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Changes in Kisspeptin, Growth and Thyroid Hormones in Thalassemic Patients of Pubertal Age Group

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ABSTRACT

Beta thalassemia syndrome are a group of hereditary blood disorders in which or absent beta globin chain synthesis, results in reduced Hemoglobin, decreased RBC production and anemia. Total 300 individuals were divided into 4 groups according to age and gender *i.e* ≤13 years females, >13 years females, ≤13 years and >13 years males. Height in centimeter, weight in kilogram was measured to calculate BMI Kg/m^2. Serum ferritin (ng/mL) and hemoglobin (gm/dl) alongwith hormonal assay of GH (ng/mL), T_3 (ng/mL), T_4 (µg/dL) TSH (µIU/mL), and kisspeptin (ng/ml) was done. BMI and hemoglobin were significantly reduced (P<0.001), while serum ferritin were significantly increased (P<0.001) in all four thalassemic groups on comparison with control. Kisspeptin levels were significantly reduced in ≤13 years female (P<0.001). While significantly high levels were observed in >13 years of male (P<0.01). T_3 levels were significantly increased in both thalassemic groups of female (P<0.01). While T_4 levels were significantly reduced in ≤13 years of male alongwith significantly reduced (P<0.05) TSH levels. In >13 years male significantly increased (P<0.01) TSH levels were obtained. Growth hormone levels were significantly reduced (P<0.001) in both male and female thalassemic groups of ≤13 years. While significantly raised (P<0.001) hormone levels were observed in male and female thalassemic groups of >13 years. In >13 thalassemic female T_3 had a negative correlation (P<0.05) with BMI and hemoglobin, while a positive correlation (P<0.001) of T_3 with hemoglobin was observed in thalassemic male of ≤13 years. In >13 years male T_3 had a positive correlation (P<0.05) with kisspeptin. T4 in all four thalassemic groups had a significant positive correlation with hemoglobin (P<0.05). TSH in >13 years female had a significant positive correlation with BMI, ferritin and hemoglobin (P<0.001). Results revealed that hypothalamic pituitary axis had proper production, other factors miught be involved in delaying the growth spurt.

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SJ designed the study. SA and HU collected blood samples and performed hormonal analysis. SA wrote the article.

Key words
Thalassemia, Ferritin, Kisspeptin, Thyroid Hormones.

INTRODUCTION

Beta thalassemia syndrome are a group of hereditary blood disorders characterized by reduced or absent beta globin chain synthesis, resulting in reduced Hemoglobin in red blood cells (RBC), decreased RBC production and anemia. In thalassemia major defective gene are inherited from both parents and clinical features appear by 6 to 24 months of age. Transfusion with chelation therapy has significantly extended life expectancy but, leads to complications due to iron overload (Borgna-Pignatti *et al*., 2004; Qurat-ul-Ain *et al*., 2011). Iron toxicity causes development of Reactive oxygen species (ROS) that lead to DNA damage (Mehrvar *et al*., 2008). Iron deposition in gonads (primary), pituitary gland (secondary) and hypothalamus (tertiary) leads to Hypogonadism. Whereas, overloaded pituitary iron is most prevalent in thalassemia major (Wood *et al*., 2010; Farmaki *et al*., 2010). Early recognition of pituitary iron over load can only partially be reversed by intense chelation therapy therapeutic (Kohgo *et al*., 2008; Chatterjee and Bajoria, 2010). Disturbance of the hypothalmo pituitary gonadal (HPG) axis leads to reduced target height and delayed puberty. Gonadotropin releasing hormone (GnRH) is main regulator for onset of puberty (Kyriakou and Skordis, 2009). Primary excitatory neurotransmitter of GnRH secretion is glutamate along with leptin, kisspeptin (Chatterjee and Katz, 2000; Apter *et al*., 1993). Currently, the role of kisspeptin for the onset of puberty and fertility has been recognized, it functions through the G-protein coupled receptor (GPR54), which stimulates GnRH neurons (Shander and Cappellini, 2009; Roseweir and Millar, 2009). Pituitary iron deposition occurs in second decade of life (Marshall and Tanner, 1969). Primary gonadal dysfunction is a late finding during which, irreversible damage to HPG axis has already occurred, strong association has been observed between pituitary volume and appearance of clinical disease which suggest that secondary hypogonadism is the dominant etiology, whereas tertiary hypogonadism

