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Trajectories and Transitions of Physical Frailty in Chronic Kidney Disease: A Scoping Review

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Abstract

Introduction: Frailty is associated with increased vulnerability to a poorer state of health. There is a growing interest in understanding the associations between frailty and chronic kidney disease. The present review explores the current knowledge regarding trajectories and transitions of frailty in patients with chronic kidney disease.

Material & Method: We conducted a search in different databases such as PubMed, Web of Science, Oxford Academic, Redalyc.org, and the Cochrane Library to identify articles addressing the topic, including those published between July 2015 and July 2022. Two independent researchers assessed the eligibility of the articles following PRISMA guidelines.

Results: The literature search yielded 38 articles, of which 7 met the inclusion criteria and were analyzed in the review. We found that frailty is a dynamic process in patients both before and after kidney transplantation, regardless of age. It initially worsens after the surgical procedure but then improves significantly, probably associated with renal function improvement. Pre-transplant assessment and interventions such as rehabilitation can successfully increase the number of recipients whose frailty improves after transplantation.

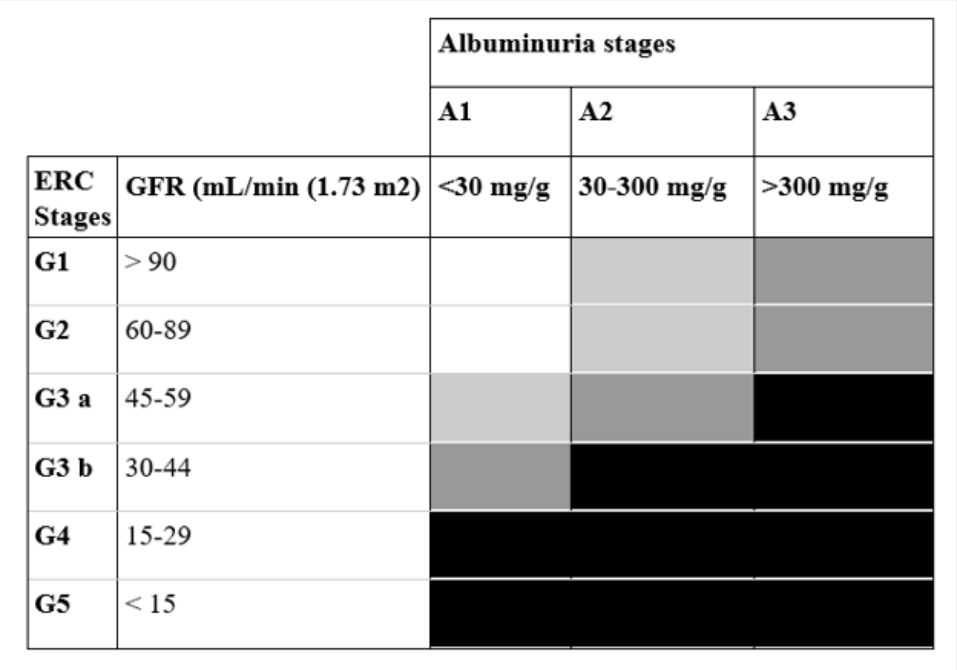
Conclusion: Physical frailty assessment and treatment seems crucial in pre and post kidney transplant patients.

Keywords: Chronic nephropathy; Hemodialysis; Renal transplant; Post-transplant; Physical frailty, trajectories; Frailty transitions

