Frailty syndrome in hemodialyzed patients: a pilot study

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Introduction: Frailty refers to clinical syndrome in chronic patients with heightened stressors sensitivity and decreased physiological reserve resulting from diminished capacity of body systems and organs. Frailty leads to increased morbidity and mortality.

Research objective: The objective was to determine the prevalence of frailty in hemodialyzed patients and to investigate correlations of epidemiological data and laboratory tests with psychosocial functioning in the study group.

Material and Methods: The study involved 42 patients of one hemodialysis center: 12 women and 30 men. Participants were asked to anonymously complete the Kidney Disease Quality of Life (KDQOL-SF™) questionnaire consisting of closed-end questions about their opinions about their health, well-being, and ability to perform everyday activities. Independent researchers collected clinical records. The data was compared with the questionnaire responses.

Results: Patients with the lowest scores on the KDQOL-SF™ and individual scales (frail individuals) revealed lower concentrations of potassium (p=0.031), albumin (p=0.008), total protein (p=0.035), PTH (p=0.018) before HD and higher urea concentrations after HD (p=0.014). They also took cinacalcet more often (p=0.049). Frail females exhibited high concentration of CRP (p=0.009) and longer weekly dialysis time ($p \leq 0.05$). Frail males were characterized by lower hemoglobin ($p<0.05$) and were more concerned by the burden of kidney disease and dialysis therapy than females (p=0.016).

Conclusions: KDQOL-SF™ instrument is useful for identifying hemodialyzed patients with frailty syndrome. The study identified the most significant parameters for diagnosis of frailty: low concentrations of albumin, total protein, potassium, and elevated levels of CRP. These parameters may be used to develop screening test for frailty.

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Key words:
- frailty syndrome
- renal insufficiency
- hemodialysis

Zespół kruchości u pacjentów hemodializowanych: badanie pilotażowe

Wstęp: Kruchość to określenie zespołu klinicznego dotyczącego przewlekle chorych, charakteryzującego się zwiększoną wrażliwością na czynniki stresogenne oraz zmniejszeniem rezerwy czynnościowej, co wynika z obniżonej wydolności różnych układów i narządów. Prowadzi to do wzrostu chorobowości i umieralności.

Cel badania: Celem pracy było określenie występowania zespołu kruchości u chorych przewlekle dializowanych oraz związku danych epidemiologicznych i wyników badań laboratoryjnych z funkcjonowaniem psychospołecznym w badanej grupie.

Materiał i Metodyka: W badaniu wzięło udział 42 pacjentów z jednej stacji dializ: 12 kobiet i 30 mężczyzn. Wypełnili oni anonimową ankietę „Choroba nerek a jakość życia (KDQOL-SFTM)", w której odpowiadali na pytania zamknięte dotyczące ich subiektywnej opinii o własnym zdrowiu, samopoczuciu i zdolności wykonywania codziennych zajęć. Niezależni badacze zbierali dane kliniczne, które zostały zestawione z wynikami ankiety.

Wyniki: Pacjenci z najniższą punktacją uzyskaną w KDQOL-SFTM i poszczególnych podskalach testu (tzw. „krusi") uzyskiwali niższe stężenie potasu (p=0,031), albumin (p=0,008), białka całkowitego (p=0,035), PTH (p=0,018) przed HD oraz wyższe stężenia mocznika po HD (p=0,014). Otrzymywani oni także częściej cinacalcet (p=0,049). Kruche kobiety miały wysokie stężenie CRP (p=0,009) i były dłużej dializowane ciągu tygodnia ($p \leq 0,05$). Krusi mężczyźni mieli natomiast niższy poziom hemoglobiny ($p<0,05$), a przy tym gorzej radzili sobie z chorobą nerek i dializoterapią niż kobiety (p=0,016).

Wnioski: Skala KDQOL-SF™ jest pomocnym narzędziem w identyfikowaniu pacjentów hemodializowanych z „zespołem kruchości". Wykazano także parametry, które mają istotny wpływ na identyfikację kruchości: niskie stężenie albumin, białka całkowitego, potasu, a także podwyższone wartości białka ostrej fazy. Parametry te mogłyby zostać użyte w przesiewowym panelu badań tego zespołu.

