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RENAL STONE FORMATION IN SPACEFLIGHT

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ABSTRACT

The microgravity environment of space increases bone resorption in astronauts, increasing urinary calcium excretion. Dehydration may also occur due to decreased fluid intake and increased fluid loss through insensible losses and space motion sickness. These factors increase the risk of renal stone formation. Renal stones can cause sudden incapacitating pain, requiring immediate treatment. Definitive treatment options are currently unavailable in space, necessitating a return to Earth. Thus, preventative strategies should be employed.

Dietary intake of calcium, oxalate and sodium should be controlled. Citrate intake can help decrease stone formation risk but may not be readily available in space. Potassium-magnesium citrate can be used as a supplement. Exercise and bisphosphonates help significantly mitigate bone mass loss due to microgravity but is inadequate to completely prevent stone formation risk. Thiazides have been trialed with good effect.

Various countermeasures have been investigated for general use and in spaceflight. They can potentially be used to mitigate stone formation risks in future missions. Risk of stone formation can be monitored using urinary biochemistry analyte normograms. These risk mitigation strategies can be employed in the general public to prevent recurrences and manage stone formation risks.

INTRODUCTION

The environment of spaceflight poses unique risks on astronauts, predisposing them to a multitude of health issues. Renal stones have been identified as a possible risk that astronauts can face[(1)]. Renal stones can present as an acute and severe pain that may be incapacitating. If such an episode occurs on a safety critical personnel, the mission may need to be aborted, necessitating a hasty return to Earth for definitive treatment. To date, Apollo 13 was the farthest spaceflight mission that required termination and emergency return to Earth. The mission lasted less than 6 days. The National Aeronautics and Space Administration (NASA) is planning future missions that may be significantly longer in duration, such as human exploration of Mars or establishing a base on the moon. These extended duration missions may increase the risks of developing a multitude of health issues, including renal stones. Furthermore, renal stone risk remains elevated post-flight[(2)].

Between 2006 and 2007, 131 out of 100 000 Australians were admitted to hospital for kidney stone diseases[(3)]. There has only been a single reported case of renal stone occurring during spaceflight which presented as severe lower abdominal pain that spontaneously resolved1. As of 2007, 7 crew members have also experienced renal stone within 12 months post flight[(4)].

Crews may not be able to return to Earth to receive definitive medical treatment in a reasonable amount of time. Thus, it is prudent to analyse the factors of spaceflight that predisposes astronauts to renal stones, and the possible methods of investigation, treatment and prevention.

PATHOPHYSIOLOGY OF KIDNEY STONES IN SPACEFLIGHT

A significant majority of kidney stones mainly consist of calcium(5). Calcium oxalate stones form about 75% of stones, while calcium phosphate stones form 15%(5). Other stones can be composed of uric acid, cystine or struvite(5). The main principle behind stone formation is the concentration of stone substrates and their supersaturation(5-7). Several factors of spaceflight can affect these factors, increasing the risk of renal stones.

The microgravity environment has been known to alter bone homeostasis. It reduces bone formation, whilst increasing bone resorption(8). This manifests as osteopenia(8-10). This has been attributed to decreased mechanical loading on the bones(8-10). As such, it has been observed that load bearing bones are affected first(8). However, the exact cellular mechanisms remain unknown(8). In addition to the musculoskeletal issues, bone resorption causes a release of calcium from the bones, leading to hypercalciuria(10). Studies conducted on Skylab missions reported an average increase of urinary calcium excretion by 81%(10). This elevation in urinary calcium increases risk of stone formation. Furthermore, the risk of renal stone formation remains elevated after landing as renal calcium excretion slowly returns to pre-flight levels(2,9). However, current studies have only compared calcium excretion between microgravity and Earth's gravity. Future missions may involve long term habitations in partial gravity environments such as the moon or Mars. There has been a lack of studies in partial gravity environments, as opposed to microgravity experienced during spaceflight. The reduced gravitational forces experience may cause a degree of bone resorption, leading to increased renal calcium excretion.

Current space analogue studies have used bed rest on humans and suspension on animal models to emulate the effects of microgravity. It has been shown that they approximate the loss of bone mass due to microgravity quite well, allowing researchers to investigate the mechanism of bone resorption in microgravity, other factors that influence calcium homeostasis and possible countermeasures in a safer and practical environment(8). Other factors such as physiological stress have been thought to contribute towards issues with calcium homeostasis through the release of cortisol. The steroid hormone reduces bone formation and increases bone resorption, further aggravating calcium loss(10). Future missions would need to consider the stress of spaceflight and mission requirements and its effects on bone metabolism.

