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Original Research Article.

To Study Thyroid Profile, Short Stature, Delayed Puberty in Children With β – Thalassemia Major

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ABSTRACT

Background: Thalassemias are a common cause of hypochromic microcytic anaemia which arises from reduced or absent synthesis of globin chain of haemoglobin. Endocrine abnormalities are the most common complications of thalassemia. They include Delayed puberty, hypogonadism, Hypothyroidism, Impaired glucose tolerance and diabetes mellitus, Hypoparathyroidism, Adrenal insufficiency and short stature.

Objectives: To study Thyroid profile, short stature and delayed puberty in children with β- Thalassemia major.

Materials and methods: It was a cross-sectional study among 100 β-Thalassemia patients conducted within 1 year (April 2021-April 2022) amongst patients registered with Thalassemia Centre, Department of Paediatrics Rajindra Hospital, Patiala.

Results: A total of 100 patients were enrolled meeting the inclusion criteria. Out of 100, 36 (36%) had short stature while 64(64%) had normal growth. Out of 100, 24(24%) of patients had delayed puberty while 76(76%) patients had normal pubertal growth. Out of 100, 27(27%) were Hypothyroid whereas 73(73%) were Euthyroid.

Conclusion: Endocrine complications namely short stature, delayed puberty and hypothyroidism are seen in β- Thalassemia patients on multiple transfusions and chelation therapy due to high serum ferritin levels. Detection of these complications is important since regular screening of these patients, early detection and timely treatment could improve the life expectancy and quality of these patients.

Keywords: Thalassemia, Hypothyroidism, Serum Ferritin, Serum T3, Serum T4, Serum TSH, Blood transfusions.

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INTRODUCTION

Thalassemias are a common cause of hypochromic microcytic anaemia which arises from reduced or absent synthesis of globin chain of haemoglobin. The basic defect in Beta Thalassemia is reduced or absent production of beta globin chains with relative excess of alpha chains.[1] Peripheral haemolysis occurs when insoluble alpha globin chains induce membrane damage to the peripheral erythrocytes and cause anemia. The first response to ineffective erythropoiesis and anaemia is an increased production of erythropoietin causing a marked erythroid hyperplasia, which in turn may produce skeletal deformities, osteoporosis and occasionally extramedullary masses and contribute to splenomegaly. Untreated or undertreated thalassemia major patients have retarded growth as a result of anaemia and the excessive metabolic burden imposed by erythroid expansion. Ineffective erythropoiesis is also associated with increased intestinal absorption of iron caused by deficiency of hepcidin, a 25- amino acid peptide produced by hepatocytes that plays a central role in the regulation of iron haemostasis.

Clinical presentation of beta thalassemia major usually occurs between 6 and 24 months with severe microcytic anaemia, mild jaundice and hepatosplenomegaly. In untreated or poorly transfused patients, growth retardation, pallor, jaundice, poor musculature, genu valgum, leg ulcers, hepatosplenomegaly, development of masses from extramedullary haematopoiesis and skeletal changes resulting from expansion of bone marrow may occur.[2]

In thalassemias, Iron overload occurs due to red blood cell transfusion being the major cause and increased absorption of iron through GI tract being the other cause. Iron accumulation is toxic to many tissues, causing heart failure, cirrhosis, liver cancer,

growth retardation and multiple endocrine abnormalities Iron overload causes pituitary damage, leading to hypogonadism, growth retardation and delayed puberty. Endocrine complications namely diabetes, hypothyroidism, hypoparathyroidism, are present.[2] Despite early establishment of appropriate chelation therapy, problems such as delayed growth and sexual maturation and impaired fertility may persist.[3]

Endocrine abnormalities are the most common complications of thalassemia. They include Delayed puberty, hypogonadism, Hypothyroidism, Impaired glucose tolerance and diabetes mellitus, Hypoparathyroidism, Adrenal insufficiency and short stature.

