

Prevalence and Correlates of Frailty among Patients on Maintenance Hemodialysis

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Abstract

Background: Frailty has been recognized as a syndrome resulting from cumulative declines in multiple physiologic systems, leading to impaired homeostatic reserve and decreased capacity to withstand stress. Frailty is common in dialysis patients of all ages and is a more sensitive marker of morbidity and mortality than chronological age. Prevention of frailty in hemodialysis patients of all ages could form an active part of nephrology management.

Objective: To determine the prevalence and correlates of frailty among hemodialysis patients

Patients and Methods: Cross section study was carried out in the hemodialysis unit of the Zagazig university hospital in between Oct 2013 to Nov 2014. The total number of the study was 165 hemodialysis patients, 25 were excluded from the study and thus the final included numbers became 140 hemodialysis patients. All participants were subjected to complete clinical examination. Routine laboratory investigations including corrected serum calcium (Ca) mg/dL, serum phosphate (P) mg/dL and serum intact PTH (i-PTH) (pg/mL) were performed. Anthropometric measurements, including mid arm circumference (MAC), mid-calf circumference (MCC) and body mass index (BMI). Frailty diagnoses and scoring by fried frailty criteria

Results: The prevalence of frailty among hemodialysis patients in Zagazig university hospital was 60%, prefrail 15.7% and non-frail 24.3%. Frailty was started early at mean age of 44.11 ± 6.7 and significantly increase with aging $P < 0.05$. Although gender, smoking, blood pressure, anthropometric measures, diabetes, serum albumin, Ca, P, iPTH, C-reactive protein (CRP), hemoglobin (Hb) % g/dl, RBCs $\chi 106$, Platelets $\chi 103$, WBCs $\chi 103$ venous access line were assessed for correlation with frailty. Only female gender $P < 0.001$, diabetes $P < 0.05$, hypoalbuminemia $P < 0.001$, severity of secondary hyperparathyroidism $P < 0.02$, inflammatory state $P < 0.002$, anemia $P < 0.001$, and absence of permanent venous access $P < 0.001$ were correlated with frailty. Administration of erythropoietin (EPO) and L.carnitine were negatively correlated with frailty

Conclusion: The prevalence of frailty among hemodialysis patients in this study was an extremely high 60%, approximately 8-9 folds of the general population. Frailty increases with, female gender, diabetics, absence of permanent venous access for hemodialysis, anemia, hypoalbuminemia and secondary hyperparathyroidism.

Keywords: Frailty; Fried phenotype; End-stage renal disease (ESRD); Hemodialysis

Introduction

Frailty is a multi-dimensional geriatric syndrome [1]; theoretically defined as a clinically recognizable state of increased vulnerability resulting from aging-associated decline in reserve and function across multiple physiologic systems such that the ability to cope with every day or acute stress is comprised and increased risk for poor health outcomes including falls, incident disability, hospitalization, and mortality [2,3].

Frailty remains an evolving concept lacking unique diagnostic criteria for use in clinical practice and epidemiological research [4-7]. However, the Fried criteria are the most widely implemented objective approach to the classification of frailty as meeting three out of five phenotypic criteria indicating compromised energetics: low grip strength, low energy, slowed waking speed, low physical activity, and/or unintentional weight loss [8].

The prevalence of frailty in community dwelling men and women aged 65 years and older defined by Fried were 7% [8]; however, it varied from 17% in French [9] varied from 8.6% in Sweden to 27.3% in Spain [10] and 6.9% in US [8]. Frail older adults, regardless of their Co morbidity and disability status, are at twice the risk of mortality and hospitalization [11].

