# Editorial: An Insight into the Symptomatology of β-thalassaemia Major – I

β-thalassaemia major is an important autosomal recessive disorder in many ethnic groups across the world. Blood transfusion and iron chelation is the mainstay of treatment in a vast majority of patients [1]. Most of the symptomatology of β-thalassaemia major is considered to be due to low haemoglobin level and effects of massive deposition of iron in the body. Iron chelation is the standard of care and recommended as soon as 10-20 blood transfusions have been given to the patient [1].

Recently, haemoglobin-F augmentation using Hydroxyurea (HU) is explored as a potential treatment option in transfusion dependent and non-transfusion dependent β-thalassaemia patients to ameliorate the need of blood transfusion [2]. Many groups from France, Iran, India and Pakistan have reported encouraging results in a subgroup of study patients [3-6]. Other groups reported additional benefit of iron chelation, along with HbF induction; when used in combination with other chelators, showed the maximum chelation effect [7, 8].

Mechanism of many of the clinical benefits of HU reported in β-thalassaemia is poorly understood. Despite of maintaining a haemoglobin level between 6-7 g/dl, they have a significantly improved quality of life and marked improvement in physical activity. Effects of HU at sub-cellular level *i.e.* on intracellular anti-oxidant levels, handling of trace elements required for enzymes in different metabolic pathways, oxygen binding and dissociation from haemoglobin-F are not known. Our group started to explore proteomics, metabolomics, genomics and metallomics in β-thalassaemia patients with and without the use of HU to understand the disease biology better [9-12].

Recently, metallomic profile of β-thalassaemia patients before and after treatment with HU was reported. Of 19 elements analysed in serum of these patients, 8 showed correction of impaired levels to the same levels as found in healthy control subjects. Exposure to HU not only improves Hb levels in β-thalassaemia patients but also reduces biometal dysregulations and normalization of many metabolic pathways [9]. This possibly translates into improved quality of life and exercise tolerance. These eight elements including Vanadium (V), Chromium (Cr), Iron (Fe), Cobalt (Co), Nickel (Ni), Copper (Cu), Rubidium (Rb), and Lead (Pb) have differential distribution when compared with HU untreated samples. There have been contradictory reports about copper in β-thalassaemia patients; some studies claimed that thalassaemia patients had elevated levels of serum copper, whereas others reported copper deficiency in some of the patients.

A significantly higher copper level was also reported in transfusion dependent thalassaemia patients (before the start of HU in them) as compared to healthy controls. After starting HU, these patients showed a significant reduction in serum copper level similar to those found in normal healthy individuals. These results indirectly support the lower oxidative stress in HU-treated patients as the copper levels return to normal. Elements such as vanadium, chromium, cobalt, lead, nickel and rubidium are found in ultra-trace levels in the human body. Except Rb, they all are toxic. The concentrations of V, Cr, Co, and Pb were found to be significantly elevated in thalassaemia patients before HU treatment as compared to those of healthy controls [13]. However, their levels decreased after HU treatment. Excess vanadium has been reported to cause biochemical imbalances in the body, resulting in body aches, arthritis, a weakened immune system, gastrointestinal disorders and various other symptoms. High lead level causes anaemia, brain damage, kidney disease, impaired growth, impaired reproductive function, and impaired mental functions in children. Our group found lower serum concentration of Ni and Rb in untreated β-thalassaemia patients as compared to healthy controls [13]. Treatment with HU normalized these levels to those of healthy and untreated subjects. Zinc is an essential trace element. Its deficiency results in growth retardation, hypogonadism in males, skin changes, and delayed wound healing. These clinical signs are seen in severe thalassaemia.

Zinc deficiency was consistently found in HU treated and untreated β-thalassaemia patients; lower in those of HU-treated patients as compared to healthy controls. Selenium is a component of Glutathione Peroxidase (GPx) and Thioredoxine

 

Reductase (TrxR). Our group reported significantly higher selenium levels in β-thalassaemia patients and even higher in those of HU-treated patients as compared to healthy controls [13]. Scientific literature shows contradictory reports about selenium in thalassemia patients.

This metallomic data in β-thalassaemia indicates that beta globin gene mutations may have some indirect functions in controlling metallomic pathways at cellular level. Many clinical manifestations in this disease may not be attributed to a low haemoglobin level. This data shows some evidence that part of the symptomatology may be attributed due to dysregulation of these trace elements in the body. HU to some extent reverses this dysregulation and directly or indirectly reduces oxidative stress at cellular level thereby improving the bodily functions in β-thalassaemia patients.

More studies are needed on metallomic regulation in this group of patient. Correction of deficiencies of some of these trace metals by supplementation along with HU treatment to reduce those trace elements which are present in higher concentration will bring them in equilibrium. This may add a new dimension in improving the treatment modalities of this disease, improving quality of life and exercise tolerance.

Studying metabolome of β-thalassaemia patients for disease prognosis and to understand unclear pathophysiological mechanisms of thalassaemia started to unveil many interesting and important differences in serum metabolites of β-thalassaemia patients and normal subjects.

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