Mortality in patients with 5D chronic kidney disease associated with obesity: A narrative review

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Abstract

Introduction: The Rico-Fontalvo classification of chronic kidney disease associated with obesity (CKD-OA) proposes four main pathophysiological mechanisms of renal function impairment with obesity. Type 4 CKD-OA addresses the issue of obesity in the group of patients undergoing dialysis programs. An increase in body mass index >of 30 kg/m² in the general population is associated with a higher risk of developing cardiovascular and metabolic diseases and higher mortality. In the group of patients undergoing hemodialysis therapies, the opposite occurs.

The objective of the review: The aim is to provide the reader with an update on the effect of weight, body composition, and body mass index in patients undergoing hemodialysis therapy in the short, medium, and long term.

Methods: A systematic search was performed in PubMed (Medline, United States Library of Congress); the search was restricted to references with no publication date limit. Keywords in English were used.

Conclusion: The increase in body mass index >25 Kg/m² in the population group of patients undergoing hemodialysis treatments has a protective effect, decreasing mortality in studies carried out with 3 to 5 years of follow-up; At a longer follow-up time (12 years), according to observational studies, an increase in body mass index >30 kg/m² seems to have a harmful effect equal to that of the general population. The benefit of an increase in BMI >25 kg/m² and a decrease in mortality is more significant in men, African Americans, Hispanics, and those over 65.

Keywords:

MESH: Obesity; Kidney Dialysis; mortality; Muscle, Skeletal
C lassification of obesity-associated chronic kidney disease (OA-CKD) addresses the pathophysiological mechanisms underlying the relationship between morbidity and mortality with obesity. Type 1 OA-CKD: presents with obesity and potentially non-reversible functional alterations. Type 2: Obesity and potentially non-reversible histopathological structural alterations (including obesity-associated glomerulopathy and focal segmental glomerulosclerosis). Type 3: Obesity-related to chronic diseases (Diabetes, Hypertension, Pulmonary Hypertension, Heart Failure), and Type 4: Obesity in patients with renal function replacement therapy [1].

It is known that in the population without chronic kidney disease and those with chronic kidney disease but without the need for renal replacement therapy, a body mass index (BMI) above 30 kg/m2 is associated with a greater risk of developing pathologies. Cardiovascular (hypertension, heart disease, and stroke), metabolic diseases, diabetes being the most prevalent, musculoskeletal complications such as osteoarthritis, and various types of cancer [2].

Despite this, obesity is related to better survival in hemodialysis patients, so researchers have called it the "obesity survival paradox" [2].

Several observational studies, meta-analyses, and systematic reviews have shown a good association between a higher body mass index (BMI) and lower mortality on dialysis, a lower percentage of abdominal fat, and greater muscle mass.

Probable causes of this paradoxical phenomenon are attributed to better hemodynamic stability, less inflammation related, especially with tumor necrosis factor-alpha (TNF alpha), more efficient control of the neurohormonal system, lower prevalence of malnutrition-inflammation complex (MIC) in patients with high BMI [2]. There are also non-modifiable factors associated with this phenomenon, such as ethnicity, gender, age, and short-term effect on the region [2].

It is for this reason that this paradoxical phenomenon has been widely studied by various observational studies, meta-analyses, and systematic reviews and has yet to have experimental studies to date.

This narrative review analyzes this phenomenon from the epidemiological and pathophysiological aspects. It explains probable mechanisms and their repercussions in patients with chronic kidney disease who receive renal replacement therapy (peritoneal dialysis and hemodialysis), excluding transplant patients.

Generalities and epidemiology

An increase in the prevalence of obesity among patients starting dialysis may influence the growth of the total population of patients with stage 5 chronic kidney disease on dialysis due to improved survival and decreased likelihood of transplantation [3]. For example, the retrospective study by Kramer H et al. investigated the increase in obesity in incident patients on hemodialysis at five years by age group. Finding a prevalence of obesity of 36% (95% CI: 35 - 38%), and in people with diabetes, a higher prevalence of obesity at 44.6% (95% CI 43.0 to 46.2%) [3, 4]. In the same study, the age group between 64 and 75 years had the most significant increase in obesity concerning other age groups (45% type I obesity and 97% type II obesity), being more remarkable for the non-Hispanic white race, both in diabetic and non-diabetic subgroups [3, 4].