The risk of dehydration in astronauts is higher due to multiple factors within their environment. Reduced urine volumes have been reported in astronauts during spaceflight(9). Cabin humidity is lower than on Earth, leading to higher insensible losses(9). Furthermore, a diminished sense of thirst has been reported during spaceflights(4). Additionally, vomiting due to space motion sickness and challenges of voiding in space during busy schedules can reduce fluid intake by the crew(4,9). The decreased urine volume raises the concentration of all solutes, raising the risk of renal stones.

The concept of nanobacteria has been a contentious topic in microbiology(11-12). The controversy stems from its initial classification as a living organism that only spans 0.08 – 0.5 μm in diameter(11-12). Much doubt exists as to whether such a miniscule organism could contain the necessary biological machinery that would classify it as an organism(11-12). As such, it is also commonly referred to as a 'calcifying nanoparticles'. Despite its controversial nature, many studies have investigated its ability to promote renal stone formation(11-12). It is thought to inhibit fetuin, a protein that inhibits calcification(11). Their rate of replication has been noted to increase by 4.6 times in simulated microgravity environments, which potentially increases stone formation risk during spaceflight(13).

IMPACT ON SPACEFLIGHT

Renal stones can be asymptomatic if they are small or situated in areas where they do not impede renal function. Renal stones can progress to a dull loin or back ache that may radiate to the groin(14-15). However, the pain can be severe and colicky, to the point of incapacitation(16). The pain may not be relieved by analgesics available to astronauts, necessitating the termination of the mission and a prompt return to Earth for definitive treatment(16). Furthermore, a complete obstruction may cause hydronephrosis or pyelonephritis(15). This would necessitate emergency medical treatment.

INVESTIGATIONS FOR SPACEFLIGHT

Urine dipsticks can be a quick and simple test to detect for nitrates or leucocytes in the urine, suggesting the presence of urinary tract infections which can alter the course of treatments(17). Vacuum urine collection devices are already employed as part of normal toileting facility in space. A full urinalysis can also be conducted to detect biochemistry abnormalities and infective processes that predispose stone formation(6,15). Examples of such biochemistry abnormalities include extremes of pH, hypercalciuria, hyperoxaluria, hyperuricosuria and hypocitraturia(6-7).

Blood collection during spaceflight is already done as part of other studies. Automated equipment can be used to analyse the blood samples to assess renal function and investigate possible infections[14-15].

Non-contrast computed tomography (CT) scans of the kidneys, ureters and bladder (KUB) have been the first line option for imagine renal stone diseases[14-15]. It can rapidly detect and differentiate renal stones of different compositions[14-15]. Its high sensitivity also allows it to exclude stone diseases if none are visualised during the scans[14].

Full body CT scanners are large and bulky. Although recent advances have allowed it to be portable and battery operated, such CT scanners still weigh more than 1.5 tons and measure 205.7 cm × 256.6 cm × 104 cm in dimensions[18]. Although its bulk may be a concern in the cramped conditions of a spacecraft, the cost of sending heavy equipment to space may pose a greater challenge. Furthermore, maintaining complex equipment may require specialized training. However, a CT scanner can be used for a myriad of other medical conditions. Thus, mission planners should carefully consider the benefit of such an equipment against its disadvantages.

Approximately 90% of renal stones are radiopaque and visible on a plain film x-ray KUB14. Plain film x-rays have a 60% sensitivity in detecting renal stones[14]. It is associated with much lower doses of radiation, compared to CT KUB. As such, it can be useful to monitor the progression of patients with renal stones visible on plain x-rays[14].

Battery operated handheld x-ray equipment are commercially available. They weigh slightly above 11 kg and are slightly larger than 3 reams of office paper[19]. Thus, it addresses the concerns of a CT scanner in spacecrafts. Thus, it can be a useful, multipurpose medical imaging tool for future spaceflight missions. However, it may not detect all radiopaque kidney stones due to the presence of overlying soft tissues, gastrointestinal contents and bony structures, small calculi may not be detectable[14].