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has not been explored. Similarly, previous studies did not explore the level of dysfunction in hypothalmic pituitary HP axis. Biochemical parameters are more reliable than clinical parameters as patients with profound pituitary iron overload may have no clinical proof of hypogonadism (Fung *et al*., 2006; Chatterjee and Bajoria, 2010). Age of iron deposition and stage at which it causes HP dysfunction is unknown, presence of iron in an organ does not necessarily suggest that damage has occurred, a silent period of pituitary siderosis occurs before hypogonadism develops (Chatterjee and Katz, 2000). Serum ferritin levels >1000 ng/ml lead to iron overload in various organ like heart, liver and endocrine gland (Olivieri and Brittenham, 1997; Vichinsky, 2001). Iron toxicity on the adipose tissue causes altered physiological function of leptin that affects body mass index (BMI) and body growth (D'anglemont *et al*., 2007; Plant and Durant, 1997). Definite levels of serum ferritin causing significant iron toxicity and organ damage are still unknown.

Advancement in medical treatment has improved the survival rate of thalassemic patients (Olivieri and Brittenham, 1997). Alongwith endocrine complications growth retardation is a frequent problem encountered by the thalassemic patients. Etiology of growth retardation is based on a number of factors like disease itself, toxic effects of the drugs used for chelation therapy (Caruso *et al*., 1998; De Sanctis *et al*., 1996), toxicity of iron overload and malnutrition and endocrine complications (Fuchs *et al*., 1997). The mechanism of growth retardation in these patients is not fully exemplified however, regarding endocrine complications along with thyroid and gonadal dysfunction (Roth *et al*., 1997; Jain *et al*., 1995), Growth Hormone (GH), insulin like growth factor (IGF),insulin like growth factor binding protein (IGFBP) also play an important role (Ashraf *et al*., 1998; Low *et al*., 1998).

Cause of retarded growth in thalassemic patient is complex and multi-factorial various factors like chronic hypoxia secondary to anemia (pre-transfusion Hb is below 8.5g/l), deficiency of Growth Hormone due to defective hepatic, biosynthesis of somatomedin, insulin like growth factor-1 (IGF-1) and sex steroid deficiency play main their role. Children treated with modern transfusion and chelation therapy are entering early adulthood so, evaluation of various endocrine complication secondary to iron overload can be evaluated in such individuals for future interventions. Therefore, exploration of the effects of iron overload on Kisspeptin and anterior pituitary hormones like GH, TSH and Thyroid hormones T_3, T_4 were evaluated. Also correlation of these hormones with body mass index (BMI), Ferritin and Hemoglobin (Hb) and Kisspeptin levels were further evaluated in beta thalassemic patients undergoing regular blood transfusion with chelation therapy.

