Renal Replacement Therapy

REVIEW

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# Nontraditional risk factors for cardiovascular disease in patients on peritoneal dialysis

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## Abstract

Patients on peritoneal dialysis (PD) have a high prevalence of cardiovascular complications and are at increased risk of cardiovascular mortality. Dialysis increases the likelihood of developing various cardiovascular complications, including ischemic heart disease, cardiac valvular disease, hypertensive cardiomyopathy, and arrhythmias. However, noncardiac circulatory failure can also occur in the absence of obvious cardiac disease in PD patients as a result of excessive fluid volume. Other important causes of nontraditional circulatory failure in these patients include mineral imbalance and severe anemia. In this review, I focus on nontraditional risk factors for cardiovascular disease in PD patients, including ultrafiltration failure, chronic kidney disease–mineral bone disorders, anemia, inflammation, and sarcopenia.

**Keywords** Cardiovascular disease, Peritoneal dialysis, Nontraditional factors, Mortality

## Introduction

According to a Japanese Society for Dialysis Therapy (JSDT) Renal Data Registry survey conducted at the end of 2018, there were 344,640 patients receiving chronic dialysis therapy in Japan at the time [1]. The number of incident dialysis patients was 40,885, 5.7% of whom were on incident peritoneal dialysis (PD). Among all patients receiving dialysis treatment, the proportion of those on PD remained low at 2.9%. The mean age of patients receiving PD was 70.42 years, and the age group with the highest proportion of patients on PD was 70–74 years for both men and women. The most common cause of death in patients on PD were heart failure (22.7%), infection (21.5%), and malignancy (11.1%), in that order. Cardiovascular mortality in patients on PD (including heart failure, cerebrovascular disease, and myocardial infarction) was 32.3%. This statistic indicates that prevention and treatment of cardiovascular disease (CVD) are essential to improve the prognosis of patients on PD.

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### Heart failure as a CVD

Heart failure is an important and growing public health problem worldwide [2]. Even though evidence-based therapies have continuously developed, most patients with heart failure will progress to advanced stages. Fluid overload is a prominent condition in the patients with chronic heart failure and is a primary reason for hospitalization and relating to the progression of heart failure [3]. Reduction in renal function and diuretic resistance are frequently associated with fluid overload, causing pulmonary congestion.

Heart failure is a clinical syndrome arising from structural and functional cardiac abnormalities that impair ventricular filling (diastolic function) and reduce ejection fraction (contractile function); it is highly associated with hypoxia [4]. Among the symptoms most commonly experienced by patients with heart failure, dyspnea and fatigue, limited exercise tolerance, and fluid retention leads to pulmonary congestion and peripheral edema. Myocardial fibrosis is a major complication in patients with chronic kidney disease (CKD) [5]; it is the abnormal

deposition of extracellular matrix in the myocardium [6]. Despite the significant burden of myocardial fibrosis in CKD patients, the molecular mechanisms involved in collagen metabolism are known.

Patients on dialysis are more likely to develop cardiac complications, including ischemic heart disease, cardiac valvular disease, hypertensive cardiomyopathy, and arrhythmias [7]. Abnormality in left ventricular mass and structure are common in CKD patients [8]. Among patients on hemodialysis or PD, it has been reported that the prevalence of left ventricular hypertrophy is approximately 75% [9]. However, noncardiac circulatory failure owing to noncardiac origin not accompanied by obvious cardiac disease, but caused by excessive fluid volume can also occur in dialysis patients. Other important causes of noncardiac circulatory failure include severe anemia [10].

