Fiscal Year:	FY 2016	**Task Last Updated:**	FY 05/01/2017
PI Name:	Kassemi, Mohammad Ph.D.		
Project Title:	Integrated Medical Model		
Division Name:	Human Research		
Program/Discipline:	HUMAN RESEARCH		
Program/Discipline--Element/Subdiscipline:	HUMAN RESEARCH--Operational and clinical research		
Joint Agency Name:		**TechPort:**	Yes
Human Research Program Elements:	(1) **ExMC**:Exploration Medical Capabilities		
Human Research Program Risks:	(1) **Medical Conditions**:Risk of Adverse Health Outcomes and Decrements in Performance Due to Medical Conditions that occur in Mission, as well as Long Term Health Outcomes Due to Mission Exposures (2) **Renal Stone**:Risk of Renal Stone Formation		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
PI Email:	mohammad.kassemi@nasa.gov	**Fax:**	FY 216-433-5033
PI Organization Type:	NASA CENTER	**Phone:**	216-433-5031
Organization Name:	NASA Glenn Research Center/Case Western Reserve University		
PI Address 1:	NASA Glenn Research Center		
PI Address 2:	21000 Brookpark Road, MS110-3		
PI Web Page:			
City:	Cleveland	**State:**	OH
Zip Code:	44135	**Congressional District:**	10
Comments:	NOTE (Dec 2019): former affiliation included National Center for Space Exploration Research (NCSER), per information from J. McQuillen/GRC		
Project Type:	Ground	**Solicitation / Funding Source:**	Directed Research
Start Date:	01/01/2011	**End Date:**	12/31/2015
No. of Post Docs:	0	**No. of PhD Degrees:**	0
No. of PhD Candidates:	0	**No. of Master' Degrees:**	0
No. of Master's Candidates:	0	**No. of Bachelor's Degrees:**	0
No. of Bachelor's Candidates:	1	**Monitoring Center:**	NASA JSC
Contact Monitor:	Antonsen, Erik	**Contact Phone:**	281.483.4961
Contact Email:	erik.l.antonsen@nasa.gov		
Flight Program:			
Flight Assignment:	NOTE: End date is 12/31/2015 per D. Griffin/GRC (Ed., 11/18/15) NOTE: Title change to "Integrated Medical Model - Renal Stone Module" and end date change to 12/15/2015 per M. Urbina/JSC (Previous title "Probabilistic Analysis of Renal Stones in US Astronauts")--Ed., 10/8/15 NOTE: End date change per M. Urbina/JSC and PI (Ed., 9/17/15) NOTE: Addition of ExMC 4.13 Gap per IRP Rev E (Ed., 3/19/14) NOTE: End date shows as 5/31/2015 per JSC MTL dtd 12/28/12 (Ed. 1/25/13) NOTE: End date is 8/8/2014, per D. Griffin/GRC (Ed., 5/30/12)		
Key Personnel Changes/Previous PI:	NOTE: Previous PI was Jerry Myers until January 2011. See project with title "Probabilistic Analysis of Renal Stones in US Astronauts" and PI=Myers for previous information.		
COI Name (Institution):	Myers, Jerry (NASA Glenn Research Center)		
Grant/Contract No.:	Directed Research		

