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Review Article

Educational Tips for Students and Physiology Instructors Regarding Reabsorption of Kidney's Proximal Tubule and Autoregulation: Different Perspectives of Medical and Postgraduate Students

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Abstract
The authors opinions in physiology books are different on some issues, and this mixes up the readers. The purpose of this article is to clarify the differences between two examples in renal physiology (the autoregulation and the reabsorption of the materials in the proximal tubule) to help better understand; therefore, this paper is especially beneficial for medical students. The latest editions of several physiology books are used in this study including Brenner and Rector›s "The Kidney", Seldin and Giebisch's "The Kidney Physiology and Pathophysiology", Koeppen Stanton›s "Renal Physiology", Vander's "Renal Physiology", Boron's "Medical Physiology", Ganong's "Review of Medical Physiology", Rose's "Clinical Physiology of Acid-Base and Electrolyte Disorders", "Renal Pathophysiology: the Essentials" by Rennke and Denker, "Color Atlas of Physiology", "Renal Physiology: a Clinical Approach", and "Medical Physiology" by Guyton. It is concluded that the two above-said methods, in general, adopt similar approaches. However, there are some differences in terms of details that are explained and clarified in this study.
Keywords: Renal autoregulation, Proximal tubule reabsorption, Tubular fluid to plasma concentration ratio, Physiology books

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Introduction

While reviewing and studying various physiology books it is realized that the authors' opinions are somewhat different, and it is confusing to readers, especially students. This study aimed to compare two different perspectives regarding the physiology of the kidney to help understand the subject. One of these controversial issues is kidney blood flow autoregulation. The second issue, which is expressed differently in various physiology books, is the reabsorption of materials in the proximal tubule. The perspective of various physiology books was reviewed to clarify these issues.

Material and Methods

For this review, the latest editions of several available physiology books, in the field of autoregulation and reabsorption of materials in the kidney proximal tubule, are used in this study including Brenner and Rector's "The Kidney", Seldin and Giebisch's "The Kidney Physiology and Pathophysiology", Koeppen Stanton's "Renal Physiology", Vander's "Renal Physiology", Boron's "Medical Physiology", Ganong's "Review of Medical Physiology", Rose's "Clinical Physiology of Acid-Base and Electrolyte Disorders", "Renal Pathophysiology: the Essentials" by Rennke and Denker, "Color Atlas of Physiology", "Renal Physiology: a Clinical Approach", and Guyton's "Medical Physiology" were examined separately in this article.

Autoregulation

"The Kidney" by Brenner and Rector (1), states that autoregulation of blood flow requires changes in vascular resistance alongside changes in blood pressure. This book attributes the change of resistance to something more over

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than afferent arterioles, from the preglomerular arteries, which include relaxation of arcuate to the interlobular arteries due to the reduction of blood pressure from 120 to 95 mm Hg, while the blood pressure is reduced to 70 mm Hg in afferent arterioles (2). In general, since the smaller diameter of small vessels compared to the larger vessels has a more significant effect on their resistance, Brenner and Rector believe that the greatest change in resistance occurs due to the change in diameter of afferent arterioles (3).

"The Kidney Physiology and Pathophysiology" (4) states that, in a physiological range, kidney blood flow can be autoregulated independent of blood pressure (5). The autoregulation of the kidney is controlled by at least two mechanisms of tubuloglomerular feedback (TGF) and the myogenic response of the arteries' smooth muscles. These regulatory systems have different but interconnected operating frequencies. The dynamic frequency of the two systems shows a degree of interference, and contraction of afferent arterioles by TGF increases the pressure in the upper vessels, which increases the myogenic response (6). From the two mentioned systems, only myogenic response to blood pressure change is adequate and necessary for kidney autoregulation (5). The myogenic response occurs along the preglomerular vascular tree. TGF is a dynamic process by which alterations in the NaCl concentration in Henle's loop fluid that enters the macula densa cause an inverse change in the glomerular filtration rate (GFR).

