Synergetic effect of testosterone and phophodiesterase-5 inhibitors in hypogonadal men with erectile dysfunction: A systematic review

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Abstract

Testosterone deficiency seems to impair the clinical response to phophodiesterase-5 (PDE-5) inhibitors in patients with erectile dysfunction (ED). In hypogonadal men, testosterone repletion was associated with enhanced sexual function in patients who failed initial treatment with sildenafil or tadalafil. We conducted a systematic review of studies that evaluated combination therapy of testosterone and PDE-5 inhibitors in patients with ED and low, low-normal testosterone levels who failed monotherapy. The studies we examine are heterogeneous with several methodological drawbacks and that, overall, the addition of testosterone to PDE-5 inhibitors might benefit patients with ED associated with testosterone <300 ng/dL (10.4 nmol/L) who failed monotherapy. Further studies, with a randomized placebo-controlled and double blind design, are needed to describe the appropriate target patient group, testosterone cut-off and to define the optimal dose and duration of combination therapy.

Introduction

Experimental studies have shown that testosterone deficiency is associated with marked decline in nitric oxide synthetase (NOS) activity and protein expression – two factors important for proper erectile function.[1,2]

Testosterone-treated castrate rats restored their erectile response and NOS activity.[3-5] Furthermore, testosterone supplementation restored cavernosal phosphodiaesterase-5 (PDE-5) gene and protein expression in a rabbit model with hypogonadotropic hypogonadism.[6-8] On the ultra-structural scale, castrate animals had a thinner and less elastic tunica albuginea,[9] a significantly reduced trabecular smooth muscle content, an increased connective tissue deposition in the corpora cavernosa[10,11] and deleterious changes in the penile dorsal nerve.[9] Nevertheless, testosterone replacement restored most of these penile changes.[12] There is now evidence to show that testosterone replacement is recommended to improve sexual desire and erectile function in patients with unequivocally low serum testosterone and sexual dysfunction, loss of libido and erectile dysfunction (ED).[13-15] Furthermore, there is mounting clinical evidence to show that in hypogonadal men with ED who failed previous treatments with monotherapy (testosterone or PDE-5 inhibitors), combination therapy might normalize testosterone blood levels and possibly enhance the response to PDE-5 inhibitors.[16-18] This is highly pertinent given that 30% to 35% of patients with ED fail to respond to treatment with PDE-5 inhibitors partly due to low blood testosterone levels.[17,19]

Few uncontrolled studies have shown a beneficial effect when testosterone was added to PDE-5 inhibitors, however, the small sample size, lack of controls and the different serum testosterone cut-offs used made these studies subject to criticism.[20-24] A systematic review of the literature demonstrates that most trials examining combination therapy or testosterone alone suffer from methodological problems or report inconsistent results; these studies also show oral PDE-5 inhibitors may be enhanced by testosterone adjunction whenever necessary.[19] A relatively recent meta-analysis identified three small-randomized controlled trials in hypogonadal men with ED refractory to previous PDE-5 inhibitors. The results were inconsistent on whether oral PDE-5 inhibitors plus testosterone improved sexual function more than did PDE-5 inhibitors alone.[25] Conversely, a recent randomized controlled trial showed that the addition of testosterone to daily tadalafil helped hypogonadal men with baseline testosterone levels ≤300 ng/dL (≤10.4 nmol/L).[17]

The objective of this study was to conduct an up-to date systematic review of the clinical studies on combination therapy in order to gain further insight on the clinical impact of hypogonadism (if any) on PDE-5 inhibitors action.

Methods

Search strategy and selection criteria

We searched the Medline database from 1995 to 2011 using the following MESH terms: "erectile dysfunction," "hypogonadism," "phophodiesterase-5 inhibitors," in combination with "testosterone therapy," "combined modality therapy," "sildenafil," "tadalafil." Additional studies were identified from the study reference lists. Two investigators (NA, SC) independently reviewed the papers for eligibility.

Eligibility criteria

Only full articles published in English were retrieved. All studies, either controlled or not, evaluating the role of combination therapy were included, provided they stated a pre-treatment cut-off value of testosterone. Due to the scarcity of high quality studies, we included less evidence-based studies.

