ORIGINAL ARTICLE

Low-Dose Tadalafil and Cabergoline versus Cabergoline alone in Management of Erectile Dysfunction in Patients with End-Stage Renal Disease and Hyperprolactinemia Undergoing Hemodialysis

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Abstract

Background: ***Hyperprolactinemia in chronic kidney disease (CKD) is associated with high rates of hypogonadism and erectile dysfunction (ED). This study compares the efficacy, safety, and side effects of cabergoline monotherapy versus low-dose tadalafil combined with cabergoline in treating ED in end-stage renal disease (ESRD) patients undergoing hemodialysis with hyperprolactinemia.***

Patients and Methods: ***A total of 120 male ESRD patients on hemodialysis with ED and hyperprolactinemia were enrolled from November 2023 to December 2024 at Al-Azhar Hemodialysis Units, Cairo, Egypt. Patients were randomly assigned to two groups: Group 1 received 0.5 mg of cabergoline weekly, while Group 2 received 5 mg of tadalafil daily along with 0.5 mg of cabergoline. Efficacy was assessed using the International Index of Erectile Function-5 (IIEF-5) and hormonal assays for prolactin and testosterone after 6 weeks of treatment.***

Results: ***The combined Cabergoline/Tadalafil group showed a significant improvement in IIEF-5 scores (from 14.79 to 22.8, P<0.001), whereas the Cabergoline-only group showed no significant change. Prolactin levels decreased significantly in both groups (P<0.05), with no significant change in testosterone levels. Side effects were more common in the combined Cabergoline/Tadalafil group: 35% had back pain, 8.3% dizziness, and 48.3% headaches, compared to 11.6%, 1.7%, and 11.7%, respectively, in the Cabergoline-only group (P<0.05).***

Conclusion: ***Low-dose tadalafil combined with cabergoline is a promising treatment for ED and hyperprolactinemia in ESRD patients. Although side effects were more common, most were mild and self-limited.***

Keywords: Cabergoline; Erectile dysfunction; Hemodialysis; Hyperprolactinemia; Tadalafil

1. Introduction

Chronic kidney disease (CKD) is commonly associated with gonadal dysfunction, leading to symptoms such as decreased libido, erectile dysfunction (ED), and impaired ejaculation.[1] Several factors contribute to the pathophysiology of ED in CKD, including vascular abnormalities, neurogenic issues, hormonal imbalances, and medications used to manage CKD-related conditions.[1]

In patients with advanced CKD and end-stage renal disease (ESRD), elevated serum prolactin levels are often observed, primarily due to increased production and, to a lesser extent, reduced clearance.[2] Elevated prolactin is believed to contribute to the high prevalence of hypogonadism and sexual dysfunction in these patients, as prolactin inhibits gonadotropin release.[2]

Cabergoline, a dopamine agonist, is the drug of choice for hyperprolactinemic men with ED due to its positive impact on male sexual function.[3] Tadalafil, a phosphodiesterase type 5 inhibitor, is a well-established first-line treatment for ED, known for its safety and effectiveness.[4]

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Given the high prevalence of ED among CKD patients, addressing this issue is crucial to improving their quality of life.[5] However, limited research has explored the combined use of tadalafil and cabergoline, or cabergoline alone, in improving sexual performance or the relationship between serum prolactin and ED in dialysis patients.

This study aims to compare the efficacy, safety, and adverse effects of two treatment regimens—cabergoline alone versus low-dose tadalafil combined with cabergoline—in managing ED in hemodialysis patients with ESRD and hyperprolactinemia.

2. Patients and methods

This prospective, randomized, comparative trial was conducted from November 2023 to December 2024 at the hemodialysis units of Al-Azhar University hospitals, Cairo. A total of 120 adult, sexually active male patients with ESRD undergoing hemodialysis and experiencing ED were enrolled. Inclusion criteria required patients to have an IIEF-5 score of < 22 and a serum prolactin level > 20 ng/mL. Exclusion criteria included patients with known contraindications for the study medications, those currently receiving ED treatment, or those with prior ED treatments that did not yield adequate results. Before participation, all patients provided written informed consent after receiving a detailed explanation of the study protocol. Ethical approval was obtained from the Al-Azhar Faculty of Medicine's ethics committee.

Prior to treatment, all patients underwent a comprehensive clinical evaluation, including the IIEF-5 score questionnaire. Laboratory tests included total testosterone and serum prolactin (with normal prolactin levels defined as ≤ 20 ng/mL). The data collected included age, smoking status, number of dialysis sessions per week, dialysis duration, etiology of ESRD, body mass index (BMI), blood pressure, and baseline IIEF-5 scores. Laboratory tests included complete blood count (CBC), hemoglobin A1c, serum creatinine, and prolactin and total testosterone levels.

