

*Original Article*

## **Erectile dysfunction and the effects of sildenafil treatment in patients on haemodialysis and continuous ambulatory peritoneal dialysis**

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### **Abstract**

**Background.** Sexual dysfunction, including erectile dysfunction, is common in patients with uraemia. Despite successful treatment of male sexual dysfunction with sildenafil in non-uraemic population, its efficacy in dialysis patients is unknown.

**Patients and methods.** In this study, 35 male HD patients (mean age  $48 \pm 12$  years) and 15 male CAPD patients (mean age  $44 \pm 12$  years) were included. In the baseline period, haemoglobin, serum urea, and albumin, Kt/V, several hormonal parameters, Beck depression scale, and penile Doppler blood flow, (peak systolic velocity after intracavernous papaverine administration) were measured. The international index of erectile function (IIEF) form was used to evaluate erectile dysfunction. Sildenafil was given to patients with erectile dysfunction at a dose of 50–100 mg/day twice a week.

**Results.** The percentage of erectile dysfunction was similar between patients on HD (71%) and those on CAPD (80%). Patients with erectile dysfunction were significantly older and had lower free-testosterone serum levels and penile blood flow than those without. In linear regression analysis for baseline IIEF score, penile blood flow was the only independent variable associated with erectile dysfunction. IIEF score increased to a similar extent after sildenafil treatment in both HD patients (from  $8.10 \pm 5.54$  to  $21.70 \pm 9.61$ ,  $P < 0.001$ ) and CAPD patients (from  $9.90 \pm 3.87$  to  $21.60 \pm 10.18$ ,  $P = 0.011$ ). Changes in IIEF scores after sildenafil treatment were associated with baseline penile blood flow as an independent variable by linear regression analysis. Adverse events observed during sildenafil treatment were dyspepsia in two patients and headache in one patient.

**Conclusion.** The rate of erectile dysfunction is high in dialysis patients. Penile blood flow is the most important factor for predicting both the development of erectile dysfunction and the response to sildenafil therapy in such patients. Oral sildenafil is an effective, reliable, well-tolerated treatment for uraemic patients with erectile dysfunction.

**Keywords:** CAPD; erectile dysfunction; haemodialysis; penile blood flow; sildenafil

### **Introduction**

Erectile dysfunction (ED) is the persistent inability to achieve and/or maintain an erection for satisfactory sexual activity. More than 50% of uraemic men complain of symptoms that include ED, decreased libido, and marked declines in the frequency of intercourse [1,2]. Sildenafil has been successfully used for treatment of male sexual dysfunction in the non-uraemic population [3,4]. Except a few preliminary reports [5,6], no data have been published in the literature on the efficacy and safety of this agent in dialysis patients with ED.

The aim of this study was to evaluate the factors involved in ED and the efficacy and the safety of sildenafil in the treatment of ED in haemodialysis (HD) and continuous ambulatory peritoneal dialysis (CAPD) patients.

### **Patients and methods**

In this study, 35 male HD patients, mean age  $48 \pm 12$  years and 15 male CAPD patients, mean age  $44 \pm 12$  years, each having regular partners, were included. No difference was found between study groups regarding age, primary renal disease and time on dialysis. None of the patients

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had hypertension or used any antihypertensive drug. Demographic features of the patients are shown in Table 1. Patients were evaluated by history, physical examination, and electrocardiogram and echocardiography for cardiac evaluation. Patients with congestive heart failure, acute ischaemic heart disease or recent ( $\leq 6$  months) history of cardiovascular disease, stroke or myocardial infarction, concomitant treatment with nitrates or presence of hypotension were excluded. Sildenafil treatment was not given to five HD and two CAPD patients for cardiovascular reasons. Patients with penile anatomical defects or major haematological and/or liver abnormalities were not included. All patients were  $> 18$  years of age. Written informed consent was taken from all patients. The Helsinki Declaration guiding physicians in biomedical research was followed.

