Turkish Journal of Endocrinology and Metabolism, (2004) 4 : 143-145 **CASE REPORT**

Testosteron Replacement Therapy: Another Contributing Factor to Heart Failure in β Thalassemia Major ?

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Iron-overload alone does not seem to explain the pathogenesis of heart failure (HF) associated with beta-thalassemia major (BTM). Further contributing factors i.e. myocarditis, HLA haplotypes are being claimed to play important roles in the development of HF especially in case of predominantly left-sided involvements. Here we report a case of BTM plus secondary hemochromatosis, in whom the testosteron replacement therapy was temporally associated with initiation and aggrevation of HF. We propose that gonadal replacement therapy can be considered as a potential contributing factor to the heterogenous and multifactorial nature of BTM-associated HF.

Key words: **Hypogonadism, beta-Thalassemia, heart failure, testosteron enanthate**

Introduction

Heart failure (HF) in beta-thalassemia major (BTM) has previously been attributed almost only to iron-overload (1,2). However predominantly left-sided HF has been reported to develop in younger and less hemosiderotic BTM patients in contrast to the involvement of elderly and severely hemosiderotic cases by predominantly right-sided HF (3,4). This is the reason why, Kremastinos et al. emphasized the importance of other risk factors apart from iron-overload in the pathogenesis of HF associated with BTM (5,6).

Androgenic anabolic steroids -including testosteron- are known to be associated with hypertension, ventricular remodelling, myocardial ischemia, and sudden cardiac death, even in healthy men who are taking these drugs to increase athletic performance (7). Testosteron is the preferred ligand of the human androgen receptor in myocardium, and modulates some cellular actions similar to those seen in HF and cardiomyopathy (7). In an experimental model, Zaugg et al., have demonstrated for the first time that, androgenic anabolic steroids -including testosteron- induced apoptotic cell death in rat myocytes (8). These findings were regarded as a molecular evidence to understand the underlying pathogenesis of cardiac morbidity and mortality in case of androgenic anabolic steroid abuse (8).

Beyond the heart as an organ to be damaged directly, fluid retention and erythrocytosis are well known side effects of testostesteron therapy which could precipitate pre-existing heart failure (9).

Despite the lack of comparative clinical evidences in human, searching whether the testosteron therapy in physiologic- or supraphysiologic regimens might have different cardiotoxic profiles, it seems reasonable that at least for some instances, testosteron therapy is a potentially cardiotoxic agent depending on host factors. Thus, here we report the first beta-thalassemic case of the literature, in whom the role

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of testosteron therapy has been discussed as a contributing factor to the development of HF.

Case Report

A 16-year-old white male with BTM plus secondary hemochromatosis was referred to the endocrinology department due to delayed puberty. Following the physical examination, basal and dynamic hormonal evaluations, and pituitary magnetic resonance imaging, he was diagnosed on hypogonadotropic hypogonadism with pituitary hemochromatosis due to diffuse reduction in pituitary signal intensity on T2-weighed images at a background presence of hepatic hemochromatosis and concomitant high levels of serum ferritin levels. Normal TSH and ACTH responses to TRH and CRH stimulation tests were obtained respectively. GH axis was also evaluated as normal (Table 1). Upon these findings, testosteron replacement therapy -testosteron enanthate, 50 mg, IM, once in every 3 weeks- was started. Instead of hCG and/or hMG, testosteron was preferred due to patients' expectations of a less frequent injection. On the 14th month of testosteron therapy, while he had no cardiovascular sign or symptom, an echocardiography was obtained for routine purposes to screen for probable complications, and suggested diastolic dysfunction with completely normal systolic measurements. Thereafter the dosage of testosteron was increased to 125 mg/month. On the 5th month of dose increment, he admitted to the hospital with palpitation and dyspnea on exertion, and his cardiopulmoner auscultation revealed a systolic murmur over the cardiac base, Gallop rythm and bibasal fine crackles. M-mode, 2-dimensional and Doppler echocardiography was done, reported as the systolic dysfunction of the left ventricle with second degree tricuspid insufficiency, and confirmed the clinical diagnosis of congestive heart failure (Table 2). Despite the compliance with desferrioxamine iron chelation therapy, ferritin was measured as 1550 ng/ml at time of HF-diagnosis. With these findings of heart failure, diuretics, digoxine, angiotension converting enzyme inhibitors plus beta-blockers were administered, and testosteron therapy was stopped. At the 18th month of his follow-ups, congestive heart failure seemed to be stable on therapy with an ejection fraction of 51%.

