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ORIGINAL ARTICLE

Cavernosal Uric Acid Level in Vasculogenic Erectile Dysfunction Patients Before and After Allopurinol Alone Versus Allopurinol Plus Daily Tadalafil 5 mg: Comparative Study

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Abstract

Background: **Erectile dysfunction (ED) is the inability to sustain an erection that is firm enough to engage in satisfactory sexual intercourse. Previous literature reported a link between hyperuricemia and ED and others found Allopurinol could reduce the risk of ED in patients with hyperuricemia.**

Aim: **We aim in our study to assess the impact of hyperuricemia on ED and the effect of Allopurinol on this population either alone or with Tadalafil.**

Patients and methods: **We recruited a sample of 80 participants. Patients with vasculogenic ED and hyperuricemia underwent uric acid (UA) measurement before and after receiving Allopurinol for 2 months, then after receiving Allopurinol plus Tadalafil daily dose for another 2 months. The participants were divided into three groups based on their baseline International Index of Erectile Function questionnaire (IIEF5): mild to moderate ED, mild ED, and no ED.**

Results: **Baseline UA levels and IIEF5 showed significant variation among all groups ($P < 0.001$). Similarly, IIEF5 scores at 2 months ($P < 0.001$) and 2-month UA levels ($P < 0.001$) significantly differed among groups. IIEF5 scores at 4 months also showed significant differences ($P < 0.001$), while 4-month UA levels did not ($P > 0.05$). Participants' comparison at the different time points revealed highly significant differences in all the variables being compared ($P < 0.001$).**

Conclusion: **Substantial differences were observed in UA levels and IIEF5 scores at baseline, 2 months, and 4 months, indicating the efficacy of Allopurinol alone and Allopurinol plus Tadalafil in decreasing UA levels and improvement of ED.**

Keywords: Allopurinol, Erectile dysfunction, International index of erectile function questionnaire, Tadalafil, Uric acid

1. Introduction

Erectile dysfunction (ED), is a prevalent condition that can adversely affect the quality of life for both men and their partners. The National Institutes of Health's definition of ED, which is the most commonly cited, states that it is the inability to attain or sustain an erection that is firm enough to engage in satisfactory sexual intercourse.[1,2]

ED has many different causes. The most prevalent one is psychogenic ED, which is often tied to stress, depression, and anxiety, leading to the apprehension of not achieving or maintaining an erection during sexual intercourse.[3,4] These psychological factors often coexist with this condition because noradrenaline inhibits erectile function. Nonendocrine causes include neurogenic and vascular factors. Neurogenic ED results from nerve signaling issues caused by conditions like spinal cord injuries, multiple sclerosis, and diabetes.[3,5] Vascular causes stem from vascular diseases and endothelial dysfunction, reducing blood flow and arterial insufficiency. Risk

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factors include atherosclerosis, hypertension, and diabetes.[3,6,7] Iatrogenic ED can result from surgeries or medications, including thiazide diuretics and β-blockers. Endocrine-related causes are linked to hormonal imbalances, particularly testosterone. The use of testosterone replacement therapy is controversial.[2,3]

Allopurinol, functioning as a xanthine oxidase inhibitor, holds the promise of ameliorating endothelial dysfunction through the reduction of uric acid (UA) concentrations and the manifestation of antioxidative characteristics.[8,9] Only a limited number of investigations have explored the prospective advantages of urate-lowering therapy (ULT) in the context of ED. A prior meta-analysis disclosed a 27% risk reduction in ED among patients with hyperuricemia following ULT.[10] In our study, we aim to assess the impact of hyperuricemia on ED and the effect of Allopurinol on this population either alone or with Tadalafil, a phosphodiesterase-5 inhibitor well established for treating ED.[11]

2. Patients and methods

2.1. Study design and participants

This study employed to compare and analyze the effect of hyperuricemia on ED and the effect of Allopurinol and Tadalafil on treating this ED. We recruited a sample of 80 participants. Patients with vasculogenic ED and hyperuricemia underwent UA measurement in cavernosal blood before (as baseline), after receiving Allopurinol 100 mg alone for 2 months and after receiving Allopurinol 100 mg plus Tadalafil 5 mg daily dose for another 2 months.

