Hyperuricemia Is an Independent Risk Factor of the Erectile Dysfunction: a Systematic Review and Meta-analysis

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Abstract

Background and Aims: Serum uric acid can affect endothelial function, and hyperuricemia-induced endothelial dysfunction is involved in the pathogenesis of cardiovascular diseases. As endothelial dysfunction is also a main pathogenic mechanism of erectile dysfunction (ED), the present study aims to evaluate the relationship between hyperuricemia and ED via systemic review and meta-analysis.

Methods: Five cohort studies and five cross-sectional studies on hyperuricemia and ED, including a total of 454256 participants, were recruited. Odds ratio (OR) and the 95% confidence intervals (CI) were adopted to estimate the relationship between hyperuricemia and ED. Overall risk were effects of urate-lowering therapy (ULT) analyzed. In addition, subgroup analyses on study design, populations, age stratification and the object were conducted.

Results: In the patients with hyperuricemia, the risk of ED was 1.55-fold higher than (pooled OR=1.55, 95%CI (1.24,1.94)) the non-hyperuricemia counterparts. urate-lowing therapy (ULT) in these hyperuricemia patients reduced the risk of ED by 27% (OR=1.27, 95%CI (1.14,1.41)). After subgroup analysis and meta-regression, the association between hyperuricemia and ED remained significant apart from in the ≥ 55 y subgroup.

Conclusions: Hyperuricemia is an independent risk factor of ED, while ULT can reduce the risk of ED in hyperuricemia. This study suggests that hyperuricemia-associated endothelial dysfunction may also underlie the pathogenesis of ED in these patients.

Introduction

Erectile dysfunction (ED), a consistent and recurrent inability to acquire or sustain an erection of sufficient rigidity and duration to engage in satisfactory sexual intercourse, greatly compromises the quality of life [1]. A systematic review showed the prevalence of ED varies in different ages and populations [2]. In an Australian research, the overall prevalence of ED was 23%[3]. The pathogenesis of ED involves vasculogenic and structural conditions, endocrine disorders, and neurogenic conditions[4]. Meanwhile, ED has been reported to be an important effector on the incidence and mortality of cardiovascular disease (CVD) [5] and diabetes mellitus (DM)[6]. Moreover, the same risk factors, e.g. age, obesity, smoke and DM, contribute to ED and CVD, suggesting that these conditions may have similar pathogenic mechanisms [5], in which endothelial damages resulting from NO reduction may play a crucial role [7].

Hyperuricemia, the serum uric acid higher than 7.0mg/dl in men and more than 6.0mg/dl in women[8], has been demonstrated to induce endothelial dysfunction [9, 10]. Indeed, hyperuricemia is also an independent risk factor of hypertension, coronary heart disease and atrial fibrillation[11]. Actually, previous clinical studies have reported that many hyperuricemia patients were inflicted with ED [12–14]. Nevertheless, the contribution of uric acid to ED remains to be defined, and the relationship between hyperuricemia and ED is controversial. In the present study, a systematic review and meta-analysis was performed to evaluate the relationship between hyperuricemia and ED.

Materials And Method

The protocols for reporting Meta-analysis Of Observational Studies in Epidemiology (MOOSE) were employed in this study. Literature-search strategies, inclusion and exclusion criteria, and statistical analyses were performed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines[15, 16] (PRISMA checklist in supplemental-1).

1. Literature-search strategies

PubMed, Embase, Cochrane Library and Web of Science were used as the source of data. The following MeSH terms and their combinations were searched: ((((((hyperuricemia [MeSH Terms]) OR (uric acid [MeSH Terms])) OR (gout [MeSH Terms])) OR (hyperuricemia [Title/Abstract])) OR (uric acid [Title/Abstract])) OR (gout [Title/Abstract])) AND (((erectile dysfunction [MeSH Terms]) OR (male sexual impotence [Title/Abstract])) OR (male impotence [Title/Abstract])) OR (sexual dysfunction [Title/Abstract])). In addition, the references of retrieved studies were reviewed for more pertinent studies.