Data extraction

We selected studies that evaluated the effect of combination therapy (testosterone + PDE-5 inhibitors) on erectile function in hypogonadal men. We recorded the type of study (randomized controlled trial vs. uncontrolled study), testosterone threshold levels, type and regimen of PDE-5 inhibitors (on demand vs. daily), form of testosterone replacement, method of ED assessment, timing of combination therapy (simultaneous vs. interval), effect on libido and orgasm, and tolerance of combination therapy (side effects). We used different thresholds for testosterone blood levels, different forms (oral, intramuscular, topical) and durations of testosterone therapy.

Results

The search process revealed initial 528 citations. Only 14 articles (12 testosterone + sildenafil and 2 testosterone + tadalafil studies) examined the combination therapy in patients with ED and low/low-normal testosterone. These articles included 684 patients, ranging from 8 to 173 patients in each study (Table 1). Ten studies used the International Index of Erectile Dysfunction (IIEF) as the main scoring system for baseline and follow-up assessment of treatment response, while the other 4 studies used the Androgen Deficiency in Aging Male (ADAM) questionnaire,[23] National Institute of Health (NIH) consensus criteria,[26] nocturnal penile tumescence (NPT) and penile colour duplex ultrasound[27] and one study used only nocturnal penile tumescence and rigidity monitoring.[28]

We identified 5 out of 14 studies that had a prospective randomized controlled design,[16-18,28,29] while the remaining studies, although prospective, lacked either a control group, randomization or both. All included studies showed improved, subjective and objective, response to combination therapy over monotherapy with either drug alone. Among the 10 studies that reported varying improvement in IIEF domains after combination therapy (erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction), 8 studies showed increase in the erectile function domain from an average 13 ± 1.8 at baseline to an average 20.25 ± 3.9 post-treatment with an overall efficacy of 34% to 100%. Treatment with testosterone ranged from 4 to 52 weeks (average 16.4 ± 12.5 weeks). The transdermal patch (5 mg/day) was used in 2 studies, 1% testosterone-gel in 5 studies, intramuscular testosterone in 4 studies, and oral undecanoate in the remaining 3 studies (Table 1). All studies reported an increase in blood testosterone at least to mid-normal levels after treatment; nevertheless, no major adverse effects (i.e., significant increase in PSA or polycythemia) occurred.

Interestingly, different thresholds were reported for the initiation of testosterone therapy; however, testosterone blood levels were either low, <300 ng/dL (10.4 nmol/L) or low-normal (lower quartile of normal range). After converting testosterone blood units to one common unit (ng/dL), the average pre-treatment testosterone level was 296 ± 85 ng/dL (10.2 ± 2.9 nmol/L) (range: 198-400 ng/d; 6.8-13.8 nmol/L). Most studies used on-demand sildenafil in adjunct to testosterone, except 2 studies that used tadalafil either daily[17] or twice weekly.[24] Despite the lack of a clear definition of PDI-5 inhibitor failure, the main indications to start combination therapy were failure of PDE-5 inhibitors and low-borderline testosterone.[16-18,22-24,29,30] The remaining studies reported good response with other indications, like ED and hypogonadism unresponsive to testosterone replacement alone,[21] initial combination therapy (not monotherapy) in patients with ED and hypogonadism after renal or bone marrow transplant, and in patients on hemodialysis not responding to erythropoietin and/or testosterone;[20,26,31] moreover, initial combination therapy benefited patients with severe hypogonadism, testosterone <200 ng/dL (<6.9 nmol/L) and ED.[27,28]

Discussion

We identified 14 studies (12 testosterone + sildenafil, 2 testosterone + tadalafil) involving combination therapy for 4 to 52 weeks in heterogeneous patient groups. We observed a superior positive impact of combination therapy (overall efficacy 34% to 100%) on sexual dysfunction in patients who failed on either drug alone or in patients who experienced partial improvement on monotherapy. This salvage treatment is clinically relevant; 23% to 50% of patients did not respond to PDE-5 inhibitors alone,[32] and hypogonadism was prevalent in 37% of impotent men treated with sildenafil.[33] Interest in