Introduction

Physical frailty is defined as a clinical syndrome with multiple causes and contributors, characterized by a decline in strength, endurance, and physiological function that increases vulnerability to developing dependence or death, which can be preventable and treatable [1]. Although frailty increases the risk of adverse outcomes such as falls, delirium, and disability [2], there are currently no universally accepted criteria for its clinical definition. In this regard, two theoretical concepts attempt to address the assessment of frailty: the frailty phenotype (FP) and the frailty index (FI). The FP was proposed by Fried [3] and is based on the evaluation of 5 physical components: unintended weight loss, weakness or decreased muscle strength, slow walking speed, fatigue, and low level of physical activity. Those who meet three or more of these criteria are considered frail, those with one or two of the components are considered pre-frail, and those with none are non-frail [3]. The FI was proposed by Rockwood, considering frailty as the accumulation of deficits in multiple systems, including social and psychological aspects [4]. It is worth mentioning that currently, multiple screening or assessment tools are derived from both concepts of frailty. Frailty can be understood as a continuum between being robust and frail, with an intermediate state known as pre-frailty [3]. This imparts a dynamic nature to frailty, involving progression or regression between stages of frailty [5]. Transitions in frailty are defined as changes or fluctuations between stages of frailty, exhibiting changing intraindividual variability over time, while trajectories are defined as groups of individuals displaying a similar progression of frailty over time [6]. The concept of transition can be seen as a sign of loss of homeostasis, vulnerability to the level of frailty, and its long-term change [7]. Chronic Kidney Disease (CKD) is defined as structural or functional abnormalities in kidney function that persist for

more than three months. The most commonly used diagnostic criteria include an increase in the albuminuria/creatinuria ratio ≧30 mg/g, or a reduction in the estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 [3]. Renal biopsy, renal ultrasound abnormalities, and renal hematuria have also been used as diagnostic criteria. CKD is divided into 5 stages based on eGFR and albuminuria values, as shown in Figure 1. Patients with CKD, especially those with an eGFR < 45 ml/min/1.73 m^2, have an increased risk of death from any cause and cardiovascular causes, a phenomenon associated with all age groups, with greater risk observed in individuals over the age of 75 [8].



		Albuminuria stages		
		A1	A2	A3
ERC Stages	GFR (mL/min (1.73 m2)	<30 mg/g	30-300 mg/g	>300 mg/g
G1	> 90			
G2	60-89			
G3 a	45-59			
G3 b	30-44			
G4	15-29			
G5	< 15			

Figure 1: Chronic kidney disease (CKD) stages (KDIGO 2012).

The definition of End-Stage Renal Disease (ESRD) is based on two criteria [9]: establishing the presence of uremia and the chronic need for renal replacement therapy (RRT) (lasting more than three months). Defining ESRD presents some challenges [9]: Firstly, defining it based on an eGFR <15 mL/min/1.73 m^2 is controversial, as this condition is diagnosed when the nephrologist determines that the benefits of RRT outweigh the risk of being on a waiting list for kidney transplantation. Secondly, when RRT is prescribed (whether dialysis or transplantation), independent of whether it is initiated or not, ESRD is considered the diagnosis. Thirdly, in the context of acute kidney injury (AKI) requiring RRT or leading to death, it is also considered to be ESRD. The classification of CKD by The Kidney Dialysis Outcome Quality Initiative (K-DOQI) is mainly based on the degree of renal function rather than the etiology of the pathology, which includes transplant recipients [10]. One of the major benefits of including transplant patients in this classification is that it also encompasses those who require nephroprotection management.

Little is known about changes in frailty status in individuals with chronic kidney disease. The prevalence of physical frailty has been evaluated across various stages of CKD, with fatigue and muscle weakness being the most frequently observed characteristics. The presence of frailty also independently and significantly increases short-term mortality in CKD patients. In 2009, Wilhelm-Leen estimated the prevalence of frailty in patients with chronic kidney disease to be approximately 2.8%, and in patients with moderate-severe CKD (eGFR < 45 ml/min/1.73 m^2), frailty was found to have a prevalence of 20.9% [11]. Some strategies have been made to assess the impact of frailty in hemodialysis. Bao et al. [12] demonstrated that the presence of frailty is significantly associated with an increased risk of hospitalization and long-term mortality in a cohort of 1,576 patients [12]. McAdams Di Marco et al. [13] evaluated the physical frailty phenotype in 537 patients who were on the waiting list for kidney transplantation and described that manifest frailty was present in 20% of the patients, pre-frailty in 33%, concluding that over 50% of the patients on the list had an increased vulnerability to endogenous and exogenous stressors. The aim of this review is to search the databases for publications on trajectories and transitions among different stages of physical frailty, its components, and associated factors in various stages of chronic kidney disease.

Materials and Methods

Search Strategy

We conducted a review based on PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [14].

