

Nontraditional factors influencing the quality of life of hemodialysis patients

Diana-Cristina Varela¹, Mayra Guarín-Parra², Natalia-Andrea Hincapié³,
Sandra-Patricia Hincapié³, Konniev Rodríguez⁴

1 Department of Clinical Research, Dially-Ser, Bogotá, Colombia

2 Department of Statistics, National University of Colombia, Bogotá, Colombia

3 End-of-Life Care Units, University of Buenaventura, Medellín, Colombia

4 Department of Nephrology, Dially-Ser, Bogotá, Colombia

Abstract

Introduction: The prevalence of CKD patients in advanced stages with dialysis requirement continues to grow. A goal for the medical team, the patient and their caregivers is to provide a treatment that offers an impact on the prognosis and quality of life (QOL).

Methods: In 100 patients with CKD on hemodialysis, randomized assigned, the quality of life by SF-36 was assessed, it was evaluated the functional capacity using the Karnofsky, ability to perform basic tasks of daily life through the index Barthel, presence of depression using the Beck test, family functioning through family APGAR, cognitive state through Minimental and presence of comorbidities using the Charlson index correlated with the sum of physical components (PCS) and mental components (MCS) of the SF-36 in patients in two renal units in Medellín and Bogotá, Colombia.

Results: A decrease in QOL in the physical components (PCS) Mental components (MCS) regarding the general population. A significant correlation between low PCS and diabetes mellitus (-16 p=0.008 95% CI 2.49) was found. Low MCS showed relation with PTH (p=0.046 95% CI 0.000-0.014), Karnofsky index (p=0.034 95% CI 0.244 to 5.984) and Beck depression test (p=0.000 95% CI -13.606 to 6.253).

Conclusions: The QOL of hemodialysis patients is affected with more impact on PCS, there is significant relationship between MCS with functional status and depression. To improve QOL in hemodialysis patients, non traditionally-measured variables should be measured and monitored and the therapeutic focus should be optimized addressed to physical rehabilitation, nutritional, functional and psychological state.

Key words: Chronic kidney disease, hemodialysis, quality of life.

Factores no tradicionales influyentes en la calidad de vida de los pacientes de hemodiálisis

Resumen

Introducción: La prevalencia de pacientes con enfermedad renal crónica (ERC) en fases avanzadas, con requerimiento de diálisis, continúa creciendo. Una meta para el equipo tratante, el paciente y sus cuidadores es lograr un tratamiento que brinde un impacto en el pronóstico y en la calidad de vida (CV).

Metodología: En 100 pacientes con ERC en hemodiálisis, asignados en forma aleatoria, se evaluó la calidad de vida por medio del SF-36, se evaluó: capacidad funcional por medio del Karnofsky, capacidad de realizar las labores básicas de la vida diaria por medio del índice de Barthel, presencia de depresión por medio del test de Beck, funcionalidad familiar por medio del APGAR familiar, estado cognoscitivo por medio del Minimental y presencia de comorbilidades por medio del índice de Charlson correlacionado con la sumatoria de componentes físicos (PCS) y mentales (MCS) del SF-36, en pacientes pertenecientes a 2 unidades renales en Medellín y Bogotá, Colombia.

Resultados: Se encontró una disminución de la CV en los componentes físicos (PCS) y mental (MCS) respecto a la población general. Se encontró una correlación significativa entre PCS bajo y diabetes mellitus ($p=0,008$ IC95% 2,49-16). MCS bajo presentó relación con PTH ($p=0,046$ IC95%: 0,000-0,014), el índice de Karnofsky ($p=0,034$ IC95% 0,244-5,984) y el test de depresión de Beck ($p=0,000$ IC95% -13,606- -6,253).

Conclusiones: La CV de los pacientes en hemodiálisis se encuentra afectada con mayor impacto en PCS, existe relación significativa entre el MCS con estado funcional y depresión. Para mejorar la CV del paciente en hemodiálisis, se debe medir y hacer el seguimiento a variables no tradicionalmente medidas y optimizar el enfoque terapéutico dirigido a rehabilitación física, estado nutricional, funcional y psicológico.

Palabras clave: Enfermedad renal crónica, hemodiálisis, calidad de vida.

