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Peritonitis risk in peritoneal dialysis
Exploring the role of calcium homeostasis

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Ο κίνδυνος περιτονίτιδας στην περιτοναϊκή κάθαρση: Διερεύνηση του ρόλου της ομοιόστασης του ασβεστίου

Περίληψη στο τέλος του άρθρου

Despite the theoretical acknowledgment that dysregulation of calcium homeostasis plays a substantial role in the development of peritoneal dialysis (PD)-related peritonitis, the supporting evidence for this hypothesis is currently constrained and lacks comprehensive validation. The dysregulation of calcium homeostasis, a critical physiological process, can instigate a cascade of diverse biochemical and pathological alterations within the body, significantly heightening susceptibility to PD-related peritonitis. When calcium regulation becomes imbalanced, it can precipitate secondary hyperparathyroidism, leading to an abnormal accumulation of calcium within cells. Simultaneously, heightened phosphates can trigger an elevation in fibroblast growth factor 23 (FGF23) levels. These interconnected disturbances in calcium metabolism may synergistically contribute to the development of peritoneal fibrosis and vascular calcification. The intricate interplay of these factors not only disrupts the delicate equilibrium of cellular environments but also sets the stage for an increased risk of PD-related peritonitis, underscoring the intricate relationship between calcium dysregulation and the pathogenesis of PD-related peritonitis. In conclusion, the pivotal role of calcium homeostasis dysregulation emerges as a critical factor intricately intertwined with the pathogenic processes, exerting a fundamental influence on the development and progression of PD-related peritonitis.

Key words

Calcium
Pathogenesis
Peritoneal dialysis
Peritonitis
Phosphate

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1. INTRODUCTION

Peritoneal dialysis (PD)-related peritonitis continues to pose a challenge among PD patients. The prevalence of PD-related peritonitis varies widely, influenced by factors such as the patient's age, comorbidities, duration of PD, and the type of PD employed. A study reported a cumulative prevalence of PD-related peritonitis at approximately 1–6%, with an incidence of 0.24 episodes per patient-year.[1] The mortality rate of PD-related peritonitis was reported to be between 10% and 20%.[2] The pathogenesis of PD-related peritonitis is complex and not widely understood. While it is generally recognized that the onset of PD-related peritonitis involves the entry of microbes into the peritoneal cavity through a catheter or other sources, several factors may contribute to the susceptibility of PD-related peritonitis. These factors include poor catheter hygiene, contamination of the dialysis fluid, impaired host immune function, exposure to antibiotic-resistant microorganisms, and dysregulation of calcium homeostasis.[3] Among these factors, dysregulation of calcium homeostasis is predicted to be a crucial element as it involves disturbances in several organs.[4]

Calcium homeostasis refers to the maintenance of a stable balance of calcium in the body. The regulation of calcium homeostasis involves complex interactions among various organs, hormones, and signaling pathways. The primary organs involved in calcium homeostasis are the bones, kidneys, and intestines. Disorders in these pathways may result in imbalances in calcium homeostasis, leading to various conditions such as osteoporosis, hypercalcemia, and hypocalcemia, which can have serious health consequences.[5] Calcium is an essential mineral that plays several important roles in the human body, including bone health, muscle function, nerve function, blood clotting, enzyme function, and hormone secretion.[6] Additionally, calcium signaling is also critical for the proper functioning of immune cells and the generation of an effective immune response against pathogens,[7] indicating that the dysregulation of calcium homeostasis may have a critical impact on the risk of infection, including PD-related peritonitis. Moreover, the dysregulation of calcium homeostasis may also implicate the excessive accumulation of calcium in the peritoneum and contribute to an increased risk of inflammation and

infection.[8] However, reports regarding the role of calcium homeostasis in the case of PD-related peritonitis are very limited. Therefore, this article aims to discuss the potential mechanism of calcium homeostasis dysregulation in the development of PD-related peritonitis.

