REVIEW ARTICLE

# Health risk of travel for chronic kidney disease patients

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The number of people with chronic kidney disease (CKD) has increased and so has their demand for travel. However, the health risk posed by travel in these patients is unclear. Few reports document the travel risk in CKD and dialysis patients. The aim of this study is to summarize the existing evidence of the influence of travel on risks in CKD patients. We aim to describe the association between the impact of travel risks and patients with CKD. A detailed review of recent literature was performed by reviewing PubMed, Google Scholar, and Ichushi Web from the Japan Medical Abstracts Society. Screened involved the following keywords: "traveler's thrombosis," "venous thromboembolism," "deep vein thrombosis," "altitude sickness," "traveler's diarrhea," "jet lag syndrome," "melatonin," with "chronic kidney disease" only, or/and "dialysis." We present a narrative review summary of the literature from these screenings. The increased prevalence of thrombosis among travelers with CKD is related to a decrease in the estimated glomerular filtration rate and an increase in urine protein levels. CKD patients who remain at high altitudes are at an increased risk for progression of CKD, altitude sickness, and pulmonary edema. Traveler's diarrhea can become increasingly serious in patients with CKD because of decreased immunity. Microbial substitution colitis is also common in CKD patients. Moreover, time differences and disturbances in the circadian rhythm increase cardiovascular disease events for CKD patients. The existing literature shows that travel-related conditions pose an increased risk for patients with CKD.

**Key words:** Chronic kidney disease, dialysis, travel-related illness

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## INTRODUCTION

Air travel is becoming increasingly popular due to time and cost advantages. However, the risk of long-travel periods in chronic kidney disease (CKD) patients is unclear. This review aims to summarize the existing evidence on the influence of travel on the health risks of CKD patients. We describe the association between travel risks (traveler's thrombosis, altitude sickness, traveler's diarrhea, and jet lag syndrome) and their impact on CKD patients. We performed a detailed review of the recent literature. A literature screen was conducted by reviewing PubMed, Google Scholar, and Ichushi Web from the Japan Medical Abstracts Society. We screened the following keywords: "traveler's thrombosis," "venous thromboembolism," "deep vein thrombosis," "altitude sickness," "traveler's diarrhea," "jet lag syndrome," "melatonin," with "chronic kidney disease" only, or/and "dialysis." Moreover, we present a narrative review summary of the literature obtained from these screenings.

The existing literature shows that travel-related conditions pose an increased risk for CKD patients. We have described the mechanism of disease onset in detail and the most recent information on travel risks for CKD patients.

## TRAVELER'S THROMBOSIS

Traveler's thrombosis is defined as travel-related venous thromboembolism (VTE), i.e., deep vein

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thrombosis (DVT) and subsequent pulmonary thromboembolism (PTE). Virchow described three factors contributing to venous thrombosis: enhanced blood clotting, venous stasis, and damage to venous blood vessel walls. Most reports of VTE relate to air travel, wherein all the aforementioned factors are present. The inside of an airplane is a low-pressure, low-oxygen, low-humidity environment, set at 0.8 bar and 5%–15% humidity. In a low-pressure environment, leg venous return decreases and venous stasis occurs, while hypoxemia leads to a depressed fibrinolytic system. Coupled with dehydration caused by low humidity, these two factors combine to increase blood coagulation. Restricted movement in narrow seats often causes leg veins to be compressed, causing damage to vein walls.

Few epidemiological studies have statistically investigated thrombosis in Japan. A 2006 study showed that thrombosis is a multifactorial disease and that the Japanese population has a specific thrombotic predisposition that is different from that of Western populations.[1] Traveler's thrombosis in Japanese air travelers is more likely to affect women, middle-aged to elderly individuals, those with a short physical stature, and those seated in the window or middle seat. VTE typically develops immediately after a person first stands and starts walking after prolonged sitting.[2] Countermeasures during air travel include rehydrating, avoiding alcohol, wearing loose-fitting clothing, performing moderate exercise such as occasionally moving the legs, and wearing elastic stockings.[3,4] Currently, aspirin is the preferred choice for preventing traveler's thrombosis, but new oral anticoagulants have recently appeared on the market which may be useful for VTE prevention in high-risk persons.[2] It is also becoming increasingly common for travelers at high risk of thrombosis in Western countries to receive subcutaneous injections of low-molecular weight heparin before or after long flights.[3]

