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NOTE

Physiology

The urinary lipid profile in cats with idiopathic cystitis

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ABSTRUCT. Although feline idiopathic cystitis (FIC) distresses of many cats, its pathogenesis is unknown and the diagnosis is challenging. Polyunsaturated fatty acids (PUFAs) are metabolized into various lipid mediators. Lipid mediators such as prostaglandins (PGs) modulate inflammation and many of them are excreted into the urine. Thus, the investigation of the urinary lipid profile may reveal pathogenesis and help diagnosis of FIC. We collected urine samples from five FIC cats by spontaneous urination and analyzed 158 types of lipid mediators in urines using liquid chromatography-mass spectrometry. The urinary levels of PUFAs were higher in FIC compared to those of the healthy group. The excretions of a major inflammatory mediator, PGD_2, were less in FIC. Other well-known inflammatory mediators such as PGE_2, PGI_2, and their metabolites did not show a difference. In contrast, the levels of $PGF_{2\alpha}$ and its 2 metabolites and $PGF_{3\alpha}$ were higher in FIC. These results may provide new insights into the future management of cat FIC.

KEYWORDS: feline idiopathic cystitis, lipid mediator, prostaglandin, urine

Feline lower urinary tract disease (FLUTD) is a collective term of diseases that cause damage and dysfunction in the lower urinary tract, bladder and urethra, of cats. The reported morbidity rate of FLUTD is 1.5–8% [9, 11, 20, 28]. Around two-thirds of FLUTD are comprised of feline idiopathic cystitis (FIC), which is characterized by bladder inflammation without any obvious etiology [9, 11, 20, 28]. FIC represents severe symptoms such as dysuria, hematuria, periuria, pollakiuria, and stranguria and they decrease the quality of life of both cats and their owners [3]. Although neuronal stimulation by stress is considered a major cause of FIC, the detailed pathogenesis remains unclear [5]. There are no other means for the definite diagnosis of FIC than excluding all of the other causes of symptoms such as infection, tumor, calculosis, and so on [11, 23, 30]. Thus, elucidation of pathogenesis and the development of diagnostic techniques are required.

Polyunsaturated fatty acids (PUFAs) are principal components of cell membranes which have more than one double bond in their carbon chain. PUFAs, such as arachidonic acid (AA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), are metabolized into various lipid mediators via non-enzymatic or enzymatic reaction by cyclooxygenase (COX), lipoxygenase (LOX), or cytochrome P450 (CYP) [7]. Lipid mediators, such as prostaglandins (PGs) and leukotrienes, are bioactive molecules that regulate inflammation [13]. The production of lipid mediators varies with the pathophysiological states of cells, and it reflects the progression or resolution of diseases.

Many lipid mediators are excreted into the urine. Several studies suggested that the profile of urinary lipid mediators can be a remarkable index and can uncover the mechanism of disease [24, 25]. In the previous study, we first analyzed urinary lipid metabolites of healthy cats and showed that the lipid production differs depending on the animal species. Their urine contained less LOX- and CYP-metabolites compared with humans and mice [17]. We next reported that infectious inflammation in the bladder increased the excretion of major inflammatory lipid metabolites of PGI_2, PGE_2, and linoleic acid in cat urine [18]. However, there are no study about whether and how FIC pathology affects lipid mediators in urine. In the present study, we comprehensively analyzed lipid metabolites in the urine of cats with FIC in order to elucidate its pathogenesis and find a novel urinary biomarker.

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The procedures for collecting samples were conducted in accordance with the guidelines of the Animal Care Committee of the University of Tokyo (approval number: P18-056). Six urine samples from clinically healthy cats and 5 samples from FIC cats were obtained from 2019 to 2020 at the Department of Veterinary Clinical Pathology and Surgery, The University of Tokyo, Tokyo, Japan and Koyama Animal Hospital, Tochigi, Japan. All urine samples were collected by spontaneous urination. Surplus urine samples remaining after the clinically routine tests have been completed were provided with informed consent from the owners. The specimens were centrifuged at 500 × *g* for 15 min and the supernatants were used. The samples were stored at −28°C for 1–11 months.