Introduction

According to the World Health Organization (WHO), 60% of all deaths in the world are caused by chronic diseases, 80% of these deaths occur in low- and middle-income countries, including Colombia.

The number of people with chronic kidney disease (CKD) has been steadily increasing in recent years. The annual USRDS 2013 data report that 112,788 patients received renal replacement therapy (RRT), an adjusted incidence rate of 357 per million; The prevalence of dialysis therapy was 395,656 people during the year 2011¹. It is evident that disease rates vary substantially according to race and ethnicity. Colombia has a prevalence of 621 patients per million (ppm) and 22,300 patients on dialysis therapy; and the incidence rate was 81.7 ppm in 2012².

Studies have shown that CKD is associated with increased mortality and morbidity, especially increasing the risk for cardiovascular disease³. Quality of life (QOL or CV) is an important indicator of health care, patient experience and the assessment of efficacy in various chronic diseases. Evaluation of quality of life becomes a mandatory measure in the evaluation of results and the efficacy of treatment in patients with various diseases, such as end-stage renal disease⁴⁻⁶. In patients with CKD, quality of life not only provides important information in daily life, but also perceptions of functional status^{7,8}. Quality of life in patients with CKD has repeatedly a low score compared to that of the general population⁹⁻¹¹.

Among the traditional factors known to influence the quality of life of hemodialysis patients are demo-

graphic factors such as age, gender, socioeconomic level, religion, spirituality, proximity to the dialysis site and family support^{12,13}; among the clinical factors are: anemia¹⁴⁻¹⁷, hypoalbuminemia, catheter use, alteration of parathyroid hormone and serum phosphorus¹⁸ and the presence of comorbidities such as diabetes, arterial hypertension and depression¹⁹⁻²¹.

Subjects and methods

Patients

In this study were included 100 patients belonging to 2 kidney units located in Medellín and Bogotá, Colombia. These patients had been in the hemodialysis program at the institution for more than 3 months. The informed consent was signed after receiving verbal and written information about the study, and was endorsed by the institution's ethics committee.

The study involved 100 patients (41 women and 59 men) over 18 years of age. A data collection document was made, which included socio-demographic and clinical aspects such as: age, sex, marital status, educational level, occupation, vascular access, BMI, and comorbidities; laboratory data such as hemoglobin, albumin, potassium, calcium, phosphorus, glucose and parathyroid hormone PTH were obtained.

Instruments

Subjects' quality of life (QOL) was assessed using the Medical Outcome Study 36 Item Short-form-survey (SF-36), which is a generic instrument for

measuring quality of life. It includes 8 subscales: physical function, limitation for physical health, limitation for emotional health, mental health, social functioning, body pain, vitality and general health. All subscales are in the range of 0 to 100, the higher the value, the greater the health perception, the SF-36 is validated in Spanish²²⁻²⁷. In addition, there are summation measures of the physical and mental component (PCS and MCS).

The functional ability to perform daily tasks was measured with the Karnofsky index. Karnofsky's performance scales range from 0 to 100. A higher score has a better ability to perform everyday activities. It can be used to determine a patient's prognosis, measure the patient's changes to work; is an independent predictor of mortality²⁸.

The ability to perform the basic tasks of daily living was assessed using the Barthel Index. The Barthel scale is a functional assessment scale, assesses dependency or independence for 10 activities of daily living such as: eating, bathing, dressing, grooming, bowel movements, urination, toileting, transfer chair/bed, walking, stairs and assigns a score of 0-5-10-15, depending on the time taken for its realization and the need to carry it out obtaining a final score of 0-100. The maximum independence score is 100 and the maximum dependency is 0; the changes occur 5 out of 5, it is not a continuous scale²⁹.

Beck Depression Test is a questionnaire of 21 multiple-choice questions, measures the severity of depression, is composed of items related to depressive symptoms, such as hopelessness and irritability, cognitions such as guilt or feelings of being punished, as well as symptoms Related to depression³⁰.

Charlson's comorbidity index is a system of evaluation of life expectancy at 10 years, depending on the age at which it is evaluated and the subject's comorbidities. In addition to age, it consists of 19 items, which, if present, have been shown to have a concrete influence on the life expectancy of the subject. Initially adapted to assess survival at one year, it was finally adapted to its final form for survival at 10 years. It has been used for many other purposes, including costing because of the suffering of a chronic illness in primary care patients³¹.