**Table 1** Traditional and nontraditional risk factors for cardiovascular disease (CVD) in patients with chronic kidney disease (CKD)

| Traditional factors | Nontraditional factors |
|---|---|
| Aging | Albuminuria |
| Male | Anemia |
| Hypertension | Hyperphosphatemia |
| Dyslipidemia | Oxidative stress |
| Diabetes mellitus | Inflammation |
| Smoking | Malnutrition |
| Left ventricular hypertrophy | Reduction in nitric oxide |
| Past history of CVD | Overhydration |
| | Thrombosis |
| | Sleep disturbance |
| | Renin–angiotensin–aldosterone |
| | Sarcopenia |

## Risk factors for CVD

Risk factors for CVD are classified into traditional and nontraditional [10] (Table 1). Advanced age and diabetes mellitus are important traditional risk factors for atherosclerosis and increase the risk of cardiovascular death. Patients on chronic dialysis therapy in Japan are typically older, with a high prevalence of diabetic nephropathy. Abnormal mineral metabolism is considered a nontraditional risk factor and is a component of chronic kidney disease–mineral bone disorder (CKD–MBD) concept, which includes vascular calcification (Fig. 1) [11]. Another nontraditional risk factor is malnutrition, markers of which include a low serum albumin level and a low body mass index, both of which are measured routinely in clinical practice. The concept of protein–energy wasting has recently been proposed [12], and is garnering

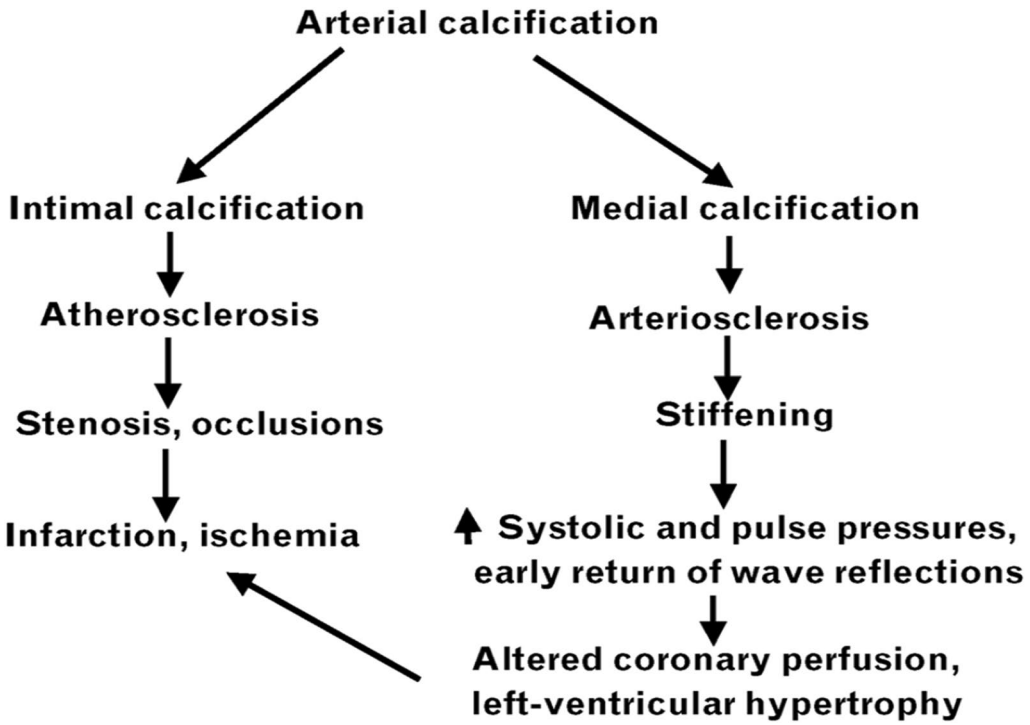



**Fig. 1** Vascular calcification and cardiovascular disease. Vascular calcification is a component of CKD–MBD and is associated with atherosclerosis and arteriosclerosis, which leads to cardiovascular disease

attention as a determinant of the prognosis in dialysis patients. A recent meta-analysis found that age, primary CVD, diabetes mellitus, and a high alkaline phosphatase level were associated with all-cause and cardiovascular mortality in patients on PD [13]. However, it also mentioned that the precise relationships between the prognosis and serum concentration of magnesium, potassium, and uric acid remain to be investigated in patients on PD.

