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In Context

Cosmic kidney disease: a spaceflight-induced tubulopathy

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IN CONTEXT

Spaceflight is taking off both in terms of space tourism and planned missions into deep space. This brings renewed attention to the health impact of spaceflight, which is primarily driven by the effects of microgravity and, for deep space missions, galactic cosmic radiation (GCR) [1]. While the impact of spaceflight on muscles, bones and the cardiovascular system has been extensively studied, the effects on the kidneys have been somewhat overlooked. This is surprising, as spaceflight leads to an unusually high risk of kidney stones and the kidney is exquisitely sensitive to radiation [1, 2]. Siew *et al.* [1] fill this gap by identifying several spaceflight-induced kidney perturbations for which they coined the term 'cosmic kidney disease'.

The authors investigated blood, urine, stool and kidney tissue from humans, mice and rats before and after exposure to actual spaceflights or simulations of microgravity and GCR. They challenged the long-held belief that kidney stone formation during spaceflight is a secondary phenomenon due to bone resorption (Fig. 1) [2]. Proteomic analysis of mouse kidney tissue revealed a striking dephosphorylation of several channels and transporters in the distal tubule, including the sodium–potassium–chloride cotransporter 2 (NKCC2, *SLC12A1*). Dephosphorylation of NKCC2 reduces its activity and results in hypercalciuria, which was observed in astronaut urine samples during spaceflight. In addition to hypercalciuria, hyperoxaluria was identified as another pro-lithogenic factor contributing to kidney stone risk (Fig. 1). Although the origin of hyperoxaluria could not be established with certainty, a microbiome analysis of human stool samples showed that spaceflight increases *Oxalobacter* species, the bacterium responsible for gut oxalate metabolism.

The third factor contributing to kidney stone formation is the antidiuretic effect of spaceflight (Fig. 1), which was clearly visible as a decrease in free water clearance in astronauts [1]. A previous animal study demonstrated that microgravity (simulated by hindlimb unloading) enhanced hypotension-induced vasopressin secretion [3]. This suggests that antidiuresis occurs secondarily to the haemodynamic changes provoked by microgravity. Although vasopressin or copeptin was not measured by Siew *et al.* [1], they did provide an alternative explanation. In their multi-omics dataset from humans, rats and mice, they observed downregulation of *SLCO2A1*, which encodes a prostaglandin transporter in the collecting duct. Reduced activity of this transporter causes prostaglandin E2 to accumulate in tubular fluid, enabling it to activate its EP4 receptor and subsequently aquaporin-2 water channels. This form of nephrogenic antidiuresis has also been implicated in the pathogenesis of thiazide-induced hyponatraemia [4].

One of the strengths of the study by Siew *et al.* [1] is that it combines a 'pan-omics' approach with classic physiological and morphological analysis of the kidney. A crude but interesting observation is that both microgravity and GCR increased kidney weight in mice and rats relative to body weight. This is reminiscent of chronic potassium depletion in which kidney hypertrophy is attributed to an increase in insulin-like growth factor 1, which also occurs during spaceflight [2, 5]. When zooming in on the architecture of the distal convoluted tubule, known for its plasticity, a clear pattern of tubular remodelling