A retrospective study conducted in Japan with 266 incident hemodialysis patients older than 65 years divided into three groups according to their BMI in kg/m2 (<18.5 low, 18.5–23.9 normals, and >24 high) demonstrated an all-cause mortality of 40.4%, 16.4%, and 10.5%, respectively. A BMI >24 kg/m2 was associated with better survival at three years of follow-up to the other groups and represented a protective factor against mortality from any cause (the most common being infectious) after two weeks of starting renal replacement therapy (HR: 0.38; 95%; CI: 0.18–0.81, P =<0.001) [3, 5].

These results were consistent with a meta-analysis study that also demonstrated that a BMI > 25 kg/m2 was associated with lower all-cause mortality in hemodialysis patients (OR 0.67; 95%; CI: 0.65–0.68, P =<0.01) compared to a BMI below this value, which was even maintained in the adjusted model (OR: 0.94; 95%; CI: 0.92–0.96, P <0.01). It has not been shown whether extreme BMIs, for example, >50 kg/m2, also confer protection against any cause of mortality in hemodialysis since these types of patients were not included in the studies [3, 6].

Johansen et al. investigated the relationship between BMI and survival using USRDS (United States Renal Data System) data collected from 418,055 patients who had started hemodialysis and found that a high BMI was associated with increased survival during an average follow-up period of two years afterward. Of adjustment for demographic, laboratory, and comorbidity data, even in subjects with highly high BMI. Furthermore, a high BMI was also associated with a lower risk of hospitalization. These results were seen in Caucasian, African American, and Hispanic subjects but not in Asians [3, 7].

Another meta-analysis showed that for every 1 kg/m2 increase in BMI, the risk reduction for all-cause mortality was 3% (HR: 0.97; 95% CI: 0.96–0.98, n=89,332), and the risk of cardiovascular mortality was reduced by 4% (HR 0.96; 95% CI: 0.92–1.00, n = 8916) [3, 8].

It has also been reported that the association between weight variation and mortality is less evident in obese patients on hemodialysis. In a prospective study by Cabezas-Rodriguez et al. with data collected at 6-month intervals in 6,296 European patients older than 64 years at 3-year follow-up with a BMI of 25.3 ± 4.9 kg/m2 examined the influence of short-term BMI variation on higher or lower mortality [3, 2].

Compared with stable weight (±1%), weight loss (>1% decrease) in the entire cohort was strongly associated with increased mortality, while weight gain (>1% increase) was associated with lower mortality; this held when using categories of non-obese and especially in underweight patients [3, 2].

For obese patients, the association of weight loss with mortality attenuated and was no longer statistically significant HR: 1.28 (95% CI: 0.74–2.14), and no survival benefit associated with increased
weight HR: 0.98 (95% CI: 0.59 –1.62), indicating a potential resistance to the development of wasting in obese patients on hemodialysis [3, 9].

Pathophysiological aspects

There are some hypotheses to explain the decrease in mortality with the presence of obesity in dialysis patients; among the most relevant are stable hemodynamic status, high levels of tumor necrosis factor-alpha (TNF-α) receptors in blood cells and decreased neurohormonal response [2].

Better hemodynamic stability

The vast majority of patients undergoing renal replacement therapy endure some heart failure or have a relative period of fluid overload, with which the redistribution of this excess in the different body compartments becomes essential [2]. Because 90% of intracellular water is deposited in muscle mass, greater muscle mass can receive most of the total body water and redistribute it to the body level.

According to the meta-analysis of Oreopoulos et al., compared with chronic heart failure patients with normal BMI, those with obesity (RR: 0.60; 95%; CI: 0.53-0.69) and overweight (RR: 0.81; 95%; CI: 0.72-0.92) are associated with lower cardiovascular mortality, whereas low weight or normal BMI is associated with relatively higher cardiovascular mortality (RR: 1.20; 95%; CI: 1.04-1.38) with a P value < 0.01 in the groups described [10].

