Title
Perspiration interventions for conservative management of kidney disease and uremia.

Journal
Current opinion in nephrology and hypertension, 29(1)

ISSN
1062-4821

Authors
Keller, Raymond W
Kopple, Joel D
Kalantar-Zadeh, Kamyar

Publication Date
2020

DOI
10.1097/mnh.0000000000000569

Perspiration interventions for conservative management of kidney disease and uremia

Raymond W. Keller Jr[a], *Joel D. Kopple*[b], *and Kamyar Kalantar-Zadeh*[c]

Purpose of review
There has been an increasing interest in developing novel technologies to treat patients with chronic kidney disease as evidenced by KidneyX, the public–private partnership between government and industry. Perhaps a simple technology for treating kidney failure would be to utilize perspiration. It is a physiological process, and when used properly it might not be an unpleasant experience. This review will explore the current state of knowledge regarding perspiration therapy in the setting of far advanced kidney failure.

Recent findings
A literature review using the PubMed database was conducted between 1 April 2019 and 3 September 2019. Search terms are shown in Table 1. Major themes of the results include diaphoresis therapy for patients with chronic kidney disease, excessive perspiration causing kidney disease, analysis of sweat to diagnose cystic fibrosis, and analysis of sweat to replenish lost electrolytes. This review will focus on intentional perspiration for the treatment of patients with end-stage renal disease (ESRD). Studies have shown that perspiration, or sweat-based therapies, can provide some of the most important currently recognized therapeutic goals in treating ESRD. These goals include decreased interdialytic weight gain, reduced serum potassium levels, and benefits to cardiovascular status. Research has shed light on some of the mechanisms, both molecular and clinical, that may be involved in induced perspiration therapy in ESRD.

Summary
There is a long history of humans using perspiration for both recreation and therapy. Perspiration therapy for ESRD experienced a surge in the United States in the 1960s but does not have much modern momentum. With the continued growth of the ESRD population worldwide this could be considered an appropriate time to conduct more research into this promising therapy.

Keywords
dialysis, kidney disease, kidney failure, perspiration, sauna

INTRODUCTION

Interest in the use of sweating to treat renal diseases has been with us since antiquity, being suggested by Hippocrates, Aristotle, Galen, and numerous contemporary authors [1–7,8▪,9–13]. Galen was the first to publish that perspiration could reduce edema from any cause [14]. Perhaps the most interesting way of inducing perspiration in early Anno Domini history was hot sand baths. In current times, the most common methods of inducing passive diaphoresis, defined as diaphoresis induced by heat stress from exogenous sources with no increase in basal metabolic levels [15], includes the traditional dry (Finnish) sauna, the infrared (IR) 'sauna,' and the wet (Turkish) bath. Renewed interest in perspiration to treat renal failure was the genesis of this article and likely of another recent article reviewing the therapeutic value of perspiration in patients with kidney failure [16]. With the continued rise in the prevalence of end-stage renal disease (ESRD) in the United States, most recently at 726,331 patients, and with a current cost of $35 billion (8–10% of the Medicare budget) [17] it is reasonable to explore physiologic alternatives and less expensive treatments for patients with chronic kidney disease and especially ESRD. Although this article focuses

[a]Third Kidney, Inc, Biddeford, Maine, [b]UCLA Schools of Medicine and Public Health and Lundquist Institute at Harbor-UCLA Medical Center, Torrance and [c]University of California Irvine Nephrology, Orange, California, USA

Correspondence to Raymond W. Keller, DO, Third Kidney, Inc., 546 Pool St, Biddeford, ME 04005, USA. Tel: +1 207 929 0576; e-mail: raykeller@gmail.com

Curr Opin Nephrol Hypertens 2020, 29:57–63
DOI:10.1097/MNH.0000000000000569

KEY POINTS

- Perspiration therapy for treatment of chronic kidney disease.
- Therapeutic value of sauna in humans.
- Sweat therapy in dialysis patients.

on ESRD in the United States, ESRD is not unique to the United States. The benefits of perspiration may be applicable to any human suffering from chronic kidney disease or ESRD (Table 1).

Physiology of sweating

There are three main types of sweat glands: eccrine sweat glands, apocrine sweat glands, and apoeccrine sweat glands. A brief review can be found by Wilke *et al.* [18]. The present article will focus on the eccrine sweat glands which can produce a copious, watery hypotonic solution whose osmolality is mainly due to electrolytes [18,19].

