Anatomy of Lymphatic system in Kidney — Poorly understood and important in future

Abstract
The cortex of a healthy kidney contains a significant number of renal lymphatics, though these have often been overlooked in discussions related to kidney diseases. These lymphatics originate within the renal lobule's core as capillaries that come to a closed end. They can either accompany the main arteries and veins towards the hilum or breach the kidney's outer covering to connect with capsular lymphatics. Valves are absent in the interlobular lymphatics, allowing lymph created in the cortex to exit the kidney in either direction. The medulla contains only a sparse number of lymphatics.

Lymph is produced from the interstitial fluid within the cortex. It is primarily composed of capillary filtrate, yet it also holds fluid that has been reabsorbed from the tubules. The formation of renal lymph depends mainly on two factors: the volume of interstitial fluid and the pressure within the veins inside the kidney.

The interplay between renal lymphatic dysfunction and renal interstitial edema creates a reciprocal negative effect. These interactions are expected to reduce renal function due to alterations in pressure within the enclosed kidney. This mechanism holds significance in numerous common renal conditions.

Introduction

Lymphatic vessels initiate as blind-ended capillaries within the interstitial space throughout the body. Over time, these capillaries merge to form larger collecting vessels that eventually link up with veins. This intricate network plays a crucial role in the body, including the kidneys, by draining both fluid and large molecules from the interstitial space and returning them to the systemic circulation. This essential function prevents the buildup of interstitial fluid that could hinder the delivery of oxygen to tissues. The kidneys, in particular, possess a substantial network of lymphatic vessels, indicating a significant role for the renal lymphatic system in normal and demanding physiological conditions.[1] Nonetheless, the role of renal lymphatics in disease, as well as the overall anatomy and physiology of renal lymphatics, have been surprisingly disregarded in recent times.

Lymphatic dysfunction is defined as an inability to effectively drain interstitial fluid, and its causes can vary (e.g., valve dysfunction, blockage of lymphatic vessels, disruption of pressure gradients, or loss of smooth muscle contractility). While this condition is evident as peripheral pitting edema when it affects a limb, its impact on the kidney is less apparent. Nevertheless, due to the inflexibility of the renal capsule, inadequate lymphatic drainage could lead to increased intra-renal pressure and contribute to impaired kidney function. We hypothesize that this often neglected mechanism might be at play in a range of clinical scenarios, such as congestive heart failure (CHF), acute kidney injury (AKI) associated with systemic inflammatory response syndrome (SIRS), chronic renal failure, failure of renal transplant grafts, and other instances.

Consequently, numerous clinical situations could potentially involve a significant role for renal lymphatics, yet there is a surprising scarcity of recent literature addressing this important subject. This comprehensive review seeks to address this knowledge gap regarding renal lymphatics. We initiate by examining the comparative anatomy of these structures in both humans and animals. This is followed by an exploration of the physiology of the renal lymphatic system under normal circumstances and during periods of stress. Finally, we provide a concise overview of the consequences of renal lymphatic dysfunction in various disease states.

Renal Lymphatic Anatomy: Exploring the Structure

Approaches to Investigating Renal Lymphatic Anatomy
The initial record of renal lymphatics is attributed to Paolo Mascagni in 1787, who injected mercury into cadaver kidneys.[2] Subsequently, most studies have utilized dyes like tryptan blue, India ink, and Evans blue dye, introduced either intravenously or into the renal tissue, to scrutinize renal microstructures under a microscope. Nevertheless, recent years have witnessed remarkable

progress in comprehending renal lymphatic anatomy, propelled by advancements in imaging methodologies and the emergence of markers specific to Lymphatic Endothelial Cells (LECs).

Distinctive Markers for Lymphatic Endothelial Cells

Though LEC markers are not exclusively confined to LECs, they do enable differentiation between these cells and endothelial cells within blood vessels. The most commonly employed markers encompass podoplanin, LYVE-1, vascular endothelial growth factor receptor 3 (VEGFR-3), and the prospero-related homeo-box transcription factor 1 (Prox1).[3] Among these, podoplanin, a transmembrane protein of the mucin type, is particularly reliable for human kidneys and can be specifically identified within paraffin-embedded tissue through the use of a podoplanin antibody.[4]

