gavage (24.94 ± 9.4 vs 6.85 ± 3.0 umol/day, $p<0.001$) while uncolonized RYGB animals showed no significant difference in urinary oxalate (17.2 ± 4.2 vs 14.0 ± 3.3, $p=0.62$). Compared to sham, the RYGB procedure increased intestinal tissue permeability of oxalate by 36% and transcellular [14C]-oxalate net secretion more than 2-fold. When compared to non-colonized RYGB, RYGB + OXWR animals had 46% increase in net oxalate efflux with no significant changes in tissue permeability.

CONCLUSIONS: In our model, RYGB-related hyperoxaluria can be reduced to that of sham controls by OF colonization because of a dual action of the bacteria. OF colonization enhanced net secretion of oxalate across the large intestine. Because intestinal permeability was similar between both RYGB groups, the mechanism for this change in urinary oxalate appears to be primarily due to luminal oxalate degradation by OF resulting in a reduction of passive oxalate absorption across the distal colon. This in vivo study suggests that OF colonization may benefit RYGB patients with hyperoxaluria and warrants a clinical trial in patients.

Source of Funding: NIH, AUA Foundation, Astellas Global Development, Ethicon Endo-Surgery.

MP33-04

HETEROGENEOUS NUCLEATION DRIVES THE FORMATION OF NON-CALCIUM URINARY STONES IN HUMANS AND *DROSOPHILA MELANOGASTER*

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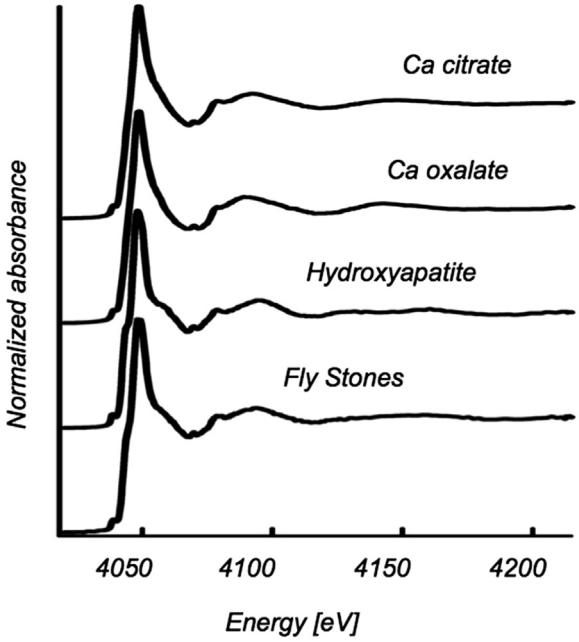
INTRODUCTION AND OBJECTIVES: Heterogeneous nucleation is the process whereby calcium hydroxyapatite is thought to serve as a nidus for nephrolithiasis formation. This nucleation process is not traditionally held to be important for most non-calcium stones. Xanthine stones have been described as being composed entirely of xanthine. We applied a *Drosophila* model for xanthinuria renal stones to test the hypothesis that heterogeneous nucleation may be equally important for non-calcium based nephrolithiasis.

METHODS: We utilized the GAL4-UAS targeted gene knockdown system to create a single gene knockdown model for xanthinuria in *Drosophila melanogaster*. Fly stone samples were collected and compared to human stones collected from a patient with xanthinuria type I utilizing inductively coupled plasma optical emission spectroscopy (ICP-OES) as well as Fourier transform infrared spectroscopy (FTIR). Fly stones were analyzed for the presence of hydroxyapatite utilizing a bisphosphonate stain as well as synchrotron radiation based analyses.

RESULTS: Upon xanthine dehydrogenase (*Xdh*) inhibition, flies formed significant tubule stones, confirming a similar phenotype compared to human xanthinuria type I. FTIR confirmed the presence of xanthinuria in both human and fly stones. ICP-OES demonstrated that in fly stones, calcium, magnesium, and zinc were present in a 4:2:1 ratio ($p<0.01$) measured by percent of total composition. This ratio was preserved in human xanthine stones. The presence of hydroxyapatite in fly stones was confirmed with a bisphosphonate dye stain as well as micro X-ray absorption near edge spectroscopy (μXANES) (Figure 1).

CONCLUSIONS: The significant presence of calcium compared to other divalent cations in both fly and human xanthine stones supports the idea that "pure" non-calcium kidney stones are not homogeneous in nature as previously reported in the literature. Hydroxyapatite's ubiquitous presence in fly stones supports the idea that heterogeneous nucleation plays an important, previously unrecognized role in the initiation of not just calcium based nephrolithiasis, but potentially all kidney stones. The implication of this finding is that disrupting a universal pathway leading to renal stone formation of all types may be a therapeutic strategy for the treatment of nephrolithiasis.

