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Do Iron Chelators Affect Fertility in Thalassemic Men?

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Authors' contributions

This work was carried out in collaboration between all authors. Author SA designed the study, author AA selected the patients, author MMA performed the ultrasound for the patients. Authors DA and MR analyzed the endocrine data of the patients. Author AK performed the statistical analysis, wrote the protocol and wrote the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Background: Iron overload is a major complication in patients with thalassemia, however, development of iron-chelating therapy has partly overcome this problem.
Objectives: The aim of this study was to evaluate the effect of iron chelator drugs on testicular volume, semen parameters and serum FSH, LH, and Testosterone concentrations in 62 young male patients with major and intermedia thalassemia.
Materials and Methods: Sixty two young male patients with major and intermedia thalassemia, aged 18–41 years who had different iron chelator drug using status were evaluated.
Results: At the time of the study their serum ferritin levels ranged from 182 to 11053 ng/mL (mean 2067 ng/mL). The mean volume of patients' ejaculate was 2.3 cc. The mean concentration of sperm was 61.04 million per milliliter. The mean size of right testis was 11.4 cc and the mean size of left

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testis was 11.7 cc. Hypogonadism and hypothyroidism were seen in 22.6% and 17.7% of patients, respectively. The mean level of FSH was 3.7 mIU/ml, LH was 4.6 mIU/ml, and Testosterone was 4.8 ng/dl. The mean level of serum ferritin was 2067 ng/dl.

Conclusion: This study suggests that in thalassemic men, concentrations of serum Testosterone, LH, FSH has significant correlation with sperm parameters and testicular volume but iron chelators mostly do not impact the elements of fertility in these patients.

Keywords: Thalassemia major; thalassemia intermedia; spermatogenesis; puberty; testicular volume; gonadal hormones; iron chelators.

1. INTRODUCTION

Beta thalassemia is a hereditary hemoglobinopathy that can cause severe anemia. The life expectancy of these patients has noticeably extended by the combination use of transfusion and effective chelation therapy [1]. Transfusions can prevent mortality and promote normal development, but the iron in the transfused red cells accumulates and in the long run damages the liver, heart, and other organs. Involvement of different organs including the endocrine system lessens the quality of thalassemic patients' lives. In fact, pubertal failure, sexual dysfunction and infertility, due to hypogonadism have been reported in 51% to 66% of thalassemic patients [2-4].

The etiologies of male infertility in general population are several though in β-thalassemia are classically considered to be the result of iron deposition in the endocrine glands. The adverse reactions of the drugs they use for different reasons including iron chelation could be an important factor influencing thalassemia fertility [5].

The prevalence of acquired hypogonadism in β-thalassemia has been reported to depend mainly on the degree of compliance with blood transfusion and chelation programs [6]. This means that iron chelator drugs could be a protector against iron deposition in gonads but at the same time could have toxic effects on gonads and sperms.

The aim of this study was to evaluate the effect of iron chelator drugs on pubertal development, sexual hormone status and sperm parameters in adolescent and young adult males with Beta-thalassemia major and intermedia.

2. MATERIALS AND METHODS

This prospective study was conducted between January 2001 and January 2003 at a teaching hospital in Tehran, Iran. The study included 62 males with Beta-thalassemia major and intermedia, whose ages ranged between 18 and 41 years. Among the patients, 52 had been regularly transfused since early childhood and underwent different chelation therapies using subcutaneous desferrioxamine and/or oral deferasirox and/or deferriperone.

The requisite of the study was that the participants being competent and cooperative.

Puberty was evaluated in the patients according to Tanner's classification of testicular development [7]. Testicular size ≤4 mL (long axis of ≤2.5 cm) was considered stage I (prepubertal genitalia), and size ≥25 mL (≥5 cm in length) was considered adult genitalia [8]. Testicular volumes were calculated with scrotal ultrasound.

After overnight fasting, blood samples were collected from patients for evaluation of their basal LH, FSH, and Testosterone.

Conventional semen analysis was carried out after an abstinence interval of 3–4 days using manual procedures and light microscopy in the central hospital laboratory according to the last World Health Organization guidelines [9].

