

Hormonal Replacement Therapy (HRT) and PDE 5 Inhibitors Response

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Abstract

Objectives: To evaluate PDE-5 inhibitors response in combination to hormonal replacement therapy in patients complaining of erectile dysfunction with low-normal serum testosterone and poor response to sildenafil citrate, vardenafil and tadalafil.

Methods: We have been following 77 men with age between 28 to 88 (mean \pm 59 years) years old with androgen deficiency and using hormonal replacement therapy since 2004. They were seen every month to check the Testosterone levels and see responses with PDE5 inhibitors answering the SHIM score. We decided to use Testosterone 1%, 2% and 3% gel and testosterone cypionate injections. All men had a clinical examination and blood drawn for hormonal profiles every month, the Prostate specific antigen level was included in males >40 years old with digital rectal examination.

Results: The prevalence of men complaining with the symptoms of androgen deficiency was associated with erectile dysfunction and loss of libido. Most of these patients did not achieve a good erection before HRT with PDE5 inhibitors (sildenafil citrate, tadalafil or vardenafil). The libido changes dramatically after HRT and increases proportionally to testosterone level and response to PDE-5 inhibitors.

Conclusions: We concluded that hormonal replacement therapy is necessary for achieving better erections, to improve the PDE-5 inhibitors response, sexual performance improvement, quality of life and even retarding the signals of elderly.

Keywords: Androgen deficiency; Hormonal therapy; Erectile dysfunction; PDE-5 response

Abbreviations: ED: Erectile Dysfunction; AD: Androgen Deficiency; HRT: Hormonal Replacement Therapy; DRE: Digital Rectal Examination; PSA: Prostate Specific Antigen

Introduction

Hormonal Replacement Therapy for males has been used in a different ways for many physicians worldwide. A progressive decline in Testosterone levels, Androgen Deficiency [1], is a common finding in males after their forties. Physical and psychological changes are related to low Testosterone level. Erectile Dysfunction is often associated with aging and can be a symptom of late-onset hypogonadism. Although low testosterone levels do not necessarily cause ED, many men may not respond adequately to treatment with PDE5 inhibitors unless testosterone levels are sufficient. It is therefore important to screen men who present with ED for low serum testosterone and hypogonadism, especially if they fail treatment with PDE5 inhibitors [2].

Various symptoms are associated with to AD including: ED, loss of libido, loss of memory, decrease muscle strength and depression, poor response to PDE-5 inhibitors. All patients came to the consultation office complaining of ED, Loss of Libido, and inadequate response to

PDE5-Inhibitors. Clinical Examination, Hormonal profile (Serum T and Free T levels) were realized in all patients. DRE and PSA Levels only in patients >40 years old. Different choices of testosterone preparation are currently available, which are characterized by different routes of administration and various pharmacokinetic profiles. Intramuscularly injections of testosterone enanthate and testosterone cypionate have been widely prescribed [2].

In our experience Testosterone gel transdermal was effective with minimal side effects and very well tolerated. Transdermal testosterone led to a significant increase in cavernous arterial inflow and a significant improvement in erectile function domain score of the IIEF and was also shown to improve arterial flow and subsequent response to tadalafil treatment [2]. The most important thing in HRT is increasing testosterone levels physiologically, we observed when using testosterone cypionate injections that testosterone levels increased very quickly sometimes above maximum normal limit [3].

Every patient who presented an increase in PSA level passes for a screening for Prostate Cancer. Maintaining the average level of Testosterone was enough to reduce symptoms, restore libido and improve potency and PDE-5 inhibitor response.

Patients and Methods

Between January 2004 and March 2006 we evaluated 77 men age 28 to 88 years old (mean \pm 59 years) with AD. All patients presented with

ED and poor response to PDE-5 inhibitors (Sildenafil, Vardenafil and Tadalafil) determined with SHIM Score (Sexual Health Inventory of Man) [4]. The patients came to the consultation office complaining of ED, Loss of Libido, and inadequate response to PDE5-Inhibitors. Clinical Examination, Hormonal profile (Serum T and Free T levels) were realized in all patients, the blood was drawn between 7-8 am. DRE and PSA Levels only in patients >40 years old. All of them had a SHIM score before and after HRT.

