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Optimizing dialysis dose in the context of frailty: an exploratory study

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Abstract

Introduction Frailty is a multicausal syndrome characterized by a decrease in strength, resistance and physiological function, which makes the individual vulnerable and dependent, and increases his/her mortality. This syndrome is more prevalent among older individuals, and chronic kidney disease patients, particularly those on dialysis. Dialysis dose is currently standardized for hemodialysis (HD) patients regardless of their age and functional status. However, it has been postulated that the dialysis dose required in older patients, especially frail ones, should be lower, since it could increase their degree of frailty. Then, the purpose of this study was to evaluate if there would be a correlation between the dose of Kt/V and the degree of frailty in a population of adult patients on HD.

Materials and methods A cross-sectional study with 82 patients on HD in Barranquilla (Colombia) and Lobos (Argentina) was conducted. Socio-demographic and laboratory data, as well as dialysis doses (Kt/V) were recorded and scales of fragility, physical activity, gait and grip strength were applied. Then these data were correlated by a Spearman's correlation and a logistic regression.

Results CFS, social isolation, physical activity, *gait speed,* and *prehensile strength tests* were outside the reference ranges in the studied group. No significant correlation was found between dialysis dose and all the above mentioned functional tests. However, a significant and inverse correlation between physical activity and CFS was documented (score − 1.41 (CI − 2.1 to − 0.7).

Conclusion No significant correlation was documented between Kt/V value and different parameters of the frailty status, but this status correlated significantly and inversely with physical activity in this group. Frailty status in hemodialysis patients was significantly higher in older individuals, although young individuals were not exempt from it.

Keywords Frailty · Dialysis dose · Hemodialysis

Introduction

Frailty is a multicausal clinical syndrome characterized by a decrease in strength, resistance and body physiological condition, making the individual vulnerable, and increasing his/her risk of dependence and death. It should be noted the difference between frailty syndrome and comorbidity, as well as between frailty syndrome and disability. Comorbidity is the coexistence of two or more chronic diseases of systemic significance, while disability is the inability to perform at least one of the activities of daily living. However, these conditions can be overlapped and linked, since the burden of comorbidities can lead to a state of frailty, and this in turn, can finally induce disability [1].

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The importance of detecting the frailty phenotype lies in its close association with a high risk of hospitalization and death [2]. This diagnosis can be established through various tests validated for that purpose, such as a clinical scale based in the degree of autonomy in the performance of daily activities (clinical frailty scale (CFS), the evaluation of the gait speed (gait test) and/or a register of the grip strength of the individual (prehensile strength test) [3].

In chronic conditions frailty phenotype is even more prevalent, as is the case of chronic kidney disease (CKD), a condition characterized by a progressive and irreversible deterioration of renal function due to the reduction of the nephron mass for a period of at least three months [3].

It has been documented that the prevalence of frailty phenotype in adult patients suffering from non-dialysis chronic kidney disease (14%) is higher than in the general population (7%). Likewise, the prevalence of frailty in patients on chronic hemodialysis (HD) is around 42% (35% in young people and 50% in older people) and pre-frailty is 29%, presenting these patients (frailty phenotype) a 2.60-fold higher risk of mortality and 1.43 fold higher number of hospitalizations, regardless the age, comorbidity and disability [4].

The most validated and universally used parameter to evaluate the dialysis dose is the assessment of the urea removal rate by means of the Kt/V. In this parameter, "K" is the effective urea clearance (commonly accepted as the solute marker of uremic toxicity), «t» is the time of duration of the dialysis session and «V» is the urea volume of distribution [5]. The Kt/V is a crucial determinant in the clinical outcome of the patients on chronic HD, considering as an adequate Kt/V value ≥ 1.2 per session [6, 7].

This dialysis dose is standardized for the population on HD regardless of the age and functional status (robust or frail). It has been postulated that the dose of dialysis required in older patients, especially frail patients, would be lower (since the rate of urea production and its volume of distribution are reduced), and that even the conventional HD (three-weekly sessions of 4–5 h) could increase their degree of frailty by induction of hypotension and gait instability [6].

Then, the purpose of this study was to evaluate if there would be a correlation between the dose of Kt/V and the degree of frailty in a population of adult patients on chronic HD.

Material and methods

A cross-sectional study was conducted with 82 adult patients on chronic HD. The subjects evaluated attended two HD centers, one in the city of Barranquilla (Colombia) and the other in the city of Lobos (Argentina), during the period of time comprised between January 2017 and May 2018. Only those who had a HD treatment longer than 3 months, over 18 years of age and who had agreed to participate in the present study, signing the informed consent, were included in the study.

