



Immunity and chronic kidney disease

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Abstract

Chronic kidney disease (CKD) is a worldwide public health problem and is associated with a rise in prevalence, costs, and undesirable outcomes. Patients with chronic renal failure are prone to develop a variety of complications. Immune system impairment is one of the most important and serious complications in these patients. These patients often suffer from immune suppression and are susceptible to a variety of infections. Changes in the immune system predispose patients to develop infections which in turn lead to an increased risk of inflammatory and cardiovascular diseases and exacerbate them. In order to prevent infections in these patients it is recommended to vaccinate against common infectious diseases. Of course, the value of educating patients about the risks and of infection and related prevention methods must not be underestimated. It is of great importance to train patients, families, and health care professional who take care of patients, because such trainings can have a major effect on the prevention of infections and other serious complications in CKD patients.

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Introduction

While renal dysfunction happens slowly, kidney disease may be present as a latent disease for many years. Gradual loss of kidney function is called chronic kidney disease (CKD) or decreased kidney function. People who suffer from CKD gradually will be faced with progressed renal insufficiency (1). CKD is a public health crisis and is associated with an increase in the prevalence, costs, and undesirable adverse outcomes (2).

The efforts made for the prevention, early detection, evaluation, and treatment of CKD can prevent complications of decreased renal function; it can also reduce the progress of CKD toward the end stage disease and related complications. Patients with chronic renal failure are at risk of many complications (3). Immune system complications are one of the serious groups of complications which occur in these patients. This group of patients is faced with both hormonal and cellular disorders in their immune. These patients are often immunosuppressed and susceptible to infection (4).

Many kidney diseases are caused by immune disorders; the kidney disease itself can affect the immune system. When CKD occurs, kidney structure is damaged as a result of the disease which leads to protein excretion from the body. Protein plays an important role in immune system. Many factors in-

Key Point

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involved in immune system, such as enzymes and antibodies, are made of proteins; hence, protein excretion reduces the amount of materials available for making these factors. In addition, kidney damage causes the accumulation of toxins in the body (4).

Many of these substances are dangerous for body organs and can disrupt the body's immune system. For example, bone marrow is one of the most important organs involved in the body's immune system however the mentioned toxins can inhibit bone marrow cell proliferation (5). Anemia is a common complication of CKD which is caused by bone marrow deficiency; some studies have investigated the use of new substances such as erythropoietin for the treatment of this complication (6).

To reduce pain and sufferings of the patients and to reduce health care costs, it is

necessary to pay special attention to patients' immunity, prevention of infections, and prevention of other complications of CKD. As kidney patients always receive repeated treatments, the diagnosis and treatment methods used for this group of patients must be less invasive as much as possible; overall, the invasive actions must be used rarely. Some remarkable studies have been conducted so far to investigate and detect less invasive methods of diagnosis and treatment (7).

This study aimed to make a review of the literature and previously published studies to investigate and introduce an appropriate method for the prevention and treatment of infectious complications of CKD.

Materials and Methods

In this review article first we searched several keywords including immune system, infection, immunodeficiency, immune therapy and CKD. The keywords were searched in scientific databases of PubMed/Medline, Scopus, EMBASE, EBSCO, directory of open access journals (DOAJ) and Google Scholar. We reviewed the results of the relevant papers. Several studies have pointed out the complication of CKD, among which cardiovascular diseases and other infections have been identified as the two serious complications that are associated with immunity.

Infections in CKD patients

A study by Kato et al showed a high rate of mortality in CKD patients with cardiovascular complications and infections; the results suggested that these two common groups of CKD complications are associated with chronic inflammation and wastes resulting from protein metabolism. The findings of that study indicated that neutrophil to lymphocyte ratio is higher in patients with CKD hence this marker can be used to detect high-risk patients with chronic inflammatory diseases (8).

Dalrymple and Go (9) conducted a study and investigated the epidemiology of acute infections in CKD patients. They note that infection in dialysis patients is a primary problem, thus there is a need for further studies to determine an approach for effective prevention of infection in these patients.

According to some other studies, the high prevalence of infections in CKD patients may be attributed to changes in immune system of this group of patients. In this group of patients, the function of PMN, lymphocytes and monocytes undergo some changes and the host shows an impaired immune response to infection. Malnutrition, increased intracellular calcium, iron overload, dialysis membranes, and uremic toxins are involved in PMN dysfunction. After the onset of kidney failure, T lymphocyte and monocytes will have an impaired function (10-12). According to the results of a study by Kato et al (13), CKD is associated with high rates of mortality and morbidity; in addition, 20% of all cases of death from CDK are due to infections. The study shows that uremia can lead to immune system disorder via generating infections. The study also suggests that the incidence of cardiovascular events in in-

fections in CKD patients is associated with changes in the immune system. Moreover, immune system dysfunction is introduced as the underlying cause of high mortality in this group of patients (13). In line with the mentioned study, McDonald et al reported the high risk of acute infections in patients with CKD; the authors concluded that special measures must be taken to prevent infections in this group of patients (14).