Etiology of short stature is multifactorial. Growth failure has been attributed to GH deficiency (hypothalamic or pituitary), chronic anemia and hypoxia, hypothyroidism, delayed sexual maturation, hypogonadism, diabetes mellitus, zinc deficit, low Hb levels, bone disorders and desferrioxamine toxicity.[4]

Hypothyroidism is a common complication and is attributed to iron overload majorly. Thyroid dysfunction occurs due to gland infiltration, chronic tissue hypoxia, free radical injury, and organ siderosis.[5] Investigations of thyroid function should be performed annually, beginning at the age of 9 years. T4 and TSH are the key investigations. Thalassemia patients with overt hypothyroidism have been reported to exhibit stunted growth, delayed puberty, cardiac failure and pericardial effusion. Sexual complications in TM present the commonest endocrine complication in almost all studies. These include: Delayed Puberty, Arrested Puberty and Hypogonadism. Delayed puberty is defined as the absence of any pubertal sign in girls (breast enlargement) and in boys (testicular enlargement) by the age of 13 and 14 years respectively. Delayed puberty in TM is almost always due to Hypogonadotrophic Hypogonadism, which still remains the most stressful complication.[6] Hypogonadism, mostly hypogonadotropic hypogonadism, is usually detected during puberty.[7] Iron deposition on gonadotrophic cells of the pituitary leads to disruption of gonadotrophin production which is proven by the poor response of FSH and LH to GnRH stimulation and clinically manifested as Hypogonadotrophic Hypogonadism. The patients with the more severe defects have a greater rate of iron loading through higher red cell consumption and probably a different vulnerability to free radical damage.[8] Other complications include Diabetes mellitus, hypoparathyroidism, adrenal insufficiency, dental abnormalities.

Iron overload is measured using Serum Ferritin concentration and is measured every 3 months. The target value is between 500-1000 microgm/L The aim of chelation therapy is to maintain safe levels of iron by balancing iron intake from blood transfusions with excretion of iron from body. Three iron chelators are currently in clinical use: DFO (Deferoxamine), DFP (Deferiprone) and DFX (Deferasirox).

MATERIALS AND METHODS

A cross-sectional study of 1 year (April 2021-April 2022) was conducted amongst patients registered with Thalassemia Centre, Department of Paediatrics Rajindra Hospital, Patiala. Consent was obtained from the parents of the children in their own vernacular language.

Inclusion Criteria:

1) Age group 10 years to 18 years.
2) Registered with Thalassemia Centre, Department of Paediatrics Rajindra Hospital, Patiala.

Exclusion Criteria:

1) Non transfusion dependent Thalassemia patients.
2) Patients not consenting.

METHODOLOGY

Following was done and assessed:

1. Thorough History.
a. Age of Diagnosis.
b. Pre- Transfusion Hb levels (Initial Hb at diagnosis of Thalassemia)
c. Complete chelation history
2. Accurate measurement of height and weight.
3.Evaluating pubertal status according to Tanner stages (breast development (girls) and testicular volume (boys) and classification into various stages (I-V).
4. Routine Investigations.
5. Special investigations such as Thyroid Profile – T3, T4, TSH.

Venous blood samples were withdrawn under aseptic conditions and used for estimation of Thyroid profile. All samples were collected in vacutainers. After centrifugation the serum was separated, and samples were preserved in refrigerator at 2-4^{0}C.

Statistical Analysis

Data was analysed using SPSS 25 software version. The descriptive statistics were used to analyse socio demographic characteristics of the subjects. To study the relationship between short stature, delayed puberty and hypothyroidism and serum ferritin levels, chi-square test was used, $p<0.05$ was considered as significant level.

OBSERVATIONS

A total of 100 patients were enrolled meeting the inclusion criteria. Out of 100, 65(65%) were males and 35(35%) were females. Table 1 shows patient wise distribution with Thyroid profile, short stature and delayed puberty among subjects.

Hypothyroidism: Out of 100 subjects, Hypothyroidism was seen in 27 patients whereas 73 patients were Euthyroid.

In our study population of 100 thalassaemic patients, hypothyroidism was seen in 27(27%) patients whereas 73 patients (73%) had normal thyroid levels. Out of 27 patients with hypothyroidism, 19 (70.4%) patients were males, and 8 (29.6%) patients were females.

In a study done by Eshragi et al[9] in Iran ,among a study of 130 patients (56 males and 74 females) suffering from Thalassemia major with age ranged from 10 to 47 years was done. Hypothyroidism was seen in 19 (14.6%) patients.

In a study conducted by Khandelwal R et al [10], 6.8% had overt hypothyroidism, 13.6% had subclinical hypothyroidism and 79.7% had euthyroid status.

