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The pathophysiology of edema formation in the nephrotic syndrome

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The mechanism of edema formation in the nephrotic syndrome has long been a source of controversy. In this review, through the construct of Starling's forces, we examine the roles of albumin, intravascular volume, and neurohormones on edema formation and highlight the evolving literature on the role of primary sodium absorption in edema formation. We propose that a unifying mechanism of sodium retention is present in the nephrotic syndrome regardless of intravascular volume status and is due to the activation of epithelial sodium channel by serine proteases in the glomerular filtrate of nephrotic patients. Finally, we assert that mechanisms in addition to sodium retention are likely operant in the formation of nephrotic edema.

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Edema is the classic clinical presentation of the nephrotic syndrome. The mechanisms of edema formation in the nephrotic syndrome have long been a subject of investigation and are continually debated. The 'underfill' hypothesis states that a decrement in oncotic pressure leads to excess filtration of fluid from the intravascular space to the interstitial space, causing hypovolemia, renal hypoperfusion, activation of the renin–angiotensin–aldosterone system, and secondary renal sodium retention. The 'overfill' hypothesis states that the nephrotic syndrome causes primary renal sodium retention, leading to edema. The purpose of this review is to describe in detail the state of current knowledge in this area and ultimately to provide a unifying model of edema formation in the nephrotic syndrome. We will individually discuss the contribution of plasma oncotic pressure, the state of intravascular volume, perturbation in hormonal systems, and the role of primary sodium retention by the kidney using the framework provided by Starling:

$$J_v = K_f([P_c - P_i] - \sigma[\pi_c - \pi_i])$$

- J_v is the net fluid movement between compartments.
- $[P_c - P_i]$: Capillary-interstitial hydrostatic pressure
- σ: reflection coefficient to proteins; which varies between 0 and 1 and reflects in this particular context some attribute of the permeability of capillaries to albumin and other large proteins
- $[\pi_c - \pi_i]$: oncotic pressure (c is capillary and I is interstitial)
- K_f = overall filtration permeability constant to volume flow (hydraulic conductivity and includes a term for surface area)

Both K_f and σ are measures of vascular permeability. K_f, the product of hydraulic conductance and capillary surface area, is essentially a measure of capillary permeability to volume flow.[1] When the capillary is modeled as a surface with many pores, then its hydraulic conductance depends on the number of pores present, the radius of the pores, and the thickness of the capillary wall.[1] However, this parameter is not a true constant, rather it is known to increase in response to increases in intravascular pressure[2,3] and hyperglycemia.[4] Also, σ is some measure of the permeability of the capillary to

proteins. A σ value of 1 signifies that a capillary is completely impermeable to proteins, whereas a value of 0 signifies complete permeability to proteins.[1] This parameter has been shown to decrease in response to inflammatory mediators such as histamine and bradykinin.[5] Although an increase in K_f does not necessarily produce a change in σ,[4] an decrease in σ (as with an increase in pore size) necessitates an increase in K_f. Further complicating matters is that vascular permeability is calculated rather than directly measured. It is therefore difficult to separate changes in permeability to different substances from current experiments in large part because of the lack of knowledge of the actual path that fluid flow takes across a complex biological structure such as a capillary. For this reason, for the remainder of the review, we will refer to K_f and σ under the general term of vascular permeability.

CHANGES IN ONCOTIC PRESSURE GRADIENTS [$\pi_c - \pi_i$]

A fundamental aspect of the 'underfill' theory is that a decrement in plasma albumin (and hence oncotic pressure) reduces the intravascular-to-interstitial albumin gradient producing an increase in the driving force for fluid filtration out of the intravascular space into the interstitial space. Several studies have addressed this important issue.