2.2. Recruitment and inclusion criteria

Participants were recruited from the Andrology Outpatient Clinics in Al-Azhar University Hospitals. Our study was approved by the ethical committee of our institution, where we collected the cases. All patients and control signed informed consent before recruitment. Inclusion criteria for this study included adult male patients aged 30 years or older who have vasculogenic ED and hyperuricemia and who provided informed consent. Participants were classified into three groups according to their baseline International Index of Erectile Function questionnaire (IIEF5) scores, as follows: mild to moderate ED ($N = 24$) (group 1), mild ED ($N = 36$) (group 2), and no ED ($N = 20$) (group 3). The first two groups were patients with vasculogenic ED and hyperuricemia, and the third group were normally healthy individuals serving as controls.

2.3. Data collection

Data collection involved recording participants' ages as part of their demographic information, determining the presence or absence of hypertension through medical records and patient interviews, and obtaining cavernosal blood samples for UA levels at baseline, 2 months, and 4 months under completely aseptic conditions. These samples were drawn into vacuum plain tubes, then centrifuged at 4000 rpm for 10 min to separate the serum for UA determination using the Cobas chemistry auto analyzer (COBAS INTEGRA 400 plus; Roche Diagnostics Ltd, Rotkreuz, Switzerland). Additionally, erectile function was assessed using the IIEF5 questionnaire, a validated tool for evaluating male sexual function, at baseline, 2 months, and 4 months, and ED was also assessed using a penile duplex.

2.4. Statistical analysis

Mean values were calculated for age, UA levels, and IIEF5 scores at each time point, and SD were computed to measure the variability within the groups. Group differences were analyzed using nonparametric analysis of variance (Kruskal–Wallis) for continuous variables such as age, UA levels, and IIEF5 scores. Additionally, the paired samples *t*-test results, as indicated by the Wilcoxon rank (nonparametric paired *t*-test), were used for detecting the difference of the same individuals at different time points. Spearman's rank correlation coefficients (rho) were used to explore associations between variables, including UA levels and IIEF5 scores at different time points. Multiple linear regression analysis was conducted to assess the impact of UA levels at different time points (baseline, 2 months, and 4 months) on corresponding IIEF5 scores. Statistical analyses were performed using IBM-SPSS software package, version 27.0 (IBM Corp., Armonk, New York, USA), and significance levels were set at P value less than 0.05.

3. Results

Our study encompassed 80 participants; three groups were compared based on their IIEF5 scores: group 1 ($N = 24$), group 2 ($N = 36$), and group 3 ($N = 20$). The groups exhibited significant differences in various aspects.

Age disparities were evident, with group 3 being the youngest (mean age of 43.9 years), followed by group 1 (mean age of 49.3 years), and group 2 as the eldest (mean age of 50.8 years). However, the

presence of hypertension did not significantly differ among these groups ($P = 0.402$).

Notable variations were observed in the UA levels and IIEF5 scores. Baseline UA levels were significantly different among the groups (mild to moderate ED: 8.3, mild ED: 7.9, no ED: 5.1; $P < 0.001$), as were baseline IIEF5 scores (mild to moderate ED: 15.5, mild ED: 17.8, no ED: 23.4; $P < 0.001$). Similarly, IIEF5 scores at 2 months (mild to moderate ED: 17.2, mild ED: 18.6, no ED: 23.4; $P < 0.001$) and 2 months UA levels (mild to moderate ED: 6.7, mild ED: 6.8, no ED: 5.1; $P < 0.001$) significantly differed among the groups. IIEF5 scores at 4 months also exhibited significant differences (mild to moderate ED: 19.8, mild ED: 19.7, no ED: 23.4; $P < 0.001$), while 4 months UA levels did not differ significantly (mild to moderate ED: 5.4, mild ED: 5.7, no ED: 5.1; $P > 0.05$) (Table 1).

The paired samples *t*-test results, as indicated by the Wilcoxon rank (nonparametric paired *t*-test) and the corresponding *P* values in Table 2, reveal highly significant differences in all the variables being compared. For 'baseline UA,' '2 months UA,' and '4 months UA,' the *P* values are all less than 0.001, indicating statistically significant changes in UA levels over time. Similarly, for the erectile function measures, 'baseline IIEF5 score,' 'IIEF5 score at 2 months,' and 'IIEF5 score at 4 months' all exhibit *P* values below 0.001, demonstrating significant alterations in erectile function scores between these time points.

Correlation analysis highlighted strong positive correlations between 2 months UA levels and 4 months UA levels (rho = 0.79, $P < 0.001$), as well as with baseline UA levels (rho = 0.75 and 0.51, respectively, both $P < 0.001$). Conversely, negative correlations were observed, with baseline IIEF5 scores negatively correlating with baseline UA levels (rho = −0.55, $P < 0.001$). Additionally, IIEF5 scores at two months negatively correlated with 2-month UA levels (rho = −0.23, $P = 0.040$).