In "Renal Physiology" by Vander (7), it is stated that in healthy kidneys, renal arterial pressure is similar to systemic arterial pressure which means that the pressure is not constant and its potential for changing the GFR is very strong. Also, the pressure in glomerular capillaries is higher than that of the capillaries in other parts of the body, and if this pressure increases significantly it can damage the vessels. In order to maintain a healthy GFR in various blood pressures and protect the glomerular capillaries against damages caused by high blood pressure, changes in GFR and renal blood flow (RBF) are minimized by the autoregulation mechanism. In the normal range of mean arterial pressure, blood pressure alterations slightly change the GFR and RBF due to the existence of autoregulation. Two mechanisms are involved in the autoregulation process, one of which is the myogenic mechanism that is the contraction and relaxation of vessels' smooth muscles in response to changes in vascular pressure. This mechanism acts very quickly and protects the glomeruli against short-term blood pressure changes, while the second mechanism, TGF, helps to maintain the appropriate filtered load for sodium and other waste products.

The book "Review of Medical Physiology" by Ganong (8), states that when the kidney is perfused with mean pressure (90-220 mm Hg) the renal vascular resistance changes, which is called autoregulation. Therefore, the renal blood flow is almost constant. Autoregulation also exists in the denervated and isolated kidneys. This phenomenon is likely to be partially caused by a direct contracting reaction to stretch in the afferent arterioles. Contraction of efferent arterioles plays a role in low perfusion pressure; therefore, GFR remains constant.

The book "Medical Physiology" by Boron (9) explains that autoregulation is an important feature of renal blood flow which is the ability to maintain RBF and GFR in a narrow range, while mean arterial pressure can change in the range of 80-170 mm Hg. Autoregulation plays a role in situations where arterial pressure changes, such as change body position, light to moderate exercise, and sleep. Afferent arterioles are the place of autoregulation response. In contrast, the resistance of efferent arterioles, capillaries, and venules makes a very small change in the wide range of renal arterial pressure. Two basic mechanisms are the myogenic response of afferent arterioles' smooth muscles and the TGF mechanism.

The "Renal pathophysiology: the essentials and acid-base and electrolyte disorders" (10) indicates that GFR and renal plasma flow (RPF) are almost constant in a wide range of arterial pressure (11,12). This phenomenon is intrinsic and occurs in denervated, and perfused kidneys, and is called autoregulation. Increasing the resistance of arteries increases the overall kidney resistance and prevents increased pressure from being transmitted to the downstream capillaries, while the effects of reducing systematic blood pressure are mitigated by dilation of afferent arterioles and preserves the GFR and RPF. However, the kidney's ability to maintain hemodynamic function in mean arterial pressures below 70 mm Hg becomes disrupted, so the GFR ceases when the systemic pressure reaches 40 to 50 mm Hg. The autoregulation of GFR in the initial decrease of arterial pressure is mediated mostly by TGF and stretch receptors in the wall of afferent arterioles (13). Greater reduction in blood pressure activates the renin-angiotensin system and the production of angiotensin II, which maintains the GFR by increasing efferent arteriole resistance (11,14,15).

The book "Renal Physiology" by Koeppen (16) introduces two mechanisms for autoregulation of renal blood flow and GFR. One mechanism responds to changes in arterial pressure, and the other one responds to variations in sodium chloride concentration in the tubular fluid. Both mechanisms regulate the tonicity of afferent arterioles. The pressure-sensitive mechanism called the myogenic mechanism is related to the intrinsic nature of vessels' smooth muscles. The second mechanism is responsible for TGF's autoregulation. This mechanism affects the resistance of afferent arterioles and consequently the GFR. The autoregulation of GFR and RBF is an efficient tool for separating renal function from arterial pressure and ensures that as long as the extracellular fluid volume is normal the removal of fluid

and soluble material remains constant. There are three facts about autoregulation to be considered: 1) There is no autoregulation in arterial pressure below 90 mm Hg. 2) Autoregulation is not a 100% process, and the GFR and RBF change briefly with changes in blood pressure. 3) Despite the autoregulation, GFR and RBF can change by specific hormones and alterations in sympathetic nerve activity.

The "Color Atlas of Physiology" (17) indicates that autoregulation occurs in systemic blood pressure between 80 and 180 mm Hg, and is also seen in the denervated kidneys. If the blood pressure changes, the interlobular arteries and afferent arterioles automatically adjust their resistance.

The book "Renal Physiology: A Clinical Approach" (18) refers to autoregulation as the vessel's ability to change its resistance in response to pressure changes. In young people, kidneys are able to maintain their blood flow in decreased blood pressure (down to 90 mm Hg), further decrease in blood pressure affects the blood flow. This is while in old people, who have lost the ability to regulate vasoactivity in the afferent and efferent arterioles, the blood supply to the kidneys decreases in higher systolic blood pressures. Although it has been argued that the efficacy of myogenic responses to constant changes in systemic blood pressure is limited and its significance is in preventing changes in GFR due to continuous and transient blood pressure fluctuations that are common during the day; and also myogenic responses have no effect on long-lasting changes like congestive heart failure or loss of blood volume. The mechanism involved in autoregulation is the regulation of tonicity in afferent and efferent arterioles. (In the autoregulatory process, only the afferent arterioles have been mentioned, and in the section on extra-renal agents and peptides such as epinephrine and norepinephrine, the contraction of efferent arterioles has been explained).