Patients were randomly assigned to two treatment groups using blocked randomization with a 1:1 allocation ratio via a random number generator program. Group 1 (Cabergoline-only group) received 0.5 mg of cabergoline once weekly, while group 2 (combined Cabergoline/Tadalafil group) received 5 mg of tadalafil daily before bed, along with 0.5 mg of cabergoline once weekly. Patients were encouraged to engage in sexual intercourse at least once per week.

After 6 weeks, patients were re-evaluated with follow-up assessments, including clinical evaluation, measurement of IIEF-5 scores, and hormonal assays for prolactin and testosterone to assess efficacy and adverse effects. The primary outcome was the change in IIEF-5 score, while secondary outcomes included hormonal changes (prolactin and testosterone) and the occurrence of adverse effects.

Statistical Analysis:

Data were analyzed using SPSS version 26 (SPSS Inc., Chicago, IL). Categorical variables were expressed as numbers and percentages and compared using the chi-square test (X^2) or Fisher's exact test. Numerical variables were expressed as mean ± standard deviation (SD) and compared using Student's t-test, Mann-Whitney U test, or Kruskal-Wallis test, as appropriate. A p-value of < 0.05 was considered statistically significant.

3. Results

A total of 336 patients were assessed for eligibility, and 140 were initially enrolled. However, treatment was discontinued in 3 patients from the Cabergoline-only group and 6 patients from the Cabergoline/Tadalafil group due to drug-related side effects. Additionally, 3 patients from the Cabergoline-only group and 4 patients from the Cabergoline/Tadalafil group were lost to follow-up. Furthermore, 4 patients in the Cabergoline-only group were excluded due to non-compliance with sexual engagement instructions. As a result, the final analysis included 120 patients (60 per group). A flow diagram illustrating patient disposition is provided in Figure 1.

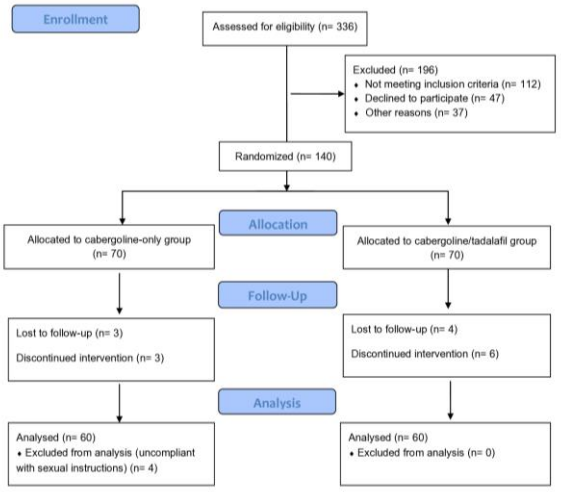

Figure 1. The flow diagram illustrating patient disposition.

The mean age of patients was 57.4 ± 1.73 years (range: 54–62 years), and the mean BMI was 29.55 ± 1.03 kg/m² (range: 20–31.5 kg/m²). A total of 79 patients (65.8%) were smokers. The mean dialysis duration was 2.9 ± 1.07 years (range: 6 months–6 years), with a mean frequency

of 3.02 ± 0.79 sessions per week. Baseline demographic and clinical characteristics were comparable between groups (Table 1).

Table 1. Demographic data and clinical characteristics of the studied patients, overall and in each group

	OVERALL (N=120)	CABERGOLINE-ONLY (N=60)	CABERGOLINE/ TADALAFIL (N=60)	P VALUE
AGE YRS, MEAN±SD	57.36±1.7	57.38±1.7	57.33±1.7	0.932
BMI, KG/M^2, MEAN±SD	29.55±1.0306	28.9±0.90	30.03±0.85	0.323
SMOKING STATUS, N (%)	79 (65.8)	40 (66.7)	39 (65.0)	0.874
DIABETES MELLITUS, N (%)	26 (43.3)	23 (38.3)	49 (40.8)	0.577
HYPERTENSION, N (%)	20 (33.3)	17 (28.3)	37 (30.8)	0.553
DURATION OF HEMODIALYSIS, YRS, MEAN±SD	2.917±1.0766	3.039±1.0477	2.790±1.0997	0.196

The mean baseline IIEF-5 score for the entire study cohort was 13.5 ± 2.20 (range: 10–20), with no significant difference between the two groups. ED severity was classified as mild in 12 patients (10.0%), mild to moderate in 90 patients (75.0%), and moderate in 18 patients (15.0%). Post-treatment, Cabergoline/Tadalafil group demonstrated a significant improvement ($p < 0.001$), whereas Cabergoline-only group showed a non-significant increase. The mean post-treatment IIEF-5 score was significantly higher in Cabergoline/Tadalafil group compared to Cabergoline-only group ($p < 0.001$).