Ultrasound sonography (USS) provides a rapid method to visualise renal stones without the use of radiation. It can detect renal stones as small as 0.5 mm regardless of composition[5,14]. Therefore, it can also detect cystine or uric acid stones that are radiolucent on plain film x-rays[5]. USS can also detect complications such as abscesses and hydronephrosis[5,14]. Furthermore, it can also be used for monitoring in recurrent stone disease patients without the risk of radiation exposure[5]. Portable USS equipment is available as small handheld transducers that connect with commercially available handheld devices[20]. USS equipment is already used in the International Space Station to investigate other health conditions during spaceflight[21]. Thus, it can be a useful tool to monitor for renal stones in future spaceflight missions.

Stones within the ureters can be difficult to visualise with USS due to overlying anatomical structures and bowel contents[14]. Furthermore, rates of stone detection on USS is highly dependent on the operator's skills[5,14]. Currently, all spaceflight missions have a crew medical officer rostered[21]. They may not be physicians and would have only received 40 to 80 hours of medical training[21]. Thus, their proficiency with USS imaging may be limited, reducing its potential for use in renal stone diseases. NASA has considered introducing physicians into future long duration spaceflight missions. However, their expertise with USS imaging may be variable. Fortunately, USS imaging training can significantly improve the operator's skills in detecting various pathologies, possibly providing an avenue in improving renal stone detection rates[22-23].

MANAGEMENT DURING SPACEFLIGHT

Fortunately, up to 70% of renal stones smaller than 6 mm pass spontaneously[15]. These stones can be managed with non-steroidal anti-inflammatories for analgesia[15]. The use of α1 receptor antagonists such as tamsulosin can help larger stones pass without interventional treatments[15,24]. Imaging should be repeated in 6 weeks to confirm the resolution of renal stones[15].

However, interventional treatments are required when the likelihood of spontaneous resolution is low, complications arise or when the pain becomes inadequately controlled with simple analgesia[15,17]. In common practice, a referral to a urologist is often made for definitive treatments such as extracorporeal shockwave lithotripsy (ESWL), laser lithotripsy or percutaneous nephrolithotomy[15,17].

Laser lithotripsy is the most common interventional treatment for renal stones and provides high rates of success[15,17]. However, it is an invasive procedure that requires a ureterorenoscope inserted into the genitourinary tract[15,17].

Percutaneous nephrolithotripsy is more invasive, requiring surgical access to the kidneys[17]. It is now generally reserved for larger stones[15]. Percutaneous lithotripsy may not be a viable option in spaceflight without access to specialists.

ESWL provides a non-invasive method of managing renal stones. However, its efficacy is limited to stones smaller than 1 cm positioned in the renal calyces or pelvis[15,17]. Furthermore, its efficacy can be further decreased with increasing body mass[17]. However, this can be limited through careful selection of crew members. ESWL equipment also requires training in its operation[17].

Currently, a crew flight surgeon is available to spaceflight crew members via audiovisual communication links[21]. Thus, specialist assistance may be possible onboard. However, on deep space missions, communications delay would be present and will be aggravated by increasing distance between the spacecraft and Earth. Currently, the delay from low earth orbit lasts a few seconds[21]. However, two-way communications to Mars may experience delays more than half an hour[21]. This may make live telemedicine impractical on such missions. Furthermore, all interventional treatment for renal stones requires the use of specialised equipment. The size and weight constraints of spacecraft may decrease the value of a single-purpose medical equipment. Thus, it would be more prudent to prevent renal stone formation during spaceflight.

PREVENTION

Medical screening of crew members can reduce the risk of stone formation. Renal stone patients have a 50% chance of a recurrence within 5 years[6,15]. Furthermore, anatomical pathologies with the genitourinary system can also increase stone formation risk[15]. Metabolic disorders can cause biochemistry disturbances that increases renal stone substrate concentration in the urine. Examples include hyperthyroidism and hyperparathyroidism[6]. Renal issues can also affect reabsorption of calcium and oxalate, increasing renal stone risk[7]. Of note, cystine stones result from a genetic condition affecting the reabsorption of certain amino acids in the proximal convoluted tubule[7]. As cystine has low solubility, it precipitates out of the solution, forming cystine stones[7]. Furthermore, gastrointestinal issues such as inflammatory bowel diseases can increase dietary oxalate absorption, increasing risks of renal stones[7]. Certain medications and supplements can also promote renal stone formation through altering urinary biochemistry composition or inducing crystallisation[6]. Previous stone analyses can also be useful to target risk factors specific to the formation of the stone[15].

Dietary intake forms an important source of stone substrates and stone formation inhibitors. Dietary modifications can significantly alter renal stone formation risk through addressing intake of stone substrates and stone formation inhibitors[25]. Thus, through regulating meals provided in spaceflight, renal stone formation risk can be addressed.