2. PD-RELATED PERITONITIS

PD-related peritonitis is the infection of the peritoneum caused by bacteria, which may enter through the open ends of the PD catheter during exchanges. The morbidity rate of PD-related peritonitis was reported to be between 1% and 6%, and it has been identified as the primary concern for critical outcomes in patients with PD.[1] This phenomenon has been associated with higher treatment costs and hospitalization.[9,10] Moreover, this phenomenon has also been associated with the transition to hemodialysis. Furthermore, the annual mortality rate of PD-related peritonitis was reported to be approximately 10–20%.[2,11]

The bacteria causing PD-related peritonitis vary according to the findings of several studies. However, the most frequently reported bacterium was *Staphylococcus epidermidis*. On the other hand, at least 40 species of coagulase-negative *Staphylococcus* have also been identified as the causes of PD-related peritonitis. This is probably due to the fact that *S. epidermidis* is the most common among coagulase-negative *Staphylococci*.[12] The reported microorganisms identified as the causes of PD-related peritonitis were as follows: Coagulase-negative *Staphylococci, Staphylococcus aureus*, *Streptococcal* species, *Enterococcus* species, *Corynebacterium* species, Gram-negative enteric bacteria, *Pseudomonas aeruginosa, Acinetobacter* species, *Stenotrophomonas maltophilia, Candida* species, and *Mycobacterium tuberculosis*.[13,14] *S. aureus* commonly causes severe peritonitis due to its many virulence factors. Streptococcal peritonitis is less common, with a prevalence of approximately 5–10% among all PD-related peritonitis patients. The severity depends on the species; β-hemolytic *Streptococci* groups A and B have clinical manifestations similar to *S. aureus*. *Enterococcus* species are normal inhabitants of the gastrointestinal tract and may colonize or infect the genitourinary tract. *Corynebacterium* species commonly colonize human skin and mucous membranes and are generally low-virulence pathogens. Gram-negative enteric bacteria are part of the normal flora of the gastrointestinal tract, and colonization may result from infections in the upper aerodigestive tract and urinary tract.[12]

While many studies have succeeded in identifying the microorganisms causing PD-related peritonitis,[12,13] the risk of developing PD-related peritonitis differs for each individual. The risk factors for PD-related peritonitis are classified into modifiable and non-modifiable categories. Modifiable risk factors include malnutrition, overweight, smoking, immunosuppression, lack of oral active vitamin D use, psychosocial factors, low socioeconomic status, PD against patient choice, and prior hemodialysis as a modality. Non-modifiable risk factors encompass female gender, ethnicity, chronic lung disease, coronary artery disease, congestive heart failure, cardiovascular disease, hypertension, hepatitis C infection, diabetes mellitus, lupus nephritis, glomerulonephritis, and no residual renal function.[15,16]

The pathogenesis of PD-related peritonitis is complex and may involve a wide variety of inflammatory biomarkers. In the literature, the pathogenesis of PD-related peritonitis is classified into the first hit and second hit. The first hit is the pathological pathway where microorganisms enter and infect the peritoneum, while the second hit is the mechanism where complications occur.[17] In the majority of cases of PD-related peritonitis, the source of infection is the PD catheter. The catheter acts as a gateway for microorganisms to enter the normally sterile peritoneum. In females, microorganisms may also enter from vaginal infections.[12,18] Coagulase-negative staphylococcal species, such as *S. epidermidis*, commonly found on human skin and hands, along with *S. aureus*, are the most frequently occurring pathogens in PD-related peritonitis. On the other hand, the abdomen itself less commonly may be the source of infection, such as diverticulitis, appendicitis, cholecystitis, or a perforated viscus, as well as intra-abdominal surgery, colonoscopy, hysteroscopy, and transmigration of bowel flora from constipation. The infecting organisms originating from the intra-abdomen are usually Gram-negative enteric bacteria, *Streptococci*, and anaerobic bacteria. After entering the peritoneum, microorganisms may rapidly grow and proliferate. The peritoneum provides a favorable environment for microorganisms due to its warm and dark conditions, abundance of nutrients such as glucose, and the lack of effective host defenses. This includes a low number of peritoneal macrophages and a limited presence of host-defense proteins such as immunoglobulins and complement. Subsequently, Gram-positive bacteria may produce cell-wall components, and Gram-negative bacteria may produce endotoxin. The infiltration of polymorphonuclear leukocytes (PMNLs) and activated macrophages into the peritoneum leads to inflammation and clinical symptoms such as fever, abdominal pain, cloudy dialysate, and peripheral blood leukocytosis.[12]