Figure 1: Micro X-ray absorption near edge spectroscopy (μXANES) demonstrates the presence of hydroxyapatite in fly xanthine stones.



Source of Funding: This research was supported by the NIH NIDDK RFA-DK-12-003: Planning Centers for Interdisciplinary Research in Benign Urology (IR-BU) (P20), K12-DK-07-006: Multidisciplinary K12 Urologic Research Career Development Program. This work was also supported in part by a grant from the AUA Foundation Research Scholars Program and Boston Scientific Corporation, The Endourological Society, and the "Friends of Joe."

MP33-05

IN VITRO STUDY ON URETERAL SMOOTH MUSCLE CONTRACTILITY WITH TAMSULOSIN, NIFEDIPINE, AND TERPENE MIXTURE (ROWATINEX¢Ç)

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INTRODUCTION AND OBJECTIVES: The aim of this study was to evaluate whether tamsulosin, an alpha-blocker, has an effect on decreasing spontaneous ureteral contractility with or without phenylephrine, an alpha-agonist. Additionally, nifedipine, terpene mixure (Rowatinex¢ç) were tested and compared with each other.

METHODS: We obtained ureteral segments from freshly killed eight-week-old rabbits. Preparation was performed in aerated Krebs buffer (95% oxygen and 5% carbon dioxide) at a constant temperature of 37°. All segments were suspended into organ tissue baths containing aerated Krebs buffer using stainless steel hangers and clips. The ureter divided into four segments; upper, middle, low and uretero-vesical junction. Each ureteral segment was suspended longitudinally and circularly by opposite corners, respectively. Tamsulosin, nifedipine, and terpene mixture were separately applied into the segments. Contractile activities of each drug was recorded and analyzed by PowerLab data acquistition system (AD instruments CO., USA). Area under the curve was compared between before and after each drug application for each 5 minutes with or without pheylephrine. Statistical analysis was performed using the unpaired Student's t test.

RESULTS: Under Krebs solution, ureteral smooth muscle Contractility was significantly decreased in all segments over 10-6M in tamsulosin, 10-7M in nifedipine and 0.001x1 concentrations in terpene mixture (p=0.038). However, under Krebs solution with 10-5 M phenylephrine, there was no significant difference at all concentrations in tamsoluin and nifedipine. In contrast to tamsulosin and nifedipine, there was a significant decrease in ureteral smooth muscle Contractility in most of segments at 0.01x1 concentrations (p=0.042) in terpene mixture.

CONCLUSIONS: Tamsulosin, nifedipine, and terpene mixture showed the effect on spontaneous ureteral contractility. In particular, terpene mixture might have the better effect on decreasing ureteral smooth muscle contractility.

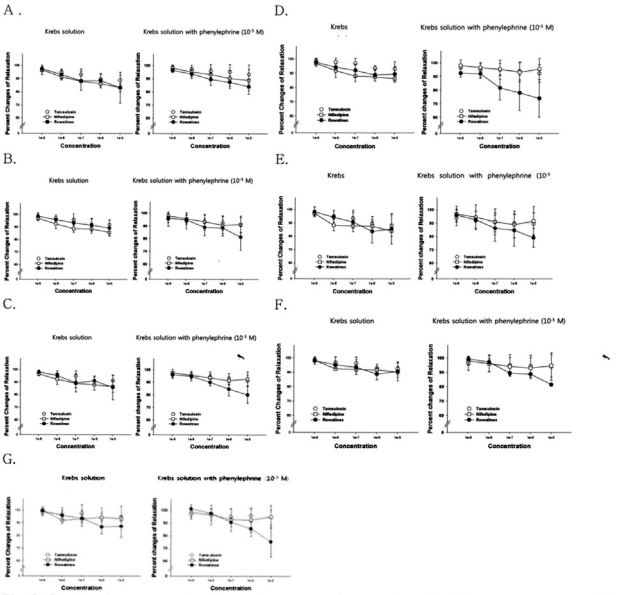

Fig. 2. Graphs of concentration-dependent contractions produced by four segments; upper (A, D), middle (B, E), low (C, F) and ureterovesical junction (G). Each ureteral segment was suspended longitudinally (A, B, C) and circularly (D, E, F) by opposite corners, respectively.

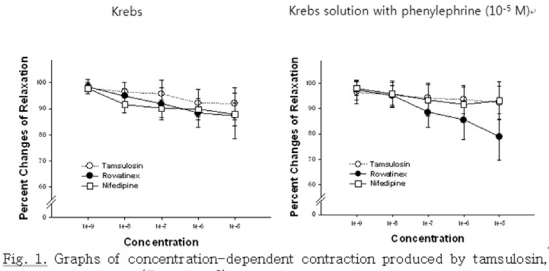

Fig. 1. Graphs of concentration-dependent contraction produced by tamsulosin, nifedipine, and terpene mixture (Rowatinex®) ureteral segments in eight-week-old rabbits.