Hypoalbuminemia is accompanied by a parallel decrease in interstitial albumin

Joles[6] showed that analbuminemic Nagase rats had no difference in transcapillary colloid osmotic pressure gradient when compared with Sprague-Dawley rats of similar age owing to increases in nonalbumin proteins in the Nagase rats. Fiorotto and Coward[7] utilized a starvation model of hypoproteinemia to study the driving forces for edema formation in rats. The experiments showed that as serum oncotic pressure decreases there is a parallel decrease in interstitial oncotic pressure of greater magnitude (Figure 1). Also notable was that the normally negative interstitial hydrostatic pressure approached zero at the time of edema formation. For these reasons, despite the decrement in plasma oncotic pressure in the protein malnourished rats, the net driving force for edema formation was not significantly different from control rats. Preservation of the oncotic pressure gradient due to parallel decreases in serum and interstitial oncotic pressures has also been demonstrated in humans with the nephrotic syndrome.[8–10] Finally, in a review of 21 cases of congenital analbuminemia by Russi and Weigand,[11] 43% had no edema, whereas 38% had only mild ankle edema. Hence, a reduction in the serum to interstitial oncotic pressure gradient due to hypoalbuminemia is not supported by existing data.

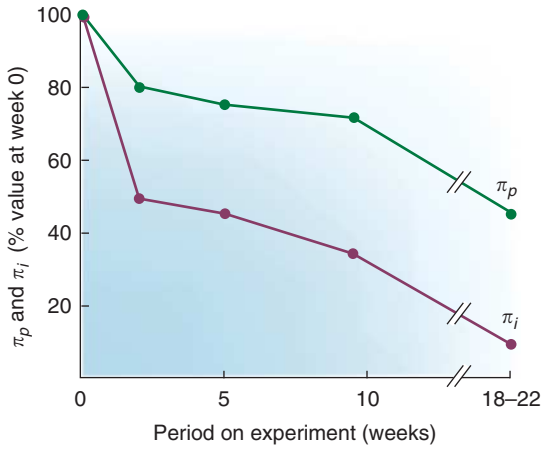

Figure 1 | As serum oncotic pressure declines, there is a parallel decline in interstitial oncotic pressure of greater magnitude in rats fed a very low protein diet (adapted from Fiorotto and Coward[7]).

Mechanisms for decrease in interstitial albumin

It has been proposed by Aukland and Nicolaysen[12] that two safety factors protect against edema formation in the presence of hypoalbuminemia. An increase in filtration of fluid from the intravascular space to the interstitial space will dilute or 'washdown' the interstitial protein concentration. In addition, an increase in fluid delivery to the interstitial space will produce an increase in lymphatic flow that will 'washout' interstitial proteins by bulk flow. Both washdown and washout, as may occur with loss of fluid from the intravascular to interstitial space in hypoproteinemia, serve to maintain the plasma to interstitial protein ratio close to normal and thus defend against edema. Edema formation would follow when the interstitial protein concentration was reduced to zero and no further reduction could occur in response to further intravascular protein decline.

Koomans *et al.*[13] studied the influence of colloid osmotic pressure and plasma protein concentration on blood volume and blood pressure in nephrotic patients and those with chronic renal failure who were admitted to the hospital with extracellular fluid volume (ECFV) expansion. As compared with the chronic renal failure patients, the nephrotic patients had significantly lower plasma protein and oncotic pressures and higher hematocrits. An elevation of the ECFV to 300% of normal produced no significant change in blood volume compared with baseline in nephrotic patients; blood pressure similarly was not significantly different. In contrast, the blood volume and blood pressure were significantly elevated in the chronic renal failure patients at an ECFV of 200% above baseline. Thus, the ECFV excess expands both the intravascular and interstitial space in chronic renal failure, whereas the excess is largely confined to the interstitial space in nephrotic patients. The authors hypothesize that nephrotic patients have no edema despite marked hypoproteinemia at normal ECVF because of the protective effects of interstitial protein washdown and washout. They further hypothesize that expansion of the ECFV to 300% of normal does not raise the intravascular volume because the interstitial protein concentration is near zero and no further washdown or washout can occur.