The average human body has between 2 and 4 million eccrine sweat glands that share some functional and morphological characteristics with the nephron [1,19]. The main function of the eccrine sweat glands is to produce copious fluid that can provide evaporative cooling for the human body. In normal people, moderate thermal stress can stimulate the sweat glands to produce an average of 500–1000 ml sweat per hour [6]. In heat trained humans hourly sweat production can approach 2 L/h [6]. Daily sweat production can exceed 12 L in warm climates [14]. Sweat is always hypotonic to serum, but paradoxically, if persons sweat profusely and drink large amounts of water with little sodium intake, they may become hyponatremic.

Table 1. Review of the literature related to perspiration and uremia

Search term	Hits
Sauna uremia	3
Sauna kidney disease	13
Sauna renal failure	10
Sauna dialysis	5
Sauna ultrafiltration	2
Sauna toxin	9
Perspiration kidney disease	409
Perspiration renal failure	189
Perspiration uremia	33
Perspiration dialysis	107
Perspiration ultrafiltration	9
Perspiration toxin	553
Sweat kidney disease	252
Sweat renal failure	82
Sweat uremia	21
Sweat dialysis	58
Sweat toxin	252

Composition of sweat

The solute composition of sweat varies greatly. The major determinants of sweat composition include sweat rate, nutritional status, and disease states. The osmolality of sweat can range between 5 and 60 mEq/l [19]. The major constituents in sweat include sodium, chloride, potassium, lactic acid, urea, and ammonium [18,19]. Other constituents include phosphorus, creatinine, calcium, glucose, and heavy metals [20–23]. At minimal sweat rates, the majority of solutes are reabsorbed by the sweat duct, thus promoting the reabsorption of most of the perspired water; under these conditions sweating is not a useful excretory mechanism. At maximal sweat rates the concentration of sodium in sweat can reach 50–60 mEq/l while the potassium and urea concentrations can be quite large. Sweat potassium, urea, and lactic acids concentrations can approach or exceed serum concentrations [15]. Sweat potassium and urea can reach up to four times their plasma concentrations [16]. An interesting phenomenon with sweat potassium and urea concentrations is that they increase proportionately as the serum levels rise. This fact might be important for potential diagnosis and treatment of patients with ESRD.

Changes occur at the molecular and transporter level in the sweat glands of patients with ESRD. Although the evidence is sparse, rodent and human studies show that urea and aquaporin transporters are regulated in eccrine sweat glands in the setting of chronic kidney disease (CKD) [24,25]. The kidney also shows distinct changes in urea transport in the setting of advanced CKD [26].

METHODS OF NATURALLY INDUCING PERSPIRATION

There are many ways to induce passive sweating in humans, a passive sweat being one that requires no effort from the participant. Current practice favors thermal and pharmaceutical stimulation as the most reliable methods. Thermal stimulation can take the form of endogenously produced heat during exercise, convective, conductive, or radiative

transfer of energy. This review will focus on traditional Finnish sauna and water immersion (convective and conductive heating) recognizing that there are many other methods to warm the human body and activate sweat glands. The focus on sauna and water immersion is based on trends in published research. We specifically exclude IR 'sauna' techniques as they are likely not robust enough to induce large water losses.

Exercise is perhaps the most variable inducer of sweat, varying widely with ambient temperature, humidity, and exercise intensity, leading to variable rates of sweat generation. Saunas produce a dry heat, usually in the range recommended by the Finnish Sauna Society of 80–100 °C, or 176–212 °F. Depending on exposure times, 200 °F can be a sustainable temperature. Since hot tubs mostly abolish the evaporative cooling effect of sweat, they usually do not exceed 106 °F. All three methods of thermally induced sweat have shown benefits in CKD patients.