Chronic kidney disease (CKD) is a major public health problem affecting roughly 10% in the general population, the disease increases

with age, affecting more than one third of all individuals over age 65 years [12]. This population is associated with additional Co morbid conditions; a higher risk of cardiovascular disease and increasing prevalence of frailty and disability [13]. CKD and frailty are associated with many of the same clinical manifestations such as advanced age, inactivity, loss of muscle mass (sarcopenia), Co morbid conditions, and decline in physical and cognitive functioning [14]. In the geriatric literature, these clinical manifestations have been identified as important contributors to a frailty phenotype [15]. Many of the pathological changes resulting from CKD are altered mineral metabolism, chronic inflammation and atherosclerosis. These pathological changes directly or indirectly influence sarcopenia and weakness, which are core domains of the frailty construct [16]. In the hemodialysis population, the condition of frailty is significantly represented not only among older people, but also in people younger than 50 years [17] and more

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sensitive marker of morbidity and mortality than chronological age [18].

The objective of the current study is to describe the prevalence and correlates of frailty among patients on maintenance hemodialysis, in Zagazig university hospital.

Patients and Methods

Study design

Cross section study was carried out in hemodialysis unit of the Zagazig university hospital between October 2013 and November 2014. The total number of the study was 165 hemodialysis patients, 25 were excluded from the study, thus the enrolled final number became 140 hemodialysis patients, and all patients gave informed consent to participate in this study in compliance with the Helsinki Declaration

Demographic information was collected, their age ranged from 19-70 years (mean age 48.09 ± 18.3), among them 80 were males and 60 females (1.3:1) and the main causes of ESRD were chronic glomerulonephritis 45 (32.1%), diabetic nephropathy 30 (21.4%), interstitial nephropathies 21 (15%), obstructive uropathy 9 (6.4%) and unknown 35 (25%).

Eligible participants included adults with stable clinical condition, good verbal agreement to questionnaire and on maintenance hemodialysis therapy for at least 6 months and the mean period of dialysis was 8.96 ± 4.9 year (6 m-21 years). Dialysis was performed three times weekly using 3.5 mEq/l dialysate calcium, duration of each dialysis was 4 hours; protocols were not changed during the study with adequate dialysis treatment ($Kt/V > 1.2$), follow-up visits were conducted at the dialysis center and were conducted on average within 12 months after enrollment

Participants were excluded from the study if suffered from unstable angina, lower extremity amputation without prosthesis, orthopedic disorder that would be exacerbated by activity, chronic liver disease, thyroid dysfunction, severe psychological disorders, chronic heart and lung diseases that results in significant desaturation with exercise or shortness of breath at rest and cerebral vascular disease.

Physical examination and measurements

All participants in this study were subjected to complete clinical examination, anthropometric measurements, including MAC, MCC and BMI, hand grip strength test by handgrip dynamometry (HGD) to measure muscle strength,

Laboratory investigations

The results of the most recent routine laboratory testing (within 1 month) were recorded, including intact PTH (pg/mL), corrected serum calcium (mg/dL) and serum phosphate (mg/dL). Blood sample was drawn for additional tests within 1 month of the testing visit. Samples were centrifuged, aliquoted, and stored at -80°C . Samples were transported to the laboratory. We measured albumin, and C-reactive protein in duplicate on each serum sample using a Beckman Array 360 nephelometer, and the mean values were used in analyses.

Frailty

The participants were interviewed before the hemodialysis session and frailty was measured as defined and validated by Fried et al. criteria [8] (Table 1).

Muscle strength quantitatively measured by HGD and the he best

result from several trials for each hand is recorded, with at least 15 seconds recovery between each effort. Correlation of the administrated drugs EPO, L. carnitine, iron preparation and Vit. D with frailty through the period of research were studied

Statistical Analyses

Data were collected, entered and checked to an SPSS version19. Data were presented as mean \pm standard deviation, analysis of variance (ANOVA and LSD tests). The correlation between variables is calculated using the Pearson's and the Spearman correlation tests. Chi square (χ^2) test and the criterion for statistical significance was set at $p < 0.05$

Results

Demographic data and characteristic of study

The enrolled number of the study 140 participants, their mean age 48 ± 18.3 , male to female ratio 1.3/1, with a mean period of dialysis was 8.96 ± 4.9 year and complete study data was available in Table 2.

