Progression of chronic kidney disease: ambulatory experience in Santarém - Pará

Authors
Valmir José Crestani Filho[1]
Rodrigo Alexandre da Cunha Rodrigues[2]

[1] Pará State University.
[2] Brazilian Association of Nephrology. Pará State Secretary of Health. Pará State University.

Submitted on: 08/29/2012.
Approved on: 03/08/2013.

Correspondence to:
Valmir José Crestani Filho.
House of the Residents at HCFMUSP
Rua Dr. Ouvidio Pires de Campos, nº 171, apto 515, Cerqueira César, São Paulo, SP, Brazil. CEP: 05403-010.

DOI: 10.5935/0101-2800.20130017

Abstract

Introduction: Chronic kidney disease (CKD) is a growing public health problem. Nevertheless there is a little data about CKD in Brazil, mainly in its non-dialytic stages. **Objective:** To know about demographic, clinical and laboratory features of patients with CKD non-dialytic, and evaluate the impact of these variables on disease progression. **Methods:** A retrospective cohort study comprised of 65 adult patients with stages CKD 2-4, followed-up for 28.24 ± 13.3 months. **Results:** Mean age was 64.6 ± 12.6 years. The main causes of the CKD were diabetic kidney disease (DRD) (47.7%) and hypertensive nephrosclerosis (34.2%). Most patients were on stage 3 CKD (44.6%) and the minority reached therapeutic targets in control of their co-morbidities, 40% for arterial pressure and 38.7% for glycemic control. The mean annual loss of glomerular filtration rate (GFR) was 3.1 ± 7.3 mL/min/1; 73 m² (median 1.4 mL/min/1; 73 mL/min/1; 73 m²) 21.5% of patients developed progressive CKD. Diastolic blood pressure (DBP) ≥ 90 mmHg increased 2.7 times the risk of developing progressive CKD (95% CI 1.14 to 6.57; p = 0.0341) as well as systolic blood pressure (SBP) ≥ 160 mmHg (RR = 3.64, 95% CI 1.53 to 8.65; p = 0.0053) and proteinuria (RR = 4.05, 95% CI; 1.55 to 10.56; p = 0.0031). It was also observed higher SBP mean (p = 0.0359) and lower HDL-c median (p = 0.0047) in patients with CKD Progressive. **Conclusion:** In this study, hypertension and proteinuria were risk factors for evolution with progressive CKD, in spite of the difficult clinical control a minority of patients had the progressive form of CKD.

Keywords: disease progression; renal insufficiency; chronic, risk factors.

Introduction

Chronic kidney disease (CKD) has become a significant global public health issue. Its impact is felt in patient quality of life and life expectancy, and significantly affects health care expenditure. Estimates indicate that ten percent of the adult population in the USA has CKD, with incidence rates among the elderly ranging between 38% and 44%.[1,2] Very little data is available in Brazil on non-dialysis dependent CKD. However, a review on lab test results of adult Brazilian patients revealed that 2.3% of the subjects had GFR < 45 mL/min/1.73 m², the equivalent to an estimated 2.9 million Brazilians with CKD stages 3B and higher.[3] Following this trend, the number of patients on renal replacement therapy (RRT) in Brazil grew significantly in the last decade, from 42,000 patients in 2000 to over 92,091 in 2010, or 483 patients per million population (pmp). The figures are lower in Northern Brazil (265) and higher in the Brazilian Southeast (591), with hypertensive nephrosclerosis ranking first among the causes of CKD in patients on RRT, followed by diabetic nephropathy.[4]

Many factors have been correlated with CKD progression: uncontrolled systemic hypertension, proteinuria, use of nephrotoxic drugs, urinary tract obstruction, diabetes mellitus, vesicoureteral reflux, high protein diet, smoking, urinary tract infection, obesity, dyslipidemia, chronic anemia, metabolic acidosis, vitamin D deficiency, hyperphosphatemia, and active baseline disease.[5,6] The correction of hyperuricemia has been correlated by some authors with lesser drops in the GFR of patients with predialysis chronic kidney disease.[7,8]

Within the last decades the management of factors connected to CKD progression has been the cornerstone of conservative therapeutic approaches for pre-dialysis CKD patients.[6,9] In the realm of drug therapies, renin-angiotensin-aldosterone system (RAAS) inhibitors have been used effectively to hinder the progression of CKD.[10,11]

This study aimed to find the demographic, clinical, and lab test characteristics of patients with non-dialysis dependent CKD and the impact of these variables in disease progression.