PHARMACOLOGIC SWEAT STIMULATION

Sweat glands, being innervated by postganglionic sympathetic cholinergic nerve fibers [18] are stimulated unlike other cholinergic nerve targets. Thus, pilocarpine and other cholinergic agonists are the most reliable ways to activate eccrine sweat glands. The effect of pilocarpine on the skin of hemodialysis patients has not gone unnoticed by scholars, with at least one trial being conducted on electrodermal resistance [27]. There are many other studies of cholinergic agonists on sweating. They are not included in this review because the evidence for their effectiveness did not appear to be strong. Although pilocarpine is a classic producer of perspiration, capsaicin, a regularly available drug, also affects sweating. However, publications could not be found in which capsaicin was evaluated for its effects on systemic sweat production or sweat composition. Exposure to different pharmaceuticals, environmental conditions, and steroids produces different sweat compositions [21,28–30]. Thus, Capsaicin, other TRPV1 (transient receptor potential vanilloid) agonists, cholinergic agonists, and other sweat modulating compounds when ingested or applied topically might be promising targets for maximizing sweat production, but the long-term effectiveness and safety of these pharmacological agents in CKD and ESRD patients are unknown.

KINETICS OF HEMODIALYSIS

The largest proportion of small solute removal occurs within the first 2 hours of a typical 4-hours hemodialysis treatment. Most solute is removed within the first 2 h of initiating dialysis including potassium and phosphorus [31,32▪]. Limitations on the rate at which water can be safely removed is a major factor requiring hemodialysis sessions to last upward of 4 h and that sometimes necessitate more than three hemodialysis sessions per week [33]. Volume control can be an indication for quotidian hemodialysis or peritoneal dialysis.

SHORTCOMINGS IN DIALYSIS

Despite its life-saving effects, there are many unresolved problems associated with chronic dialysis treatment. These challenges include appropriate control of body water and sodium chloride [33,34▪▪] and managing hyperkalemia [35]. Chronic hemodialysis patients are often volume overloaded, even after completing a hemodialysis treatment. Models of volume overload indicate that increases in fluid overload are associated with increasing mortality [36]. Fluid overload is a cause of hypertension, left ventricular hypertrophy, heart failure and premature mortality in maintenance hemodialysis patients [37]. The dilemma of controlling fluid is highlighted by the addition of fluid management to KidneyX's prize competition. Hyperkalemia not rarely requires emergent dialysis and can be fatal in ESRD patients. There are, of course, many other uremic toxins [38,39], but it could be argued that no others have as strong as a pathophysiological relationship to morbidity and mortality as sodium chloride and water overload and hyperkalemia.

REVIEW OF PRIOR DIAPHORESIS STUDIES

Despite the long history of sweat-based therapies there is still no consensus as to whether this therapy would be beneficial for patients with different stages of CKD or ESRD. To our knowledge, our own group and that of Dr. Pruijm is the most recent group to do basic research and clinical trials of perspiration therapy for patients with ESRD [7,25].

Table 2 provides a summary of researchers and their experiences using diaphoretic therapies to treat ESRD. The first and most obvious benefit to sweating is natural fluid removal. Copious amounts of water may be removed from the body when sweating. During diaphoresis, there may be increases in cutaneous blood flow of 8–10 times normal which result in a water loss of up to 2 L of water per hour. In an acclimatized, healthy human this sweat rate can maintained for many hours and even days [19]. While we know there are changes at the molecular and structural level the effect of kidney disease on sweat rates is unknown. For patient comfort a realistic treatment goal might be 1 L/h.

Table 2. Review of published studies relevant to perspiration and uremia

Year published	First author	Study population	Temperature	Exposure time	Blood sample collection	Frequency	BUN	BP	K+	Water	Miscellaneous
1997	Al-Tamer [23]	11 Females, once weekly dialysis	40–45 °C (air)	Once, day of dialysis session, summer	Not reported		BUN is seasonal, lower in summer				Highly trained sweaters
2003	Michalsen [40]	15 CHF EF 30–40%	40 °C (water)	10 min thrice daily	Not reported	6 Weeks, daily exposure	N/A	5 Point systolic decrease	N/A	N/A	Quality of life improved
1966	Snyder [9]	8 Uremic (2 dialysis), GFR avg. 2.8	75 °C (air)	30 min	Before and after sauna	4× weekly for 12 weeks	Sweat: Plasma 3 : 1, 4.2 g per treatment			780 ml/day (26 ml/min)	EKG sinus tachycardia (normal), pH 4.8–7.1, resolution of pruritis
1978	Man in't Veld [6]	1	70 °C (air)	1–2 h	Prior to dialysis	Thrice weekly	27 → 18, protein intake 55 → 60 g/day		5.9 → 3.2, intake 50–90 mEq/day		30 min hot water bath daily as effective as 2 h sauna thrice weekly
1982	Henderson [13]	10, anuric, hypertensive, under 40	80 °C (air)	1 h	Before and after sauna	Sporadic	No change	MAP 125 → 110	No change	N/A	All participants commented on feeling of well being
1978	Lacher [3]	ESRD under 50 years of age, not on dialysis	40 °C (water)	3 h	Not stated	6 Consecutive days, daily	110 → 80, still trending downward	135/85 → 84/52 (best example)		Rehydration challenging	Decreased muscle cramping
2013	Pruijm [7]	$n = 14$	37–43 °C (air and water)	30 min	Weekly, before dialysis session	4× weekly	27 → 23	Trend to lowered	5.9 → 5.5	IDWG 2.34 → 1.84	Anti-HTN medications decreased from 2.8 to 1.9