Live Imaging of the Renal Lymphatic System

Traditionally, studies delving into renal lymphatic anatomy necessitated the removal of kidneys for microscopic or microradiographic examination. However, contemporary techniques have been developed to visualize larger lymphatics while the organ remains in vivo (e.g., pedal lymphangiography, lymphangiography, and lymphoscintigraphy),[5] although these approaches currently do not facilitate the visualization of renal lymphatics. Nonetheless, it is feasible to image the central lymphatic system by introducing contrast agents into inguinal lymph nodes (intranodal lymphangiography) or by directly catheterizing the cisterna chyli through a trans-abdominal route.[5] Furthermore, minimally invasive procedures for examining lymphatics have been outlined. Injection of embolization materials, such as N-butyl cyanoacrylate (N-BCA) glue (TRUFILL, Codman Neuro, Rayhnam, MA, United States), into lymph node interstitium can lead to downstream propagation and embolization.[5] For liver lymphatics, imaging can be accomplished by introducing contrast agents into the peri-portal space.[6] Collectively, these advancements suggest that injecting contrast materials (or probes) into the renal interstitium for imaging renal lymphatics might become feasible in the future.

Embryonic Structural Formation

Sabin's proposition in 1909, suggesting that Lymphatic Endothelial Cells (LECs) originate from sprouts emerging from embryonic veins, has been corroborated through contemporary lineage tracing studies employing LEC markers.[7,8] Lee et al., utilizing LYVE-1 expression, scrutinized the embryonic development of renal lymphatics in mouse embryos.[9] Within 13-day-old embryos, intra-renal lymphatics, interconnected with extra-renal lymphatic plexuses, were first discerned. These lymphatics then established meticulously organized networks that accompanied the burgeoning arcuate and interlobular vessels in subsequent days. Remarkably, no such lymphatics were identified within the renal medulla during any developmental stage.

Lee et al. noted that LYVE-1+ cells were sporadically detected in developing arcuate veins, particularly within branching buds.[9] Lymphatic vessels primarily localized around emerging veins until post-natal day 4. Interestingly, immature macrophages and dendritic cells, also expressing LYVE-1, emerged before LYVE-1+ lymphatic vessels. These cells were found closely intertwined or even integrated into the lymphatic vascular wall. The conclusion drawn was that LYVE-1+ cells initially sprout from veins, but it is the pivotal involvement of LYVE-1+ macrophages and dendritic cells that orchestrates a branching process, linking these cells with extra-renal lymphatic vessels. Notably, VEGF-C seems to play a crucial regulatory role in this branching mechanism.[9, 10] Correspondingly, Tanabe et al. observed a parallel pattern in rat kidneys, where renal lymphatic vessels stem from existing extra-renal lymphatic vessels, extending towards the cortex along the renal vascular framework.[11] Intra-renal lymphatic vessels were initially observable around embryonic day 20. Despite these observations, the question of whether the mammalian kidney harbors intrinsic lymphatic precursors participating in the formation of intra-renal lymphatic vessels remains unresolved.[10]

Renal Vascular Structure

Renal lymphatics closely adhere to the configuration of the renal vascular system.[12] Thus, a concise exploration of the kidney's arterial supply becomes pertinent. Ordinarily, each kidney is supplied by a solitary renal artery. This artery, within the renal sinus, branches into five segmental

arteries: posterior, superior, anterosuperior, anteroinferior, and inferior.[13] The kidney's structure comprises segments, each encompassing a renal pyramid covered by a section of renal cortex. These segments are further subdivided into renal lobules, comprising nephrons encircling a single medullary ray that empties into a solitary collecting duct. Arteries stemming from segmental arteries conform to this lobular pattern (Figure 1). An interlobar artery radiates between lobes and gives rise to arcuate arteries, which traverse the cortex-medulla juncture. From each arcuate artery, interlobular arteries emerge, coursing between lobules towards the outer capsule. These interlobular arteries release afferent arterioles that lead to the glomerulus. The venous structure mirrors the arterial, except for the existence of interconnections between veins from various segments, unlike the segmental arteries which culminate as end arteries.

