Conceptual Approach to Body Fluids and Edema, Education Determines Clinical Outcomes in Nephrotic Syndrome Management

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The objective of our paper is to reemphasize the importance of critical thinking in clinical practice and education in the field of internal medicine using the example of edema. We provide an in-depth and interactive investigation of physiological concepts as a foundation for the understanding of body fluid dynamics. Four fundamental concepts described are the hydrostatic and oncotic pressure gradients, capillary permeability, and lymphatic drainage. Furthermore, we visit the causes of edema in nephrotic syndrome. Traditional teaching considers hypoalbuminemia as a primary cause of edema formation in nephrotic syndrome. It has been proven that other etiologies causing edema include salt and water retention by the kidneys and a possible increase in capillary permeability are more important causes in the development of edema in nephrotic syndrome.

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INTRODUCTION

Generally, traditional medical education at times skims over information to emphasize more practical points for memorization. It is no surprise then that disease treatments might often be assessed superficially by trainees, prior to the consideration of their very basic underlying mechanisms.[1] Textbooks, on the other hand, provide too much detail, and unfortunately are a medium where regular updates take longer, reducing their effectiveness in an ever-changing field; especially when new information conflicts with traditional teachings. These factors allow for misunderstandings of concepts in medicine, which may persist among clinicians despite recent evidence and scientific developments.[2] Our goal is to restructure the way edema is addressed, by moving away from classical lecturing and textbook-based learning; instead we provide a concise and thought-provoking discussion of the basic underlying principles of edema for greater clinical understanding.

Cells operate through chemical reactions, all of which requiring a medium to proceed. Therefore, life's most versatile solvent, water, is mainly (~⅔) located intracellularly. Extracellular fluid is the environment in which that cell is maintained. A unicellular eukaryotic cell requires a living volume space hundreds of times larger than its own volume to sustain life. However, given the vast number of cells in the body, meeting each individual cell's biological requirement is not feasible by simply surrounding them with the remaining one third of extracellular fluid.[3]

To meet cell demands, a much smaller volume of fluid is used with an established "Active Circulatory Vascular system» and "Dynamic Diffusive Capillary system". The terminology for the above two systems are being suggested for the first time in literature to describe the process of body fluid dynamics that

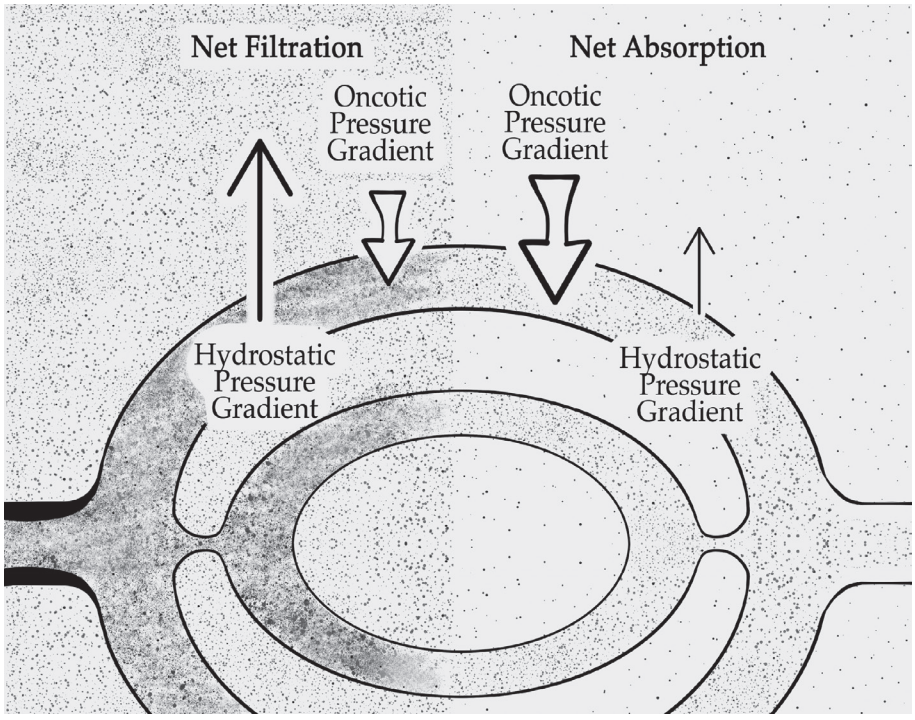
Brief Communication

pertain to the intravascular and extravascular space. The dynamic diffusive system requires a volume much larger (~ 3/4) than the active circulatory vascular system for it to dilute waste and maintain the immediate cell environment.

Active Circulatory Vascular System: At an average baseline cardiac output of 5 L/min, 7,200 liters of fluid circulate daily in a capillary network of 800 to 1000 m^2. The active pumping of the heart creates the mean arterial pressure (MAP) to provide tissue perfusion and maintain local gradients. With constant circulation, the effective extracellular fluid volume for cells is expanded exponentially.[4,5] In contrast to traditional teachings, which emphasizes oncotic and hydrostatic pressures per se, we emphasize net pressure gradients as the drivers of fluid movement. The hydrostatic pressure gradient is the difference between interstitial and intravascular pressures (Figure). In dynamic equilibrium with the hydrostatic pressure gradient, the oncotic pressure gradient opposes fluid movement by drawing fluid towards regions with a higher density of particles. Net fluid exchange is determined by four factors in equilibrium; hydrostatic pressure gradient, oncotic pressure gradient, capillary permeability, and lymphatic drainage.[6]