In Guyton and Hall's "Medical Physiology", which is the main source of medical students in Iran, there is another approach to autoregulation. The model proposed in this book is not an isolated and denervated kidney separated from hormonal effects, but the kidney is in *in vivo* condition. According to this book, the main effect of autoregulation in kidneys is the relative maintenance of GFR stability to the accurate control of renal excretion of water and soluble materials. The range of autoregulation in this book is from 75 to 170 mm Hg, and it states that in this pressure range, only a few percentages of change occur in the GFR (19). Afferent and efferent arterioles are responsible for autoregulation (19).

Concentration ratio of substances in the tubular fluid to the plasma in the proximal tubule

In terms of the concentration ratio of substances in the tubular fluid to plasma (TF/P) in the proximal tubule, there are slight variations in different books regarding the absorption ratio of substances, the maximum amount of reabsorption, and the main location of reabsorption. This issue led to the formation of different diagrams in these books (Figure 1).

1. In Guyton's "Medical Physiology" (Figure 1A) (19), and many other physiology books, the concentration ratio of TF/P for Na, K, and osmolality is "1", while in Rector's, Ganong's, and Boron's books, concentration ratio of Na in the tubular fluid to plasma is "less than 1". This ratio also shows a slight increase compared to the iso-osmolar line of the filtrate fluid along the tubule.
2. Regarding chloride, in the book "The Kidney" (1), it is shown that the TF/P ratio in the first 25% of the proximal tube reaches a maximum of 1:3 then reaches the plateau and in the rest length of the tube, it remains almost constant. Other books almost agree on this issue; their only difference is the location of reaching the peak in the proximal tube, which has been reported to be between 20% and 30% from the beginning of the proximal tube. The maximum ratio of reabsorption is also slightly different.
3. In the case of the TF/P ratio of inulin or creatinine, all books show a maximum of "2", while in the book "Medical Physiology Principle for Clinical Medicine" (20), this ratio is 3:2 (21).
4. "The Kidney" suggests that the reabsorption of organic materials occurs at the beginning of the proximal tubule. At the first 25% of the tube length, severe glucose and amino acid reabsorption occur, and these materials leave the tube when the ratio is about 0.1 (Figure 1B) (1). Other books also show the same values, however in "Comprehensive Human Physiology", the concentration drop is more moderate, so that at the first 80% of the proximal tube, severe reabsorption of organic materials occurs and at its remaining 20%, the reabsorption continues until it reaches the zero (Figure 1C) (22). In Vander's "Renal Physiology", the drop in concentration of glucose and amino acid at the beginning of the tube has been confirmed, and also final concentration is considered to be zero (Fig. 1-D) (7). The books "Medical Physiology Principle of Clinical Medicine" (20), and "Rapid Review Physiology" (23), show a gentle slope and a drop in concentration along 60% of the tube length, and also state that the amount of glucose reabsorption is higher than amino acids (Figure 1E, F) (20,23). This is while in other books, the amount of reabsorption of glucose and amino acids along the proximal tube is the same. Interestingly, Guyton's book considers the gentle slope to the end of the tubule length, on the other hand, the greater reabsorption is believed to be related to amino acids (Figure 1A) (19). According to the above, it can be argued that according to "Renal physiology" and