3. THE IMPACT OF HYPERCALCEMIA AND PARATHYROID HORMONE IN PD-RELATED PERITONITIS

Hypercalcemia has been associated with the risk of infection. Several infectious diseases, such as leprosy, *Pneumocystis* pneumonia, cat-scratch disease, *Cryptococcus neoformans*, fungal infections, rhinovirus, *Coccidioides immitis*, and *Mycobacterium avium* complex, have been reported to be associated with hypercalcemia.[19–21] Theoretically, the mechanism by which calcium homeostasis interferes with immune function is not yet fully understood. However, some previous studies have proposed that the mechanism of calcium homeostasis in immune function might occur through the disruption of the PTH feedback mechanism[4] and through fibroblast growth factor-23 (FGF23).[22]

In end-stage renal disease (ESRD) patients, secondary hyperparathyroidism occurs as a result of the failure of the feedback mechanism in calcium homeostasis, leading to an increase in PTH levels. PTH has been widely recognized as a factor that plays a pivotal role in the immune system through its role in modulating the expression of several immune cells, as well as cell migration and degranulation, such as T lymphocytes and polymorphonuclear leukocytes (PMNL).[23] In ESRD patients, it has been known that the suppression of the PTH feedback mechanism occurs, and thereafter, this circumstance may contribute to the impaired expression, migration, and degranulation of T lymphocytes and PMNL. As a result, this condition may cause a decreased capability of phagocytosis of PMNL.[4] Elevated PTH levels may implicate an increase in calcium levels in several tissues or cells, where the signals of calcium requirements in cells are regulated by inositol triphosphate (IP3). The elevated levels of calcium in cells may then interfere with the cell proliferation cycle. The prolonged resting cycle in cytosolic calcium in cells, also known as the calcium burden of cells, may occur.[23] As it has been widely known, one of the roles of calcium is to activate genes responsible for initiating the resting stage in cell proliferation,[24] suggesting that the higher calcium levels result in a longer resting cycle. As a result, the calcium burden of cells may further inhibit mitochondrial oxidation, causing a decrease in ATP levels.[23]

Mitochondrial oxidation is a biochemical pathway for the production of ATP. This process requires NADH and H^+ ions. In the context of Ca^{2+}/H^+ exchange, higher levels of Ca^{2+} entering the cells lead to higher levels of H^+ exiting from the cells. Therefore, higher levels of calcium may result in lower levels of H^+ ions and subsequently impair ATP production (fig. 1).[25] Phagocytosis is an active mechanism that requires

