Risk of urinary stone formation associated to proton pump inhibitors: A systematic review and metanalysis of observational studies

Rawa Bapir [1, 15], Kamran Hassan Bhatti [2, 15], Ahmed Eliwa [3, 15], Herney Andrés García-Perdomo [4, 15], Nazim Gherabi [5, 15], Derek Hennessey [6, 15], Vittorio Magri [7, 15], Panagiotis Mourmouris [8, 15], Adama Ouattara [9, 15], Gianpaolo Perletti [10, 15], Joseph Philipraj [11, 15], Konstantinos Stamatiou [12, 15], Musliu Adetola Tolani [13, 15], Lazaros Tzelves [8, 15], Alberto Trinchieri [14, 15], Noor Buchholz [15]

[1] Smart Health Tower, Sulaymaniyah, Kurdistan region, Iraq;
[2] Urology Department, HMC, Hamad Medical Corporation, Qatar;
[3] Department of Urology, Zagazig University, Zagazig, Sharkia, Egypt;
[4] Universidad del Valle, Cali, Colombia;
[5] Faculty of Medicine Algiers 1, Algiers, Algeria;
[6] Department of Urology, Mercy University Hospital, Cork, Ireland;
[7] ASST Nord Milano, Milan, Italy;
[8] 2nd Department of Urology, National and Kapodistrian University of Athens, Sismanoglio Hospital, Athens, Greece;
[9] Division of Urology, Souro Sanou University Teaching Hospital, Bobo-Dioulasso, Burkina Faso;
[10] Department of Biotechnology and Life Sciences, Section of Medical and Surgical Sciences, University of Insubria, Varese, Italy;
[11] Department of Urology, Mahatma Gandhi Medical College and Research Institute, Sri Balaji Vidyapeeth, Puducherry, India;
[12] Department of Urology, Tzaneio General Hospital, 18536 Piraeus, Greece,
[13] Division of Urology, Department of Surgery, Ahmadu Bello University / Ahmadu Bello University Teaching Hospital, Zaria, Kaduna State, Nigeria;
[14] Urology School, University of Milan, Milan, Italy;
[15] U-merge Ltd. (Urology for emerging countries), London-Athens-Dubai*.

Authors 1-14 have equally contributed to the paper and share first authorship.

* *U-merge Ltd. (Urology for Emerging Countries) is an academic urological platform dedicated to facilitate knowledge transfer in urology on all levels from developed to emerging countries. U-merge Ltd. is registered with the Companies House in London/ UK. www.U-merge.com*

INCLUDED STUDIES

Ferraro PCG, Gambaro G, Taylor E. Proton Pump Inhibitors, Histamine Receptor-2 Blockers and the Risk of Incident Kidney Stones. American Society of Nephrology Kidney Week; Chicago, IL 2016, p.467A

Kwak YE, Buller G, Masoud A. Increased risk of nephrolithiasis in patients using chronic proton pump inhibitor and antacid agents. Gastroenterology. 2017; 152:(5 Supp 1)(S273-).

Kim SY, Yoo DM, Bang WJ, Choi HG. Association between Urolithiasis and History Proton Pump Inhibitor Medication: A Nested Case-Control Study. J Clin Med. 2022; 11:5693.

Simonov M, Abel EA, Skanderson M, et al. Use of Proton Pump Inhibitors Increases Risk of Incident Kidney Stones. Clin Gastroenterol Hepatol. 2021; 19:72-79.e21.

Sui W, Miller NL, Gould ER, et al. Proton pump inhibitors use and risk of incident nephrolithiasis. Urolithiasis. 2022; 50:401-409.

No conflict of interest declared.

PICO TABLES

	Population	Intervention	Control	Outcome
Ferraro 2016	Health Professionals Follow-up Study (HPFS), Nurses' Health Study (NHS) I and II provided data about chronic PPI use	187,330 participants of the 3,245 incident symptomatic kidney stone events		PPI was associated with higher risk of incident kidney stones (HR 1.12, 95% CI 1.02, 1.24, p-value = 0.02). H2 blockers (HR 1.13, 95% CI 1.02, 1.24, p-value = 0.02)
Kwak 2017	Nutrition Health and Nutrition Examination Study (NHANES) 2005-12	13,836 patients with available data on nephrolithiasis, 1,259 patients (8.7%) identified with kidney stones		Subjects on PPIs 10.7% with stones Subjects without PPIa 6.8% with stones H2 blockers 3.3 vs 1.8%
Kim 2022	Retrospective nested case-control study National Health Insurance Service-National Health Screening Cohort in Korea 28,962 patients with urolithiasis and 115,848 control participants	PPIs user previous prescription history of PPI with days of PPI prescription *current* PPI users prescribed PPI within 30 days before the diagnosis of urolithiasis *past* PPI users prescribed PPI within 31 days to 365 days before the diagnosis of urolithiasis	PPIs non users randomly matched for age, sex, income, and region of residence	PPI non-user with stones 2153 without stones 16225 PPI past users with stones 9166 without stones 49026 PPI current users with stones 17643 without stones 50597 60.9% of the urolithiasis group were current PPI users. 43.7% of the control group were current PPI users The adjusted OR [aOR] for urolithiasis was 1.37 (95% CI = 1.29–1.47) in past PPI users 2.49 (95% CI = 2.33–2.66) for current PPI users Longer dates of PPI prescription were related to higher odds for urolithiasis. ORs for urolithiasis 1.65 (95% CI = 1.54–1.77) for 1–19 days 1.97 (95% CI = 1.84–2.11), for 30–364 days 2.31 (95% CI = 2.14–2.49), for 365 or more days (p > 0.001)
Conclusions: Past and current PPI use were related to a higher risk of urolithiasis in the adult population. In addition, a longer duration of PPI use was associated with a greater risk of urolithiasis in this study. This implied a dose-dependent association of PPI use with the risk of urolithiasis.				

Simonov 2021	Retrospective study Women's Veteran's Cohort Study comprising men and women 1999-2017	89,329 (19.2%) were exposed to PPIs during observation	376562 Non exposed to PPIs	PPIs exposure 4,219 with stones PPIs Non exposed 7,005 with stones HR 1.74; 95% CI, 1.67-1.82 Increased dosage of PPI was associated with increased risk of kidney stones (HR, 1.11; CI, 1.09-1.14 for each increase In 30 defined daily doses over a 3-month period)
Sui 2022	Vanderbilt Research and Synthetic Derivative 1993 to 2020 for over three million patients Single-centre retrospective study PPI naïve GERD patients who had not previously had nephrolithiasis n=55,765	40,866 exposed to PPI		Diagnosis of nephrolithiasis defined by first occurrence PPI exposed n=1516 (3.7%) PPI unexposed n=269 (1.8%) Higher risk of incident kidney stone diagnoses HR 1.19, 95% CI 1.06-1.34

Risk of Bias

Scoring of Risk of Bias according to Newcastle-Ottawa score

Study	SELECTION				COMPARABILITY	EXPOSURE/OUTCOME		
	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study		Assessment of outcome	Follow up lenght	Adequacy of follow
Ferraro 2016			★		★★	★	★	★
Simonov 2021			★		★★	★	★	★
Sui 2022	★	★	★		★★	★	★	★

Study	SELECTION				COMPARABILITY	EXPOSURE/OUTCOME		
	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study		Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate
Kim 2022			★		★★	★	★	★
Kwak 2017			★		★★	★	★	★

"Trim-and-fill" strategy