The socio-demographic data of each patient were recorded, as well as some laboratory parameters, hospital stays, and dialysis dose (Kt/V). The CFS of Rockwood et al. (2007) [8, 9] in Spanish was applied to evaluate the patients' biological frailty (Annex, Table A). For evaluating the patients' social frailty, the *Social Isolation Score* of Pantell et al. (2013) was applied [10] (Annex, Table B). In addition, the *Questionnaire of Hierarchical Physical Activity* of Reuben et al. (1993) [11] (Annex, Table C), the *Gait Speed Test* [12] (Annex, Table D), and the *Hand-Grip Strength Test* [13] (Annex, Table E) were also applied to these patients before their first dialysis session of the study week (Annex).

To evaluate if there was a significant difference in the findings depending of the patient´s age, the population was also separated into two groups according to the age: group 1 with young adult patients (18 to 64 years old), and group 2 with older patients (≥ 65 years old).

Then, to determine if there was a significant difference in the evaluated variables among patients with different functional clinical status, these were compared dividing the population in three groups: robust (CFS: 1–3), frail (CFS: 4–5), and very frail (CFS:6–7). It is worth mentioning that there was no terminal patients (CFS: 7–8) in the studied group.

Basic descriptive statistics, the test of statistical significance between two proportions, a Spearman's correlation and a logistic regression were applied to the data. The same evaluation was performed among the different functional groups. The statistical analyzes were performed with the R-CRAN statistical package.

The study was approved by the Institutional Bioethical Committee, and informed consent was obtained from all the participants included in the study.

Results

A total of 82 adult patients on chronic HD were recruited and divided into two groups: young adult patients (age 18–64 years) and older young patients (≥ 65 years), being the average age 51 ± 13 years and 75 ± 7, respectively. A predominance of males was found in both groups, 58% in the young adult patients and 68% in the older patiens. Regarding the presence of comorbidities, the proportions were similar in both groups, (p value NS), as was the case of diabetes mellitus type 2, hypertension, and heart failure. Conversely, stroke was significantly more prevalent in the older group (Table 1).

As for the functional markers; the CFS value was higher in both age groups (CFS value > 3) compared to its reference value (CFS ≤ 3 in healthy people). Additionally, CFS value

Table 1 Socio-demographic characterization and comorbidities in young and older patients groups

Socio-demographic	Young adult patients (18–64 years old)	Older patients (≥65 years old)	*p* value
No of individuals	57	25	–
Age (years)	51 ± 13 years	75 ± 7 years	< 001
Gender (%male)	58%	68%	NS
Comorbidities	Adult (age 18–64 years)	Elderly (≥65 years)	*p* value
DM2	42%	47%	NS
HP	85%	80%	NS
HF	9%	7%	NS
ST	0%	27%	< 001

DM2 diabetes mellitus type 2, *HP* hypertension, *HF* heart failure, *ST* stroke, *NS* no significant

Table 2 Evaluation of the different parameters that assess frailty status

Evaluation	Young adult patients (18–64 years old)	Older patients (≥65 years old)	*p* value	Reference range
Clinical Frailty Scale	3.8 ± 1.3	5.5 ± 5.5	< 001	≤ 3
Social isolation (low score: 4)	6%	13%	NS	≤ 1
Physical activity (low score: 0)	55%	87%	0.05	2–3
Gait speed (m/sec)	6.1 ± 3.5	8.3 ± 2.8	0.03	< 8
Hand-grip (kg)	41.5 ± 21.6	33.2 ± 13.7	NS	57–105

NS non-significant

was significantly higher in older patients (CFS: 5.5 ± 5.5) compared to CFS value the young patients (CFS: 3.8 ± 1.3), *p* value < 0.01 (Table 2).

With regards the *Social* Isolation score, it was high (sub-optimal) in a low percentage of young adult patients (6%) and older patients (13%), and there was no significant difference in this score between the age groups. Regarding the scale of *Physical Activity*, more than 50% presented a low score in both studied groups: young adult patients (55%), and older patients (87%), being slightly worse this score in the older group (*p* value = 0.05) (Table 2).

Regarding Speed Test, the average value was normal in the young adult patient group 6.1 ± 3.5 (m/sec), while it was abnormal in the older patients group: 8.3 ± 2.8 (m/sec), being this gait tests significantly worse in the older patients (*p* 0.03) (Table 2).

Finally, the hand-grip test was below the reference value in both age groups, and there was no significant difference between the young adult patient and older patient groups (*p* = NS) (Table 2).