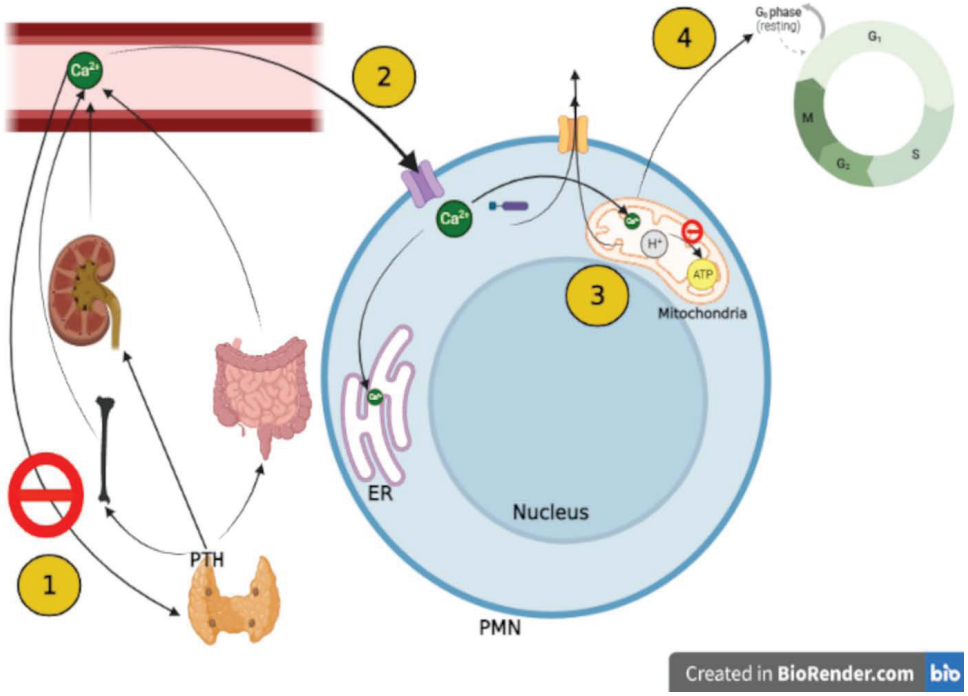

Figure 1. The potential mechanism on the imbalance of calcium homeostasis affects the impairment of immune function. (1) Secondary hyperparathyroidism occurs as the consequence of the failure of feedback mechanism in the calcium homeostasis, leading to hypercalcemia. (2) Inositol triphosphate (IP3) regulates the requirement of calcium which may transfer calcium into endoplasmic reticulum (ER), mitochondria, or extracellular space. (3) Excessive accumulation of calcium may then impair the pathway of mitochondrial oxidation in producing ATP and (4) cause the prolonged G0 of cell proliferation. PTH: Parathyroid hormone, ER: Endoplasmic reticulum, PMN: Polymorphonuclear cells.

ATP. Defects in the process of ATP formation may have implications for a decrease in the ability of phagocytosis.[23] On the other hand, a defect in the PTH mechanism has also been associated with the malnutrition-inflammation complex (MIC) in patients with ESRD.[26] MIC is a condition where a decrease in the body's protein pool occurs, either with or without fat depletion; or a condition where there is a decrease in functional capacity caused by an imbalance between nutritional intake and needs.[10,27] Hyperparathyroidism may stimulate protein-energy wasting and has been reported as a common cause of secondary immune deficiency and susceptibility to infection.[28] Taken together, they may lead to an increased susceptibility to infection, including PD-related peritonitis.

4. THE IMPACT OF FIBROBLAST GROWTH FACTOR-23 IN PD-RELATED PERITONITIS

The association between calcium homeostasis and immune disorders may also occur through FGF23. FGF23, a protein belonging to the fibroblast growth factor family, is secreted by osteocytes and osteoblasts, regulating the metabolism of phosphate and vitamin D. In healthy individuals, the levels of FGF23 may increase with phosphate loading. In the case of ESRD, the increased levels of FGF23 may result from the decline in urinary phosphate excretion. The mechanism by which FGF23 stimulates phosphaturia is by decreasing levels of calcitriol, inhibiting the secretion of parathyroid hormone, and degrading and internalizing the sodium-phosphate co-transporter.[29] In ESRD patients, elevated levels of FGF23 have been found to be associated with adverse outcomes, including cardiovascular events and mortality.[30]