Methods

Sixty-five patients submitted conservative treatment were enrolled in the study. They were 18 years and older and had CKD stages 2, 3A, 3B, and 4. The members of this retrospective cohort were followed for over a year, between June of 2006 and June of 2012 (mean of 28.24 ± 13.3 months) at the Nephrology Ward of the Low Amazon Teaching and Health Care Unit (UEASBA) maintained by the Pará State University (UEPA) in the municipality of Santarém. The service is run by a multidisciplinary team that provides patients with nutritional guidance, psychological advice, physical therapy, nursing care and the aid of social workers and physicians from other medical specialties when needed. As a routine, CKD patients on stage 2 are seen every four months by a nephrologist; stage 3 individuals are seen every quarter; and stage 4 patients are seen every two months.

All patients seen at the ward are tested for creatinine, glucose, and serum uric acid levels, in addition to undergoing simple urine testing and estimation of the glomerular filtration rate (GFR) as per the formula proposed by Cockcroft & Gault.[12] Glycated hemoglobin (for diabetic patients), total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides, and 24-hour urinary protein tests are run routinely and were considered in this study. The clinical variables considered were cause of CKD, use of renin-angiotensin-aldosterone system (RAAS) inhibitors [angiotensin-converting-enzyme (ACE) inhibitors and/or angiotensin II receptor blockers (ARBs)] and blood pressure. Age and gender were included as demographic variables.

Mean values were calculated for lab test results and blood pressure levels, and subjects were divided based on whether or not these parameters were controlled and if the comorbidities they had were adequately managed during follow-up as per the targets set in the main guidelines and trials. Patients under control had blood pressures < 140/90 mmHg;[13] glycemic control, fast glucose < 130 mg/dL (tolerable);[14] lipid control,[15] HDL-c ≥ 50 mg/dL for women and ≥ 40 mg/dL for men, LDL-c < 100 mg/dL, TGL < 150 mg/dL; uricemia control,[7] serum uric acid < 7.6 mg/dl. Levels of systemic hypertension were defined as per the categories described by the Brazilian Association of Cardiology (SBC).[16] Proteinuria was diagnosed in patients with sustained albuminuria > 300 mg/day without identified reversible cause.[9] Patients taking at least one RAAS inhibitor for at least six consecutive months were considered users of this drug class.

The clinical endpoint was progressive CKD as defined by the NICE[13] (annual decrease in GFR > 5 mL/min/1.73 m^2 or decrease greater than 10 mL/min/1.73 m^2 in five years) after at least one year of follow-up. This study was approved by the Research Ethics Committee of the Pará State University Campus XII - UEPA (permit nº 40/2012).

Study results were treated in Microsoft Excel® 2003 and analyzed using software package SPSS 15.0. Data descriptive analysis included absolute frequencies, relative frequencies, and measures of central tendency (means, medians, minimum and maximum values) and scatter (standard deviation). Inferential statistics was used to analyze the correlations and effects between qualitative variables based on relative risk. Student's t-test was used to analyze the mean values of quantitative variables. The Mann-Whitney test was used to analyze median values. Statistical calculation used levels of significance ≤ 0.05 (5%) to reject the null hypothesis, and a 95% confidence interval was adopted.