CKD reportedly increases the risk of DVT and PTE; further, a decrease in the estimated glomerular filtration rate (GFR) and an increase in the albumin/creatinine ratio are independently correlated with the risk of VTE [Table 1].[5-7]

**Table 1: Adjusted hazard ratio of venous thrombosis to estimated glomerular filtration rate and albumin-to-creatinine ratio[6]**

| eGFR (mL/min/1.73 m²) | Albumin-to-creatinine ratio | | |
|---|---|---|---|
| | 30 mg/g (3.3 mg/mmol) | 30-300 mg/g (3.4-33.8 mg/mmol) | 300 mg/g (33.9 mg/mmol) |
| 90 | Reference | 1.66 (1.11-2.48) | 1.51 (0.48-4.73) |
| 60-89 | 1.15 (0.96-1.38) | 1.47 (1.07-2.03) | 4.38 (2.64-7.26) |
| 45-59 | 1.23 (0.87-1.74) | 1.37 (0.76-2.49) | 1.51 (0.48-4.77) |
| 30-44 | 2.13 (1.26-3.62) | 2.11 (0.95-4.95) | 2.33 (0.74-7.34) |

eGFR=Estimated glomerular filtration rate, results are reported as number (range)

The global incidence of venous thrombosis is 104–183 cases/10,000 individuals/year,[8] but the risk of venous thrombosis is increased 2.3-fold for those with end-stage renal disease (ESRD) compared with the general population.[9] Previous research shows that the adjusted hazard ratio of DVT for ESRD is 13.92 times that for non-ESRD patients.[10] In addition, patients who are undergoing hemodialysis have a risk of venous thrombosis that is 4–7 times higher than that for the general population.[11] Furthermore, CKD patients who develop pulmonary embolism have a higher mortality rate than patients without CKD.[12]

Potential mechanisms for clot formation in CKD include the involvement of oxidative stress, increased inflammatory mediator levels, accumulation of asymmetric dimethylarginine, and decreased calcium–phosphorus control, which not only promote arterial disease but also promote endothelial damage to the venous system.[13]

With CKD, there are elevated levels of procoagulants such as D-dimers, C-reactive protein (CRP), fibrinogen, interleukin-6, factor VII, factor VIII, and plasmin–antiplasmin complexes.[14] These procoagulants continue to rise as renal function deteriorates.[15] Moreover, there is an increase in microparticles, which are membrane vesicles released from platelets, endothelial cells, and monocytes in the event of cell damage and apoptosis associated with CKD.[16,17] Together with an increase in circulating tissue factors, the conversion of prothrombin into thrombin is increased, thus facilitating blood clotting.[18]

The systemic inflammatory state associated with ESRD results in exacerbation of endothelial dysfunction and vascular disorders.[19] Such mechanisms promote a clotting reaction in CKD patients, increasing the risk of traveler's thrombosis.

Because of the increased hemorrhage risk associated with the use of anticoagulants, the use of anticoagulant therapy to prevent venous thrombosis in CKD patients remains controversial. However, a few recent findings support the effectiveness and safety of novel oral anticoagulants for patients with CKD who are undergoing hemodialysis.[20,21] In conclusion, there is a lack of clinical data on anticoagulant use in severe renal impairment due to differences in individual factors.[22]

## ALTITUDE SICKNESS

Altitude sickness is a general term for physical symptoms caused by low oxygen levels at altitudes above 2500 m.[23,24] For untrained individuals, however, the effect of high altitudes may need to be considered from 1500 m because

maximum oxygen consumption decreases approximately 1% for every 100 m of ascent above 1500 m.[25,26] Causes of altitude sickness include organ edema owing to reduced pressure at high altitudes and a decrease in oxygen partial pressure, creating a systemic hypoxic state. At high altitudes, peripheral veins contract and the central blood volume increases; with pressure stimulus, secretion of antidiuretic hormone and aldosterone is suppressed, resulting in diuresis. These physiological changes are related to high-altitude adaptation as is bicarbonate diuresis that occurs as compensation for respiratory alkalosis caused by hypoxia. It is generally possible to adapt to high altitudes if the altitude increases gradually, but the symptoms of altitude sickness may occur if compensatory mechanisms are unable to keep up.

