, the authors report 75 deaths, with cardiac failure noted in 24% of cases and liver failure noted in 6.7% of cases [30]. Of these, 97% had ferritin levels \(>1000\) ng/ml. Moreover, a large, retrospective analysis from US Medicare database revealed that diabetes occurs significantly more frequently in patients with MDS. When MDS patients were compared based on transfusion dependency, those receiving transfusions had an additional increased risk of diabetes than those not receiving transfusions; however, the difference was not statistically significant (44.4% versus 37.1%; \(P = 0.1\)) [33].

2.4. Diagnosis and evaluation of IO

Most data on modalities for the assessment of IO in general come from experience with transfusion-dependent thalassemia patients.

**Ferritin:** In the general population, IO is generally defined by a serum ferritin level \(>300\) \(\mu\)g/L in men and \(>200\) \(\mu\)g/L in women. Serum ferritin thresholds of \(>1000\) and \(>2500\) \(\mu\)g/L have been classically used to flag patients with increased morbidity risk and to tailor indications for chelation therapy in the thalassemia population [39]. The aforementioned studies evaluating the consequences of IO in MDS patients also relied on a serum ferritin level of \(>1000\) \(\mu\)g/L. Elderly patients with MDS present frequently with comorbidities, and chronic inflammation is a common finding. In this group of patients, C-reactive protein and other parameters are altered, and so is ferritin. It is thus a parameter which has some disadvantages, but may help in following a patient, allowing repeated exams and being rather costless and highly reproducible.

**Liver iron:** Assessment of liver iron concentration remains the gold standard for quantification of total body iron [40], with values up to 1.8 mg Fe/g dry weight considered normal, values up to 7 mg Fe/g dry weight seen in some non-thalassemic populations without apparent adverse effects and values \(>15\) mg Fe/g dry weight commonly associated with worse prognosis, liver fibrosis progression, or liver function abnormalities [39].

Liver biopsy enables pathologists to determine liver iron concentration as well as severity of liver disease in patients who are at high risk of liver involvement. However, liver biopsy is contraindicated in almost the totality of MDS patients since there is an increased risk of bleeding due to thrombocytopenia and/or platelet dysfunction [7].

**MRI:** Magnetic resonance imaging using either R2 (1/T2) or R2* (1/T2*) pulse sequences are reliable, internationally reproducible, and non-invasive methods for assessing liver iron concentration, and have been validated against liver biopsy in several diseases complicated by IO [41–43]. The upper limit to reliably estimate liver iron concentration by MRI is approximately 30–40 mg Fe/g dry weight, depending on the scanner specifications [43]. This method is expensive, requires a skilled radiologist, needs accurate software and is not readily available in all hematologic centers treating MDS patients. Moreover, not all MDS patients on chelation really require this determination, unless ferritin is increasing or some cardiac failure signs have appeared, or transfusion history prior to therapy is not clear [8]. Cardiac siderosis is measured using T2* MRI (normal: \(>20\) ms) a functional analysis in the end, which correlates with subsequent risk of heart failure. It is now validated as a true measure of cardiac iron, correlating with chemical measurement on post-mortem cardiac biopsies [42].

**Hepcidin:** Serum hepcidin measured by mass spectrometry or ELISA (EIA-5258) revealed that highly transfused patients were shown to have significantly higher hepcidin levels while patients with low hepcidin levels had significantly higher hemoglobin and transferrin, and lower serum ferritin and transferrin saturation [8,10,44]. A correlation between hepcidin and OS was seen with a hepcidin level according to EIA-5258 at or above the median of 17.5 ng/ml associated with a significantly worse survival (\(P = 0.03\)) [44]. However, the clinical reliability of hepcidin is still a subject of active research.

Practically, the best approach should be to assess iron intake by registering all transfusions carefully, which is not frequently done in clinics. For patients with significant transfusion burden, cardiac function (by ultrasound), liver function, and glucose tolerance test should be performed.
Iron 3.1. Iron chelation therapy

Early every three months. In case of increasing ferritin levels without specific inflammatory or infective causes during iron chelation therapy (ICT), as well as in case of cardiac or liver dysfunction, more accurate exams, like cardiac MRI (T2*) should be performed.