Patients with heart failure on hemodialysis programs are more prone to systemic arterial hypertension despite having similar pulmonary capillary wedge pressure and cardiac indices (cardiac output x body surface area in m2) [2, 11].

Therefore, there seems to be a better hemodynamic tolerance in this group of patients with chronic heart failure and obesity or overweight because most are treated for their hypertension with drugs that reduce cardiac afterload, such as converting enzyme inhibitors, ACE inhibitors, known to prolong the life of patients on renal replacement therapy and contribute to the redistribution of body fluids [2, 11].

Role of tumor necrosis factor (TNF)-α receptors

TNF-α is a proinflammatory cytokine with a potent effect on the host immune system and is also involved in regulating lipid and glucose metabolism [12]. Adipose tissue is an essential endogenous source, and its expression is elevated in obesity. It is believed to operate primarily through autocrine and paracrine mechanisms in both adipose tissue and skeletal muscle [12].

Two structurally distinct TNF receptors have been identified, TNFR type I and TNFR type II. TNFR-I is thought to regulate most of the functions of TNF-α, while the actions of TNFR-II are still unclear and perhaps mainly cell-specific; both receptors are expressed in human adipose tissue and exist in soluble forms in the circulation [12].

Patients with heart failure and those on renal replacement therapies have elevated levels of circulating TNF-α, particularly those with intermittent fluid overload episodes [12].

TNF-α can cause cardiac damage due to its adverse ionotropic and pro-apoptotic effects. In turn, adipose tissue generates type I and type II soluble TNF-α receptors, leading to higher circulating levels of both receptors in overweight and obesity. These receptors neutralize the undesirable biological effects of TNFα at the cardiac level, playing a cardioprotective role that confers survival benefits to obese patients [13].

Altered neurohormonal response

Obesity is related to an alteration of the sympathetic neurohormonal systems and the renin-angiotensin system (RAS), as corroborated by a comparison study carried out in thin and obese subjects, which showed remarkably elevated levels of adrenaline and renin in plasma in lean subjects during exercise, despite a similar baseline between both groups [2].

Sympathetic and RAS stimulation is associated with adverse effects in heart failure and the transient state of fluid overload in hemodialysis patients. Therefore, the decreased response of these neurohormonal systems may confer a favorable prognosis in obese patients on hemodialysis. However, some observational studies have shown that obese hemodialysis patients have lower blood pressure readings than underweight hemodialysis patients [2].

Protective role of inflammation

Inflammation in hemodialysis patients may be due to processes associated with renal failure itself, secondary to renal replacement therapy, oxidative damage, altered immune function related to uremia, protein-energy malnutrition, dialysis fluid, accumulation of end products glycation, dialysate reflux, vascular access, and old age [2].

High BMI plays a protective role in inflamed dialysis patients through several mechanisms:

- It may be related to increased catabolism and loss of muscle mass and probably reflects energy stores and preserved appetite, which is essential when renal function declines and uremia develops.

- Secondly, the production of uraemic toxins is relatively higher in patients with low BMI; it is possible that the adipose tissue, as what happens with benzodiazepines, constitutes a storage space and prevents the free circulation of fat-soluble uremic toxins, which would not occur in patients with low BMI.

- Lastly, endothelial progenitor cell density is related to obesity; there is a possibility that endogenous repair mechanisms are well preserved in patients with a high BMI [2].

A prospective study of 609 dialysis patients in the ACTIVE/ADIPOSE survey found that the percentage of visceral and subcutaneous fat appears to have opposite associations with biomarkers of inflammation and nutrition and that subcutaneous fat may be an indicator of nutritional status [14].