Regarding the serum laboratory parameters and Kt/V value, there was no significant differences between both studied groups, except for serum creatinine value which was significantly lower in the older group (*p*: < 0.001) (Table 3).

There was no significant correlation (Spearman) between Kt/V value and different parameters of the frailty status, such as the clinical frailty scale, grip strength, gait speed and physical activity. Through a logistic regression, when adjusting for the potential confounding effect of the dialysis dose (Kt/V) and the age, it was found that there was a significant association between CFS and the *Physical Activity* level, with a score of − 1.41 (CI − 2.1 to − 0.7) in the CFS. i.e., for each point of increase in frailty, the level of *Physical Activity* descends 1.4.

Then, the obtained data was reevaluated dividing the studied patients in three groups depending on their functional status: robust (R), frail (F), and very frail (VF).

Table 3 Serum parameters of the studied patients

Parameter	Young group (18–64 years)	Older group (≥65 years)	*p* value
Hemoglobin (g/l)	10.1 ± 2.4	10.8 ± 2.1	NS
Hematocrit (%)	29.9 ± 5.1	30.8 ± 6.5	NS
Serum creatinine (mg/dl)	10.1 ± 3.3	7.3 ± 2.7	< 0.001
BUN (mg/dl)	64 ± 22.3	57.5 ± 19.8	NS
Serum calcium (mg/dl)	10.2 ± 1	8.8 ± 0.6	NS
Serum phosphate (mg/dl)	4.8 ± 1.4	4.4 ± 1.2	NS
Serum albumin (g/dl)	3.4 ± 0.6	3.3 ± 0.6	NS
Kt/V	1.13 ± 0.25	1.15 ± 027	NS

NS no significant, *BUN* blood urea nitrogen

Table 4 Socio-demographic characterization and comorbidities in robust, frail and very frail patients groups

Socio-demographic	Robust	Frail	Very frail	*p* value
No of individuals	29	29	24	–
Age (years)	52 ± 15	56 ± 15	68 ± 13	< 0.001
Gender (% Male)	52%	66%	67%	NS
Comorbidities	Robust	Frail	Very frail	*p* value
DM2	39%	38%	57%	NS
HP	89%	94%	80%	NS
HF	6%	13%	7%	NS
ST	0%	13%	14%	NS

DM2 diabetes mellitus type 2, *HP* hypertension, *HF* heart failure, *ST* stroke, *NS* no significant

Table 5 Evaluation of frailty parameter among different frailty status

Evaluation	Robust	Frail	Very frail	*p*	Reference range
Clinical Frailty Scale	1–3	4–5	6–7	–	≤ 3
Social isolation (low score 4)	17%	6%	0%	0.07	≤ 1
Physical activity (low score 0)	33%	69%	100%	< 0.001	2–3
Gait speed (m/sec)	5.4 ± 2.6	7.7 ± 2.0	7.5 ± 5.4	NS	< 8
Hand-grip (kg)	19.3 ± 11	20.7 ± 14	19.1 ± 16	NS	57–105

NS non-significant

From this perspective, it was documented that the oldest individuals were in the VF group ($p = < 0.001$), while there was a slightly preponderance of male gender in all the functional groups. Regarding the documented comorbidities, such as diabetes mellitus, hypertension, heart failure, and stroke, there was no significant difference in their prevalence among the three functional groups (Table 4).

Regarding the frailty parameters, there was a significant difference in the percentage of individuals with the lowest social isolation and physical activity scores among the three studied groups: the percentage of individuals with the lowest social isolation score was slightly higher in the R group ($p = 0.07$), and the percentage of individuals with the lowest physical activity score was significantly higher in the F and VF groups, particularly in the last one ($p = < 0.001$) (Table 5). Even though gait-speed and hand-grip tests showed abnormal value in the three studied groups, there was no significant difference among them (Table 5).

Finally, regarding the evaluated serum parameters: hemoglobin, hematocrit, and albumin were abnormally reduced, while creatinine, and BUN were abnormally increased in the three groups. As regards serum calcium and phosphorus, the former showed variable values (low and high) among the studied groups, while the latter showed normal values among them. However, there was no significant difference regarding all the above mentioned serum parameters among the three groups, except for serum hemoglobin, creatinine, and albumin which were significantly lower in the VF group (Table 6). Concerning Kt/V value, there was no significant difference in its value among the three functional groups (Table 6).