Baseline prolactin levels were 20.25 ± 3.20 µg/L (range: 20.0–36.0 µg/L) and were comparable between groups. Post-treatment, prolactin levels significantly decreased in both groups ($p < 0.001$), with no significant difference between them. The mean baseline total testosterone level was 9.00 ± 4.48 nmol/L (range: 8.5–17.0 nmol/L). Although both groups exhibited an increasing trend, the change did not reach statistical significance (Table 2).

Table 2. Changes in hormonal profiles within each group and between-group comparisons.

	CABERGOLINE-ONLY (N=60)	CABERGOLINE/ TADALAFIL (N=60)	P VALUE**
IIEF-5 SCORE			
PRE-TREATMENT, MEAN±SD	12.30±1.10	14.79±2.42	0.545
MIN. TO MAX.	10-14	11-20	
POST-TREATMENT MEAN±SD	13.30±0.70	22.80±2.40	< 0.001
MIN. TO MAX.	11-15	19-24	
P VALUE*	0.497	< 0.001	
PROLACTIN (µG/L)			
PRE-TREATMENT MEAN±SD	22.28±0.49	23.31±1.40	0.128
MIN. TO MAX.	20-26	21-36	
POST-TREATMENT MEAN±SD	19.15±1.14	20.35±2.61	0.280
MIN. TO MAX.	16.8-20.5	16.4-24.2	
P VALUE*	< 0.001	< 0.001	
TOTAL TESTOSTERONE (NMOL/L)			
PRE-TREATMENT MEAN±SD	9.10±1.10	10.82±2.57	0.348
MIN. TO MAX.	8.8-17	8.5-16.5	
POST-TREATMENT MEAN±SD	11.10±0.15	13.82±0.55	< 0.001
MIN. TO MAX.	11.5-13.2	13.2-18.2	
P VALUE*	< 0.001	< 0.001	

P value*, intergroup comparisons; P value**, between groups comparisons

Side effects were generally mild and self-limited in both groups. However, the incidence of side effects was significantly higher in Cabergoline/Tadalafil group. No serious adverse events were reported (Table 3).

Table 3. Adverse effects in each group.

	CABERGOLINE-ONLY (N=60)	CABERGOLINE/ TADALAFIL (N=60)	P VALUE
BACK PAIN	7 (11.6%)	21 (35.0%)	< 0.001
DIZZINESS	1 (1.7%)	5 (8.3%)	< 0.001
GASTROINTESTINAL UPSET	16 (26%)	19 (31.7%)	0.348
HEADACHE	7 (11.7%)	29 (48.3%)	< 0.001
STUFFY NOSE	8 (13.3%)	11 (18.3%)	0.320

4. Discussion

The prevalence of ED in ESRD patients receiving hemodialysis can reach up to 80%, which is significantly higher compared to the general population.6 In these patients, ED can arise from both organic and psychogenic factors, with hormonal imbalances, vascular changes, and the adverse effects of dialysis being key contributors.[2] The present study provides valuable insights into the management of ED in ESRD patients undergoing hemodialysis with hyperprolactinemia. Our findings demonstrate that the combination of low-dose tadalafil and cabergoline significantly improves erectile function, as measured by the IIEF-5, when compared to cabergoline monotherapy. This highlights the potential synergistic effects of tadalafil and cabergoline in treating ED in this patient population.

The combination therapy of tadalafil and cabergoline showed a statistically significant improvement in the IIEF-5 scores, with a marked increase from 14.79 to 22.8 ($p<0.001$). This improvement aligns with the findings by Bolat et al.[7] who demonstrated that tadalafil therapy is an effective treatment for ED in ESRD patients undergoing HD, with manageable side effects. The combination of tadalafil and cabergoline offers a more comprehensive approach, addressing both the hormonal and vascular components of ED.

Moreno[8] also emphasized the synergistic effects of phosphodiesterase-5 inhibitors like tadalafil and dopamine agonists such as cabergoline in improving erectile function in patients with complex conditions like ESRD. These findings are further supported by Mohammad et al.[9], who showed that a combination of cabergoline and tadalafil significantly improved erectile function in men with psychogenic ED, further reinforcing the potential benefits of this combination therapy.

In contrast, our study showed no significant improvement in IIEF-5 scores in the cabergoline-only group. This is consistent with Elbardisi et al.[10] who found that cabergoline alone did not lead to significant improvements in erectile function in patients with chronic kidney disease. However, our findings contradict those of De Piccoli et al.[11] who reported that cabergoline treatment significantly restored sexual function in their cohort. These conflicting results may reflect differences in study design, patient characteristics, or the duration of treatment.