Comparing Renal Lymphatic Structure Across Species

Renal Lymphatic System in Non-Mammalian Vertebrates

The emergence of the lymphatic system is thought to coincide with the transition of aquatic organisms to terrestrial habitats. While fish lack a well-developed lymphatic system, amphibians exhibit such a system.[14] Reptiles, certain amphibians, and bird embryos possess lymph "hearts," which aid in lymph movement. These rhythmic chambers are positioned where lymph vessels intersect veins. Notably, these chambers exhibit variations in wall thickness, encompass valves, and pulsate independently of the heart's rhythm.[15] Fish and anuran amphibians rely on the kidney for a supplementary lymphoid function, whereas this role diminishes in amniote kidneys.[16] Although reptile and avian renal anatomy reports often omit mention of renal lymphatics.[17,18]

Mammalian Renal Lymphatic Structure

Predominant research on renal lymphatic architecture pertains to mammals, notably dogs. In a seminal investigation, Pierce et al employed India ink injections into dog, rabbit, and guinea pig kidneys, along with intravenous administration of tryptan blue, to meticulously delineate renal lymphatics microscopically.[19] Pierce observed that renal lymphatics originate within the cortex as intralobular lymphatics—sparse, blind-ended tubules in close proximity to renal tubules. These intralobular lymphatics pass near, but do not infiltrate, renal corpuscles, subsequently merging into interlobular lymphatics. These interlobular lymphatics interconnect with larger arcuate and interlobar lymphatics, eventually draining into hilar lymphatics (Figure 1). The dog typically possesses 6–8 hilar lymphatics and 4–6 lymphatic channels exiting the renal capsule. Following capsule departure, capsular lymphatics appear to interconnect with hilar lymphatics within the renal sinus and hilum. In dogs, the volume of cortical lymph is approximately equivalent to only 1% of the blood volume in cortical peritubular capillaries.
This renal lymphatic structure is generally consistent across species, albeit with some exceptions. For instance, rabbit kidneys appear devoid of intralobular lymphatics, while sheep kidneys lack a capsular system (Table 1). The extent of intra-cortical lymphatics corresponds to urine concentration ability; the rabbit, with the least extensive system, has lower concentration ability, while the golden hamster, with the most extensive system, boasts higher concentration ability. In humans, the outlined renal lymphatic architecture closely mirrors that of other mammals (Figure 1). Autopsy microscopy and radiographic studies affirmed these findings, which have been further validated using LEC markers. The interstitial spaces surrounding interlobular, arcuate, and interlobar arteries and veins host a profusion of lymphatic vessels, as established by Ishikawa et al. (2006) through podoplanin antibody application (Figure 2).

Lymphatic Communication and Pathways

Within humans, lymphatic vessels surrounding interlobular veins exhibit greater development compared to those around interlobular arteries . Abundant lymphatics are situated in the interstitium around interlobar arteries, but those encircling interlobar veins are distributed within the vascular wall, encompassing the media and intima beneath the endothelium. Although renal lymphatics and vessels run in proximity, conclusive evidence of intra-renal lymphatic-venous shunts remains elusive. However, lymphovenous connections have been observed at the renal

