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ORIGINAL ARTICLE

Efficacy of sildenafil in male dialysis patients with erectile dysfunction unresponsive to erythropoietin and/or testosterone treatments

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The aim of this study was to evaluate the effects of recombinant human erythropoietin (Epo), testosterone (T) or a combination of them in the treatment of erectile dysfunction (ED) in hemodialysis patients, as well as the efficacy of sildenafil in patients unresponsive to combination treatment. A total of 23 patients with ED were divided into two groups. The international index of erectile function (IIEF) was used to evaluate ED and treatment response. Patients received Epo or T treatments for 12 weeks. Later on both groups received combination treatment for another 12 weeks. Although IIEF scores increased significantly in both groups after the combination treatment, the score changes were similar. After combination treatment, 16 patients still having IIEF score <26 were given sildenafil treatment in combination with Epo while T was discontinued. Although the IIEF scores increased significantly in all patients (17.4%), only eight of them attained an IIEF score of $\geqslant 26$. The baseline IIEF scores of the patients with satisfactory response to the sildenafil treatment were higher than those with unsatisfactory response. The patients with a score of $\geqslant 22$ responded better to the treatment. Although Epo and/or T therapies could partially improve ED in male dialysis patients besides correcting renal anemia and hypogonadism, sildenafil treatment could improve ED in unresponsive patients. Especially, those with higher baseline IIEF scores benefited more.
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Introduction

Sexual dysfunction is a frequent disorder in men with end-stage renal disease (ESRD).[1] Erectile dysfunction (ED) is the persistent inability to achieve or maintain an erection sufficient for satisfactory sexual activity.[2] ED is the most common disorder of sexual dysfunction in dialysis and predialysis patients that impairs the quality of life of such patients, with a varying range reported upto 82% among dialysis patients.[3–8] The pathogenesis of ED includes physiological, psychological and organic causes. Hormonal disturbances, zinc deficiency, medications, peripheral neuropathy, biochemical imbalances from dialysis, autonomic insufficiency and peripheral vascular pathologies are the suggested organic components.[1] The psychogenic component of ED seems to arise from chronic illness and lifestyle limitations. Patients with ESRD have chronic fatigue, anxiety and a decline in self-esteem, which results in decreased sexual interest.

Previously, several methods, for example, external vacuum devices, intracavernosal injection of vasoactive medications and penile prosthesis, have been recommended for treating ED in patients with ESRD.[9,10] However, most patients rejected or were dissatisfied with these methods and therefore discontinued them. For the patients with ESRD together with ED, the traditional treatment consisted of correction of anemia by recombinant human erythropoietin (Epo), optimization of dialysis, removal of the implicated medication and administration of testosterone (T).[1,6,9,11] Recently, sildenafil, a selective inhibitor of phosphodiesterase type-5,

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which is the predominant isozyme inactivating cyclic guanosine monophosphate in the corpus cavernosum, has been shown to be an effective, well tolerated treatment for nonuremic men with ED.[12] Its use results in increased smooth muscle relaxation and improved erection when nitric oxide is released in the presence of sexual stimulation. Several studies have indicated that sildenafil is a well-tolerated and effective treatment for ED in men receiving maintenance hemodialysis (HD).[7,13–15] However, no study specifically addressed the comparison of efficacy and safety of Epo, T, combination of both drugs and sildenafil together with Epo on ED in the same patient population with ESRD. We aimed to evaluate the effects of Epo, T and combination of both drugs in treatment of ED in HD patients with ESRD and the efficacy of sildenafil as an adjunct to Epo in patients unresponsive to combination treatment.

Materials and methods

Patient selection

The study was carried out between June 1999 and May 2000. Stable male subjects older than 18 years receiving routine outpatient HD therapy were recruited for participation in this study. A total of 94 male patients were evaluated by a detailed medical and sexual history, a systemic and urologic physical examination, psychological profile and electrocardiogram and echocardiography, if required for cardiac evaluation. Patients with congestive heart failure, acute ischemic heart disease or recent ($\leq$6 months) history of cardiovascular disease, stroke or myocardial infarction, concomitant treatment with nitrates, presence of hypotension or hypertension, penile anatomical defects and hematological and/or hepatic diseases were excluded.

