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Long-Term Phosphodiesterase Type 5 (PDE5) Inhibitor Therapy and Serum Uric Acid Levels in Men With Erectile Dysfunction: A Retrospective Analysis

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Abstract

Background: Serum uric acid (UA) is linked to metabolic dysfunction and endothelial impairment, both of which play a role in erectile dysfunction (ED). Phosphodiesterase type 5 inhibitors (PDE5is) are first-line therapy for ED; however, their effect on UA metabolism remains unclear. This study evaluated changes in serum UA levels in men with ED receiving long-term PDE5i therapy and explored clinical factors associated with UA.

Methods: We retrospectively reviewed the medical records of men with ED receiving PDE5i therapy at a tertiary care center. Patients with endocrine disorders, conditions affecting UA metabolism, recent infections, or use of medications influencing sex steroid levels were excluded. Demographic characteristics, body mass index (BMI), comorbidities, and laboratory parameters - including serum UA, lipid profile, fasting glucose, HbA1c, vitamin D, and total testosterone - were collected. Pre- and post-treatment UA measurements were summarized, and associations between baseline UA and clinical variables were assessed using Pearson and Spearman correlation coefficients.

Results: Mean age was 59.4 ± 9.4 years, and mean BMI was 30.1 ± 5.0 kg/m². Mean serum UA decreased from 360.8 ± 79.3 µmol/L before treatment to 352.8 ± 77.7 µmol/L after treatment, corresponding to a mean change of -8.1 µmol/L and a median paired change of -1.0 µmol/L. Baseline UA correlated positively with BMI (Pearson r = 0.253; Spearman ρ = 0.293) and age (Pearson r = 0.335; Spearman ρ = 0.346).

Conclusions: Long-term PDE5i therapy does not significantly affect serum UA levels in men with ED. BMI emerged as the primary determinant of UA, highlighting the close relationship between obesity, hyperuricemia, and metabolic dysfunction. Serum UA appears to reflect systemic metabolic and vascular health rather than a treatment-responsive marker in men receiving PDE5 inhibitors. These findings do not denote a causal relationship but instead underscore the importance of addressing metabolic risk factors as part of comprehensive ED management.

Categories: Urology, Endocrinology/Diabetes/Metabolism
Keywords: cardiovascular diseases, erectile dysfunction, obesity, phosphodiesterase inhibitors, uric acid

Introduction

Erectile dysfunction (ED) is defined as the inability to achieve or maintain an erection sufficient for satisfactory sexual performance. Although not life-threatening, ED negatively affects quality of life and interpersonal relationships and is increasingly recognized as a sentinel marker of cardiovascular disease (CVD) [1,2]. Organic causes predominate in most cases, including vascular, neurogenic, and hormonal factors, often mediated by dysfunction of the nitric oxide-cyclic GMP pathway. Because of this vascular basis, ED is considered an early indicator of systemic vascular disease, and its presence warrants metabolic and cardiovascular evaluation [3].

Serum uric acid (UA), the final product of purine metabolism, has been implicated in endothelial dysfunction, oxidative stress, inflammation, and vascular smooth muscle proliferation [3,4]. Epidemiological studies have linked hyperuricemia with hypertension, metabolic syndrome, diabetes, and CVD [5,6]. Elevated UA has also been associated with ED in patients with cardiovascular comorbidities, suggesting a potential role as a marker of systemic vascular and metabolic health [7,8].

Observational evidence has examined relationships between metabolic parameters and erectile function in patients with hyperuricemia [9]. Additionally, a 2024 Mendelian randomization study provided genetic evidence supporting relationships between serum UA and male sexual hormones, including testosterone; however, its adjusted association with ED was not statistically significant [10].

Phosphodiesterase type 5 inhibitors (PDE5is) remain the first-line therapy for ED, improving penile hemodynamics through nitric oxide-mediated smooth muscle relaxation. While PDE5is may modulate endothelial and inflammatory pathways, their effects on systemic UA metabolism remain unclear [11].

Given this background, the primary objective was to evaluate the within-patient change in serum UA between pretreatment and follow-up measurements after at least 12 months of PDE5i therapy. The secondary objective was to examine observational associations between UA and selected clinical and biochemical variables, including body mass index (BMI), lipid parameters, and total testosterone.

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Materials And Methods

Study design and population

This retrospective chart review evaluated 300 records of men diagnosed with ED and treated with PDE5 inhibitors at our tertiary hospital between January 2014 and August 2019. Records with paired serum UA measurements obtained before treatment and during follow-up were included. Treatment categories comprised tadalafil alone, sildenafil alone, vardenafil alone, and multiple-agent prescriptions.

Inclusion/exclusion criteria

Men older than 18 years with ED who had used PDE5is continuously for at least 12 months and had serum UA measurements available before treatment and at follow-up were eligible.