#### Ultrafiltration failure

The peritoneal capillary wall and its surrounding tissues serve as a biologic membrane for fluid and solute transport during peritoneal dialysis, and therefore the major determinants of peritoneal permeability to fluid and solutes [14]. The peritoneum is a heterogeneous membrane consisting of various structures: methothelium, interstitial tissue, and endothelial cells of the microvascular wall. The endothelium is suggested to be an important structure for peritoneal transport.

The incidence of ultrafiltration failure increases after about 5 years of standard PD therapy owing to an increase in peritoneal solute permeability [15]. Ultrafiltration failure results from a decreased osmotic gradient caused by increased glucose reabsorption from the dialysate, which leads to increased fluid retention and consequently to hypertension and left ventricular hypertrophy; these conditions are considered to contribute to an increase in CVD-related mortality in these patients. Peritoneal permeability increases with expansion of the peritoneal capillary bed.

Pathology studies have revealed fibrous thickening and angiogenesis in the submesothelial compact zone of the peritoneum, and the severity of these changes increases with increasing duration of dialysis [16]. Factors involved in ultrafiltration failure include patient-related factors (e.g., peritonitis, inadequate dialysis, chronic inflammation, and diabetes mellitus), exposure of the peritoneum to acidic dialysate, glucose and glucose degradation products, and insertion of foreign materials (e.g., catheters) into the body. Measures that should be taken to prevent ultrafiltration failure include adequate dialysis, use of a dialysate solution with the lowest concentration possible to ensure preservation of residual renal function, prevention of peritonitis, and restriction of salt and water intake by the patient.

The length of time during which patients can be maintained on PD is expected to be extended with the advent of icodextrin and neutralized dialysates, and icodextrin may contribute to a reduction in CVD-related mortality. The approach to ultrafiltration failure is summarized in Table 2. Icodextrin is a water-soluble glucose polymer and acts as a colloidal osmotic agent. Previous meta-analyses have reported some advantages of icodextrin compared with glucose, including improvement of peritoneal ultrafiltration, especially in patients with high or high-average peritoneal status [17, 18]. There is also evidence for a reduction in events of uncontrolled fluid overload.

#### CKD–MBD

The JSDT published a Clinical Practice Guideline for the Management of Chronic Kidney Disease–Mineral and Bone Disorder in 2013 [19]. In this guideline, the target MBD marker levels are as follows: serum phosphorus, 3.5–6.0 mg/dL; serum calcium, 8.4–10.0 mg/dL; and serum parathyroid hormone (PTH), 60–240 pg/mL. The KDIGO (Kidney Disease: Improving Global Outcomes) has also published an international guideline [11], which has contributed to improved management of CKD–MBD. However, in Japan, it has been difficult to achieve the target levels of phosphorus, calcium, and PTH specified in the revised KDIGO guidelines [20]. One possible reason for this is that use of phosphorus adsorbents (P binders) in patients on PD differs from country to country.

The mainstream treatment for MBD in patients on PD is management of serum phosphorus [20]; more specifically, a phosphorus-restricted diet, maintenance of residual renal function, and treatment with phosphorus binders. Given that continuous ambulatory peritoneal dialysis is a continuous blood purification therapy, the serum calcium concentrations remain constant, except that it is affected by the calcium concentration in the dialysates. When using a dialysate with a low calcium concentration, the patient should be monitored for the possible development of secondary hyperparathyroidism. However, when a low calcium dialysate is used in patients on continuous ambulatory PD who are in a low bone

**Table 2** Approach to ultrafiltration failure in patients on peritoneal dialysis (PD)

| | |
|---|---|
| 1. | Attainment of normal volume status is important for the wellbeing of patients on PD |
| 2. | There is a different diagnosis in the volume overload patients on PD. Do not assume it is membrane failure |
| 3. | Early versus late ultrafiltration failure have different causes |
| 4. | Management includes dietary sodium restriction, pushing urine output by diuretics, and changes to the PD prescription |
| 5. | Consider a transition to hemodialysis (HD) if the patient remains chronically volume overloaded despite these interventions |