In the case of FGF23 and infection among ESRD patients, the reports are still limited. FGF23 has been elucidated to have a crucial role in innate immunity by inhibiting CYP27B1 in peripheral blood mononuclear cells, monocytes, and the kidney,[31] a major enzyme involved in the production of $1,25(OH)_2D$.[32] Moreover, FGF23 was also associated with the negative effect on intracrine production of $1,25(OH)_2D$ and the suppression of antibacterial cathelicidin production. In the case of infection, the expression of CYP27B1 and the vitamin D receptor is increased in immune cells, leading to the conversion of 25(OH)D to $1,25(OH)_2D$. This circumstance may subsequently alleviate cathelicidin transcription,[31] a potent antimicrobial for many pathogens, including both Gram-positive and Gram-negative bacteria, fungi, parasites, and enveloped viruses. Subsequently, cathelicidins may cause neutrophils and mast cells degranulation, stimulating upregulation of neutrophils and mast cells and leading to phagocytosis,[33] and may indirectly trigger the immune host to produce specific pro-inflammatory cytokines against microbes, such as: TNF-α, IL-1b, IL-6, and IL-36 by interacting with the toll-like receptor (TLR) system.[34] The interaction between cathelicidins and TLRs may be responded to by MyD88 and TNF receptor-associated factor 6 (TRAF6), eventually stimulating nuclear factor kappa B (NFκB), mitogen-activated protein kinases (MAPKs), and the activator protein-1 (AP-1) to subsequently produce specific pro-inflammatory cytokines. Additionally, cathelicidins may also act directly as antimicrobial agents by destroying the stability of the microbial cell membrane, leading to cell death.[33] Meanwhile, increased levels of FGF23 are associated with the suppression of CYP27B1 expression in monocytic cells, causing decreased production of $1,25(OH)_2D$ (fig. 2). Therefore, this condition may inhibit antibacterial cathelicidin production, leading to an increased risk of infection, including PD-related peritonitis.[31]

5. THE IMPACT OF VASCULAR CALCIFICATION AND FIBROSIS IN PD-RELATED PERITONITIS

The role of calcium homeostasis imbalance in the risk of infection may also occur through vascular calcification and fibrosis. Vascular calcification is defined as the deposition of mineral complexes (calcium-phosphate complexes) in the vasculature. This circumstance may occur in all arterial beds, both in intimal and medial layers, and therefore, vascular calcification is classified into intimal calcification and medial calcification. Intimal calcification is associated with lipid deposits and the infiltration of inflammatory cells. On the other hand, in cases of ESRD, diabetes mellitus, and arterial stiffness, medial calcification is more prevalent.[35] The potential contributing factors for the development of vascular calcification are diabetes mellitus, ESRD, hypertension, dyslipidemia, smoking, aging, inflammation, oxidative stress, FGF23, and imbalances in calcium homeostasis.

The mechanism of how an imbalance in calcium homeostasis affects vascular calcification is complex. Briefly, an imbalance in calcium homeostasis may cause the loss of vascular smooth muscle cells (VSMC) markers, such as smooth muscle (SM) alpha-actin and SM22α. On the other hand, an imbalance in calcium homeostasis may also increase the expression of osteochondrogenic markers, such as Runx2, osterix, osteopontin, and alkaline phosphatase. High phosphate and or calcium may also initiate the regulation of matrix mineralization through elastin degradation, leading to the induction of VSMCs mineralization.[36] In patients with PD, this condition might be defined as peritoneal calcification.[37] In this condition, a vigorous