In the baseline period, haemoglobin, serum urea, creatinine, albumin, Kt/V, hormonal parameters including total testosterone, FSH, LH, iPTH, prolactin (immunometric assay, Immulite 2000 catalogue nos L2KTT2, L2KFS2, L2KLH2, LKPH1, L2KPR2; Diagnostic Product Corporation, Los Angeles, CA) and free-testosterone levels (Radioimmunoassay, catalogue no. TKTF1; Diagnostic Product Corporation) were measured. All patients underwent colour Doppler ultrasonography (Hitachi EUB-555 Sony colour video printer) for measurement of penile blood flow after pharmacological stimulation by intracavernous papaverine (30–60 mg). At least 20 min after papaverine injection, peak systolic velocities were measured. The Beck depression scale was used for determination of the psychological status of patients [7]. The International index of erectile function (IIEF) form was used to evaluate ED [8]. In this form the patients were asked questions 1, 2, 3, 4, 5 and 15 (all shown below). Total score was 30. IIEF score

below 26 was accepted as ED. IIEF score measurements were repeated after sildenafil treatment.

- Q1: Erection frequency
- Q2: Erection firmness
- Q3: Penetration ability
- Q4: Maintenance frequency
- Q5: Maintenance ability
- Q15: Erection confidence

Initially, sildenafil (Viagra<sup>®</sup>) was recommended to and accepted by 30 (20 HD and 11 CAPD) patients. Sildenafil (50 mg/day) was administered to the patients with ED twice a week. At the end of 4 weeks, the dosage of sildenafil was increased to 100 mg if there was no response to 50 mg ( $n = 12$  patients). Side-effects were recorded.

### Statistics

The data was evaluated by SPSS 10.0 for Windows. Data are given as mean  $\pm$  SD.

Data are shown as median and 25–75th percentiles. Numerical values under or above the median levels represents the values below the 10th percentile and above the 90th percentile. Numerical variables with normal distribution were compared with paired and non-paired Student's *t*-tests and when variables had non-normal distribution, Mann–Whitney U or Wilcoxon test were used. Correlations between two numerical variables were sought with Pearson bivariate correlation test and Spearman rho test when appropriate. For non-numerical variables, Chi-square test was used. For 2\*2 contingency tables, Yates' correction was made. When assumptions were violated in 2\*2 tables, Fisher's exact test was used. Factors that affect baseline IIEF score and increase in IIEF score after sildenafil treatment were examined with multiple linear regression analysis. Independent variables were age, penile blood flow, free-testosterone, and Beck depression scale. *P* value  $< 0.05$  was accepted as significant.

**Table 1.** Baseline parameters in HD and CAPD patients

|                            | Haemodialysis<br><i>n</i> = 35 | CAPD<br><i>n</i> = 15 | <i>P</i> |
|----------------------------|--------------------------------|-----------------------|----------|
| Demographic features       |                                |                       |          |
| Age (years)                | 48 $\pm$ 12                    | 44 $\pm$ 12           | NS       |
| Time on dialysis (months)  | 39 $\pm$ 34                    | 42 $\pm$ 29           | NS       |
| ED* duration (months)      | 25 $\pm$ 27                    | 16 $\pm$ 16           | NS       |
| Primary renal disease      |                                |                       |          |
| Glomerular disease         | 20                             | 8                     | NS       |
| ADPKD                      | 5                              | 1                     |          |
| DM                         | 4                              | 3                     |          |
| Unknown                    | 6                              | 3                     |          |
| Biochemical results        |                                |                       |          |
| Haemoglobin (g/dl)         | 11.7 $\pm$ 1.5                 | 11.9 $\pm$ 2.0        | NS       |
| Albumin (g/dl)             | 4.1 $\pm$ 0.3                  | 4.2 $\pm$ 0.3         | NS       |
| Urea (mg/dl)               | 131 $\pm$ 36                   | 142 $\pm$ 45          | NS       |
| Kt/V/week                  | 4.05 $\pm$ 0.76                | 1.96 $\pm$ 0.37       |          |
| Beck scale                 | 12.5 $\pm$ 5.8                 | 8.3 $\pm$ 4.6         | = 0.03   |
| Endocrine work-up          |                                |                       |          |
| iPTH (pg/ml)               | 187 $\pm$ 164                  | 96 $\pm$ 70           | = 0.04   |
| Prolactin (ng/ml)          | 16.1 $\pm$ 16.8                | 18.9 $\pm$ 12.7       | NS       |
| Total testosterone (ng/dl) | 344 $\pm$ 173                  | 296 $\pm$ 165         | NS       |
| Free testosterone (pg/ml)  | 16 $\pm$ 9                     | 18 $\pm$ 7            | NS       |
| FSH (mIU/ml)               | 11.6 $\pm$ 12.3                | 6.8 $\pm$ 5.9         | NS       |
| LH (mIU/ml)                | 7.2 $\pm$ 8.4                  | 6.9 $\pm$ 3.7         | NS       |
| IIEF score                 | 13.4 $\pm$ 10.9                | 14.1 $\pm$ 7.9        | NS       |
| ED* number <i>n</i> (%)    | 25 (71%)                       | 12 (80%)              | NS       |

ED, erectile dysfunction.