2. Inclusion and exclusion criteria

Inclusion criteria: **a.** all original cohort and cross-sectional studies available on the relationship between hyperuricemia and ED; **b.** studies providing primary descriptive data or the odds ratio and 95% confidence intervals; **c.** no limitations on publication time or language.

Exclusion criteria: editorials, letters to the editor, reviews, case reports, case-control studies and animal experimental studies.

3. Data extraction and Quality assessment

The titles, first authors, publication year, populations, mean age, study design, assessment of ED, number of participants, the years of follow-up, OR and 95%CI of the included studies were extracted and summarized independently by two of the authors. The disagreement was settled by consensus or a third author for adjudication.

The methodological quality was assessed by the NEWCASTLE-OTTAWA Quality Assessment Scale [17] for cohort studies, and Agency for Healthcare Research and Quality (AHRQ) [18] recommended for cross-sectional studies[19]. The cohort study quality assessment consisted of three factors: patient selection, comparability of the study groups and outcomes/exposures. A score of 0–9 (allocated as stars) was allocated to each cohort study. The studies acquiring 3 or 4 stars in the selection domain, 1 or 2 stars in the comparability domain, and 2 or 3 stars in outcome/exposure domain simultaneously were defined as good quality. Those acquiring 2 stars in the selection domain, 1 or 2 stars in the comparability domain, and 2 or 3 stars in the outcome/exposure domain were moderate quality, while 0 or 1 star in selection domain, 0 stars in comparability domain, and 0 or 1 stars in the outcome/exposure domain as poor quality.

The cross-sectional study quality assessment consisted of 11 questions that could be answered with “YES, NO, or UNCLEAR”. An item would be scored “0” if it was answered “NO” or “UNCLEAR”; while an item was scored “1” if it was answered “YES”. Article quality was assessment as: low quality at 0–3; moderate quality at 4–7; and high quality at 8–11 scores[20].

4. Evidence synthesis process & statistical analyses

Based on the incidence of ED reported in each study, the pooled OR and 95%CI were calculated to evaluate the relationship between serum uric acid and ED. Heterogeneity between studies was assessed using the Chi-square test. If $I^2 > 50\%$ and $P < 0.05$, random effect, subgroup analysis and meta-regression analysis were employed to identify the source of high heterogeneity. Publication bias was evaluated using the Egger’s test and Harbord test with a visually symmetric plot. STAT v14.0 and the forestplot package of RStudio were employed for statistical analyses.

Results

1. Characteristics of included studies

Five cohort studies [12, 21–24] and five cross-sectional studies [13, 25–28], containing 454256 participants, were included in the final analysis (Fig. 1). Two of the selected studies were in abstract form [24, 27]. Baseline patient characteristics of the included studies, e.g., populations, mean age, study design, assessment of ED, participants, follow-up years and the quality score were summarized in Table 1.

Table 1

Characteristics of included studies.

Study	Year	Populations	Mean age (years)	Study Design	Assessment of ED	Population ED group control group events/total events/total	Follow-Up (years)	Result OR (95%CI)	Quality Score
Y.F. Chen	2015	Taiwan	42.7 ± 12.0	Cohort study	ICD-9-CM Code 607.84	186/19368 558/77472	N.A.	1.21(1.03-1.44)	□□□□□□□□
Sultan, A.	2017	England	18-64	Cohort study	Medical code	1736/9653 4124/38218	17	1.31(1.24-1.40)	□□□□□□□□
C.Y. Hsu	2015	Taiwan	49.6 ± 16.2	Cohort study	PED (ICD-9-CM codes 302.72) OED (ICD-9-CM codes 607.84)	476/35265 634/70529	11	1.21(1.07-1.37)	□□□□□□□□
Naomi. S.	2018	United Kingdom	63.6±12.3	Cohort study	Read code: E227311	2290/38438 8447/154332	5	1.15(1.09-1.21)	□□□□□□□□
Maynard JW	2010	USA	68.7 ± 11.3	Cohort study	Professional diagnosis of ED	102/256 677/2349	N.A.	1.51(0.85-1.53)	N.A.
Naomi. S.	2015	USA	56.67±14.3	Cross-sectional study	SHIM questionnaire	23/83 19/118	3	2.92(1.41-6.06)	6
ALPAY. A.	2014	Turkey	56.2±8.9	Cross-sectional study	SHIM questionnaire	110/200 90/200	N.A.	1.76(1.28-2.41)	8
J.H. Kim.	2017	Korea	52(44-59)	Cross-sectional study	IIEF-5	42/80 27/70	N.A.	0.62(0.11-3.53)	8
Edward. R.	2013	England	59.9	Cross-sectional study	Read code diagnosis of ED	116/1292 429/5168	N.A.	0.97(0.78-1.22)	N.A.
F.B. Gao.	2017	Chinese	55.5±10.8	Cross-sectional study	IIEF-5	852/1365 513/1365	11	0.996(0.99-1)	10