After the urine samples were centrifuged at 20,000 × *g* for 5 min, 200 µl of supernatant was mixed with 350 µl 0.1% formic acid water and 50 µl internal standard solution (Supplementary Table 1). The mixed solutions were applied to a solid-phase extraction cartridge (OASIS µElution plate, Waters, MA, USA) preconditioned with 200 µl methanol and distilled water. After washing with 200 µl distilled water and 200 µl hexane, the lipid fractions were eluted with 100 µl methanol. The 5 µl sample solution was injected into high-performance liquid chromatograph (Nexera 2, Shimadzu, Kyoto, Japan) equipped with a mass spectrometer (LCMS-8060, Shimadzu). We measured 3 types of PUFAs, 155 types of lipid metabolites, and 16 types of internal standards and analyzed using the Method Package for Lipid Mediators Version 2 with LabSolutions software (Shimadzu). Each metabolite was identified by the retention time and selected reaction-monitoring ion transition. The level of each lipid mediator in urine samples was assessed by comparing the peak area ratio calculated using the following formula: Peak area of each metabolite/peak area of internal standard.

Statistical differences were determined by the Mann-Whitney *U* test for two-group comparisons. A value of $P<0.05$ was considered statistically significant.

Sample information is presented in Supplementary Table 2. Healthy cats (two castrated males and four unspayed females, 4.2 ± 0.5 years old) recruited in this study were diagnosed as healthy based on the results of general examination. These cats had no underlying diseases or intake of medications during the urine collection. FIC cats (four castrated males and one spayed female, 4.5 ± 1.1 years old) were diagnosed as FIC by clinical signs and eliminating other causes of symptoms [22, 23, 30].

We analyzed 158 types of lipid mediators in urine using liquid-chromatography mass spectrometry. AA, EPA, DHA, and 79 types of lipid mediators were detected in 80% and more of urine samples in either healthy or FIC group (Supplementary Table 3). The detection rates of most lipids were similar between the healthy and FIC groups. Among them, the urinary levels of two PUFAs and nine lipid mediators significantly ($P<0.05$) or slightly ($0.05<P<0.06$) changed (Figs. 1–3).

As illustrated in Fig. 1, we first compared the levels of three types of PUFAs between healthy and FIC urines. The levels of AA, EPA, and DHA were slightly higher in FIC urines than healthy ones ($P=0.052$, 0.082, and 0.052, respectively). As shown in Fig. 2, the urinary levels of four COX- and one LOX-catalyzed metabolite of AA in FIC group had differences compared to healthy group ($P<0.06$). In detail, the level of PGD_2 tended to be lower in FIC urines (Fig. 2A, $P=0.052$). The levels of major inflammatory lipid mediators, such as PGI_2, PGE_2, or their metabolites did not change in FIC. Of note, the urinary levels of $PGF_{2\alpha}$ ($P=0.017$) and its two sequential metabolites ($P=0.052$ and 0.039) were significantly or slightly higher in common in FIC urines compared to healthy ones (Fig. 2B–D). The LOX-mediated metabolite of AA, 5(S),6(R)-lipoxin A_4, was also increased in FIC urines (Fig. 2E, $P=0.030$).

Other lipid mediators were increased in the urine of FIC (Fig. 3). The level of a COX metabolite of EPA, $PGF_{3\alpha}$, was higher in FIC urine (Fig. 3A, $P=0.045$). The inactive form of platelet-activating factor (PAF), lyso-PAF, was also significantly increased in FIC urine compared to healthy one (Fig. 3B, $P=0.017$). The levels of the two types of DHA metabolites were changed. The 10-hydroxy-4Z,7Z,11E,13Z,16Z,19Z-docosahexaenoic acid (10-HDoHE) level was slightly higher (Fig. 3D, $P=0.054$) while that of the resolvin D_2 level was lower in FIC urines compared to healthy ones (Fig. 3C, $P=0.056$).