A total of 30 patients, each having regular partners and a hematocrit (Hct) less than 30%, matched the inclusion criteria. A total of 23 HD patients with ED (International Index of Erectile Function (IIEF) score $<$26 and normal penile erection response with intracavernosal papaverine, having primary or secondary hypogonadism) were included in the study. The study was carried out in accordance with the guidelines of the Helsinki Declaration of Human Studies. An informed written consent was taken from all patients before study entry.

Study design

The multi-tier treatment study consisted of three periods. In the first period, the patients were divided into two groups based on age and time on dialysis. The first group of patients were given Epo treatment (subcutaneously, at a dose of 50 U/kg three times per week after each dialysis session) (Epo group, *n*:12) and the second group received T treatment (intramuscular T ester compounds once every 15 days—Sustanon® 250 mg; 30 mg T propionate, 60 mg T phenpropionate, 60 mg T isocaproate and T decoanate, Organon) (T group, *n*:11) for 12 weeks.

In the second period, both groups had received Epo and T combination treatment for 12 weeks (Combination group). In the third period, patients having IIEF score still $<$26, totally 16, had been given sildenafil treatment (Viagra®; Pfizer Inc.) for 12 weeks in combination with Epo by discontinuing T (Sildenafil group). Patients were instructed to take 1 tablet of sildenafil 1 h before sexual activity, 2–3 h after a meal. The initial dose for all patients was 25 mg; after two subsequent failures with 25 mg they were instructed to increase the dose to 50 and 100 mg until satisfactory erection was maintained but not to exceed more than one tablet daily. Patients were asked to use sildenafil on the days after dialysis.

In all periods the erectile function response to treatment was evaluated according to the IIEF. After using the treatment a score of $\geqslant$26 was accepted as indicating restored erectile function.

Laboratory measurements

Medical and demographic data were obtained for each subject from the dialysis records. In the baseline period, hemoglobin (Hb), Hct, efficacy of dialysis (Kt/V), normalized protein catabolic rate (nPCR), serum creatinine, albumin, iron, total iron binding capacity, transferrin saturation (TS), ferritin, alanine aminotransferase (ALT) and serum hormone levels including follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin, total T (TT, normal range (NR): 2.7–17 ng/ml in 20–49 years and 2.1–8 ng/ml $>$50 years) and free T (FT, NR: 12.4–40 pg/ml in 20–49 years and 10.8–24.6 pg/ml $>$50 years), dehydroepiandrosterone sulfate (DHEA-S), androstendion (AD), sex hormone binding globulin (SHBG) and intact parathyroid hormone (iPTH) were measured. The hematological, biochemical and hormonal measurements were repeated with 3-month intervals.

Primary hypogonadism was biochemically defined as a low or low normal FT level in the presence of elevated LH and FSH. Secondary hypogonadism was diagnosed by a low-FT level accompanied by a low or low normal LH or FSH. The lack of secondary sexual characteristics combined with small testicles suggested hypogonadism.

Assessment of erectile function

After pharmacological stimulation by intracavernosal injection of 30–60 mg papaverine under basal conditions, penile tumescence and rigidity were

recorded after 15 min by measuring the length and the circumference of the penis.

All patients filled in the IIEF form, which included ED criteria consisting of 15 questions (Qs).[16] The IIEF has five domains: erectile function (Q1–Q5 and Q15, total score 1–30), intercourse satisfaction (Q6–Q8, total score 0–15), orgasmic function (Q9–10, total score 0–10), sexual desire (Q11–12, total score 2–10) and overall sexual satisfaction (Q13–14, total score 2–10). The erectile function domain consisted of 6 Qs (erection frequency – Q1, erection firmness – Q2, penetration ability – Q3, maintenance frequency – Q4, maintenance ability – Q5, and erection confidence – Q15). Subjects who scored <26 in this domain were considered to have ED. The score for each item ranges from 0 to 5 for Qs 1–10, 0 meaning no sexual activity/no attempt at sexual intercourse, and from 1 to 5 for Qs 11–15.