Effect of rapid reduction of plasma albumin

In some causes of nephrotic syndrome, particularly due to minimal change disease (MCD), the onset of nephrosis is abrupt and plasma protein levels can decline rapidly. A question then is what, if any, are the effects of acute reductions in plasma oncotic pressure on edema formation? Plasmapheresis with isotonic fluid replacement has been used to produce acute reductions in serum oncotic pressure in order to study the effect of plasma oncotic pressure on blood volume maintenance. Repeated episodes of plasmapheresis to produce moderate levels of hypoproteinemia in dogs (mean 4.6 g/dl) led to increased ECFV, no change in blood volume, and stable renin and aldosterone levels, whereas plasmapheresis to severe hypoproteinemia (mean 2.4 g/dl) produced a decrease in plasma volume and blood volume, an increase in renin and aldosterone, and a positive sodium balance.[14–16] Despite the significant decrease in blood and plasma volume, there was a significant increase in sodium space (indicating interstitial fluid volume expansion) in the dogs with severe hypoproteinemia. These studies suggest that severe acute hypoproteinemia can cause edema formation and intravascular volume depletion. It is not clear if the explosive onset of MCD in some patients could cause a similar reduction in intravascular volume with interstitial fluid volume expansion. The development of acute renal failure in a small subset of patients (typically with MCD) suggests that hypovolemia may play a role, but this cannot be conclusively proven without formal blood volume measurements.[17–21] In a retrospective review of 95 cases of adult MCD at a single center, acute renal failure occurred in 24 patients. Those with acute renal failure were older, were hypertensive, and had lower serum albumin and more proteinuria compared with those who did not have acute renal failure.[22]

CHANGES IN HYDROSTATIC PRESSURE GRADIENTS [$P_c - P_i$]

Assessment of blood volume in nephrotic patients

There are few studies on this subject and they assess different end points, which makes comparisons difficult. A significant issue in the consideration of this problem is the lack of a gold standard for the assessment of intravascular volume. At least three methods of intravascular volume assessment have been utilized in the nephrotic syndrome literature: neurohumoral hormone assays, blood volume measurement with radioactive labeling techniques, and presence or absence of hypovolemic symptoms and signs. This section will review some of the more important studies assessing blood volume in the nephrotic syndrome.

Pioneering work on neurohumoral assessment of blood volume in the nephrotic syndrome was done by Meltzer *et al.*,[23] who studied patients with untreated nephrotic syndrome and separated them into two groups by renin levels. Patients with high renin all had MCD and significantly higher aldosterone, higher creatinine clearance, lower urine sodium, and lower serum albumin than the low-renin group. There was a suggestion of low plasma volume as measured by ^{125}I serum albumin in the high-renin group and elevated plasma volume in the low-renin group, but no definitive conclusions could be made because not all subjects had their plasma volume measured.

In one of the largest studies of nephrotic patients, Geers *et al.*[24] compared 28 patients with MCD and 24 with nephrotic syndrome due to other histologic lesions; patients included all had a low fractional excretion of sodium. The group with MCD had significantly lower plasma volume as assessed by ^{131}I-albumin, higher plasma aldosterone, and lower serum albumin (1.5 vs. 2.1 g/dl) than the other histologic lesion group, but blood volume was not significantly different. There was no correlation between blood volume and plasma renin activity (PRA) or serum albumin and blood volume.

In a study of 88 patients with the nephrotic syndrome, 33 of whom had MCD, it was found that plasma and blood volumes as assessed by ^{131}I-albumin were no different than those of healthy controls.[25] Other studies have also found that patients with the nephrotic syndrome have normal or expanded blood volumes.[24,26,27]

Conversely, there are also studies supporting the presence of hypovolemia in the nephrotic syndrome. Vande Walle *et al.*[28] compared children with nephrotic syndrome due to MCD with those with non-MCD and further divided each group by the presence or absence of symptoms or signs of hypovolemia. Patients in both groups with hypovolemic symptoms had significantly higher levels of norepinephrine, PRA, and aldosterone, and lower fractional excretion of sodium than their nonsymptomatic counterparts. When considering only the group with hypovolemic symptoms, the non-MCD group (comprising mostly Finnish type nephrotic syndrome patients) had a lower albumin (0.8 g/dl) and greater elevation in norepinephrine, PRA, and aldosterone than did the MCD group whose albumin was 1.5 g/dl. When analyzing the entire cohort, it was found that there was a significant negative correlation between aldosterone and both serum colloid osmotic pressure and fractional excretion of sodium. Thus, neurohumoral activation was associated with hypovolemic symptoms and those with the most severe neurohumoral activation had the lowest serum albumin. These data suggest that severe hypoalbuminemia is associated with hypovolemia.

