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(REVIEW ARTICLE)

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The potential benefits and risks of sex-steroids therapy in thalassemic patients with hypogonadism

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Abstract

Introduction: A recent review from 14 Mediterranean and Middle East countries (n =4477, mean age = 16.5 years) showed that the pooled prevalence of delayed puberty / hypogonadism in patients with BTM was 45.6%. Studying the consequences of hypogonadism and the potential benefits versus unwanted side effects of sex-steroid hormone replacement therapy (HRT) in children and adolescents with Beta Thalassemia Major (BTM) represent an important issue for these patients.

Objectives: We reviewed the literature (Pubmed, Google scholar, Scopus, Research gate) (1995: 2022) on the consequences of hypogonadism and benefits versus side effects of using sex Steroid therapy (HRT) in hypogonadal adolescents with BTM. Thirty-five papers were included and analyzed.

Results: HRT had a variable but significant beneficial effect on improving bone mineral density (BMD), pubertal growth spurt, development of secondary sexual characteristics and subsequently improved quality of life (QOL) in children and adolescents with BTM. Increased side effects of HRT in these patients may occur due to their state of hypercoagulability especially in splenectomized patients and those with cardiomyopathy, chronic hepatitis, and dysglycemia. Gynecomastia and local pain in the site of injection confirmed in a considerable number of males on testosterone therapy. Local reaction to sex steroid patches appeared in around 30% of patients. Based on this review recommendations for using HRT in these patients were updated.

Conclusion: Proper and wise use of sex steroid therapy in patients with BTM can significantly improve many consequences of hypogonadism.

Key words: Hypogonadism; Beta Thalassemia; Sex Steroid Therapy; Benefits; Side Effects.

1. Introduction

The worldwide prevalence of hypogonadism in patients with thalassemia major is still considerably high and differs among studies from different countries. In a recent review of 22 studies between 2017 and 2022 the prevalence of hypogonadism ranged between 22.2% and 82% and in another review from 14 Mediterranean and Middle East countries (n =4477, mean age = 16.5 years) the pooled prevalence of hypogonadism/delayed puberty was 45.6%.

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Several studies have reported that as many as 51% to 66% of patients may have pubertal failure, sexual dysfunction, and infertility, due to hypogonadism (1,2).

Hypogonadism may reveal during puberty and may represent delayed onset with spontaneous/slow progression, arrested puberty, or failure of puberty. Primary or secondary amenorrhea may occur in females. The high variability in the proportion of patients affected by hypogonadism could be explained by ethnic factors, different accessibility and compliance to therapy, economic status, and genetic susceptibility (3,4).

The goals of Hormone replacement therapy (HRT) (estrogen for females and testosterone for males) in hypogonadal Thalassemic patients can be summarized in the following:

- To stimulate the development of and maintain secondary sexual characteristics and normal sexual function.
- To support pubertal growth spurt
- To build and sustain normal bone accretion and muscle mass.
- To relief the symptoms of hypogonadism
- To assist in the proper psychosocial adjustment of adolescents with hypogonadism
- To increase the quality-of-life (QOL) (5,6).

HRT is extremely complex in transfusion dependent BTM (TDBTM) patients because of the existence of associated co-morbidities, such as iron overload, thrombophilic status, chronic liver disease, impaired glucose tolerance or diabetes, and cardiomyopathy. BTM females with hypogonadism receive different hormone replacement therapy (HRT). The majority receive either oral conjugated estrogens (CE) or oral contraceptive pills (CO). Relatively few uses transdermal estrogen patch or vaginal ring (7,8).

In BTM males with delayed puberty, low doses of intramuscular depot-testosterone esters (25 mg) can be given monthly, at a bone age of about 12 years, for 6 months, to stimulate growth velocity. This may induce pubertal development. In patients with hypogonadism, therapy continues, and the dose increases to 100 mg/monthly until the growth rate begins to wane. The full virilizing dose is 75-100 mg of depot-testosterone esters every 10 days administered intramuscularly or 100 mg/m2 twice a month (9,10). The same effects can be achieved with topical testosterone gel (9-12).

Both beneficial and negative side effects of using HRT have been reported in non-thalassemic hypogonadal patients, however the use of HRT in patients with BTM may have higher risk because of the coexistence of other morbidity factors in these patients including hypercoagulability, iron overload with hepatic, pancreatic and cardiac toxicity, and other endocrinopathies (13).