Table 1. Studies on combination therapy for ED and low, low-normal T level

Study, yr	N/R	Total T level	T form	PDE-Is	ED assessment	Control/ medication	Finding	Evidence
Aversa, 2003[16]	20/yes	Low-normal 10-13 (nmol/L) = 288-374 (ng/dL)	Transdermal patch (5 mg/ day) for 1 month	Sildenafil (100 mg) on demand	IIEF	ED/placebo and sildenafil	Significantly improved response to sildenafil; significant increase in cavernous blood flow	1b
Shabsigh, 2004[18]	75/yes	400 (ng/dL) or less ≤13.8 (nmol/L)	1% T-gel for 12 weeks	Sildenafil (100 mg) on demand	IIEF	ED/placebo and sildenafil	Significant improvement in erectile function and overall satisfaction	1b
Shamloul, 2005[29]	40/yes	7.3±1.4 (nmol/L) = 210±40 (ng/dl)	Oral undecanoate 120 mg/day for 8 weeks	Sildenafil (50-100 mg) on demand	-IIEF-5 -PADAM rating score	ED/ Sildenafil alone	Significant increase in T levels, IIEF-5 score and PADAM score	1b
Kalinchenko, 2003[30]	120/none	6.9±1.3 (nmol/L) = 198±37 (ng/dl)	Oral undecanoate 80-120 mg/d for 4-6 weeks	Sildenafil (100mg) on demand	IIEF	DM patients with ED/ and good response to Sildenafil	Significant increase in libido, erections and IIEF score in type 2 DM on OHA	3b
Greenstein, 2005[21]	49/none	Less than 400 (ng/dL) = <13.8 (nmol/l)	T-Gel 1% for 6 months	Sildenafil (100 mg) on demand	IIEF GAQ	None	Significant improvement in libido and erectile function	4
Buvat, 2011[17]	n=173/ yes	T ≤ 400 ng/dL ≤13.8 (nmol/L) Bioavailable T ≤ 100 ng/dL	T-Gel 1% for 12 weeks	Tadalafil 10 mg daily	IIEF SEP	ED/ Placebo Gel plus daily Tadalafil	Combination therapy beneficial only when baseline T level ≤ 3 ng/ml	1b
Chatterjee, 2004[20]	n=12/ no	11.45 nmol/L (median) = 329 (ng/dL)	Monthly T cypionate 250 mg IM injection for 12 months	Sildenafil 50-100mg (1-2/week)	IIEF NIH	None	Combination therapy improves sexual performance, including erectile function, in post-renal transplant and hemodialysis patients	4
Hwang, 2006[22]	n=32/ none	T=259 (ng/dL) (mean) = 8.9 (nmol/L)	T undecanoate 80 mg (bid or tid) for 2 ms	Sildenafil 100 mg (on demand)	IIEF	None	Two thirds of patients showed significant improvement in IIEF score with combination therapy	4
Rosenthal, 2006[23]	n=24/ none	Less than 400 ng/dL = 13.8 (nmol/L)	1% T-Gel for 16 weeks	Sildenafil 100 mg (on demand)	ADAM	None	Improvement in erectile quality observed after 3 months of combined therapy	4
Tas, 2006[31]	n=23/ none	300±40 ng/dL	Testers 250 mg IM every 15 days for 12 weeks	Sildenafil 25-100mg (on demand)	IIEF	Erythro-poietin± Testosterone	Hemodialysis patients: significant improvement in IIEF score with Sildenafil after 3 months T therapy (not in combination)	3b
Yassin, 2006[24]	n=69/ Yes	≤ 340 ng/dL = 11.8 (nmol/L)	1% T-gel for 4 vs. 10 weeks	Tadalafil 20 mg 2/week	IIEF Partner satisfaction	None	Significant improvement in erectile function as early as 4 weeks of combination therapy Increased response at 10 weeks	2b
Chatterjee, 2002[26]	n=8/ none	8.3 – 17.9 nmol/L = 239-515 (ng/dL)	IM T cypionate 250 mg 4/weekly for 6 months	Sildenafil 50-100 mg	NIH consensus criteria	Yes (non-specified)	Bone marrow transplant Combination therapy is safe and effective in high-dose chemotherapy recipients	4
Foresta, 2004[27]	15/ none	Less than 200 ng/ dL ≤6.9 nmol/L	T patch (5 mg) for 6 months	Sildenafil 50 mg (on demand)	NPT P-CDU	20 men with psychogenic ED	Testosterone restores erectile response to sildenafil and apomorphine (vascularization, erection numbers)	4
Rochira, 2006[28]	24/yes	Less than 200 ng/dL ≤ 6.9 nmol/L	Testosterone enanthate IM, 250 mg every 21 days	Sildenafil 50 mg (bed time)	NPTRM	24 eugonadal volunteers	Combination therapy results in maximum positive effect on sleep-related erections	1b