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Słowa kluczowe:
- zespół kruchości
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Introduction

Frailty refers to a widespread clinical presentation which carries a higher risk of health deterioration, hospitalization, impairment of daily functioning, falls, disability, morbidity, and mortality [1]. This state is characterized by heightened susceptibility to stressors and decreased physiological reserve due to the faltering capacity of the various body systems and organs [2].

The key pathogenetic process underlying the frailty syndrome is a state of chronic inflammation, which affects the musculoskeletal, endocrine, cardiovascular, and hematopoietic systems [2,3]. The activity of inflammatory mediators, in conjunction with coagulation disturbances and hormonal changes, leads to sarcopenia, osteopenia, anemia, cardiovascular diseases, as well as vitamin and albumin deficiency [2,3]. This in turn results in reduced strength and exertion tolerance, impaired cognitive function, and increased vulnerability to stressors [4].

"Frailty" in its present understanding dates back to 1974, when Charles Fahey and the US Federal Council on the Aging (FCA) used the term "frail elderly" to denote a certain segment of the elderly population [5-7]. However, it was not until 1990 that it appeared in the medical subject index to the Journal of the American Geriatrics Society [5,8]. In the 1990s, the notions of frailty, comorbidity, and disability were often used interchangeably to identify a particularly susceptible group of older individuals requiring greater care. However, subsequent research and geriatric reports have shown that these concepts, albeit interrelated, represent separate clinical entities entailing different medical approaches due to their specific characteristics and challenges.

The first and most widely used diagnostic criteria were proposed by Fried et al. in 2001. According to them, a diagnosis of frailty can be made if at least 3 out of the following 5 conditions are met: unintentional weight loss (more than 5 kg/year), self-reported exhaustion, muscular weakness, slow walking speed, and low physical activity [1,9]. Still, since those early propositions, a number of other methods (clinical tests, questionnaires) have been developed to evaluate frailty in patients. They examine the various constituent elements of the frailty syndrome: physical (physical activity, nutritional status, grip force), mental (cognitive function, mood), and social (social support vs. isolation). The best known instruments include the Cardiovascular Health Study Scale (CHS), the Edmonton Frail Scale (EFS), and the Tilburg Frailty Indicator (TFI) [10].

The frailty syndrome, which was once thought to be limited to the geriatric population, is now diagnosed also in younger patients suffering from serious chronic diseases. It has been extensively studied in cardiological patients [11-13], type 2 diabetics [14], individuals with COPD [15,16], and those with renal diseases [17-22]. At a particularly high risk of frailty are hemodialyzed patients as a result of complications from chronic renal insufficiency [17,23] and prevalent malnutrition accompanied by low protein, hemoglobin, and phosphate levels [24,25]. Of significance are also the time-consuming and exhausting hemodialysis procedures and their consequences. Another factor contributing to frailty in dialyzed patients is widespread comorbidity in this this clinical population [23].

The objective was to assess the prevalence of the frailty syndrome in regularly dialyzed patients and to determine the correlations of epidemiological data and laboratory test results with psychosocial functioning.