BP, blood pressure; BUN, blood urea nitrogen; CHF, congestive heart failure; EF, ejection fraction; EKG, electrocardiogram; ESRD, end-stage renal disease; GFR, glomerular filtration rate; IDWG, interdialytic weight gain; MAP, mean arterial pressure.

As ultrafiltration rates rise the chance of symptoms of hypovolemia increase, markedly so after an ultrafiltration rate of 600 ml/h [37]. Because sweat clearances are physiological, they might be capable of clearing fluid without the symptoms and sequalae of hypovolemia encountered with high ultrafiltration rates. Since restriction of water intake is onerous for a large proportion of maintenance hemodialysis patients, the prospect of augmenting chronic hemodialysis treatments with diaphoresis therapy and thereby allowing patients much less restriction or no restriction on their water intake may be very attractive to many patients. In fact, a small pilot study performed at the University of Colorado found that daily sauna sessions did allow hemodialysis patients to have an unrestricted fluid intake [9].

The potential benefits of urea removal by sweating are unclear. On the one hand, urea is overwhelmingly the major nitrogenous product of protein and amino acid metabolism in ESRD patients. On the other hand, urea tends to be to be only mildly toxic [41]. Urea removal is also the benchmark for dosing dialysis. It is noteworthy that the eccrine sweat gland concentrates urea. The sweat : serum concentration gradient approaches 4 : 1. It may be of value to characterize the dose of perspiration therapy in terms of urea clearance as well of water removal. Future research may answer this question.

Hyperkalemia has been associated with higher mortality in patients on dialysis [35]. The increased mortality during the 3-day 'dialysis weekend' may be at least partly due to arrhythmias induced by hyperkalemia. Sweat glands are capable of concentrating potassium, and the sweat : plasma ratio of potassium approaches 3 : 1. A seminal study in 1982 at the Royal Infirmary in Glasgow reported a trend toward significant reductions in serum potassium after a single 1-h sauna treatment [9]. Other studies using different methods of inducing diaphoresis have described similar results [6,7].

Many chronic dialysis patients experience pruritus. The constant itching in patients receiving dialysis may severely reduce quality of life. A reduction in pruritus with diaphoresis therapy was demonstrated in a study done in 1966 at the Brigham and Women's Hospital in Boston. After 6 days of daily sauna treatment all patients reported a complete resolution of pruritus [9]. Advances in dialysis membranes appear to have decreased pruritus, but have far from eliminated it [42▪▪]. The mechanism of dialysis might dehydrate the stratum corneum leading to pruritus [43]. Sauna and water immersion therapy may serve to provide hydration to the skin and relieve pruritus. Water immersion may be particularly suited to reduce pruritus because emollients or oils may be added to the bath water. Moreover, sweat itself may contain oils that could lubricate skin and possibly reduce pruritus.

OTHER POTENTIAL USES FOR PERSPIRATION THERAPY

In addition to its use to augment the benefits of chronic dialysis therapy, diaphoresis might be used to delay the need for dialysis treatments, particularly if it were employed in conjunction with high calorie and low protein, sodium, potassium, and phosphorus diets. This use of diaphoretic therapy might be particularly useful in parts of the world where chronic dialysis therapy is not available at no cost to all members of society. Perspiration therapy might also be useful for people with treatment-resistant nephrotic syndrome with severe edema or other medicine-resistant edematous states including chronic severe heart failure or ascites.