The percentage of subcutaneous or peripheral body fat had no association with C-reactive protein (CRP) in mg/L (0.03 [95% CI, -0.10 to
blood pressure levels have a better prognosis than patients with normal blood pressure, so the inverse relationship between obesity and mortality may be related to hypertension [2]. The better control of hypertension among obese patients may be due to the following reasons:

Obese patients can more efficiently redistribute excess volume at the level of the extracellular space, which thin people cannot do, resulting in better blood pressure control. There could be increased expression of the renalase enzyme in response to increased muscle mass in patients with a high BMI. Renalase is an enzyme predominantly expressed in skeletal muscles. It metabolizes catecholamines (adrenaline, norepinephrine), decreasing their blood levels, related to a lower prevalence of hypertension and better control in obese patients [2]. This is demonstrated by a retrospective study in which thinner patients on dialysis have a higher prevalence of hypertension with poorer control and more significant evidence of extracellular volume excess compared to patients who are overweight and obese OR 2.85(95%; CI: 1.28-6.34, P = 0.01). However, the excess volume only partly explains the higher prevalence or worse control of hypertension; thinner patients have an accelerated mortality rate in the first two years, but better blood pressure control is not entirely explained [19].

Reverse causality
There is a probability that BMI is not a cause but a consequence of the complications involved in renal replacement therapy; for example, cardiac cachexia produced by muscle deterioration generates higher mortality in dialysis, as does Sarcopenia (decrease in muscle mass). However, this relationship between higher BMI and lower mortality in hemodialysis patients does not fully explain this opposite relationship, with the possibility that treatments that produce weight gain in hemodialysis patients result in better survival, regardless of the causal pathway [2]. A meta-analysis investigated this possibility precisely and reiterated that hemodialysis patients with a high BMI had lower all-cause mortality compared with other BMIs (BMI ≥25, OR 0.67, 95% CI: 0.63-0.68, P < 0.01); this relationship is maintained even in the risk-adjusted sensitivity analysis (adjusted hazard ratio 0.94, 95%, CI: 0.92-0.96, P <0.01) [11].

Non-modifiable mechanisms
Other non-modifiable mechanisms influence this paradox of obesity, among which are:

Ethnicity
A retrospective study compared the obesity paradox in three ethnic groups (African, Hispanic, and non-Hispanic white) with a mean age of 62 on hemodialysis. The results suggest a higher BMI is associated with better survival in all three groups. Ethnic. However, the African American group (OR 0.57 [95%, CI: 0.49-68, P =<0.01]) and Hispanics (OR 0.63 [95%, CI: 0.58-0.70, P =<0.01]) experienced lower mortality with BMI ≥40 kg/m² compared with non-Hispanic whites among BMI categories 23 to 25 kg/m² [20]. Suggested reasons for this finding include higher muscle mass and higher food intake in Black and Hispanic ethnicities with any BMI compared with other races, regardless of differences in health status, income, and education [20].
**Age**

Hoogeveen et al., in a prospective study of hemodialysis patients at 7-year follow-up, found that younger HD patients (<65 years) with BMI > 30 kg/m² have a mortality rate almost twice as high (OR 1.7; 95% CI: 1.1–2, P <0.05) compared to those of older age [20]. This direct relationship between mortality and obesity is even more pronounced among individuals <50 years [21].

The inverse relationship between BMI and all-cause mortality is more evident when the average age of individuals is ≥65 years, even though these HD patients have a high overall mortality rate compared to younger ones, precisely by competing risk factors such as infections, low weight and MIC syndrome which could block the long-term effects of obesity. Therefore obesity is not a risk factor for mortality in patients under 65 on hemodialysis [21].

**Sex**

A prospective study conducted in Korea with hemodialysis patients older than 55 years showed that male HD patients with a BMI greater than 25.1 kg/m² have more remarkable survival than those with a BMI less than 25.1 kg/m² HR = 0.43 (95% CI: 0.25–0.75, P = 0.003). In contrast, no statistically significant association was found in the survival of female patients according to body mass index [22].