Table 6 Serum parameters in each frailty group

Parameter	Robust	Frail	Very frail	*p* value
Hemoglobin (g/l)	11.3 ± 2.2	10.2 ± 2.5	9.3 ± 1.9	0.05
Hematocrit (%)	29.9 ± 6.2	31.2 ± 4.8	29.2 ± 5.8	NS
Serum creatinine (mg/dl)	10.3 ± 3.4	9.7 ± 3.0	7.3 ± 2.8	0.002
BUN (mg/dl)	62 ± 23	63.4 ± 23	60.7 ± 19.2	NS
Serum calcium (mg/dl)	8.9 ± 0.7	8.7 ± 0.8	12.0 ± 16	NS
Serum phosphate (mg/dl)	4.6 ± 1.4	4.9 ± 1.4	4.5 ± 1.2	NS
Serum albumin (g/dl)	3.5 ± 0.5	3.6 ± 0.4	3.1 ± 0.7	0.025
Kt/V	1.13 ± 0.3	1.16 ± 0.2	1.10 ± 0.2	NS

NS no significant, *BUN* blood urea nitrogen

Discussion

The majority of patients in both age groups were male. This phenomenon can be explained due to the higher prevalence of male gender among CKD patients [14]. Regarding the similar prevalence of hypertension and diabetes mellitus type 2 documented in both age groups, this finding can be

explained by the importance of these both conditions as CKD etiology, as well as the high prevalence that hypertension has in CKD patients [15, 16]. In regards with the higher prevalence of stroke in the older group, it can be explained due to the higher prevalence of this disease in the older individuals, particularly in those suffering from chronic nephropathy [17].

As for the biochemical parameters, the significantly lower serum creatinine in older patients can be attributed to the characteristic sarcopenia of this group, since the magnitude of muscle mass directly impacts on serum creatinine levels [18].

In both age groups, it was documented similar degree of anemia and hypoalbuminemia, being both groups on adequate and similar dialysis (Kt/V) and erythropoietin doses. This phenomenon could reflect a state of malnutrition and/or chronic inflammation (erythropoietin resistance) [16].

With regard to the frailty status, which was evaluated by applying the CFS, gait-speed test, and physical activity score, it was significantly more marked in the older group. Nevertheless, it was found some degree of biological and social frailty in the young group. It should be noted that although there was no significant difference in the grip strength between the groups, it was low for both of them. Moreover, CFS correlated significantly and inversely with physical activity in the studied group, regardless patients' age and dialysis dose. Therefore, these findings reflect the significantly negative influence that CKD have on the deterioration of muscle functionality [19–22].

This is consistent with other literature reports that have documented not only frailty in young CKD patients, but even in children suffering from this condition, reinforcing the concept that frailty should be evaluated even in pediatric population with CKD [20].

Finally, no significant correlation was found between the Kt/V value and the frailty markers. Although this could be attributed to the fact that the study did not gather the necessary number of patients to be able to find such correlation, its lack could be interpreted as at that level of Kt/V the state of frailty does not depend on the delivered dialysis dose but rather on other variables. In consonance with this finding it is documented that the prognosis of the population on chronic dialysis worsens (higher mortality) when the Kt/V is < 1.1 [21].

As expected, the oldest individuals and percentage of those individuals with the lowest physical activity scores were in the VF group, since prevalence and degree of frailty progressively increases with aging (Tables 4 and 5) (4). The slightly preponderance of male gender among the three functional groups could be explained due to the higher prevalence of chronic nephropathy in men (7). The fact that there was no significant difference in the prevalence of comorbidities among the three functional groups reinforces the concept that comorbidity and frailty are related clinical scenarios but not identical ones (Table 4) (4).

Regarding the evaluated frailty parameters, the percentage of individuals with the lowest social isolation score was slightly higher in the R group ($p = 0.07$), perhaps because these patients were able to perform self-care, and consequently had no need of social support network (Table 5). In addition, there was no significant difference in the gait-speed and hand-grip tests values among the three functional groups, since these tests showed abnormal low values in all of them. This phenomenon could be explained by the sarcopenia and peripheral neuropathy usually present in chronic dialysis patients (4, 7) (Table 5).

Regarding the evaluated serum parameters, most of them showed no significant difference among the three studied groups, and their values were the expected for chronic dialysis patients. Serum hemoglobin, creatinine, and albumin were significantly lower in the VF group, phenomenon which could be explained due to the higher inflammatory status (erythropoietin resistance, low serum albumin), and sarcopenia (lower serum creatinine value) which characterized this functional group. Some VF patients also showed hypercalcemia, which could be associated to their immobility syndrome (Table 6). Finally, concerning Kt/V value, there was no significant difference in its value among the studied groups since the same dialysis dose target was sought during renal replacement treatment prescription for every patient.