SHORT STATURE

Short stature: Out of 100 36 (36%) had Short stature while 64(64%) had normal growth.

- In our study out of 100 patients' short stature was seen in 36(36%) patients and 64(64%) patients had height above 3rd centile for age.
- Out of 36 patients with short stature 13 patients were females and 23 males, Out of 36 patients with short stature,

19 patients had Serum ferritin <2000 µgm/L whereas 17 patients has Serum ferritin >2000 µgm/L.

- In a similar study done by Eshragi et al[11] in Babol, out of 133 thalassemic patients, 41(31.3%) patients were found to be short, with their height less than the 3rd percentile for age whereas in 53 (40.8%) patients weight was under normal range.
- In a study conducted by S Sharma et al[12] in a tertiary care centre in North East India, among 50 children with Thalassemia major,68% patients had Short stature as evidenced by Height for age less than 3rd centile. It was 67.7% in males and 68.4% in females.
- In all of above-mentioned studies including our study, short stature is one of the most commonest prevalent endocrinopathy in thalassemic patients.

DELAYED PUBERTY

In our 100 patients, 24(24%) of patients had delayed puberty while 76(76%) patients had normal pubertal growth.

- In our study out of 100 thalassemic patients,24 (24%) patients had delayed puberty, whereas 76 (76%) patients had normal pubertal development. Delayed puberty is defined as the absence of any pubertal sign in girls (breast enlargement) and in boys (testicular enlargement) by the age of 13 and 14 years respectively. Delayed Puberty is said to be when the patient has not achieved appropriate tanners stage for that age.
- In a study by N Abdelrazek et al[13], at University Children's Hospital, Egypt among 40 (20 Males and 20 Females) patients with age group 12-22 years, delayed puberty as assessed by Tanner's Staging was seen in 16 boys (80%) and 15 girls (75%).
- In a study by Moayeri et al[14] in a tertiary centre in Tehran,62 (69%) patients out of total of 138 patients showed failure of puberty out of which 33 (73.2%) were males and 29 (64.8%) females.

Table 2 shows Ferritin levels in relation to Hypothyroidism. In Patients with Serum Ferritin levels <2000ng/ml 9(17.6%) patients were Hypothyroid and 42(82.4%) were Euthyroid. Whereas in patients with Serum Ferritin levels >2000ng/ml 18 patients (37.7%) were Hypothyroid and 31(62.3%) were Euthyroid. The correlation was significant statistically. (p value = 0.03)

In our study among patients with serum ferritin levels <2000 ng/ml, 9 patients (17.6%) were hypothyroid whereas 42 patients (82.4%) were Euthyroid. In patients with serum ferritin levels >2000 ng/ml, 18 patients (37.7%) were hypothyroid whereas 31 patients (62.3%) were Euthyroid. The association of serum ferritin levels with Hypothyroidism was statistically significant. (p value = 0.03).

In a study conducted by S Baul[15] at Thalassemia centre, NRS Medical college, Kolkata conducted from January 2016 to December 2017 out of 50 β-thalassemia patients, A total of 22 (44%) patients showed thyroid dysfunction; overt hypothyroidism seen in 6 (12%) patients with mean ferritin level of 1077 ng/ml and subclinical hypothyroidism seen in 16 (32%) patients with mean ferritin level of 1200 ng/ml. Normal thyroid function seen in 28 (56%) of patients with mean ferritin level of 1155 ng/ml.

Table 3 shows correlation between S. ferritin levels and short stature. In 51 patients with Ferritin levels <2000, 19 patients (34.7%) had short stature and 32(62.7%) had normal growth, whereas in 49 patients with Ferritin levels >2000, 17 patients (34.7%) had short stature and 32 patients (65.3%) had normal growth.

In a similar study done by Eshragi et al[11] in Babol, out of 133 thalassaemic patients, 41(31.3%) patients were found to be short, with their height less than the 3rd percentile for age whereas in 53 (40.8%) patients weight was under normal range.

In a study conducted by S Sharma et al [12]in a tertiary care centre in Northeast India, among 50 children with Thalassemia major, 68% patients had short stature as evidenced by height for age less than 3rd centile. It was 67.7% in males and 68.4% in females.