Men with Free T (1.90 to 29.00 pg/ml) and Total T (70.0 to 350.0 ng/dL) started a hormonal replacement with Testosterone transdermal gel application and Testosterone Cypionate 200 mg injections. The preparations of testosterone gel (3 g) contained 30 mg (1%), 60 mg (2%) and 90 mg (3%) of Testosterone (Equilibra Pharmacological Institute, Campo Grande, MS, Brazil), applied on the skin, upper arm (changing left to right) once a day. The dose applied to the skin daily resulted in serum testosterone in the normal range in most hypogonadal men. Dose adjustments to either a lower or higher dose should shift serum testosterone concentration to the desired range in those who do not achieve this range with this dose [5]. Testosterone Cypionate 200 mg injections in 15 patients every 21/21 days and Testosterone Gel were using for 62 patients. After 2 weeks of treatment the patients were asked to try in two different opportunities to use sildenafil citrate 50 mg and 100 mg, if there were poor response to 50 mg, vardenafil 20 mg and tadalafil 20 mg. The follow up occurred every month for a new SHIM score and get a blood drawn to measure free T, total T and PSA.

Results

A total of 77 men with ED and (28 to 88 years) complaining of loss of libido and poor response to PDE-5 inhibitor were evaluated and start a treatment for AD and ED. The SHIM score realized before and after HRT (Table 1) shows an important improvement to erections using PDE-5. The hormones levels have an increasing, free T from 12.64 ± 0.7784 before treatment to 17.62 ± 0.8686 after treatment (Figure 1). Total T from 212.1 ± 7.042 before treatment to 467.0 ± 20.21 after treatment (Figure 2). The data statistical analysis was realized with test T demonstrating that a significant ($p < 0.0001$) between pre and post HRT. Most of all, the patients were feeling well and have their sexual life back. The results of this study support the use of Testosterone gel with sildenafil citrate, vardenafil and tadalafil in men with low serum testosterone levels in whom PDE-5 inhibitor alone failed.

SHIM score	Patients before HRT	Patients after HRT
≤ 7	7	none
08-Nov	18	none
Dec-16	34	2
17-21	18	15
22-25	none	60

Table 1: In accordance to the SHIM score realized to PDE-5 inhibitors before and after HRT.

Comment

Androgen Deficiency in male is considered a syndrome that is characterized by the presence of defined signs/symptoms in

conjunction with low testosterone levels [6]. Testosterone deficiency is the commonest hormonal deficiency in men but its clinical presentation may be subtle and its diagnosis overlooked unless actively considered [1]. The crude incidence rate of androgen deficiency was 12.3 per 1,000 person-years, and the rate increased significantly ($P < 0.0001$) with age. Available data suggest that the prevalence of low Testosterone in older men is around 20% and that prevalence increases with age. Estimates of the incidence of androgen deficiency are non-existent [6]. Several epidemiological studies have demonstrated a gradual decrease of serum testosterone with aging in men. Testosterone levels in adult men decline at an average rate of 1 to 2 per year. This change can be caused by the normal physiologic changes of aging, testicular dysfunction [7]. Classical androgen deficiency is caused by testicular disorders that reduce testosterone production and by hypothalamic-pituitary disorders that reduce pituitary secretion of gonadotropins, the tropic drive to testosterone secretion [8].