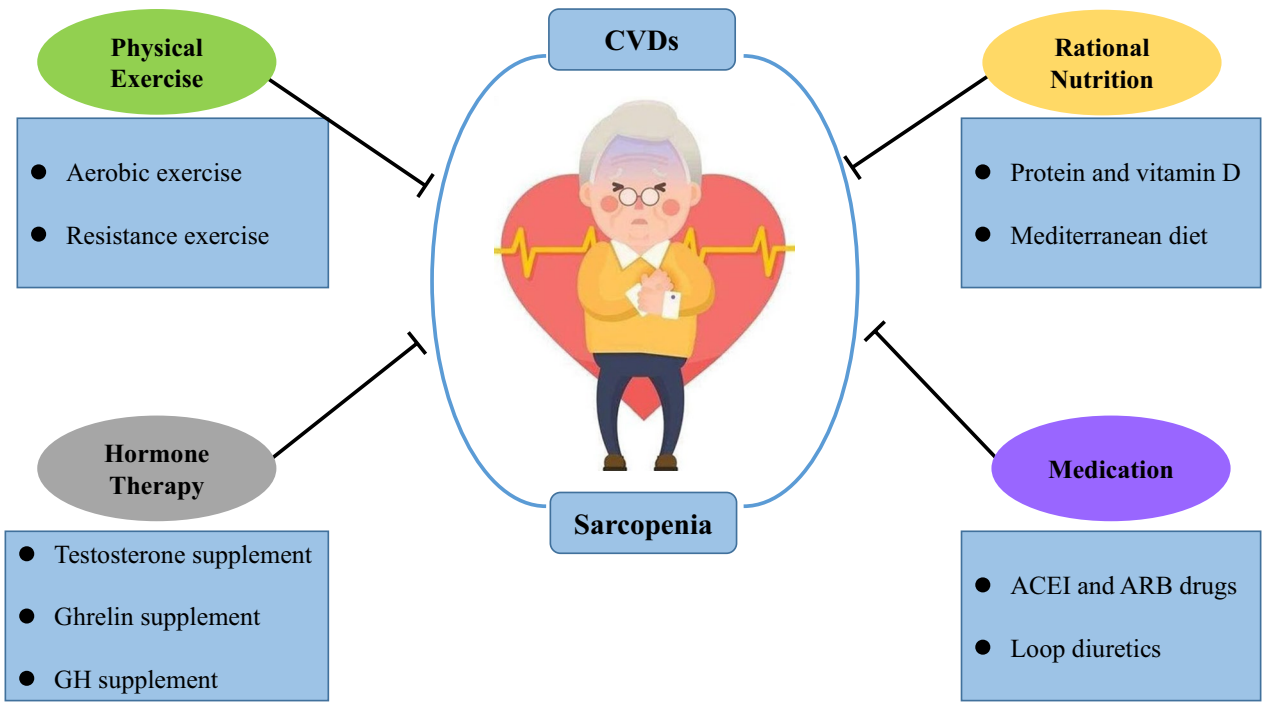
turnover state owing to a low serum PTH levels, bone turnover increases with elevating PTH concentration. Therefore, the bone turnover rate should be taken into consideration when selecting the dialysate.

MBD and mortality in patients on PD were investigated in the multicenter Netherlands Cooperative Study on the Adequacy of Dialysis [21]. The cardiovascular death rate relative to the all-cause death rate was 52% in patients on PD, which was higher than the reported rate of 45% in patients on hemodialysis (HD), although the difference was not statistically significant ($p=0.07$). Cardiovascular mortality was analyzed further according to serum calcium, phosphorus, and PTH concentrations. The risk of death was 1.5-fold higher (95% confidence interval: 1.1–2.1) in patients on HD and 2.4-fold higher (95% confidence interval 1.3–4.2) in those on PD when the serum P concentration was elevated (> 5.5 mg/dL) than when was in the normal range (3.5–5.5 mg/dL). Considering that the serum phosphorus concentration is a determinant of cardiovascular mortality, we believe that serum phosphorus needs to be managed more aggressively in patients on PD than those on HD.