Usberti *et al.*[29] subjected nephrotic patients and control patients with glomerulonephritis or hematuria to water loading. The nephrotic patients (8/16 with MCD) had a significantly lower blood volume and serum albumin than controls (1.5 vs. 4.0 g/dl). In response to water loading, a significant direct correlation between plasma osmolality and arginine vasopressin (AVP) levels was seen in control, but not in nephrotic patients. In contrast, a significant negative correlation was seen between blood volume and plasma AVP in nephrotic but not in control patients. This suggests that a volume-mediated stimulus was driving vasopressin release in nephrotic patients. In 1995, Usberti *et al.*[30] studied two groups of nephrotic patients with normal renal function, one who had a positive sodium balance and the other in sodium

balance. The group in positive sodium balance (7/12 with MCD) had significantly lower measured blood volume, lower serum albumin (1.4 vs. 2.2 g/dl), and higher renin, angiotensin II, and aldosterone than the group in sodium balance. In both groups there was a direct relationship between serum albumin and blood volume. As discussed above, this finding is at odds with other studies.

In summary, most edematous patients with the nephrotic syndrome have a normal to expanded intravascular volume, whereas a minority of patients have a depleted intravascular volume. Those patients with intravascular volume depletion typically have MCD and more severe hypoalbuminemia. It is worth noting that although MCD and severe hypoalbuminemia are associated with intravascular volume depletion in some studies, most patients with MCD and significant hypoalbuminemia do not show evidence of intravascular volume depletion.

Neurohormonal changes

Renin, angiotensin II, and aldosterone. The renin, angiotensin II, and aldosterone system has frequently been implicated as a cause of sodium retention in the nephrotic syndrome, particularly in patients who have intravascular volume depletion.

Although Geers *et al.*[24] found no correlation between PRA and blood volume in their large study of nephrotic patients,[24] significant negative correlations have been found between ECFV and log PRA,[13] plasma volume and PRA,[31] and blood volume and PRA.[30]

In a study of nephrotic patients with active sodium retention with high plasma renin, ACE inhibition with captopril did not lead to negative sodium balance or weight loss despite a reduction in plasma aldosterone.[32] In a similar study of nephrotic patients with low and high renin, captopril failed to produce negative sodium balance despite a decline in aldosterone levels.[33] Several studies have shown that patients with MCD have higher renin or renin activity and aldosterone levels than those with other histologic lesions despite similar blood volumes.[23,34] A large study of nephrotic patients failed to show a difference in PRA in patients with MCD vs. those with histologic lesions, although those with MCD did have significantly higher aldosterone concentrations.[24] Studies of children with the nephrotic syndrome showed that patients with hypovolemic symptoms had greater elevations in renin activity and aldosterone, despite similar measured blood volumes.[27,28,35]

Blockade of aldosterone in a small group of nephrotic patients who were retaining sodium and who were fed a high salt diet resulted in marginal negative sodium balance.[36] This study did not, however, control for the degree of proteinuria reduction caused by aldosterone blockade. An inverse relationship has been shown between plasma aldosterone and urinary sodium excretion by several investigators,[28,31,37,38] whereas other investigators have found no relation.[39] It is noteworthy that in several studies the development of edema occurred without significant elevations in serum aldosterone levels.[24,28,40]

The above suggest that renin–angiotensin–aldosterone system is not a major mechanism of sodium retention in the nephrotic syndrome. MCD is phenotypically associated with elevated PRA and aldosterone, although in most cases the blood volume is not different from those who have other histologic lesions and normal PRA and aldosterone. It is not clear if this MCD phenotype suggests an alternate pathophysiology.