Prevalence of frailty

Among 140 participants, 84 were fulfilled 3 or more components

Components of physical frailty	Phenotype of frailty used in the Cardiovascular health study (CHS)
Shrinking: unintentional weight loss	Self-reported unintentional weight loss ≥ 10 pounds in prior year
Weakness	Grip strength: lowest 20% at baseline adjusted for sex and BMI
Poor endurance; exhaustion	Self-reported exhaustion identified by two questions from the CES-D scale: Everything I do is an effort; I cannot get going
Slowness	Walking time/15 feet; slowest 20% (by sex and weight)
	Kcals/week: lowest 20%
Low physical activity	Males < 383 /week are frail. Women: < 270 /week are frail

Table 1: Phenotype of frailty used in the Cardiovascular health study (CHS), Center for Epidemiological Studies-Depression (CES-D scale). A score of 3 points or higher was considered frail; Prefrail=1-2; Non frail (Robust)=none.

Characteristic	No or mean%
Enrolled participant number	140
Age	48.09 ± 18.3 (19-70)
Male/female	80/60=1.3:1
Period of dialysis/year	8.96 ± 4.9 (6m-21 years)
Venous access Catheter/A-V fistula	24/116=1/4.8
Smoker/Non smoker	32/108=1/3.7
Diabetic/non diabetic	30/110=1/3.6
BMI(kg/m ²)	22.4 ± 4.25
MAC (cm)	24.7 ± 4.6
MCC (cm)	34.1 ± 6.48
Mean arterial blood pressure(MAP) mmHg	96.2 ± 14.45
Serum albumin(mg/dL)	3.2 ± 0.64
Mean i-PTH (pg/mL)	431.3 ± 279.4
Mean corrected serum Ca (mg/dl)	9.4 ± 1.0
Mean serum p (mg/dL)	5.52 ± 2.02
CRP (mg/dL)	83.3 ± 44.6
Hb g/dl; RBC X ¹⁰	8.8 ± 1.3 ; 3.16 ± 0.7
WBC X ³	11.12 ± 4.25
PLT X ³	168.4 ± 67.5
KT/V	1.45 ± 0.2 (1.2-1.8)

Table 2: Demographic data and characteristics of the patient study.

of frailty, 22 were fulfilled only 1-2 components and 34 free from any components, hence the prevalence of frailty in hemodialysis unit Zagazig universality hospital was 60% frail, 15.8% prefrail and 24.2% robust (Table 3).

The common components of frailty among all participants was muscle weakness and the prevalence of all components of all frailty was shown in Table 4

Correlates of frailty

Although gender, smoking, blood pressure, anthropometric measures, diabetes, serum albumin, Ca, P, iPTH, CRP, Hb % g/dl, RBCs $\chi 10^6$, Platelets $\chi 10^3$, WBCs $\chi 10^3$ and venous access line were assessed for correlation with frailty. Only female gender $P < 0.001$, diabetes $P < 0.05$, hypoalbuminemia $P < 0.001$, severity of 2nd hyperparathyroidism $P < 0.02$, inflammatory state $P < 0.002$, anemia $P < 0.001$, and absence of permanent venous access $P < 0.001$ were correlated with frailty (Table 5).

In hemodialysis population frailty was started early with a mean age of 44.11 ± 6.7 but frail subjects were significantly older than the prefrail and robust $P < 0.05$. Frailty significantly increased with aging process as 45% of patients younger than 40 y were frail increased to 60%; 66% and 73% in aged patients 40-50; 50-60 and 60-70 years respectively.

Pearson correlation of the administrated medications and frailty showed statistically significant negative correlation with erythropoiesis stimulating agents and L.carnitine and non-statistically significant correlation with vit D and iron preparation (Table 6).

Discussion

The prevalence of frailty in community dwelling men and women aged 65 years and older defined by Fried were 7% [8] Frailty might be expected to be more common among hemodialysis patients than community-dwelling older adults. So we conducted the current study to evaluate the prevalence and correlates of frailty among hemodialysis patients in Zagazig university hospital.

The prevalence of frailty among hemodialysis patients in this study was an extremely high 60% of all participants were fulfilled 3 or more components of frailty, approximately 8-9 folds of the community dwelling men and women aged 65 years and older. However, this high prevalence was consistent with previous research of Johansen et al. [17], who found 67.7% of dialysis patients were frail. Another strikingly high result of Yeran Bao et al. study [19] who found 73% of hemodialysis patients were frail but their mean age higher than our study and this may explain this striking high result.