Aim of the study

We performed an electronic search in PubMed, Google Scholar, and Web of Sciences to evaluate the prevalence of hypogonadism and its consequences, and possible benefits versus side effects of HRT in TD-BTM patients in the past 25 years. Sixty-five papers were included and analyzed (figure 1).

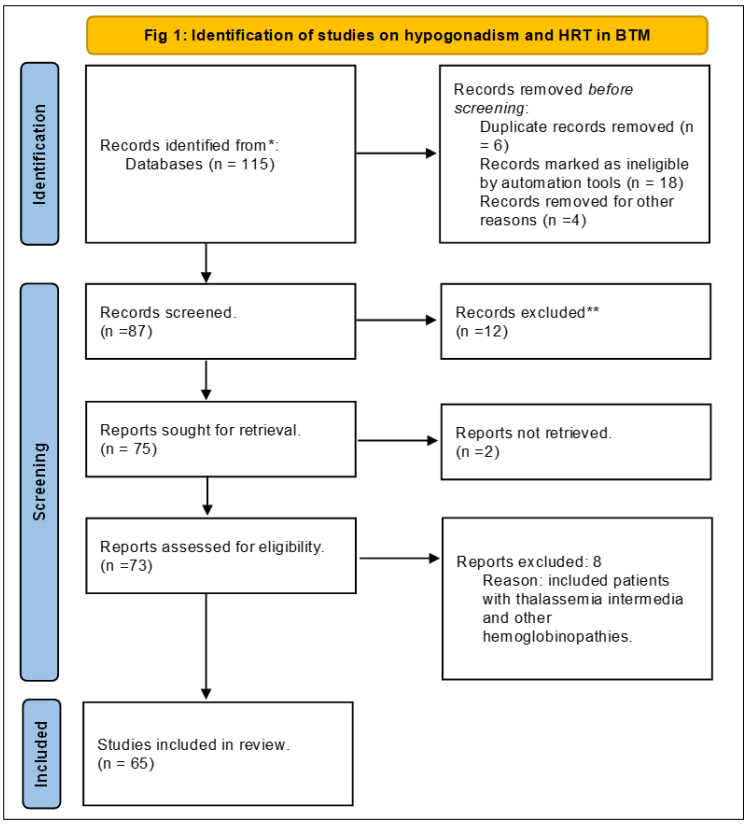

Figure 1 Identification of studies on hypogonadism and HRT in BTM databases

2. Results of the review

The global prevalence of hypogonadism in BTM is still high and varies among studies, related especially to whether pubertal status is taken into consideration. In a recent review of 22 studies between 2017 and 2022 the prevalence of hypogonadism ranged between 22.2% and 82% and in another review from 14 Mediterranean and Middle East countries (n =4477, mean age = 16.5 years) the pooled prevalence of hypogonadism/delayed puberty was 45.6%. Several studies have reported that as many as 51% to 66% of patients may have pubertal failure, sexual dysfunction, and infertility, due to hypogonadism (1,2).

In the studied articles, hypogonadism presented during puberty in the form of delayed onset with spontaneous and/or slow progression, arrested puberty, or complete failure of puberty. Primary or secondary amenorrhea occurred variably in females. The high variability in the proportion of patients affected by hypogonadism could be partially explained by ethnic factors, different accessibility and compliance to therapy, economic status, and genetic susceptibility (14-32).

Comorbidities in BTM patients that increase the risk of thrombosis and other side effects of using HRT:(33- 47).

a. Hypercoagulable state: Natural coagulation inhibitors (protein C, protein S, and antithrombin-III) are significantly lower in thalassemic children, while D-dimers are significantly increased. The pathogenesis of hypercoagulability mainly involves a double role of triggered platelets and hemolyzed red blood cells with generation of thrombin.
b. Splenectomy significantly increases the prevalence of thrombotic events. Post-splenectomy thrombocytosis is common. Splenectomized thalassemic patients had significantly lower levels of protein C, protein S and thrombin activatable fibrinolysis inhibitor (TAFI), when compared to non-splenectomized thalassemic patients.
c. Inadequate transfusion may increase the risk of thrombosis secondary to increased release of procoagulant red cell particles.
d. Patients with thalassemia (βTM), have high prevalence of metabolic syndrome, insulin resistance, and glycemic abnormalities (IFG, IGT, DM). Hyperglycemia and insulin resistance cause changes in platelet number and activation, as well as qualitative and/or quantitative modifications of coagulation and fibrinolytic factors,

resulting in the formation of fibrinolysis-resistant clots. Metabolic syndrome significantly increases levels of Fibrinogen, Factor VIII and Plasminogen Activator Inhibitor1 (PAI1) and increases the risk of hypercoagulability. On the other hand, HRT may lead to deterioration of glycemic state.