Conclusion

In this study, it was found no significant correlation between Kt/V value and different parameters of the frailty status, but this status correlated significantly and inversely with physical activity in this group. Frailty status in hemodialysis patients was significantly higher in older individuals, although young individuals were not exempt from it. Finally, very frail dialysis patients showed the highest proportion of patients with low physical activity score.

It is worth pointing out that dialysis dose should be individualized in all patients, but particularly in older and frail individuals since not only standard dialysis dose could be unnecessary high for these patients because dialytic adequacy have been designed based on a series of parameters which are usually significantly modified in these clinical groups, such as patient´s total body water, water compartmental distribution, body surface area, and urea generation rate; but also standard dialysis dose could have deleterious effect on these patients by inducing or accelerating frailty status.

Because of that, there is a tremendous need of performing a prospective controlled study, based on these concepts, to

document, on one hand: which would be an adequate KtV value in these particular groups, and on the other hand: to explore if dialytic adequacy evaluation should also be based on patient´s clinical functional markers, such as clinical frailty scale, hand grip score, and gait rate test, or most likely a combination of them.

Annex

Table A: Clinical Frailty Scale

1. Very fit	People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age
2. Well	People who have no active disease, symptoms but are less fit than category 1. Often, they exercise or are very active occasionally
3. Managing well	People whose medical problems are well controlled, but are not regularly active beyond routine walking
4. Vulnerable	While not dependent on others for daily help, often symptoms limit activities. A common complaint is being "slowed up", and/or being tired during the day
5. Midly frail	These people often have more evident slowing and need help in high orders (finances, medication, transportation, heavy housework)
6. Moderately frail	People need help with all outdoor activities. Indoors they need help with housekeeping, and often have problems with stairs. They also need help with bathing and might need minimal assistance with dressing
7. Severely frail	Completely dependent for personal care, from either cause (physical or cognitive). Even so, they seem stable and not at high risk of dying
8. Very severely frail	Completely dependent, and approaching the end of life (within 6 months)
9. Terminally ill	Approaching the end of life. This category applies to any people with a life expectancy < 6 months, who are not otherwise evidently frail

If dementia, the degree of frailty usually corresponds to the degree of dementia

- Mild dementia: includes forgetting the details of a recent events though still remembering the event itself, repeating the same question/story and social withdrawal
- Moderate dementia: recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting
- Severe dementia: they cannot do personal care without help

Table B: Social Isolation Score

- Four type of relationships (1 point for each). Score ranges from 0 (highest isolation) to 4 (lowest isolation).
- Marital status: being married or living together with someone.
- Frequency of contact with other people: having 3 or more interactions with other people per week.
- Participation in religious activities: attending church or religious services 4 or more times per year.
- Participation in other club or organization activities: being member of a club or organization.

Table C: Physical Activity–Reuben Scale

3. Do you participate at least three times a week in a sporting activity or exercise such as swimming, jogging, tennis, cycling, aerobics, gymnastics or other activities, that cause sweating or leave without breathing?
2. Do you walk, at least three times a week, between 9 and 20 blocks (1.6 km) without rest?
1. Do you walk at least three times a week less than 8 blocks (0.5 km) without rest?
0. None of the above.

Table D: Gait speed

- Seconds it takes you walking four and a half meters at usual pace. The patient is instructed to walk a further meter to avoid slowing near the end point.
- Two measurements are taken and the shortest time (highest speed).

Men		Women	
Height (cm)	Cut point (seg)	Height (cm)	Cut point (seg)
≤ 173	≥ 7 (0.65 m/s)	≤ 159	≥ 7 (0.65 m/s)
> 173	≥ 6 (0.76 m/s)	> 159	≥ 6 (0.76 m/s)

Table E: Hand-Grip

- The individual should be seated in a chair with an adduction and neutral rotation shoulder, 90° flexion elbow, mid prono-supination forearm, and wrist with 0–30° dorsal flexion and 0–15° ulnar deviation. The subject is asked to perform the grip with the maximum force by means of a fast but continuous impulse, until reaching the maximum power, registering the measurement of maximum strength reached by the dynamometer needle. The best result of 3 trials of the dominant hand is recorded, with at least 15 s of recovery between each effort.
- The values given below give guidance on the expected scores for adults according to Fried et al.

Men		Women	
BMI	Cut point (kg)	BMI	Cut point (kg)
≤24	≤29	≤23	≤17
24–26	≤30	23–26	≤17.3
26–28	≤30	26–29	≤18
>28	≤32	>29	≤21

Compliance with ethical standards

Conflict of interest All the authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from the patient.

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