Folstein's Mini Mental State Examination (MMSE) provides a brief and standardized mental state analysis. The 35-point version explores 5 cognitive areas: orientation, fixation, concentration and calculation, memory and language³².

The family functionality was evaluated through APGAR (Appearance, Pulse, Gesticulation, Activity and Breath) familiar, which is an instrument that shows how family members perceive the level of functioning of the family unit globally, scores suggest a very functional family, a moderately dysfunctional family or a family with severe dysfunction^{33,34}.

To guarantee standardized conditions, the questionnaires were administered during the hemodialysis session and the participants answered the questionnaire under the assistance of a trained psychologist. All 100 subjects completed the questionnaires completely.

Statistical analysis

The statistical analysis was structured in 4 phases, starting with a univariate descriptive analysis of the variables of interest observed in the group of 100 patients, after which the normality test of the continuous variables was performed, in order to determine the test of Correlation to be implemented in accordance with the assumptions it fulfilled. Following this process, we calculated the correlation of the continuous variables, if these, in the normality test, did not have a normal distribution, the Spearman correlation test was implemented, in the case where they complied with this distribution; we used the Pearson's correlation test.

The performance of the correlation tests allowed to select the variables for the linear regression model that was proposed at the end of the analysis, if there were co-linear or correlated variables, those that contributed more information to the model were selected and the others were excluded, at the end of the process, a multiple linear regression model that considered categorical and continuous variables within the regressor was raised, and allowed to calculate or estimate the value of the variables of interest (PCS and MCS).

Results

One hundred patients were analyzed, 50 belonged to one renal unit in Medellín and the other 50 belonged to one renal unit in Bogotá, Colombia.

The gender distribution was 41% female and 59% male, the average age was: 57 ± 1.8 years. The clinical variables are expressed in Table 1.

Regarding the presence of comorbidities, 53% of the patients were on hemodialysis due to diabetic nephropathy and 47% had another pathology precursor of renal damage; the minimum Charlson index for the population was 2 (14%) because of their hemodialysis condition, the maximum score was 9 (1%), the Charlson index in the total population was 4 (78%).

The distribution for each item of the applied tests is expressed in table 2.

The quality of life measured by the SF-36 showed a decrease in all items with respect to the general population, a more marked decrease in the sum of the physical components with respect to the sum of the mental components was found (Table 3).

In the model for PCS, the variable that best represents to explain the low PCS is suffering from diabetes mellitus ($p=0.008$ IC95% 2.49-16), which explained the low PCS in 43.5%.

In the model for MCS, the variables that best explained a low MCS were PTH ($p=0.046$ 95% CI: 0.000-0.014), the Karnofsky index ($p=0.034$ 95% CI 0.244, 5.984) and the Beck depression test ($P=0.000$ CI 95% -13,606-6,253), which indicates that the proposed model explained the low MCS score in 64.6%.

Discussion

For medicine in the XXI century, the traditionalist approach to alleviate or mitigate the disease should not only achieve the benefit of improving the prognosis, but also, to improve the quality of life, thus achieving a treatment that provides years of useful life for the patient.

Table 1

Clinical characteristics of the population		
Clinical variable	Average	IC 95%
KTV	1.96	[1.39; 2.52]
Hemoglobin	11.61	[11.20; 12.01]
Albumin	5,41	[2,93; 7,89]
Potassium	4.90	[4.73; 5.06]
Calcium	8.71	[8.51; 8.92]
Phosphorus	5.39	[4.99; 5.80]
PTH	610,55	[507.1; 713.9]
BMI	24.29	[23.37; 25.22]

Hemodialysis patients in different studies have a lower quality of life than the general¹⁹⁻¹¹ population, which may not improve significantly after initiating dialysis.

Interdisciplinary teams in charge of patients with chronic kidney disease should address early on the risk factors known as traditional, to provide the patient with adequate nutritional status, early construction of arteriovenous fistula, proper management of anemia, training and education to the patient and the family, among others.