Sympathetic nervous system. The renal vasculature, particularly the afferent and efferent arterioles, as well as the tubules are innervated by the sympathetic nervous system.[41] Activation of the renal sympathetic nerves causes an increase in afferent and efferent vascular resistance (independent of angiotensin II[42]) and increased renin release with subsequent increases in angiotensin II, all of which serve to increase sodium reabsorption.[41] In a study of nephrotic rats in the edema-forming stages, DiBona[41] showed that compared with control rats, nephrotic rats have higher basal renal sympathetic nerve activity, decreased excretion of intravenous isotonic saline, and less suppression of renal sympathetic nerve activity following isotonic saline infusion. Following renal sympathetic denervation, the nephrotic rats had increased excretion of isotonic saline.

Vasopressin. Patients with the nephrotic syndrome have been shown to have higher basal AVP levels than controls[43] and to have higher AVP levels and reduced free water clearance in response to water loading vs. controls.[29,44] Albumin loading has been shown to reduce serum vasopressin levels in some nephrotic patients, suggesting a volume-mediated stimulus for vasopressin release.[29,45] In a study of puromycin aminonucleoside (PAN) nephrosis in rats vs. controls, it was noted that nephrotic rats had higher serum vasopressin levels and higher hypothalamic AVP mRNA than controls.[46] Vasopressin thus appears to play a role in free water retention and edema formation in some patients with the nephrotic syndrome.

Atrial natriuretic peptide. Atrial natriuretic peptide (ANP) is another hormone that has been implicated in the sodium retention seen in the nephrotic syndrome. ANP is released by the atria in response to atrial distension. As the intravascular volume status is difficult to judge, and nephrotic patients could have normal, increased, or decreased plasma volumes, interpretation of ANP levels at baseline and in response to treatment are difficult.

Rats rendered nephrotic after exposure to adriamycin had expanded plasma volumes and significantly increased ANP levels vs. control rats.[47]

A unilateral adriamycin nephrosis model in rats showed that the proteinuric kidney was resistant to the diuretic and natriuretic effects of ANP, whereas the normal kidney had appropriate natriuresis and diuresis in response to ANP.[47] Other groups have also noted diminished natriuresis in response to ANP infusion in PAN nephrotic rats.[48–50] Rats with nephrosis due to Heymann nephritis and PAN have been shown to have similar levels of ANP at baseline and after volume expansion as controls, but had diminished diuresis in

response to volume expansion vs. controls.[50,51] In a study of nephrotic rats, ANP infusion resulted in a blunted natriuresis and diuresis compared with controls.[52] In the same experiment, renal sympathetic denervation resulted in a greater diuresis and natriuresis in nephrotic rats in response to ANP infusion.

A study comparing nephrotic patients with controls showed a reduced diuretic response to head-out water immersion despite similar ANP levels.[53] This study also showed lower baseline ANP in nephrotics vs. controls. A study analyzing nephrotic patients based on their urine sodium excretion showed that basal ANP correlated with their basal urinary sodium excretion.

In summary, there is evidence for decreased renal responsiveness to ANP in some nephrotic patients, whereas others have low baseline ANP levels that could be pathologic or could be reflective of an underfilled circulation. Increased renal sympathetic nerve activity may play a role in ANP resistance in the nephrotic syndrome.

Role of primary renal sodium retention

Ichikawa *et al.*[54] created a unilateral PAN nephrosis model in the rat such that one kidney was nephrotic and the other functioned normally. They showed that although the nephrotic kidney was proteinuric and sodium avid, the contralateral normal kidney had no proteinuria and handled sodium normally as in control rats. This suggested that an intrarenal defect caused sodium retention. Micropuncture studies from superficial nephrons showed that there was a significant increase in sodium reabsorption beyond the distal convoluted tubule in the nephrotic kidney vs. the normal kidney.