Dynamic Diffusive Capillary System: In conjunction with the movement of fluid in the active circulatory vascular system, the dynamic diffusive capillary system is the site of continuous exchange with the internal environment. Further increasing the complexity of the dynamic interaction between fluids and particles are the membranes through which these substances are transferred. Transport of particles across the capillary wall occurs via capillary permeability, which contributes to the gradients. Organs such as the kidneys, require larger and more plentiful fenestration to support higher filtration and absorption rates, while the brain has limited fenestrations to restrict capillary exchange, helping to maintain a stable environment by reducing the entry and exit of substances that can alter the brain's function. In addition, there is a required energy expenditure associated with the movement of particles against their gradients or by transcellular transportation (transcytosis). Paracellular transport is more economical since this pathway does not involve the movement against concentration gradients of a cell compartment.[7]

A common misconception is that albumin is restricted primarily intravascularly, accounting



Simplified Dynamic Diffusive Capillary System (Arrows denote net fluid movement. Densely shaded regions denote higher oncotic pressure).

for the oncotic pressure. However, primarily a multipurpose carrier for nutrients, vitamins, drugs and toxins, albumin must be exchanged between interstitial and intravascular spaces, and thus has persistently higher intravascular concentration and higher interstitial content (almost 60% located in the interstitial space).[8,9] Intuitively, it is the latter that constitutes the main oncotic pressure gradient exerting a pull on fluids. The albumin concentration gradient provides an adequate osmotic gradient, which approximately matches the hydrostatic pressure gradient.[10] Thus, filtration and absorption in the dynamic diffusive capillary system are balanced.

In the arteriolar side of the capillary, the hydrostatic pressure gradient is greater than the oncotic pressure gradient, favouring filtration and albumin transport outside. However, in the venular side of the capillary the oncotic pressure gradient is more than the hydrostatic pressure gradient, favouring absorption and albumin transport back into the intravascular space (Figure).

In order to excrete waste, albumin must be filtered into the nephron where it is able to unload substances. It is then reabsorbed via pinocytosis and broken down into amino acids. Based on the balance between glomerular filtration and the reabsorptive capacity of the nephron, only a negligible amount of albumin is normally excreted in the urine.[9] The lymphatic system, responsible for drainage of remaining protein rich interstitial fluid, prevents gelatinous fluid accumulation not easily absorbable by typical pressure gradients. The action of skeletal muscle contractions force fluid through unidirectional lymphatic valves and return fluid to the thoracic duct.[11] Edema is defined as a clinically identifiable accumulation of interstitial fluid. Such an accumulation occurs whenever forces (including lymphatic drainage) favour fluid filtration over absorption. Edema could develop due to local processes or diffuse systemic processes such as; nephrotic syndrome. Generalized versus localized edema are defined based on the ability of edema to redistribute.

It was traditionally believed that the basis of edema in nephrotic syndrome is solely due to a hypoalbuminemic state and lower oncotic pressures.[12] When the cause of edema is understood through the hypoalbuminemia hypothesis, the obvious solution is to infuse albumin to the patient, which may not be best practice. This way of thinking might seem counterintuitive at first. However, as a carrier molecule, albumin continuously picks up and delivers substances from and to the cells.[8] Therefore, even with higher intravascular gradient, albumin distributes between the two compartments, leaving the net gradient unchanged. Also, due to rapid excretion of albumin in the urine following IV infusion, albumin becomes a negligible solution to the gradients favouring filtration over absorption.

Furthermore, many facts are against the hypoalbuminemia hypothesis as the sole reason causing edema: a) peripheral edema and hypertension in some patients develop prior to significant hypoalbuminemia in a nephrotic patient; b) treatment of a nephrotic patient leads to alleviation of edema and high blood pressure in hypertensive patients; and c) normalization of hypoalbuminemia does not occur until 2-3 weeks following alleviation of edema. Multiple studies have shown an absence of edema in analbuminemic rats and humans.[13] Thus, intuitively, fluid exchange is relatively maintained despite hypoalbuminemia, since a drop in albumin concentration affects both interstitial and intravascular spaces.

The overfill hypothesis has been validated more in its explanation of edema in nephrotic syndrome. However, most textbooks such as Harrison›s principles of internal medicine focus merely on the hypoalbuminemia theory, with no mention of the overfill hypothesis. Medical education should emphasize the more validated hypothesis as the plausible cause of edema which could guide enriched diagnostic and therapeutic approaches. This hypothesis highlights primary salt and water retention as the main mechanism of edema formation. It is postulated that fluid retention is achieved either by the pathological over activation of the sympathetic nervous system, through the renin angiotensin aldosterone system and other mediators, or primary sodium reabsorption directly by the renal tubules.[14] There are studies demonstrating that loss of plasmin and other serine proteases in the urine due to proteinuria promote the up-regulation of epithelial sodium channels (ENaC), causing salt and fluid retention.[5]

Currently, there is no evidence that systemic or peripheral capillary permeability leakage is restricted to the glomerular capillary system. Steroids are one of the commonly used treatments

for nephrotic syndrome, minimizing inflammation by reversing increased glomerular capillary permeability, decreasing edema, and suppressing polymorphonuclear activity. This favors increased capillary permeability as a contributing factor of edema formation.[15]

The treatment of edema in nephrotic syndrome aims to create a negative sodium balance; to alleviate symptoms, patients must restrict their sodium and fluid intake. Steroids in some patients (indirectly) and diuretics (directly) can reduce fluid overload and enhance salt and water excretion. Albumin transfusion, as a human product, is resource limited, could cause adverse reactions, and is an ineffective treatment of edema in nephrotic syndrome.[13]

CONCLUSION

In conclusion, many clinical challenges in the management of edema may be due to shortcomings of classical medical education. As a novel approach, fluid dynamics are defined using an active circulatory system and dynamic diffusive capillary system that work in conjunction to perfuse tissue and remove waste. It is shown that a critical thinking approach to address various clinical scenarios is imperative to modify the previous understanding of edema and promote accurate learning of the topic.

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