3. Iron chelation therapy

3.1. Chelation therapy

The rationale behind using ICT is removing the increased iron burden specifically LCI to minimize production of ROS thereby decreasing cellular and organ damage. Patients most likely to benefit from chelation therapy include those with low or intermediate-1 IPSS risk MDS who have a long life expectancy and are anticipated to receive more than 20 red blood cell transfusions and/or whose serum ferritin level is >1000 μg/L [1,45]. Chelation therapy efficacy can be monitored by monitoring trends and levels of serum ferritin.

Multiple drugs have been developed to decrease iron burden from IO states. The three iron chelators approved for use include deferoxamine (DFO), Desferal®, Novartis Pharma AG, Basel, Switzerland), deferasirox (Exjade®, Novartis Pharma AG, Basel, Switzerland) and recently deferiprone (Ferriprox®, Apotex Inc., Toronto, ON, Canada) (Table 1). DFO binds to NTBI or to iron that is found in ferritin and hemosiderin but not transferrin forming the ferroxamine molecule which is later excreted via the kidneys [46] (Fig. 1). Ferroxamine renders iron unavailable to chemical reactions and hence prevents formation of ROS. DFO promotes ferritin degradation in lysosomes by inducing autophagy [47]. Both deferiprone and deferasirox are likely to chelate cytosolic iron and iron which is extracted from ferritin prior to ferritin degradation by proteasomes [47] (Fig. 1). Besides its efficacy as an iron chelator, deferasirox administration has been associated with increased levels of hepcidin that results in the removal of ferroportin from the enterocyte membrane and its subsequent degradation by lysosomes [48]. Lately, Deferasirox has been used frequently in the treatment of IO in MDS patients. The oral administration in fact allows higher compliance of elderly patients who do not accept such prolonged infusions and may be subject to bleeding at the subcutaneous insertion site. Despite these positive characteristics, in a recent Italian study, the percentage of drop out from a chelation study in lower risk MDS was pretty high and related to compliance and side effects, even if mild which impaired MDS patients compliance [49]. Fig. 2 shows one suggested algorithm on the management of IO in MDS patients with the use of the aforementioned iron chelators.

3.2. Effect of chelation therapy on survival in MDS

Evidence supporting the fact that IO causes severe complications comes from the demonstration of prolonged survival in MDS patients undergoing ICT. At present, all the evidence comes from retrospective studies. These studies demonstrated that low risk MDS patients receiving chelation therapy had a better median OS compared to non-chelated ones [52–55]. Recently, significant improvement in survival was reported in low risk MDS patients exhibiting non-RARS features but the same was not achieved for patients with RARS [56]. Median OS in the RARS who received chelation therapy was 134.4 months versus 99 months; however, it did not reach statistical significance. The retrospective nature of these trials does not exclude potential bias that arises from the possibility that patients with a better performance score had a greater chance of being started on ICT. This bias can only be excluded once a prospective randomized placebo controlled trial is undertaken. A large phase 3 trial (TELESTO, Clinical trials.gov: NCT00940602) is currently recruiting patients with low and intermediate-1 risk MDS patients to receive either deferasirox monotherapy or placebo. Although the retrospective studies consistently show a survival advantage of chelation therapy, these results cannot be confirmed until results of this phase 3 trial are available.

3.3. Efficacy of chelation therapy in MDS patients

Results on the efficacy of chelation therapy in decreasing serum ferritin levels, LPI and liver iron concentrations come from prospective trials (Table 2). Most available data on the

