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In Chronic Kidney Disease, Protein-Energy Wasting and Mortality

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Abstract

Protein-energy wasting (PEW) is a common complication of chronic kidney disease (CKD) and is linked to an increased risk of death from cardiovascular illnesses. Despite the fact that even minor renal impairment is an independent predictor of poor cardiovascular prognosis, PEW manifests clinically at a later stage, either before or during dialysis. Loss of muscle protein and fat is caused by a variety of abnormalities that stimulate protein degradation and/or decrease protein synthesis. These abnormalities are not always linked to anorexia, but they are linked to several abnormalities that stimulate protein degradation and/or decrease protein synthesis. Furthermore, data from experimental CKD shows that uremia selectively inhibits the regeneration ability of skeletal muscle stem cells. The loss of kidney excretory and metabolic functions occurs in the course of CKD, along with the activation of endothelial damage, inflammation, acidosis, insulin signalling changes, and anorexia, all of which are believed to orchestrate net protein catabolism and the PEW syndrome.

Keywords: Protein-energy wasting • Malnutrition • Chronic kidney disease • Cardiovascular risk • Skeletal muscle

Introduction

Despite advances in current renal replacement therapy approaches, death rates in patients with CKD remain high [1]. This rise in mortality is not confined to dialysis patients, but affects people with all GFR levels as CKD progresses, and is mostly caused by cardiovascular disease (CVD) and, in advanced stages, infections [2-4]. Protein energy waste (PEW), a disease characterised by a loss of muscle and visceral protein reserves that is not totally explained by insufficient nutritional intake [5], worsens with the loss of residual renal function and is particularly prevalent in dialysis patients. Uremia-induced changes in protein metabolism and gastrointestinal tract function can lead to poor nutritional status, which raises the risk of cardiovascular disease and infection. The traditional CVD risk factors (such as age, lifestyle, smoking, hypertension, dyslipidemia, diabetes, left ventricular hypertrophy, and heart failure) are over-expressed in CKD patients, partly due to the clinical characteristics of the CKD population (which consists primarily of elderly people, many of whom have CVD or type II diabetes) [6]. The increased cardiovascular risk associated with CKD may be attributable in part to a higher prevalence of non-traditional risk factors unique to CKD, which may promote endothelial dysfunction and/or atherogenesis in and of itself. The phenomenon of "reverse epidemiology" among dialysis patients is an example of the importance of non-traditional risk variables. While a high BMI (kg/m2) is associated with increased cardiovascular risk and all-cause mortality in the general population, the effect of overweight or obesity in dialysis patients is surprisingly in the other direction, with a higher BMI leading to enhanced survival. Several other established risk factors, including as blood pressure and serum cholesterol, homocysteine, and creatinine concentrations, are also involved in the "reverse epidemiology" phenomena [7]. Furthermore, due to the development of other risk factors, such as progressive wasting, the profile of risk for death may shift over time as renal function declines. Only in the short run, according to Chmielewski et al., the apoB/apoA-I ratio is related with improved survival in hemodialysis (HD) patients (1-year mortality). Another study found that the reverse link between hypercholesterolemia and all-cause mortality gradually decreased after the first year of follow-up. Due to the time impact of competing hazards, this is most likely the case. The contradictory link between cholesterol levels and mortality, according to Liu et al., could be explained by the existence of complicated malnutrition-inflammation (defined as BMI 23 kg/m2 or C-reactive protein > 10 mg/L) in the dialysis population. Contreras et al. recently investigated the prevalence of malnutrition-inflammation and its moderating effects on the risk-relationship of cholesterol levels with later CVD events in African Americans with hypertensive CKD. They discovered that in participants without malnutrition-inflammation, the hazard ratio for the primary CVD outcome increased as total cholesterol increased, whereas it tended to decrease in those with malnutrition-inflammation. It's worth noting that the phenomena of “reverse epidemiology” aren’t limited to renal patients; it's also seen in ageing sarcopenia. The goal of this study is to look at the mechanisms that cause PEW as well as a list of non-traditional factors that enhance cardiovascular risk in CKD patients. The loss of kidney metabolism and function, as well as the activation of pathways of endothelial damage, inflammation, acidosis, and altered intracellular IGF-1 and insulin signalling, are among the mechanisms underlying the causes of the wasting syndrome. These elements are expected to orchestrate the PEW syndrome, as they overlap with those that currently operate in ageing and concomitant illnesses like diabetes and sepsis. Several biomarkers have been linked to poorer outcomes in individuals with CKD and dialysis. Those of PEW appear to be the most effective predictors of survival. In dialysis patients, lower levels of serum albumin, prealbumin, cholesterol, serum transferrin, creatinine, and bicarbonate are linked to death. Hormones such as testosterone, leptin, visfatin, adiponectin, and thyroid hormones are other biochemical indicators that are directly or indirectly connected to PEW and outcomes. The mechanisms of action that causes the negative outcomes associated with PEW markers are unknown: it is more likely that a mix of factors, rather than a single etiologic process, is to blame.

