Pathophysiology of oedema in idiopathic nephrotic syndrome

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Abstract
The decrease in plasma protein and colloid osmotic pressure (COP) in the nephrotic syndrome is accompanied by a decrease in tissue-fluid protein and COP. The latter protects against a fall in blood volume. However, the range and speed of this protective mechanism are limited, and a decrease in blood volume can be expected if plasma COP is below \(\sim 10\) mmHg, or (temporarily) if the protein loss starts very fast. In addition, due to this protective mechanism volume retained by the kidneys cannot effectively expand blood volume, explaining that hypertension is rarely grave and pulmonary congestion unusual, whereas peripheral oedema can be gross. The renal derangement leading to volume retention involves a decreased filtration per nephron, increased tubular reabsorption, and decreased sensitivity to ANP but the relation between these changes is incompletely resolved.

Keywords: nephrotic syndrome; oedema; pathophysiology

Transcapillary fluid balance

The notion that plasma volume (blood volume) is decreased in the nephrotic syndrome (NS) stems from the fact that in the Starling equilibrium, which dictates that the plasma colloid osmotic pressure (pCOP) is a major driver for plasma fluid to be retained in the vascular compartment. According to this equation, a decrease in pCOP such as follows from renal protein loss results in an increased fluid shift to the interstitium. But how about interstitial COP (iCOP)? Would that remain unchanged during hypoproteinenaemia? Of course not. There is a continuous dynamic exchange and equilibrium between vascular protein, in particular albumin, and interstitial albumin, which is essential for normal blood volume regulation [1]. This exchange is so effective, that if pCOP drops from the normal value of 24–14 mmHg, i.e. by 10 mmHg, the iCOP will drop by approximately the same amount, say from 14 to 4 mmHg [2]. Consequently, the drop in pCOP is compensated for by an equal drop in iCOP, which prevents a fluid shift from plasma to interstitium, or, in other words, prevents a drop in plasma and blood volume.

Indeed, blood volume measurements are generally normal or even somewhat increased in the NS [3]. Blood pressure is also mostly normal or even increased, which would be difficult to understand if blood volume would be low. A good case for the idea that blood pressure is indeed elevated rather than low is made by the observation in adults [4] as well as in children [5] that blood pressure drops after steroid-induced recovery from the NS. In these patients, plasma renin activity is often higher after recovery from the NS [4,6], also pointing against a decreased blood volume in the nephrotic phase. However, the case for plasma renin is more complex, as some patients may have extremely high concentrations [7].

The parallel decreases in plasma and iCOP help to maintain a normal fluid distribution and blood volume during normal hydration state, but at the same time have great consequence for the distribution of volume that is retained by the kidneys. In normoproteinaemic conditions such retained fluid will expand both blood volume and interstitial volume. As it is, interstitial expansion will accelerate lymphatic flow and replace albumin from interstitial space to the blood. The increased blood albumin mass will keep part of the retained fluid in the blood compartment, which is important, as that will form the physiological basis for stimulation of renal volume excretion, and restoration of the balance.

During hypoproteinenaemia, interstitial albumin concentration is low, virtually zero if hypoproteinenaemia is severe. In these conditions, fluid retained by the kidney will not, or in any case less, expand blood volume, as
there is no tissue-fluid albumin to be replaced to the blood. Therefore, in the NS the excess volume is mainly distributed to the interstitium, and blood volume remains within normal limits irrespective whether total hydration is normal or increased. Consequently, fluid overload can in general be removed without causing hypovolaemia. The absence of a blood volume increase despite overhydration averts severe hypertension and pulmonary congestion, which are uncommon in the NS. This explains why patients with the NS have a much higher tolerance for fluid retention and are more severely overhydrated when referred for treatment than patients with chronic renal failure. We found that out when we followed patients with chronic renal failure or with the NS during their clinical treatment for overhydration [8].

