Does Testosterone Replacement Therapy Promote an Augmented Risk of Thrombotic Events in Thalassemia Major Male Patients with Hypogonadism?

Sir,

Hypogonadotropic hypogonadism (HH) is the most frequent endocrinopathy in transfused patients with thalassemia major (TM). Hypogonadism is likely to be caused by iron deposits in the gonads, pituitary gland, or both. The treatment of pubertal disorders in thalassaemia is a complex issue due to the frequent coexistence of other factors such as severity of iron overload, chronic liver disease, insulin-dependent diabetes, and/or the identification of a hypercoagulable state.[1,2] In addition, splenectomy can contribute to, and increase, the risk of thrombosis.

As the current literature is very limited regarding the potential risks of venous thromboembolism and cardiovascular in TM patients with hypogonadism, the main aim of the present retrospective study was to investigate the incidence of venous thromboembolism (deep venous thrombosis and pulmonary embolism) in three cohorts of hypogonadal men with TM treated with depot testosterone, in Muscat (Oman), Doha (Qatar), and Ferrara (Italy).

The registry database included 424 male patients followed regularly or occasionally in Muscat (96 patients), in Doha (56 patients), and in Ferrara (272 patients). In the latter group, all patients were of Italian ethnic origin. Forty-one of 96 TM patients in Muscat (42.7%), 22 of 56 TM in Doha (43%), and 95 of 272 TM patients in Ferrara (34.9%) developed a pubertal disorder: delayed puberty (1.8%), arrested puberty (1.7%), HH (91.1%), or acquired HH (5.4%).

One of the coauthors (ATS) observed the development of left atrial thrombosis in a 19-year-old adolescent male with TM and diabetes mellitus, who had been on testosterone replacement therapy (100 mg testosterone enanthate, monthly) for 1 year. His laboratory and hormonal profile is reported in Table 1.

Diabetes mellitus (blood glucose at 2 h oral glucose tolerance test = 220 mg/dl) developed 7 months after starting testosterone therapy. He was on insulin therapy with HbA1c = 8%, and he did not show any of the side effects of testosterone therapy apart from this acute incidence. The hormone replacement therapy (HRT) with testosterone was stopped. Unfortunately, no further information was available after his admission to the Cardiac Intensive Care Unit.

No cases of thrombosis were reported in our thalassaemic patients with spontaneous pubertal development.

In conclusion, male hypogonadism and its treatment is a

Table 1: Laboratory and hormonal levels of our patient who developed a left atrial thrombosis

Variables	Results	Normal values
CBC		
Erythrocytes (RBCs)	4.3×10^4	$4.5\text{-}6\times10^4$ (men)
Hemoglobin (g/L)	111	130-150
Platelets ($10^3/\mu L$)	454	200-450
aPTT (s)	32.7	30-45
INR	1.2	0.8-1.2
CK-MB (U/L)	5	5-130
LDH (mmol/L)	2	1-1.8
AST (U/L)	47	5-35
Cholesterol (mmol/L)	2.88	<5.2
Triglycerides (mmol/L)	4.15	0.45-1.71
Creatinine (µmol/L)	47	50-107
CRP (mg/L)	8	<8
Serum ferritin (peak level) (µg/L)	4928	24-336
FT4 (pmol/L)	15.7	8.5-15.2
TSH (mU/L)	0.84	0.4-5.0
Hormonal levels before treatment with testosterone		
LH (IU/L)	<0.5	1.8-8.6 (<18 years)
FSH (IU/L)	<0.5	1.5-12.4 (<18 years)
Testosterone (nmol/L)	0.44	14.0-33.1 (adults: 3rd-97th centile)

CBC: Complete blood count, RBCs: Red blood cells, aPTT: Activated partial thromboplastin time, INR: International normalized ratio, CK-MB: Creatinine kinase-MB, LDH: Lactate dehydrogenase, AST: Alanine aminotransferase, CRP: C-reactive protein, TSH: Thyroid-stimulating hormone, LH: Luteinizing hormone, FSH: Follicle-stimulating hormone

rapidly evolving area. Much of the controversy surrounding testosterone therapy stems from intense attention on recent reports suggesting increased risk of venous thromboembolism or cardiovascular events in young and aging men.[3-5] HRT has numerous benefits that can greatly enhance a patient's quality of life. Before prescribing testosterone, physicians should be aware of the potential side effects of testosterone therapy and how best to address them. Particular attention should be made in TM patients with a clinical history of splenectomy and/or thrombophilia before administration of exogenous testosterone. Patients receiving testosterone therapy should be followed according to a standardized monitoring plan to ensure any potential side effects are detected early. Therefore, we urge health-care professionals to report side effects involving prescription testosterone products and to encourage a regular endocrine follow-up of multitransfused TM patients on HRT.

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Conflicts of interest

There are no conflicts of interest.

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