Our results revealed that how the urinary lipid profile changed due to FIC. The level of three types of PUFAs, AA, EPA, and DHA, were higher in FIC urines than the healthy ones. Of interest, while the excretion of major inflammatory lipid mediators did not change, the levels of $PGF_{2\alpha}$ and its two types of metabolites were significantly higher in FIC urines.

Bladder epithelial cells contain some types of PUFAs [36]. FIC disrupts glycosaminoglycan coverage and damage bladder epithelial cells [3]. Therefore, the increase of three types of PUFAs in FIC urines might reflect the epithelial cell damages and direct release of PUFAs into urines.

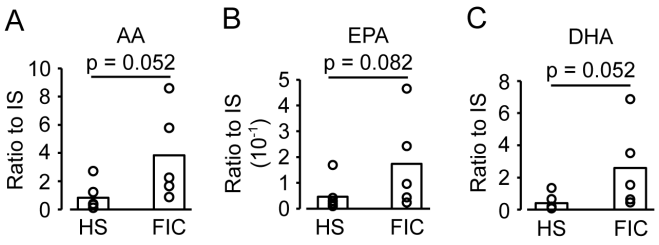

Fig. 1. The urinary levels of polyunsaturated fatty acids (PUFAs). The levels of (**A**) arachidonic acid (AA), (**B**) eicosapentaenoic acid (EPA), and (**C**) docosahexaenoic acid (DHA) in urines of healthy (HS) or idiopathic cystitis (FIC) cats. The values are represented as a ratio to internal standards (IS). Each dot means the value of each cat. The height of bar represents average value of each group.