An increase in cortical collecting duct (CCD) Na/K ATPase activity[55–58] mRNA,[58] and amount[57] has been shown in the PAN model of nephrotic syndrome. CCD Na/K ATPase activity has also been shown to be increased in the $HgCl_2$ and adriamycin nephrosis models.[56] An inverse linear relationship between CCD Na/K ATPase activity and urinary sodium excretion has been noted.[56] The increase in Na/K ATPase activity was found to be independent of serum aldosterone in studies of adrenalectomized rats.[55,58]

The expression[58–61] and apical targeting[60] of epithelial sodium channel (ENaC) has been shown to be increased in the CCD in the PAN model of the nephrotic syndrome and is aldosterone dependent.[58,59] Increased apical targeting of ENaC in the CCD has also been shown in the $HgCl_2$ model of the nephrotic syndrome.[62] A linear correlation between plasma aldosterone and ENaC abundance was found in the PAN model of nephrosis.[58] Prevention of hyperaldosteronemia by adrenalectomy prevents the increase in apical ENaC targeting, but does not prevent the development of the nephrotic syndrome in PAN-treated rats.[58,59] Adrenalectomized rats with PAN nephrosis that do not show an increase in ENaC expression have a similarly low urinary sodium excretion as adrenal-intact nephrotic rats with increased ENaC expression.[58] Furthermore, treatment with amiloride prevented the sodium retention in the rat PAN model of nephrosis,[58,63] whereas treatment with an aldosterone receptor blocker did not.[63] It is notable that in the study by Lourdel *et al.*[58] with adrenalectomized nephrotic rats, amiloride returned sodium excretion to normal despite the fact that ENaC expression was not increased.

The above suggests that the observed increase in ENaC that occurs in animal models of the nephrotic syndrome is because of aldosterone, and that development of nephrotic edema is not dependent on aldosterone. The importance of the ENaC channel in the development of nephrotic edema, however, is underscored by the reversal of sodium retention by amiloride in the above animal models. Evidence suggests that the Na/K-ATPase activity is increased in the nephrotic syndrome and appears to be important in the sodium retention seen in the nephrotic syndrome.

Regulation of ENaC occurs through two primary mechanisms: regulation of channel density at the apical membrane and regulation of the open channel probability.[64] The ENaC receptor density is regulated by both aldosterone and vasopressin. Open channel probability is regulated by proteolytic processing[65] and by anionic phospholipids present on the inner cell membrane.[66]

ENaC is composed of three subunits: α, β, and γ.[67] The α and γ have been shown to have regulatory roles.[67] An ENaC channel with uncleaved α and γ chains has a low open channel probability and conducts little sodium.[64,67] Proteolytic activation of ENaC is a normal intracellular event with sequential cleavage of the α and γ chains resulting in progressive increases in its open channel probability.[67] Some ENaC channels have been shown to be present at the apical membrane in a closed (uncleaved α and γ chain) state.[67]

Carattino *et al.*[68] showed that proteolytic removal of an inhibitory domain from the γ subunit of ENaC by a serine protease results in near complete activation of ENaC. This same group then showed that the serine protease plasmin can activate ENaC through removal of the γ inhibitory chain.[69] Furthermore, they demonstrated that plasminogen and plasmin are present in the urine of proteinuric rats with the metabolic syndrome but not control rats. Simultaneously, Svenningsen *et al.*[70] showed that plasmin present in the urine of nephrotic rats and humans can activate ENaC through removal of an inhibitory γ chain domain. Additionally, they showed that urokinase-type plasminogen activator present in the rat and human kidney can convert inactive plasminogen (which is filtered by the nephrotic kidney) to the active-form plasmin (Figure 2). In the rat PAN nephrosis model, they showed that amiloride increases urine sodium excretion and reduces ascites volume. This effect was attributed both to the ability of amiloride to inhibit ENaC and the ability of amiloride to inhibit urokinase-type plasminogen activator and thus reduce the amount of active plasmin present.