**Region-related short-term effect**

In third-world countries, malnutrition is a significant cause of morbidity and mortality, translating into a shorter life expectancy. Likewise, the short-term survival benefits in obese patients on hemodialysis may outweigh the long-term adverse effects of obesity on cardiovascular disease [2]. Therefore, there is a possibility that obese patients may have a higher survival rate in the short term but not necessarily in a long time [2]; this is supported by a long-term prospective study conducted over 12 years by Kaizu et al., which showed no obesity survival paradox on dialysis [23].

In the short term, another prospective study conducted over three years by Yen et al. found the existence of the obesity survival paradox (Kaplan-Meier: higher mortality with low weight on hemodialysis about average or high weight (P = 0.0392)) [23].

**Muscle mass**

A retrospective study conducted by Beddhu et al., in incident patients over 64 years of age on hemodialysis at four years of follow-up, analyzes the relationship between an increase in BMI about muscle mass or an increase in body fat with more remarkable survival in hemodialysis, using urinary creatinine excretion (CrU in grams day) in twenty-four-hour urine as a measure of muscle mass [2, 25]. As a result, Beddhu et al. observed that the protective effect of high BMI occurred only in patients with normal (18.5 to 24.9 kg/m²) or high (>25 kg/m²) BMI, with increased muscle mass (CrU > 0.55 g/d) and low body fat (HR, 0.85; 95% CI: 0.83–0.87, P <0.001) in addition to a lower risk of cardiovascular death in this study group (HR: 0.89; P <0.001). These results were consistently similar in subgroup analyses by gender and race [25].

High BMI patients with low muscle mass (CrU ≤0.55 g/d) and thus higher body fat were at increased risk of all-cause death (HR, 1.14; P <0.001) and cardiovascular death (HR, 1.19; P <0.001) [25].

Lean people (low muscle mass) have an accelerated mortality rate due to poor nutritional status and high levels of inflammation. It is important to note that muscle mass was reflected in urinary creatinine in these studies. Different theories have explained this relationship between muscle mass and mortality, the most accepted being that uremic toxins are redistributed in the muscle compartment. High muscle mass allows better redistribution of excess fluids in patients undergoing renal replacement therapy [25].

**Acetyl-ghrelin**

Ghrelin is a hormone that is secreted in the stomach and, in addition to stimulating the secretion of growth hormone (GH) in the pituitary, favors the regulation of energy metabolism, leading to an increase in body weight and adiposity since this hormone stimulates specific hypothalamic neurons causing an increase in appetite. Ghrelin has the physiological roles of regulating energy and glucose homeostasis, gastrointestinal, cardiovascular, pulmonary, and immune functions, cell proliferation and differentiation, and bone physiology [26]. There are two primary molecular forms of plasma ghrelin, acetyl ghrelin (AG), with an n-octanoylated serine residue at position 3, and diacetyl ghrelin (DAG). AG represents about 10% of total circulating ghrelin.

Acetyl ghrelin improves cardiovascular outcomes by attenuating pressure overload-induced cardiac hypertrophy, reversing endothelial dysfunction, and improving overall survival. As an appetite-related hormone, high levels of acetyl ghrelin may also contribute to better nutritional status in hemodialysis patients [2].

A prospective cohort demonstrated that high FA levels improve the association between high BMI and survival in hemodialysis patients, showing lower cardiovascular mortality (OR: 0.31; 95%, CI: 0.16 – 0.62, P =0.001) and lower death from any cause (OR: 0.35; 95%, CI: 0.13 – 0.91, P =0.03) Independent of appetite, nutritional status, and inflammation [26].

**Discussion**

Several observational studies, meta-analyses, and systematic reviews have shown a protective effect of increased body mass index against all-cause mortality in hemodialysis patients, especially cardiovascular events, compared to normal and low BMIs. In a descriptive study of the body composition of hemodialysis patients, high BMI is related to greater muscle mass and lower visceral fat percentage with smaller abdominal circumference [25]. Greater muscle mass allows for a better redistribution of excess body fluid and uremic toxins. It is also related to increases in the renalase enzyme (generated in skeletal muscle) that metabolizes the catecholamines adrenaline and norepinephrine, decreasing their blood levels and conferring better hemodynamic stability [2, 25]. Increased muscle mass is also related to reduced production of inflammatory cytokines (especially TNF-α, which is associated with cardiovascular damage), decreased production of uremic toxins, and
prevents malnutrition-inflammation complex (MIC) syndrome by maintaining the appetite thanks to increased production of acetyl ghrelin [2, 11].