Haghpanah and Karimi reviewed the literature and reported that out of 152 thalassemic patients with cerebral thromboembolic events; 48% were splenectomized. Cerebral thrombosis was linked with older age, poor transfusion status, splenectomy, thrombocytosis, and diminished protein C level (48).

De Sanctis et al studied 42 BTM females on HRT and reported two severe adverse events (AE) during the long-term HRT treatment: a stroke with right hemiparesis in a 31-year-old splenectomized who had been taking sequential ethinyl estradiol (20 μg/d) combined with medroxyprogesterone (MPA) for the last 3 years, and an episode of transient monocular visual loss in a 29-year-old splenectomized patient treated, with HRT for 4 years. Skin irritation at the patch application site, or patch detachment under conditions of heat, humidity, and exercise occurred in 7/9 (77.7%) patients (49).

Observational studies and meta-analyses advocated that transdermal estrogen therapy does not increase thrombotic risk. However, no RCTs were conducted in thalassemic patients. Therefore, HRT in hypogonadal thalassemic patients should be used cautiously, preferably in a transdermal form (50).

De Sanctis V, et al studied the risk of testosterone replacement therapy on the risk of thrombotic events in 424 BTM males, only 1 patient (19-year-old), who had diabetes mellitus, developed atrial thrombosis during testosterone therapy (51).

e. Cardiovascular Risk

Cardiomyopathy secondary to iron toxicity occurred in BTM patients especially those with high ferritin levels. Cardiomyopathy in thalassemic patients was characterized by 2 distinct patterns, a dilated phenotype, with left ventricular dilatation and impaired contractility, and a restrictive phenotype, with restrictive left ventricular filling, pulmonary hypertension, and right heart failure. Patients with impaired cardiac performance were believed to have a higher risk of venous thromboembolism (VTE). Three meta-analyses in hypogonadal non-thalassemic males indicated that testosterone replacement therapy did not increase the risk of adverse cardiovascular events (52-54). However, Dadelen S et al, reported the occurrence of heart failure in an adolescent with BTM after starting testosterone therapy (55).

f. Dysglycemia: Patients with BTM have a prevalence of glucose abnormalities including insulin resistance, impaired fasting glucose, impaired glucose tolerance and diabetes mellitus. De Sanctis V et al reported deterioration of glucose tolerance in 4 BTM patients on oral contraceptives (OC), from normal tolerance to impaired glucose tolerance in 3 and from impaired to diabetes in 1 (with chronic HCV liver disease) (49).

2.1. Potential Benefits versus side effects of HRT Use in hypogonadal patients with BTM

Tables 1 and 2 summarize the consequences of hypogonadism in patients with BTM and the potential benefits and side effects of using sex steroid replacement.

Since not all published papers were not randomized controlled trials (RCT), the recommendations have been scored according to the following standards:

g. High confidence indicates that further research is unlikely to change the confidence in the estimate of effect (●●●).
h. Moderate confidence indicates that further research may change the confidence in the estimate of effect (●●○).
i. Low confidence indicates that further research would likely have a significant impact on the confidence in the estimate of effect (●○○).
j. Insufficient indicates that the evidence is unavailable or does not permit a conclusion (○○○).

Table 1 Consequences of hypogonadism in BTM patients and potential benefits of HRT