In contrast to our results a lower prevalence of frailty recorded by Mansur HN, et al. 40.3%, but among a lower mean age hemodialysis participant [20], also other lower prevalence recorded in other studies, 14.0%, 20.9%, 36% [20-22] respectively in CKD stage 1-4 on conservative treatment. It seems that mean age of participants; stages of CKD and maintenance hemodialysis are important contributors to frailty. Our data showed that commonest component of the frailty phenotype was muscle weakness followed by exhaustion and weight loss. The predominance of muscle weakness was expected as significant sarcopenia and associated weakness is commonly seen in hemodialysis patients [23,24].

The factors associated with frailty in our study were age, female gender, diabetes and severity of secondary hyperparathyroidism, hypoalbuminemia, leukocytosis, high CRP and lack of permanent venous access.

Contrary to the definition of frailty as a geriatric syndrome [1], we observed that the frailty, not only started early in the hemodialysis population with mean age 44y and 45% of patients younger than 40 y were frail but also progress rapidly with aging to 60%; 66% and 73% at age 40-50; 50-60 and 60-70y respectively. Certainly several previous researches were noted similar results [17,20,25]

Female gender more liable to frailty, actually several researchers observed such correlation [17,26,27], while others showed that male gender more susceptible to frailty than female [28,29], however such debate may be attributed to the racial difference between those studies

Diabetes and severity of secondary hyperparathyroidism as comorbid diseases were associated with frailty. Consisting with previous researches of Johansen et al. [17] and Mansur et al. [20] respectively. Despite of proving an association between frailty and smoking, blood pressure in other searches [17,30] respectively, in the current study we cannot find such association. This may be explained by a few number of smokers included in the study (only 22.8% of participants were smoker) and the blood pressure of the most participants was controlled (MAP 96.2 ± 14.45). Anthropometric measures MAC, MCC and BMI, not significantly associated with frailty in this study, however, several studies supported our result and denied such association [24,31].

In the current study, we found an association between anemia and hypoalbuminemia and frailty, a similar results were observed by other authors in both community-dwelling older adults [32] and hemodialysis populations [17,29,33]. An increase in the total WBC counts is recognized as a clinical indicator for systemic inflammation, and associated with cardiovascular and cerebrovascular events [34,35]. In the current study, we observed increase prevalence of frailty with leukocytosis and elevated C reactive protein as a marker of inflammation, these findings proved the potential roles of inflammation in the pathogenesis of frailty, however the association of frailty and inflammatory state was established by other authors [36,37].

Concerning vascular access, A-V fistula believed to be the best way of vascular access to perform hemodialysis. In the current study the prevalence of frailty was increased in patients with venous catheter. Lack of permanent vascular contributes to complications, actually these

Frailty components	NO/%	Frailty score		
		Frail	Prefrail	Robust
Weight loss No/yes	52(37.1%)/88(62.9%)	84 (60%)	22 (15.8%)	34 (24.2%)
Gait speed Normal/Slow	56(40%)/84(60%)			
Hand gripe strength Normal/Low	42(30%)/98(70%)			
Physical activity Normal/Low	70(50%)/70(50%)			
Exhaustion Non/exhausted	56(40%)/42(60%)			

Table 3: Component and prevalence of frailty among hemodialysis population

Frailty component	Robust	Prefrail	Frail	X ²	P
Weight loss	0%	36.4%	95.2% ^{a,b}	34.38	0.001
Gait speed	0%	63.6%	83.3% ^{a,b}	18.66	0.001
Hand gripe	0%	63.3%	100% ^{a,b}	36.6	0.001
Physical activity	0%	27.3%	76.2% ^{a,b}	11.52	0.001
Exhaustion	0%	18.2%	95.2% ^{a,b}	34.3	0.001

^aSignificant difference as compared to robust. ^bSignificant difference as compared to prefrail.