Patients were excluded if they lacked either UA measurement, had not used PDE5is, had discontinued treatment before completing 12 months, or had a documented UA-related disease, including gout.

Data collection

Demographic characteristics, comorbidities, BMI, duration of PDE5i therapy, and laboratory parameters were collected from medical records. Treatment regimens included tadalafil 5 mg daily or 20 mg every other day, sildenafil 50 or 100 mg every other day, and vardenafil 20 mg every other day. Serum UA was measured before PDE5i initiation and repeated six to nine months after treatment initiation. Additional laboratory parameters included lipid profile (high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, and total cholesterol), glucose, HbA1c, vitamin D, and total testosterone.

Statistical analysis

Continuous variables were summarized as mean ± standard deviation or median with the 25th and 75th percentiles, as appropriate. Categorical variables were presented as frequencies and percentages. Changes in serum UA were calculated as follow-up minus baseline values. Associations between baseline UA and clinical and laboratory variables were described using Pearson and Spearman correlation coefficients. Available-case analyses were performed for each association, with the corresponding sample size reported. Missing values were not imputed. HbA1c results recorded as “>12” were excluded from numeric correlation analyses without assigning an arbitrary value.

Ethical approval

The study was approved by the institutional Medical Research Center (approval number: MRC-01-19-406). The requirement for informed consent was waived because of the retrospective study design.

Results

Patient characteristics

The analysis included 300 records, with a mean age of 59.4 ± 9.4 years and a mean BMI of 30.1 ± 5.0 kg/m². Recorded PDE5i use comprised tadalafil alone in 200 records (66.7%), sildenafil alone in 31 (10.3%), vardenafil alone in 15 (5.0%), and more than one PDE5i in 54 (18.0%). Baseline characteristics are summarized in Table *1*.

Variable	Value (mean ± SD or n, %)
Number of analyzed records	300
Age (years)	59.4 ± 9.4
BMI (kg/m²)	30.1 ± 5.0
Tadalafil alone, n (%)	200 (66.7)
Sildenafil alone, n (%)	31 (10.3)
Vardenafil alone, n (%)	15 (5.0)
Multiple-agent codes, n (%)	54 (18.0)
UA pre-treatment (μmol/L)	360.8 ± 79.3
UA post-treatment (μmol/L)	352.8 ± 77.7
Mean ΔUA (post - pre, μmol/L)	-8.1
Pre-treatment UA, median (Q1-Q3), μmol/L	360.5 (314.0-420.0)
Post-treatment UA, median (Q1-Q3), μmol/L	365.0 (317.0-387.0)
Paired ΔUA, median (Q1-Q3), μmol/L	-1.0 (-42.0-28.3)

TABLE 1: Baseline Characteristics and Serum Uric Acid Levels

Values are mean ± standard deviation unless otherwise indicated. ΔUA is follow-up minus baseline. Q1-Q3 denotes the 25th-75th percentiles. BMI, body mass index; Q1, first quartile (25th percentile); Q3, third quartile (75th percentile); SD, standard deviation; UA, uric acid; ΔUA, change in uric acid (post-treatment minus pre-treatment); n, number of records.

Serum UA levels

Mean serum UA was 360.8 ± 79.3 μmol/L before treatment and 352.8 ± 77.7 μmol/L at follow-up, corresponding to a mean paired change of -8.1 μmol/L. Median baseline and follow-up UA levels were 360.5 μmol/L (Q1-Q3: 314.0-420.0) and 365.0 μmol/L (Q1-Q3: 317.0-387.0), respectively. The median paired change was -1.0 μmol/L (Q1-Q3: -42.0 to 28.3). Descriptive results are summarized in Table *1*.

Correlation analyses

Baseline serum UA correlated positively with BMI (Pearson r = 0.253; Spearman ρ = 0.293) and age (Pearson r = 0.335; Spearman ρ = 0.346). Negative correlations were observed with HbA1c, total cholesterol, HDL, LDL, and total testosterone, whereas triglycerides showed a positive correlation. Pearson and Spearman coefficients and the number of available observations for each analysis are presented in Table *2*.

Variable	Available records, n	Pearson r	Spearman ρ
Age	300	0.335	0.346
BMI	300	0.253	0.293
HbA1c	291	-0.176	-0.269
Total cholesterol	300	-0.18	-0.128
HDL	300	-0.08	-0.033
LDL	300	-0.224	-0.162
Triglycerides	300	0.201	0.201
Total testosterone	265	-0.261	-0.17

TABLE 2: Correlations Between Baseline Serum Uric Acid and Clinical and Laboratory Parameters

BMI, body mass index; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; UA, uric acid; r, Pearson correlation coefficient; ρ, Spearman rank correlation coefficient.

Discussion

In this retrospective cohort of men with ED, findings did not demonstrate a statistically significant change in serum UA during long-term PDE5 inhibitor therapy. However, the study design does not permit definitive conclusions regarding the effect of treatment on UA levels or metabolism.