Consequences of Hypogonadism in BTM	**Potential Benefits of Sex Steroid therapy**
Secondary osteopenia and osteoporosis (Low bone mineral density (BMD) were identified in both pediatric and adult populations. The prevalence of osteoporosis in BTM patients varies; the highest rate is 40-72%. Untreated hypogonadal BTM patients had the lowest BMD and the highest were observed in those on the continuous replacement group (●●●) (56,57).	HRT can maintain BMD of thalassemic patients, with significant improvement of BMD Z score in thalassemic females who received sex steroid replacement for around 5 years (●●●). The BMD values increased during the first 2-3 years of HRT treatment by an average of 7.7% at lumbar spine and of 8.9% at left femoral neck (●●) (58.59).
Short stature (disproportionate); A recent metanalysis included 74 studies from five continents between 1978 and 2019. The pooled prevalence of short stature was 48.9% and was higher in males vs females (61.9%, vs 50.9%) (20) The studied etiology included disturbed GH-IGF1 axis, loss of pubertal growth spurt, and nutritional factors (●●●) (60)	Low dose sex steroid therapy priming (6-12 months) for induction of puberty was successful in 80% with increase in height, growth spurt and completed pubertal maturation in patients younger than 15 years with minimal iron load. (61) The use of sex steroids improved the final adult height of the hypogonadal patients comparable to those with patients with normal puberty (62) Use of HCG in boys improved pubertal growth spurt in 58%. of patients. (63) (●●●)
Delayed/absent puberty and amenorrhea (primary (PA) and secondary (SA). The largest cohorts on BTM identified the prevalence of primary amenorrhea in 47% and secondary amenorrhea in 25% of patients and in another recent review between 44.5% and 82%. (●●●) (2, 64)	50% of BTM females with PA respond to 2-3 years of sex steroid treatment with a mature, heart-shaped uterine configuration and endometrial thickness, and 45.2% presented a smaller sized uterus (transitional) with normal endometrial thickness. In the rest of patients there was a failure of endometrium to respond. (●●) (6) Use of HCG in boys improved pubertal development and testosterone secretion in 58%. (18) In hypogonadal BTM males with azoospermia HCG therapy increased testosterone level (5/5), testicular volume (4/5) and spermatogenesis (2/5) (●●) (65).
Decreased Quality of life BTM adolescents had poor perception of their general health and scored significantly lower in all the subscales compared with the controls. (●●) (66,67). The high prevalence of short stature and pubertal delay was associated with lowest scores for physical and psychological domains. (●●) (32).	HRT can greatly enhance a patient's QOL. Inducing secondary sexual characteristics, improving erectile abilities. improving pubertal growth spurt, increasing muscle performance are among factors that can markedly improve QOL (●●). A metanalysis confirmed the broad and sustained benefits of TRT across major QOL dimensions, including sexual, somatic, and psychological health, which were sustained over 36 months in our treatment cohort (●●●) (68).

Table 2 Risks associated with BTM and potential side effects of HRT

Consequences and risks associated with BTM	**Potential Side Effects of Sex Steroid therapy**
Increased risk of thrombo-embolism: In 1 study on 8860 Thalassemic patients approximately 1 to 2 percent of BTM patients and 5 percent of beta thalassemia intermedia (BTI) patients experience a serious thrombosis. (●●●) (69).	In 42 splenectomized BTM females on long-term HRT, 2/42 had severe adverse events (a stroke with right hemiparesis and an episode of transient monocular visual loss). (●●) (6) Out of 424 males with BTM, only 1 patient (19-year-old) with DM, developed atrial thrombosis during testosterone therapy. (●) (51).

An Italian survey disclosed that in a total of 735 (683 BTM and 52 BTI), 3.95% and 9.61%, respectively had VTE episodes and the CNS was the main location (16/32) involved. (●●●) (702) The increased risk was due to: the hypercoagulability state (dual role of activated platelets and hemolyzed red blood cells with thrombin generation potential), splenectomy, inadequate transfusion, metabolic syndrome, glycemic abnormalities, cardiomyopathy and advancing age (●●●) (71,72).	
Dysglycemia (Impaired fasting glucose, IGT, DM) The prevalence of DM in BTM varies from 9.7% to 29% and the overall prevalence of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) is 17.2% and 12.4% respectively (●●●) (73).	Deterioration of glycemia (9.5%) (3 from NGT to IGT and 1 from IGT to diabetes.) and mild dyslipidemia occurred in 7.1% occurred in BTM females on HRT. (●●) (6).
Cardiomyopathy: BTM is considered a condition with a high level of cardiovascular risk due to iron-related myopathy, atherosclerosis and arrhythmias. According to recent statistics, the prevalence of heart failure (HF) in patients born later than 1970 at age 35 is ≈7%. Another study HF occurred in 2.5% of 202 well-treated patients BTM (27+/-6 years). The BTM cardiomyopathy had 2 phenotypes, a dilated phenotype, with left ventricular dilatation and impaired contractility and a restrictive phenotype, with restrictive left ventricular filling, pulmonary hypertension, and right heart failure (●●●) (74).	Out of 424 males with BTM, only 1 patient (19-year-old) with DM, developed atrial thrombosis during testosterone therapy. A case report described the occurrence of heart failure in a BTM male that occurred concomitantly with increasing the dosage of testosterone. (●) (51).
Chronic hepatitis – Liver cirrhosis: Current HBsAg positivity in thalassemia major ranges from <1% to >20% and Hepatitis B infection remains a significant cause of chronic liver disease and hepatocellular carcinoma in BTM. (●●●) (75) Anti-HCV positive was present in 87% of thalassemic patients based on an Italian registry, 39.6%-74.4% in two Greek studies, and 18%-70% in studies from the Middle East (●●●) (76).	Mild elevation of liver enzymes and bilirubin occurred in (3/42= 7.1%) of BTM females on HRT. (●) (6). In 2 prospective studies, for 1 year (n =117) and for 8 years (n = 312), Testosterone treatment improved liver function in non-thalassemic hypogonadal males with hepatic steatosis (●) (77,78).