Table 4: The prevalence of frailty component among the three groups.

Character	Robust 34 (24.2%)	Prefrail 22 (15.8%)	Frail 84 (60%)	Significance test	P value
Age	36.4 ± 18.9	42.6 (18.6 ^a)	44.1 (16.7 ^a)	F=4. 52	0.05*
Male/Female	40%/8.6%	11.4%:20%	48.6%:71.4% ^{a,b}	X ² =14. 25	0.001*
Smoker/nonsmoker	37.5%:38.9%	12.5%:20.4%	50%/40.7%	X ² =0. 66	0.7
MAP (mmHg)	102.1 ± 14.8	98.3 ± 13.7	93.8 ± 13.4	F=2. 5	0.09
Diabetes	20%	33.3% ^a	46.7% ^{a,b}	X ² =6. 25	0.05*
MAC(cm)	26.0 ± 3.9	24.9 ± 5.7	24.0 ± 4.5	F=1. 11	0.33
MCC(cm)	34.1 ± 5.6	34.9 ± 7.3	33.8 ± 6.67	F=0. 14	0.83
BMI(kg/m ²)	22.3 ± 3.2	24.1 ± 15	21.9 ± 4.6	F=1. 46	0.2
Albumin ((mg/dL)	3.6 ± 0.52	3.6 ± 0.63	2.9 ± 0.53 ^{a,b}	F=13. 3	0.001*
Ca(mg/dL)	9.65 ± 1.0	9.4 ± 1.2	9.1 ± 0.9	F=1. 7	0.18
P(mg/dL)	5.0 ± 1.97	4.8 ± 1.8	5.0 ± 1.6	F=1. 9	0.17
iPTH (pg/mL)	310 ± 128	439 ± 304 ^a	477 ± 253 ^a	F=4. 09	0.02*
CRP (mg/dL)	58.11 ± 30.98	64.9 ± 27.94 ^a	98.42 ± 46.83 ^{a,b}	F=7.141	0.002*
Hb% g/dl	10.4 ± 1.0	8.5 ± 1.5 ^a	8.5 ± 1.2 ^a	F=31.6	0.001*
RBCs ×10 ⁶	3.5 ± 0.5	3.0 ± 0.7 ^a	2.8 ± 0.8 ^a	F=6.1	0.002*
Platelets ×10 ³	154.9 ± 42	145.7 ± 71.7	177.4 ± 70.4	F=1.57	0.21
WBCs ×10 ³	8.1 ± 2.0	9.3 ± 2.0	13.0 ± 4.3 ^{a,b}	F=17.5	0.001*
A-V fistula/Cath.	27.6%:8.3%	15.5%:16.7%	56.9%:75% ^{a,b}	X ² 19.3	0.001*

*Significant difference as compared to robust, ^aSignificant difference as compared to prefrail.

Table 5: Correlates of frailty.

	Frailty score	
	r	P value
Vit D	-0.22	NS
Iron	-0.03	NS
EPO	-0.35	0.05
L.Carnitine	-0.40	0.01

Table 6: Correlation between administrated drugs and frailty.

results compatible with other studies [17,38]. Regarding the correlation between certain hemodialysis medications and frailty, in the current study we, found probable beneficial effects of EPO and L.carnitine on frailty and insignificant effect of Vit. D. These results are generally compatible with Johansen et al. [17] study, which also observed this negative correlation between EPO and L. carnitine on frailty. Contrary to our results Mansur et al. study showed beneficial effects of Vit. D. However, the absent beneficial effect of Vit D in the current study was attributed to, the higher iPTH level in frail group which exceeding the target of the National Kidney Foundation “K/DOQI” target [41].

Conclusion

The prevalence of frailty among hemodialysis patients in this study was an extremely high 60%, approximately 8-9 folds the general population and frailty was started early in the hemodialysis population than the general population. Aging, female gender, absent permanent access for dialysis, hypoalbuminemia, anemia and secondary hyperparathyroidism were identified as correlates of frailty. Frailty in hemodialysis populations highlights the need for strategies to minimize inflammatory state also hemodialysis patients may get benefit from EPO, L carnitine.