Quality of life was analyzed in both the physical component and the mental component. The physical component comprised by the subscales: physical function, social role, body pain and limitation by physical problems, which make up the sum of the physical component (PCS), in this aspect diabetes mellitus was found as the most important aspect that deteriorates the Quality of life of patients receiving hemodialysis.

Diabetes mellitus is a precursor of macro and micro-vascular damage that leads not only to the loss of renal function but also is a significant cause of visual limitation, neuropathy and amputations, so diabetes mellitus has a negative impact on the quality of life of The patients and increase the mortality with respect to the population of hemodialysis^{19,35,36}.

Table 2	
Distribution of the Population in the tests applied. KARNOSFKY	
KARNOSFKY	
1. Invalid, in bed more than 50%	1,0%
2. Great care, in bed less than 50%	8,0%
3. Requires occasional attention	6,0%
4. Is able to take care of himself but not to work	2,0%
5. Perform normal activities with effort	6,0%
6. Normal activities with mild symptoms	24,0%
7. Normalç	53,0%
BARTHEL	
1. Total dependant	3,0%
2. Serious dependant	1,0%
3. Moderate dependant	3,0%
4. Light dependant	28,0%
5. Independent	65,0%
BECK	
1. Normal	67,0%
2. Slight disturbance	17,0%
3. Intermittent depression	7,0%
4. Moderate depression	7,0%
5. Severe depression	2,0%
MINIMENTAL	
1. Terminal phase	2,0%
2. Dementia	1,0%
3. Impairment of cognitive ability	10,0%
4. Pathological suspicion	7,0%
5. Normal	80,0%
APGAR Familiar	
1. Severely dysfunctional	3,0%
2. Moderately functional	12,0%
3. Highly Functional	85,0%

Table 3	
SF-36 scores for each item and physical and mental summations	
Physical function	38,8±13,76
Limitation due to physical problems	38,7±13
Body ache	48,4±14
Functioning or social role	50,5±9,7
Mental health	48,9±14,8
Emotional problems	46,36±13,8
Vitality	50,9±12,4
Perception of general health	45,9±10,5
PCS	38,3±12,2
MCS	53,4±13,7

As for the mental component, the subscales: vitality, perception, mental health and emotional problems make up the sum of the mental component (MCS). In this aspect, the relationship between the parathyroid hormone and the functional capacity of daily tasks measured with the Karnofsky's index and the presence of depression evaluated with the Beck test were found to be the most relevant aspects that influence this component.

The PTH parathyroid hormone is involved in the metabolism of calcium and phosphorus, bone mineral regulation disorder has a negative impact on the quality of life, previously described, in incident hemodialysis patients¹⁸ because of a greater propensity to suffer fractures due to bone disease and a higher incidence of events Associated with extra-skeletal qualification.

Karnofsky's index has been described as a scale that impacts on mortality in the hemodialysis population, describing a one-year mortality rate of 68% in patients with Karnofsky's index below 40³⁶. High scores on this scale have been related to a good quality of life in hemodialysis^{37,38}.

The Beck test is an instrument created to measure depression. The presence of depression is described as a factor that negatively impacts the quality of life and has been reported in up to 41.7% of hemodialy-

sis patients³⁹. In this study a prevalence of 33% was found.

For the integrated model of care, clinical decisions should focus primarily on the priorities and preferences of the individual patient, and the treatment focuses on influencing modifiable factors that prevent the patient from enjoying health and survival is only one of the objectives of the attention⁴⁰.

The issue of the quality of life of the patient on dialysis must be placed in a context of humanization, as an ethical imperative of care, so that decisions are made regarding their dignity as a human being and taking into account their perception of quality of life, particularly in those patients with high comorbidity, low functional status or compromised brain function.

The interdisciplinary teams responsible for the management of these patients should pay greater attention to variables not usually considered in the therapeutic plan, but not less real, such as quality of life, emotional condition, pain, suffering, the caregiver's

burden or the indirect and intangible costs associated with dialysis.

We have the challenge of going beyond biological clinical indicators and transcending the other components of health, such as the patient's psychological, spiritual and social well-being. In other words, make the patient's care on dialysis an art with a moral component of equal value to the scientist.