Materials and Methods

The study involved 42 out of 83 (50.6%) patients of one dialysis center: 12 (28.6%) females and 30 (71.4%) males. The study excluded patients receiving hemodialysis therapy for less than a year. Participation was voluntary. The patients were requested to anonymously complete the Kidney Disease Quality of Life (KDQOL-SF™) questionnaire consisting of 24 closed-end questions concerning their subjective opinions about their health (items 1-11), kidney disease (12-14), effects of the disease on their daily lives (15-22), and satisfaction with care (23-24). All analyses were performed on recoded items; the higher the score, the more favorable the health performance. Independent researchers collected clinical data, such as age, BMI, the duration of the disease and dialysis therapy, the cause of renal insufficiency, and comorbidities. They also gathered records concerning weekly dialysis time, the administration of erythropoietin preparations (EPO), cinacalcet (Mimpara), and iron. Finally, the input included laboratory test results concerning the concentration of hemoglobin (Hb), urea before and after hemodialysis, potassium, calcium, phosphates, CRP, PTH, cholesterol, triglycerides, total protein, and albumin, as well as the calculated indicators Kt/V and URR. The clinical, therapeutic, and laboratory data were compared with the questionnaire results expressed as indicators of self-reported physical health (PH), mental well-being (MWB), emotional functioning (EWB), social functioning (SF), perception of one's disease (PD), disease burden (DB), interactions with one's family and friends (IFF), perceived social support (PSS), and dialysis staff encouragement (DSE). These indicators were developed on the basis of the original subscales of the KDQOL-SF™ [26]. However, in the present study the subscales were rearranged into a different set of configurations (scales) to make sure that the resulting indicators would better reflect the functioning of individuals with the frailty syndrome. Statistical analysis was carried out using IBM SPSS ver. 22 software (Student's *t*-test and Pearson's correlation). The adopted significance level was $p<0.05$. Results for which $0.05<p<0.1$ were regarded as close to statistical significance.

Results

The mean patient age was 60 years (23-87). The mean duration of renal disease prior to the initiation of dialysis therapy was 13 years (1-28). The patients had been dialyzed for an average of 6 years (1-22). The mean weakly dialysis time was 13.58 h (11-24 h) (Tab. I).

The main causes of renal disease were: chronic glomerulonephritis (31.1%), with the most common type being IgA nephropathy (10.3% of all causes), autosomal dominant polycystic kidney disease (ADPKD) (12.8%), diabetic nephropathy (12.8%), interstitial nephritis (10.3%), renal cell carcinoma (5.1%), vesicoureteral reflux (2.6%), and others – unknown (15.3%). Major comorbidities included hypertension (73.8%), diabetes (35.7%), cardiovascular complications (28.6%), such as a history of heart infarction (14.3%), atrial fibrillation (9.5%), and cerebral stroke (4.8%), as well as cancer (14.3%). As compared to men, women were younger ($p=0.061$), had a shorter dialysis time per week ($p=0.039$), were less frequently given EPO ($p=0.035$), exhibited higher total cholesterol levels ($p=0.003$), revealed lower BMI ($p=0.071$), smaller comorbidity ($p=0.096$), lower urea concentration after HD ($p=0.078$), and lower phosphate levels ($p=0.095$). The results are given in Table II. The other parameters did not differ significantly between males and females. In the questionnaire survey, the patients could score between 89 and 174 points (the mean score was 129.51; SD 25.809; median 128). Patients who scored below the median (<128) were deemed at a higher risk of frailty. Among all parameters evaluated by means of the questionnaire, the patients had the highest opinion of their social and emotional functioning, while most of them did not accept their disease, as indicated by the mean score on perception of the disease ($p=0.001$). Interestingly, the degree of dialysis staff encouragement did not significantly affect the patients' perceptions ($p=0.926$). Women were more accepting of their disease than men ($p=0.039$), less bothered by it ($p=0.042$), and also reported better physical and mental health ($p=0.092$). Patients with the lowest scores on the KDQOL-SF™ and on its component scales (frail individuals) revealed a lower potassium concentration before HD ($p=0.031$), as well as lower levels of albumin ($p=0.008$) and total protein ($p=0.035$), which may be considered an indicator of poor nutritional status, translating into worse physical, mental, and emotional health. They also exhibited a higher concentration of urea after HD ($p=0.014$). Frail patients were found to have lower PTH ($p=0.018$) and they were more frequently given cinacalcet ($p=0.049$). These results are shown in Table III.

More differences emerged when the data were analyzed by sex. Males at a high risk of frailty additionally exhibited lower levels of hemoglobin ($p<0.05$), which in particular translated into worse physical health ($p=0.006$), mental well-being ($p=0.02$), and emotional functioning ($p=0.042$). They were also more bothered by the burden

Table I
Clinical data.
Dane kliniczne.