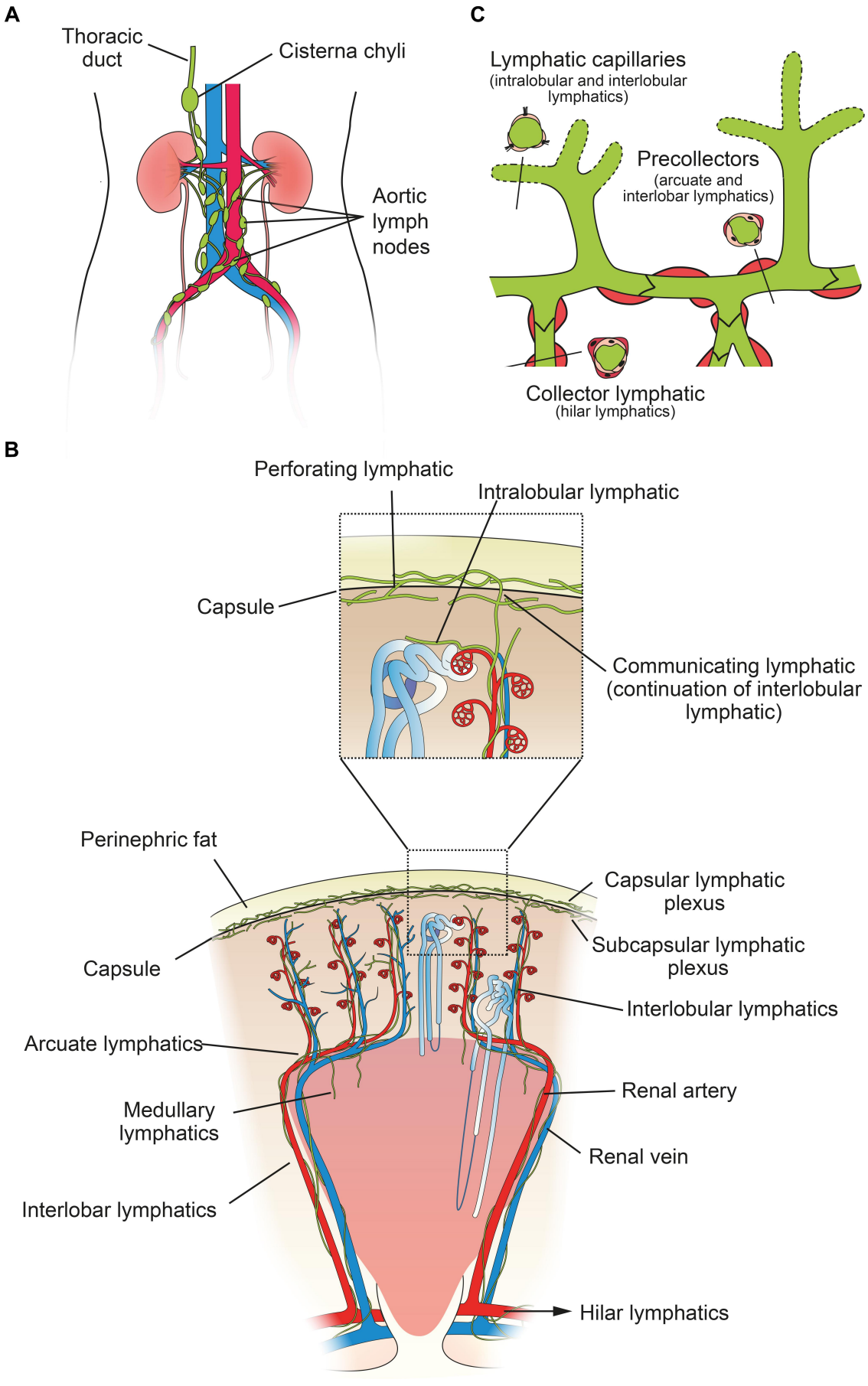

FIGURE 1. Structure of the human renal lymphatic system. **(A)** Lymph passes from 4–5 renal hilar lymphatics on each kidney to various groups of aortic lymph nodes. Most lymph draining from the kidney collects in the cisterna chyli and is drained via the thoracic duct into the central venous circulation in the neck. **(B)** Schematic diagram of a human renal lobe. **(C)** Schematic showing morphology of renal lymph vessels.

vein level in rats and primates, but not in human autopsy studies.[20]

Summarizing Human Renal Lymphatic Anatomy

The fundamental structure of human renal lymphatic anatomy parallels that of other mammals. Lymphatic capillaries, commencing near renal tubules, traverse the vicinity of glomeruli before accompanying renal arteries as interlobular, arcuate, and interlobar lymphatics. Notably, interlobular lymphatics lack valves in the cortex, enabling lymph to flow either toward the hilum or penetrate the capsular lymphatic plexus and exit the kidney through distinct routes. Although the cortex harbors relatively abundant lymphatic capillaries, they are rare within the medulla. These capillaries, tethered to surrounding interstitial tissue, lack a basement membrane, and incorporate intercellular gaps between endothelial cells. Larger arcuate, interlobar, and hilar lymphatics feature valves to ensure unidirectional flow and are equipped with smooth muscle cells for lymph propulsion.

Renal Lymphatic Function Under Physiological Conditions

Methods for Investigating Renal Lymphatic Physiology

Much like studies on renal lymphatic anatomy, research into renal lymphatic physiology has primarily relied on animal models. While in vivo sampling of renal lymph has been achieved in dogs[21] and rats[22], analogous studies in humans have not been successfully conducted. Assessing renal lymphatic flow rates in animals has proven intricate due to the kidney's unique lymphatic arrangement, yet noteworthy progress has been made, as detailed in the subsequent sections.