Results

The mean age of the 65 included patients was 64.6 (± 12.6) years. Sixty-seven percent of the enrolled individuals were 60 and older, and 59% were females. The main etiologies for CKD were diabetic nephropathy (47.7%), hypertensive nephrosclerosis (34.2%), and adult polycystic kidney disease (7.6%). Most patients (44.6%) had stage 3 disease at the time of hospitalization - 18.5% on IIIA and 26.1% on IIIB - and had a mean GFR of 40.8 ± 17.8 mL/min/1.73 m^2. Eighty-three percent of the patients had hypertension. Only 40% of them had mean blood pressure levels under control. Uncontrolled patients had very high levels of systolic blood pressure (161.6 ± 17.9

mmHg). Only 38.7% of the diabetic patients had fast glucose levels under control. Proteinuria was observed in 31% of the patients. Patients had a mean of 3.11 ± 0.93 comorbidities. Most (77%) were on RAAS inhibitors. Almost all patients had one type of dyslipidemia, most (73.8%) had more than one type of dyslipidemia, 40% had high cholesterol levels (LDL, HDL, TGL), and 28% had hyperuricemia. Progressive CKD was seen in 21.5% of the patients. The mean and median annual decrease in GFR was 3.1 ± 7.3 mL/min/1.73 m^2 and 1.43 mL/min/1.73 m^2 respectively (Table 1).

Univariate analysis revealed that mean systolic blood pressures were significantly higher in patients with progressive CKD (p = 0.0359). Median HDL-c levels were significantly lower in progressive CKD patients (p = 0.0047), as seen in Table 2.

Dichotomized variable analysis showed that diastolic blood pressures ≥ 90 mmHg increased by 2.7 times the risk for progressive CKD (95% CI; 1.14-6.57; p = 0.0341). Other risk factors were systolic hypertension ≥ stage 2 (RR = 3.64; 95% CI; 1.53-8.65; p = 0.0053) and proteinuria (RR = 4.05; 95% CI; 1.55-10.56; p = 0.0031) (Table 3).

Table 1 Clinical and demographic characteristics of the studied population

Female gender %	59%
Age in years at admission (mean ± SD)	64.6 ± 12.6
Elderly subjects (≥ 60 years) %	67%
Octogenarians and above (≥ 80 years) %	15.4%
CKD etiology	
- Diabetic nephropathy	47.7%
- Hypertensive nephrosclerosis	34.2%
- Adult polycystic kidney disease	7.6%
- Other	10.5%
GFR (mL/min/1.73m^2) at admission (mean ± SD)	40.8 ± 17.8
CKD stage at admission, %	
- 2	18.5%
- 3A	18.5%
- 3B	26.1%
- 4	36.9%
Patients on RAAS inhibitors, %	77%
Hypertensive patients %	83%
Hypertensive subjects with controlled mean levels of BP, %	40%
SBP (mean ± SD) in uncontrolled hypertensive patients, mmHg	161.6 ± 17.9
DBP (mean ± SD) in uncontrolled hypertensive patients, mmHg	96 ± 4.2
Patients with proteinuria, %	31%
Diabetic patients, %	49.2%
Diabetic patients with glucose levels under control %	38.7%
Glucose levels (mean ± SD) of patients with uncontrolled glucose levels, mg/dL	186.8 ± 34.57
HbA1C (mean ± SD) of patients with uncontrolled glucose levels, %	9.1% ± 1.2
Number of comorbidities, (mean ± SD; median)	3.11% ± 0.93; 3
Patients with dyslipidemia	96.9%
- Increased LDL-C	75.4%
- Decreased HDL-C	67.7%
- Hypertriglyceridemia	67.7%
Hyperuricemia	28%
Annual GFR decrease (mean ± SD), mL/min/1.73 m^2	3.1 ± 7.3

SD: Standard deviation; CKD: Chronic kidney disease; GFR: Glomerular filtration rate; RAAS: Renin-angiotensin-aldosterone system; BP: Blood pressure; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HbA1C: Glycated hemoglobin; LDL-C: Low-density lipoprotein; HDL-C: High-density lipoprotein; GFR: Glomerular filtration rate.