In conclusion, functional and depression scales should be included as routine measures in hemodialysis patients, as a measure of the quality of life of this population, it is important a multidisciplinary approach which should include physical rehabilitation, since this is the aspect which has the greatest impact on the quality of life of this group and is the one that less intervention and interdisciplinary management routinely has in the renal units.

Interest conflict

The authors declare no conflict of interest

Bibliographic references

1. U.S. Renal Data System, USRDS 2013 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2013.
2. Gómez RA. Renal disease in Colombia. *Ren Fail.* 2006;28(8):643-7.
3. Weiner DE, Tighiouart H, Amin MG et al. Chronic kidney disease as a risk factor for cardiovascular disease and all-cause mortality: a pooled analysis of community-based studies. *J Am SocNephrol* 2004;15:1307-1315.
4. Kalantar-Zadeh K, Kopple JD, Block G et al. Association among SF36 quality of life measures and nutrition, hospitalization, and mortality in hemodialysis. *J Am SocNephrol* 2001;12:2797-2806.
5. Lopes AA, Bragg-Gresham JL, Satayathum S et al. Health-related quality of life and associated outcomes among hemodialysis patients of different ethnicities in the United States: the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis* 2003;41:605-615.
6. Lowrie EG, Curtin RB, LePain N et al. Medical outcomes study short form-36: a consistent and powerful predictor of morbidity and mortality in dialysis patients. *Am J Kidney Dis* 2003;41:1286-1292.
7. Unruh M, Benz R, Greene T et al. Effects of hemodialysis dose and membrane flux on health-related quality of life in the HEMO Study. *Kidney Int* 2004;66:355-366.
8. Kimmel PL, Emont SL, Newmann JM et al. ESRD patient quality of life: symptoms, spiritual beliefs, psychosocial factors, and ethnicity. *Am J Kidney Dis* 2003;42:713-721.

9. Kusek JW, Greene P, Wang SR et al. Cross-sectional study of health-related quality of life in African Americans with chronic renal insufficiency: the African American Study of Kidney Disease and Hypertension Trial. *Am J Kidney Dis* 2002;39:513-524.
10. Perlman RL, Finkelstein FO, Liu L et al. Quality of life in chronic kidney disease (CKD): a cross-sectional analysis in the Renal Research Institute-CKD study. *Am J Kidney Dis* 2005;45:658-666.
11. Tsai YC, Hung CC, Hwang SJ, et al. Quality of life predicts risks of end-stage renal disease and mortality in patients with chronic kidney disease. *Nephrol Dial Transplant*. 2010;25(5):1621-6.
12. Davison SN, Jhangri GS. The Relationship Between Spirituality, Psychosocial Adjustment to Illness, and Health-Related Quality of Life in Patients With Advanced Chronic Kidney Disease. *J Pain Symptom Manage*. 2012 Aug 20.
13. Davison SN, Jhangri GS. Existential and religious dimensions of spirituality and their relationship with health-related quality of life in chronic kidney disease. *Clin J Am Soc Nephrol*. 2010 Nov;5(11):1969-76.
14. Farag YM, Keithi-Reddy SR, Mittal BV, et al. Anemia, inflammation and health-related quality of life in chronic kidney disease patients. *Clin Nephrol*. 2011 Jun;75(6):524-33.
15. Clement FM, Klarenbach S, Tonelli M, et al. The impact of selecting a high hemoglobin target level on health-related quality of life for patients with chronic kidney disease: a systematic review and meta-analysis. *Arch Intern Med*. 2009 Jun 22;169(12):1104-12.
16. Finkelstein FO, Story K, Firaneck C, et al. Health-related quality of life and hemoglobin levels in chronic kidney disease patients. *Clin J Am Soc Nephrol*. 2009 Jan;4(1):33-8.
17. Covic A, Seica A, Gusbeth-Tatomir P, et al. Hemoglobin normalization trials in chronic kidney disease: what should we learn about quality of life as an end point? *J Nephrol*. 2008 Jul-Aug;21(4):478-84.
18. Johansen KL, Chertow GM. Chronic kidney disease mineral bone disorder and health-related quality of life among incident end-stage renal-disease patients. *J Ren Nutr*. 2007 Sep;17(5):305-13.
19. Mucsi I, Kovacs AZ, Molnar MZ, et al. Co-morbidity and quality of life in chronic kidney disease patients. *J Nephrol*. 2008 Mar-Apr;21 Suppl 13:S84-91.
20. Soni RK, Porter AC, Lash JP, et al. Health-related quality of life in hypertension, chronic kidney disease, and coexistent chronic health conditions. *Adv Chronic Kidney Dis*. 2010 Jul;17(4):17-26.
21. Porter A, Fischer MJ, Brooks D, et al. Quality of life and psychosocial factors in African Americans with hypertensive chronic kidney disease. *Transl Res*. 2012 Jan;159(1):4-11.
22. McHorney CA, Ware JE Jr, Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health construct. *Med Care*. 1993 Mar;31(3):247-63.
23. McHorney CA, Ware JE Jr, Lu JF, et al. The MOS 36-item Short Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. *Med Care*. 1994 Jan;32(1):40-66.
24. Vilagut G, Valderas JM, Ferrer M, et al. [Interpretation of SF-36 and SF-12 questionnaires in Spain: physical and mental components]. *Med Clin (Barc)*. 2008 May 24;130(19):726-35.
25. Alonso J, Prieto L, Anto JM. [The Spanish version of the SF-36 Health Survey (the SF-36 health questionnaire): an instrument for measuring clinical results]. *Med Clin (Barc)*. 1995 May 27;104(20):771-6.
26. Alonso J, Regidor E, Barrio G, et al. [Population reference values of the Spanish version of the Health Questionnaire SF-36]. *Med Clin (Barc)*. 1998 Oct 10;111(11):410-6.
27. Ayuso-Mateos JL, Lasa L, Vázquez-Barquero JL. [Internal and external validity of the Spanish version of SF-36]. *Med Clin (Barc)*. 1999 Jun 12;113(1):37.
28. Karnofsky DA, Abelman WH, Craver LF, Burchenal JH. The use of nitrogen mustards in the palliative treatment of cancer. *Cancer* 1948;1:634-6456.
29. Mahoney F, Barthel D. "Functional evaluation: the Barthel Index". *Md Med J* 1965;14:61-65.