	N	Min	Max	Mean
Age	42	23	87	57.5
BMI	21	16.43	31.16	24.43
Disease duration [year]	38	1	28	13.03
Dialysis therapy duration [year]	39	1	22	5.97
Weekly dialysis time [h]	37	11	24	13.58
Comorbidity	37	1	6	2.24

Table II
Selected parameters for male and female patients.
Wybrane parametry dla mężczyzn i kobiet.

	Men	Women	*p*
Age	60.1±15	50.8±11	0.061
BMI	25.3±2.9	22.2±4.4	0.071
Weekly dialysis time [h]	14±2.3	12.5±0.9	0.039
Comorbidity	2.5±1.4	1.6±1.2	0.096
Urea before HD	138.2±28.9	124.18±30.9	0.180
Urea after HD	43.1±11.9	33.8±13.7	0.038
URR	69.6±6	70.6±8.4	0.658
Kt/V	1.43±0.2	1.46±0.36	0.717
Total protein	6.67±0.5	6.56±0.95	0.550
Albumin	3.86±0.3	3.72±0.51	0.328
Hb	11.0±1.2	10.5±0.92	0.239
Fe	65.7±34.7	63.6±25.2	0.853
Total cholesterol	152.8±47.1	203.4±35.6	0.003
TG	191.0±170.1	176.3±55.6	0.782
Calcium	8.8±0.7	9.2±1.1	0.151
Phosphates	5.5±1.7	4.4±1.8	0.095
PTH	508.7±324.7	550.6±389.8	0.736
EPO	1.7	1.3	0.038

Table III
Results for all patients.
Wyniki dla wszystkich pacjentów.

		KDQOL-SF	PH	MWB	EF	PD	DB	PSS
Urea before HD	**Pearson's correlation**	ns	ns	ns	ns	ns	ns	ns
	p	ns	ns	ns	ns	ns	ns	ns
Urea after HD	**Pearson's correlation**	-0.518	ns	ns	ns	-0.404	ns	-0.377
	p	0.014	ns	ns	ns	0.009	ns	0.015
Kt/V	**Pearson's correlation**	ns	ns	ns	ns	ns	ns	ns
	p	ns	ns	ns	ns	ns	ns	ns
URR	**Pearson's correlation**	ns	ns	ns	ns	ns	ns	ns
	p	ns	ns	ns	ns	ns	ns	ns
Potassium	**Pearson's correlation**	0.645	0.375	0.364	0.473	ns	ns	ns
	p	0.031	0.017	0.027	0.003	ns	ns	ns
Protein	**Pearson's correlation**	ns	0.338	ns	ns	ns	ns	ns
	p	ns	0.041	ns	ns	ns	ns	ns
Albumin	**Pearson's correlation**	0.016	0.474	0.402	0.397	ns	ns	ns
	p	0.008	0.005	0.025	0.018	ns	ns	ns
PTH	**Pearson's correlation**	ns	0.392	ns	ns	ns	ns	ns
	p	ns	0.018	ns	ns	ns	ns	ns
EPO	**Pearson's correlation**	ns	ns	ns	ns	ns	ns	0.362
	p	ns	ns	ns	ns	ns	ns	0.049

KDQOL-SF – total score in Kidney Disease Quality of Life questionnaire; PH – physical health; MWB – mental well-being; EF – emotional functioning; PD – perception of one's disease; DB – disease burden; PSS – perceived social support

Table IV
Results for men.
Wyniki *w grupie* mężczyzn.