Table 2 Comparison between clinical and workup findings and outcomes

Variables	Chronic Kidney Disease				*p*-value
	Progressive		Non-progressive		
	Mean ± SD	Median	Mean ± SD	Median	
Age	65.36 ± 12.14	62	64.43 ± 12.93	65	0.8109*
Mean SBP, mmHg	156.50 ± 32.48	158.54	139.87 ± 20.77	139.09	0.0359**
Mean DBP, mmHg	82.95 ± 14.16	84.17	78.71 ± 10.86	77.73	0.2313*
Mean glucose level, mg/dl	118.87 ± 33.32	113.93	122.58 ± 50.81	99.33	0.7979*
HbA1C, mean %	8.51 ± 0.84	8.35	8.24 ± 1.60	8.30	0.6299*
Mean total cholesterol, mg/dl	208.15 ± 31.78	210.05	199.43 ± 36.69	197.20	0.4229*
Mean LDL-c, mg/dl	118.59 ± 27.89	125.67	122.31 ± 31.12	122.14	0.7003*
Mean HDL-c, mg/dl	40.98 ± 8.15	37.40	41.52 ± 7.21	41.05	0.0047**
Mean triglycerides, mg/dl	218.30 ± 128.43	182.65	192.86 ± 73.99	185.17	0.8455**
Mean uric acid, mg/dl	5.69 ± 1.27	5.83	5.80 ± 1.51	5.80	0.8021*

* Student's *t*-test; ** Mann-Whitney test; SD: Standard deviation; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HbA1C: Glycated hemoglobin; LDL-C: Low-density lipoprotein; HDL-C: High-density lipoprotein.

Table 3 Correlation between possible risk factors and outcomes

Variables	Chronic Kidney Disease		Total	RR	*p*-value
	Progressive n (%)	Non-progressive n (%)	n (%)	95% CI	
Gender (n = 65)					
Female	8 (57.1)	31 (60.8)	39 (60.0)	0.89	0.4754
Male	6 (42.9)	20 (39.2)	26 (40.0)	(0.35-2.26)	
Age (n = 65)					
< 60 years	5 (35.7)	16 (31.4)	21 (32.3)	1.16	0.4941
≥ 60 years	9 (64.3)	35 (68.6)	44 (67.7)	(0.44-3.05)	
Hypertension (n = 65)					
Yes	12 (85.7)	41 (80.4)	53 (81.5)	1.36	0.4738
No	2 (14.3)	10 (19.6)	12 (18.5)	(0.35-5.29)	
Diabetes (n = 65)					
Yes	10 (71.4)	22 (43.1)	32 (49.2)	2.58	0.0578
No	4 (28.6)	29 (56.9)	33 (50.8)	(0.90-7.39)	
Mean SBP ≥ 140 mmHg					
Yes	10 (71.4)	23 (45.1)	33 (50.8)	2.42	0.0744
No	4 (28.6)	28 (54.9)	32 (49.2)	(0.85-6.95)	
Mean DBP ≥ 90 mmHg					
Yes	6 (42.9)	8 (15.7)	14 (21.5)	2.73	0.0341
No	8 (57.1)	43 (84.3)	51 (78.5)	(1.14-6.57)	
Mean SBP ≥ 160 mmHg					
Yes	7 (50.0)	7 (13.7)	14 (21.5)	3.64	0.0053
No	7 (50.0)	44 (86.3)	51 (78.5)	(1.53-8.65)	
Glucose level (n = 65)					
Altered	9 (64.3)	18 (35.3)	27 (41.5)	2.53	0.0501
Normal	5 (35.7)	33 (64.7)	38 (58.5)	(0.95-6.72)	

Continued Table 3.