Hypoalbuminemia

In dialysis patients, hypoalbuminemia is the most often utilised surrogate for PEW, and it has a clear link to increased mortality and morbidity. In HD and CAPD patients, hypoalbuminemia is linked to the development of de novo and recurrent heart failure. In dialysis patients, serum prealbumin has been suggested as a superior proxy of nutritional status than albumin. The fact that serum albumin and prealbumin are both negative acute phase reactants whose serum levels are greatly influenced by the existence of an inflammatory response is a confusing element. When nutritional intake is restricted, albumin levels are conserved while fat and muscle mass are reduced, according to experiments conducted in the 1940s (the "Minnesota Experiment"). A significant drop in blood albumin levels is not seen in CKD patients who adhere to a reduced protein and calorie consumption. Hypoalbuminemia may be aided in dialysis patients by the loss of amino acids and/or protein during renal replacement therapy. As a result, it's unclear if the poor clinical outcome associated with hypoalbuminemia in advanced CKD patients is due to nutrition, the inflammatory response, or both. It's also unclear if the link between hypoalbuminemia and increased mortality in dialysis patients is due to albumin's intrinsic effects or whether hypoalbuminemia is the result of a series of events linked to an increased mortality risk. Low albumin levels have been linked to hypercoagulable conditions and high blood viscosity. Low oncotic pressure may also have an unfavourable effect on water transfer between the intravascular and interstitial spaces. Albumin also serves as a free radical scavenger, a binding agent for hazardous chemicals, and a transporter for a number of medicines and hormones. Uremia is characterised by decreased albumin binding of medications and endogenous ligands. Persons over the age of 65 are predicted to soon make up the majority of people requiring renal replacement treatment in several Western countries [8]. Nutritional issues are widespread in senior dialysis patients with ESRD, and they contribute to their debility and morbidity. Decreased BUN and serum creatinine levels can occur even in the midst of severe renal failure due to low food intake and decreasing muscle mass in the elderly. One of the most noticeable signs of

ageing is a decrease in body protein. It mostly affects muscle proteins and is linked to a loss of muscle strength and functional impairment. When results are expressed per lean body mass, whole-body protein production and breakdown are similar in young and elderly persons. However, some muscle protein components, such as myosin heavy chain and mitochondrial protein, are associated with specific deficiencies. Furthermore, a decline in insulin sensitivity in relation to protein metabolism has been seen in aged people. Senescence-related changes in protein metabolism are expected to amplify the effects of uremia. Weight loss in elderly people is linked to an increased risk of morbidity and mortality. Weight loss in elderly persons is influenced by a number of factors. Excess cytokine elaboration appears to be a key role in the induction of unintentional weight loss in older persons, according to available evidence. Increased levels of TNF-alfa, IL-6, IL1 receptor antagonist, and soluble TNF receptor are linked to ageing. Acute phase proteins like C-reactive protein and serum amyloid are also high, indicating that the full inflammatory cascade has been activated. Chronic uremia is a kind of acquired immunodeficiency, and CKD patients are more vulnerable to infection [9]. Infection was the leading cause of death in 23% of patients in the HEMO Study who died during follow-up. During an infection-related hospitalisation, the overall chance of death was 15%. CKD patients are susceptible to infections for a variety of reasons, including advanced age, diabetes, hypoalbuminemia, immunosuppressive therapy, dialysis catheters, the dialysis technique, and uremia. Malnutrition impairs immune function by increasing susceptibility to infections and slowing the healing of wounds. Nutrients like arginine and glutamine have been shown to boost immunological response. Uremia-induced changes in muscle metabolism of particular amino acids may impede muscle regeneration. Reduced muscle release of valine and leucine is believed to be the cause of their lower blood levels in CKD patients. The poor release of this amino acid from peripheral tissues has been attributed to increased muscle valine breakdown, which is thought to be caused by metabolic acidosis and/or decreased glucose use. The treatment of metabolic acidosis raises both plasma and muscle BCAA levels via reducing transamination and decarboxylation in muscle, according to studies in rats and humans with CKD. During the course of CKD, anomalies induced by decreased food intake overlap those caused by acidosis, and lowering plasma valine levels have been described as a sign of inadequate nutrition and a loss of lean body mass. It's worth noting that leucine works in tandem with IGF-1 to activate myogenic satellite cells. In a variety of scenarios, such as damage-induced muscle loss, ageing, and progressive neuromuscular disorders, these cells are important for muscle regeneration. Satellite cells are activated by leucine via the mammalian target of rapamycin (mTOR) signalling pathway, which is one of the most important mechanisms for protein synthesis and cell proliferation [10]. These effects appear to be caused by Beta-hydroxy-beta-methilbutyrate (HMB), a leucine catabolite that can cause myoblast proliferation, Akt phosphorylation, and muscle wasting prevention. Finally, PEW is frequent in people with CKD and is linked to an increased risk of death. Despite the fact that even minor renal impairment is an independent predictor of poor cardiovascular prognosis, PEW manifests clinically at a later stage, either before or during dialysis. Loss of muscle protein and fat is caused by a variety of abnormalities that stimulate protein degradation and/or decrease protein synthesis. These abnormalities are not always linked to anorexia, but they are linked to several abnormalities that stimulate protein degradation and/or decrease protein synthesis. Furthermore, data from experimental CKD shows that uremia selectively inhibits the regeneration ability of skeletal muscle stem cells. The loss of renal excretory and metabolic functions occurs as CKD progresses, along with the activation of endothelial damage and inflammatory pathways.

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