Partner assessment

Partner satisfaction was assessed by a form that consisted of seven Qs evaluating previous 1 year (intercourse enjoyment, intercourse satisfaction, intercourse frequency and overall satisfaction, and change in partners' desire level, maintenance ability and erection confidence). Partners whose scores ranged from 0 to 4 were considered 'not satisfied' with the sexual function of their partners, while those that ranged form 4 to 5 were considered 'satisfied'.

Statistical analysis

The data were evaluated by SPSS v. 10.0 statistical software for Windows. Clinical and laboratory data were presented as mean $\pm$ s.e. Statistical analysis was performed with nonparametric Wilcoxon's signed rank test and Mann–Whitney *U*-test in intra- and intergroup comparisons, respectively. Fischer's exact test was used for categorical variables. The correlations between numerical parameters were evaluated with the Pearson bivariate correlation test. The ROC curve was used to determine the threshold for predicting sildenafil treatment outcome. *P*-values less than 0.05 were considered to be significant.

Results

Two patients in the T group decided to discontinue the therapy on their own will. The results of the rest 21 patients were evaluated. No difference was detected between the characteristics of the Epo and T groups (Table 1).

Erectile function response

There was no significant difference in the baseline IIEF scores between Epo and T groups. After the treatment, IIEF scores were significantly increased in both groups ($P<0.05$, Table 2). But, the percentage changes in IIEF score of Epo and T groups were similar (37.5 vs 14.7%, respectively). IIEF score of one patient from each group was $\geqslant 26$. In the combination period, although the IIEF scores of three patients in addition to the previous two patients increased to $\geqslant 26$, the changes in IIEF scores were insignificant. In the third period sildenafil treatment was given to a total of 16

Table 1 Characteristics of patients in all periods

	1 period		*2 period*	*3 period*
	Epo (n: *12*)	*T* (n: *9*)	*Epo + T* (n: *21*)	*Epo + sildenafil* (n: *16*)
Age (y)	37.5 ± 3.6	38.8 ± 3.1	38.1 ± 2.4	41.2 ± 2.6
Dialysis duration (y)	3.4 ± 0.8	4.7 ± 1.0	4.0 ± 0.6	4.7 ± 0.8
BMI (kg/m^2)	23.0 ± 0.9	22.1 ± 1.0	22.6 ± 0.6	23.4 ± 0.7
SBP (mmHg)	135 ± 5.1	131 ± 6.3	133 ± 3.9	136 ± 4.6
DBP (mmHg)	81 ± 2.4	79 ± 2.9	80 ± 1.8	83 ± 2.1
Kt/*V*	1.03 ± 0.1	1.02 ± 0.05	1.02 ± 0.06	1.03 ± 0.07
Albumin (g/dl)	3.9 ± 0.1	4.1 ± 0.1	4.0 ± 0.1	4.0 ± 0.1
nPCR	1.1 ± 0.07	1.03 ± 0.03	1.07 ± 0.04	1.07 ± 0.04
iPTH (pg/ml)	333 ± 124	345 ± 114	273 ± 76	333 ± 91
Primary diseases				
Idiopathic	4	3	7	5
Hypertension	1	1	2	2
Glomerulonephritis	3	2	5	2
Policystic kidney D.	—	2	2	2
Pyelonephritis	1	1	2	2
Diabetes mellitus	3	—	3	3

Epo: recombinant human erythropoietin; T: testosterone; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; Kt/V: dialysis adequacy; nPCR: normalized protein catabolic rate; iPTH: intact parathyroid hormone.

Table 2 Changes in body mass indexes, blood pressure, hematological parameters, erectile function domain scores and testosterone levels of the patients before and after different treatment regimens