30. Craven, J.L., Rodin, G.M., Littlefield, C. "The Beck Depression Inventory as a screening device for major depression in renal dialysis patients". *Int J Psychiatry Med* 1988;18(4):365-374.
31. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chron Dis*, 1987;40(5):373-383.
32. Folstein, M., Folstein, S.E., McHugh, P.R. "Mini-Mental State" a Practical Method for Grading the Cognitive State of Patients for the Clinician. *Journal of Psychiatric Research*, 1975;12(3);189-198.
33. Smilkstein G. The family APGAR: a proposal for a family function test and its use by physicians. *J FamPract* 1978;6:1231-9.
34. Bellon JA, Delgado A, Luna del Castillo JD, Lardelli P. Validez y fiabilidad del cuestionario de función familiar Apgar-familiar. *Aten Primaria* 1996;18(6):289-96.
35. Mandoorah QM, Shaheen FA, Mandoorah SM, et al. Impact of demographic and comorbid conditions on quality of life of hemodialysis patients: a cross-sectional study. *Saudi J Kidney Dis Transpl.* 2014 Mar;25(2):432-7.
36. Van Diepen M, Schroijen MA, Dekkers OM, et al. Predicting mortality in patients with diabetes starting dialysis. *PLoS One.* 2014 Mar;4;9(3):e89744.
37. Arogundade FA1, Zayed B, Daba M, Barsoum RS. Correlation between Karnofsky Performance Status Scale and Short-Form Health Survey in patients on maintenance hemodialysis. *J Natl Med Assoc.* 2004 Dec;96(12):1661-7.
38. Grincenkov FR1, Fernandes N, Chaoubah A. Factors associated with the quality of life of incident patients on PD in Brazil (BRAZPD). *J Bras Nefrol.* 2011 Mar;33(1):38-44.
39. Andrade CP, Cruz MC, Urrutia M, et al. Evaluation of depressive symptoms in patients with chronic renal failure. *J Nephrol.* 2010 Mar-Apr; 23(2):168-74.
40. Tinetti ME, Fried T. The end of the disease era. *Am J Med.* 2004 Feb 1;116(3):179-85.