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References

- Bauer JM, Sieber CC (2008) Sarcopenia and frailty: a clinician's controversial point of view. *Exp Gerontol* 43: 674-678.
- Gill TM, Gahbauer EA, Allore HG, Han L (2006) Transitions between frailty states among community-living older persons. *Arch Intern Med* 166: 418-423.
- Ensrud KE, Ewing SK, Cawthon PM, Fink HA, Taylor BC, et al. (2009) A comparison of frailty indexes for the prediction of falls, disability, fractures, and mortality in older men. *J Am Geriatr Soc* 57: 492-498.
- Bergman H, Ferrucci L, Guralnik J, Hogan DB, Hummel S, et al. (2007) Frailty: an emerging research and clinical paradigm--issues and controversies. *J Gerontol A Biol Sci Med Sci* 62: 731-737.
- Hogan DB, MacKnight C, Bergman H; Steering Committee, Canadian Initiative on Frailty and Aging (2003) Models, definitions, and criteria of frailty. *Aging Clin Exp Res* 15: 1-29.
- Hubbard RE, O'Mahony MS, Woodhouse KW (2009) Characterising frailty in the clinical setting--a comparison of different approaches. *Age Ageing* 38: 115-119.
- Rothman MD, Leo-Summers L, Gill TM (2008) Prognostic significance of potential frailty criteria. *J Am Geriatr Soc* 56: 2211-2216.
- Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, et al. (2001) Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 56: M146-156.
- Avila-Funes JA, Helmer C, Amieva H, Barberger-Gateau P, Le Goff M, et al. (2008) Frailty among community-dwelling elderly people in France: the three-city study. *J Gerontol A Biol Sci Med Sci* 63: 1089-1096.
- Santos-Eggimann B, Cuénoud P, Spagnoli J, Junod J (2009) Prevalence of frailty in middle-aged and older community-dwelling Europeans living in 10 countries. *J Gerontol A Biol Sci Med Sci* 64: 675-681.
- Puts MT, Monette J, Girre V, Wolfson C, Monette M, et al. (2010) Does frailty predict hospitalization, emergency department visits, and visits to the general practitioner in older newly-diagnosed cancer patients? Results of a prospective pilot study. *Crit Rev Oncol Hematol* 76: 142-151.
- Stevens LA, Nolin TD, Richardson MM, Feldman HI, Lewis JB, et al. (2009) Comparison of drug dosing recommendations based on measured GFR and kidney function estimating equations. *Am J Kidney Dis* 54: 33-42.
- Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, et al. (2007) Prevalence of chronic kidney disease in the United States. *JAMA* 298: 2038-2047.
- Fried LF, Unruh ML (2010) Aging in kidney disease: key issues and gaps in knowledge. *Adv Chronic Kidney Dis* 17: 291-292.
- Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G (2004) Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. *J Gerontol A Biol Sci Med Sci* 59: 255-263.
- Walston J, Hadley EC, Ferrucci L, Guralnik JM, Newman AB, et al. (2006) Research agenda for frailty in older adults: toward a better understanding of physiology and etiology: summary from the American Geriatrics Society/ National Institute on Aging Research Conference on Frailty in Older Adults. *J Am Geriatr Soc* 54: 991-1001.