Iron overload was assessed by direct and indirect methods. It was evaluated by measuring serum ferritin level. Iron status was classified as mild (ferritin < 1000 ng/ml), moderate (ferritin >1000 ng/ml and < 2500 ng/ml) or severe (ferritin >2500 ng/ml). T2* MRI of heart and liver was assessed for iron overload. Standard computer program SPSS for Windows, release 16.0 was used for data entry and analysis. P≤0.05 was considered statistically significant.

The study was approved by the University's ethical Committee.

Patient informed consent was obtained, as appropriate, before beginning the study.

3. RESULTS

The patients' age range was between 18 to 41 years. Their mean age was 27.2 years. Among the patients, 75.8% were major and 24.2% were intermedia and totally 83.9% were transfusion dependent. Among our patients, 4.8% did not use any kind of iron chelator drugs, 54.8% used deferoxamine, 50% used deferasirox and 21% used deferiprone. On an additional glance, 14.5% had history of using both deferoxamine and deferasirox, 12.5% used deferoxamine and deferiprone at the same time and 3.2% used deferasirox and deferiprone simultaneously.

The mean volume of patients' ejaculate was 2.3 cc. Five patients (8.1%) had dry ejaculate and 24.2% o patients had unacceptable ejaculate volume (<1.5 ml).

Having dry ejaculate significantly correlated with having the history of using deferiprone (p=0.025). However, patients who had the history of using deferoxamine had significantly lower ejaculate volume comparing with patients who did not use deferoxamine (1.7 ml versus 2.6 ml). This was also true about the patients who had the history of using deferiprone (1.2 ml versus 2.3 ml). But having the history of using deferasirox had not impacted ejaculate volume in our study.

The mean concentration of sperm was 61.04 million per milliliter. Totally, 61.3% of patienst had acceptable sperm concentration (≥15 M/ml) but 21% had azospermia and 22.4% had oligospermia. In patients who used deferiperrone, oligospermia was significantly more frequent (P=0.04).

Considering the sperm motility, respectively, in 22.4% and 34.6% of patients the number of motile sperms and progressively motile sperms were less than normal. Considering the sperm morphology, in 44.8% of patients the number of sperms with normal morphology were less than normal. The drugs did not impact the sperms' motility and morphology in our study.

The mean size of right testis was 11.4 ml and the mean size of left testis was 11.7 ml. Only 3.2% of patients had testicular volume less than 4 ml which is indicative of the puberty process not being started and this was significantly correlated with using deferiprone. This means that deferiprone usage was associated with delayed puberty.

The mean level of FSH was 3.7 mIU/ml, LH was 4.6 mIU/ml, and Testosterone was 4.8 ng/dl. The frequency of hypogonadothropic hypogonadism and hypergonadotropic hypogonadism was 16.1% and 6.5%, respectvely. The chelator drug usage did not correlate with the gonadal hormones' serum level.

The mean level of serum ferritin was 2067 ng/dl. Serum ferritin level correlated significantly with deferoxamine and deferiprone usage and not with deferasirox usage. In 74.2% of patients cardiac MRI was normal. In 21% of patients hepatic MRI was normal. Interestingly, cardiac and hepatic MRI involvements did not correlate with chelators' usage. All the same, no significant correlation was found between the iron overload determinants and sperm parameters or having hypogonadism. Variables' characteristics according to history of drug usage are summarized in Table 1.

4. DISCUSSION

Iron overload in beta-thalassemia patients is the mutual outcome of multiple blood transfusions and improperly increased iron absorption due to ineffective erythropoiesis. Tissue iron deposition affects all organ systems, especially the cardiac, hepatic, and endocrine systems. Observational records advocate that iron loading in endocrine organs may precede that in the heart and liver. There is now considerable evidence on the role of iron overload in endocrine morbidity in these patients [10,11]. Hypogonadism and delayed puberty are the most common endocrinopathy in thalassaemic patients (40–91%) [1,12,13]. It has been shown to be correlated with early onset of transfusion therapy, serum ferritin levels of approximately 2000 ng/mL [14] and HU treatment [12] in beta thalassemia patients. Iron chelation therapy could prevent long-term complications of iron overload [15]. Chelation regimens are improving and studies show the preventability and reversibility of hypogonadism by intensive combined chelation [16]. ElAlfy et al. documented that combination chelation using deferiprone and desferrioxamine in a 3 year time priod in polytransfused males (>14 years) with thalassemia who had good pituitary–testicular function led to progression of pubertal development; meanwhile, their semen quality was still impaired [17].