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The following English terms were used to identify articles that assessed trajectories or transitions of frailty in chronic kidney disease: 'end stage renal disease' OR 'kidney disease' OR 'chronic nephropathy' AND 'frailty transitions' OR 'frailty trajectories'. The following databases were searched: PubMed, Web of Science, Oxford Academic, Redalyc.org, and the Cochrane Library, including articles published between July 2015 and July 2022. The reference lists of key articles were also evaluated.

Selection criteria

Inclusion criteria embraced articles that analyzed trajectories and transitions between stages of frailty in chronic kidney disease across any stage, including dialysis and transplantation. Articles were excluded if they were written in a language other than English or Spanish. In cases where multiple analyses were conducted on the same study population, the analysis most aligned with the objectives of this review was selected for analysis.

Data Extraction

Two reviewers independently examined the abstracts of the studies according to the outlined criteria. In the event of differences of opinion on whether to include a study, a third reviewer was consulted. A data extraction table was created, including demographic information, sample size, method for assessing frailty, evaluated chronic kidney disease, and outcomes such as changes in frailty stage.

Results

A total of 34 publications were identified. After removing duplicates, the abstracts and titles of 31 articles were reviewed. Finally, 10 articles were chosen, of which six met the inclusion criteria. The selection process is illustrated in Figure 2. Among the selected publications, three [15-17] describe frailty trajectories under the concept of FP. Three studies [18-20] described transitions between stages of frailty, two of which used FP and one used the Groningen Frailty Indicator (GFI), consisting of 15 elements that encompass physical, cognitive, psychological, and social components of frailty; with a score ≥ 4, the patient is classified as frail [21]. The characteristics of the selected studies are presented in Table 1.

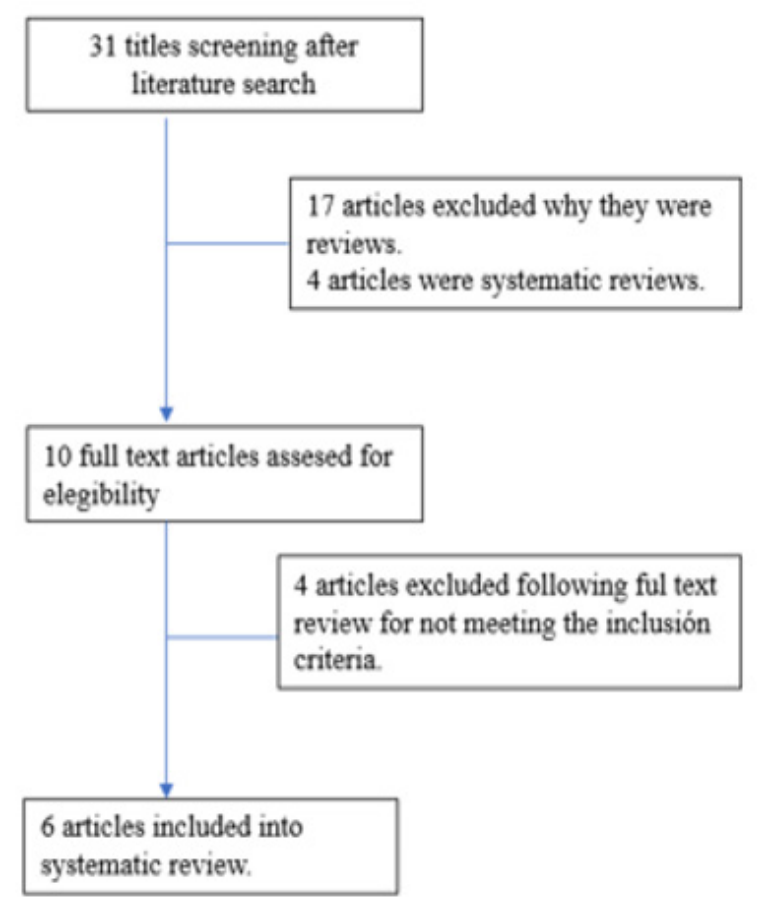

Figure 2: Selection process.

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Table 1: Characteristics of the chosen studies.