MATERIALS AND METHODS

The present study included total 300 individuals out of which 200 were thalassemic patients and 100 were control matched for age and gender with the thalassemic group. The study was carried out after approval from Ethics committee of Quaid-e-Azam University. It was a case control study carried out at Quaid-e-Azam University in collaboration with Jamila Sultana Foundation, Thalassemia House, and Pakistan Institute of Medical Sciences (PIMS) from 2010-2014. The total individuals were divided into 4 groups according to age and gender *i.e.* ≤13 years females, >13 years females, ≤13 years and >13 years males. The patients selected for the study were diagnosed as beta thalassemia major according to hemoglobin electrophoresis. These patients were on regular blood transfusion with chelation therapy (desferroxamine injections). Informed consent and a detail proforma including history and clinical examination were filled on the patients visit to the thalassemia center. Patients suffering from any other blood disorders other than beta thalassemia major or any other pathology besides spleen and liver enlargement or Hepatitis B and C were not included. Height in centimeter and weight in kilogram were measured to calculate the BMI Kg/m^2. Serum ferritin (ng/mL) and hemoglobin (gm/dl) were done when patients came for their routine blood transfusions. The blood samples were taken for hormonal assay of GH (ng/mL), T_3 (ng/mL), T_4 (µg/dL) TSH (µIU/mL), and kisspeptin (ng/ml). The samples were collected in comfortable sitting position and arm rest was provided under the elbow. The sampling area was disinfected with a spirit swab. Blood sample (3ml) was drawn from the right median cubital vein of both female and male patients. Blood was then collected in labeled serum separator tubes containing Ethylene diamine tetra acetic acid (EDTA). The blood samples were centrifuged at 3000 rpm for 10 mins, and serum separated was stored at 2-8 ^{0}C until analyzed. Serum hormone concentration for qualitative determination of GH was done by Enzyme Amplified Sensitivity Immunoassay, T_3 was done by using Micro Particle Enzyme Immuno Assay (MEIA), while T_4 was analyzed using Fluorescence Polarization Immunoassay (FPIA). TSH was detected by Chemiluminescent Microparticle Immunoassay (CMIA) and detection of specific peptide and its related peptides of kisspeptin were analyzed by using principal of competitive enzyme immuno assay (CEIA).

Statistical analysis

Data was analyzed through Graph Pad Prism 5.01, and data was reported as mean±SEM. Comparison

amongst hormones, BMI, hemoglobin and serum ferritin level with the control group was done by using unpaired t-test. Further non parametric co-relation (Spearman) was done for each hormone with rest of the variables through pad prism. P<0.05 was considered statistically significant in both cases.

RESULTS

Thalassemic patients included in the study were divided in 4 different groups. Mean±SEM of age in male and female patients of ≤ 13 years was 10.3± 0.20 years. Male patients >13 years had mean±SEM of age 16.7±0.42 years, whereas the female patients of >13 years had mean±SEM of age 17.8±0.70 years. Mean±SEM of BMI, serum ferritin and hemoglobin levels of thalassemic and control groups are presented in Table I. BMI and hemoglobin levels in all thalassemic groups were significantly (P<0.001) less than the respective control group. In both, male and female thalassemic patients (≤13, >13years) significantly high (P<0.001) level of ferritin were noticed between the patient and corresponding control group. Comparison of serum kisspeptin levels in control and thalassemic male and female patients of different age groups are represented in Figure 1A. Serum kisspeptin levels in thalassemic females ≤13 years (5.60±0.26 ng/ml) were significantly lower (P<0.001) as compared to the control group (10.1±0.95 ng/ml); whereas, serum kisspeptin levels of thalassemic males >13 years were 28.00±0.76 ng/ml and were significantly higher (P<0.01) as compared to the control group (25.00±0.18 ng/ml). Comparison of serum T_3 levels of males and females thalassemic patients with their corresponding control of different age groups is shown in Figure 1B. Serum T_3 levels in ≤ 13 years thalassemic females (27.0±8.44 ng/mL) was significantly higher (P<0.05) than the control group (1.50±0.03 ng/mL), similarly thalassemic females >13 years (1.88±0.115 ng/mL) also had significantly higher (P<0.001) T_3 levels than the control group (1.38±0.05 ng/mL). On comparison, serum T_3 levels in thalassemic males ≤ 13 and >13 years of age, there was no significant difference with the control groups. Comparison of serum T_4 levels of males and females thalassemic patients with their corresponding control of different age groups is shown in Figure 1C. Serum T_4 levels in ≤13 years thalassemic male patients (6.60±0.39 µg/dL) were significantly lower (P<0.001) than that in the control group (8.26±0.22 µg/dL), whereas serum T_4 levels in >13 years males and ≤13 and >13 years thalassemic females were not significantly different from those in the control groups.