Up to 98% of dietary citrate is absorbed[6,25]. It forms an important source of citrate, which is an inhibitor of renal stone formation[6,25]. Citrate forms soluble complexes with common stone substrates such as calcium, reducing the risk of crystal formation[6-7]. Furthermore, citrate interacts with the surface of crystals that have already formed, slowing their growth[25]. This allows for their expulsion before they become pathological. Thus, it is important that spaceflight meals contain adequate amounts of citrate. Citrus fruits and vegetables are a common source of dietary citrate but may be of limited supply in a long duration missions[6]. Citrate salts have been proposed as a supplement to dietary citrate intake[26]. Potassium citrate supplementation has been trialed on crew members of the International Space Station, showing similar effects of lowering urinary calcium excretion and raising pH during spaceflight and after landing[27]. This suggests that citrate salts can provide an adequate source of citrate to prevent renal stones in spaceflight. Potassium-magnesium citrate has been suggested as a more efficacious citrate supplement due to its inclusion of magnesium. The magnesium would interact with intestinal oxalates, further decreasing its absorption[4, 25, 28]. Thus, potassium-magnesium citrate may be a superior agent compared to potassium citrate.

A high sodium diet has been associated with increased urinary calcium excretion. Sodium causes a state of relative hypervolaemia, decreasing sodium and water reabsorption in the kidneys[29]. As calcium is passively reabsorbed with sodium and water, this cause hypercalciuria[29]. Furthermore, a high sodium diet is also associated with decreased citrate levels, further increasing stone formation risk6. Numerous studies have shown significant decreases in urinary calcium levels and rates of renal stone formation when dietary sodium intake is controlled[29]. Dietary sodium can be reduced by replacement with potassium salts. Furthermore, increased potassium intake has been associated with increased urinary citrate levels, further decreasing renal stone risks[4, 8, 15, 29]. As such, NASA has already reduced the daily sodium intake from meals from 5300 mg to 3000 mg[8]. Further improvements in sodium intake can further reduce stone formation risk[29]. However, its effect on palatability and shelf life should be considered for future missions where the absence of an established supply line can limit the variety and availability.

Oral intake of calcium can influence hypercalciuria. Due to the lack of sun exposure in spacecrafts, crew members are issued vitamin D supplementation, further augmenting intestinal calcium absorption[2,7]. Thus, calcium intake needs to be carefully regulated. However, excessively low calcium intake has been associated with hyperoxaluria. Dietary calcium interacts with oxalate, forming complexes that are not easily absorbed through the intestines[6,25]. Thus, careful timing of calcium intake can significantly influence stone formation risk[6,25]. Calcium intake or supplementation should be avoided unless taken with foods[6,25]. Furthermore, dietary oxalates should be avoided whenever possible[6].

Excessive protein intake has also been associated with increased stone formation risk. Sulfur-containing amino acids contribute towards hyperuricosuria and the resulting low pH[7]. This causes uric acid to remain undissociated in the urine, decreasing the solubility of stone substrates[7]. Higher acid loads associated with protein intake also increases bone resorption, mobilising phosphate and carbonate to counteract changes in pH[25]. Calcium is also released in the process, which is excreted via the kidneys. Restricting proteins to less than 60 g a day has been associated with reduced stone formation risk. As such, NASA has already limited proteins to constitute 12% - 15% of the daily energy intake in meals provided to astronauts[4,25].

Adequate hydration is vital in preventing renal stone formation. It helps dilute the urine, reducing the concentration of substrates within. For the general population, the daily recommended intake to prevent renal stone formation is 2.5 litres[7]. Adequate hydration has been investigated as a countermeasure for use in spaceflight. It does not fully counter urine biochemistry abnormalities encountered during spaceflight, but can augment other countermeasures[30]. However, it is effective as a sole countermeasure to prevent renal stones after spaceflight2, 30. Currently, NASA recommends 2 litres of fluid daily for their spaceflight crew[4,25]. However, compliance has been variable due to many factors[4, 9, 16, 25]. Space motion sickness and busy schedules may affect adherence to the guidelines[4,9]. Thus, it is important to reiterate the importance of renal stones and adequate hydration to spaceflight crew.