| Table 1: Iron chelators available for the management of IO. |  |
| --- | --- | --- | --- | --- | --- |
| Agent | Approval (US, FDA) | Administration | Schedule and dose | Clearance | Most common adverse events |
| Deferoxamine [46] | Chronic ID due to transfusion-dependent anemias | Subcutaneous, intravenous | 20–40 mg/kg/d over 8–24 h 5–7 d/wk | Renal | Hypersensitivity reactions, tachycardia, gastrointestinal events, increased transaminases |
| Deferasirox [50] | Chronic ID due to blood transfusions or non-transfusion-dependent thalassemia | Oral | 20–40 mg/kg/d | Hepatobiliary | Gastrointestinal events involving diarrhea, nausea, constipation and abdominal pain; skin rashes and increased serum creatinine level |
| Deferiprone [51] | Transfusional ID due to thalassemia syndromes when other chelation therapy is inadequate | Oral | 25–33 mg/kg 3 x/d for a total daily dose of 75–99 mg/kg | Renal | Gastrointestinal symptoms, granulocytosis, agranulocytosis and elevation of liver enzymes |
use of ICT in MDS patients come from deferasirox trials, because they are more recent and data were collected in an appropriate and complete manner. Few and relatively small studies have been conducted with other iron chelators in patients with MDS.

Decreases in liver iron concentration depended on the dose of deferasirox administered and transfusion requirements [57,60]. Both Gatterman et al. and Breccia et al. reported a significant decrease in serum ferritin regardless of chelation history [60,63] suggesting that deferasirox is effective in patients receiving chelation therapy for the first time and in patients switching from other chelation therapies. However, the same result was not achieved in the EXtend and eXjange trials where a significant decrease in serum ferritin was seen only in patients not receiving prior chelation therapy [61]. Also, the decrease in serum ferritin level was

<table>
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<tr>
<th>Study</th>
<th>Patients</th>
<th>Treatment</th>
<th>Duration (months)</th>
<th>Decrease in LIC</th>
<th>Decrease in ferritin</th>
<th>Decrease in LPI</th>
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<tr>
<td>Porter et al. [57]</td>
<td>47</td>
<td>Deferasirox</td>
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<td>Metzegeroth et al. [58]</td>
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<td>Deferasirox</td>
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<td>Greenberg et al. [59]</td>
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<td>Deferasirox</td>
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<tr>
<td>EPIC trial, Gatterman et al. [60]</td>
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<td>Deferasirox</td>
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<td>US03 trial, List et al. [62]</td>
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<td>Deferasirox</td>
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<td>Breccia et al. [63]</td>
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<td>Nolte et al. [64]</td>
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<td>Gonzalez et al. [65]</td>
<td>28</td>
<td>DFO</td>
<td>12</td>
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<td>Kersten et al. [66]</td>
<td>18</td>
<td>Deferiprone</td>
<td>12</td>
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</tbody>
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S: significant; NR: not reported; NS: not significant; LPI: labile plasma iron; LIC: liver iron concentration; DFO: deferoxamine.
associated with a significant improvement in alanine transaminase ($P < 0.00001$), which is an indicator of hepatocellular injury that can lead to cirrhosis [60].

### 3.4. Hematological improvement with iron chelation

Evidence of hematological improvement with the use of iron chelation was reported previously in a study by Jensen et al. with the use of DFO. DFO was successful in decreasing transfusional requirements and 5/11 patients became transfusion independent [67]. Further improvement in platelet and neutrophil counts was also reported. In patients who showed improvement in erythropoietic output, an increase in serum transferrin receptor was detected.

Similarly, a post hoc analysis evaluated hematologic response to deferasirox in a cohort of iron-overloaded
patients with MDS enrolled in the EPIC trial. Erythroid, platelet and neutrophil responses were observed in 21.5% (53/247), 13.0% (13/100) and 22.0% (11/50) of the patients after a median of 109, 169 and 226 days, respectively. Median serum ferritin reductions were greater in hematologic responders compared with non-responders at end of study; although these differences were not statistically significant [68]. In another retrospective Italian study, 42.7% of patients receiving chelation with DFO or deferasirox achieved a hematologic response. Eighteen patients became transfusion independent; 12 of which received deferasirox and the remainder DFO [69]. Median time to response was 15 months for DFO and 3 months for deferasirox.