Serum TSH levels in thalassemic males and females of different age groups are shown in Figure 1D. Serum TSH levels in thalassemic females of ≤ 13 years and >13 years females were not significantly different when compared with the control group, respectively. The serum TSH levels were significantly lower (P<0.05) in thalassemic males of ≤ 13 years of age (1.50±0.08 µIU/mL) as compared to the control group (2.20±0.34 µIU/mL). Whereas >13 years thalassemic males (6.70±1.2 µIU/mL) TSH levels were significantly higher (P<0.01) than the control group (1.40±0.11 µIU/mL). Serum GH levels in thalassemic male and female patients of different age groups are shown in Figure 1E. Serum GH levels in thalassemic female ≤13 years were (1.33±0.00 ng/ml**)** which were significantly low (P<0.01) than the control group (1.80±0.27 ng/ml). Whereas, thalassemic females of >13 years (2.29±0.30 ng/ml) had significantly high levels (P<0.01) when compared with the control group (1.02±0.19 ng/ml).

Table I.- Mean±SEM of BMI, hemoglobin and serum ferritin levels in control and thalassemic male and female patients in different age groups.

Age (Years)	Gender	Groups	BMI (Kg/m^2)	Hb (gm/dl)	Ferritin (ng/mL)
≤ 13	Females	Control (n=25)	19.6±0.51	13.1±0.27	74.8±2 .92
		Thalassemic (n=75)	16.0±1.42***	7.60±0.17***	3900±301***
> 13		Control (n=25)	23.1±0.48	13.5±0.26	150±7.02
		Thalassemic (n=75)	13.7±0.92***	6.71±0.30***	3630±368***
≤ 13	Males	Control (n=25)	21.8±0.44	13.5±0.28	75.8±3.00
		Thalassemic (n=75)	17.2±0.61***	7.06±0.23***	4240±255***
> 13		Control (n=25)	22±0.45	15.00±0.27	130±13
		Thalassemic (n=75)	18±0.63***	8.00±0.47***	4300±320***

BMI, body mass index; Hb, hemoglobin. ***= P<0.001 is considered significant.