Regression analysis indicated varying influences of UA levels at different time points on erectile function scores. 'Two months UA' had a significant negative impact on 'IIEF5 scores at 2 months' (coefficient of −1.07, $P < 0.001$), while 'baseline UA' had a strong negative effect on 'baseline IIEF5 scores' (coefficient of −1.48, $P < 0.001$). For the 'IIEF5 score at 4 months,' the predictor '4 months UA' had a negative coefficient of −0.37, though it was not statistically significant ($P = 0.126$).

Regarding penile duplex results, there was no significant difference in cavernosal peak systolic velocity, end-diastolic velocity, and resistance index in the studied groups after 2 months. There was a significant increase in cavernosal peak systolic velocity after 4 months of treatment, a decrease in end-

Table 2. Wilcoxon rank (nonparametric paired t-test) for the assessed parameters.

	P value
Baseline UA	
Two months UA	<0.001
Four months UA	<0.001
Baseline IIEF5 score	
IIEF5 score at 2 months	<0.001
IIEF5 score at 4 months	<0.001
IIEF5 score at 2 months	
IIEF5 score at 4 months	<0.001

IIEF, International Index of Erectile Function questionnaire; UA, uric acid.

Table 1. Characteristics and comparison between groups stratified to bassline International Index of Erectile Function questionnaire.

	Group 1 ($N = 24$)	Group 2 ($N = 36$)	Group 3 ($N = 20$)	Total ($N = 80$)	*P* value
Age					<0.001[a]
Mean (SD)	49.3 (4.4)	50.8 (6.6)	43.9 (5.5)	48.6 (6.3)	
Hypertension					
Yes	14.0 (58.3)	17.0 (47.2)	0.0	31.0 (51.7)	0.40[b]
Baseline UA					<0.001[a]
Mean (SD)	8.3 (0.4)	7.9 (0.5)	5.1 (1.8)	7.3 (1.6)	
Baseline IIEF5 score					<0.001[a]
Mean (SD)	15.5 (0.5)	17.8 (0.7)	23.4 (1.1)	18.5 (3.1)	
IIEF5 score at 2 months					<0.001[a]
Mean (SD)	17.2 (1.1)	18.6 (1.4)	23.4 (1.1)	19.4 (2.7)	
Two months UA					<0.001[a]
Mean (SD)	6.7 (0.3)	6.8 (0.6)	5.1 (1.8)	6.4 (1.2)	
IIEF5 score at 4 months					<0.001[a]
Mean (SD)	19.8 (1.4)	19.7 (1.6)	23.4 (1.1)	20.6 (2.2)	
Four months UA					0.052[a]
Mean (SD)	5.4 (0.4)	5.7 (0.5)	5.1 (1.8)	5.5 (1.0)	

IIEF, International Index of Erectile Function questionnaire; UA, uric acid.
[a] Nonparametric analysis of variance (Kruskal–Wallis).
[b] Chi-square test.

diastolic velocity, and an increase in resistance index of the studied groups after 4 months.

4. Discussion

In our study, 80 participants were grouped by their IIEF5 scores into mild to moderate ED, mild ED, and no ED, and significant differences were observed. Notable variations were found in UA levels and IIEF5 scores at baseline, 2 months, and 4 months. UA levels and IIEF5 scores showed significant differences among the groups at all three-time points, indicating the efficacy of Allopurinol alone and Allopurinol plus Tadalafil in decreasing UA levels and increasing IIEF5 scores and consequently indicative of ED improvement. Correlation analysis showed strong positive correlations between UA levels at different time points negative correlations between baseline IIEF5 scores and baseline UA levels, as well as between IIEF5 scores at 2-month and 2-month UA levels. Regression analysis indicated that UA levels at different time points had varying impacts on erectile function scores, with 2-month UA negatively affecting 2-month IIEF5 scores and baseline UA negatively affecting baseline IIEF5 scores.

However, the association between hyperuricemia and ED remains a topic of debate in clinical studies. Several investigations have documented a favorable correlation between UA levels and ED. These encompass a study involving hypertensive males in Turkey, a case–control analysis involving individuals recently diagnosed with ED, and an extensive population-based study involving Chinese male patients.[12–14] In contrast, an investigation encompassing males with suspected coronary artery disease failed to reveal a substantial correlation between UA and ED when considering multiple variables in a regression model.[15] Similarly, in a series of Finnish men participating in the Harmonica Project, UA was not found to be associated with ED in both univariate and multivariable analyses.[16] Further research and additional well-designed clinical studies are needed to clarify the existence and extent of the association between hyperuricemia and ED.