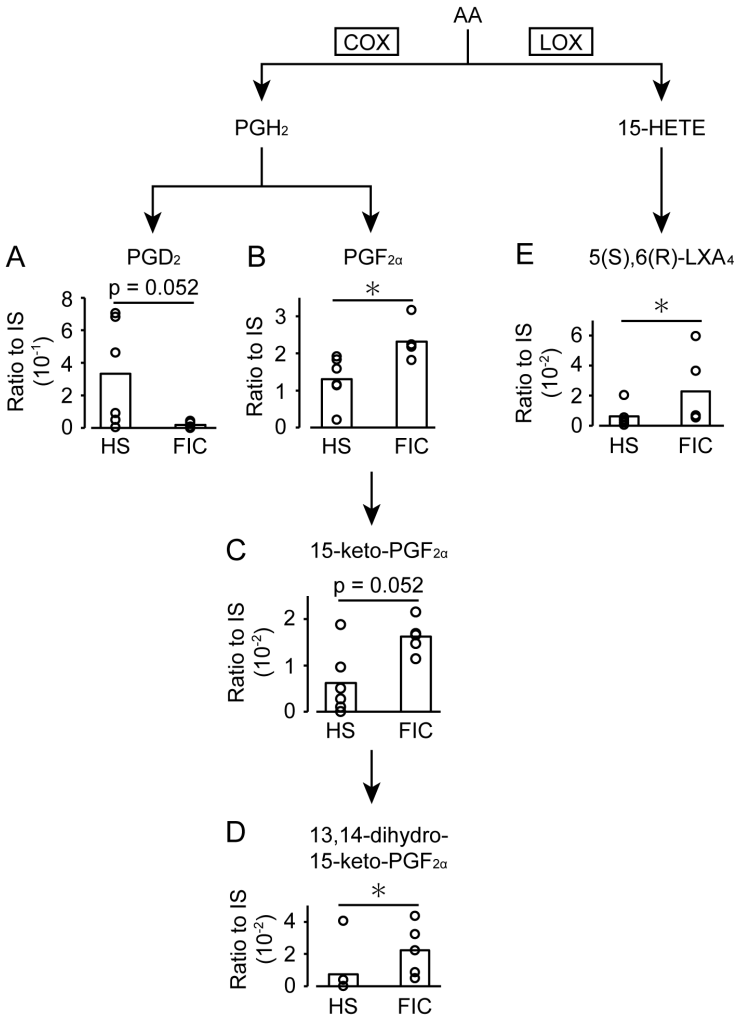

Fig. 2. The levels of arachidonic acid (AA) metabolites. (A–E) The levels of AA metabolites in urines of healthy (HS) and idiopathic cystitis (FIC) cats *P*-values of which are <0.06. The values are represented as a ratio to internal standards (IS). Each dot means the value of each cat. The height of the bar represents the average value of each group. Indicated names of enzymes are those which catalyze each metabolic reaction. *: $P<0.05$ compared between healthy and FIC group. COX, cyclooxygenase; LOX, lipoxygenase; PG, prostaglandin; HETE, hydroxyeicosatetraenoic acid.

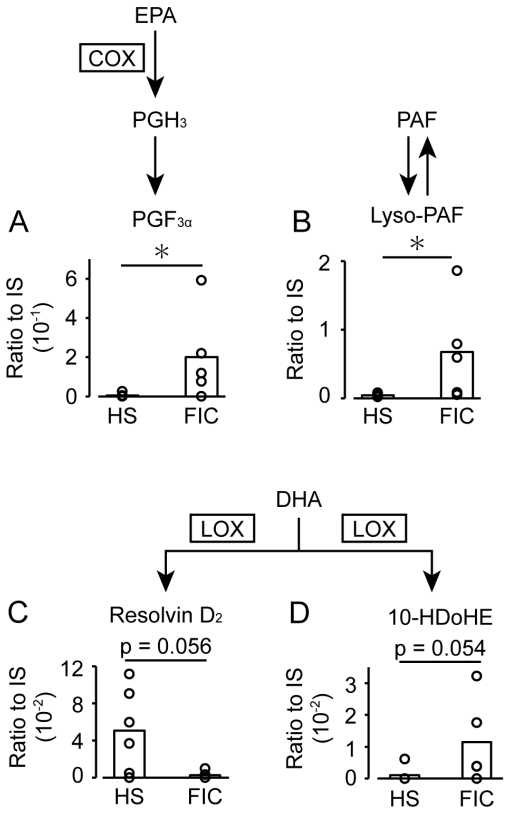

Fig. 3. The levels of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) metabolites and lyso- platelet-activating factor (PAF). The levels of (**A**) $PGF_{3\alpha}$, (**B**) lyso-PAF, (**C**) Resolvin D_2, and (**D**) 10-HDoHE in urines of healthy (HS) and idiopathic cystitis (FIC) cats, with *P*-values <0.06. The values are represented as a ratio to internal standards (IS). Each dot means the value of each cat. The height of the bar represents the average value of each group. Indicated names of enzymes are those which catalyze each metabolic reaction. *: $P<0.05$ compared between healthy and FIC group. EPA, eicosapentaenoic acid; COX, cyclooxygenase; PG, prostaglandin; PAF, platelet-activating factor; DHA, docosahexaenoic acid; LOX, lipoxygenase; HDoHE, hydroxydocosahexaenoic acid.

PGD_2, PGE_2, and PGI_2 are major well-known inflammatory mediators. They have the potentials to promote vasodilation, leukocyte migration, and pain in inflammation [8, 14, 16]. Previous reports showed that excretions of these lipid mediators are increased in various types of inflammatory diseases of humans as well as animals [2, 24, 34]. Therefore, also in FIC, these inflammatory mediators are anticipated to increase in urine. However, they did not increase in the urines of FIC. The current observations imply that the pathological condition in the bladder of FIC cats is distinct from typical inflammation. Although non-steroidal anti-inflammatory drugs (NSAIDs), inhibitors of PG synthesis, were used to ameliorate inflammatory diseases, they were reported to be ineffective for FIC [10, 27]. Our finding might explain the ineffectiveness of NSAIDs against FIC.