Total cholesterol (n = 64)					
Altered	9 (64.3)	23 (46.0)	32 (50.0)	1.80	0.1822
Normal	5 (35.7)	27 (54.0)	32 (50.0)	(0.68-4.78)	
Triglycerides (n = 64)					
Altered	10 (71.4)	35 (70.0)	45 (70.3)	1.06	0.4100
Normal	4 (28.6)	15 (30.0)	19 (29.7)	(0.38-2.95)	
LDL-c (n = 62)					
Altered	10 (76.9)	39 (79.6)	49 (79.0)	0.88	0.4313
Normal	3 (23.1)	10 (20.4)	13 (21.0)	(0.28-2.75)	
HDL-c (n = 61)					
Altered	9 (69.2)	35 (72.9)	44 (72.1)	0.87	0.4658
Normal	4 (30.8)	13 (27.1)	17 (27.9)	(0.31-2.45)	
Proteinuria (n = 65)					
Yes	9 (64.3)	11 (21.6)	20 (30.8)	4.05	0.0031
No	5 (35.7)	40 (78.4)	45 (69.2)	(1.55-10.56)	
Uric acid (n = 62)					
Altered	3 (23.1)	15 (30.6)	18 (29.0)	0.73	0.4253
Normal	10 (76.9)	34 (69.4)	44 (71.0)	(0.23-2.36)	
RAAS inhibitors (n = 65)					
On	10 (71.4)	40 (78.4)	50 (76.9)	0.75	0.4236
Off	4 (28.6)	11 (21.6)	15 (23.1)	(0.27-2.05)	

SD: Standard deviation; CKD: Chronic kidney disease; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; LDL-C: Low-density lipoprotein; HDL-C: High-density lipoprotein; RAAS: Renin-angiotensin-aldosterone system.

Discussion

A significant portion of the studied population was made up of elderly patients (64.6%), and the sample's mean age was 64.6 ± 12.6 years. The high number of comorbidities per subject (3.11 ± 0.93) was consistent with the literature,[17,18] in addition to being expected in cases of CKD.

The predominance of diabetic nephropathy in the etiology of CKD seen in this study was not reported in other Brazilian studies, but was consistent with the findings described in the CKD population in the USA[17] and agreed with the etiologies found in RRT patients treated in Santarém.[19]

Most of the patients in the sample (44.6%) were referred to a nephrologist when they had stage 3 CKD. This is a positive finding, as other studies carried out in Brazil indicated that most patients on RRT were referred to nephrology services only when they had stage 4 disease.[18,20,21]

The low rates of controlled systemic hypertension (40%) and glucose levels (38.7%) are preoccupying, once both are part of the goals of CKD treatment.[6] Batista *et al*. reported similar rates: 34.4% and 65% for controlled BP and glucose levels, respectively.[21] On the other hand, a significant number of patients was on RAAS inhibitors (77%). Another Brazilian retrospective study reported similar findings.[18] Batista *et al*. and Kausz *et al*. assessed the fact that only 65% of the patients enrolled in the study were on RAAS inhibitors as a negative finding.[21,22] These studies used different methods and cutoff points, but their authors showed how difficult it is to conservatively manage patients with chronic kidney disease and reach treatment goals.

Dichotomized analysis revealed that proteinuria, high levels of systolic blood pressure, and diastolic hypertension were risk factors for unfavorable renal outcome (progressive CKD) and worse disease evolution.[6]

The correlation observed in this study between proteinuria and renal disease progression has been reported by other authors.[23,24] Despite the benefits introduced by the use of RAAS inhibitors, many authors have described correlations between

proteinuria and death, and identified the use of these drugs as an independent risk factor for morbidity and cardiovascular death.[25-28] Pereira *et al*. reported correlations between higher levels of proteinuria at the time of admission in an outpatient service for CKD treatment with death and RRT.[18]

Many authors have described the benefits of blood pressure management as a protective factor against CKD progression.[29,30] Nonetheless, targets vary between the main guidelines and the most recent studies. Although the World Health Organization (WHO)[31] and the Kidney/Disease Outcomes Quality Initiative (K/DOQI)[32] recommend blood pressure levels ≤ 130/85 mmHg, a recent meta-analysis[33] concluded that no additional benefit was produced when BP was kept at these levels when compared to 140 x 90 mmHg and under, with the exception of patients with proteinuria between 300 and 1,000 mg/24h, as also supported by the NICE.[13] In this study, patients with systolic BP equal to or greater than 160 mmHg (SBC stage ≥ 2)[16] and individuals with systolic hypertension were at higher risk of developing progressive CKD. Additionally, patients with unfavorable CKD progression had significantly higher mean systolic BP levels than patients evolving favorably.