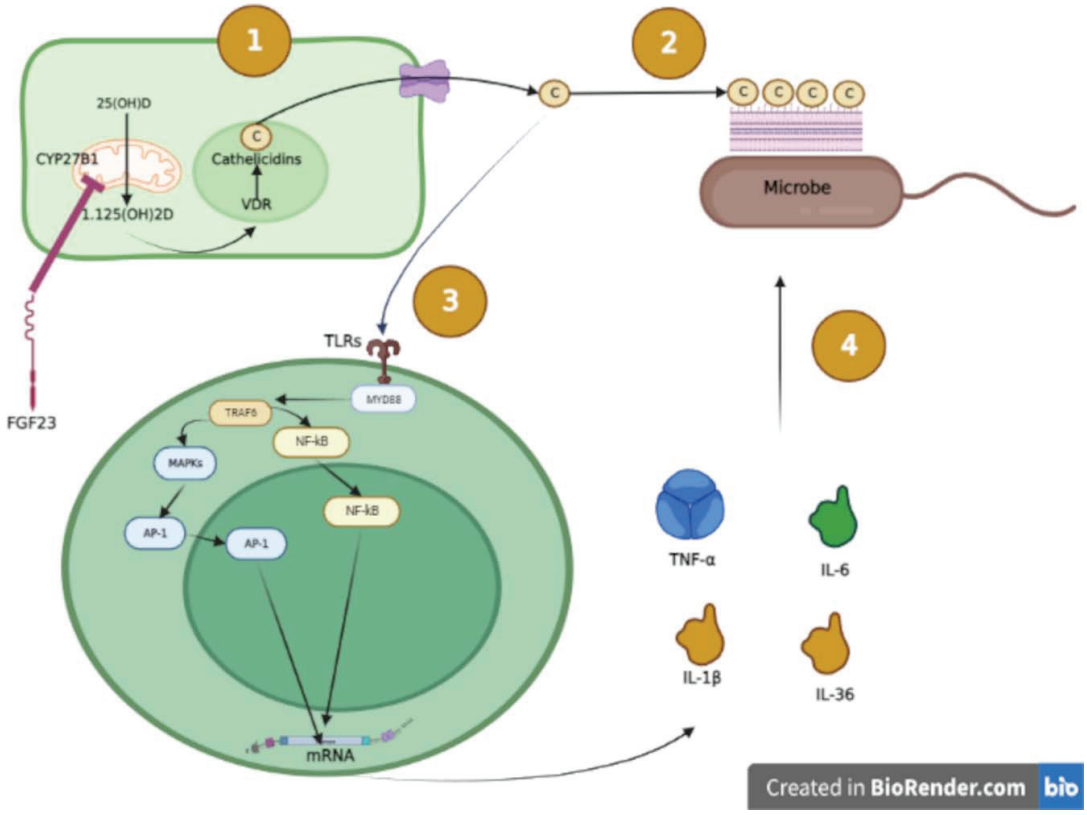

Figure 2. The proposed mechanism of cathelicidins as the antimicrobial which is inhibited by FGF23. (1) The pathway of cathelicidin production. (2) Cathelicidins have an impact to cause the disruption of microbial membrane wall. (3) Cathelicidins indirectly stimulate the production of pro-inflammatory cytokines, (4) which may further be against the microbes. CYP27B1: Cytochrome P450 family 27 subfamily B member 1, FGF23: Fibroblast growth factor 23, VDRE: Vitamin D response element, TLRs: Toll-like receptors, TRAF6: TNF receptor-associated factor 6, MAPKs: Mitogen-activated protein kinases, NFκB: Nuclear factor kappa B, AP-1: Activator protein 1, mRNA: Messenger ribonucleic acid, TNF-α: Tumor necrosis factor alpha, IL-6: Interleukin 6, IL-1β: Interleukin 1β, IL-36: Interleukin 36.

inflammatory reaction might occur in the peritoneum, involving vascular smooth muscle cells, interleukin 6, and tumor necrosis factor alpha. The accumulation of these pro-inflammatory cytokines is known to cause the inflammatory process in the peritoneum.[38] On the other hand, the phagocyte-microbe complex may trigger the adhesion process in the basal membrane of the peritoneum. Consequently, FGF23 may stimulate peritoneal mesothelial cells to undergo mesothelial-to-mesenchymal transition (MMT) or epithelial-to-mesenchymal transition (EMT), causing low polarization of mesothelial cells and subsequently inducing the secretion of extracellular matrix (ECM). Furthermore, the secreted ECM and MMT may gather to cover the adhesive immune complex and may trigger fibrosis (fig. 3). As fibrosis develops, the structure of ECM may change to become stiffer, as well as the anatomy of the peritoneum.[39] This circumstance eventually may cause impaired production of key immune molecules, such as complement pathway proteins,[40] leading to increased risk of infection including PD-related peritonitis.