ED: erectile dysfunction; T: testosterone; N: number; R: randomization; PDE-Is: phophodiesterase-5 inhibitors; IIEF: International Index of Erectile Function; PADAM: Partial Androgen Deficiency of Aging Male; GAQ: Global Assessment Question; NPT: nocturnal penile tumescence; P-CDU: penile colour Doppler ultrasound; NIH: National Institute of Health; SEP: sexual encounter profile diary; OHA: oral hypoglycemic agents; IM: intramuscular; NPTRM: Nocturnal Penile Tumescence Rigidity Monitoring test.

combining testosterone and PDE-5 inhibitors has increased due to the role of testosterone in the maintenance of the nitric oxide pathway and in the expression of the gene and protein of phophodiesterase-5. On the other hand, while some studies comparing testosterone to placebo in hypogonadal men with ED were inconsistent regarding the effect on erectile function,[25] few other studies showed only mild or moderate improvement in frequency of sexual intercourse[34] or slightly higher mean IIEF erectile function domain score,[35] especially in middle and older age group. This could be explained by the coexistence of vasculogenic or neurogenic ED,[36] together with hypogonadism, that might respond better to the augmented vasodilatation effect generated by both drugs.[16]

Combination therapy was shown to be beneficial in different clinical settings. In their uncontrolled study, Greenstein and colleagues reported a 100% success rate (erectile function and libido) when they combined testosterone-gel 1% with on-demand 100 mg sildenafil for 6 months in borderline eugonadal men (testosterone less than 400 ng/dL) who failed initial treatment with testosterone-gel alone.[21] Interestingly, combination therapy was also shown to be safe and effective in hypogonadal men with comorbidities. Chatterjee and colleagues reported an improvement in sexual performance in all 12 patients on hemodialysis and post-renal transplant who had a median serum testosterone 329 ng/dL (11.45 nmol/L) and ED; these patients had monthly intramuscular testosterone cypionate 50 to 100 mg sildenafil orally once or twice weekly for 12 months.[20] Another study by the same group used similar drug regimen for 6 months in 8 bone marrow transplant patients; the authors demonstrated that combination therapy was safe and effective in high-dose chemotherapy recipients. Furthermore, sildenafil improved IIEF scores in hemodialysis patients with serum testosterone 300 ng/dL who failed initially with erythropoietin and/or testosterone for 3 months.[31]

Interestingly, combination therapy resulted in increased sexual response in the setting of severe hypogonadism, testosterone <200 ng/dL (<6.9 nmol/L). One study reported that treatment with testosterone and sildenafil resulted in a maximum positive effect on sleep-related erections.[28] Another study showed that testosterone therapy improved response to sildenafil as assessed by erection numbers at sleep and cavernosal vascularization (penile colored duplex).[27]

On the other hand, most studies in our systematic review examined the effects of combination therapy after failure of initial treatment with PDE-5 inhibitors alone, not testosterone therapy. Combination of testosterone undecanoate and sildenafil have been reported to reverse ED in 120 diabetic patients with serum testosterone 198 ng/dL (6.9 nmol/L) who failed sildenafil therapy alone.[30] Furthermore, testosterone was shown to be helpful in small, uncontrolled trials.[22-24]