There are some limitations to the compensatory power of the transcapillary albumin redistribution mechanism. First, there is an end to the amount of interstitial albumin. The normal interstitial albumin mass in an average adult is ~250 g, and the iCOP ~14 mmHg (but less in depending extremities). This means that when pCOP has dropped by >14 mmHg (or <10 mmHg), the gradient between pCOP and iCOP must have decreased. In those circumstances the blood volume cannot be maintained. This is the case in severe NS, such as occurs in children with minimal lesions NS, or, particularly, congenital nephrosis [9]. In adults such extreme situations occur less often, and then mostly in MLNS or amyloidosis (‘malignant proteinuria’). We have confirmed this principle in dogs, in whom progressive hypoproteinaemia was induced by repetitive plasmapheresis. These dogs, who, in contrast to the NS, have normal kidneys, appeared able to excrete a volume challenge when the artificially decreased pCOP was allowed to rise above 9 mmHg [10].

The second limitation concerns the speed of albumin circulation between plasma and interstitial compartment, probably 24 h for a complete circle. This means that with a sudden strong loss of plasma proteins, such as can occur in the initial phase of a minimal lesions NS, mobilization of interstitial albumin may be too slow to compensate for the decrease in pCOP. A temporary decrease in effective blood volume is the result, but the circulation can recover within a day, when mobilization of interstitial protein is completed. This leads to the interesting situation that initially a patient may show symptoms of hypovolaemia at a moderately decreased plasma protein concentration, whereas these symptoms have disappeared later, although plasma protein has dropped further. This sequence of events is found particularly in the initial phase of minimal lesions NS, again more often in children than in adults [11].

The third limitation is that the physiological decrease in blood volume that occurs during standing is enhanced during hypoproteinaemia. This implies that upon standing a subnormal effective circulation may arise in patients in whom pCOP is around the critically low level [12].

**Sodium retention in the NS**

The observation that patients with NS retain volume in the absence of a low blood volume implicates that it is an intrinsic renal abnormality. However, measurements of blood volume have been criticized as not sufficiently accurate to exclude (impending) hypovolaemia [13]. Other observations in humans present convincing evidence that the kidney in the NS indeed has an intrinsic inability to excrete sodium. Patients with incipient minimal lesions NS start to retain sodium when plasma albumin is still normal [11,14]. Patients with established minimal lesions NS, in whom recovery is induced with steroids start to excrete the excess volume when plasma albumin concentration has hardly changed from its hypoproteinaemic level [6,15]. The other observation is that experimental hypervolaemia, either induced by head-out water immersion or by iso-osmotic albumin infusion (iso-osmotic, to avoid the acute sodium retaining effect of hyperoncoticity) induces only limited increase in sodium excretion in NS patients, not in proportion with the large amounts of fluid overload [16,17].

The nature and localization of the renal impairment to excrete sodium has not yet been elucidated. Understandably, evidence in humans is indirect and circumstantial. The general notion is that, when patients are actively retaining sodium (i.e. in a positive sodium balance), increased tubular sodium reabsorption occurs throughout the nephron. Instead, when patients have stable nephrotic oedema, but are not actively retaining sodium, their renal sodium handling appears to be normal [14].

In rats with experimental puromycin nephrosis, a model of minimal lesions NS, proximal tubular sodium reabsorption was increased, and insufficiently suppressable by volume loading [18]. In unilateral puromycin nephrosis, sodium retention by the affected kidney was localized in some distal part of the nephron, as proximal reabsorption was decreased [19]. There is evidence that the distal nephron in the NS has decreased sensitivity to the action of atrial natriuretic peptide. In humans, studies using various forms of volume expansion showed insufficient natriuretic response despite elevation of plasma ANP to at least normal levels [20,21]. ANP resistance can be demonstrated specifically in the affected kidney of experimental unilateral nephrosis [22], and isolated kidneys of nephrotic rats [23]. Isolated inner medullary collecting cells from rats with experimental nephrosis show diminished sensitivity to atrial natriuretic peptide, a disturbance that can be resolved by inhibition of degradation of its second messenger cGMP [24]. This is indeed an intriguing finding, however, it is completely unresolved how this abnormality is related to the glomerular disturbance of the NS.

**References**