There are three international classifications for altitude sickness [Table 2]:[23] acute mountain sickness (AMS), high-altitude pulmonary edema (HAPE), and high-altitude cerebral edema (HACE). AMS is cause for stopping any further increase in altitude, and if HACE or HAPE are suspected, then a lower altitude must be reached as soon as possible. Prevention involves gradually increasing altitude, taking acetazolamide, and rehydrating, because dehydration occurs at higher altitudes and exacerbates the symptoms of altitude sickness. Acetazolamide prevents altitude sickness by expanding cerebral blood vessels, increasing the blood flow, and mitigating the lack of oxygen. The mechanism of action is through suppression of carbonic anhydrase, resulting in elevated bicarbonate urinary excretion, which causes metabolic acidosis; the respiratory center is stimulated, and ventilation is increased to mitigate the hypoxemia.

**Table 2: Classification criteria for the different types of altitude sickness[23]**

| Condition | Criteria | |
|---|---|---|
| Acute mountain sickness | Headache and at least one of the following symptoms<br>Anorexia, nausea<br>Whole-body fatigue, weakness<br>Vertigo, light-headedness<br>Sleep disorders | |
| High altitude pulmonary edema | At least two each of the following symptoms and signs | |
| | **Symptoms** | **Signs** |
| | Dyspnea at rest<br>Coughing<br>Whole-body weakness<br>Decreased activity<br>Chest tightness sense of strangulation | Moist rales wheezing<br>Cyanosis<br>Rapid breathing<br>Tachycardia |
| High altitude cerebral edema | Patients with acute mountain sickness experiencing impaired consciousness or ataxia<br>Patients who have not had acute mountain sickness experiencing impaired consciousness and ataxia<br>Early diagnosis is possible with the tandem gait eyes-closed standing up, and finger-nose tests | |

## Physiology of healthy kidneys at high altitudes

Renal function at high altitude is affected by various factors including respiration, cardiac output, sympathetic activity, and erythropoietin. When a sharp drop in oxygen partial pressure occurs, natriuresis and increased potassium and bicarbonate excretion develop via peripheral oxygen receptors. The respiratory compensation and natriuresis responses to hypoxia take place during the 24–48 h that follow hypoxic exposure and vary by as much as 10-fold between individuals. Hypoxia and hypocapnia caused by high altitude increase the following: adrenosympathetic activity, epinephrine, atrial natriuretic peptide, brain natriuretic peptide, and endogenous digitalis. Kidney hypoxia increases endothelin-1 and adrenomedullin and results in decreased levels of antidiuretic hormone, renal sensitivity to antidiuretic hormone, renin, aldosterone, and renal sympathetic nerve activity. These mechanisms result in increased natriuresis and diuresis.[27,28] These substances have been implicated in natriuresis, along with nitric oxide secretion due to the stimulus of hypoxia-inducible factors (HIFs).[29] Through this HIF stimulus, erythropoietin production and angiogenesis in the renal cortex are promoted, thus improving oxygen supply.[30]

## Kidney disease at high altitudes

With the increasing popularity of travel to and residence in mountainous regions, and the 10%–11% prevalence rate for adult CKD in developed countries, it is important to consider the association between these two factors.[31] Hypoxia develops in kidneys at high altitudes, which may promote CKD progression;[32] the Navajo Native Americans who reside at altitudes of 1600–3200 m have twice the incidence of end-stage renal failure than do other Native Americans.[33] When patients with type 2 diabetic nephropathy who live at sea level and those who live at a high altitude of 1700 m were compared, those who lived at high altitudes reported a higher urinary protein levels and a lower GFR despite having the same blood sugar management as those who lived at sea level.[34]

Chronic, systemic hypoxemia among long-term high altitude residents accelerates CKD progression; in addition, hypoxia is believed to cause glomerulosclerosis and tubulointerstitial damage.[35] High-altitude sickness is accompanied by renal hypoxia and is associated with significant proteinuria, and the appearance of urine protein at high altitudes further exacerbates CKD.[36] Because protein reabsorption requires energy, oxygen consumption in the kidneys increases, leading to an increase in fibrotic matter due to hypoxia.[37,38] CKD patients who live at high altitudes, therefore, have the potential to progress to ESRD earlier than those living at sea level.[39]

A short-duration of stay at high altitudes results in a 2–3-fold increase in the amount of protein excreted in the urine by sudden hypoxemia.[40] Patients with elevated urine protein levels are reportedly more likely to experience altitude sickness.[41]

Regarding anemia, CKD patients living at high altitudes take lower amounts of erythropoietin but have a higher frequency of thrombosis and hypertension than CKD patients living at sea level.[42] Erythropoietin may react differently at high altitudes than at sea level, and the erythropoietin and hemoglobin target values in this population warrant further investigation.