	1 period				*2 period*		*3 period*	
	Epo (n: *12*)		*T* (n: *9*)		*Epo + T* (n: *21*)		*Epo + Sildenafil* (n: *16*)	
	Pretreatment	*Post-treatment*	*Pretreatment*	*Post-treatment*	*Pretreatment*	*Post-treatment*	*Pretreatment*	*Post-treatment*
BMI (kg/m^2)	23.0±0.9	23.1±0.9	22.1±1.0	23.2±1.0*	23.2±0.6	23.0±0.6	23.4±0.7	23.6±0.7
SBP (mmHg)	135.8±5.1	142.5±7.6	131.1±6.3	131.1±7.7	137.6±5.4	135.7±3.9	136.8±4.6	143.7±5.4
DBP (mmHg)	81.6±2.4	84.1±3.3	79.4±2.9	78.8±5.6	81.9±3.0	80.9±1.9	83.1±2.1	86.2±2.5
Hemoglobin (g/dl)	7.65±0.4	8.53±0.5*	8.38±0.5	9.27±0.4**	8.85±0.3	9.4±0.3	9.96±0.3	10.0±0.3
Hematocrit (%)	22.6±1.2	25.6±1.4*	24.8±1.7	27.8±1.6**	26.6±1.1	28.8±1.1	30.6±1.1	31.1±1.2
Ferritin (ng/ml)	242±64	219±49	233±82	246±82	231±44	212±40	194±45	243±66
TS (%)	15.6±1.9	13.8±1.7	28.8±7.2	19.6±3.2	16.3±1.8	13.6±1.3	13.7±1.2	17.8±2.2
Epo dosage (U/kg/w)	156.2±6.8	146.6±13.3			126.3±11.8	113.1±13.4	100.1±14.4	86.9±15.1
Albumin (g/dl)	3.9±0.19	3.9±0.14	4.1±0.12	4.0±0.08	4.0±0.08	3.9±0.1	4.0±0.11	3.8±0.35
IIEF score	15.5±1.6	19.5±1.6*	19.1±1.4	21.7±1.6*	20.5±1.1	21.6±1.0	19.8±1.0	23.0±1.4*
TT (ng/ml)	3.6±0.3	3.8±0.3	3.0±0.4	5.0±0.7*	4.3±0.3	3.9±0.4	4.2±0.5	4.1±0.5
FT (pg/ml)	8.6±1.3	20.1±2.6*	9.7±2.2	23.7±3.8*	21.7±2.2	12.8±1.1*	12.7±1.3	12.0±1.4

Epo: recombinant human erythropoietin; T: testosterone; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; TS: transferrin saturation; IIEF: International Index of Erectile Function; TT: total T; FT: free T. *$P<0.05$ and **$P<0.01$, compared with pretreatment values of same group.

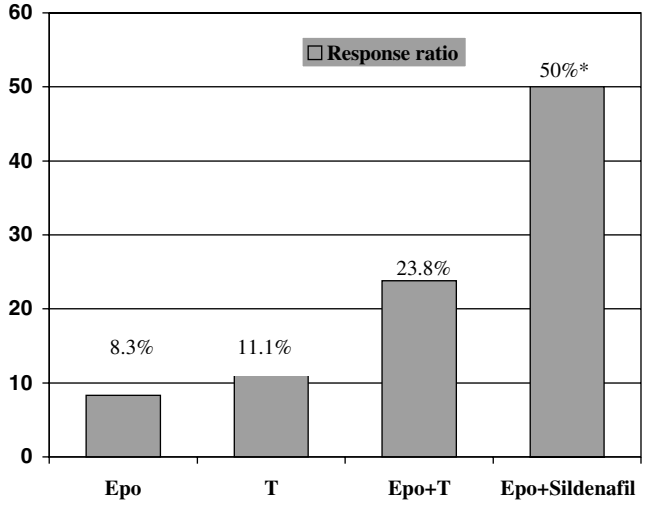

Figure 1 The comparison of ratios of patients with IIEF scores ⩾26 after different treatment regimens. Epo: recombinant human erythropoietin, T: testosterone; *$P<0.05$, compared with Epo group.

