Relationship Between Chronic Kidney Disease and Diabetic Foot Ulcers

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Abstract: Diabetic foot ulcer (DFU) is a significant complication of diabetes. Chronic kidney disease (CKD) can exacerbate the risk and worsen the prognosis of DFU, leading to a substantial economic burden on both individuals and society. There may be a relationship between CKD and DFU. This review primarily explores the potential mechanisms underlying the occurrence of DFU in CKD patients, aiming to provide a foundation and guidance for subsequent clinical treatment and management.

***Keyword*:** hemodialysis, type 2 diabetes, diabetic foot ulcer

1. Introduction

Diabetes mellitus (DM) is a prevalent chronic metabolic disease in clinical settings, with Diabetic Foot Ulcer (DFU) being a serious complication. Patients who develop DFU usually have a very poor prognosis, with ulcer recurrence rates of nearly 65% within 3 years after healing[1], approximately 19% of DFU patients will require lower limb amputation[2], and mortality rate of nearly 50% within 5 years[3]. Approximately 39.3% of diabetic foot patients also have Chronic Kidney Disease (CKD)[4]. The incidence of foot ulcers in patients with diabetes and end-stage renal disease increased by 3.35 times in the first year after starting renal replacement therapy and by 4.65 times between the second and fifth years. Additionally, severe amputations occurred in 31.98% of cases in the first year and 34.01% between the second and fifth years[5]. Patients entering the dialysis stage, whether hemodialysis or peritoneal dialysis, face a risk of DFU that is more than four times higher[6], and the incidence of amputation and sepsis will be more frequent, and the hospital stay will be longer[7]. The survival rate of DFU maintained dialysis patients was significantly lower than that of patients without foot ulcers[8]. There may be a relationship between CKD and DFU, and some specific measures taken for patients receiving dialysis can also affect the prognosis of DFU. Therefore, to gain a deeper understanding of the relationship between the two diseases, this article reviews relevant clinical research progress, with a view to providing basis and guidance for subsequent clinical treatment and management.

2. Proteinuria

About 30%-47% of ESKD originates from diabetic nephropathy[9], and albuminuria is an important feature. Hyperglycemia can alter the phenotype of podocytes through various mechanisms. These include inducing the loss of Nephrin protein, affecting the production or degradation of extracellular matrix components, enhancing the signal transduction of procytokine transforming growth factor β1 (TGF-β1), remodeling the actin cytoskeleton, down-regulating α3β1 integrin, and causing podocyte hypertrophy and apoptosis[10]. Simultaneously, the increase in advanced glycation end products can bind to the receptor for advanced glycation end products (RAGE) expressed by podocytes[11]. This further worsens podocyte injury and leads to proteinuria. Studies have shown that proteinuria plays a specific role in the occurrence and development of DFU, and increased urinary protein excretion is associated with long-term non-healing, amputation rate, mortality, and other poor prognosis of DFU[12]. Compared with the decrease in eGFR, proteinuria may be a more predictive risk factor for vascular complications of type 2 diabetes[13]. Proteinuria is associated with atherosclerosis, which leads to the deterioration of PAD[14][15]; at the same time, increased albumin excretion rate may lead to decreased blood osmotic pressure, which induces foot edema, affects the blood supply of the affected limb, aggravates local hypoxia and inflammation, and leads to poor ulcer healing[16]. Furthermore, as diabetic foot infections worsen, complications such as diabetic foot osteomyelitis and systemic inflammatory response syndrome (SIRS) frequently arise. This results in the release of numerous inflammatory mediators, increased capillary permeability, and eventual kidney damage, leading to elevated urinary protein excretion[12].

3. Decreased glomerular filtration rate

With the increase of dialysis age and the decline of residual renal function, uremic toxin accumulation and water

and electrolyte disturbance often occur in patients. Accumulated uremic toxins such as protein-binding toxins (PBUTs), phosphates, indole sulfate (IS), and indole-3-acetic acid (IAA) can induce inflammation and lead to structural damage, phenotypic changes, and impairment of the protective and repair mechanisms of endothelial cells, leading to the prethrombotic state of endothelium and participating in the formation and rupture of atherosclerotic plaques[17]. On the other hand, the accumulation of inositol, guaninosuccinic acid, methylguanidine, polyamines, phenol derivatives, and parathyroid hormone, along with increased free radical activity due to oxidative stress[18][19], can result in motor, sensory, and autonomic nerve damage, leading to uremic neuropathy. At the same time, patients with end-stage renal disease are often accompanied by hyperkalemia, which disrupts the normal ionic gradient and then activates calcium-mediated processes, leading to further aggravation of axonal damage[20]. The goal of hemodialysis is to remove uremic toxins from the blood, and unfortunately, protein-bound toxins are not completely removed. On the other hand, it removes many valuable low molecular weight compounds, such as vitamins, hormones, etc. Large fluid transfers (and the resulting hemodynamic changes) during dialysis in diabetic dialysis patients can lead to microcirculatory hypoperfusion and poor oxygen delivery to the skin of the lower extremities[21], which may worsen any underlying PAD and lead to skin vulnerability and impaired wound healing. The autonomic nervous system dysfunction caused by diabetes and uremia is prone to intradialytic hypotension, and the blood flow is usually set at a low level during dialysis, which affects the adequacy of dialysis[22].