Metabolic acidosis with CKD causes hypoxic pulmonary vasoconstriction, which plays a role in the pathogenesis of HAPE, and has the potential to worsen altitude sickness.[43] ESRD involves mild-to-moderate pulmonary hypertension, with various causes, in 40% of patients.[44] The fact that pulmonary hypertension and HAPE frequently occur together makes altitude sickness, an increased health risk for patients with ESRD.[39]

To the best of our knowledge, no previous studies have investigated whether patients with CKD receive the same treatment for AMS and HAPE as healthy individuals. However, in general, time or acetazolamide, which adjusts the bicarbonate ion levels, is effective for adapting to high altitudes,[45] and the administration of various other drugs has also been proposed as a treatment for lowering the risks of exposure to high altitudes.[23,39]

At high altitudes, patients with CKD have an increased risk of secreting an excess of body fluid owing to reduced urinary sodium excretion; improper functioning of sodium excretion in patients receiving hemodialysis increases the risk of pulmonary edema.[39] Indeed, the higher the altitude at which a hemodialysis patient is, the higher the weight gain between dialyses.[46] CKD patients therefore require daily body weight monitoring, if excess fluid retention associated with AMS occurs, then an increased dosage of diuretics is necessary. The monitoring of blood pressure and blood sugar is recommended.[39]

Nonsteroidal anti-inflammatory drugs impair renal vasodilatation, reduce kidney oxygen supply, increase sodium reabsorption, and increase oxygen consumption and should therefore be avoided.[39] It is considered that angiotensin-converting enzyme inhibitors should be prescribed to minimize altitude-related proteinuria.[47] Thus, although CKD patients with high altitude stays pose an increased risk for progression of CKD, altitude sickness, and pulmonary edema, management strategies to counter the risks remain poorly understood, and the most effective treatment to prevent altitude sickness is to strive for gradual increases or decreases in altitude.

## TRAVELER'S DIARRHEA

Traveler's diarrhea most frequently occurs during travel in Southeast Asia, Latin America, and Africa and is chiefly a bacterial infection associated with the ingestion of contaminated water or food. It is defined as four or more bouts of diarrhea within 24 h, or three or more bouts of diarrhea within 8 h, along with abdominal pain and vomiting.[48] The causative pathogens of traveler's diarrhea varies depending on the season; 15 different pathogens were detected from 3537 patients among 5842 Tokyo metropolitan travelers (61%) who went abroad and developed diarrhea between 1978 and 1995. They include, in the descending order of frequency, enterotoxigenic *Escherichia coli* (35%), *Salmonella* (8.4%), *Vibrio parahaemolyticus* (6.5%), *Campylobacter* (6.4%), *Plesiomonas* (5.6%), and *Shigella* (5.5%).[49] *Salmonella*, *Campylobacter*, and *Rotavirus* occur not only in summer but also during winter.[50] Relevant risk factors include being ≤30 years old, the area visited (e.g., about 4% in Europe, but 80% in Nepal), travel during rainy season, length of stay, reduction of stomach acid (patients taking H2-blockers, proton pump inhibitors, etc.), certain genetic factors, reduced immune function, and diabetes. Residence in a developing country for over 6 months allows for conditioning of the digestive tract and reduces the frequency of diarrhea.[51] Common symptoms are abdominal pain, vomiting, and a fever up to 38.5°, onset is typically on day 3 from the date of arrival (the incubation period can range from 6 h to several days), and the disease duration is 3–4 days if untreated. It can be prevented by washing hands with soap, consuming only bottled or boiled water, and only eating cooked food.[52]