The above suggests a dominant role of ENaC in the sodium retention of the nephrotic syndrome and provides a rationale for specific diuretic blockade of ENaC. The only study addressing this showed that a combination of diuretic

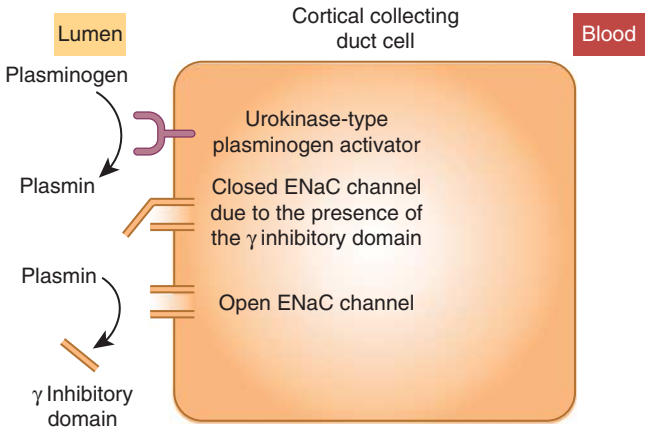

Figure 2 | Plasminogen filtered by the nephrotic glomeruli is converted to plasmin by urokinase-type plasminogen activator in the cortical collecting duct cells. Plasmin then proteolytically removes the γ inhibitory domain from epithelial sodium channel (ENaC), resulting in near full activation of ENaC.

therapy with amiloride and furosemide resulted in greater natriuresis and weight loss than monotherapy with either diuretic in 13 pediatric patients.[71]

These important findings provide a mechanism of an intrinsic renal defect whereby abnormally filtered proteins in nephrotic patients can cause sodium retention via ENaC activation. It also explains the predictable course of recovery seen in MCD patients treated with steroids. First, there is a decrement in urinary protein excretion, then a reduction in aldosterone (urine and serum), followed by natriuresis, and then diuresis.[31,38,72–74]

CHANGES IN VASCULAR PERMEABILITY (K_f and σ)

The clinical observation that nephrotic patients with similar degrees of proteinuria can have significant differences in the degree of edema is curious. It is often assumed that differences in sodium intake (or diuretic compliance) account for the individual patient differences in edema, but patient- and disease-specific factors also seem possible.

One such possibility is an abnormality of systemic vascular permeability. In 1993, Gamble *et al.*[75] showed that mercury-in-silastic strain gauge plethysmography could be used to measure capillary filtration capacity. Whereas hydraulic conductance (K_f, capillary permeability) can be measured for a single capillary, capillary filtration capacity measures hydraulic conductivity of a tissue.[76] Lewis *et al.*[76] showed that although the capillary hydrostatic pressure is normal at the nail bed in nephrotic patients, the capillary filtration capacity was significantly higher in nephrotic patients vs. controls. This argues that capillary permeability is a possible etiology of edema formation in the nephrotic syndrome. Oqvist *et al.*[77] showed that there was no difference in clearance of albumin from the plasma to the interstitium in PAN nephrotic rats vs. controls, which argues against an abnormality in capillary permeability. Rostoker *et al.*[78] used the Landis isotope method to assess capillary permeability in patients with the nephrotic syndrome, healthy controls, and those with idiopathic cyclic edema, a disease considered to be related to abnormal vascular permeability. Capillary permeability was found to be significantly higher in those with idiopathic cyclic edema and the nephrotic syndrome vs. controls. Another noteworthy finding was the significant decrease in capillary permeability after treatment with steroids in patients with MCD.

CONCLUSION

The nephrotic syndrome is characterized by proteinuria, edema, and hypoalbuminemia. Renal sodium retention and changes in variables of the Starling equation are fundamental to the pathophysiology of nephrotic edema. There is evidence for both intravascular volume expansion (overfilling) and intravascular volume depletion (underfilling) in patients with nephrosis.

Microvascular fluid exchange is described using a formulation of the Starling driving forces (ΔP and $\Delta\pi$) and it is through this equation that nephrotic edema is conceptualized. Previous theories have focused on abnormalities in ΔP and $\Delta\pi$ to explain nephrotic edema. Studies have shown that hypoalbuminemia (and thus $\Delta\pi$) is not a likely cause of edema formation in most nephrotic patients owing to a parallel decrease in interstitial fluid albumin and an increase in interstitial fluid pressure, both of which serve to maintain edema driving forces constant. There is limited evidence suggesting that abnormalities in vascular permeability (K_f and σ) may contribute to edema formation.