Table 1. Variables' characteristics according to history of drug usage

History of drug usage		Mean ejaculate volume (ml)	Mean sperm concentration (M/ml)	Mean percent of progressively motile sperms%	Mean percent of Normal morphology sperms%	Mean volume of Right testis (ml)	Mean volume of Left testis (ml)	Mean FSH	Mean LH	Mean Testostrone	Mean Ferritin
Deferoxamine	Pos	1.7	58.82	31	19	11.33	12.06	3.95	5.21	5.37	2576
	Neg	2.6	63.74	32	20	10.92	11.44	3.59	4.04	4.19	1450
Deferasirox	Pos	2.3	61.83	32	19	10.72	11.11	3.62	4.00	4.54	1745
	Neg	1.9	60.26	31	21	11.56	12.46	3.96	5.37	5.13	2389
Deferiprone	Pos	1.3	50.49	26	14	9.31	9.94	3.13	3.43	4.92	3277
	Neg	2.3	63.84	33	21	11.63	12.27	3.97	5.01	4.82	1746

Although different chelators are being used and serum ferritin is strictly controlled, the harmful effect of iron overload to the reproductive system of patients with thalassemia major is still common [18].

To our knowledge, no study has assessed the impact of iron chelator drugs on fertility indicators. In this study we illustrated that ejaculate volume and sperm concentration in beta thalassemic men could be affected by the use of iron chelator drugs.

The iron chelator desferrioxamine was first introduced more than 50 years ago [19], and has been proven to prevent the iron-mediated damage of parenchymal organs and to improve growth, sexual maturity, and survival time. But achieving these positive effects seems to require very early and aggressive chelation therapy [20] which have been confirmed to have toxic effects on acoustic and visual neurosensorial pathways [21,22]. De Virgiliis et al. showed that impairment of longitudinal growth and pseudorachitic bone changes should be added to the list of the negative side effects of high doses of desferrioxamine [23]. We found that patients who had the history of using deferoxamine had significantly lower ejaculate volume comparing with patients who had not used deferoxamine.

Deferasirox is an orally absorbed once-daily iron chelator developed for the management of chronic iron overload from blood transfusions. Its safety, tolerability and efficacy in reducing body iron burden have been demonstrated in patients with transfusion-dependent beta thalassaemia [24]. The most notable adverse events reported after this drug usage has been transient gastrointestinal symptoms and skin rash. Mild, stable increases in serum creatinine and reversible increases in liver enzymes have been noted [25,26]. In our study, having the history of deferasirox usage did not impact sperm parameters, testicular volumes and gonadal hormones' serum levels.

Deferiprone is an orally active iron chelator which its adverse effects in clinical trials include agranulocytosis, arthropathy, gastrointestinal symptoms, increased ALT levels and progression of hepatic fibrosis (Hoffbrand et al., 1998, Bartlett et al., 1990, Agarwal et al., 1992) . In our study,patients who had the history of using deferiprone had significantly lower ejaculate volume and having dry ejaculate and oligospermia was more frequent in these patients comparing to patients who had never used deferiprone. Considering testicular volume in ultrasound assessment, in patients who used deferiprone testicular volume less than 4ml which is indicative of delayed puberty was much more frequent.

Our study has a number of limitations, including the retrospective design and the lack of dose and duration of drug usage being specified. Therefore, further prospective studies on a larger population would improve the quality of the research.

6. CONCLUSION

In conclusion, we observed that in thalassemic men, concentrations of serum Testosterone, LH, FSH has significant correlation with sperm parameters and testicular volume but iron chelators mostly do not impact the elements of fertility in these patients. Taking into account the important role of reproduction and fatherhood in the quality of lives of these patients, we advocate the necessity of the care givers to be alert of the mentioned side effects.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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