Reference Study	Study Characteristics	Study population	Primary outcome	Study design and methods	Frailty assessment	GFR estimation and Average GFR	Results
Long-Term Trajectories of Frailty and Its Components After Kidney Transplantation Nadia M. Chu et al. Journals of Gerontology: Medical Sciences cite as: J Gerontol A Biol Sci Med Sci, 2022, Vol. XX, No. XX, 1–8 https://doi.org/10.1093/gerona/glac051	N: 1 336 % female=40 Mean age = 53 years	2-center cohort study of frailty in KT recipients (December 2008–May 2019) from the Johns Hopkins Hospital in Baltimore, Maryland and the Michigan Medical Center in Ann Arbor, Michigan.	Evaluate longer-term post-KT trajectories of the physical frailty phenotype (PFP) and its components in adult patients at 2 centers.	Cohort study. Physical Frail phenotype components were measured at admission, 1, 3, 6 months, 1 year, and annually thereafter post-KT.	Fried	End stage CKD post KT	Frailty improvements in the first 2.5 years, recipients' frailty worsened after 2.5 years post-KT. Specifically, they experienced gains in strength, activity, and exhaustion in the first 2.5 years post-KT, but declined in strength and activity after 2.5 years post-KT
Dynamic Frailty Before Kidney Transplantation—Time of Measurement Matters Nadia M. Chu et al. Transplantation Publish Ahead of Print, 2019 DOI:10.1097/TP.0000000000002563	N= 569 % female=60,8 Mean age=51,7 years	English-speaking KT recipients (≥18 years old) at Johns Hopkins Hospital, Baltimore, Maryland (November 2009 - September 2017), for whom frailty was measured both at time of evaluation and admission for KT.	Change in frailty between time of evaluation and KT.	Cohort study. Using three approaches, including change between: 1) binary states (frail vs. nonfrail) 2) 3-category states (frail vs. intermediately frail vs. nonfrail, and 3) raw frailty score.	Fried	End stage CKD at evaluation of wait list and KT time.	Between evaluation and KT, 22.0% became more frail, while 24.4% became less frail. Black race (RRR=1.98, 95%CI:1.07-3.67) was associated with frail-to-nonfrail transition; diabetes (RRR=2.56, 95%CI:1.22-5.39) was associated with remaining stably frail. Candidates who became more frail between 3-category states (HR=2.27, 95%CI:1.11-4.65) or frailty scores (HR=2.36, 95%CI:1.12-4.99) had increased risk of post-KT mortality and had higher odds of length of stay (LOS) ≥2 weeks (3-category: OR=2.02, 95%CI:1.20-3.40; scores: OR=1.92,95%CI:1.13-3.25).

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Frailty component trajectories after restoration of kidney function among kidney transplant recipients Nadia M. Chu et al. Innovation in Aging, 2020, Vol. 4, No. S1.	N= 1,410 KT recipients %female= Mean age=53	Two-center prospective cohort study (2009-2019) of adult patients undergoing KT.	known about how an acute stressor, like KT, can impact the five physical frailty phenotype (PFP) criteria	PFP criteria were measured at KT admission, 1 month, 3 months, 6 months, 1 year, and annually thereafter post-KT.	Fried	End stage CKD at admison to KT and 10 years later.	Followed for a mean of 1.9 years (IQR=0.1-3.2), 46.8% had low activity, 46.7% weakness, 29.0% exhaustion, 16.1% slowness, and 14.3% unintentional weight loss at KT admission. Among continuous components, weight worsened (0.3lb/month, 95%CI:0.2,0.4), while grip strength (0.09kg/month, 95%CI: 0.07,0.11) and activity (5.8Kcal/month, 95%CI: 3.3, 8.2) improved post-KT; gait speed remained stable (-0.0004s/ month, 95%CI: -0.01, 0.0005). Trajectories differed by age, such that improvements were observed among younger recipients (<0.05).
Changes in Frailty After Kidney Transplantation McAdams-De Marco et al. J Am Geriatr Soc. 2015 October; 63(10): 2152–2157. DOI:10.1111/jgs.13657	N=349 %female= 38.1% Mean age= 53.3 ± 14.2	Johns Hopkins Hospital, Baltimore, Maryland, between December 2008 and March 2014.	Characterize the change in frailty over time after transplantation and identify predictors of long-term changes in frailty score.	Prospective cohort study (December 2008–March 2014)	Fried	End stage CKD after KT. The median number of years on dialysis was 2.1 (IQR 0.4–3.9), 20% were preemptive KT, and 37.3% were live donor recipients.	Three months after KT, of those who were nonfrail at KT, 21.6% were intermediately frail, and 11.7% were frail (Table 2); of those who were intermediately frail at KT, 52.0% were nonfrail, and 20.0% were frail; and of those who were frail at KT, 33.4% were nonfrail, and 40.7% were intermediately frail. Of those who were less frail after KT, 47% improved (from frail to nonfrail for the component) in grip strength, 14% in weight loss, 55% in physical activity, 25% in exhaustion, and 19% in walk speed Of those who were more frail after KT, 20% worsened (from nonfrail to frail for the component) in grip strength, 36% in weight loss, 43% in physical activity, 50% in exhaustion, and 27% in walk speed. The only post-KT factor associated with change in frailty score was DGF (RR = 1.30, 95% CI = 1.10–1.53, P = .003). Recipient diabetes mellitus (RR = 1.26, 95% CI = 1.08–1.46, P = .003), and pre-KT frailty (RR = 1.49, 95% CI = 1.29–1.72, P < .001) remained significantly associated with frailty score change after adjusting for DGF (RR = 1.22, 95% CI = 1.04–1.43, P = .02).