The current study, which included 120 male ESRD patients with hyperprolactinemia undergoing HD, observed a mean age of 57.40 years and a mean body mass index (BMI) of 29.55 kg/m². These findings are consistent with studies by Vietri and Stenmark[12] and Tang et al.[13] who reported similar mean ages of around 55–60 years for ESRD patients. This suggests that age is an important factor in the development of ED in this patient population. Franz et al.[14] reported a lower mean age (47.6±10.1 years) in their cohort of hemodialysis patients, with a mean BMI of 24.3±4.2 kg/m². Abdelaal et al.[15] also observed a similar average age (48.77±9.66 years) in their study of 100 hemodialysis patients. These differences in age highlight the variability in the demographic characteristics of ESRD patients with ED, which may influence the treatment outcomes and response to therapy.

Regarding hormonal abnormalities, the average total testosterone level in our study was 9.003 nmol/l, which is low compared to the general population and aligns with findings from Gungor et al.[16] who reported similar hormonal disturbances in ESRD patients. Uremic toxins, oxidative stress, and the inflammatory environment that accompanies chronic kidney disease are known to contribute to reduced testosterone levels. Franz et al.[14] found a mean testosterone level of 7.2±1.7 mmol/L, with only four patients within the normal range, while Abdelaal et al.[15] reported a significantly lower mean testosterone of 2.93±1.4 ng/dL in their cohort of hemodialysis patients. In contrast, Albaaj et al.[17] observed that 26.3% of ESRD patients exhibited abnormally low testosterone levels, further emphasizing the widespread hormonal dysregulation in this population.

Our study showed that although testosterone levels in the combination therapy group demonstrated an improvement, the change was not statistically significant. This result is consistent with Elbardisi et al.[10] who found that cabergoline treatment reduced hypothalamic-pituitary-gonadal (HPG) axis inhibition, facilitating luteinizing hormone (LH) production and consequently stimulating testosterone synthesis. However, despite this theoretical mechanism, the expected increase in testosterone levels did not occur in our study. Age, uremic effects on Leydig cells, and comorbid conditions, particularly DM, are likely contributing factors to the persistent low testosterone levels in these patients. This finding contrasts with research by Nickel et al.[18] who reported statistically significant associations between cabergoline treatment and improved testosterone serum concentrations. These discrepancies could be due to variations in study designs, patient selection, or the presence of additional factors influencing testosterone production in ESRD.

The significant reduction in prolactin levels observed in both groups after treatment is in line with studies by Chen et al.[19] who demonstrated the efficacy of cabergoline in managing hyperprolactinemia. Prolactin is a known inhibitor of gonadotropin release, and its elevated levels in ESRD patients contribute significantly to the development of ED. Our findings support the idea that cabergoline can effectively reduce prolactin levels, as evidenced by the significant decrease in prolactin in both treatment groups. This is further supported by Elbardisi et al.[10], who confirmed that cabergoline treatment reduced prolactin levels and improved sexual function in patients with CKD.

Although the combination therapy showed significant efficacy, it was not without its drawbacks. The incidence of side effects was notably higher in the combination group, with 35% of patients reporting back pain, 48.3% headaches, and 8.3% dizziness. These adverse effects, though mild and self-limited, were significantly more common in the combination group than in the cabergoline-only group. This increase in side effects in the combination group can likely be attributed to the combined pharmacological actions of tadalafil and cabergoline, with tadalafil potentially exacerbating certain adverse effects, such as musculoskeletal discomfort and headaches. Lui et al.[20] observed that phosphodiesterase-5 inhibitors like tadalafil are commonly associated with similar adverse effects. Nonetheless, it is important to emphasize

that these side effects were not severe and generally resolved without requiring discontinuation of treatment. This indicates that while combination therapy offers substantial clinical benefits, patient monitoring for side effects remains critical. Moreover, the relatively benign nature of these side effects may not preclude the use of this combination in clinical practice, particularly given the overall improvement in erectile function and quality of life that patients experienced.

This study provides robust evidence for the effectiveness of combining tadalafil and cabergoline in treating ED in hemodialysis patients with hyperprolactinemia. The combination therapy addresses multiple underlying mechanisms of ED, including hormonal imbalances and vascular dysfunction, and offers a promising strategy for improving both erectile function and quality of life in these patients.

Despite its strengths, our study has several limitations, including its single-center design, short follow-up duration, and the lack of a placebo control group.

In conclusion,.

4. Conclusion

This study demonstrates that low-dose tadalafil combined with cabergoline is an effective and safe treatment for ED in ESRD patients with hyperprolactinemia undergoing hemodialysis. The combination therapy significantly improves erectile function and reduces prolactin levels, although it is associated with a higher incidence of mild, self-limiting side effects. These findings suggest that combination therapy may be a promising approach for managing ED in this population. Larger, multi-center randomized controlled trials with longer follow-up periods are needed to confirm these findings and provide further insights into the long-term safety and efficacy of combination therapy in ESRD patients.

Disclosure

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Authorship

All authors have a substantial contribution to the article

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Conflicts of interest

There are no conflicts of interest.

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