ED: Erectile Dysfunction; SHIM: Sexual Health Inventory in Men; ICD-9-CM: International Classification of Diseases, 9th ed, Clinical Modification; OED: organic erectile dysfunction; PED: psychogenic erectile dysfunction; OR: odds ratio; 95%CI: 95% confidence interval. N.A. Not available.

2. Analyses of Sensitivity

After removing two studies [24, 27] published in abstract form, the remaining four cohort studies [12, 21–23] and four cross-sectional studies [25, 26, 28] were included in the sensitivity analysis. By omitting each study by turn, no significant changes occurred in the outcome regarding the heterogeneity and the OR of the effect ranged from 1.47 to 1.67 (Table 2). No single study had a crucial effect on the combined outcome (Supplementary Fig. 1).

Table 2
Sensitivity analysis after each study omitted.

Study Omitted	OR	95%CI for Remainders	Heterogeneity			
			tau ²	df	I ² (%)	P
A. ARIBAS. 2014	1.64	1.24 2.16	0.0005	6	98	0.00
CY, Hsu 2015	1.64	1.21 2.22	0.0013	6	98	0.00
FB, Gao. 2017	1.47	1.15 1.89	0.0021	6	96	0.00
JH. Kim. 2017	1.62	1.24 2.13	0.0004	6	98	0.00
N. Schlesinger. 2018	1.74	1.43 2.12	< 0.0001	6	88	0.00
N. Schlesinger. 2015	1.59	1.22 2.08	0.0007	6	98	0.00
Sultan, A 2017	1.59	1.18 2.51	0.0026	6	96	0.00
YF, Chen 2015	1.67	1.25 2.24	0.0005	6	98	0.00
Pooled estimate	1.62	1.25 2.10	0.0003	NA	97%	0.00

3. Publication bias and quality assessment

While the funnel plot displayed a scattered distribution around the effect size (Fig. 2), no significant publication bias was detected in the included studies, upon examination by the Egger's plot ($P = 0.61$, $Z = 0.53$) and the Harbord test ($P = 0.58$, $Z = 0.58$). Based on the methodology and reported data, the overall quality of the four included cohort studies [12, 21–23] was assessed to high quality (Supplementary Table 1). Of the five included cross-sectional studies, three [25, 26, 28] were considered high quality, while the study by N. Schlesinger (2015) was assessed to be of moderate quality (Supplementary Table 2).

4. Relationship between hyperuricemia and ED

As shown in Fig. 3A, the combined effect estimate suggested that the incidence of ED in hyperuricemia group was approximately 1.55-fold higher than their non-hyperuricemia counterparts (pooled OR 1.55, 95%CI (1.24,1.94), $Z = 3.87$, $P < 0.001$). Three included studies [12, 21, 28] investigated the effects of urate-lowering therapy on the risk of ED. Meta-analysis results showed that ULT reduced the risk of ED in hyperuricemia by 27% (pooled OR = 1.27, 95% CI (1.43–1.41)) (Fig. 3B). These results suggest that hyperuricemia is a risk factor of ED, and that ULT can alleviate ED development in these patients.

5. Subgroup analysis

An obvious heterogeneity was detected between the included publications ($\text{Chi}^2 = 254.54$, $df = 9$, $\text{Tau}^2 = 0.1068$, $I^2 = 96.5\%$, $P < 0.001$). Therefore, subgroup analyses on study design, populations, age stratifications, research object of the studies, and meta-regression analysis were conducted to identify the factors affecting heterogeneity (Fig. 4).