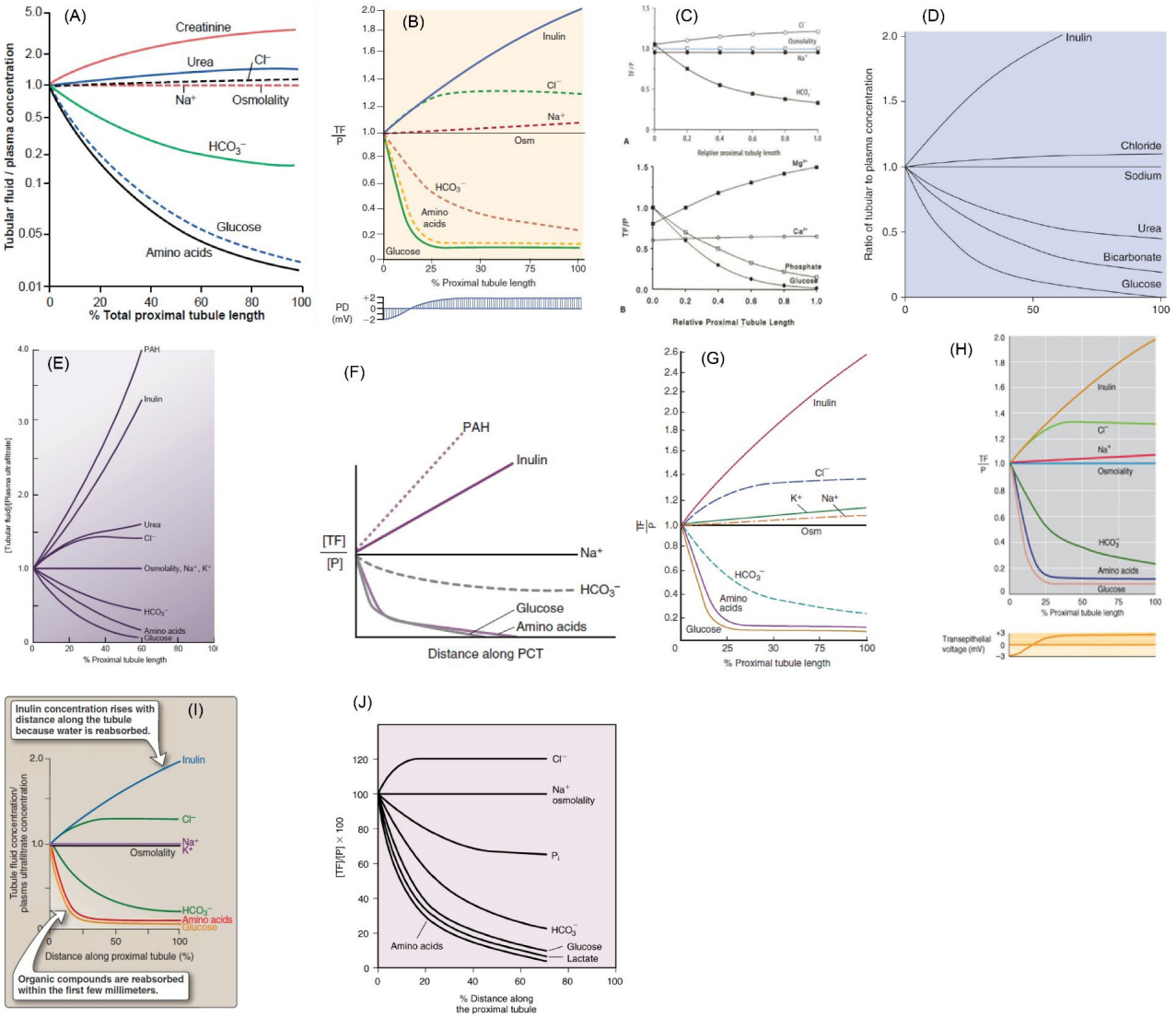

Figure 1. Reabsorption of different substances along the proximal tubule illustrated by the tubular fluid-plasma concentration ratio. A: Medical physiology (19), B: The kidney (1), C: Comprehensive Human Physiology (22), D: Vander's renal physiology (7), E: Medical Physiology Principles for Clinical Medicine (20), F: Rapid review physiology (23), G: Ganong's review of medical physiology (8), H: Medical physiology (9), I: Lippincott's Illustrated Reviews (24), J: Renal Physiology (16)

"Comprehensive physiology" (Figure 1D, C) (7,22), the concentration of these materials in the proximal tubule before reaching the end of the tube is zero, while other authors, including Brenner and Rector, Ganong, Boron, and Lippincott, believe that 10% of these materials remain at the end of the tube (Figure 1B, G, H, I) (1,8,9,20).

5. In regard to bicarbonate, Guyton's book shows a drop with a gentle slope in the TF/P ratio and at the end of the proximal tube, this ratio is 0.2 (Figure 1A) (19). Other books agree on the same reabsorption trend for bicarbonate.
6. In two reviewed books ("The Kidney" and "Medical Physiology" by Boron), the potential difference in the epithelial cell membrane of the proximal tube is also suggested as a mechanism for reabsorption of materials. The difference in potential in "Medical physiology" is between -3 and + 3 mV, while in "The Kidney" it is between -2 and + 2 (1,9).