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Transitions in frailty state after kidney transplantation Quint et al. Langenbeck's Archives of Surgery (2020) 405:843–850 https://doi.org/10.1007/s00423-020-01936-6	N= 176 % female= 63,1% Mean age= 51.8 (± 14.1)	This study was part of a previously published cohort on frailty in KTR at the University Medical Center Groningen (UMCG), the Netherlands	The primary aim of this study was to determine transitions in frailty states after KT over a period of 1 to 3 years. Our secondary aim was to assess which domains and/or patient characteristics contributed most to these transitions.	Cohort study in KT recipients between 2015-2017 176 of 233. Measured frailty by GFI before KT and following for three years.	Groningen Frailty Indicator (GFI)	End stage CKD after KT. Dialysis and KT	Thirty patients were considered frail (GFI ≥ 4) at baseline. After a mean follow-up of 22.8 ± 8.3 months, 34 non-frail patients (19.3%) became frail, 125 patients (71.0%) remained the same, and 17 frail patients (9.7%) Thirty patients were considered frail (GFI ≥ 4) at baseline. After a mean follow-up of 22.8 ± 8.3 months, 34 non-frail patients (19.3%) became frail, 125 patients (71.0%) remained the same, and 17 frail patients (9.7%) became non-frail (GFI < 4). In the domain psychosocial Thirty patients were considered frail (GFI ≥ 4) at baseline. After a mean follow-up of 22.8 ± 8.3 months, 34 non-frail patients (19.3%) became frail, 125 patients (71.0%) remained the same, and 17 frail patients (9.7%) became non-frail (GFI < 4). In the domain psychosocial functioning, 28.4% of the patients had an increase in GFI score after follow-up. Patients who scored a point in the domain cognition at baseline had a greater chance of becoming frail (OR 4.38, 95% CI 0.59–32.24).