More convincing, 5 randomized controlled trials support this observation, but some had methodological shortcomings. In one study, although it included small numbers and a short duration, 100-mg sildenafil plus 5-mg/d testosterone patch improved sexual intercourse success and erectile function compared with sildenafil and placebo in borderline eugonadal men, testosterone 288 to 374 ng/dL (10-13 nmol/L).[16] Shabsigh and colleagues reported significant improvement in erectile function and overall satisfaction as early as 4 weeks, but not at 8 or 12 weeks, on the sildenafil plus 1% testosterone-gel arm compared to men randomly assigned to sildenafil and placebo in a group of patients with low-normal testosterone, <400 ng/dL (<13.8 nmol/L).[18] In a third trial, oral testosterone 120 mg/d plus sildenafil was associated with a small but significant increase in the erectile function domain and Partial Androgen Deficiency of Ageing Male (PADAM) scores compared with sildenafil and placebo in hypogonadal men with serum testosterone 210 ± 40 ng/dL (7.3 ± 1.4 nmol/L).[29] Interestingly, Rochira and colleagues reported similar improvement in nocturnal erections when sildenafil or testosterone used as monotherapy in patients with very low serum testosterone levels; however, the effects of testosterone plus sildenafil were greater than the sum of the effects of each drug used alone.[28] More recently, a multicentre, double-blind; placebo-controlled study (TADTEST study) examined 173 men, non-responders to treatment with different PDE-5 inhibitors with baseline testosterone ≤400 ng/dL (13.8 nmol/L). Men were treated first with tadalafil (10 mg) once daily for 4 weeks; if this was unsuccessful, they were randomized to placebo or 1% testosterone-gel. Surprisingly, no additional effect of testosterone in men optimally treated with PDE-5 inhibitors was found at 12 weeks when the baseline mean testosterone level was 337 ± 14.8 ng/dL (11.7 ± 0.5 nmol/L). In contrast, the testosterone-gel group had a statistically significant positive effect over placebo, IIEF-erectile function domain and rate of successful intercourse in men with baseline testosterone ≤300 ng/dL (≤10.4 nmol/L).[17]

Conversely, a meta-analysis of three controlled trials yielded inconsistent results on whether PDE-5 inhibitors plus testosterone enhance sexual function more than PDE-5 inhibitors alone in hypogonadal men with ED refractory to previous PDE-5 inhibitors alone.[25] Furthermore, sildenafil treatment was associated with increase in erectile function whether or not the patient received prior testosterone supplements, even when testosterone blood levels were lower than normal range.[33] A testosterone threshold below which sexual function is impaired could exist.[37] This threshold is controversial because although consistent in one individual, it is markedly variable among individuals.[38] Nevertheless, testosterone deficiency is most often defined as a serum testosterone <300 ng/dL (10.4 nmol/L)[39] and there is a general agreement that total testosterone levels above 346 ng/dL (12 nmol/L) do not require substitution.[40-41] In this review, the average testosterone level for all studies was just below

300 ng/dL (296 ± 85 ng/dL) despite the fact that most studies included low-normal levels of testosterone, up to 400 ng/dL (13.8 nmol/L). Furthermore, the fact that some hypogonadal men respond fully to PDE-5 inhibitors[28] suggests that their efficacy may depend on minimal levels of circulating testosterone.[39]

A limitation of this review is the inclusion of low-evidence, heterogeneous population-based studies. However, this work confirmed the safety and potential positive impact of combination therapy with 6 of our 14 high-level evidence studies (≥2) showing its synergistic efficacy in hypogonadal men. Prospective well-designed trials are needed to better define the target population who will benefit from this approach

Conclusion

There is an emerging body of evidence to show that combination therapy is safe and could be beneficial. The most widely accepted cut-off below which hypogonadism is diagnosed is a serum testosterone level <300 ng/dL (10.4 nmol/L). Furthermore, adding testosterone for a short time in cases of low-normal testosterone levels (300 to 400 ng/dL) seems helpful in some men who did not respond to initial treatment with PDE-5 inhibitors alone and in whom testosterone therapy is not contraindicated. The lower the baseline testosterone level, the more likely combination therapy will have a superior improvement in sexual function over monotherapy.

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