Table 4 shows association between Serum Ferritin levels and Delayed puberty. Among 51 patients with S. ferritin levels <2000 ng/ml, 10(29.6%) patients had delayed puberty and 41 patients (80.4%) had normal pubertal growth. Among 49 patients with S. ferritin levels >2000 ng/ml, 14 patients (28.6%) had delayed puberty whereas 35 patients (71.4%) had normal pubertal growth. The correlation between Serum ferritin levels and delayed puberty was statistically insignificant. (p value = 0.29)

In our patients with serum ferritin levels <2000ng/ml, 10 patients (29.6%) had delayed puberty whereas 41 patients (80.4%) had normal pubertal development. In patients with ferritin levels >2000 ng/ml, 14 patients (28.6%) had delayed puberty whereas 35 patients (71.4%) had normal pubertal development.

In study done by Shamshiraaz et al[16] in Tehran the average ferritin levels were 1441±1111.3µg/l ,in this study population out of 220 thalassaemic patients evaluated, 80.8% of boys and 72.6% of girls had impaired puberty. Serum ferritin level in this group was 1407 ± 971 µg/l, which was not statistically significant. Hypogonadism was seen in 22.9% of boys and 12.2% of girls with the mean serum ferritin level equal to 1787 ± 988 µg/l that was significantly higher than patients without hypogonadism (P = 0.036).

Table 1: Thyroid profile, short stature and Delayed puberty of β-thalassemia study subjects (n=100)

Thyroid Profile	**No.**	**%**
Hypothyroidism	27	27.0
Normal	73	73.0
Short stature		
No	64	64
Yes	36	36
Delayed Puberty		
No	76	76
Yes	24	24

Table 2: Association of serum ferritin level with Hypothyroidism

Thyroid status	Upto 2000	>2000	P value
Hypothyroidism	9 (17.6%)	18 (37.7%)	0.03
Euthyroid	42 (82.4%)	31 (62.3%)	

Table 3: Association of serum ferritin level with short stature

Short stature	Upto 2000	>2000	P value
No	32 (62.7%)	32 (65.3%)	0.79
Yes	19 (37.3%)	17 (34.7%)	

Table 4: Association of serum ferritin level with delayed puberty

Delayed puberty	Upto 2000	>2000	P value
No	41 (80.4%)	35 (71.4%)	0.29
Yes	10 (29.6%)	14 (28.6%)	