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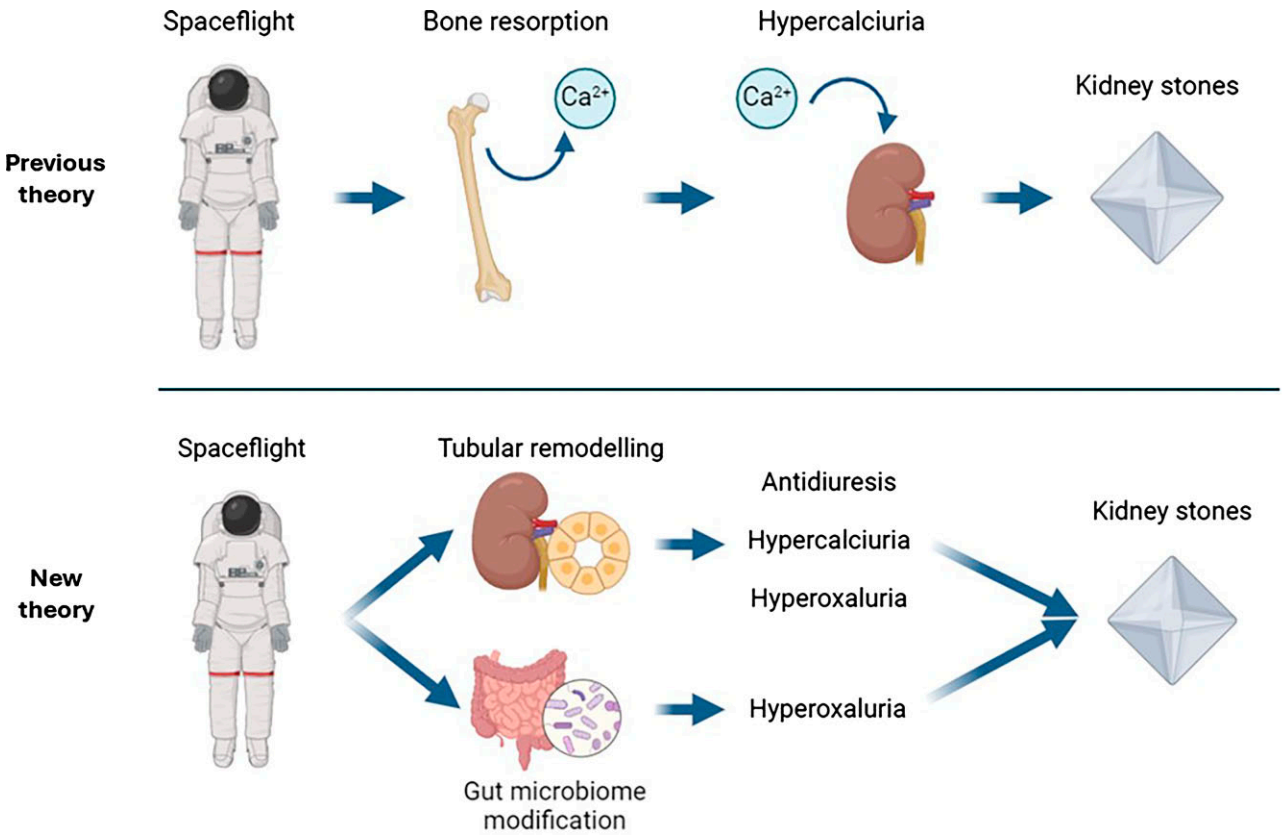

Figure 1: A new theory for kidney stone formation during spaceflight. According to the previous theory, the main cause was the impact of microgravity on bone, leading to bone resorption, which in turn caused hypercalciuria and increased the risk of kidney stone formation. The new theory proposed by Siew *et al.* [1] suggests that the primary cause is the direct effect of microgravity on the kidneys and gut microbiome. This leads to tubular remodelling, resulting in antidiuresis, hypercalciuria and hyperoxaluria, all of which contribute to the risk of developing kidney stones [1]. The figure was created using BioRender.

was identified, characterized by increased tubule size but a loss of overall density [1]. Tubular remodelling is increasingly recognized as a response of the kidney tubule to adjust transporter capacity to changes in homeostasis [6].

Siew *et al.* [1] also investigated the effect of long-term exposure to GCR (≈1.5- or ≈2.5-year dose equivalent) on the mouse kidney. This revealed overt thrombotic microangiopathy in several cases, possibly triggered by micro-RNAs causing vascular damage in the inner stripe of the outer medulla. Of interest, in back-to-back articles, the use of antagomirs against three micro-RNAs was effective in mitigating the vascular damage from simulated deep space radiation [7]. In addition to the vascular kidney lesions, GCR caused proximal and distal tubular injury leading to albuminuria and magnesiuria.

Some questions regarding cosmic kidney disease remain to be addressed, including what exactly triggers tubular remodelling and how reversible is it, considering that kidney stone risk remains increased after returning to Earth [2]. Another question is how to reconcile hypercalciuria with the observation that the sodium–chloride cotransporter (NCC, *SLC12A3*) was also dephosphorylated, which would be expected to cause hypocalciuria. This is also relevant when considering whether astronauts might benefit from thiazide diuretics to prevent kidney stones and bone loss. Preventing cosmic kidney disease is clearly relevant for those traveling to Mars, if only because a renal colic in this setting would be rather inconvenient, to say the least.

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DATA AVAILABILITY STATEMENT

No new data were generated or analysed in support of this research.

CONFLICT OF INTEREST STATEMENT

None declared.

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