17. Abboud H, Henrich WL (2010) Clinical practice. Stage IV chronic kidney disease. *N Engl J Med* 362: 56-65.
18. Johansen KL, Chertow GM, Jin C, Kutner NG (2007) Significance of frailty among dialysis patients. *J Am Soc Nephrol* 18: 2960-2967.
19. Brown EA, Johansson L (2010) Old age and frailty in the dialysis population. *J Nephrol* 23: 502-507.
20. Bao Y, Dalrymple L, Chertow GM, Kaysen GA, Johansen KL (2012) Frailty, dialysis initiation, and mortality in end-stage renal disease. *Arch Intern Med* 172: 1071-1077.
21. Mansur HN, Damasceno Vde O, Bastos MG (2012) [Prevalence of frailty in patients in chronic kidney disease on conservative treatment and on dialysis]. *J Bras Nefrol* 34: 153-160.
22. Roshanravan B, Khatri M, Robinson-Cohen C, Levin G, Patel KV, et al. (2012) A prospective study of frailty in nephrology-referred patients with CKD. *Am J Kidney Dis* 60: 912-921.
23. Wilhelm-Leen ER, Hall YN, K Tamura M, Chertow GM (2009) Frailty and chronic kidney disease: the Third National Health and Nutrition Evaluation Survey. *Am J Med* 122: 664-671.
24. Johansen KL, Shubert T, Doyle J, Soher B, Sakkas GK, et al. (2003) Muscle atrophy in patients receiving hemodialysis: effects on muscle strength, muscle quality, and physical function. *Kidney Int* 63: 291-297.
25. Campistol JM (2002) Uremic myopathy. *Kidney Int* 62: 1901-1913.
26. Bao Y, Dalrymple L, Chertow GM, Kaysen GA, Johansen KL (2012) Frailty, dialysis initiation, and mortality in end-stage renal disease. *Arch Intern Med* 172: 1071-1077.
27. Painter P, Kuskowski M (2013) A closer look at frailty in ESRD: getting the measure right. *Hemodial Int* 17: 41-49.
28. Reese PP, Cappola AR, Shults J, Townsend RR, Gadegbeku CA, et al. (2013) Physical performance and frailty in chronic kidney disease. *Am J Nephrol* 38: 307-315.
29. Biavo BM, Tzanno -Martins C, Cunha LM, Araujo ML, Ribeiro MM, et al. (2012) Nutritional and epidemiological aspects of patients with chronic renal failure undergoing hemodialysis from Brazil, 2010. *J Bras Nefrol* 34: 206-215.
30. Oriandi FS, Cucumber BG, Pavarini SC, Santos DA, Mediondo MS (2012) Assessment of the level of life expectancy in the elderly with chronic renal hemodialysis. *Rev Esc Enferm USP* 46: 500-505
31. Bastos-Barbosa RG, Ferrioli E, Coelho EB, Moriguti JC, Nobre F, et al. (2012) Association of frailty syndrome in the elderly with higher blood pressure and other cardiovascular risk factors. *Am J Hypertens* 25: 1156-1161.
32. Johansen KL, Dalrymple LS, Delgado C, Kaysen GA, Kornak J, et al. (2014) Association between body composition and frailty among prevalent hemodialysis patients: a US Renal Data System special study. *J Am Soc Nephrol* 25: 381-389.
33. Reuben DB, Cheh AI, Harris TB, Ferrucci L, Rowe JW, et al. (2002) Peripheral blood markers of inflammation predict mortality and functional decline in high-functioning community-dwelling older persons. *J Am Geriatr Soc* 50: 638-644.
34. Chaves PH, Semba RD, Leng SX, Woodman RC, Ferrucci L, et al. (2005) Impact of anemia and cardiovascular disease on frailty status of community-dwelling older women: the Women's Health and Aging Studies I and II. *J Gerontol A Biol Sci Med Sci* 60: 729-735.
35. Leng SX, Xue QL, Huang Y, Ferrucci L, Fried LP, et al. (2005) Baseline total and specific differential white blood cell counts and 5-year all-cause mortality in community-dwelling older women. *Exp Gerontol* 40: 982-987.
36. Margolis KL, Manson JE, Greenland P, Rodabough RJ, Bray PF, et al. (2005) Leukocyte count as a predictor of cardiovascular events and mortality in postmenopausal women: the Women's Health Initiative Observational Study. *Arch Intern Med* 165: 500-508.
37. Leng SX, Xue QL, Tian J, Walston JD, Fried LP (2007) Inflammation and frailty in older women. *J Am Geriatr Soc* 55: 864-871.
38. Puts MT, Visser M, Twisk JW, Deeg DJ, Lips P (2005) Endocrine and inflammatory markers as predictors of frailty. *Clin Endocrinol (Oxf)* 63: 403-411.
39. National Kidney Foundation (2003) K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis* 42: S1-201.