Source of Funding: none

MP33-06

A NEW PORCINE MODEL OF ENTERIC HYPEROXALURIA MIMICS EFFECTS OF HIGH OXALATE ABSORPTION IN HUMANS

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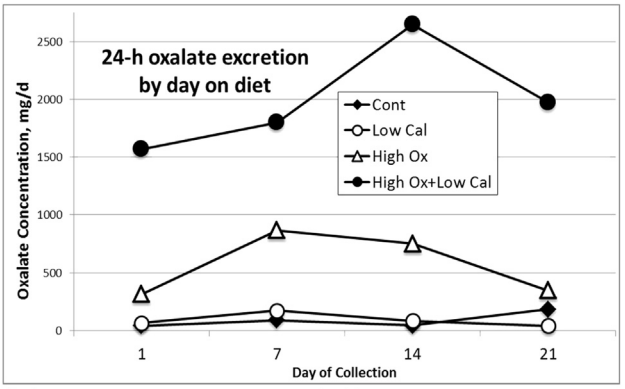
INTRODUCTION AND OBJECTIVES: Adult swine can be made to manifest hyperoxaluria and calcium oxalate stone formation with a diet enriched with hydroxyproline, an oxalate precursor, to emulate primary hyperoxaluria (Sivalingam *et al*, 2013; Patel *et al*, 2012). In an effort to emulate enteric hyperoxaluria, a more common condition in humans, we examined whether pigs would respond similarly to an oxalate-rich diet.

METHODS: With IACUC approval, we randomized 32 gilts (adult, virgin sows) to 1 of 3 dietary treatments: high-oxalate/normal-calcium; high-oxalate/low-calcium; or normal-oxalate/low-calcium. Oxalate was provided as sodium oxalate. A fourth group was fed the usual adult sow diet. The high- and normal-oxalate diets provided approx. 8,100 and 1,110 mg oxalate/d, respectively. The normal- and low-calcium diets provided 13,000 and 4,000 mg calcium/d respectively. Animals were treated up to 21 d. Foley catheters were inserted for 24-h urine collections. Fecal “grab” collections were made at time points throughout the intervention. Animals were sacrificed at various time points. Urinary oxalate excretion from 24-h urine collections and fecal oxalate was compared within and between groups.

RESULTS: Gilts fed the high-oxalate diets achieved the highest urinary oxalate excretion (figure); this effect was significantly potentiated when dietary calcium was reduced. Fecal oxalate excretion, presumably representing unabsorbed gastrointestinal oxalate, was highest in the high-oxalate/normal-calcium treated gilts and lower in those with reduced calcium. H&E and Yasue staining revealed crystals in cortical and medullary regions of renal tubules (which were birefringent upon polarization), inflammation, and fibrosis in oxalate-treated gilts. No such sequelae were observed in gilts fed the normal adult sow diet.

CONCLUSIONS: Adult female pigs, closely related to humans for renal function and urinary tract physiology, are useful in studying hyperoxaluria and oxalate-related pathologies. We have previously defined dietary methods that induce increased endogenous oxalate synthesis and now, in the current study, enteric hyperoxaluria. Pigs demonstrate similar renal pathology to humans who have hyperoxaluria and can be made to form calcium oxalate stones via methods that increase either oxalate synthesis or absorption. Work is underway to further characterize the effects of hyperoxaluria and oxalosis in this porcine (swine) model and to identify specific calcium oxalate-related human conditions for which future porcine studies may be designed.



Day 1:
Control v. high oxalate, P=0.041
Control v. high oxalate/low calcium, P<0.0001
Low calcium v. high oxalate/low calcium, P=0.028
High oxalate v. high oxalate/low calcium, P=0.013

Day 7:
Control v. high oxalate/low calcium, P=0.004
Low calcium v. high oxalate/low calcium, P<0.0001
High oxalate v. high oxalate/low calcium, P<0.0001

Day 14:
Control v. low calcium, P=0.009
Control v. high oxalate, P=0.010
Control v. high oxalate/low calcium, P<0.0001
Low calcium v. high oxalate, P<0.0001
Low calcium v. high oxalate/low calcium, P<0.0001
High oxalate v. high oxalate/low calcium, P=0.022

Day 21:
Control v. high oxalate/low calcium, P=0.018
Low calcium v. high oxalate, P=0.005
Low calcium v. high oxalate/low calcium, P<0.0001
High oxalate v. high oxalate/low calcium, P=0.012

Source of Funding: UW-Madison Clinical and Translational Science Award program, NCATS grant UL1TR000427 (awarded to KLP)