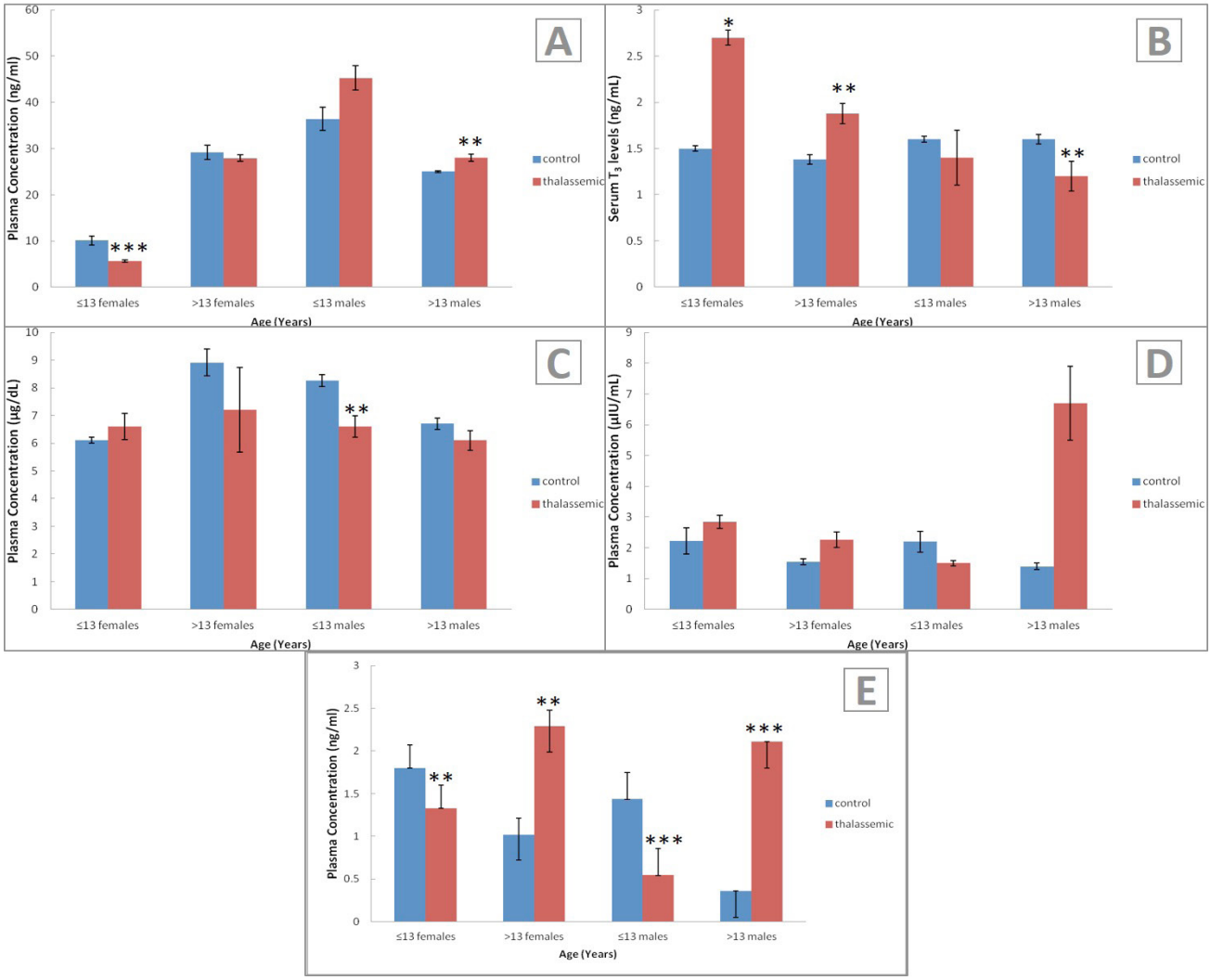

Fig. 1. Kisspeptin (A), kriiodothyronine (B), thyroxin (C), thyroid stimulating hormone (D), and (E) of male and female thalassemic patients with their corresponding control of different age groups. Mean±SEM. *P<0.05, value *vs* corresponding control; **, P<0.01, value *vs* corresponding control; ***, P<0.001, value *vs* corresponding control.

Similarly, serum GH levels in thalassemic males of ≤13 years (0.55±0.01 ng/ml) were significantly, lower than (P<0.001) control group (1.44±0.31 ng/ml), while thalassemic males >13 years (2.11±0.31 ng/ml) were significantly raised as compared to the control group (0.36±0.00 ng/ml) respectively. Correlation of T_3 and T_4 with BMI, serum ferritin, hemoglobin and kisspeptin levels in control and thalassemic males and females patients in different age groups is shown in Table II.

In thalassemic female of >13 years T_3 has a significant (P<0.001) negative correlation with BMI (r= -0.408), (P<0.05) with Hb levels (r= -0.329). While T_3 has a positive correlation (P<0.05) with serum ferritin levels of thalassemic males of ≤ 13 years (r = 0.523) similarly, T_3 has a positive correlation (P<0.05) with kisspeptin levels (r=0.317) in thalassemic males of >13 years.T_4 has a significant positive correlation (P<0.05) with BMI (r= 0.333), serum ferritin (r=0.317) and Hb levels (r=0.328) in thalassemic females of >13 years of age. While T_4 has a positive correlation (P<0.05) with Hb levels (r=0.332) in ≤ 13 years thalassemic females. Similarly, T_4 has a positive correlation (P<0.001) with Hb levels (r=0.516) in thalassemic males of > 13 years of age and (P<0.01) with Hb levels of ≤13 years thalassemic male (r= 0.422).