On the other hand, other non-modifiable factors confer protection against mortality related to high BMI on hemodialyses, such as age over 65 years [less or no protective effect in those under 65], and male gender [less effect in females], black and Hispanic ethnicity (about greater muscle mass and greater intake related to these ethnicities), and the long-term or short-term effect about the region [20-22].

There is also the possibility of reverse causation where low BMI could be a sequel and not cause increased mortality in chronic kidney disease on hemodialysis [2].

Other studies have classified obesity in hemodialysis as chronic kidney disease associated with type 4 OA-CKD, where they propose that obesity could be a protective factor for mortality with the lower production of adiponectin, which are peptides that act as hormones. Or messengers that regulate metabolism (generated by adipocytes and related to higher mortality in patients without dialysis), observing better survival at three years [27]. However, more studies are needed to correlate adiponectin as a protective factor in dialysis [27].

A low BMI in renal replacement therapies is related to higher mortality due to lower muscle mass (sarcopenia) and increased frailty syndrome [25, 26]. For example, in a 3-year prospective study in patients on hemodialysis programs with a 65.7% prevalence of frailty (measured by the Fried frail method), it was correlated with higher mortality in those patients with frailty (significant correlation between Charlson index and frailty, r= 0.54; P<0.0001) [28].

Last, a high BMI with low muscle mass and increased body fat are correlated with higher all-cause mortality (HR, 1.14; P <0.001) and cardiovascular death (HR, 1.19; P <0.001) [25]. Therefore, it is concluded that the more remarkable survival in hemodialysis patients is related to a BMI >25 kg/m2 in those over 65 years of age as a consequence of a greater muscle mass and not of the percentage of body fat, for which the term "paradox of survival of obesity" in hemodialysis should be ruled out if the phenomenon is explained by an increase in BMI due to muscle mass. More studies are needed to support this theory based on muscle mass, especially with bioimpedance, in geriatric patients with frailty and sarcopenia.

**Conclusion**

The increase in body mass index >25 kg/m2 in the population group of patients undergoing hemodialysis treatments has a protective effect, reducing mortality in studies carried out within 3 to 5 years of follow-up. At a longer follow-up time (12 years), according to observational studies, an increase in body mass index >30 kg/m2 seems to have a harmful effect equal to that of the general population. The benefit of an increase in BMI >25 kg/m2 and a decrease in mortality is more significant in men, African Americans, Hispanics, and those over 65. The most important benefit of reducing mortality in the hemodialysis group is increased subcutaneous adipose tissue versus visceral adipose tissue.

**Abbreviations**

AG: acetyl ghrelin
BMI: Body Mass Index.
MIC: malnutrition and inflammation complex.
TNF: tubular necrosis factor

**Supplementary information**

Supplementary materials have not been declared.

**Acknowledgments**

Does not apply.

**Author contributions**

Santiago David Silva Tobar: Conceptualization, Data Curation, Formal Analysis, Fundraising, Research, Methodology, Project Management, Resources, Software, Writing – original draft.
Franklin Mora Bravo: Conceptualization, Supervision, Validation, Visualization, Writing: review and edition.
All authors read and approved the final version of the manuscript.

**Financing**

The authors provided the costs of the research.

**Availability of data or materials**

The data sets generated and analyzed during the current study are not publicly available due to participant confidentiality but are available from the corresponding author upon reasonable scholarly request.

**Statements**

**Ethics committee approval and consent to participate**

Does not apply.

**Consent for publication**

It does not apply when images or photographs of the physical examination or patients’ X-rays/CT/MRI are not published.

**Conflicts of interest**

The authors report having no conflicts of interest.

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DOI: Digital Object Identifier. PMID: PubMed Identifier.

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