6. LIMITATIONS

Several important limitations were also discussed. Firstly, the pathogenesis of PD-related peritonitis is complex. While a wide variety of bio-markers may speculatively play a crucial role in the development of PD-related peritonitis, in fact, studies reporting the direct impact of those bio-markers in PD-related peritonitis are limited. Therefore, this limitation poses a challenge in establishing the potential mechanism of calcium homeostasis in the development of PD-related peritonitis. Secondly, studies on PD-related peritonitis cases were very limited. Most articles only reported on peritoneal membrane transport. Hence, this limitation also contributes to our difficulty in compiling potential mechanisms of calcium homeostasis in PD-related peritonitis.

7. CONCLUSIONS

Theoretically, this article has proposed a possible mecha-

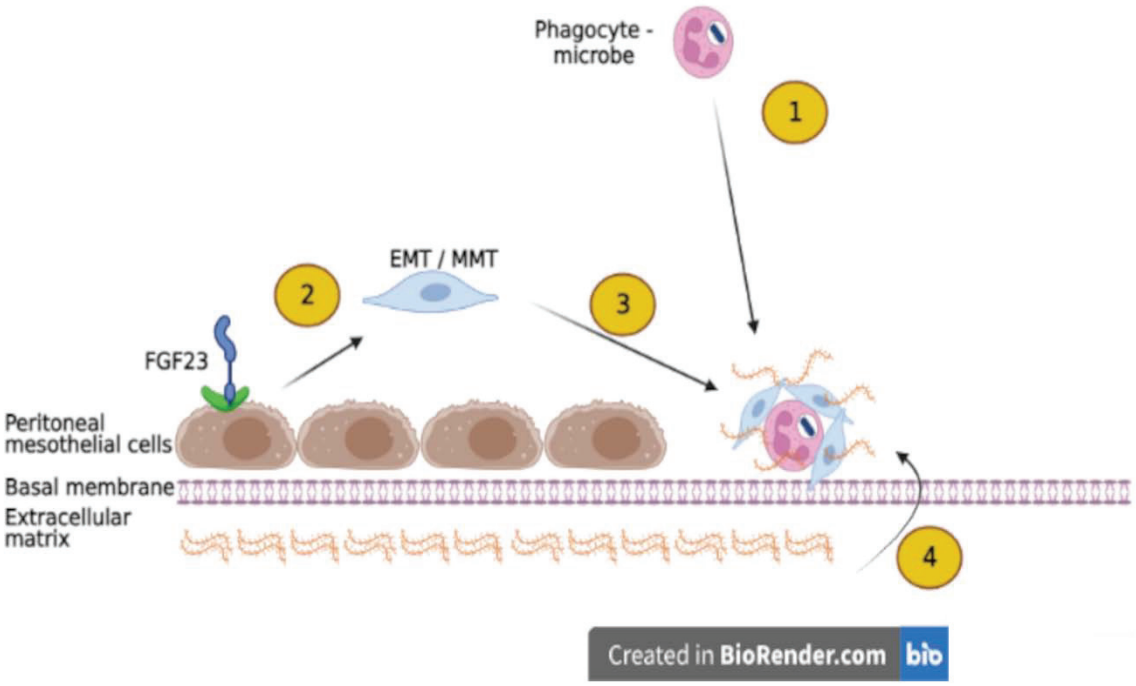

Figure 3. The potential mechanism of fibrosis in peritoneal dialysis (PD)-related peritonitis. (a) The immune complex of phagocyte-microbe causes the adhesion in basal membrane of peritoneum. (b) FGF23 may stimulate peritoneal mesothelial cells to lead MMT or EPT. (c) EMT/MMT together with secreted ECM may accumulate in the adhesive site and causing fibrosis. ECM: Extracellular matrix, EMT: Epithelial to mesenchymal transition, FGF23: Fibroblast growth factor 23, MMT: Mesothelial to mesenchymal transition.