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Factors Associated with Frailty and Its Trajectory among Patients on Hemodialysis Johansen, 2017. Clin J Am Soc Nephrol 12: 1100–1108, 2017. DOI: https://doi.org/10.2215/CJN.12131116	N= 762 % female= 40.7% Mean age= 57.2 ±14.2	Participants in the A Cohort to Investigate the Value of Exercise/Analyses Designed to Investigate the Paradox of Obesity and Survival in ESRD cohort study	Known about changes in haemodialysis frailty people over time and the factors associated with those changes.	Cohort to Investigate the Value of Exercise/Analyses Designed to Investigate the Paradox of Obesity and Survival in ESRD (ACTIVE/ADIPOSE) enrolled 771 patients from 14 dialysis facilities in the San Francisco Bay area and the Atlanta, Georgia metropolitan area during 2009–2011 and followed them with annual assessments for up to 2 years through 2013.	Fried	End stage CKD. Hemodialysis	Most participants scores changed, with patients improving almost as often as worsening (overall change, 0.2 points per year; 95% confidence interval, 0.1 to 0.3). Hispanic ethnicity (0.6 points per year; 95% confidence interval, 0.0 to 1.1) and diabetes (0.7 points per year; 95% confidence interval, 0.3 to 1.0) were associated with higher frailty scores and higher serum albumin concentration with lower frailty scores (21.1 points per g/dl; 95% confidence interval, 21.5 to 20.7). In addition, patients whose serum albumin increased over time were less likely to become frail, with each 1-g/dl increase in albumin associated with a 0.4-point reduction in frailty score (95% confidence interval, 20.80 to 20.05). To examine the underpinnings of the association between serum albumin and frailty, we included serum IL-6, normalized protein catabolic rate, and patient self-report of hospitalization within the last year in a second model. Higher IL-6 and hospitalization were statistically significantly associated with worse frailty at any point and worsening frailty over time, whereas normalized protein catabolic rate was not independently associated with frailty

Trajectories and transitions between frailty stages

a) Frailty in hemodialysis

In the study by Johansen et al. [17], the mean frailty scores measured by FP changed over a 2-year follow-up period, with an overall change of 0.2 points per year (95% CI: 0.1-0.3). Being Hispanic (0.6 points per year; 95% CI: 0.0-1.1) and having diabetes mellitus (0.7 points per year; 95% CI: 0.3-1.0) were associated with higher frailty scores. Conversely, a normal level of serum albumin was associated with lower frailty scores (21.1 points per g/dL; 95% CI: 21.5-20.7). Additionally, patients whose serum albumin concentration increased over time were less likely to become frail, with a reduction of 0.4 points in frailty score for every 1 g/dL increase in albumin (95% CI: 20.8-20.05). High levels of IL-6 and hospitalization were significantly associated with worse frailty stage and worsening over time, noting that normalized catabolic protein rate did not have an independent association with frailty.

b) Frailty on the transplant waiting list and on transplant recipients

In the study by Chu et al. [18], 22% of patients progressed to a higher frailty stage, while 24% regressed to lower stages. Being of Black race showed a Relative Risk Ratio (RRR) of 1.98 (95% CI: 1.07-3.67) and was associated with transition from frail to non-frail stage. Diabetes mellitus was associated with stability between frailty stages (RRR: 2.56, 95% CI: 1.22-5.39). High frailty scores increased the risk of post-transplant mortality (HR: 2.36, 95% CI: 1.12-4.99), and a greater likelihood of hospital stay exceeding 2 weeks (OR: 2.02, 95% CI: 1.20-3.40).

c) Frailty after kidney transplantation

Chu et al. [15] reported an improvement in frailty stage within the first 2.5 years, followed by a worsening after this time. Specifically, patients showed improvement in physical frailty components: strength, level of physical activity, and fatigue, with

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a decline in strength and physical activity after 2.5 years. The study by McAdams-DeMarco et al. [19] demonstrated that within the first 3 months after transplantation, among those who were not frail prior to the procedure, 21.6% progressed to pre-frailty and 11.7% to frailty. Among those who were pre-frail prior to the procedure, 52% reverted to a non-frail stage and 20% progressed to frailty. The only factor associated with a change in frailty score post-transplantation was delayed graft function (DGF) (RR: 1.30; 95% CI: 1.1-1.53, p=0.003). Transplanted patients with diabetes mellitus (RR = 1.26, 95% CI: 1.08–1.46, P = .003) and pre-transplant frailty (RR=1.49, 95% CI: 1.29–1.72, P < .001) had a significant association with frailty score modification, even after adjusting for DGF (RR: 1.22, 95% CI: 1.04-1.43, P=0.02). In the study by Quint et al. [20], thirty patients were considered frail (GFI ≥ 4) at baseline, and after a follow-up of 22.8 ± 8.3 months, 34 non-frail patients (19.3%) became frail, 125 patients (71%) remained stable, and 17 frail patients (9.7%) reverted to non-frailty. In the psychosocial functioning domain, 28.4% of patients increased their GFI score after follow-up, and those with cognitive domain scores at baseline were more likely to become frail (OR 4.38, 95% CI: 0.59–32.24).