In contrast, a significant positive association between UA and BMI was observed, reinforcing the well-established link between obesity, insulin resistance, and hyperuricemia. Obesity contributes to elevated UA through multiple mechanisms, including increased purine turnover, reduced renal urate excretion mediated by hyperinsulinemia, and low-grade systemic inflammation [6,12]. The observed association between BMI and UA in our cohort is consistent with prior studies demonstrating that adiposity is a primary determinant of UA levels across diverse populations [12,13]. These results align with prior research indicating that increased adiposity contributes to elevated UA through insulin resistance, increased purine turnover, and decreased renal excretion [1,2]. This finding indicates an association within the studied cohort but does not establish a causal relationship or identify BMI as the primary determinant of UA.

Baseline UA showed negative correlations with HbA1c, total cholesterol, HDL, LDL, and total testosterone, whereas triglycerides showed a positive correlation. These findings should be interpreted cautiously because of the descriptive nature of the analyses, incomplete laboratory data, and potential confounding. In particular, the observed coefficients do not establish the absence or presence of clinically meaningful hormonal or lipid-related relationships. Elevated UA has been associated with endothelial dysfunction, oxidative stress, and systemic inflammation, which are recognized contributors to ED pathophysiology [3,4]. Furthermore, hyperuricemia has been identified as an independent risk factor for ED, with genetic studies supporting a causal link between UA and male sexual hormones [9,10]. Therefore, UA may serve more as a surrogate marker of metabolic and vascular compromise than a direct target for PDE5i therapy.

Prior studies have suggested associations between hyperuricemia and ED, particularly in patients with comorbid hypertension, diabetes, or coronary artery disease [5,6]. The causal relationship, however, remains unclear. Our findings support the concept that elevated UA primarily reflects underlying metabolic derangements, most notably obesity, rather than being modifiable via PDE5i therapy. These results emphasize the importance of comprehensive cardiovascular and metabolic evaluation in men presenting with ED.

Mechanistically, PDE5is improve penile hemodynamics through the nitric oxide-cGMP pathway [7]. While endothelial dysfunction contributes to both ED and hyperuricemia, the lack of UA reduction in our cohort suggests that PDE5is improve endothelial function without substantially affecting systemic UA metabolism. This is consistent with recent meta-analytic evidence indicating that PDE5is modulate inflammatory markers but do not significantly alter UA levels [11].

This study has several limitations. First, its retrospective, observational design limits causal interpretation. Although paired serum UA measurements allowed us to compare values before and after long-term PDE5i therapy, the absence of an untreated or PDE5i-naïve control group prevents us from attributing any observed change specifically to treatment. Furthermore, the absence of a statistically significant pre-post difference should not be interpreted as proof that PDE5i therapy has no effect on UA levels. Second,

selection bias may have arisen from the retrospective inclusion criteria and the requirement for available paired laboratory measurements. Patients with complete data may differ from those without complete follow-up measurements, potentially limiting the generalizability of the findings. Third, detailed information on PDE5i agents, doses, treatment frequency, treatment changes, and adherence may not have been consistently available in the medical records. In addition, the timing of follow-up laboratory measurements may have varied between patients, which could have introduced variability into the pre-post comparison. Fourth, residual confounding cannot be excluded. Although several clinical and biochemical variables were assessed, factors potentially associated with UA - including renal function, dietary intake, alcohol consumption, physical activity, and concomitant medications - may not have been comprehensively documented or accounted for in the analyses. Mechanisms such as insulin resistance and altered renal urate handling were not directly assessed and therefore cannot be established as explanations for the observed findings. Finally, the positive association between BMI and UA was modest and observational. It does not establish a causal relationship or demonstrate that BMI is an independent determinant of UA. The study was also not designed to establish equivalence or exclude small treatment effects. These findings should therefore be interpreted cautiously and confirmed in prospective controlled studies with standardized laboratory measurement intervals, detailed treatment-exposure data, and more comprehensive assessment of potential confounders.

Conclusions

In this retrospective cohort of men with ED receiving long-term PDE5 inhibitor therapy, no statistically significant change in serum UA was observed between pretreatment and follow-up measurements. The absence of a control group limits the ability to determine whether PDE5 inhibitor therapy affects UA levels. BMI showed a modest positive association with UA, but this observational finding does not establish causality or identify BMI as the primary determinant of UA. Prospective controlled studies with standardized follow-up and appropriate adjustment for potential confounders are needed to clarify these relationships.

Clinically, these findings emphasize the importance of addressing metabolic risk factors, especially obesity, alongside ED therapy through lifestyle modification and risk reduction strategies. Future studies with larger cohorts are needed to clarify the links between UA, metabolic dysfunction, and ED, and to assess whether targeting UA or metabolism can improve ED outcomes.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. Hamad Medical Corporation issued approval MRC-01-19-406. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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