4. Immunity and infection

Infection is one of the common complications of DFU, and patients with diabetes and end-stage renal disease are vulnerable to infection, especially those undergoing hemodialysis. Uremic patients accumulate uremic toxins and reduce the production of renin, erythropoietin, and vitamin D due to a disorder of renal metabolic activity and impaired glomerular filtration, thus affecting the systemic immunity and presenting various immune abnormalities and neutrophil dysfunction[23]. These abnormalities and neutrophil dysfunction can be exacerbated by underlying diseases and complications, immunosuppressive drug use, malnutrition and micronutrient deficiencies, iron overload, hyperparathyroidism, and specific dialysis procedures[24]. Urinary toxins and hyperglycemia lead to the damage of intestinal epithelial cells and the destruction of barrier function in patients, thus increasing the systemic inflow of microbial products and the spread of intestinal infection[25][26]. Meanwhile, repeated puncture of the arteriovenous fistula and catheter placement in dialysis patients increase the potential sources of infection in diabetic dialysis patients. The presence of diabetes also increases the susceptibility of ESRD patients to infection, especially in hemodialysis patients. Higher HbA1c levels are associated with higher diabetic foot infections and higher skin and soft tissue infection rates[27]. The blood glucose of patients with CKD is affected by a variety of interacting factors, including insulin secretion, insulin resistance, renal insulin clearance, renal gluconeogenesis, and renal function. Commonly used blood glucose assessment indicators may have errors due to hemoglobin abnormalities, iron therapy, and the use of erythropoietic stimulants, as well as chronic inflammation caused by uremia. Therefore, blood glucose management and monitoring in patients with CKD and diabetes mellitus pose great challenges[28]. Long-term hyperglycemia negatively affects the human body's immune system by inhibiting cytokine production, causing phagocytosis defects, and leading to immune cell dysfunction. A high glucose environment can stimulate bacterial growth, and in cases of autonomic neuropathy, abnormal sweat gland secretion function will make the skin on the feet dry and chapped, and prone to infection[29]. Once diabetic foot and lower limb infection occurs, wound healing becomes a problem. At the same time, CKD and hyperglycemia contribute to the development of atherosclerosis, which hinders the flow of nutrients to the wound. In addition, various skin cell function impairment, inflammatory reaction, and peripheral neuropathy lead to repeated wound infection in CKD patients, which is not healed for a long time.

5. Nutritional status

The occurrence and development of DFU are closely related to nutritional status[30]. Metabolic acidosis, inflammatory state, uremic toxin accumulation, abnormal eating and digestive function, and dialysis operations of end-stage renal disease caused by impaired renal function can all lead to malnutrition in patients[31]. The deficiency of protein and energy consumption, vitamins and minerals (such as magnesium, selenium, and zinc), etc., affects oxidative stress and inflammation, thus aggravating the damage to peripheral nerves and blood vessels, and can also lead to the decline of immune function in DFU patients, increase the chance of infection, and affect wound healing[32].

6. Educational nursing and cognition

Insufficient foot nursing education is one of the potential risk factors for patients with DFU[33]. DFU has high requirements on patients' daily self-care ability, but DFU patients are often affected by factors such as lack of awareness of

foot nursing knowledge and bad psychology, resulting in inadequate daily self-management behaviors and unsatisfactory blood sugar control, which is not conducive to patients' prognosis[34]. The incidence of cognitive impairment in CKD patients is higher than that of the general population[35], especially in hemodialysis patients. The prevalence of mild cognitive impairment in diabetic hemodialysis patients can be as high as 20.6%[36], and the presence of uremic toxins, vasculopathy, anemia, and multi-drug therapy may all have an impact on cognition[37]. At the same time, the prevalence of anxiety disorders and the incidence of anxiety symptoms in CKD patients were 19% and 43%, respectively[38], which further diminish quality of life and hinder daily activities.

In recent years, some progress has been made in researching the risk factors for DFU in hemodialysis patients. It is understood that these risk factors are numerous and complex, with interactions among them that can lead to the gradual development of foot ulcers and necrosis, potentially resulting in amputation in severe cases. Currently, preventing and treating DFU issues in dialysis patients with diabetic nephropathy remains challenging, necessitating further research. To address this, guiding patients to adopt a proper mindset, implementing early intervention for high-risk factors, conducting regular foot screenings, tailoring treatment plans to individual needs, and optimizing DFU prevention and treatment are essential.

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