Few papers have investigated the relationship between management of MBD and mortality in patients on PD. A study in Taiwan reported an association of serum calcium > 9.5 mg/dL and/or a serum phosphorus > 6.5 mg/dL with increased mortality [22]. However, that study also reported that when the reference range for serum PTH was set at 150–600 pg/mL, a PTH concentration > 600 pg/mL was associated with lower mortality, whereas a PTH concentration < 150 pg/mL was associated with increased mortality. Further studies are needed to investigate the relationship between management of MBD and mortality, including cardiovascular death in patients on PD by country (Fig. 1).

## Anemia

The concept of anemia in cardiorenal syndrome has been proposed (Fig. 2) [23], in which ischemia and oxidative stress induced by anemia cause fluid retention and inflammation, contributing to deterioration of clinical status in patients with cardiac and renal diseases. It is known that the higher the New York Heart Association functional class for cardiac disease, the worse the anemia,




The treatment of sarcopenia and CVDs. At present, the joint intervention of sarcopenia and CVDs is mainly from physical exercise, rational nutrition, hormone therapy and medication.

**Fig. 2** Anemia is a risk factor for cardiac hypertrophy. Cardiorenal anemia syndrome (CRAS) is known as a vicious circle, since heart failure, chronic kidney disease, and anemia are exacerbated by each other

and the worse the anemia, the higher the rate of hospitalizations for heart failure, resulting in a poor prognosis. According to the guidelines for treatment of renal anemia published by the JSDT [24], the target hemoglobin level in adult patients with PD should be maintained in the range of > 11 g/dL to < 13 g/dL. Furthermore, the guidelines recommend that treatment for renal anemia should be started when multiple tests reveal a hemoglobin level of < 11 g/dL. According to the guidelines, the protocol for administration of erythropoiesis-stimulating agents in patients on PD should be the same as that used before dialysis in patients with chronic kidney disease (Fig. 2).

The treatment of anemia and CVD in patients on PD has been the subject of only a few studies. Inferences can only be made from the results of large-scale studies conducted in predialysis patients. In the CREATE study, the group treated to maintain hemoglobin at a high target level (> 13.5 g/dL) had better quality of life than the group treated to maintain the hemoglobin at a lower target level (11.5 g/dL). However, a noteworthy finding in this study was that although there was no differences in the estimated glomerular filtration rate or frequency of cardiovascular events between the groups, the time to initiation of dialysis was shorter in the group with a higher target hemoglobin level [25]. Moreover, in the CHOIR study, the prognosis was worse in the group treated to maintain hemoglobin at > 13.5 g/dL than in the group treated to maintain hemoglobin at around 11.5 g/dL [26]. On the basis of the above findings, the JSDT guidelines for the treatment of renal anemia recommend dose interruption or reduction of erythropoiesis-stimulating agents in dialysis patients with a hemoglobin levels of > 12 g/dL or > 13 g/dL (for relatively young patients with high physical activity levels) and in patients with a predialysis or nondialysis hemoglobin > 12 g/dL (severe CVD) or > 13 g/dL (history or complications of severe CVD).

The hemoglobin value might change longitudinally in PD patients owing to the presence of various disease status and treatment measures; measurement of a single hemoglobin level does not reflect an accurate assessment of a patient's exposure to the effects of anemia management over time. To address this problem, a clinical study analyzed the time-averaged hemoglobin value from each patient to validate the longitudinal burden of anemia by averaging all individual measurements and considering the duration of any individual value [27]. Results from a study from Taiwan demonstrated that a lower hemoglobin level was associated with significantly higher all-cause and CV mortality in PD patients [28] and were similar to those of the study by Molnar et al. on PD patients [29].