Correlation of TSH and GH with BMI, serum ferritin, hemoglobin and kisspeptin levels in control and thalassemic males and females patients in different age groups is shown in Table II.

Table II.- Correlation of T_3 and T_4, TSH and growth hormone with BMI serum ferritin, hemoglobin and kisspeptin levels in control and thalassemic male and female patients in different age groups.

Age (Years)	Gender	Hormone	Groups	BMI (Kg/m²)	Ferritin (ng/mL)	Hb (gm/dl)	Kisspeptin (ng/ml)
≤ 13	Females	T_3 (ng/mL)	Control (n=25)	0.0	0.155	-0.274	0.111
			Thalassemia (n=75)	0.148	-0.223	0.085	0.031
> 13			Control (n=25)	0.443	0.441	0.311	0.155
			Thalassemia (n=75)	-0.408**	-0.038	-0.329*	0.243
≤ 13	Males		Control (n=25)	0.284	0.162	0.155	-0.122
			Thalassemic (n=75)	-0.263	0.523***	0.187	0.202
> 13			Control (n=25)	0.0734	0.018	0.107	0.460
			Thalassemic (n=75)	0.164	-0.207	0.208	0.317*
≤ 13	Females	T_4 (µg/dL)	Control (n=25)	0.099	0.118	-0.237	0.083
			Thalassemia (n=75)	-0.196	0.137	0.332*	0.099
> 13			Control (n=25)	0.073	0.415	0.142	0.218
			Thalassemia (n=75)	0.333*	0.317*	0.328*	0.061
≤ 13	Males		Control (n=25)	-0.450	-0.351	-0.346	0.104
			Thalassemic (n=75)	-0.0173	-0.103	0.422**	-0.212
> 13			Control n=25	0.213	-0.191	-0.160	-0.101
			Thalassemic (n=75)	-0.229	-0.143	0.516***	0.064
≤ 13	Females	TSH (µIU/mL)	Control (n=25)	0.457	-0.138	0.083	-0.015
			Thalassemia (n=75)	-0.0627	-0.115	0.042	-0.052
> 13			Control (n=25)	0.215	0.151	0.059	0.194
			Thalassemia (n=75)	0.487***	0.531***	0.394**	0.021
≤ 13	Males		Control (n=25)	0.191	0.137	0.141	-0.118
			Thalassemic (n=75)	0.192	0.187	0.124	-0.056
> 13			Control (n=25)	0.174	0.599	0.524	-0.101
			Thalassemic (n=75)	0.064	0.446**	-0.197	-0.220
≤ 13	Females	Growth Hormone (ng/ml)	Control (n=25)	-0.799	-0.099	-0.122	0.174
			Thalassemic (n=75)	0.207	0.229	0.159	-0.009
> 13			Control (n=25)	0.439	0.072	-0.146	-0.100
			Thalassemic (n=75)	0.016	-0.021	0.113	0.021
≤ 13	Males		Control (n=25)	-0.024	-0.348	-0.358	0.035
			Thalassemic (n=75)	0.091	0.043	0.005	0.310*
> 13			Control (n=25)	0.236	0.0	0.067	-0.761
			Thalassemic (n=75)	0.020	-0.012	-0.124	-0.101

BMI, body mass index; Hb, hemoglobin. *P<0.05, value *vs* corresponding control; **P<0.01, value *vs* corresponding control; ***P<0.001, value *vs* corresponding control.

In thalassemic females of > 13 years of age, TSH concentration showed highly significant (P<0.001) positive correlation between BMI (r= 0.487) and serum ferritin level (r= 0.531). Similarly, significant positive correlation (P<0.01) was observed with Hb levels (r=0.394); TSH had a positive correlation (P<0.01) with serum ferritin levels (r=0.446), and GH had a positive correlation with (P<0.05) with thalassemic males of ≤13 years (r=0.310).