Quinolone antibiotics may be administered to treat severe cases, but prophylactic administration should generally be avoided because it may contribute to drug resistance.[52] Rifaximin, a new antibiotic recently approved in Western countries, is a rifamycin antimicrobial that is effective against Gram-positive, Gram-negative, aerobic, and anaerobic bacteria. It shows promise as a treatment for traveler's diarrhea because it is not absorbed into the blood, often remaining in the intestine (the target organ); it is effective against a wide range of bacterial infections; and it rarely increases bacterial resistance.[53,54] Recent evidence has demonstrated that probiotics may be effective, to a certain extent, in preventing traveler's diarrhea or reducing the disease duration.[55] Notably, in about 30% of the cases, starting early treatment with antibiotics for traveler's diarrhea has no effect on the prevention of a hypersensitive state in the colon even 6 months later.[51,56]

In general, traveler's diarrhea is not life-threatening, but it may become more severe in patients with CKD due to their reduced immune function. In CKD patients, uremia lowers the functions of lymphocytes, neutrophils, monocytes, nitric oxide, and platelets, resulting in reduced phagocytosis, chemotaxis, and control of chemokines and cytokines, thus lowering the immune response.[57]

Patients on hemodialysis are frequently malnourished,[58] with vitamin deficiency,[59] reduced prealbumin levels, and elevated CRP.[60] The resulting hypotension also lowers nitric oxide activity and platelet function, causing anemia[61] and a consequent loss of immune ability.

Microbial substitution colitis is also common. CKD patients also experience *Clostridium difficile* colitis 1.95 times more often than the general population, whereas the rate for ESRD patients is 2.63 times higher.[62] *Cryptosporidium* is about four times more common in hemodialysis patients than in healthy individuals,[63] and ESRD patients also have parasitic infections more often than healthy individuals.[64] Irrespective of colitis, sepsis-related deaths among hemodialysis patients are 100–300 times more common than among healthy patients;[65] therefore, it is essential to pay attention to the worsening of infections.

Although there is no epidemiological research on traveler's diarrhea in hemodialysis patients, severe dehydration represents a high risk for vascular access occlusion, cardiovascular disease (CVD) events, and other sequelae, and it is also important to take appropriate measures, such as oral rehydration, to prevent dehydration.

## PSYCHOLOGICAL EFFECTS: JET LAG SYNDROME

Travel is generally thought to improve quality of life (QOL), but there are few epidemiological reports regarding how CKD patients' state of mind is affected by travel. Psychological stress due to travel, insufficient sleep, autonomic nervous system tone, and disturbed circadian rhythm due to time differences may also negatively impact fluctuations in blood pressure.[66,67] A proposed mechanism for hypertension and CVD events due to jet lag disorder is that jet lag syndrome causes circadian rhythm disorder, which leads to an elevated level of aldosterone, increased autonomic nervous activity, and increased salt sensitivity. These result in hypertension and CVD events.[66,67]

Air travel to regions with a time difference of 4–5 h or more may result in a transient state of disharmony, defined as jet lag syndrome. The diagnostic criteria for circadian rhythm sleep disorder and the jet lag type (jet lag disorder) in the International Classification of Sleep Disorders, Second Edition are adapted from a study by Kario [Table 3].[67]

**Table 3: Diagnostic criteria for circadian rhythm sleep disorder, jet lag type (jet lag disorder) in the International Classification of Sleep Disorders-2[67]**

| |
|---|
| Diagnosis must satisfy the following three items |
| A. Complaint of insomnia or intense drowsiness during the day in association with transmeridian travel exceeding at least two time zones |
| B. Impaired function during the day, systemic undefined complaints, or physical symptoms such as gastrointestinal disorders within 1-2 days after travel |
| C. This sleep disorder cannot be explained with other currently known sleep disorders, physical disease, neurological disease, mental illness, medication, or substance abuse |