$PGF_{2\alpha}$ and $PGF_{3\alpha}$ are increased in FIC urine. Both metabolites are produced by the aldo-keto reductase 1 (AKR1) enzyme family or 9-keto PGE_2 reductase (9KPGR) [12]. These observations imply the upregulation of PGF synthases in FIC. Although expressions of COX1 and COX2 were reported to be elevated in the bladder or urethra of FIC cats, those of AKR1 and 9KPGR remain to be studied [19]. Further investigations are needed to reveal the expression of these enzymes in the feline bladder.

$PGF_{2\alpha}$ contracts the smooth muscle of the uterine as well as the bladder of a pig, guinea pig, and humans [1, 4, 6, 33]. The increase of $PGF_{2\alpha}$ and its metabolites might change the motility of the bladder and contribute to the progression of FIC. Except for luteal regression during pregnancy in a mammal, few reports are showing that the endogenous $PGF_{2\alpha}$ production is involved in some kinds of pathophysiological condition [31]. Previously, we showed that urinary $PGF_{2\alpha}$ and/or its metabolites were increased in mice and humans with dermatitis, and the expressions of COX2 and AKR1 were upregulated in thickened murine keratinocyte

[26]. Dermatitis is characterized by barrier dysfunction with activated epidermal nerves [35]. FIC is also considered to damage epithelium by neuronal stimulation [3]. This similarity suggests that $PGF_{2\alpha}$ can be a responsive marker to such conditions that epithelium is damaged involving neuronal activity.

Some of the other bioactive lipid mediators showed changes. 5(S),6(R)-lipoxin A_4 is reported to have an anti-inflammatory and pro-resolving property in several inflammatory diseases [15, 21, 37]. PAF is known to act as a promoter of broad inflammatory processes [29]. The bioactivity of 10-HDoHE is unelusive. Resolvin D_2 is a well-known anti-inflammatory and pro-resolving lipid mediator [32]. The pathophysiological implication and mechanisms of these changes in urinary lipid mediators are unknown. Further investigations are required to reveal these points.

Bacterial cystitis is another cystitis that frequently occurred in cats and must be distinguished from FIC. We previously analyzed urinary lipid profile of cats with bacterial cystitis [18]. Consistently with the current expectation that damaged epithelium releases PUFAs into the urine, the levels of AA, EPA, and DHA have significantly higher in the urines of cats with bacterial cystitis. In contrast, the urinary levels of PGE_2, PGI_2, and their metabolites, linoleic acid metabolites were significantly higher in urines of bacterial cystitis, suggesting relatively broad inflammation of the bladder. These differences may help to distinguish between infectious and idiopathic cystitis and may provide some implication of their pathology.

There is some limitation to this study. The production and metabolism of lipids are affected by some factors including diet and medication. The procedure of urine collection also affects the detection of urinary lipid mediators. Spontaneously excreted urine contains lipids produced in the urethra, while catheterized and punctured urine does not. In contrast, catheters could increase lipid release by stimulating the epithelium of the urethra. Since some cats have difficulty in urination due to cystitis, the optimal urine collection method must be selected for FIC diagnosis.

In conclusion, our findings revealed several lipid mediators remarkably changes in the urines of FIC cats compared to healthy ones. Although broad changes in major inflammatory lipid mediators were not observed, the levels of $PGF_{2\alpha}$ and its metabolites represent a characteristic increase in FIC urine. These results will provide a new insight for future diagnosis and unveil the mechanisms of FIC.

POTENTIAL CONFLICT OF INTEREST. The authors have no conflicts of interest relevant to the content of this article.

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