### Inflammation

Nontraditional risk factors in addition to traditional risk factors may contribute to an increased CV mortality in dialysis patients. Chronic inflammation, as one of the nontraditional risk factors, is a common condition in these patients and is associated with the high CV mortality rate. On the basis of the strong associations between malnutrition, inflammation, and atherosclerosis, malnutrition–inflammation–atherosclerosis (MIA) syndrome has been proposed in PD patients [30, 31]. Elevated serum levels of proinflammatory cytokines may play an important role in the vicious circle of MIA syndrome.

PD leads to both systemic and local peritoneal inflammation, which cause various pathophysiological processes [32]. Mesenchymal conversion of mesothelial cells is suggested to be a key feature in the pathophysiology of the peritoneum during peritoneal dialysis [33]. Systemic inflammation is a risk factor that contributes to increased mortality and CVD [34]. Local inflammation was an important factor of peritoneal transport but did not influence survival [35].

The local peritoneal inflammation in PD is induced by exogenous and endogenous factors [36], including glucose-degradation products (GDP) [37]. GDP lead to the formation of advanced glycation end-products (AGE), and continuous exposure results in cytotoxic damage and proinflammatory responses in mesothelial cells [38]. The receptor for AGE (RAGE) is a membrane receptor which mediates the damaging effects of these compounds [39]. Although local peritoneal inflammation does not directly contribute to CVD, it modulates peritoneal transport and ultrafiltration capacity. There were prominent correlations between baseline and 1-year dialysis effluent cytokine levels with peritoneal transport parameters [40]. Taken together, MIA syndrome is indirectly associated with CVD in PD patients.

### Sarcopenia

Sarcopenia is a disorder in which there is a reduction in skeletal muscle volume with diminishing muscle strength and function; it is the major cause of frailty and falls in the elderly [41]. A common complication in dialysis patients, sarcopenia is known to be associated with poor quality of life and death [42]. Dialysis-related sarcopenia has been linked to various factors, including metabolic acidosis, uremic toxins, malnutrition, loss of amino acids on dialysis therapy, and chronic inflammation. These factors ultimately result in protein degradation and a reduction in protein synthesis, resulting in a negative nitrogen balance. Moreover, physical activity is low in dialysis patients, and this is associated with loss of muscle mass [43].

Considering the differences in the diagnostic criteria used in the various guidelines, the highest prevalence (36.9%) was found in the 2019 Asian Working Group in dialysis patients [44]. A recent study found that patients on PD had a significantly lower frequency of sarcopenia than those on maintenance HD [45], potentially because of a younger age, fewer comorbidities, and greater physical independence. Most patients on PD have more time available during the day, especially when treated with nocturnal intermittent PD therapy, requiring one or two dialysate exchanges per day at nighttime. However, patients on HD have to spend about 4 h on dialysis, two or three times a week, with limited activity during their session. Moreover, some patients on HD may have fatigue, dizziness, and cramping after a session. Therefore, these patients need a longer rest period. It is known that residual kidney function is better preserved in patients on PD than in those on regular HD, which may reflect the benefit of greater reduction of protein-bound uremic toxins. It was been shown that uremic toxins impaired the regeneration of skeletal muscle by inhibiting proliferation of myoblasts, decreasing myogenic differentiation, and promoting fibrosis in muscle [46].

Previous studies in patients on HD, including a meta-analysis, found that sarcopenia was significantly associated with increased risk of cardiovascular events [47, 48] (Fig. 3). However, there is still limited information on the relationship between sarcopenia and cardiovascular events in patients on PD. Kamijo et al. [49] investigated sarcopenia and frailty in 119 patients on PD in terms of their impact on mortality, malnutrition, and inflammation. They identified sarcopenia in 8.4% of these patients and frailty in 10.9%, respectively. During follow-up, the presence of sarcopenia and frailty was associated with the risk of mortality. A recent study of the relationship between sarcopenia and pre-atherosclerotic markers and its effect on cardiovascular events and death in dialysis patients found that patients on HD were more likely to be sarcopenic than those on PD during 24 months of follow-up [50]. There was no statistically significant difference in the cardiovascular event rates or mortality according to sarcopenia status.