A number of hemodynamic changes have been described with heat exposure. Heart rate and pulse pressure may increase, and peripheral vascular resistance may decrease [44]. Blood pressure may rise or fall [45]. Renal blood flow may increase or decrease. Glomerular filtration rate seems to remain stable although renal vascular resistance may rise [45]. It is not known how many CKD and ESRD patients will undergo the same responses as normal people. Clinical trials of diaphoretic therapy conducted in ESRD patients, usually several decades ago, seem to indicate that this therapy is well tolerated (Table 2). Until more information is available, it would seem prudent to monitor carefully patients who are undergoing perspiration therapy, especially those who are very young, elderly or have a history of cardiovascular disease.

HAZARDS OF CHRONIC HEAT EXPOSURE

There is an increasing body of literature that continuous exposure to hot climates without proper hydration and nutrition can cause renal failure. Overzealous use of the sauna or hot baths can lead to dehydration and electrolyte disturbances [46,47].

POTENTIAL HAZARDS OF THE SAUNA

The published literature on diaphoresis therapy for maintenance hemodialysis patients suggest that deliberate prescribed, controlled, and monitored perspiration is safe for the great majority of these individuals. Core body temperatures of up to 104 °F have been considered safe for short exposures in healthy individuals. Research will be needed to

determine if core body temperature is an acceptable safety marker for patient with ESRD and if so what values are acceptable.

The overzealous use of sauna has been reported to cause acute kidney disease and death [46–48]. All reports were in healthy individuals and most reports are attributed to misuse of the sauna including ethanol intoxication and over-exposure [49▪].

The following considerations are important to keep in mind regarding the safe use of the sauna or hot baths:

(1) Sauna or hot baths should not be considered an instrument for body tissue mass or fat loss tool because, despite claims that sauna increases calories burned during the exposure there is no evidence or theoretical basis to support this concept [50]. Since saunas and hot baths cause weight (water) loss, it is not surprising that some people confuse this weight loss with fat loss.
(2) Patients with sickle cell disease may be at a uniquely increased risk of developing a sickle cell crisis from excessive sauna use [48].
(3) Although imbibing ethanol, at low doses, may increase sweat gland secretion [51], it can also impair judgment when the person is exposed to heat therapy. Deaths have been described during sauna treatments of healthy individuals with elevated blood alcohol levels [49▪]. Therefore, anyone participating in the methods described in this article is cautioned against ethanol intake shortly before and after their experience.

CONCLUSION

Perspiration-based therapies for the treatment of volume overload in chronic dialysis patients has been supported in previous research and deserves further research. Future studies should assess the efficacy of sauna, hot bath or other sweat-based therapies to improve symptoms and quality of life or to delay or augment dialysis therapy of patients with CKD and ESRD. Larger scale clinical trials are needed to more define the indications for diaphoresis therapy, the optimal techniques for these procedures and the safety issues involved with this treatment.

Acknowledgements

Dr. Jeff Sands for his ongoing mentorship.

Financial support and sponsorship

None.

Conflicts of interest

R.K. is an executive with Third Kidney.
Potential Conflicts of Interest: R.W.K. is the founding CEO of the Third Kidney, which is attempting to bring a medical grade perspiration device to market. Other authors have not declared relevant conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
- ▪ of special interest
- ▪▪ of outstanding interest