Multiple studies have looked into the high prevalence of dyslipidemia in CKD patients and the correlations between cholesterol and progression of renal dysfunction. In this study, significantly higher median levels of HDL-c were seen in patients with favorable CKD progression. However, controversy looms over the benefits of statin-based lipid control in limiting the progression of CKD. Most studies on the topic disagree on the main benefits offered by these drugs to such end. If, on the one hand, the 4S trial[34] showed reduced rates of CKD progression with statins, the ALLHAT[35] study did not report the same results. This disagreement does not disavow the established correlation between the use of statins and lower cardiovascular morbidity and mortality rates.[36]

The mean annual decrease in GFR was 3.1 ± 7.3 mL/min/1.73 m^2 with a median of 1.4 mL/min/1.73 m^2. Despite the difficulties achieving clinical and workup control over the variables classically correlated with CKD progression, these levels were lower than the thresholds established in the CKD guidelines (NICE).[16] Additionally, only 21.5% of the patients developed progressive CKD. Pereira *et al*. carried out a retrospective study with patients seen at an integrated predialysis CKD care center in Brazil and found lower levels of decreased renal function (0.6 ± 2.5 mL/min/1.73 m^2).[22]

Conclusion

Diabetic nephropathy was the main etiology of CKD in the studied population. Diastolic hypertension, high levels of systolic blood pressure, and proteinuria were risk factors for decreased renal function. Higher systolic blood pressure levels and lower levels of HDL-c were observed in patients with progressive CKD. The clinical and laboratory workup variables that affect the progression of renal disease are not easily controlled. Nonetheless, most patients did not develop progressive CKD.

Acknowledgement

The authors would like to thank professors Frederico Galante Neves and Romy Castro and medical students Rafael Scherer and Nayara Binda for their contributions to the study.

References

1. Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, et al. Prevalence of chronic kidney disease in the United States. JAMA 2007;298:2038-47. http://dx.doi.org/10.1001/jama.298.17.2038 PMid:17986697
2. Stevens LA, Li S, Wang C, Huang C, Becker BN, Bomback AS, et al. Prevalence of CKD and comorbid illness in elderly patients in the United States: results from the Kidney Early Evaluation Program (KEEP). Am J Kidney Dis 2010;55:S23-33. http://dx.doi.org/10.1053/j.ajkd.2009.09.035 PMid:20172445
3. Fernandes N, Bastos RMR, Bastos MG. Diagnóstico da doença renal crônica a partir da filtração glomerular estimada: CKD-EPI ou MDRD In: Congresso Brasileiro de Nefrologia; 2010;Vitória. Anais. Vitória: Sociedade Brasileira de Nefrologia. 506.
4. Sesso RCC, Lopes AA, Thomé FS, Lugon JR, Santos DR. Relatório do Censo Brasileiro de Diálise, 2010. J Bras Nefrol 2011;33:442-7. http://dx.doi.org/10.1590/S0101-28002011000400009
5. Brenner BM. Retarding the progression of renal disease. Kidney Int 2003;64:370-8. http://dx.doi.org/10.1046/j.1523-1755.2003.t01-2-00052.x PMid:12787440
6. Bastos MG, Kirsztajn GM. Doença renal crônica: importância do diagnóstico precoce, encaminhamento imediato e abordagem interdisciplinar estruturada para melhora do desfecho em pacientes ainda não submetidos à diálise. J Bras Nefrol 2011;33:93-108. http://dx.doi.org/10.1590/S0101-28002011000100013
7. Goicoechea M, de Vinuesa SG, Verdalles U, Ruiz-Caro C, Ampuero J, Rincón A, et al. Effect of allopurinol in chronic kidney disease progression and cardiovascular risk. Clin J Am Soc Nephrol 2010;5:1388-93. http://dx.doi.org/10.2215/CJN.01580210 PMid:20538833 PMCid:2924417