Performance Goal No.:	
Performance Goal Text:	
Task Description:	The Exploration Medical Capability Element of the Human Research Program carries the risk of not being able to treat ill or injured crewmembers. Gap 4.13 in the Exploration Medical Capability Research Plan is the “Lack of lithotripsy or other capability to treat a renal stone.” The description of this gap states that, “Given the high probability of kidney stone formation in crew members during long duration missions the capability to perform Lithotripsy is highly desirable.” During all spaceflight missions to date, renal stone incidence is actually lower than what would be expected in the general population or in the analog population utilized by the Lifetime Surveillance of Astronaut Health (LSAH). After astronauts return to Earth, however, the incidence rate increases and surpasses both the rate of the general population and the LSAH analog population, with the astronaut incidence rate of calcium oxalate stones approximately doubling that of the general US population. If these trends persist with the reintroduction of even fractional gravity, renal stones during a Mars mission could become a serious problem, not only in terms of astronaut health, but also in terms of the resources required to adequately treat the condition. A Bayesian update analysis of the data above suggested an approximately 5% probability of at least one crewmember developing a renal stone during a Mars mission. Given the nature of these data, the Glenn Research Center (GRC) Integrated Medical Model (IMM) team developed a proof of concept probabilistic simulation of renal stone formation during a long duration exploration mission. While somewhat limited in scope, this simulation included both probabilistic and deterministic components. The deterministic components were developed to support the probabilistic analysis. Key findings from this work included: 1) As the stone grows larger, the governing equation says the rate of growth will increase, which is why the probabilistic analysis picks up the seed size as being influential. 2) The probabilistic model demonstrates identical sensitivity for Calcium and Oxalate, suggesting that a more detailed surface chemistry simulation needs to be conducted. 3) The sensitivities for the dwell time of a stone show pronounced differences between the 2.0 L/day and 2.5 L/day cases resulting in a 68.6% change in the probability of one stone reaching the effective diameter of a nephron from heterogeneous growth only. This result has a standard deviation of 0.237. As part of the validation process for this module, the task underwent a subject matter expert review of the work done to date. The review was favorable with indication that an increase model fidelity was required, as outlined in Steps 1-3 below. 1. Determine expected incidence rate of renal stones during exploration missions and how this rate is affected by new countermeasure activities. 2. Provide a probabilistic simulation that allows the Exploration Medical Capabilities Element of the Human Research Program to develop medical kits appropriate to the level of risk of renal stone formation. 3. Provide a probabilistic simulation that allows the Exploration Medical Capabilities Element of the Human Research Program the ability to quantitatively evaluate the effect of different operations scenarios on the ability of a given medical kit to adequately treat an ill or injured crew member. The GRC IMM task team is currently working to extend the capabilities of the deterministic model used as the parameter integration function to include both promoters, inhibitors, agglomeration, wall interaction effects, and gravity components. Once this is matured, it will be wrapped with a probabilistic simulation representing the scenarios and physiological parameter variation typical of spaceflight to assess the likelihood of renal stone formation. Once completed, The Renal Stone Formation Simulation Module (RSFSM) will provide a state-of-the-art computational capability that can not only be used to more directly investigate the renal stone size distributions and the statistical propensities for developing a critical stone incident for future mission scenarios but also help to devise and evaluate different systematic chemical or physical intervention countermeasures for preventing their occurrence in future.
Rationale for HRP Directed Research:	This research is directed because it contains highly constrained research, which requires focused and constrained data gathering and analysis that is more appropriately obtained through a non-competitive proposal.
Research Impact/Earth Benefits:	Nephrolithiasis constitutes as one of the most common diseases that has afflicted man for centuries. Indeed, one of the first evidences of renal stones in humans was found in an Egyptian mummy at El- Amrah dating back to 4800 B.C. Today, approximately 5% of the U.S. population develops clinically significant urinary calculi in their lifetime. However, renal stone disease is not only a concern on Earth, but could conceivably pose as a serious risk to the astronauts’ health and safety in space. The physiological, environmental, and dietary conditions imposed by space travel and weightlessness can easily increase this risk as a recent survey of renal stone formation in U.S. astronauts has revealed 14 recorded episodes. Russian medical science investigators have also noted multiple stone events among the Soviet cosmonauts. The most serious one was an in-flight renal stone occurrence that nearly caused the the Russian mission to be aborted. The Renal Stone Formation Simulation Module (RSFSM) developed as part of this task is designed to inform NASA's Integrated Medical Model (IMM) with the likelihood and associated uncertainty of astronauts developing kidney stones upon long-term exposure to microgravity, as well as upon re-entry to a gravitational field. The computational module will be able to assess the effects of various design reference mission scenarios, thus allowing mission planners, medical kit designers, and clinicians to compare the efficacy of various countermeasures devised to reduce the probability of developing renal stone incident during the mission. The understanding that these simulations provide will also help to improve the astronauts' screening protocols. The benefits of developing this computational capability is not limited to space applications but will extend back to impact clinical and scientific medicine on Earth. As a state-of-the-art research tool and virtual hypothesis-tester, RSFSM will expand the current level of understanding of renal stone disease. It will also serve as a tool to help improve clinical procedures for screening and treating nephrolithiasis on Earth and devise physical and/or pharmaceutical

interventions to help the nearly 15 million Americans who currently suffer from this ailment today.

Task Progress:

In this work analytical Population Balance Equation (PBE) and Computational Fluid Dynamics (CFD) models were developed to predict the steady state size distribution of nucleating, growing, and agglomerating calcium oxalate (CaOx) renal calculi during their transit through the kidney in 1g and microgravity based solely on the renal biochemical profile of the subject as input. The PBE model was verified through comparison with the published results provided by several MSRPP crystallization experiments including an in-vitro calcium oxalate experiment related to renal stone formation with excellent agreements.
For the PBE renal stone formation simulation studies, four subjects were considered based on their published 1g and microgravity biochemical profiles, namely -- 1g normal, microgravity astronaut, and 1g recurrent and microgravity stone-formers. Parametric simulations were performed to assess the impact of alterations in renal biochemistry of the astronauts due to microgravity exposure on the risk of critical CaOx renal stone formation during long duration missions and to quantify the efficacy of using citrate and pyrophosphate dietary supplements and increased hydration as possible countermeasures for reducing this risk.