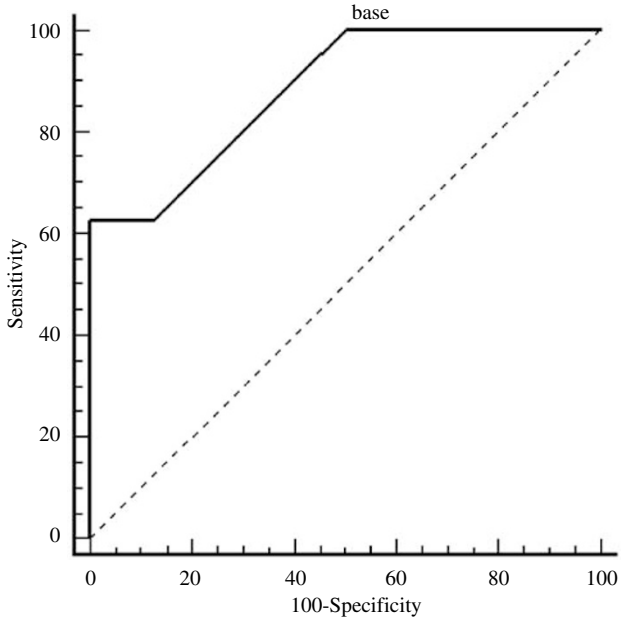

Figure 2 The ROC curve of the erectile function domain score before sildenafil treatment for predicting the outcome of the treatment in 16 patients (area under the ROC curve = 0.883, standard error = 0.090, 95% confidence interval = 0.626–0.983).

patients (76%) whose IIEF scores were <26 in addition to Epo by discontinuing T. The IIEF scores of patients increased significantly (17.4%, $P<0.05$) (Table 2). At the end of 12 weeks, the dosage of sildenafil was increased to 50 mg in 11 patients (69%) and to 100 mg in two patients (13%). Eight of them (50%) had an IIEF score ⩾26. The ratio of patients who responded to sildenafil treatment was higher than those of all groups and this ratio was only comparable with the Epo group (50 vs 8.3%, $P<0.05$, Figure 1).

The baseline IIEF scores and percentage change in IIEF scores of eight patients who had satisfactory response after the sildenafil treatment were higher than those with unsatisfactory response (22.3±0.7 vs 17.2±1.4, $P<0.01$ and 23.5 vs 11.4%, $P=0.05$, respectively). The ROC curve for the erectile function domain showed that patients with a score of ⩾22 responded better to the sildenafil treatment with a sensitivity of 62.5% and a specificity of 100% (area under the ROC curve = 0.883, Figure 2). Additionally, there was no significant difference

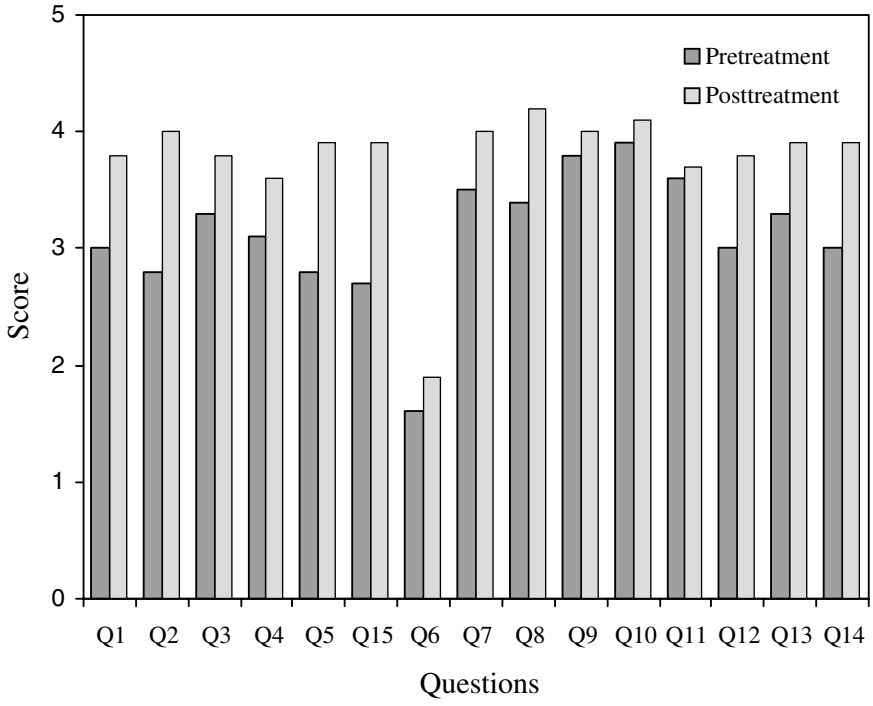

Figure 3 The changes in erectile function (Q1–5, Q15), intercourse satisfaction (Q6–8), orgasmic function (Q9, and10), sexual desire (Q11, and 12) and overall sexual satisfaction (Q13, and 14) domain questions scores in patients on sildenafil before and after the treatment ($P<0.05$ for the increases in Q1, Q2, Q5, Q15, Q8, Q12 and Q14).

concerning age, duration of dialysis, BMI, Kt/*V*, nPCR, blood pressure, albumin, hematological and hormonal values, sildenafil and Epo dosages between sildenafil-responsive and unresponsive groups.