A major advance in our understanding of the pathophysiologic basis of edema formation in the nephrotic syndrome is the discovery that proteinuria can cause primary renal sodium retention through ENaC activation. This mechanism is likely active in all patients with nephrotic syndrome, regardless of their intravascular volume status. Other causes of primary renal sodium retention include increased renal efferent sympathetic nerve activity, ANP, and in the expression and activity of the Na/K ATPase in the collecting duct in animal models (Figure 3). Furthermore, excess serum vasopressin levels have been found to contribute to free water retention in some patients with the nephrotic syndrome. It is not clear if nephrotic proteinuria underlies any of these other abnormalities. The renin–angiotensin–aldosterone system does not appear to be a primary mechanism of renal sodium retention.

An abundance of data in the last decade has implicated ENaC as a major factor in edema formation in the nephrotic syndrome. There are limited animal and human data to support the use of amiloride in nephrotic patients.[58,63,70,71] Amiloride alone would likely not be sufficient for diuresis in nephrotic patients with significant ECFV expansion given the limited amount of sodium that is delivered to the collecting duct. It may, however, be an important adjunct to furosemide and could have a role in preventing edema in those with relapsing nephrotic syndrome.

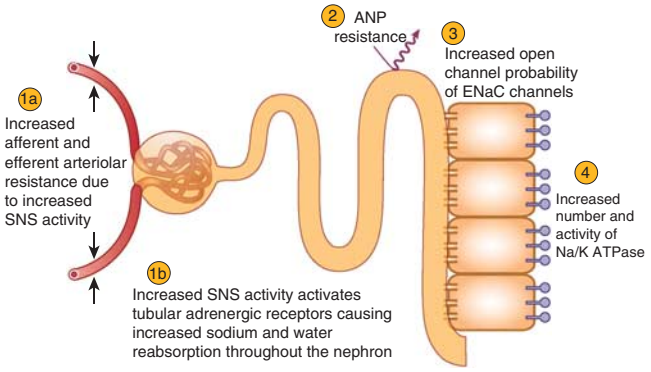

Figure 3 | Mechanisms of sodium retention in the nephrotic syndrome. (1) Increased angiotensin II-independent afferent and efferent arteriolar tone because of increased efferent sympathetic nerve activity. (2) Tubular resistance to atrial natriuretic peptide (ANP). (3) Increased number of open epithelial sodium channel (ENaC) channels in the cortical collecting duct due to proteolytic activation of ENaC by plasmin. (4) Increased number and activity of cortical collecting duct Na/K ATPase channels. SNS, sympathetic nervous system.

Although sodium retention is necessary for edema formation in the nephrotic syndrome, it is unlikely to be the sole factor. For instance, patients with Liddle syndrome who have ENaC activation and sodium retention are not known to have edema. The observation that patients with nephrotic syndrome and ECFV expansion to 300% above baseline have a normal blood volume, whereas those with chronic renal failure and ECFV expansion of 200% have a significantly increased blood volume suggests that nephrotic patients have an additional physiologic abnormality that favors preferential expansion of the interstitial space in response to an increase in ECFV.[13] It is possible that a critical reduction in the capillary-interstitial oncotic pressure gradient or abnormalities in vascular permeability are also important in edema formation.

Many problems remain in this field. First, it is difficult to obtain unambiguous measurement of the driving forces across the capillary in that the interstitial space is not readily accessible. But the greatest difficulty is to obtain a direct measurement of the capillary permeability function. Finally, in most studies the nephrotic syndrome is considered a uniform entity throughout its course. However, it is quite likely that the physiology of salt retention and edema has different phases. The initiating events have already passed by the time the patient presents to the physician with edema. This is the phase where the pathogenesis of edema needs to be studied; yet, most studies address a later phase (by necessity), and hence what is being studied is often a steady state that is reached after renal and neurohumoral compensation has set in.

DISCLOSURE

All the authors declared no competing interests.

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