Furthermore, the influence of glomerular filtration rate has been explored as a potential determinant that could affect the relationship between UA and ED.[17] In a study by Solak *et al.*,[15] comprising 312 individuals with coronary artery disease, the initially observed substantial correlation between elevated UA levels and ED became nonsignificant in multivariable analysis after accounting for glomerular filtration rate.

In the investigation conducted by Totaro and colleagues, the presence of chronic kidney disease did not seem to have an impact on the prevalence of ED in men with hyperuricemia, as revealed by the meta-regression analysis. Nonetheless, it is essential to be cautious in interpreting this result, given the limited number of studies included. In summary, their outcomes derived from the meta-regression and subgroup analyses suggested that the direct causal role of hyperuricemia in endothelial dysfunction leading to ED may be circumscribed. Hyperuricemia and ED could potentially share common risk factors associated with metabolic irregularities.[18]

Additionally, Wang and colleagues meta-analysis investigated the link between high levels of UA in the blood and ED. They found that elevated UA was a notable risk factor for ED and that reducing UA levels through treatment decreased the risk of ED in individuals with hyperuricemia. Their analysis also included subgroup analyses that confirmed the association between hyperuricemia and ED across various study types, populations, age groups, gout patients, and asymptomatic hyperuricemia patients. These findings provide evidence supporting the need for early intervention in hyperuricemia to decrease the risk of developing ED.[10]

There have been only a few studies examining the potential benefits of ULT for ED. In a previous meta-analysis, it was reported that ULT reduced the risk of ED by 27% in patients with hyperuricemia.[10] Chen *et al.*[19] demonstrated that patients with gout who received ULT for at least 90 days had a lower risk of developing ED compared to those who did not receive ULT. However, Abdul Sultan *et al.*[20] found no significant impact on ED incidence when ULT was taken within 1–3 years after a gout diagnosis.

Allopurinol stands as the predominant ULT employed globally, including in patients with chronic kidney disease.[21] A multitude of investigations have demonstrated the potential of Allopurinol, operating as a xanthine oxidase inhibitor, to ameliorate endothelial dysfunction through UA reduction and the display of antioxidant attributes.[8,9] Its influence on endothelial function was assessed in heart failure patients via venous occlusion plethysmography. Allopurinol notably augmented forearm blood flow in response to acetylcholine, enhancing nitric oxide availability and reducing plasma malondialdehyde levels, indicative of oxidative stress.[9] Two additional studies corroborated the beneficial effects of Allopurinol on endothelial function, demonstrating reductions in allantoin levels, a marker of oxygen free-radical generation, and tumor necrosis factor-alpha levels, a pro-inflammatory cytokine, within the same patient

cohort.[22,23] Nonetheless, limited direct data exists regarding the impact of ULT, particularly Allopurinol, on ED.[10,19,20]

ED in individuals with hyperuricemia may be attributed to the activation of penile vascular endothelial cells induced by oxidative stress. Allopurinol, a pharmaceutical agent that lowers UA levels, can play a role in ameliorating endothelial dysfunction by diminishing the activity of reactive oxygen species and neutralizing oxygen-free radicals, consequently mitigating oxidative stress.[24] To summarize, both Allopurinol and benzbromarone, as conventional UA-lowering medications, can alleviate endothelial oxidative stress associated with elevated UA levels. By reducing UA levels, these medications can enhance endothelial function and potentially alleviate ED. Allopurinol can enhance NO availability in endothelial cells and reduce oxidative stress through mechanisms independent of UA, leading to an improvement in ED.

In our study, although we had a robust design and analysis, we were not free of limitations. Being all patients selected from our institutional clinic, this could attribute us to the selection bias. Also, we had a relatively small sample size and a small number of controls. Lastly, many confounders needed to be stratified, but this was not feasible with our collected data.

4.1. Conclusion

Our study encompassed 80 participants grouped into mild to moderate ED, mild ED, and no ED; we noted substantial differences in UA levels and IIEF5 scores at baseline, 2 months, and 4 months, indicating the efficacy of Allopurinol alone and Allopurinol plus Tadalafil in decreasing UA levels and improvement of ED.

Ethics

Its was approved by faculty.

Conflicts of interest

There are no conflicts of interest.

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