Through comprehensive numerical case studies performed by the PBE model the following assessments were made:

1. The PBE model was successful in clearly distinguishing between a 1g normal and a 1g recurrent stone-former based on their published 24 hr urine biochemical profiles.

2. The predicted CaOx crystal aggregate size distribution for a microgravity astronaut were closer to those of a recurrent stone-former on Earth than a normal risk free subject in 1g underscoring the detrimental effect of space altered renal biochemistries.

3. Due to microgravity renal biochemical alterations, the increase in risk level for developing renal stone in microgravity was relatively more significant for a normal person going to space than a stone former. However, numerical predictions also clearly underscore that the stone-former subject has still by far the highest absolute risk of critical stone formation during space travel.

4. For stone-formers both on Earth and in Space depletion of calcium and oxalate is an important factor to be considered. This points to the shortcoming of the relative supersaturation levels determined by the 24 hr urine measurements performed distal to the growth process as a definitive measure of the risk.

5. Agglomeration was found to be a crucial mechanism for stone size enhancement both in 1g and microgravity.

6. Citrate was found to be an effective inhibitor of both growth and agglomeration. Our numerical predictions indicate that urine, due to its normal citrate content, is already, to a large extent, inhibited against growth and agglomeration of CaOx crystals. Any additional increase in citrate beyond its average normal urinary levels on Earth through dietary supplements is beneficial but only to a limited extent. However, the model also predicts that any decline in the citrate levels during space travel below its normal urinary values on Earth could easily move the microgravity astronaut subject into the stone-forming risk category. So the current results strongly recommend for use of citrate as a dietary countermeasure to prevent the adverse effect of any space-induced hypocitraturia during the future missions.

7. Pyrophosphate was also found to be an effective direct inhibitor of growth. Results indicate that minimal pyrophosphate concentrations in urine can move the maximum CaOx aggregate size predicted for the microgravity astronaut from a near critical value of 140 microns to a definitively safe range below 10 microns. These promising predictions suggest that more comprehensive experimental assessment of use of pyrophosphate and other similar inhibitors such as phytic acid, and osteopontin as dietary countermeasures for the space program are warranted.

8. Hydration can act as an effective promoter or inhibitor of renal stone development in 1g and microgravity. Our results indicate that dehydration during space travel that may cause astronaut urinary volumes below 1.5 liters/day can easily move a preflight non-stone-former to the population densities and renal stone size ranges resembling the 1-g recurrent stone formers. Augmented hydration levels that produce up to 3 liters/day urinary output were also simulated and numerical results indicate that urinary volumes from 2.5 - 3 liters/day can serve as an excellent and effective countermeasure. Thus based on our results, a ½ liter increase in urine output from the current guideline level of 2.0 liters/day to 2.5 liters/day is recommended because it is predicted that it will provide considerable inhibitive benefits, moving the astronaut well into a risk free range.

In this work, we only investigated the effect of variation in the direct inhibitive action by citrate and pyrophosphate. For the citrate case there is also an indirect inhibition due to speciation. This contribution was included in our model only at a fixed level representative of a standard urine biochemistry. In order to consider the impact of indirect inhibition as a function of citrate concentration, the use of speciation codes such as JESS or Equil2 is required to account for the bounding of calcium ions with citrate in forming soluble complexes that lowers the supersaturation levels of CaOx. Coupling of JESS computations with the current PBE renal stone model will be undertaken as part of our ongoing work in this area with the goal of providing a more comprehensive assessment of both direct and indirect inhibition potentials of the citrate and hydration countermeasures in near future.

There are two main factors that will determine whether a critical stone incident will occur or not. First is the renal biochemistry that dictates the rate of stone size enhancement due to growth and agglomeration and the second is the residence time of renal calculi that is determined by their transport through the nephron by the urinary flow. The lag that might occur due to nonslip boundary condition (in both 1g and microgravity) or due to gravity effects in upward flowing tubules (only in 1g) or due to nucleation and growth on Randall plaque surfaces or on injured sections of the nephron could not be included in the present “lumped” PBE transport analysis.