DISCUSSION

Thalassemic patients are dependent on blood transfusions to maintain the levels of hemoglobin and packed cell volume in their blood. Transfusion and iron-chelation therapy has prolonged and improved the quality of life in these patients (Borgna-Pignatti *et al*., 2004). Such a treatment, however, leads to chronic iron overload

affecting the endocrine glands (Abdulzahra *et al*., 2011). In our study, we observed that thalassemia major patients suffered from endocrine disorders and presented with delayed puberty. In another study carried out by Al-Rimawi *et al*. (2005) reported that there was a significant difference in the frequency and regularity of using chelation therapy between pubertal and delayed pubertal groups. Whereas in our study the age of starting chelation therapy was 6-8 months and the patients were on regular blood transfusion and chelation therapy. In a previous study carried out by Al-Hakeim and Mohsen (2013), comparison of measured parameters between male and female thalassemic patients of 3-11 years of age group were done which showed high hemoglobin levels in male patients as compared to the female thalassemic patients. The change in hemoglobin levels can be easily explained by the genetic changes between male and female as males have higher hemoglobin levels than females (Al-Hakeim and Mohsen, 2013). While comparing with our study, hemoglobin levels of thalassemic males and females were significantly lower than that in the control groups. Similarly, we also observed that the serum ferritin level was higher than the control group which was similar to the results reported by Adil *et al*. (2012), suggesting that increased serum ferritin levels was related to the endocrinopathies involving various endocrine structures like pancreas, interior pituitary, thyroid, parathyroid and adrenal glands. Increased serum ferritin levels were associated with increased incidence of endocrinopathies alongwith subsequent increase in the serum levels of calcium (Ca), alkaline phosphate and parathyroid hormone levels (Al-Hakeim and Mohsen, 2013). Thalassemic children frequently reflect growth retardation which may be attributed to their diversion from caloric resources resulting from ineffective erythropoiesis, alongwith the effects of anemia. Since hyper-transfusion has been shown to frequently restore normal growth rates, however, the adolescent growth spurt is often delayed, even in children who are hyper-transfused, unless intensive iron chelation therapy is instituted early in life (Viprakasit *et al*., 2001; Theodoridis *et al*., 1998). Previous studies on thalassemic patients revealed that average age of 12±8 years occasionally suffered from growth failure as 77.4% of these patients had normal BMI, while 4.8% were overweight and 6.5% were categorized as obese (Adil *et al*., 2012), whereas, thalassemic patients males and females of all groups included in the present study had reduced BMI ($P<0.001$) as compared to the control group. A high prevalence of endocrine abnormalities in β thalassemia major patients has been reported (Zervas *et al*., 2002). Relationship between the level of ferritin and the development of endocrinopathies suggested that serum ferritin was used as a prognostic marker for survival of these thalassemic patients; prognosis for survival was excellent when serum ferritin concentration was below 2500 ng/ml in thalassemic patients (Costin *et al*., 1979); however, Zervas *et al*. (2002) reported the absence of any such relation. During the course of β-thalassemia major, multiple endocrine disorders may develop mainly due to iron overload. Growth retardation and HPG axis dysfunction represent the commonest disorders of the endocrine system (De-Sanctis *et al*., 2002). Thyroid dysfunction has been reported in thalassemia major, but its prevalence and severity varies. Decreased thyroid levels can lead to growth problems in thalassemic patients (Abdulzahra *et al*., 2011; Pirinççioğlu *et al*., 2011). Study carried out by Hegazi *et al*. (2013), reported no significant difference in thyroid (free T_4, free T_3 and TSH) function tests between thalassemic patients and the control group.