Discussion

In general, the definition of autoregulation is mostly similar in almost all physiology books (preserving the stability of blood flow and GFR according to blood pressure alteration by changing blood vessels' resistance). While "Medical Physiology" by Guyton and Hall considers the blood flow stability in the range of 75-170 mm Hg, as mentioned above, this range is different in other books. For example, according to "Review of Medical Physiology", "Renal Physiology", and "Renal Physiology: A Clinical Approach" (8,16,18), a severe drop in kidney blood flow occurs when the pressure is under 90 mm Hg, while as stated in "Medical Physiology" by Boron and "Color Atlas Of Physiology" (9,17), it occurs

with pressure under 80 mm Hg; and according to "The Kidney" and "Renal Pathophysiology" (1,15), the drop occurs with pressure under 70 mm Hg. Concerning the mechanism of autoregulation and the vessels involved in it, "Medical Physiology" by Guyton and Hall (19), in addition to the role of afferent arterioles, mentions the role of efferent arterioles in the process of autoregulation, while some of the above said references only attribute the afferent arterioles ("Renal Physiology" (1), Boron's "Medical Physiology" (9), "Clinical Physiology of Acid-Base and Electrolyte Disorders" (10), "Renal Physiology" by Koeppen (16), and "Color Atlas of Physiology" (17). "Renal Physiology" by Vander, "Review of Medical Physiology", and "Renal Physiology: A Clinical Approach" (7,8,18) attribute afferent and efferent arterioles. In addition, "The Kidney" and "Color Atlas of Physiology" attribute the arcuate and interlobular arteries in autoregulation (1,17). Most books have mentioned the role of myogenic mechanisms and TGF in autoregulation. Both of these mechanisms have also been mentioned in the "Control of Glomerular Filtration Rate" by Guyton, according to which, these mechanisms are not related to the intrinsic and inner effects of kidneys, but are caused by the kidneys' external factors (Table 1) (25).

In the book "The Kidney", like Guyton's "Medical Physiology", 60% of filtered materials reabsorption occurs in the primary region of the nephron (1). However, with defining different histology of the cells in this area which is divided into three parts, "The Kidney" expresses that there is a significant difference in the primary, middle, and end parts of the proximal tubule (1), and also it is stated that sudden drop of chloride and bicarbonate reabsorption after the first one millimeter of the tubule (21) and Guyton's Medical Physiology believes that the most reabsorption capability is related to the S1 section with a large brush border and abundant mitochondria. In the case of organic materials such as glucose and amino acids, the most reabsorption occurs in the S1 section, and this heterogeneity is seen throughout the proximal tubule (26). It has also been argued that the negative potential difference inside the lumen causes paracellular chloride reabsorption and sodium leakage from the extracellular space into the tube. The beginning of the proximal tubule, has great power in the reabsorption of bicarbonate through the coupling of the apical sodium-proton exchanger, carbonic anhydrase, and basolateral sodium-bicarbonate co-transport, in addition to sodium-dependent reabsorption of organic materials (26). Contrary to the beginning of the tube, the negative potential difference in the rest of the proximal tubule changes to a positive potential difference that is produced by inactive chloride diffusion (27). This positive potential difference inside the tube causes the paracellular sodium reabsorption, and the concentration gradient of chloride leads to its paracellular transfer. The total active and inactive transfer of sodium-chloride in this section reabsorbs 60% of the filtered sodium-chloride, and this is while the activity of the Na-K-ATPase pump in the proximal tubule is significantly less than that of the distal part of the nephron (28). Guyton's "Medical Physiology" does not consider the inactive route in this way, and considering the role of the proximal tubule in the reabsorption of the high volume of filtered materials, the reader may wrongly conclude that the pump activity in this section is greater. In in the book "Review of Medical Physiology" by Ganong's (8), it has been mentioned that 60% of the reabsorption of sodium in the proximal tube occurs through the sodium-hydrogen exchanger in the proximal tube. In this book, it has been argued that almost all the filtered glucose is reabsorbed, and only a very small amount (in milligrams) appears in the 24-hour urine (8). Boron's "Medical Physiology" divides sodium transfers into *transcellular* and *paracellular* methods. It states that the electrochemical dragging force is an agent for the transfer of materials into the extracellular space. This net dragging force is positive for sodium in the S2 and S3 sections of the proximal tube and at the thick ascending part of the loop of Henle, and has a tendency towards the inactive reabsorption of sodium; in addition, the solvent drag, also plays a role in the net inactive transfer of sodium in the S2 and S3 sections (9).