1. Diamandopoulos AA GP. Substitution of renal function through skin catharsis: evidence from the classical period to the middle ages. Kidney Int 2001; 59:1580–1589.
2. Berlyne GM, Brown C, Adler A, *et al.* Water immersion in nephrotic syndrome. Arch Intern Med 1981; 141:1275–1278.
3. Lacher JW, Schrier RW. Sweating treatment for chronic renal failure. Nephron 1978; 21:255–259.
4. Sobel J, Seifter E. Sweating in the Treatment of Chronic Uraemia. Lancet 1964; 2:760–761.
5. El-Housseini Y, Mahfoudh H, Jarraya F, *et al.* Stimulated sweating in order to improve the water-and-salt balance in hemodialysis patients. A case report. Nephrol Ther 2012; 8:472–475.
6. Man in 't Veld AJ, van Maanen JH, Schicht IM. Stimulated sweating in chronic renal failure. Br Med J 1978; 2:172–173.
7. Pruijm M, El-Housseini Y, Mahfoudh H, *et al.* Stimulated sweating as a therapy to reduce interdialytic weight gain and improve potassium balance in chronic hemodialysis patients: a pilot study. Hemodial Int 2013; 17:240–248.
8. Wurzner-Ghajarzadeh A, Braconnier P, Burnier M, Pruijm M. The skin as third
▪ kidney. Rev Med Suisse 2019; 15:418–421.
I regularly correspond with Menno. His article is similar to this one which lends validation to this article.
9. Snyder D, Merrill JP. Sauna baths in the treatment of chronic renal failure. Trans Am Soc Artif Intern Organs 1966; 12:188–192.
10. Pyrih LA, Berezovs'kyi V, Dudar IO. Infrared sweat secretion stimulation as a means of homeostatic correction in patients with kidney dysfunction. Fiziol Zh 2003; 49:25–29.
11. Krishna GG, Danovitch GM. Effects of water immersion on renal function in the nephrotic syndrome. Kidney Int 1982; 21:395–401.
12. Tapolyai MB, Faludi M, Berta K, *et al.* The effect of ambient temperature and humidity on interdialytic weight gains in end-stage renal disease patients on maintenance hemodialysis. Int Urol Nephrol 2016; 48:1171–1176.
13. Henderson IS, Podmore P, Spence MS. Diaphoretic therapy in regular dialysis patients. Scott Med J 1982; 27:234–235.
14. Diamandopoulos AA, Goudas PC. Substitution of renal function through skin catharsis: evidence from the classical period to the middle ages. Kidney Int 2001; 59:1580–1589.
15. Crandall CG, Wilson TE. Human cardiovascular responses to passive heat stress. Compr Physiol 2015; 5:17–43.
16. Hanafusa N, Lodebo BT, Shah A, Kopple JD. Is there a role for diaphoresis therapy for advanced chronic kidney disease patients? J Ren Nutr 2017; 27:295–302.
17. USRDS. 2018 USRDS annual data report: executive summary. Am J Kidney Dis 2019; 73:A9–A22.
18. Wilke K, Martin A, Terstegen L, Biel SS. A short history of sweat gland biology. Int J Cosmet Sci 2007; 29:169–179.
19. Hall JE. Guyton and Hall textbook of medical physiology. Hall JE, editor. , 12 ed. Philadelphia, PA: Saunders Elsevier; 2011. pp. 867–877.
20. Ely MR, Kenefick RW, Cheuvront SN, *et al.* The effect of heat acclimation on sweat microminerals: artifact of surface contamination. Int J Sport Nutr Exerc Metab 2013; 23:470–479.
21. Chinevere TD, Kenefick RW, Cheuvront SN, *et al.* Effect of heat acclimation on sweat minerals. Med Sci Sports Exerc 2008; 40:886–891.
22. Crinnion W. Sauna as a valuable clinical tool for cardiovascular, autoimmune, toxicant-induced and other chronic health problems. Altern Med Rev 2011; 16:215–225.
23. al-Tamer YY, Hadi EA, al-Badrani II. Sweat urea, uric acid and creatinine concentrations in uraemic patients. Urol Res 1997; 25:337–340.
24. Xie L, Jin L, Feng J, Lv J. The expression of AQP5 and UTs in the sweat glands of uremic patients. Biomed Res Int 2017; 2017:8629783.
25. Keller RW, Bailey JL, Wang Y, *et al.* Urea transporters and sweat response to uremia. Physiol Rep 2016; 4:.
26. Sands JM. Molecular mechanisms of urea transport. J Membr Biol 2003; 191:149–163.

27. Marczewski K, Janicka L, Cudny J. The effect of pilocarpine on electrodermal resistance in chronic hemodialyzed patients. Clin Nephrol 1993; 39:88–91.

28. Taussig LM, Braunstein GD. Effects of vasopressin on sweat rate and composition in patients with diabetes insipidus and normal controls. J Invest Dermatol 1973; 60:197–202.

29. Sato K, Sato F. Pharmacologic responsiveness of isolated single eccrine sweat glands. Am J Physiol 1981; 240:R44–R51.

30. Saga K, Sato F, Sato K. K+ efflux from the monkey eccrine secretory coil during the transient of stimulation with agonists. J Physiol 1988; 405:205–217.