Generation of Renal Lymph

Lymphatic vessels are responsible for draining fluid and macromolecules from the interstitial space between tubules and capillaries. The entry of lymph into lymphatic capillaries is determined by the balance between hydrostatic and oncotic pressures, governed by the Starling equation.[23] In all blood capillaries, proteins are released into the interstitium, a phenomenon especially prominent in the presence of endothelial fenestrations. In the kidney, these fenestrations are more prevalent on the side of capillary walls facing renal tubules due to their close proximity. Consequently, proteins entering the interstitium are prone to accumulate between capillaries and tubules, diminishing the crucial oncotic pressure gradient. This would lead to decreased fluid and electrolyte flow from tubules to peri-tubular capillaries. The kidney uniquely possesses a substantial extravascular albumin pool that is swiftly replenished and eliminated. Slotkoff and Lilienfield demonstrated this by infusing radioactively labeled red cells and albumin intravenously into dogs.[24] Subsequent perfusion with dextran revealed that a greater proportion of labeled albumin persisted in the kidneys compared to labeled red cells. This suggested the presence of a significant extravascular albumin pool, most pronounced in the medulla due to fewer lymphatics to eliminate albumin. In the medulla, interstitial albumin is essential for urine concentration, while in the cortex, lymphatics play a primary role in interstitial albumin removal, maintaining oncotic pressure gradients essential for tubular reabsorption.

Interstitial fluid and proteins readily traverse terminal lymphatics, driven by hydrostatic and oncotic pressure gradients. Notably, renal interstitial fluid pressure maintains a positive value, unlike subcutaneous tissue or muscle, leading to elevated baseline lymph flow rates.[25] Entry into lymphatic vessels primarily occurs through interjunctional gaps between lymphatic endothelial cells (LECs). These endothelial cells exhibit high endocytic activity, facilitating transcellular uptake of fluid and macromolecules.[3] Tethering filaments contribute to entry, as they connect LECs to the perivascular matrix, enlarging interendothelial gaps during edematous conditions. The absence of a basement membrane also supports fluid and protein entry. Lymph composition in terminal lymphatics closely resembles interstitial fluid, the precursor from which it derives.

Capsular Lymph vs. Hilar Lymph Formation and Flow

Renal lymph drainage differs based on cortical region. Capsular lymph vessels primarily drain the outer cortex, while the medulla and inner cortex are drained primarily by hilar lymphatics. Although most renal lymph originates in the cortex, research indicates that flow from hilar lymph

exceeds capsular lymph by 4–8 times, suggesting that the bulk of cortical lymph is drained through the hilar route. This is substantiated by the resemblance of the electrolyte composition of hilar lymph to plasma, reflecting the similarity between cortical interstitium (where most hilar lymph originates) and plasma. Since medullary interstitium has higher solute concentrations due to urine concentration mechanisms, the composition of renal hilar lymph, predominantly draining the cortex, does not reflect medullary conditions.

Composition of Renal Lymph Under Normal Conditions

Renal lymph arises from both capillary filtrate and tubule reabsorbate. Studies administering labeled substances have unveiled the combined origin of renal lymph. Inulin lymph/plasma ratios suggest both filtrate and reabsorbate contribute.[26,27] Sodium, chloride, and other solute concentrations indicate the distal tubule's independent reabsorption of solute, which blends with capillary filtrate to form renal lymph. The relative proportion of proteins in renal lymph varies widely, influenced by flow rate and anesthesia status. Renal lymph displays elevated renin and angiotensin II levels due to proximity to the juxtaglomerular apparatus. High apolipoprotein levels and similar albumin concentrations underscore renal lymph's significance in transporting various molecules.

Renal Lymph Flow Rates Under Normal Conditions

Total renal lymph flow rate quantification poses challenges as renal lymphatics do not converge before entering the periaortic chain. Experimental measurements differ due to these complexities. Although lymph flow is a minor fraction of renal fluid output, some studies suggest lymph and urine flows are comparable.[28]. Flow estimation ranges from 2% of fluid reabsorption to one-half of urine flow.[29-31] In fasted dogs, total renal lymph flow averages 0.36 ml/min/100 g kidney, with each kidney contributing 21% of thoracic duct flow.[31] The heightened value in fasted animals may reflect reduced cisterna chyla flows.[31]

Interstitial Fluid and Protein Drainage in the Medulla

Unlike the cortex, medullary fluid and proteins are predominantly cleared by vasa recta rather than lymphatics. Convective flow guides proteins alongside fluid, as medullary fluid moves toward vasa recta, facilitated by concentration gradients.[32,33] Medullary lymph composition differs from that of cortical lymph, as vasa recta play a prominent role in interstitial fluid reabsorption in the medulla.[32] Consequently, lymphatics are unnecessary for medullary interstitial fluid drainage, similar to the brain, cornea, and bone marrow.[32]

