www.nephropathol.com DOI: 10.34172/jnp.2021.36 J Nephropathol. 2021;10(4):e36

Journal of Nephropathology

Hyperoxaluria; a risk factor or a consequence of recurrent pyelonephritis?

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ARTICLE INFO

Article type:
Editorial

Article history:
Received: 5 April 2020
Accepted: 31 July 2020
Published online: 13 August 2020

Keywords:
Hyperoxaluria, pyelonephritis, gut microbiota

Implication for health policy/practice/research/medical education:
Hyperoxaluria often coexists with recurrent pyelonephritis which may be caused by the destruction of the gut microbiota. It would be logical to assume the formation of a so-called "vicious circle". On the one hand, the development of dysbiosis and intestinal barrier dysfunction, mediated by the constant use of antibiotics, are the main sources of urinary tract infection; while they lead to impaired oxalate transport and acquired hyperoxaluria. In turn, calcium oxalate deposition in the proximal renal tubules causes chronic inflammation and might be an independent risk factor for pyelonephritis recurrences. Further studies are needed to clarify the mechanism of this interaction.
Please cite this paper as: Stepanova N. Hyperoxaluria; a risk factor or a consequence of recurrent pyelonephritis? J Nephropathol. 2021;10(4):e36. DOI: 10.34172/jnp.2021.36.

Editorial

Urinary tract infection (UTI) is a global medical and social problem. It is primarily due to the high prevalence of UTI among women of sexually active age (1-3). Worldwide, UTI leads to more than 1.5 million doctor visits per day (4,5). The recurrent form of UTI is diagnosed in 25%-44% of women who have suffered from acute UTI. The burden of UTI is also reflected in significant financial losses for the patients and state budget resulting from costs for diagnostic tests and antibacterial therapy (1,4,5). Recurrent pyelonephritis is a common severe form of febrile UTI. The annual number of cases globally has grown up to 25.9 million and approximately 10% of the recurrent pyelonephritis cases result in sepsis (4,6,7).

Over the past decade, there has been an increasing and renewed interest of the scientific community in the field of recurrent pyelonephritis. However, despite significant progress in determining the identification and management of risk factors associated with recurrent pyelonephritis, antibiotics still remain the basis of the treatment and prevention of this disease (2,5).

Hyperoxaluria, defined as urinary oxalate excretion greater than 44 mg per day, is considered a major risk factor for calcium oxalate (caOx) stone disease and a key factor for oxalate saturation (8,9). It has been demonstrated that approximately 50% of oxalate is metabolized by oxalate-degrading bacteria and 25% of oxalate is excreted unchanged (8,9). Oxalobacter formigenes was first isolated and described in 1985 by Ellison et al. So far, however, there have been only limited clinical data on the prevalence and a pathogenetic role of oxalate-degrading bacteria in the development of hyperoxaluria (10). It is also worth noting that although common coexistence between recurrent pyelonephritis and nephrolithiasis has been previously described, the mechanisms underlying this interaction have not yet been fully explored (10-12).

A team of scientists from The Institute of Nephrology of the National Academy of Medical Sciences (Kyiv, Ukraine) has been working on the problem of oxalate metabolism for over 10 years. The results of our previous studies have determined a significant prevalence (>80%) of hyperoxaluria in women with recurrent pyelonephritis (5,12,14). These findings are consistent with other research and allowed us to hypothesize the following mechanism of the interaction between pyelonephritis recurrences and hyperoxaluria (Figure 1).

Women with recurrent pyelonephritis have to take antibiotics permanently, including long-term antibiotic prophylaxis. In fact, antibiotics prevent pyelonephritis

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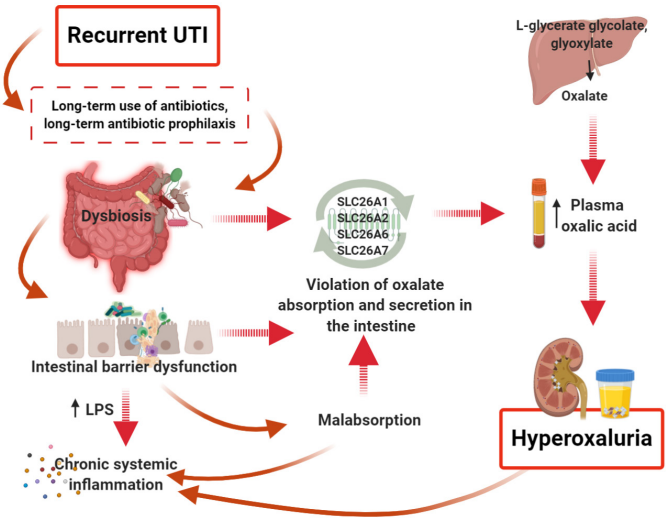

Figure 1. A proposed mechanism of the interaction between recurrent pyelonephritis and hyperoxaluria (created with BioRender.com).

recurrences. However, on the other hand, they could violate the quantitative and qualitative composition of the gut microbiota (11,13,14). Antibiotic-induced dysbacteriosis leads to increased production and accumulation of lipopolysaccharides and other toxic products of bacterial activity (P-cresol, trimethylamine-N-oxidereductase, indoxyl sulfate, etc), epithelial barrier dysfunction and increases intestinal permeability of endotoxins (11). Dysbiosis and impaired barrier function cause excessive production of cytokines and chemokines in the intestine and facilitate the translocation of the toxins, causing systemic inflammation (11,12,15). The absorption of oxalate from the intestine in a state of subclinical malabsorption, mediated by the SLC26 and SLC4 anion exchange transporters, is significantly increased leading to enteric hyperoxaluria (16). Besides, CaOx deposition in the proximal renal tubules could cause chronic inflammation with the formation of renal fibrosis (17), which may be an independent risk factor for pyelonephritis recurrences.

In turn, bacteria caused UTI might be present in oxalate deposits and potentially contribute to the development of recurrent pyelonephritis (18). Enterobacteriaceae DNA was sequenced from multiple oxalate-calcium deposits in patients with sterile urine (18). E. coli could selectively aggregate around crystals of calcium oxalate monohydrate (19). Animals inoculated with glyoxylate and E. coli had 180 times greater bacterial load in the urine compared with isolated hyperoxaluria or in the presence of pyelonephritis alone (19). Thus, hyperoxaluria increases a risk of pyelonephritis due to the predominant aggregation of bacteria around oxalate crystals and, conversely, the number of calcium oxalate deposits increases in the presence of uropathogenic bacteria (18).

Finally, it should be noted that, all extensive studies on the renal transport of oxalates, searching mechanisms for the formation of stones and their effect on PN recurrences have been conducted on the model of kidney stone disease, almost no single study exists which has been carried out on the effect of hyperoxaluria on the development and progression of recurrent pyelonephritis in non-stone-formers. Further experimental and large-scale studies are needed to clarify the interaction mechanisms and the role of hyperoxaluria in pyelonephritis recurrences.

Author's contribution

NS is the single contributor to the paper.

Conflicts of interest

The author declared no competing interests.

Ethical considerations

Ethical issues including plagiarism, double publication and redundancy have been completely observed by the author.

Funding/Support

None.

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