nism for the dysregulation of calcium homeostasis in the development of PD-related peritonitis. Dysregulation of calcium homeostasis may cause secondary hyperparathyroidism, which triggers excessive accumulation of intracellular calcium, increased FGF23 as a result of hyperphosphatemia, and the effects of vascular calcification and peritoneal fibrosis. Taken together, these factors may contribute to an increased risk of PD-related peritonitis.

ΠΕΡΙΛΗΨΗ

Ο κίνδυνος περιτονίτιδας στην περιτοναϊκή κάθαρση: Διερεύνηση του ρόλου της ομοιόστασης του ασβεστίου

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Παρά τη θεωρητική παραδοχή ότι η απορρύθμιση της ομοιόστασης του ασβεστίου διαδραματίζει σημαντικό ρόλο στην ανάπτυξη περιτονίτιδας που σχετίζεται με την περιτοναϊκή κάθαρση (ΠΚ), τα υποστηρικτικά στοιχεία γι' αυτή την υπόθεση είναι επί του παρόντος περιορισμένα και στερούνται ολοκληρωμένης επιβεβαίωσης. Η απορρύθμιση της ομοιόστασης του ασβεστίου μπορεί να προκαλέσει έναν καταρράκτη ποικίλων βιοχημικών και παθολογικών αλλοιώσεων στο σώμα, αυξάνοντας σημαντικά την ευαισθησία για περιτονίτιδα που σχετίζεται με ΠΚ. Όταν η ρύθμιση του ασβεστίου δεν είναι ισορροπημένη, μπορεί να επισπεύσει τον δευτεροπαθή υπερπαραθυρεοειδισμό, οδηγώντας σε ανώμαλη συσσώρευση ασβεστίου στα κύτταρα. Ταυτόχρονα, τα αυξημένα φωσφορικά άλατα ενδέχεται να προκαλέσουν αύξηση των επιπέδων του FGF23 στους ινοβλάστες. Αυτές οι διαταραχές στον μεταβολισμό του ασβεστίου μπορεί να συμβάλλουν συνεργιστικά στην ανάπτυξη περιτοναϊκής ίνωσης και αγγειακής ασβεστοποίησης. Η

περίπλοκη αλληλεπίδραση των εν λόγω παραγόντων όχι μόνο διαταράσσει την ισορροπία του περιβάλλοντος των κυττάρων, αλλά προδιαθέτει και για αυξημένο κίνδυνο περιτονίτιδας σχετιζόμενης με ΠΚ, υπογραμμίζοντας την περίπλοκη σχέση μεταξύ της απορρύθμισης του ασβεστίου και της παθογένεσης της σχετιζόμενης με ΠΚ περιτονίτιδας. Συμπερασματικά, ο κεντρικός ρόλος της απορρύθμισης της ομοιόστασης του ασβεστίου αναδεικνύεται ως ένας κρίσιμος παράγοντας, πολύπλοκα συνυφασμένος με τις παθογόνες διεργασίες, ασκώντας θεμελιώδη επίδραση στην ανάπτυξη και στην εξέλιξη της σχετιζόμενης με ΠΚ περιτονίτιδας.

Λέξεις ευρετηρίου: Ασβέστιο, Παθογένεια, Περιτοναϊκή κάθαρση, Περιτονίτιδα, Φωσφορικό άλας

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