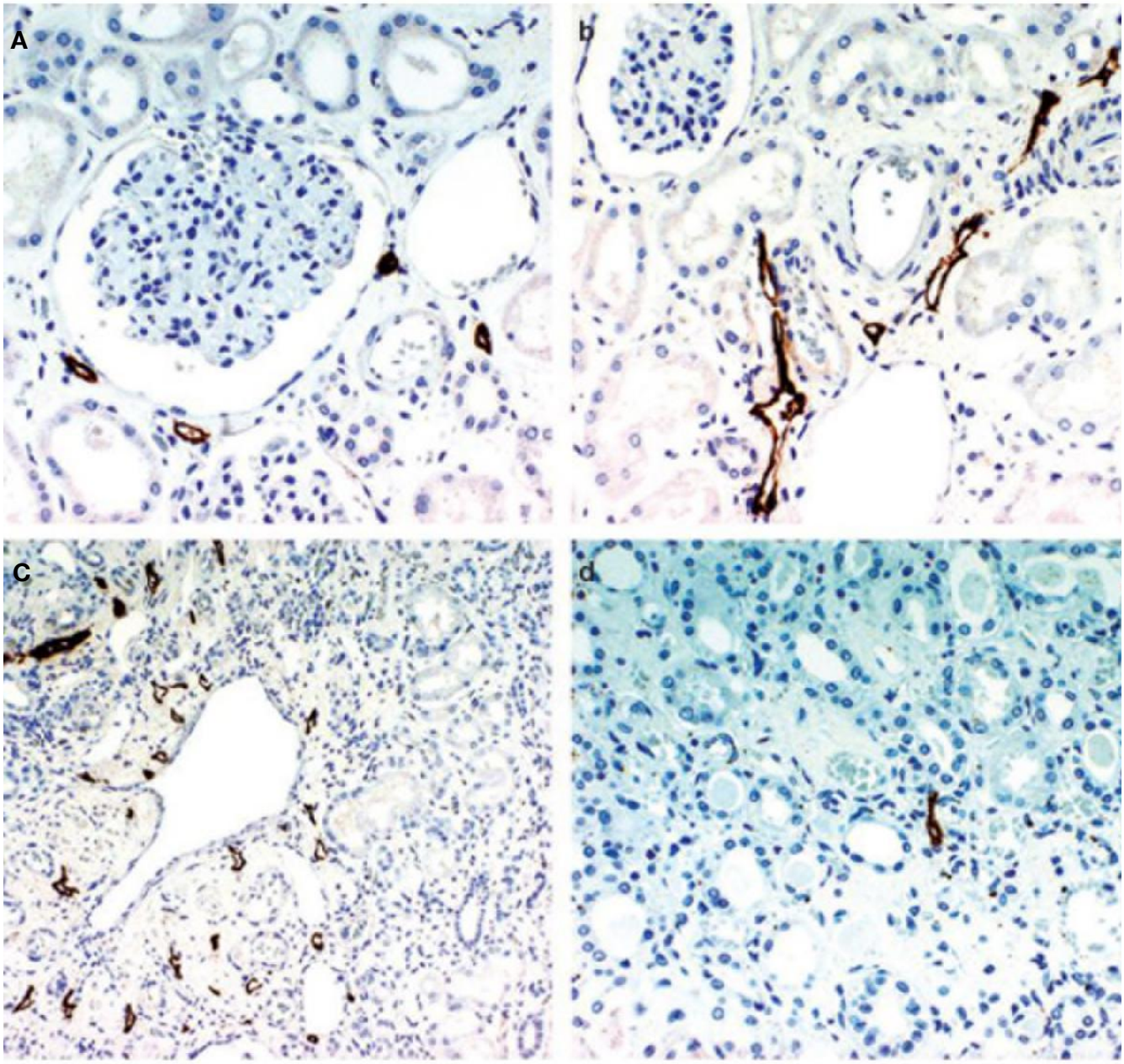

FIGURE 2. D2-40 immunostaining of lymphatics in the normal kidney. **(a)** Lymphatic capillaries in the interstitium around the glomerulus, **(b)** lymphatics exhibiting a slit-like structure are distributed around the interlobular artery and vein in the cortex, **(c)** multiple lymphatic capillaries in the interstitium around a dilated interlobular vein, a few lymphatic capillaries are present just beneath the venous endothelium, **(d)** a lymphatic capillary is recognizable in the center of the figure showing a normal medulla.