According to the study by Cohen et al, cardiovascular and infectious diseases are the two main causes of mortality in patients with CKD, and these two groups of diseases directly or indirectly have a relationship with immunodeficiency syndrome (15).

Similarly, Valizadeh et al conducted a study to assess the serum level of DPPIV/CD26 molecule in patients affected by lupus and renal involvement; the results of their study showed a significant increase of CD26 in patients with renal involvement which was attributed to autoimmune response to inflammatory process (16).

According to the results of another review study, immunodeficiency was one of the common problems in the elderly who are largely affected by the deterioration of the immune system. Many chronic inflammatory diseases such as treated HIV, tuberculosis, and CKD have a similar effect on the aging process. Vascular calcification, atherosclerosis, decreased appetite, increased muscle catabolism, osteodystrophy, and depression are very prevalent in patients which might be due to immune system disorders. The clinical symptoms of immune system disorder in these patients are different (17).

Previously conducted studies have noted the high cost of treatment in these patients which highlights the value of preventive measures (18).

Discussion

Patients with kidney diseases receive several different medications. Long-term use of hormone drugs can reduce the level of immunity (19).

High level of blood glucose in diabetic nephropathy patients reduces the immune response and causes infection; in fact, it deteriorates patient immunity (20).

Another problem of kidney patients is having trouble sleeping. Sleep is the best antiphlogistic medicine. Muramic acid, which acts as an antiphlogistic, is created when a people is sleeping. This material plays a major role in increasing the immunity level of the body. In patients with renal failure the creation of this material is disturbed due to sleep disturbances and consequently the immunity level is reduced (21).

Another factor that affects immunity level is the cognitive and psychological status of patients with kidney diseases. These patients may suffer from several side effects such as itching, nausea, vomiting, fatigue, and sleep problems. All of the mentioned items can affect the emotional, cognitive, and psychological status of patients and thus have negative effects on the immune status of the individuals (22,23).

As already mentioned above, many kidney disease are caused due to immune disorders; hence, it is very im-

portant to restructure immunity in these patients. Deposit of immune complements in kidneys is the major cause of a high percentage of kidney damages such as nephrotic syndrome, IgA nephropathy, lupus nephritis, and Henoch-Schönlein purpura nephritis (4).

After entering the body, external factors or antigens are attacked by antibodies and an immune complex is formed. Under normal conditions, when the immune system of the body is normally functioning, these immune complexes are eliminated from the body. However, when the immune system is impaired, these materials are not excreted from the body; instead they are accumulated in kidneys and cause inflammatory responses, damage to kidney cells, and damage to kidney structure. Because of damages to kidneys, patients will suffer from hematuria, proteinuria, swelling, high blood pressure, and deterioration of renal failure (24).

Kidney constantly shows pathogenic immune responses against the body antigens; these responses are associated with local systemic autoimmune protests. Recent studies on animal models and human have revealed the underlying immunity mechanisms that explain the pathology of renal diseases (25). These mechanisms include molecular patterns of renal damages which lead to sterile inflammation; they also include the molecular expression of microbial agents (25).

On the other hand, renal failure affects the immune system and leads to intestinal dysfunction, systemic inflammation, and immune deficiency, all of which are associated with mortality and morbidity in patients with kidney disease (13). Infection is one of the serious complications of CKD and is the main cause of a significant percentage of mortality and morbidity in kidney patients. Many infections in these patients are preventable (26).

Patients with CKD are susceptible to various infections caused by uremia; these infections lead to the subsequent changes in host defense mechanisms and increase the risk of bacterial infections. Damaged chemotaxis neutrophils can cause oxidative metabolism, phagocytosis, and intracellular granulation and death. Several factors are involved in neutrophils dysfunction including malnutrition, lack of chelation, iron overload, impaired glucose metabolism, hyperparathyroidism, dialysis, and urea products retention. These immunological disorders exacerbate after taking immunosuppressive drugs which are used to treat and control underlying diseases; the drugs can lead to reduced appetite, dialysis, and weakening of the mucosal barrier against infections (27-29).