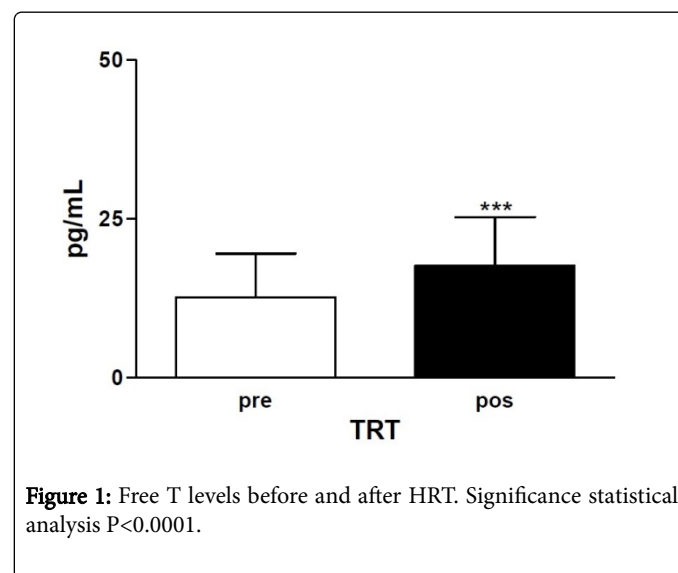


Figure 1: Free T levels before and after HRT. Significance statistical analysis $P < 0.0001$.

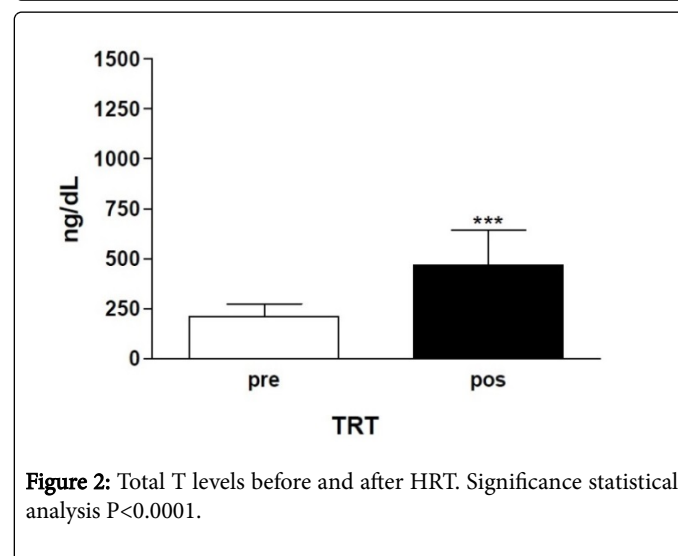


Figure 2: Total T levels before and after HRT. Significance statistical analysis $P < 0.0001$.

Testosterone has an impact on sexual and non-sexual behavior [9]; numerous clinical studies confirm the efficacy of testosterone replacement for treating testosterone deficiency. When testosterone deficiency is physiologically replaced several benefits have been

reported, including improved sexual function, libido, mood, cognition, bone mineral density and lean muscle and strength [5]. The morning erections become more frequent and erections are harder and last longer.

T-gel with sildenafil significantly improved sexual activity in hypogonadal men with ED who did not respond to sildenafil alone. Interest has increased in evaluating androgen replacement as concomitant therapy to PDE-5 inhibitors in hypogonadal men who do not respond to PDE-5 inhibitors alone [10]. Androgen replacement therapy should be started after proof of androgen deficiency and should continue lifelong with monitoring.

The major goal of androgen substitution is to replace testosterone at levels as close to physiological levels as is possible [3]. We can say for sure that HRT increases the testosterone levels and restores libido, muscle strength, enhance memory and improve the response to PDE-5 inhibitors.

Conclusion

We observed that testosterone levels went to normal range after HRT and the SHIM score demonstrated that was a 78% improvement on PDE-5 response. We concluded that Hormonal Replacement Therapy (HRT) is necessary for achieving better erections, improve the PDE-5 response, sexual performance improvement, and quality of life and even retarding the signals of elderly. Testosterone replacement effectively restores sexual health and other androgen dependent actions on mood/cognition, muscle and bone. The major goal of androgen substitution is to replace testosterone at levels as close to physiological levels as is possible and improve the response to PDE-5 inhibitor. The results of this study support the use of testosterone gel with Sildenafil citrate, Vardenafil and Tadalafil in men with low serum testosterone levels in whom PDE-5 inhibitor alone fails. It also

underscores the numbers of men with low to low-normal testosterone levels who would benefit from testosterone screening when evaluated for erectile dysfunction. Testosterone gel raised and maintained serum testosterone levels to within the normal adult range, alleviated signs and symptoms associated with hypogonadism, and was well tolerated.

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