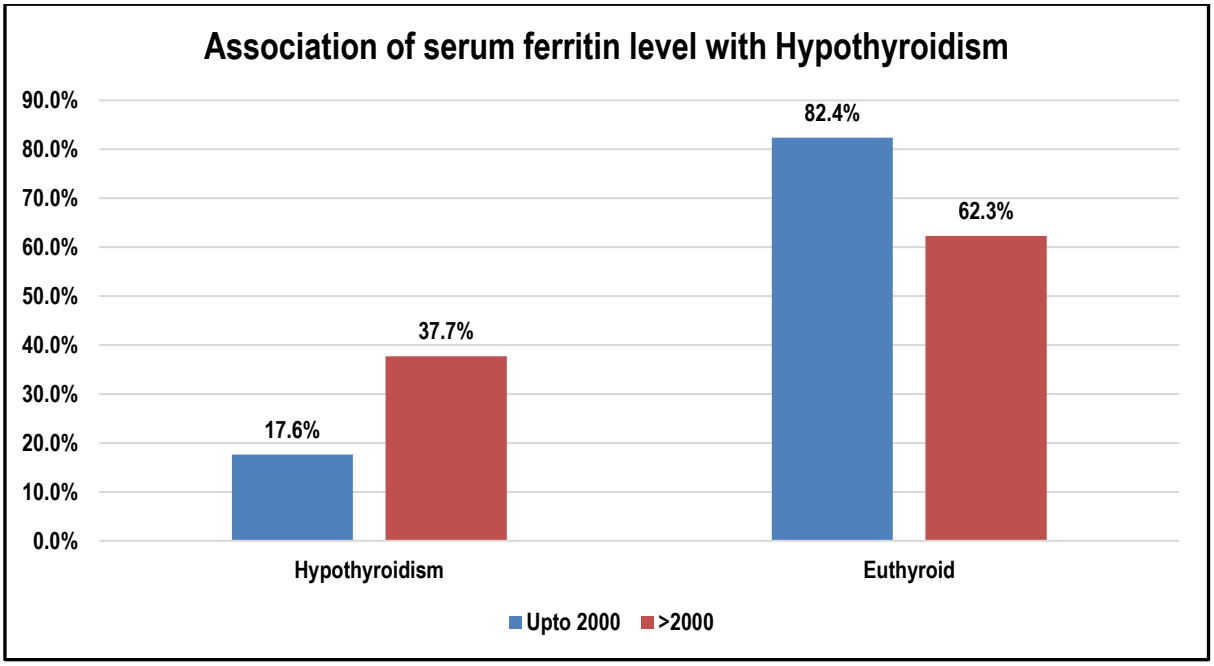

Figure 1. Association of Serum Ferritin levels with Hypothyroidism.

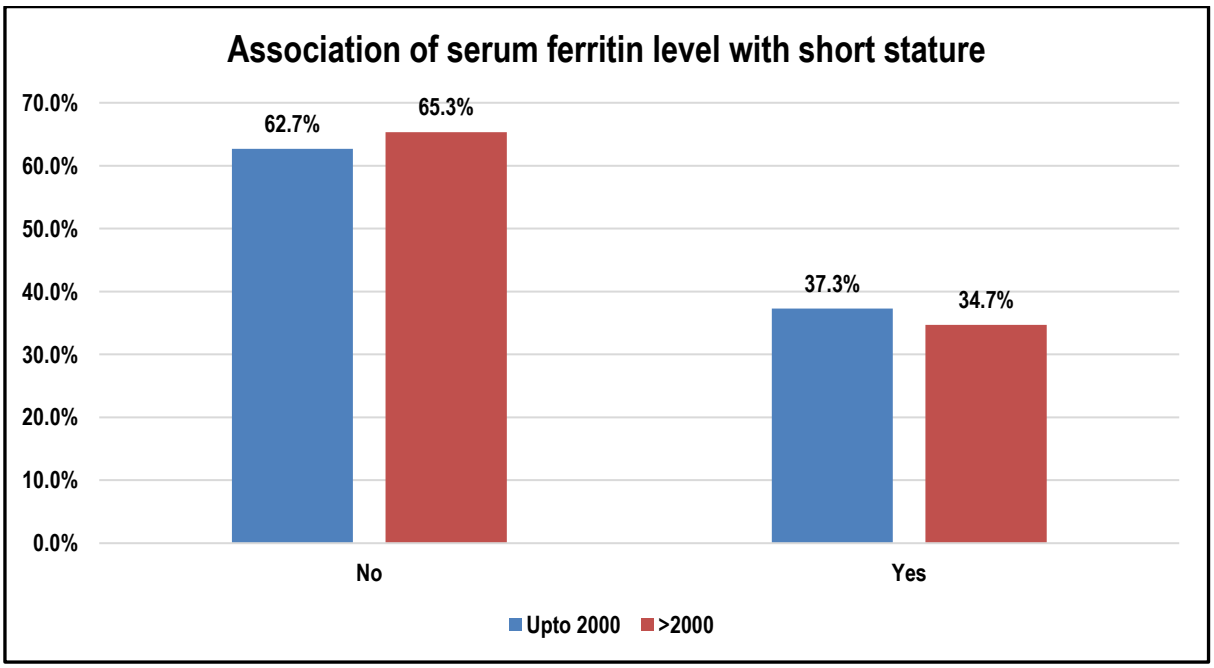

Figure 2: Association of Serum ferritin with short stature.