31. Gutzwiller JP, Schneditz D, Huber AR, *et al.* Increasing blood flow increases kt/V(urea) and potassium removal but fails to improve phosphate removal. Clin Nephrol 2003; 59:130–136.

32. ■ Pietribiasi M, Waniewski J, Wojcik-Zaluska A, *et al.* Model of fluid and solute shifts during hemodialysis with active transport of sodium and potassium. PLoS One 2018; 13:e0209553.

This article provides a nice mathematical model to describe the transfer of sodium, potassium, and urea between compartments during dialysis.

33. Chou JA, Kalantar-Zadeh K. Volume balance and intradialytic ultrafiltration rate in the hemodialysis patient. Curr Heart Fail Rep 2017; 14:421–427.

34. ■■ Twardowski ZJ, Misra M. A need for a paradigm shift in focus: from Kt/Vurea to appropriate removal of sodium (the ignored uremic toxin). Hemodial Int 2018; 22(S2):S29–S64.

This article provides major criticisms to the HEMO study, which are justified. It also raises the question of whether urea is an appropriate molecule to dose dialysis.

35. Montford JR, Linas S. How dangerous is hyperkalemia? J Am Soc Nephrol 2017; 28:3155–3165.

36. Daugirdas JT, Greene T, Depner TA, *et al.* Modeled urea distribution volume and mortality in the HEMO Study. Clin J Am Soc Nephrol 2011; 6:1129–1138.

37. J A. Fluid and solute removal: how and why (part two) https://www.home-dialysis.org/life-at-home/articles/fluid-and-solute-removal-part-two. [Accessed 10 July 2018]

38. Vanholder R, De Smet R, Glorieux G, *et al.* Review on uremic toxins: classification, concentration, and interindividual variability. Kidney Int 2003; 63:1934–1943.

39. Vanholder R, Meert N, Schepers E, *et al.* Review on uraemic solutes II – variability in reported concentrations: causes and consequences. Nephrol Dial Transplant 2007; 22:3115–3121.

40. Michalsen A, Ludtke R, Buhring M, *et al.* Thermal hydrotherapy improves quality of life and hemodynamic function in patients with chronic heart failure. Am Heart J 2003; 146:728–733.

41. Kopple JMS, Kalantar-Zadeh K. Nutritional management of renal disease. 3rd ed Amsterdam: Elsevier; 2012.

42. ■■ Hu X, Sang Y, Yang M, *et al.* Prevalence of chronic kidney disease-associated pruritus among adult dialysis patients: a meta-analysis of cross-sectional studies. Medicine (Baltimore) 2018; 97:e10633.

The article shows that although improvements in dialysis membranes have improved pruritis the problem is far from solved.

43. Park TH, Park CH, Ha SK, *et al.* Dry skin (xerosis) in patients undergoing maintenance haemodialysis: the role of decreased sweating of the eccrine sweat gland. Nephrol Dial Transplant 1995; 10:2269–2273.

44. Gayda M, Paillard F, Sosner P, *et al.* Effects of sauna alone and postexercise sauna baths on blood pressure and hemodynamic variables in patients with untreated hypertension. J Clin Hypertens (Greenwich) 2012; 14:553–560.

45. Vuori I. Sauna Bather's circulation. Ann Clin Res 1988; 20:249–256.

46. Dean S, Green DJ, Melnick SC. Hazards of the sauna. Br Med J 1977; 1:1449.

47. Hannuksela ML, Ellahham S. Benefits and risks of sauna bathing. Am J Med 2001; 110:118–126.

48. Hofmann N, Waldherr R, Schwenger V. Is the sauna a common place for experiencing acute renal failure? Nephrol Dial Transplant 2005; 20:235–237.

49. ■ Yang KM, Lee BW, Oh J, Yoo SH. Characteristics of sauna deaths in Korea in relation to different blood alcohol concentrations. Forensic Sci Med Pathol 2018; 14:307–313.

The article shows that alcohol an be a cause of morbidity and mortality when using sauna.

50. R H. The truth about that rumor that saunas can help you lose weight https://www.self.com/story/the-truth-about-that-rumor-that-saunas-can-help-you-lose-weight2016. [Accessed 10 September 2019]

51. Yoda T, Crawshaw LI, Nakamura M, *et al.* Effects of alcohol on thermoregulation during mild heat exposure in humans. Alcohol 2005; 36:195–200.