### Results

On comparing patients on HD and CAPD in the baseline period, no differences in age, time on dialysis, distribution of primary renal diseases, serum urea, creatinine, albumin levels, haemoglobin values, duration of erectile dysfunction, and IIEF score were found. Patients on HD had higher score in the Beck depression scale than patients on CAPD (12.5 vs 8.3,  $P = 0.03$ ). Regarding hormonal parameters, no difference in any parameter except serum iPTH levels was found between study groups (Table 1).

The percentage of ED was quite high (37 of the 50 patients, 74%) and similar between patients on HD (25 of the 35 patients, 71%) and CAPD (12 of the 15 patients, 80%) according to criteria derived from IIEF score mentioned above. On comparing patients with and without ED, time on dialysis, serum urea, albumin, haemoglobin, prolactin, FSH, LH, iPTH levels, and results of the Beck scale were not different. Patients with ED were significantly older and free-testosterone levels were significantly decreased in patients with ED as compared to patients without

ED. Penile blood flow was significantly decreased in ED patients as compared to without ED (Table 2).

Baseline IIEF score had positive correlation with free testosterone ( $P=0.028$ ,  $r=0.311$ ) and penile blood flow ( $P=0.001$ ,  $r=0.706$ ) and negative correlation with age ( $P=0.001$ ,  $r=-0.461$ ). There also was a negative correlation between age and penile blood flow ( $P=0.001$ ,  $r=-0.469$ ). In linear regression analysis for baseline IIEF score as dependent variable, penile blood flow was the only independent variable in development of ED in this group of patients.

After detection of ED in dialysis patients, sildenafil treatment was given to 20 HD and 10 CAPD patients. Response was defined as IIEF score above 26 after sildenafil treatment. Twelve of the 20 HD patients and six of the 10 CAPD patients had responded to the therapy. None of the patients who did not respond to 50 mg sildenafil responded to 100 mg/day sildenafil treatment. Response rate (60%) was found to be same between study groups. Patients not responding to sildenafil treatment ( $n=12$ ) had significantly lower penile blood flow than the responding patients ( $23 \pm 14$  cm/s vs  $37 \pm 9$  cm/s,  $P=0.003$ ). However, no differences in age, time on dialysis, haemoglobin, and serum free-testosterone levels were found between responding and non-responding patients.

IIEF score increased after sildenafil treatment in both HD (from  $8.10 \pm 5.54$  to  $21.70 \pm 9.61$ ,  $P<0.001$ ) and CAPD (from  $9.90 \pm 3.87$  to  $21.60 \pm 10.18$ ,  $P=0.011$ ). Increase in IIEF scores was similar between HD and CAPD ( $13.6 \pm 8.4$  vs  $11.7 \pm 8.5$  respectively,  $P=NS$ ) (Figure 1). Change in IIEF score was correlated with penile blood flow ( $r=0.66$ ,  $P<0.001$ ). In multiple linear regression analysis for changes in IIEF scores after sildenafil treatment, penile Doppler was found as an independent variable (Figure 2).

Five of seven diabetic patients had ED. Four diabetic patients received sildenafil treatment and three of them (75%) responded to therapy. Increase in IIEF score after sildenafil treatment was similar between patients with and without diabetes mellitus ( $18 \pm 6$  vs  $12 \pm 8$ ,  $P=NS$ ).