Epidemiological studies have suggested a higher risk of bacterial infection in CKD patients, especially those with urinary tract infections, pneumonia, and sepsis. The incidence of infectious complications in patients with CKD who are not on dialysis is three times more than that in the general population. Crude mortality rate is higher in CKD patients with sepsis, pneumonia, and UTI than normal patients with the same complications. The higher rates in CKD patients may be attributed to urinary tract obstruction caused by BPH, kidney stones, and cancer (30).

Compared with the general population, the annual mortality rate of dialysis patients due to sepsis is higher even after adjusting for age, race, and diabetes. The mortality rate of dialysis patients due to sepsis is approximately 100 to 300 times higher (31). The second major causes of death are urinary tract infections and pulmonary infections. Other sources of infection include skin and dialysis water treatment systems (32).

Dialysis patients are hospitalized at least once a year due to infections (33). Type of vascular access has an important role in the spread of blood-borne infections. Central venous catheters significantly increase the risk of bacteremia in dialysis patients. Temporary catheter, compared with fistula, increases the risk of septicemia by 50%. Arteriovenous fistula somewhat reduces the risk of infection (34). Old, non-functional, and flocculated arteriovenous grafts can be one of the causes of bacteremia and mortality in hemodialysis patients. Infectious grafts should be promptly removed and systemic antibiotics must be administered (35).

Prolonged hemodialysis is one of the risk factors for developing infective endocarditis which has a high rate of mortality in hemodialysis patients (36).

Cardiovascular complications are the dominant cause of mortality in hemodialysis patients however patients on peritoneal dialysis are hospitalized mainly due to infections. Peritonitis at the catheter site is the most common infection in this group of patients (37).

Peritonitis is usually caused by decreased phagocytic function which is attributable to phagocytosis suppression and phagocytic ability of peritoneal macrophages. In case of peritonitis, fluid path becomes reversed and passes the lymph ducts and peritoneal membrane and goes into the abdominal cavity. As a result, infectious agents in the blood stream are activated in this environment. Such infections affect the performance of peritoneal membrane and reduce its ultrafiltration capacity. Consequently, it makes it difficult to remove fluids from the cavity. Such a condition is usually caused by epidermidis and *Staphylococcus aureus* organisms and catheter infections (38).

Compared with hemodialysis and peritoneal dialysis patients, transplant patients are less at risk of infection; however, the annual mortality rate from sepsis in renal transplant patients is 20 times more than that in the general population (31).

Common treatments for immune disorders in CKD patients

Special attention must be paid to infections in CKD patients. In order to prevent infections, vaccination is recommended for these patients. Despite improvements in infection control methods and dialysis techniques, bacterial and viral infections are still a major cause of death in CKD patients (28).

Respiratory infections, especially pneumonia, are among the most common infections in this group of patients. Hence it is recommended to vaccinate patients against pneumonia using pneumococcal polysaccharide vaccine.

In addition, because of the high prevalence of influenza, especially in the cold seasons, it is recommended to vaccinate patients against this disease as well (39,40). Hepatitis B is one of the common viral infections in these patients. Vaccination against hepatitis B in these patients is now routinely done. The response to the vaccine in CKD patients have been reported between 60% and 80% (41). Staphylococcal infections are among the other common infections in this group of people. *Staphylococcus aureus* is the most common type of staphylococcal infections. It is also recommended to vaccinate patients against this organism though its effect has not been established. Nevertheless, available reports suggest the positive effect of vaccination during the first 40 weeks after injection (42). It is also highly recommended to train these patients, their families, and health care personnel. Training people about the infections can increase public and patient awareness of the risks of infection. In order to reduce mortality from infectious and cardiovascular complications it is recommended to recruit highly qualified and skilled health care personnel, pay more attention to infections, prevent infections, and reduce at least one source of infection and inflammatory stimuli in patients with CKD.

Conclusion

Due to uremia, immune system disorder occurs in CKD patients. As a result, it leads to the immune suppression and activates the immune system to fight the inflammatory processes caused by cardiovascular complications. Changes in the immune system prepare a favorable ground for infections which in turn lead to an inflammatory process and increase the risk of cardiovascular diseases. In order to prevent infection in these patients it is generally recommended to carry out vaccination against common infectious diseases. Nevertheless, it is necessary to consider the effects of trainings about the risks of infection and prevention methods. It is of great importance and value to train patients, family members, and health care personnel who are in contact with this group of patients, because the elimination of even a single source of infection can greatly reduce the incidence of infection and related cardiovascular complications in these patients.

Author's contribution

MRT is the single author of the paper.

Conflicts of interest

The author declared no competing interests.

Ethical considerations

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