5.1 Study design

A significant association between hyperuricemia and the risk of ED was both observed in the five cohort studies [12, 21–24] (OR = 1.45 95%CI (1.11–1.89)), and cross-sectional studies [25–29] (OR = 1.69, 95%CI (1.03–2.79)). The heterogeneity of the cohort studies ($I^2 = 98\%$, $P < 0.01$) was consistent with the cross-sectional studies ($I^2 = 96\%$, $P < 0.01$), indicating that study design had no significant effect on the high heterogeneity (Fig. 4A).

5.2 Populations

By subdividing the subjects into Asian and European populations, the significant association between hyperuricemia and ED remained valid, with OR = 1.74 95%CI (1.19, 2.52) for Asian populations (four studies containing 149436 subjects [12, 22, 26, 28]), and OR = 1.44

95% CI (1.08, 1.92) for European populations (six studies containing 200385 subjects [13, 21, 24, 25, 27, 29]) (Fig. 4B). The heterogeneity of the studies on Asian populations ($I^2 = 94\%$, $P < 0.01$) was similar to that on European populations ($I^2 = 97\%$, $P < 0.01$), basically ruling out populations as a contributor to the high heterogeneity.

5.3 Age stratification

Considering the mean age spectrum of the included studies, an age stratification of $< 55Y$, $55-60Y$, and $\geq 60Y$ was adopted for subgroup analysis. A significantly associated between hyperuricemia and the risk of ED was detected in the $< 55Y$ subgroup ($OR = 1.58$, $95\%CI (1.35, 1.86)$), whereas no such association was observed in the $55-60Y$ subgroup ($OR = 1.66$, $95\%CI (0.85, 3.23)$) or the $\geq 60Y$ subgroup ($OR = 1.31$, $95\%CI (0.88, 1.94)$) (Fig. 4C). There was a similar heterogeneity in the $< 55Y$ subgroup ($I^2 = 76\%$, $P < 0.01$), $55-60Y$ ($I^2 = 96\%$, $P < 0.01$) and $\geq 60Y$ subgroup ($I^2 = 88\%$, $P < 0.01$), suggesting that age was unlikely to contribute to the high heterogeneity.

5.4 Research objects

The result of eight included studies [12, 21–24, 26, 27, 29] reported the risk in gout patients was higher than the control group ($OR = 1.43$, $95\%CI (1.15, 1.79)$) was consistent with the result of another two studies [25, 28] detected the relationship between serum uric acid and ED ($OR = 2.09$, $95\%CI (1.15, 3.80)$). The results of heterogeneity test of the gout group ($I^2 = 96\%$, $P < 0.01$) and uric acid level group ($I^2 = 88\%$, $P < 0.01$) were accordant, suggesting that high heterogeneity was not associated with research object (Fig. 4D).

6. Meta-regression analyses

A meta-regression analysis was performed to examine potential factors affecting heterogeneity. The results failed to identify any specific factors significantly affecting the relationship between hyperuricemia and ED, including study design ($P = 0.452$, Adj R-squared = -3.66%), age stratifications ($P = 0.120$, Adj R-squared = 18.57%), study object ($P = 0.607$, Adj R-squared = -10.42%), populations ($P = 0.214$, Adj R-squared = 12.21%) and the quality of the study assessment ($P = 0.102$, Adj R-squared = 24.77%) (Supplementary Table 3)

Discussion

This meta-analysis reported that elevated serum uric acid was an independent risk factor of ED, and that ULT reduced the risk of the ED in hyperuricemia patients. Further subgroup analyses confirmed that association between hyperuricemia and ED in the different study types, different populations, < 55 -year-old group and gout patients as well as asymptomatic hyperuricemia patients. These results have provided evidence for early intervention on hyperuricemia to reduce the risk of ED.