Table 1. Endocrine evaluation of the case before testosteron replacement therapy.

Age (years)	16
Skeletal age (years)	12.5
Weight (kg)	37
Height (m)	1.48
Pubic hair (Tanner Staging)	Stage 1
Testicular volume (mL)	3
Streched penile length (cm)	5.5
Ferritin level (ng/mL)	1650
FSH levels (mIU/mL), (Basal/peak response to LHRH stimulation)	0.57/0.74
LH levels (mIU/mL), (Basal/peak response to LHRH stimulation)	0.26/0.86
Testosteron levels (ng/dL), (Basal/peak response to LHRH stimulation)	0.14/0.34
GH levels (ng/mL), (Basal/peak response to L-Dopa stimulation)	1.51/14.01
TSH levels (mU/mL), (Basal/peak response to TRH stimulation)	0.954/4.104
ACTH levels (pg/mL), (Basal/peak response to CRH stimulation)	15.7/39.0
Basal cortisol (µg/dL)	15.9
Basal IGF-1 (ng/mL)	136.0
Basal FT3 (pmol/L)	4.1
Basal FT4 (pmol/L)	14.6

Table 2. Echocardiographic findings of the case.

Parameter	Before testosteron	After testosteron
Ejection Fraction (%)	62	48
Left ventricular end-diastolic diameter (mm)	55	62
Right ventricular diameter (mm)	20	22
Pulmonary artery pressure (mmHg)	17	25

Discussion

Despite intensive iron-chelation therapy, the survivals of BTM is still limited by the occurrence of heart failure (6). Myocardial iron deposition alone does not affect left ventricular relaxation but directly causes left ventricular myocardial restriction with an elevation in pulmonary pressure, and thereafter causing predominantly right-sided heart failure (4). Left ventricular failure, which occurs in younger, less hemosiderotic populations, seems to be multifactorial in etiology (4). Apart from iron loading, immunogenetic risk factor s are claimed to trigger

the mechanisms of left-sided heart failure development in the context of dilated-type cardiomyopathy (4,6).

The clinical presentation of our case shows that there is a temporal association between the initiation of testosteron replacement therapy and HF-development. Interestingly the increase in the dosage of testosteron is also followed by the precipitation of HF. Therefore question of whether the testosteron might have played a triggering role in the development of HF in our case, is raised on.

On the contrary, androgens are well known vasodilators in the coronary (10), pulmonary (11), and peripheral vasculature (12). In fact, it has recently been shown that, testosteron therapy increased the cardiac output acutely in elderly patients with HF via the reduction of left ventricular afterload (13). Additionally, gonadectomy of adult male rats was shown to reduce the cardiac contractility which was then reversed by gonadal replacement therapy (14). On the other hand, Gao et al. (15), and Li et al. (16), have reported that testosteron was a cardiomyotoxic agent in the presence of a cardiomyopathic phenotype (beta-2-adrenergic receptor overexpressed and guanylyl cyclase-A knockout mice models, respectively). These controversies regarding the cardio-toxicity, cardio-safety and even the cardio-benefits of testosteron therapy definetly requires further explanations. However it seems reasonable that, the cardiac effects of testosteron in case of an established HF, can be ratherly different than in case of an otherwise normal heart.

Consequently we propose that, testesteron replacement therapy could contribute to the development and/or precipitation of HF, especially in predisposed individuals like with BTM-associated hemochromatosis. Regarding the underestimation of such an effect in the literature we suggest that, further clinical evidences are required to document the cardiac effects of gonadal status and gonadal replacement therapies on the HF associated with BTM.

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