8. Siu YP, Leung KT, Tong MK, Kwan TH. Use of allopurinol in slowing the progression of renal disease through its ability to lower serum uric acid level. Am J Kidney Dis 2006;47:51-9. http://dx.doi.org/10.1053/j.ajkd.2005.10.006 PMid:16377385
9. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002;39:S1-266. http://dx.doi.org/10.1016/S0272-6386(02)70054-1
10. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. N Engl J Med 1993;329:1456-62. http://dx.doi.org/10.1056/NEJM199311113292004 PMid:8413456
11. Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). Lancet 1997;349:1857-63. http://dx.doi.org/10.1016/S0140-6736(96)11445-8
12. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41. http://dx.doi.org/10.1159/000180580 PMid:1244564
13. Early identification and management of chronic kidney disease in adults in primary and secondary care [Internet]. [cited 2011 Sep 3]. Available from: http://www.nice.org.uk/cg73
14. Basevi V, Di Mario S, Morciano C, Nonino F, Magrini N. Comment on: American Diabetes Association. Standards of medical care in diabetes--2011. Diabetes Care 2011;34:S11-S61. http://dx.doi.org/10.2337/dc11-S011 PMid:21193625 PMCid:3006050
15. Sposito AC, Caramelli B, Fonseca FAH, Bertolami MC, Afiune Neto A, Souza AD, et al. IV Diretriz Brasileira sobre Dislipidemias e Prevenção da Aterosclerose: Departamento de Aterosclerose da Sociedade Brasileira de Cardiologia. Arq Bras Cardiol 2007;88:2-19. http://dx.doi.org/10.1590/S0066-782X2007000700002 PMid:17515982
16. Sociedade Brasileira de Cardiologia. VI Diretrizes Brasileiras de Hipertensão. Arq Bras Cardiol 2010;95: I-III.
17. Collins AJ, Foley RN, Herzog C, Chavers B, Gilbertson D, Ishani A, et al. US Renal Data System 2010 Annual Data Report. Am J Kidney Dis 2011;57:A8,e1-526.
18. Pereira AC, Carminatti M, Fernandes NMS, Tirapani LS, Faria RS, Grincenkov FRS, et al. Associação entre fatores de risco clínicos e laboratoriais e progressão da doença renal crônica pré-dialítica. J Bras Nefrol 2012;34:68-75. http://dx.doi.org/10.1590/S0101-28002012000100011
19. Marques RS, Maués SLS. Prevalência da adesão ao tratamento medicamentoso em pacientes submetidos à hemodiálise em Santarém-PA [Trabalho de Conclusão de Curso de Medicina]. Santarém: Universidade do Estado do Pará; 2012.
20. Fernandes NM, Chaoubah A, Bastos K, Lopes AA, Divino-Filho JC, Pecoits-Filho R, et al. Geography of peritoneal dialysis in Brazil: analysis of a cohort of 5,819 patients (BRAZPD). J Bras Nefrol 2010;32:268-74.
21. Batista LKC, Pinheiro HS, Fuchs RC. Manuseio da doença renal crônica em pacientes com hipertensão e diabetes. J Bras Nefrol 2005;27:8-14.
22. Kausz AT, Khan SS, Abichandani R, Kazmi WH, Obrador GT, Ruthazer R, et al. Management of patients with chronic renal insufficiency in the Northeastern United States. J Am Soc Nephrol 2001;12:1501-7. PMid:11423579
23. Lea J, Cheek D, Thornley-Brown D, Appel L, Agodoa L, Contreras G, et al.; AASK Study Investigators. Metabolic syndrome, proteinuria, and the risk of progressive CKD in hypertensive African Americans. Am J Kidney Dis 2008;51:732-40. http://dx.doi.org/10.1053/j.ajkd.2008.01.013 PMid:18436083
24. Hou FF, Xie D, Zhang X, Chen PY, Zhang WR, Liang M, et al. Renoprotection of Optimal Antiproteinuric Doses (ROAD) Study: a randomized controlled study of benazepril and losartan in chronic renal insufficiency. J Am Soc Nephrol 2007;18:1889-98. http://dx.doi.org/10.1681/ASN.2006121372 PMid:17494885