The association between hyperuricemia and ED reported here is consistent with previous studies [30–32]. Excessive serum uric acid can induce oxidative stress [33, 34], lower concentration of nitric oxide, and microcirculation disorder [11, 35], resulting in endothelial dysfunction. Endothelial dysfunction has been implicated in the pathogenesis of many diseases, e.g. coronary heart disease [36, 37], hypertension [38, 39], atrial fibrillation [40], and diabetes [41]. As endothelial dysfunction is also a primary pathogenic mechanism of ED, hyperuricemia-induced endothelial impairments might play a crucial role in ED seen in hyperuricemia patients. Previous clinical studies have indeed demonstrated that uric acid was significantly associated with endothelial dysfunction in patients with metabolic syndrome [42], and that ED was an early manifestation of systemic vascular endothelial injury [43].

Previous clinical studies [31, 44] have reported a positive relationship between serum urate level and the risk and severity of ED, i.e., an increase of 1 mg/dL in serum uric acid was associated with doubled risk of ED ($OR 2.07$, $95\% CI (1.63–2.64)$). These results provide basis for our findings that ULT reduced the risk of ED in hyperuricemia patients. Another meta-analysis [45] reporting that ULT with allopurinol significantly improved endothelial dysfunction. Urate-lowering drugs benzbromarone and febuxostat also alleviate endothelial impairments [46].

It is noted that no significant association was detected between hyperuricemia and risk of ED in the $\geq 55y$ subgroup. This absence of association might be due to comorbidities that are more common in older population, such as coronary heart disease, diabetes, hypertension, and renal failure, which might complicate and cover the effects of hyperuricemia on ED. Four included studies [12, 21, 22, 29] have provided the adjust OR for these comorbidities, showing that the effects of hyperuricemia on ED varied by the presence of different commodities (Supplementary Fig. 2).

The high heterogeneity ($I^2 = 96\%$, $P < 0.001$) is a major concern of this meta-analysis. Subgroup analysis and meta-regression have been performed, but unfortunately failed, to determine the source of heterogeneity. Sensitivity analysis of the included high-quality studies was conducted, where the combined OR and the overall risk were consistent without apparent fluctuations (Supplementary Fig. 1). A possible source of the high heterogeneity might derive from six of the included studies [23–28], which did not adjust some potential interfering effectors on the relationship between hyperuricemia and ED. In addition, two included studies were published as abstract with limited information provided. As a result, quality assessment on these studies was impossible, which might also contribute to the high heterogeneity. Actually, high heterogeneity has been observed in other meta-analysis studies [47].

A major limitation of this study is that it failed to acquire the dose-response relationship between urate level and the risk and severity of ED, by the lack of relevant information. After all, it is crucial to perform multi-center, large sample cohort studies to obtain more detailed evidence on hyperuricemia and ED. Given the fact that ED holds tremendous significance on social-mental life, the findings of this study provide important hints for early intervention of hyperuricemia in order to minimize the risk of ED.

Conclusions

This meta-analysis has identified hyperuricemia as an independent risk factor of ED, by demonstrating a significant correlation between hyperuricemia and ED and significant benefits of ULT on the risk of ED.

Declarations

ETHICS APPROVAL:

Not applicable.

CONSENT FOR PUBLICATION:

Not applicable.

AVAILABILITY OF DATA AND MATERIALS:

All data are fully available without restriction.

COMPETING INTEREST:

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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AUTHOR'S CONTRIBUTIONS:

Study concept and design: X Hou.

Acquisition of data: WT Wang and ZH Jing.

Analysis and interpretation of data: W Liu and L Zhu.

Drafting of the manuscript: WT Wang.

Critical revision of the manuscript for important intellectual content: X Hou and HS Ren.

Statistical analysis: WT Wang, ZH Jing and L Zhu.

All authors listed involved in the writing and revising of the manuscript and approved for publication.

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Not applicable.

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Figures

Figure 1

Flow diagram of studies identified.

Figure 2

Funnel plot for the association between hyperuricemia and ED. (OR, odds ratio)

Figure 3

Forest plot of the main result. (A.) Forest plot demonstrate the association between hyperuricemia and ED. (B.) Forest plot of the urate-lowering therapy in the risk of ED. (OR: odds ratio; LCI: lower confidence interval; UCI: upper confidence interval)

Figure 4

Forest plot of the subgroup analysis.

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