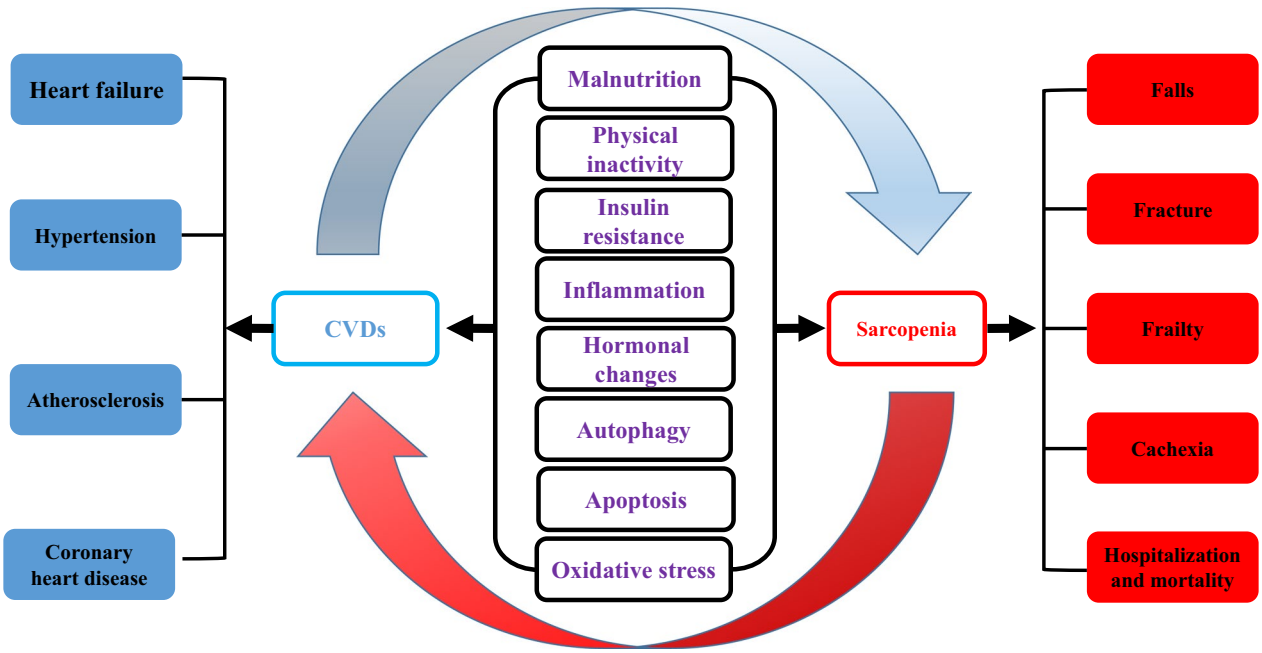



**Fig. 3** Relationship between sarcopenia and cardiovascular disease. Malnutrition, physical inactivity, insulin resistance, inflammation, hormonal changes, autophagy, apoptosis, and oxidative stress are involved in the occurrence of cardiovascular disease. The prevalence of cardiovascular disease, such as heart failure, hypertension, atherosclerosis, and coronary heart disease, in patients with sarcopenia is significantly increased

## Conclusions

In addition to traditional risk factors, such as age and diabetes mellitus, nontraditional risk factors for CVD, including ultrafiltration failure, CKD–MBD, anemia, inflammation, and sarcopenia, should be investigated to improve quality of life and mortality in patients on PD.

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KN planned the review, searched the literature, and prepared the article.

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## Declarations

**Ethics approval and consent to participate**
Not applicable.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare that they have no competing interests.

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## Publisher's Note