ICSD-2=International Classification of Sleep Disorders-2

Circadian rhythms are coordinated by a central pacemaker or clock in the suprachiasmatic nucleus of the hypothalamus.[68] A peripheral biological clock exists in organs, including liver, heart, lung, and kidney.[69] There is a relationship between jet lag syndrome and the onset of hypertension and CVD events. The proposed mechanism involves a disturbance of circadian rhythm, resulting in raised aldosterone levels, enhanced autonomic nervous activity, salt sensitivity, and ultimately in hypertension and CVD events.[67] A survey of 257 bus passengers in Japan showed that 88.3% of all bus passengers had an increased perception of this disease, with the main reported symptoms being difficulty in sleeping (67.3%), intense drowsiness during the day (16.7%), reduced ability to work (14.4%), and other undefined complaints.[68] Causes of jet lag syndrome include insufficient sleep, fatigue, hypoxia, altered meal timing, the light-and-dark cycle in the aircraft, direction of the flight, chronotype (morningness, eveningness), and age. A person's biological rhythm has a cycle that is longer than 24 h; therefore, delaying the phase of the biological rhythm makes it easier to adjust the rhythm. Thus, eastward flights (e.g., from Japan to the USA) produce more intense symptoms than westward flights (e.g., from Japan to Europe). Individuals with an eveningness chronotype adapt more quickly after westward flights to Europe and struggle to adapt more in the opposite direction. The biological clock within healthy human subjects is reset when they experience solar light, melatonin is secreted 15–16 h after this reset, and physiological sleepiness occurs.[70] Countermeasures include sleeping pills, exposure to bright light, melatonin, and melatonin receptor agonists. With sleeping pills, it is necessary to watch for transient amnesia or traveler's thrombosis, which occurs more readily when alcohol is also used. Intense light of 2500 lux or higher alters the circadian rhythm. While bright morning light advances circadian rhythm, bright light in the evening rewinds circadian rhythm. Melatonin, a pineal hormone, acts to promote re-synchronization of the circadian rhythm. If melatonin is taken at night, in contrast to bright light, then the circadian rhythm is pushed forward, whereas

it is pushed back if it is taken in the morning. Taking melatonin before bedtime reportedly improves untreated hypertension.[71]

Regarding the relationship between CKD and circadian rhythm, sleep is important for the QOL of patients with ESRD, and melatonin is also relevant for this purpose.[72] Melatonin is responsible for various biological functions, such as suppressing sympathetic nervous activity, maintaining endothelial function, bioavailability of nitric oxide, apoptosis, and adjusting vascular function; it also possesses antioxidant properties.[73-75] As CKD progresses, melatonin levels fall[76] and hemodialysis patients show reduced nocturnal melatonin secretion.[77]

This impaired melatonin secretion reportedly involves elevated levels of tumor necrosis factor in CKD-suppressing melatonin.[78] Impairment of nocturnal melatonin secretion has also been implicated in renal impairment in patients with CKD.[79] Melatonin supplements improve QOL and sleep quality in hemodialysis patients.[80]

Ramelteon, which is a melatonin receptor agonist used as a sleeping aid, is generally regarded as effective in relieving jet lag syndrome,[81,82] and it may also be effective for hemodialysis patients. Thus, the melatoninergic drugs are promising, but large trials in real-life situations are needed.[83,84]

CKD patients have a higher risk of CVD events compared with the general population, and it is therefore important to avoid disturbances to the circadian rhythm due to travel, given the association between altered melatonin homeostasis and CKD.

## CONCLUSION

Travel leads to a better QOL, and there is a steadily growing demand for travel in today's aging society. CKD patients are believed to be at a higher risk than healthy individuals when they travel, owing to the aforementioned concerns about the impact on their mental and physical well-being; thus, travel is something that should be weighed carefully. However, there is almost no epidemiological evidence regarding the effect of travel on CKD patients, and the pathophysiology of travel-related illness in this population remains poorly understood. In our conventional study,[85] we showed an association between disease severity and travel in CKD patients in terms of the degree and frequency of the disease, but not with respect to the detailed mechanism and risks.

In addition, few reports have investigated the impact of travel on CKD patients. Therefore, in the present study, we performed a detailed examination based on more recent reports and provided updated information. We offer the following tips for travelers with CKD. CKD increases the risk of traveler's thrombosis. Low-molecular-weight heparin is useful for long-distance travelers only if they are at high risk for VTE. CKD patients who remain at high altitudes pose an increased risk for progression of CKD, altitude sickness, and pulmonary edema. Rifamycin is a recommended treatment for traveler's diarrhea because it is not absorbed into the blood. Jet lag syndrome is a risk for hypertension and CVD events. The melatoninergic drugs may be effective in relieving jet lag syndrome for hemodialysis patients.

Collecting data on patients with renal failure in various altered environments will improve our ability to predict risk and improve patient safety.

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### Conflicts of interest

There are no conflicts of interest.

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