Table 1. Comparison of renal lymphatics between different species

Species	Intralobular Lymphatics	Medullary Lymphatics	Communication between renal and capsular lymphatics	Glomerular Lymphatics	Comments
Dog	Present	Present	Present	Partially surround Bowman's capsule	Species most extensively studied
Pig	Present	Present	Present		
Rat	Intermediate	Not found		Lymphatics lie close to glomerulus	Intrarenal lymphatic vessels appear at embryonic day 20
Mouse			Present		Intrarenal lymphatic vessels appear at embryonic day 20
Rabbit	Rare	Present	Not Found		Least extensive intralobular lymphatics and lowest urine concentrating ability
Guinea Pig	Extensive				Most extensive intralobular lymphatics and highest urine concentrating ability
Horse				Completely surround Bowman's capsule	
Sheep		Not found	Absent		
Human	Present	Rare and in outer medulla only or surrounding vasa recta	Present	Sporadically surround glomerulus	Medullary lymphatics seen in pathological specimen

Space left blank if no data is available

References:

1. Kaiserling, H. (1940). Lymphatics and lymphangitis of the kidney. Virchows Arch. F. Path. Anat. 306, 322–359. doi: 10.1007/BF02595100
2. Mascagni, P. (1787). Vasorum Lymphaticorum Corporis Humani Historic et Ichnographia. Siena: Pazzini Carli.
3. Seeger, H., Bonani, M., and Segerer, S. (2012). The role of lymphatics in renal inflammation. Nephrol. Dial. Transplant. 27, 2634–2641. doi: 10.1093/ndt/gfs140
4. Kalof, A. N., and Cooper, K. (2009). D2-40 immunohistochemistry – so far! Adv. Anat. Pathol. 16, 62–64. doi: 10.1097/PAP.0b013e3181915e94
5. Itkin, M., and Nadolski, G. J. (2018). Modern techniques of lymphangiography and interventions: current status and future development. Cardiovasc. Intervent. Radiol. 41, 366–376. doi: 10.1007/s00270-017-1863-2
6. Itkin, M., Piccoli, D. A., Nadolski, G., Rychik, J., DeWitt, A., Pinto, E., et al. (2017). Protein-losing enteropathy in patients with congenital heart disease. J. Am. Coll. Cardiol. 69, 2929–2937. doi: 10.1016/j.jacc.2017.04.023
7. Sabin, F. R. (1909). The lymphatic system in human embryos, with a consideration of the morphology of the system as a whole. Am. J. Anat. 9, 43–91. doi: 10.1002/aja.1000090104
8. Tammela, T., and Alitalo, K. (2010). Lymphangiogenesis: molecular mechanisms and future promise. Cell 140, 460–476. doi: 10.1016/j.cell.2010.01.045
9. Lee, H. W., Qin, Y. X., Kim, Y. M., Park, E. Y., Hwang, J. S., Huo, G. H., et al. (2011). Expression of lymphatic endothelium-specific hyaluronan receptor LYVE-1 in the developing mouse kidney. Cell Tissue Res. 343, 429–444. doi: 10.1007/s00441-010-1098-x
10. Mohamed, T., and Sequeira-Lopez, M. L. S. (2018). Development of the renal vasculature. Semin. Cell. Dev. Biol. doi: 10.1016/j.semcdb.2018.06.001 [Epub ahead of print].
11. Tanabe, M., Shimizu, A., Masuda, Y., Kataoka, M., Ishikawa, A., Wakamatsu, K., et al. (2012). Development of lymphatic vasculature and morphological characterization in rat kidney. Clin. Exp. Nephrol. 16, 833–842. doi: 10.1007/s10157-012-0637-z
12. O'Morchoe, C. C. C., and O'Morchoe, P. J. (1988). The renal lymphatic system: a brief review. Contr. Nephrol. 68, 230–237. doi: 10.1159/000416519
13. Bhimji, S. S., and Leslie, S. W. (2018). Anatomy, Abdomen and Pelvis, Kidneys. Treasure Island, FL: StatPearls Publishing.
14. Brown, P. (2005). Unlocking the drains. Nature 436, 456–458. doi: 10.1038/436456a
15. Satoh, Y., and Nitatori, T. (1980). "On the fine structure of lymph hearts in amphibia and reptiles," in Hearts and Heart-like Organs. Volume 1: Comparative Anatomy and Development, ed. G. H. Bourne (Cambridge, MA: Academic Press), 149–169. doi: 10.1016/B978-0-12-119401-7.50011-6
16. Manning, M. J. (1979). Evolution of the vertebrate immune system. J. R. Soc. Med. 72, 683–688. doi: 10.1177/014107687907200911
17. Davis, L. E., Schmidt-Nielsen, B., Stolte, H., and Bookman, L. M. (1976). Anatomy and ultrastructure of the excretory system of the lizard, Sceloporus cyanogenys. J. Morphol. 149, 279–326. doi: 10.1002/jmor.1051490302
18. Morild, I., Bohle, A., and Christensen, J. A. (1985). Structure of the avian kidney. Anat. Rec. 212, 33–40. doi: 10.1002/ar.1092120105
19. Pierce, E. C. (1944). II: renal lymphatics. Anat. Rec. 90, 315–335. doi: 10.1002/ar.1090900407
20. Karmali, R. J., Suami, H., Wood, C. G., and Karam, J. A. (2014). Lymphatic drainage in renal cell carcinoma: back to the basics. BJU Int. 114, 806–817. doi: 10.1111/bju.12814
21. LeBrie, S. J., and Mayerson, H. S. (1960). Influence of elevated venous pressure on flow and composition of renal lymph. Am. J. Physiol. 198, 1037–1040. doi: 10.1152/ajplegacy.1960.198.5.1037
22. Hargens, A. R., Tucker, B. J., and Blantz, R. C. (1977). Renal lymph protein in the rat. Am. J. Physiol. Renal Physiol. 233, F269–F273. doi: 10.1152/ajprenal.1977.233.4.F269
23. Staub, N. C., and Taylor, A. E. (1984). Edema. New York, NY: Raven Press.
24. Slotkoff, L. M., and Lilienfield, L. S. (1967). Extravascular renal albumin. Am. J. Physiol. 212, 400–406. doi: 10.1152/ajplegacy.1967.212.2.400
25. Ott, C. E., and Knox, F. G. (1976). Tissue pressures and fluid dynamics in the kidney. Fed. Proc. 35, 1872–1875.