Exercise has been shown to reduce loss of bone mass in simulated and actual microgravity environments[4, 8]. It does not affect bone resorption, but increases rate of bone formation[9]. Regular exercise has already been implemented in spaceflight crew scheduling to combat the effects of microgravity. The International Space Station crew currently utilise the Advanced Resistive Exercise Device to maintain bone and muscle mass in space. Thus, it can also be used in future spaceflight missions. Although exercise is effective in combating spaceflight osteopenia and sarcopenia, it still results in a monthly loss of 1% in bone mass[2, 9-10]. Thus, it is unsuitable as the sole countermeasure in longer duration missions[8]. Other measures have been explored to augment resistive exercises. Whole body vibrations have been shown to further reduce bone mass loss by causing increased muscle activation to dampen the vibrations[31]. Lower body negative pressures can also augment aerobic exercises to help further decrease bone mass loss by simulating the forces of gravity during running[16].

Bisphosphonates have been shown to be effective at reducing bone resorption. It reduces osteoclast numbers and activity[9-10]. Trials with alendronate on patients in bedrest have shown minimal changes in bone mass due to simulated microgravity environments[8]. NASA has investigated the concurrent use of bisphosphonates and exercise in spaceflight[1]. It has shown to be more effective than either countermeasure alone and may be used for future spaceflight[8,10]. However, bisphosphonates are associated with osteonecrosis of the jaw. Oral intake of bisphosphonates has 0.01% - 0.04% risk of the complication, which usually presents in 24 – 36 months[32]. However, this risk can be managed through good dental hygiene and the use of safer bisphosphonates[32].

Thiazides have been investigated for use in renal stone prevention due to its ability to decrease renal excretion of calcium[7,33]. It has demonstrated the ability to significantly reduce the rate of stone formation irrespective of other countermeasures employed[33]. However, similar effects have been observed with a low salt diet with potassium supplementation[7]. Thiazides can possibly be used in combination with other preventative measures to complement each other. Struvite stones usually forms in the presence of a urinary tract infection with a urease-producing organism[7]. The urease hydrolyses urea, forming ammonia. In an alkaline environment, ammonia reacts with magnesium and phosphate to form struvite stones[7]. Thus, struvite renal stones can be prevented through the prevention and early treatment of urinary tract infections. Astronauts are at risk of urinary retention due to a variety of factors[4]. The risk of infection is significantly increased during urinary retention. Therefore, there is a risk of struvite stone formation during spaceflight.

SURVEILLANCE STRATEGY

Urine biochemistry analysis has been suggested as a quick and non-invasive method to monitor the risk of renal stone formation. Studies have validated the efficacy of analysing urine biochemistry at predicting renal stone risk[34-35]. A 24-hour urine collection test has shown to have high accuracy in detecting uric acid and calcium-based stones[35]. This may prove to be useful in spaceflight use where all urine voided is already collected for recycling. Analysis of the urine may provide insight to biochemical abnormalities to the crew, allowing them to take corrective actions before a renal stone forms. Based on these studies, a risk assessment index for astronauts has been proposed for use in spaceflight[36]. It comprises of normograms of various urinary biochemical analytes that can modify stone formation risk. It provides a rapid visual assessment of renal stone formation risk. Further studies have evaluated shorter collection intervals. It has been shown that a 12-hour urine collection correlates strongly with a 24-hour urine collection[34]. This would potentially allow for more feedback, allowing astronauts to gauge the efficacy of the employed countermeasures by comparing with previous results

CONCLUSION

Renal stones can cause sudden incapacitating pain on spaceflight crew members. It can impair the abilities of the affected crew member. The microgravity environment of space can predispose astronauts to renal stone formation due to increased bone resorption.

As definitive treatment may not be possible in space, it is important to prevent the formation of renal stones, especially during long duration missions where a return to Earth may not be feasible. Diet control and exercise have already been employed. Medications such as potassium-magnesium citrate, bisphosphonates and thiazides may further improve protection from renal stones.

These countermeasures could also be employed in similar situations where the where medical care may not be readily available. Rural and remote communities may benefit from prevention of stone disease, reducing the burden on the healthcare system. The renal stone risk index assessment can be a useful tool to monitor for stone formation risk. They can possibly be used to help people in safety critical roles return to work if they can demonstrate low risks through control of urinary biochemical analytes. Exercise and bisphosphonates are countermeasures that target bone mass loss due to microgravity. Other countermeasures discussed have been trialed in recurrent stone formers and may be used in the general population. These risk mitigation strategies may improve the quality of life for patients by allowing them to return to work quicker.

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