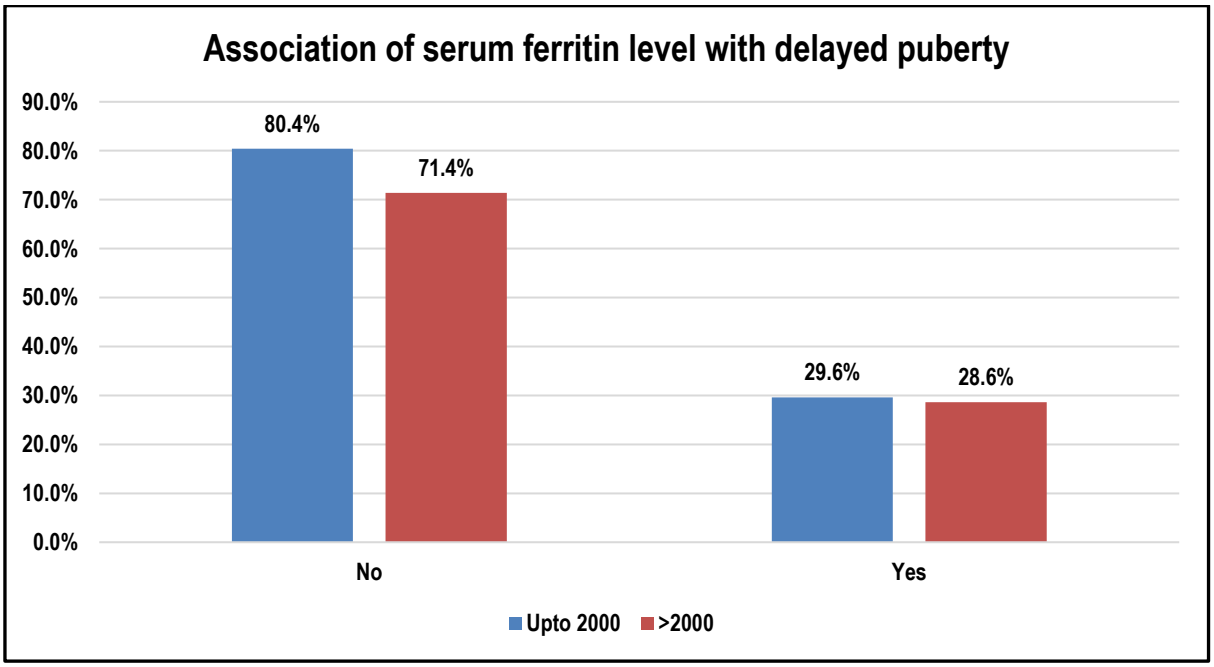

Figure 3. Association of Serum ferritin and delayed puberty.

DISCUSSION

With the emergence of safe transfusion therapies and regular monitoring, the life of Thalassemia patients has improved both in terms of duration as well as quality. But the complications related to transfusions and Iron overload are a significant cause of morbidity and mortality in these patients.

This study has been conducted to study the trends of one of the major Endocrinal complications associated with Chronic Transfusions leading to iron overload in Beta thalassemia patients i.e Hypothyroidism along with effect of the same on Growth and Pubertal development. This study 'Thyroid profile, shorts stature and delayed puberty in children with Beta- Thalassemia major' is a cross sectional study over a period of one year from April 2021 to April 2022 at Department of Paediatrics, Rajindra hospital, Patiala. The study was conducted among 100 registered transfusion dependent Thalassemia patients who met the inclusion criteria. The study consisted of 65 boys (65%) and 35 girls (35%). Thyroid function was assessed using ELISA kits for the estimation of TSH, Free T4, and the iron overload was estimated by measuring the serum ferritin levels. Anthropometric assessment for height was conducted for all children included in this study and found that 36 % patients had short stature. Tanners staging for age was done for Pubertal development and 24 patients (24%) had delayed puberty.

Beta- Thalassemia major children on regular transfusions and suboptimal chelation are at an increased risk for iron overload. Like in all organs, iron is deposited in the thyroid interstitium resulting in thyroid hemosiderosis. This slowly leads to worsening of the thyroid function. Iron deposition from repeated transfusions has been implicated as the likely mechanism causing thyroid dysfunction in BTM patients. Serum ferritin has a direct correlation to iron accumulation in the liver. Excess iron causes serious and irreversible organic damage, such as cirrhosis, diabetes, heart disease and hypogonadism. Fibrosis of the liver correlates with age, number of units transfused and liver iron concentration.

The aim of our study is to emphasise that Chronic iron overload resulting from frequent transfusions, inefficient chelation therapy in terms of monotherapy or polytherapy and its compliance is basically responsible for the most severe complications of thalassemia major (TM). Therefore, highlighting the requirement of an integrated approach to management with organisational interaction of thalassemia unit with other hospital facilities, blood banks, laboratries, patient support groups.

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Conflict of Interest: None Declared.

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