On the contrary, hypothyroidism was detected in different ratios in other studies conducted by various groups as they found hypothyroidism in 12.8, 2.1 and 11 percent of their patients, respectively (Kurtoglu *et al*., 2012; De-Sanctis *et al*., 2002). These results were further elaborated in another study done by Aruratanasirikul *et al*. (2007) that thyroid dysfunction in thalassemic patients was dependent on many factors like age of studied population, the duration of receiving blood transfusions, the amount of iron overload, the dosage of iron-chelating agent, and the procedure used for evaluation. In the present study it was observe that serum T_3 levels in ≤ 13 and >13 years of thalassemic females were significantly higher than the control group. On comparison, serum T_3 levels in thalassemic males ≤ 13 and >13 years of age, there was no significant difference with the control groups. Serum T_4 levels in ≤ 13 years thalassemic male patients were significantly lower ($P<0.001$) than the control group, whereas serum TSH levels were significantly lower ($P<0.05$) in thalassemic males of ≤ 13 years of age as compared to the control group. Similarly, in >13 years thalassemic males TSH levels were significantly higher ($P<0.01$) than the control group.

In another study, Hegazi *et al*. (2013) detected a significant positive correlation between the age and ferritin and a significant negative correlation between ferritin and free T_4. So, thyroid function tests might be affected with progress of age of those patients and increased their serum ferritin level. Whereas in our study thalassemic female of >13 years of age T_3 had a significant ($P<0.001$) negative correlation with BMI ($r= -0.408$), ($P<0.05$) with Hb levels ($r= -0.329$), whereas T_3 had a positive correlation ($P<0.05$) with serum ferritin levels of thalassemic males of ≤ 13 years ($r = 0.523$). Similarly, T_3 had a positive correlation ($P<0.05$) with kisspeptin levels ($r=0.317$) in thalassemic males of >13 years. T_4 had a significant positive correlation

(P<0.05) with BMI (r= 0.333), serum ferritin (r=0.317) and Hb levels (r=0.328) in thalassemic females of >13 years of age. T_4 had a positive correlation (P<0.05) with Hb levels (r=0.332) in ≤ 13 years thalassemic females. Similarly, T_4 showed a positive correlation (P<0.001) with Hb levels (r=0.516) in thalassemic males of > 13 years of age and (P<0.01) with Hb levels of ≤13 years thalassemic male (r= 0.422). These findings are in line with Hashemizadeh and Norri (2012), where they found that impaired thyroid function was associated with iron overload. Also, Irshaid and Mansi (2009), reported that the rate of thyroid dysfunctions increased steadily with growing age. On the contrary, Abdulzahra *et al*. (2011) and Zervas *et al*. (2002) stated that no statistically significant correlation was found between serum ferritin levels and thyroid functions.

Results of the study conducted by Hashemi *et al*. (2011) showed that mean serum ferritin level were significantly higher in the patients with a final low weight and BMI than in those with a normal final weight and BMI. Whereas, in the present study serum GH levels were low in thalassemic males and females of ≤13 years and the GH levels were high in thalassemic males and females of >13 years of age. Moreover, GH had a positive correlation (P<0.05) with kisspeptin levels (r=0.310) in thalassemic male of ≤13 years.

CONCLUSION

The study revealed that kisspeptin, TSH and GH levels were significantly raised in thalassemic males of >13 years of age. This is showing that hypothalamus production was correctly secreting kisspeptin and the levels of hormones secreted by anterior pituitary were also raised but there were reduced BMI and Hb levels in contrast to raised serum ferritin levels showing that hypothalamic pituitary axis was doing the proper production, whereas there might have been other factors involved in delaying the growth spurt. On the other hand, thalassemic females of >13 years also had raised levels of GH but low levels of kisspeptin and thyroid hormone, alongwith was reduced levels of BMI and Hb and raised serum ferritin levels. These finding revealed that the response to chelation therapy could be one of the reasons why thalassemic females had reduced outcome, whereas thalassemic males and females of ≤13 years of age had reduced response of hypothalamic pituitary axis alongwith reduced BMI and Hb levels and raised serum ferritin levels. Among all, the three groups of ≤13 years thalassemic female and males and >13 years thalassemic females were effected by iron overload due to multiple transfusion.

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Statement of conflict of interests

The authors declare that they have no competing interests.

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