**Table 2.** Baseline parameters of dialysis patients with and without erectile dysfunction (ED)

|                            | ED (+)<br><i>n</i> = 37 | ED (-)<br><i>n</i> = 13 | <i>P</i> |
|----------------------------|-------------------------|-------------------------|----------|
| Age (year)                 | 50 ± 10                 | 39 ± 13                 | = 0.002  |
| Time on dialysis (month)   | 35 ± 29                 | 52 ± 38                 | NS       |
| Urea (mg/dl)               | 132 ± 41                | 138 ± 32                | NS       |
| Hb (g/dl)                  | 11.8 ± 1.6              | 11.4 ± 1.2              | NS       |
| Albumin (g/dl)             | 4.14 ± 0.31             | 4.03 ± 0.24             | NS       |
| iPTH (pg/ml)               | 163 ± 152               | 150 ± 138               | NS       |
| FSH (mIU/ml)               | 11.0 ± 12.1             | 7.5 ± 6.3               | NS       |
| LH (mIU/ml)                | 7.13 ± 7.22             | 7.15 ± 7.74             | NS       |
| Prolactin (ng/ml)          | 17.9 ± 17.5             | 14.2 ± 8.2              | NS       |
| Total testosterone (ng/dl) | 316 ± 170               | 369 ± 171               | NS       |
| Free testosterone (pg/ml)  | 15.1 ± 7.7              | 20.1 ± 10.4             | = 0.04   |
| Beck scale                 | 11.1 ± 5.5              | 11.0 ± 6.6              | NS       |
| Penile blood flow (cm/s)   | 28 ± 14                 | 54 ± 2                  | < 0.001  |
| IIEF score (0–30)          | 8.4 ± 5.3               | 28.5 ± 1.5              | < 0.001  |

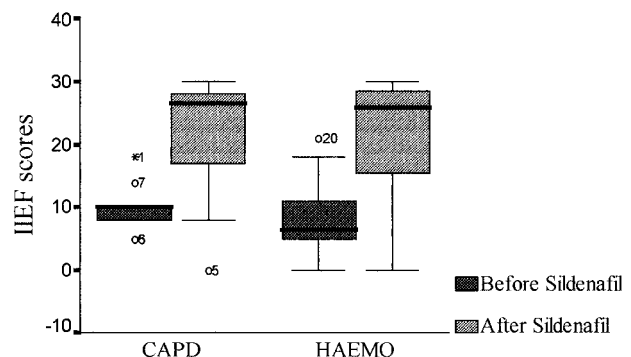
Regarding safety of the therapy, the adverse events observed during sildenafil treatment were dyspepsia in two patients and headache in one patient. These side-effects were short-lasting and did not require any treatment. None of the patients had hypotensive episode in their HD sessions during the study period.

## Discussion

Sexual dysfunction is a common problem in patients with chronic renal failure. Steele *et al.* [9] in a survey on sexual function reported that more than 80% of CAPD patients had intercourse less than or equal to twice per month, most of them never having intercourse. In our study, the percentage of ED was quite high (37 of 50 patients, 74%), similar between patients on HD and CAPD, and consistent with previous reports [9,10].

Numerous factors such as hormonal disturbances, peripheral neuropathy, autonomic dysfunction, peripheral vascular disease, psychological stress, medication, and uraemic milieu have been implicated in the development of this disorder [1,11]. Anxiety and depression are commonly present in dialysis patients. It was reported that patients with ED were more depressed and anxious, and sub-clinical depression may be underestimated as a contributory factor [9,12]. However, Procci *et al.* [1] reported no association of depression with sexual dysfunction. In addition, no difference in Beck depression scale was found between patients with and those without ED in our study.

Changes in endocrine functions due to disturbances in hypothalamic–pituitary–testicular function such as lower free-testosterone, higher LH and FSH, and elevated prolactin are well known in patients with uraemia [13]. However, the role of these disturbances on development of ED is incompletely understood. No improvement of libido or potency with administration of testosterone has been reported [14]. Lawrence *et al.* [15] reported that depot testosterone treatment fully restored sexual function in only three of the 27 male



**Fig. 1.** Changes in IIEF scores after sildenafil treatment in CAPD and haemodialysis patients. Data are shown as median and 25–75th percentiles. Numerical values below or above the median levels represent the values below the 10th percentile and above the 90th percentile.