When the questions related with ED in the IIEF form were considered, the increases in erection frequency (Q1, 26.7%), erection firmness (Q2, 42.8%), maintenance ability (Q5, 39.3%) and erection confidence (Q15, 44.4%) were found to be significant after the sildenafil treatment ($P<0.05$). The increases in penetration ability (Q3, 15.1%) and maintenance frequency (Q4, 16.1%) were insignificant. When the other domains in the IIEF form were considered, intercourse enjoyment (Q8, 23.5%), desire level (Q12, 26.6%) and relationship satisfaction (Q14, 30%) were significantly increased after the sildenafil treatment ($P<0.05$), but not others (Figure 3).

Hematological changes

There was no difference between Epo and T groups concerning baseline hematological parameters. In both Epo and T groups, Hb and Hct levels increased significantly. The changes in the combination and sildenafil periods were statistically insignificant. The weekly Epo dosages did not differ (Table 2). The changes in IIEF scores of the Epo group negatively correlate with baseline Hb ($r=-0.740$) and Hct ($r=-0.7427$) levels ($P<0.01$) but not with age, duration of dialysis, Epo dosage, changes in Hb, Hct, TS and ferritin. We did not determine any parameter correlated with the changes of IIEF scores in other treatment periods.

Hormonal changes

Nine patients in the Epo group and seven patients in the T group had primary hypogonadism while the others had secondary hypogonadism. There was no difference in baseline hormone levels between Epo and T groups. TT and FT levels in the T group increased after the treatment, although only FT level in Epo group significantly increased ($P<0.01$). In the combination period, only FT levels significantly decreased ($P<0.01$, Table 2). The changes in other serum hormone concentrations including prolactin were insignificant. Sildenafil treatment also did not affect serum hormone concentrations. In all periods baseline hormone values and percentage changes in hormone levels with the treatments did not correlated with baseline IIEF scores and percentage changes in IIEF scores.

Partner satisfaction

Seven partners participated in the partner satisfaction assessment. The response rate was 43.7%. The intercourse satisfaction improved in four (57.6%) while there was no change in three (42.4%).

Partners' desire level increased in five (71%). Four (57.6%) reported overall satisfactory sex life. The sex lives of three partners (42.4%) were moderately satisfied and one was very satisfied.

Adverse effects

All patients completed the study, except for two patients. The BMIs in the T group increased due to mild fluid retention in most patients ($P<0.05$, Table 2). Headache was reported in three subjects (18%) and rhinitis in one subject (6%) with sildenafil treatment. These side effects were short lived and did not require any treatment. No subjects reported priapism. Blood pressures were stable during all periods (Table 2). None of the patients had a hypotensive episode in their dialysis sessions during the sildenafil treatment.

Discussion

ED is one of the factors negatively influencing the quality of life of patients on HD. ED may improve in patients with renal failure after the initiation of HD therapy. Procci and Martin[17] reported that 23 patients started on chronic HD therapy and followed up prospectively for 2.5 years experienced an increase in frequency of intercourse despite stability of nocturnal penile tumescence measures. This may be caused by adequacy of dialysis or Epo administration.[11,18] Our study showed that Epo and/or T therapies could partially improve sexual dysfunction in the male dialysis population even though renal anemia and hypogonadism were corrected. The combination treatment also did not provide an additional benefit for ED. These approaches only restored ED (IIEF score >25) in five patients (23.8%), whereas sildenafil treatment improved ED in half of the unresponsive patients.