25. Hemmelgarn BR, Manns BJ, Lloyd A, James MT, Klarenbach S, Quinn RR, et al. Relation between kidney function, proteinuria, and adverse outcomes. JAMA 2010;303:423-9. http://dx.doi.org/10.1001/jama.2010.657 http://dx.doi.org/10.1001/jama.2010.39 PMid:20124537
26. Wachtell K, Ibsen H, Olsen MH, Borch-Johnsen K, Lindholm LH, Mogensen CE, et al. Albuminuria and cardiovascular risk in hypertensive patients with left ventricular hypertrophy: the LIFE study. Ann Intern Med 2003;139:901-6. http://dx.doi.org/10.7326/0003-4819-139-11-200312020-00008 PMid:14644892
27. Tonelli M, Jose P, Curhan G, Sacks F, Braunwald E, Pfeffer M; Cholesterol and Recurrent Events (CARE) Trial Investigators. Proteinuria, impaired kidney function, and adverse outcomes in people with coronary disease: analysis of a previously conducted randomised trial. BMJ 2006;332:1426-32. http://dx.doi.org/10.1136/bmj.38814.566019.2F PMid:16714328 PMCid:1479622
28. Santos AMR, Lemos CCS, Bregman R. Proteinúria-marcador clássico de comprometimento glomerular. J Bras Nefrol 2001;23:217-20.
29. Dasgupta I, Madeley RJ, Pringle MA, Savill J, Burden RP. Management of hypertension in patients developing end-stage renal failure. QJM 1999;92:519-25. http://dx.doi.org/10.1093/qjmed/92.9.519 PMid:10627872
30. Klag MJ, Whelton PK, Randall BL, Neaton JD, Brancati FL, et al. End-stage renal disease in African-American and white men. 16-year MRFIT findings. JAMA 1997;277:1293-8. http://dx.doi.org/10.1001/jama.1997.03540400043029 http://dx.doi.org/10.1001/jama.277.16.1293 PMid:9109467
31. 1999 World Health Organization-International Society of Hypertension Guidelines for the Management of Hypertension. Guidelines Subcommittee. J Hypertens 1999;17:151-83. PMid:10067786
32. Kidney Disease Outcomes Quality Initiative (K/DOQI). K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. Am J Kidney Dis 2004;43:S1-290. http://dx.doi.org/10.1053/S0272-6386(04)00369-5
33. Upadhyay A, Earley A, Haynes SM, Uhlig K. Systematic review: blood pressure target in chronic kidney disease and proteinuria as an effect modifier. Ann Intern Med 2011;154:541-8. http://dx.doi.org/10.7326/0003-4819-154-8-201104190-00335 PMid:21403055
34. Huskey J, Lindenfeld J, Cook T, Targher G, Kendrick J, Kjekshus J, et al. Effect of simvastatin on kidney function loss in patients with coronary heart disease: findings from the Scandinavian Simvastatin Survival Study (4S). Atherosclerosis 2009;205:202-6. http://dx.doi.org/10.1016/j.atherosclerosis.2008.11.010 PMid:19124121

35. Rahman M, Baimbridge C, Davis BR, Barzilay J, Basile JN, Henriquez MA, et al.; ALLHAT Collaborative Research Group. Progression of kidney disease in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin versus usual care: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Am J Kidney Dis 2008;52:412-24. http://dx.doi.org/10.1053/j.ajkd.2008.05.027 PMid:18676075 PMCid:2897819

36. Collins R, Armitage J, Parish S, Sleight P, Peto R.; Heart Protection Study Collaborative Group. Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20536 people with cerebrovascular disease or other high-risk conditions. Lancet 2004;363:757-67. http://dx.doi.org/10.1016/S0140-6736(04)15690-0