		KDQOL-SF	PH	MWB	EF	PD	DB	PSS
BMI	**Pearson's correlation**	ns	ns	-0.657	ns	ns	ns	ns
	p	ns	ns	**0.015**	ns	ns	ns	ns
Urea before HD	**Pearson's correlation**	ns	ns	ns	ns	ns	-0.453	ns
	p	ns	ns	ns	ns	ns	**0.026**	ns
Urea after HD	**Pearson's correlation**	-0.596	-0.394	ns	ns	-0.414	-0.408	ns
	p	0.019	0.038	ns	ns	0.026	**0.039**	ns
Kt/V	**Pearson's correlation**	ns	ns	ns	ns	ns	ns	ns
	p	ns	ns	ns	ns	ns	ns	ns
URR	**Pearson's correlation**	ns	ns	ns	ns	ns	ns	ns
	p	ns	ns	ns	ns	ns	ns	ns
Potassium	**Pearson's correlation**	ns	0.529	0.478	0.636	ns	ns	ns
	p	ns	**0.003**	**0.016**	**0.001**	ns	ns	ns
Protein	**Pearson's correlation**	ns	ns	ns	ns	ns	ns	ns
	p	ns	ns	ns	ns	ns	ns	ns
Albumin	**Pearson's correlation**	0.409	0.5	ns	ns	ns	ns	ns
	p	**0.047**	**0.025**	ns	ns	ns	ns	ns
Hb	**Pearson's correlation**	ns	0.5	0.464	0.409	ns	0.46	ns
	p	ns	**0.006**	**0.02**	**0.042**	ns	**0.016**	ns
EPO	**Pearson's correlation**	0.773	ns	ns	ns	ns	ns	0.362
	p	**0.009**	ns	ns	ns	ns	ns	**0.049**
TG	**Pearson's correlation**	ns	ns	ns	ns	ns	-0.405	ns
	p	ns	ns	ns	ns	ns	0.04	ns
Sleep quality	**Pearson's correlation**	ns	0.451	0.574	0.555	ns	0.375	ns
	p	ns	**0.016**	**0.003**	**0.002**	ns	**0.045**	ns

KDQOL-SF – total score in Kidney Disease Quality of Life questionnaire; PH – physical health; MWB – mental well-being; EF – emotional functioning; PD – perception of one's disease; DB – disease burden; PSS – perceived social support

Table V
Results for women.
Wyniki w grupie kobiet.

		KDQOL-SF	PH	MWB	SF	PD	DB
Age	**Pearson's correlation**	ns	ns	ns	ns	0.747	ns
	p	ns	ns	ns	ns	0.005	ns
Weekly dialysis time [h]	**Pearson's correlation**	ns	ns	ns	-0.628	ns	ns
	p	ns	ns	ns	0.038	ns	ns
Urea before HD	**Pearson's correlation**	-0.798	ns	ns	ns	ns	-0.634
	p	0.031	ns	ns	ns	ns	0.049
Urea after HD	**Pearson's correlation**	ns	ns	ns	ns	ns	ns
	p	ns	ns	ns	ns	ns	ns
Kt/V	**Pearson's correlation**	ns	ns	ns	ns	ns	ns
	p	ns	ns	ns	ns	ns	ns
URR	**Pearson's correlation**	ns	ns	ns	ns	ns	ns
	p	ns	ns	ns	ns	ns	ns
Potassium	**Pearson's correlation**	0.375	ns	ns	ns	ns	ns
	p	0.017	ns	ns	ns	ns	ns
Protein	**Pearson's correlation**	ns	0.854	0.692	ns	ns	ns
	p	ns	0.029	0.013	ns	ns	ns
Albumin	**Pearson's correlation**	ns	0.663	ns	ns	ns	ns
	p	ns	0.037	ns	ns	ns	ns
CRP	**Pearson's correlation**	-0.921	ns	ns	ns	ns	ns
	p	0.009	ns	ns	ns	ns	ns
PTH	**Pearson's correlation**	ns	0.784	0.65	ns	ns	ns
	p	ns	0.007	0.03	ns	ns	ns

KDQOL-SF – total score in Kidney Disease Quality of Life questionnaire; PH – physical health; MWB - mental well-being; SF – social functioning; PD - perception of one's disease; DB - disease burden

of their renal disease and dialysis therapy (p=0.016). They were given EPO less frequently (p=0.009). In addition, their sleep quality was lower, which adversely affected their physical health and mental well-being (p=0.016 and p=0.003, respectively), emotional functioning (p=0.002), as well as perceived burden of the disease (p=0.045) (see Table IV).