Some studies have shown improvement in sexual function in dialysis patients with the use of Epo and after renal transplantation.[19,20] Improved sexual function with Epo therapy has not been confirmed by all.[11,21] Further studies have demonstrated improved nocturnal penile tumescence[22] and increased frequency of sexual intercourse,[18] while others have suggested that Epo has direct endocrinological benefits, in addition to correction of anemia. Changes in endocrine functions due to disturbances in hypothalamic–pituitary–testicular function such as lower FT, higher LH and FSH, and elevated prolactin levels are well known in patients with uremia.[23] However, the role of these disturbances on development of ED is incompletely understood. An early study attributed improved sexual function after Epo treatment to normalization of elevated prolactin levels,[20] but other studies have not confirmed this[19,24] and in normal subjects, the acute administration of Epo does not interfere with prolactin secretion.[25] In contrast, Haley *et al*.[26] showed increment in low T levels in HD patients treated with Epo, and its acute administration in normal young males was shown to cause testicular steroidogenesis,[27] a finding that was not confirmed in male dialysis patients.[19,20,24] Although we did not observe any change in prolactin levels, the Epo treatment increased FT levels similar to T treatment. The influence of Epo on hormones affecting sexual function in this population thus remains disputed. In the hypogonadal man whose only complaint is decreased libido, T may be of benefit.[1,28] But, treatment with T has usually failed to improve libido or ED in dialysis patients.[29] A recent report showed poor effectiveness of T replacement therapy in dialysis patients with proven hypogonadism compared with vacuum tumescence therapy (18.5 vs 73.1%).[9]

Goldstein *et al*.[12] showed that 69% of 532 men with ED experienced successful coitus with sildenafil, whereas this rate was 22% in the placebo group. There have been few studies focusing on the use of sildenafil in a small number of HD patients, most of which are open-labeled uncontrolled trials. Similar to our results, these studies showed that the administration of sildenafil 25–100 mg improved ED at a rate of 60–80% within a duration of 3 weeks to 6 months.[7,13–15,30,31] In a double-blind, randomized, placebo-controlled study of oral sildenafil (50 mg) in selected patients with ESRD on HD for 1 month, an improvement was observed in 85% of 21 sildenafil patients compared with 9.5% of 20 placebo patients when the erectile function domain was used to evaluate primary efficacy.[32] Sildenafil use resulted in normal erectile function scores in 35% of sildenafil patients. After the sildenafil treatment we observed an improvement in intercourse satisfaction, sexual desire and overall sexual satisfaction together with ED, but not orgasmic function. Although only one of three diabetic patients improved sexual dysfunction, we could not draw a definite conclusion for the diabetic population. In a recent prospective pilot study, 12 patients (eight post-transplant and four on HD) with ED due to hypogonadism and cavernosal insufficiency showed a good response to intramuscular monthly injections of 250 mg T cypionate and oral 50–100 mg sildenafil once or twice weekly for 12 months. As a result of this study, authors suggested that this approach might be beneficial for those with both cavernosal arterial insufficiency and reproductive hormone abnormalities.[33] Our finding of 50% of the men experiencing some improvement in sexual function can be accessible, because they were a subgroup of the whole male dialysis population who were complaining of impotence and had proven to have primary or secondary hypogonadism and uremic impotence with multifactorial nature like intercurrent vascular disease, neuropathy and endocrine

disturbances. It has been reported that patients not responding to sildenafil treatment had a significantly lower penile blood flow than the responding patients.[7] Furthermore, patients with an IIEF score of $\geqslant 17$ responded better to sildenafil treatment.[13] In our cohort this cutoff value was found to be 22.

In our study, low FT and high prolactin levels did not relate to the effectiveness of sildenafil treatment. Sildenafil treatment did not affect the hormone levels. In a recent study, the success rate was 73% among patients with high prolactin levels and 75% in patients with low FT levels.[31] The clinical implications of elevated prolactin levels are not well understood and therapy has had inconsistent effects on libido and potency. In general, all studies suggest good tolerability of HD patients to sildenafil.[13–15] To limit the possibility of hypotension among HD patients, some clinicians recommend the use of sildenafil on nondialysis days,[34] although one small study found that sildenafil did not promote intradialytic hypotension.[35]

Conclusion

Epo and/or T treatments are effective in ED of male dialysis patients to some degree. As indicated in our study, the higher the IIEF score the higher the response rate after Epo treatment. T treatment might not be preferred in this population due to fluid retention. Oral sildenafil is an effective, reliable, well-tolerated treatment for uremic patients with ED, and might be the drug of first choice if there is no contraindication. It is effective in restoring erectile function and the ability to perform intercourse to a degree that is satisfactory for both the patient and his partner.

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