In order to consider these important transport effects, a two-phase PBE-CFD Renal Calculi Formation & Transport model was developed by coupling the PBE for nucleating, growing, and agglomerating renal calculi to a CFD model that solves for flow of urine, conservation of species, and transport of renal calculi in the nephron using a Eulerian two-phase mathematical framework.

Parametric simulations were performed using the PBE-CFD model to study steady state stone size and volume fraction distributions in the four main sections of the nephron under weightlessness conditions. These sections are: the tubule (distal, tube of Henle, proximal); the Inner Medullary Collecting Duct (IMCD); the Outer Medullary Collecting Duct

	(OMCD); and the Duct of Bellini (DoB). The CFD results reiterated that agglomeration has a profound effect on the renal stone size distributions by decreasing the population of smaller stones and increasing the number and sizes of the larger stones in all four segments of the nephron. More importantly, it was found that due to the retarding effect of the wall on the urinary flow, the volume fraction of the CaOx crystals is dramatically increased at the walls of tubule and IMCD segments. Thus for these first two nephron segments, a mixed-suspension mixed-product removal (MSMPR) continuous crystallizer model as adopted by many of the previous theoretical work is not valid. Our numerical results further show that mixing due to the cascading transition between the nephron segments produces quite uniform volume fraction distributions in the OMCD, and DoB nephron segments. Simulations using measured astronaut urinary calcium and oxalate concentrations in microgravity as input indicate that under nominal conditions the largest stone sizes developed in Space will be still considerably below the critical range for problematic stone development. However, our results also imply that since the highest stone volume fraction occurs next to the tubule and duct walls, there may be an increased propensity for wall adhesion, for example, on existing Randall Plaque surfaces or injured sections of the nephron, with a greater risk of evolution towards critical sizes. More detailed CFD models that can rigorously capture the urine-crystal-wall interactions are needed to provide a deeper understanding of renal stone formation that leads to a critical retention scenario.
Bibliography Type:	Description: (Last Updated: 03/08/2022)
Abstracts for Journals and Proceedings	Kassemi M, Thompson D, Goodenow D, Gokoglu S, Myers J. "Effect of Dietary Countermeasures and Impact of Gravity on Renal Calculi Size Distributions Predicted by PBE System and PBE-CFD Models." Exploration Medical Capability Session, 2016 NASA Human Research Program Investigators' Workshop, Galveston, TX, February 8-11, 2016. 2016 NASA Human Research Program Investigators' Workshop, Galveston, TX, February 8-11, 2016. , Feb-2016
Abstracts for Journals and Proceedings	Kassemi M, Thompson D, Goodenow D, Gokoglu S, Myers J. "Coupled CFD-PBE Prediction of Renal Stone Size Distributions in the Nephron under Weightlessness and Upon Reentry into a Gravitational Field." Presented at ExMC session, 2017 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 23-26, 2017. 2017 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 23-26, 2017. , Jan-2017
Articles in Peer-reviewed Journals	Kassemi M, Griffin E, Thompson D. "Numerical assessment of CaOx renal calculi development in space using PBE coupled to urinary flow and species transport." Int J Heat Mass Transf. 2018 Jun;121:1146-58. Epub 2018 Mar 7. https://doi.org/10.1016/j.ijheatmasstransfer.2018.01.035 , Jun-2018
Articles in Peer-reviewed Journals	Kassemi M, Thompson D. "Prediction of renal crystalline size distributions in space using a PBE analytic model. 1. Effect of microgravity-induced biochemical alterations." Am J Physiol Renal Physiol. 2016 Sep 1;311(3):F520-30. Epub 2016 Jun 8. http://dx.doi.org/10.1152/ajprenal.00401.2015 ; PubMed PMID: 27279490 , Sep-2016
Articles in Peer-reviewed Journals	Kassemi M, Thompson, D. "Prediction of renal crystalline size distributions in space using a PBE analytic model. 2. Effect of dietary countermeasures." Am J Physiol Renal Physiol. 2016 Sep 1;311(3):F531-8. Epub 2016 Jun 8. http://dx.doi.org/10.1152/ajprenal.00402.2015 ; PubMed PMID: 27279491 , Sep-2016
Papers from Meeting Proceedings	Kassemi M, Griffin E, Thompson D. "Coupled PBE-CFD Predictions of Renal Stone Size Distributions in the Nephron in Microgravity." 46th International Conference on Environmental Systems, Vienna, Austria, July 10-14, 2016. 46th International Conference on Environmental Systems, Vienna, Austria, July 10-14, 2016. Paper # 2016-276. https://ntrs.nasa.gov/archive/nasa/casi.ntrs.nasa.gov/20170000238.pdf , Jul-2016