Regarding water reabsorption that preserves the isosmotic nature of filtration along the proximal tubule, "The Kidney" explains that the major role is by the transfer from transepithelial to the paracellular route, which is done by the aquaporin-1 and aquaporin-7 channels (29-31). Different routes for water absorption may include the simultaneous transfer of water through the sodium-dependent material carriers in the proximal tubule beginning. It has also been stated that the transfer through solvent drag has a less significant role in diffusion (29-32). In Ganong's book, only aquaporin-1 is responsible for water reabsorption and isotonicity of filtra in the proximal tubule (8). In "Renal physiology" by Vander, it is explained that the mechanism of sodium reabsorption occurs via active transport and water transport by the osmosis dependent on sodium reabsorption (7). "Medical Physiology" by Boron, like Vander's "Renal Physiology", states that water reabsorption is dependent on sodium reabsorption, and in addition to that, the paracellular route in the proximal tubule is described as a leakage pathway for water movement (9).

Conclusion

It is concluded that although the general approach to the autoregulation of GFR and relative reabsorption in proximal tubule are similar in different physiology references, there are several controversies in detail. The main disagreements in autoregulation are related to the range of blood pressure in which the mechanism is

Table 1. Final operators in kidney's autoregulation in different physiology books (14)

	Author(s)/editor	Final target effector of renal autoregulation		
Textbook		**Afferent arteriole**	**Efferent arteriole**	**Angiotensin II**
Anatomy and Physiology 7th ed	Seeley et al.	√		
Essential Medical Physiology 3rd ed.	Johnson	√		
Essentials of Medical Physiology 6th ed.	Sembulingam and Sembulingam	√		
Fundamentals of Medical Physiology.	Michael and Sircar	√		
Ganong's Review of Medical Physiology 24th ed.	Barrett et al.	√	√*	√*
Human Anatomy and Physiology 9th ed.	Marieb and Hoehn	√		
Human Physiology.	Davies et al.	√		
Human Physiology 12th ed.	Fox	√		
Human Physiology 4th ed.	Rhoades and Pflanzer	√		
Human Physiology. An Integrated Approach 6th ed.	Silverthorn	√		
Human Physiology. From Cells to Systems 7th ed.	Sherwood	√		
Medical Physiology Updated 2th ed.	Boron and Boulpaep	√		
Medical Physiology. The Big Picture.	Kibble and Halsey	√		
Physiology 4th ed.	Costanzo	√		
Physiology 5th ed.	Berne et al.	√		
Principles of Anatomy and Physiology 14th ed.	Tortora and Derrickson	√		
Principles of Human Physiology 3rd ed.	Stanfield and Germann	√		
Textbook of Medical Physiology 11th ed.	Guyton and Hall	√	√*	√*
Vander's Renal Physiology 6th ed.	Eaton and Pooler	√		
Brenner & Rector's the kidney 10th ed	Skorecki et al	√*	√*	√*
Seldin and Giebisch's The Kidney: Physiology and Pathophysiology 5th ed.	Robert et al	√		√*
Rapid Review Physiology 2th ed.	Brown	√		
Lippincott's Illustrated Reviews: Physiology 6th ed.	Robin R. Preston, Thad E. Wilson	√		
Human Physiology: The Mechanism of Body Function 8th ed	Vander et al	√	√*	√*
Comprehensive Human Physiology 1st ed	Greger and Windhorst	√*		√*
Medical physiology: principles for clinical medicine 4th ed	Rhoades and Bell	√		
Renal Physiology A Clinical Approach 1st ed	Danziger et al	√*	√*	√*

activated, or the exact blood pressure that falls to control the GFR alterations; the vessels which take part in this regulation form another disagreement. In the TF/P ratio, the most different issues are seen in the part of the proximal tubule that reached the maximum reabsorption and the mechanism or pathways that are involved in the reabsorption of various substances.

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Author Contributions
SS: concept and design, data acquisition, interpretation, drafting, and final approval; MA and HA: data acquisition; MK: concept and design, reviewing the draft, interpretation, and final approval. All authors agreed to be accountable for all aspects of the work.

Conflict of Interests
The authors declare that they have no conflict of interest.

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