One proposed mechanism is the dynamic, bidirectional regulation between erythropoiesis and IO where not only ineffective erythropoiesis leads to increased intestinal iron absorption through the down-regulation of the hepatic hormone hepcidin [70], but also treatment of IO affects erythropoietic capacity and leads to improvements in hemoglobin level and red cell survival [71–73]. In a recent study from thalassemia patients, mobilization of hematopoietic peripheral progenitors (namely Erythroid Burst-Forming Units) was significantly higher in deferasirox-treated patients than those receiving other chelators, irrespective or the degree of iron depletion; which may indicate that the observed effects of deferasirox on hematologic outcomes are mediated by other factors [74]. In fact, it has been recently demonstrated that in MDS patients, IO suppresses the proliferation of erythroid progenitors cells (BFU-E), while the myeloid compartment (CFU-GM) is not affected and it was shown that ICT may revert such phenomenon [75]. It is a shared opinion that the ideal MDS patient to receive chelation is a patient with IPSS lower risk score (INT-1 and LOW), transfusion dependent but with a reasonable expectance of life, so that ICT may be effective and possibly make some difference in outcome. Nevertheless, it is becoming clearer that there is a subset of IPSS higher risk MDS patients which could benefit from ICT [45]. In particular, eligible MDS patients for whom a hematopoietic stem cell transplantation (HSCT) is programmed should be chelated because there is growing evidence that high ferritin levels before HSCT are correlated with worst outcome in patients receiving myeloablative conditioning regimen [76,77]. Therefore, it is strongly advisable to properly chelate these patients, even shortly before HSCT [78]. On the other hand, some higher risk patients who received a therapy modifying their survival and disease history could also take advantage from supportive ICT.

4. Conclusion

IO is a reality for transfusion dependent MDS patients. It is a matter of debate whether this overload has time to yield organ damage, but it is quite evident that cellular damage and DNA genotoxic effect via ROS species are induced. Another important point would be to verify the threshold of RBC transfusions leading to IO in MDS, and whether patients may be rescued by appropriate ICT [79].

The consequence of IO may be more relevant in patients with low and intermediate-1 risk MDS who may survive long enough. The causes of death in large MDS series may indicate that IO may play a critical role in exacerbating pre-existing morbidity or even unmask silent ones, especially because of the relative frailty of the large part of MDS patients. These considerations, together with the concept of “optimal” supportive care, should indicate iron chelation as an integrated tool in the management of MDS patients. Nevertheless, there is still ample skepticism in accepting this therapy, maybe due to low familiarity with the problem of IO and its diverse consequences. It is to be said that still little is known in iron homeostasis in MDS and that although MDS experts should learn the lesson from thalassemia experience, more evidence and data are required to clarify the role of iron in MDS disease manifestation and outcome. A lively debate is going on among MDS experts, and it seems as if the field was divided in “a priori” believers in IO and non-believers [80]. Prospective carefully planned randomized studies are the key to solve this issue.

Funding source

None declared.

Conflicts of interest

Sally Temraz reported no conflicts of interest. Ali Taher reported receiving research funding and honoraria from Novartis Pharmaceuticals; Khaled Musallam reported receiving research funding and honoraria from Novartis Pharmaceuticals and is currently (at the time of submission) an employee of Novartis Pharma AG, Basel, Switzerland; Valeria Santini reported receiving honoraria as a speaker from Celgene, Novartis, Janssen and GSK.

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References


Biography

Dr Ali Taher is a Professor of Medicine at the Division of Hematology–Oncology of the American University of Beirut Medical Center, Lebanon, where he is also Associate Chair for Research and the director of the Residency Research Program. In addition, he is a Consultant Hematologist at the Thalassemia Department of the Chronic Care
Center in Hazmieh, Lebanon and a fellow of the Royal College of Physicians and an Adjunct Professor at Emory School of Medicine, Atlanta, USA. Also, he is a member of the American Society of Hematology, the European Hematology Association, the International Society on Thrombosis and Hemostasis, the Mediterranean League against Thromboembolic Diseases, and of Alpha Omega Alpha honorary medical society. His research focuses on hemoglobinopathies, notably β-thalassemia and sickle cell disease, as well as thrombosis and hemostasis. Within thalassemia, his research interest lies in the detection of iron overload and the efficacy and safety of novel oral iron chelators. Moreover, he investigates the pathophysiology and clinical implications of β-thalassemia intermedia and its associated complications including mostly iron overload and hypercoagulability. In thrombosis and hemostasis, he investigates inherited thrombophilia and bleeding disorders, as well the incidence and prophylaxis of venous thromboembolism across several medical and surgical settings.