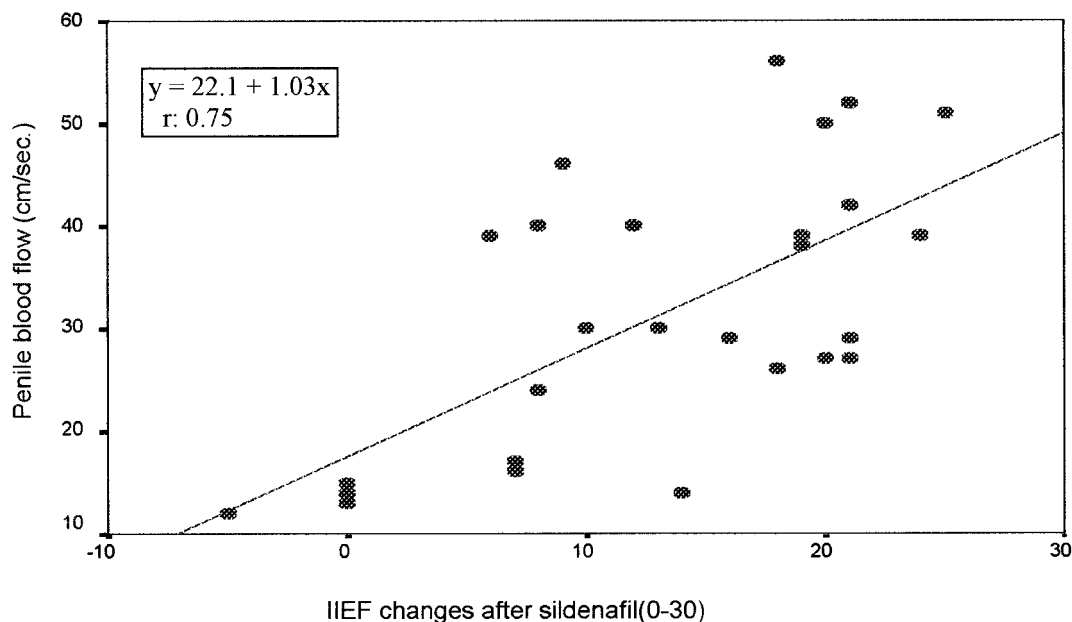


Fig. 2. Relationship between baseline penile blood flow and variation in IIEF after sildenafil treatment.

dialysis patients in their study. In our study, the only difference in hormonal parameters between patients with and without ED found was a decrease in serum free-testosterone levels in patients with ED. However, it was not an independent variable in linear regression analysis for IIEF score, and this finding was consistent with previous reports [14,15].

Ischaemic heart diseases and peripheral vascular lesions due to accelerated atherosclerosis have been reported to be much more common in patients with uraemia. A peripheral vascular lesion obstructing penile arterial blood flow was also proposed as a contributing factor to ED in this group of patients [16]. In our study, the most important factor on development of ED was penile blood flow in dialysis patients. However, resolution of ED after renal transplantation in some HD patients has been reported [17]. In these patients, peripheral arterial obstruction may not be a major factor in the development of ED. Small-vessel circulatory dysfunction due to uraemic autonomic dysfunction which improves after transplantation may be main culprit in decreased penile blood flow [18].

Sildenafil treatment as a first-line therapy has been successfully used for treating ED in non-uraemic population. However, no study specifically addressed the issue of efficacy and safety of this drug on ED in patients with chronic renal failure, except for a few preliminary reports [5,6]. In our study, sildenafil therapy was found to be effective in ED of patients on dialysis. Response rate was found to be 60% in both HD and CAPD group. In addition, increase in IIEF scores were similar between HD and CAPD. It has been reported that sildenafil treatment was also effective and safe in diabetic men with ED [19]. In our study, no differences in response rate and similar increase in IIEF scores were found between diabetic and non-diabetic patients. However, the small sample

size of diabetic patients treated precludes a definite conclusion. There is need for further study to address the efficacy of sildenafil treatment in diabetic patients with chronic uraemia.

In terms of safety, reported incidence of adverse events in non-uraemic population was low and symptoms were usually mild. The studies in men with ischaemic heart disease and hypertension sildenafil did not cause an increase in either MI or other serious cardiovascular events compared to placebo [20]. Safety for patients with uraemia is unclear. Some preliminary studies report that the drug could be utilized safely in dialysis patients if proper precautions, like not combining it with nitrates and not using it after recent coronary artery events, are taken. In our study, few mild side-effects were observed during sildenafil treatment, which suggests that sildenafil treatment is safe in uraemic men with ED.

In conclusion, ED percentage is very high in HD and CAPD patients. Penile blood flow status is the most important factor for predicting both the development of ED and response to sildenafil therapy in dialysis patients. Oral sildenafil is an effective, reliable, well-tolerated treatment for uraemic patients with ED, and should be the drug of first choice if there is no contraindication.

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