On the other hand, frail women (low KDQOL-SF™ scores) revealed high CRP levels (p=0.009), which may be attributable to generalized inflammation induced by chronic renal disease. They were subjected to a longer dialysis time per week, which adversely affected their social functioning (p=0.038). As compared to men, women were less bothered by the burden of their renal disease, being more accepting of the illness and its treatment. In particular, older women exhibited better emotional coping with the effects of their chronic kidney disease and dialysis therapy (p=0.005). They accepted their illness and its consequences. These results are shown in Table V.

Discussion

The frailty syndrome is a relatively new concept which is still in the process of being elucidated. Despite the fact that in recent years considerable advances have been made in the understanding of the pathogenesis of frailty, it still lacks a broadly accepted definition and clear diagnostic methods, reference criteria, or measures which would enable reliable estimation of its prevalence [4,23,27]. The present study used the Kidney Disease Quality of Life™–Short Form questionnaire developed by the RAND organization in collaboration with the University of Arizona to evaluate dialyzed patients. While it was not designed for the diagnosis of frailty, it comprehensively examines patient functioning, enabling in-depth assessment of factors affecting quality of life, and as such it can be used to identify aspects indicative of frailty.

Existing research has shown that patients with chronic renal disease are up to three times as likely to develop the frailty syndrome as individuals with normal kidney function [17,19]. Shlipak et al. identified a strong correlation between chronic kidney disease and frailty in older participants of the "Cardiovascular Health Study" [17]. In turn, in the study of Johansen et al., two thirds of the 2275 dialyzed adults met the criteria of frailty [20]. Even though the prevalence of the syndrome increased with age, the younger population also exhibited frailty; it was diagnosed in as many as 44% dialyzed patients under 40. Moreover, hemodialyzed patients were more susceptible to frailty than those receiving peritoneal dialysis [20]. Wilhelm-Leen et al. reported that the frailty syndrome was widespread not only among patients with end-stage renal disease, but also in patients in early or mild stages of chronic kidney disease its prevalence was twice as high as in healthy controls [22]. Moreover, according to the current state of knowledge, frail patients with chronic kidney disease are at a higher risk of hospitalization and mortality [17,20,22].

However, none of the above works concerning renal diseases examined correlations between laboratory data and the occurrence of the frailty syndrome. Such studies conducted for geriatric and cardiac patients [11,14,28] have revealed that frailty is associated with low total protein and hemoglobin levels, malnutrition, as well as high CRP, which is in agreement with the present work. The fact that our findings are consistent with results from other diagnostic tools proves that the questionnaire applied in this study is useful for diagnosing frailty.

Frail patients are characterized by: atypical symptoms, disproportionate loss of independence (as compared to the severity of their disease), early and serious consequences of their illness, as well as a slow and incomplete recovery [4]. This leads to disability, impaired independence, and the need for long-term care [3]. Therefore, diagnosis of the frailty syndrome in elderly and chronic patients is so critical, especially that some methods for the prevention and treatment of frailty have been proposed, these include avoidance of polypharmacy [29,30], increased physical activity to counteract muscle weakness [21,31,32], appropriate nutrition [21,33], and vitamin D supplementation [34].

Conclusions

The KDQOL-SF™ instrument was found to be a useful tool for identifying hemodialyzed patients with frailty syndrome, who are at a higher risk of mortality. This is true both of the questionnaire as a whole and of the reconfigured indicators used here. The study identified the parameters which are significant for diagnosing frailty in dialyzed patients and which can be subsequently used to develop a screening test. The critical indicators include low concentrations of albumin, total protein, and potassium, and elevated levels of acute-phase proteins. The most sensitive parameter is albumin concentration, which is an indicator of malnutrition and inflammatory reaction.

The study has also revealed intercorrelations between somatic and psychosocial parameters, which may suggest that conscious efforts to enhance one aspect may to a degree compensate for a deficit in the other. Indeed, frail patients require both adequate medical interventions and greater psychosocial support from family or community members and medical personnel. Moreover, the identified differences between men and women in the somatic and psychological aspects of the disease burden indicate the need to adjust therapy depending on the patient's gender. However, this observation requires further study on larger groups of patients.

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