d) Components of frailty phenotype in post-kidney transplantation

In the study by Chu et al. [16], an assessment of frailty components was conducted at admission and during follow-up, over a period of 1.9 years (IQR=0.1-3.2). At admission, 46.8% had low physical activity, 46.7% had weakness, 29% had fatigue, 16.1% showed decreased walking speed, and 14.3% had unintentional weight loss. When comparing measurements at admission and follow-up, it was observed that weight worsened (0.3 lb/month, 95% CI: 0.2-0.4), while grip strength (0.09 kg/month, 95% CI: 0.07-0.11), and physical activity (5.8 Kcal/month, 95% CI: 3.3-8.2) improved after transplantation; walking speed remained stable (-0.0004 s/month, 95% CI: -0.01 - 0.0005). Trajectories differed by age, with better outcomes observed in younger recipients (p < 0.05). In the study by McAdams-DeMarco et al. [19], among those who were frail prior to transplantation, 33.4% reverted to non-frailty and 40.7% reverted to pre-frailty. Among those who transitioned from frail to non-frail stage, improvement was observed in various components of the frailty phenotype: 47% improved grip strength, 14% reduced weight loss, 55% improved physical activity, 25% improved fatigue, and 19% improved walking speed. For those who progressed from non-frail to frail stage post-transplantation, a worsening of frailty phenotype components was observed as follows: 20% in grip strength, 36% in weight loss, 43% in physical activity, 50% in fatigue, and 27% in walking speed.

Discussion

There are few studies on trajectories and transitions of frailty in patients with chronic kidney disease, including studies involving patients on hemodialysis and transplant candidates. As has been shown in various scenarios, frailty is described as a dynamic syndrome with transitions between its stages and is amenable to intervention, especially in older individuals.

In hemodialysis [17], sex, ethnic origin, and diabetes mellitus were associated with frailty cross-sectionally but not longitudinally. The study period was likely too short to detect subtle differences in frailty trajectories among women, Hispanic patients, and those with diabetes mellitus, who are more likely to experience acute events that impact the development of frailty but not its trajectory. The study describes three trajectories (improvement, no change or stability, and worsening) based on patterns of transitions [17]. Serum albumin was associated with change in frailty stage in the initial study model, but not in subsequent explorations; inflammation and hospitalization appear to partially explain the relationship between albumin and frailty. To explain this finding, the normalized protein catabolic rate (nPCR) was calculated, which was not associated with frailty. This may indicate that low protein intake is a less significant contributor to frailty or that its contribution is not independent of other factors like inflammation or comorbidity [17]. These findings suggest that hospitalization could be a major trigger for frailty, and attention should be focused on post-hospitalization management, which could be beneficial. Further studies are needed to determine if interventions targeting inflammation management can improve frailty, or if assessment and rehabilitation immediately after hospitalization could be useful for predicting readmissions and mortality.

Most of the studies focus on various stages of the kidney transplantation process. Frailty is observed in 18.4% of kidney transplant candidates on the waiting list [22], and 19% of transplant recipients are frail at the time of the procedure [23]. A recent survey conducted in kidney transplant centers in the United States concluded that while most centers assess frailty during the initial evaluation, there is a lack of follow-up during the kidney transplantation process [24]. This is due to the extended wait times on the lists between these two points, neglecting the dynamic nature of frailty and its associated factors, as seen in community-dwelling older adults [25], hemodialysis patients [17], and transplant recipients [19]. In the study by Chu et al. [18], the average time between initial evaluation and transplantation was 1.1 years, with 46% of patients receiving a transplant within the first year of evaluation. The observed transition between frailty stages revealed that 7% remained frail, 9.5% of frail individuals reverted to non-frailty, 9% of non-frail individuals became frail, and 74.5% remained non-frail. Recipient factors associated with progression between frailty stages included age, diabetes mellitus, and the cause of ESRD. Hypertension was the most prevalent comorbidity in the transition from non-frail to frail, possibly due to hemodynamic changes inherent in the RRT required in many cases during the early post-transplant months, or it could be attributed to the effects of polypharmacy.