Other side effects of Testosterone therapy in 95 young patients with BTM included mild to moderate gynecomastia (43.1%), persistent pain in the injection site and local reactions to testosterone (T) skin patch occurred in 1/3rd of patients, priapism in 2 patients on IM T enanthate (51) (●●).

We updated and summarized the previously published ICET-A recommendations for female TM patients with hypogonadism include: (13)

3. Conclusion

Proper and wise use of sex steroid therapy in patients with BTM significantly improved many consequences of hypogonadism. Clinicians should exercise caution when considering HRT for hypogonadal males and females with BTM and disclose the benefits and potential risks prior to initiating treatment and monitor any side effects during their use.

Recommendations

- Doctors should weigh the risks against the benefits when prescribing combination estrogen plus progestin hormone therapy and counsel the patient accordingly (●●●).
- Before starting HRT, each patient should be carefully screened by a physician who should identify an increased risk of thrombophilia and tailor the laboratory testing (●●●).

- In TM patients with a known thrombophilia (such as deficiency of antithrombin, protein C or protein S) that has been identified through screening the pros and cons of HRT treatment should be discussed with a specialist (●●).
- In BTM patients with a history of VTE, HRT must be avoided (●●).
- Transdermal estradiol, micronized progesterone and natural progesterone seem to be the most "physiologic regimen" with the best safety profile, (●●).
- Splenectomized TM patients with hypogonadism on HRT should receive antiplatelet or anticoagulant therapy with aspirin or low dose warfarin (●●).
- There are minimal data on the effect of HRT on lipids, (●).
- There is evidence on the benefits of HRT on bone densitometry in hypogonadal BTM women. (●●).
- HRT is contraindicated in acute liver disease. However, once the episode of acute illness has entirely passed, HRT may be initiated (●●).
- Treatment of chronic hepatitis C with new antiviral drugs, and intensive chelation in those with severe liver siderosis (LIC > 7 mg/dry weight) prior to HRT is recommended (●●●).
- Data from studies on chronic hepatitis or its sequelae in non-TM patients suggest that COC use may improve or stop the progression of liver fibrosis or development of hepatocellular carcinoma (●●).
- If the serum liver enzymes after one month of HRT rise by more than 100 %, or if baseline serum bilirubin is elevated, liver biochemistry should be checked monthly for three months or more, and treatment needs to be reassessed (●).
- In BTM women with prediabetes HRT may increase the risk to develop diabetes. (●)
- In BTM women with insulin-dependent or non-insulin-dependent diabetes COCs use has a limited effect on daily insulin requirements and no effect on long-term diabetes control or progression to retinopathy. (●●).
- Young and adult women with hypogonadism should be counseled as to alcohol and tobacco avoidance, daily exercise for obesity prevention, and an appropriate diet to achieve optimal cardiovascular health (●●).

Compliance with ethical standards

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Disclosure of conflict of interest

Each author declares that he or she has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Author Contributions

- Conceptualization: AS; VD,
- Data collection and analysis: AS, MY, FA, NH.
- Writing original draft preparation: FA, SA, NH.
- Pharmacological review: AK
- Tabulation and figures: NA, NS.
- Revision of manuscript for important intellectual content and editing: VD, AS.

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