26. Kaplan, A., Friedman, M., and Kruger, H. E. (1942). Observations concerning the origin of renal lymph. Am. J. Physiol. 138, 553–556. doi: 10.1152/ajplegacy.1943.138.3.553
27. Keyl, M. J., Scott, J. B., Dabney, J. M., Haddy, F. J., Harvey, R. B., Bell, R. D., et al. (1965). Composition of canine renal hilar lymph. Am. J. Physiol. 209, 1031–1033. doi: 10.1152/ajplegacy.1965.209.5.1031
28. Stolarczyk, J., and Carone, F. A. (1975). Effects of renal lymphatic occlusion and venous constriction on renal function. Am. J. Pathol. 78, 285–296.
29. Sugarman, J., Friedman, M., Barrett, E., and Addis, T. (1942). The distribution, flow, protein and urea content of renal lymph. Am. J. Physiol. 138, 108–112. doi: 10.1152/ajplegacy.1942.138.1.108
30. Cockett, A. T. K. (1977). Lymphatic network of kidney. I. Anatomic and physiologic considerations. Urology 10, 125–129. doi: 10.1016/0090-4295(77)90180-7
31. Atkins, J. L., O'Morchoe, C. C. C., and Pinter, G. G. (1988). Total lymphatic clearance of protein from the renal interstitium. Contr. Nephrol. 68, 238–244. doi: 10.1159/000416520
32. Tenstad, O., Heyeraas, K. J., Wiig, H., and Aukland, K. (2001). Drainage of plasma proteins from the renal medullary interstitium in rats. J. Physiol. 536, 533–539. doi: 10.1111/j.1469-7793.2001.0533c.xd
33. Wang, W., and Michel, C. C. (2000). Modeling exchange of plasma proteins between microcirculation and interstitium of the renal medulla. Am. J. Physiol. Renal Physiol. 279, F334–F344. doi: 10.1152/ajprenal.2000.279.2.F334