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Kidney transplantation restores renal function and is the preferred treatment for end-stage renal disease. It provides numerous benefits across all age groups, doubling the remaining life expectancy and reducing mortality [26,27]. However, even after renal function is restored, transplant recipients continue to age, placing them at risk of developing or worsening geriatric conditions such as frailty. Chu et al. [15] found that transplant recipients had a lower likelihood of being frail in the first 2.5 years post-transplant, but a higher likelihood of developing frailty between 2.5 and 5 years post-transplant. These findings corroborate the dynamic nature of frailty observed in previous studies conducted before and after transplantation [18, 19], emphasizing the overall benefit of kidney transplantation and renal function recovery, independent of the physiological impact of the surgical procedure on patients with limited physiological reserves. The observations demonstrating an increased likelihood of becoming frail after 2.5 years post-transplant are reflected through the components of the frailty phenotype. Stabilization was observed in weight, gait speed, and fatigue, while a decline was noted in grip strength and physical activity. This could be explained by chronic consumption of immunosuppressive medications [28] and their impact on weight. Additionally, the contribution of comorbidities such as long-standing diabetes mellitus and its complications may also play a role. This underscores the need for more frequent monitoring with timely modifications to improve prognosis. Further research is necessary to determine factors associated with post-transplant frailty and potential interventions. All transplant recipients are at risk of secondary frailty due to chronic kidney disease, the stress of transplantation itself, and the use of immunosuppressive medications. This has been demonstrated in young patients who, with optimal immunosuppressive doses, experienced a significant increase in weight compared to older patients receiving lower doses in the first 2.5 years post-transplant. This difference reflects variations in post-operative management, as older individuals tend to be frailer, and this frailty increases the risk of immunosuppressive intolerance [29-32]. Additionally, certain medications within this class can induce glucose intolerance, hyperlipidemia, and weight gain. In the prospective cohort study conducted by McAdams-DeMarco et al. [19] at a single center with long-term follow-up, it was found that frailty exhibits a dynamic pattern. It worsened in the first month post-transplant, reverted to the pre-procedure frailty stage in the second month, and improved in the third month. At 3 months, 74% of transplanted individuals who were initially frail returned to a pre-frail or non-frail state, with a 2.6 times probability of improving frailty status, even when analyzing factors associated with the recipient, the donor, and the transplant itself. Frailty status at the time of kidney transplantation, the presence of diabetes mellitus in the recipient, and delayed graft function (DGF) were the only factors associated with long-term progression trajectories of frailty [19]. The results suggest that frailty initially worsens, presumably due to surgical stress, but then improves, likely attributable to the restoration of renal function and other benefits of kidney transplantation. These benefits include improved appetite, increased physical activity resulting from the cessation of dialysis, and an overall enhanced quality of life, which in turn contributes to the improvement of frailty status.

A likely combination of physiological and psychosocial factors may contribute to the improvement in frailty after transplantation. In the study by Quint et al. [20], frailty scores were measured using the Groningen Frailty Indicator (GFI), which provides a holistic perspective of frailty by encompassing both physical and psychological components. The study observed that one-fifth of non-frail patients became frail. The domains of frailty, specifically cognition and psychosocial functioning, appear to be the primary contributors to these changes. An initially positive cognition score was associated with a four-fold higher likelihood of becoming frail, and psychosocial functioning also contributed to the transition from a non-frail to a frail state.

Conclusion

Frailty is a dynamic process in renal transplant recipients of all ages, initially worsening after major surgical insult but subsequently showing significant improvement, likely due to the restoration of renal function. Pre-transplant assessment and interventions such as prehabilitation can successfully increase the number of transplant recipients whose frailty status improves post-transplant. The primary components of the frailty phenotype that improve after transplantation are strength, physical activity, and fatigue, but these may deteriorate in the long term, particularly strength and physical activity in older transplant recipients. The comprehensive care program for patients on the transplant waiting list and renal transplant recipients should include periodic functional assessment to detect changes amenable to intervention.

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