Prospective study of 2151 patients with chronic kidney disease under conservative treatment with multidisciplinary care in the Vale do Paraíba, SP

Authors

Eduardo de Paiva Luciano[1]
Paulo Sérgio Luconi[2]
Ricardo Cintra Sesso[3]
Claudio Santiago Melaragno[3]
Patrícia Ferreira Abreu[4]
Sandra Ferreira Stanisck Reis[5]
Rejane Maria Spindola Furtado[5]
Gilson Fernandes Ruivo[6]

[1] Nephrology Physician - Medical residency in Nephrology (Coordinator of the State Center for the Treatment of Kidney Disease of the Vale do Paraíba - SP [CETDRVP]).
[2] Master (Affiliate professor, Medicine Department of the São Paulo School of Medicine of the Federal University of São Paulo - UNIFESP).
[3] Doctor (Affiliate professor, Medicine Department of the São Paulo School of Medicine of the Federal University of São Paulo - UNIFESP).
[4] Doctor (Affiliate professor, Medicine Department of the São Paulo School of Medicine of the Federal University of São Paulo - UNIFESP).
[5] Nephrology Physician - Medical residency in Nephrology (Physician at the State Center for the Treatment of Kidney Disease of the Vale do Paraíba - SP [CETDRVP]).
[6] Doctor (Affiliate Professor of the Universidade of Taubaté - SP).

Correspondence to:
Eduardo de Paiva Luciano.
Centro Estadual de Tratamento de Doenças Renais do Vale do Paraíba (CETDRVP) faz parte do Hospital Regional do Vale do Paraíba, Hospital Público Estadual, gerido pela Sociedade Beneficente São Camilo.
Av. Conego João Maria Raimundo da Silva, nº 206, apto. 94, Estiva. Taubaté, SP, Brazil. CEP: 12050-187.

ABSTRACT

Introduction: Chronic Kidney Disease (CKD) is common, severe and treatable. Its detection involves low cost tests. **Aim:** To evaluate the effect of a multidisciplinary (nephrologist, social worker, nurse, nutritionist, and psychologist) intervention comparing clinical and laboratory parameters in patients with CKD. **Methods:** A prospective study with 2,151 patients attended at the State Center for Kidney Diseases of the Vale do Paraiba, São Paulo, from February 2008 to March 2011. The kidney function was measured using albuminuria and estimated glomerular filtration rate (eGRF) using the MDRD formula The clinical outcomes were the occurrence of cardiovascular disease (CAD), hospitalization episodes, need of renal replacement therapy (RRT) and death. **Results:** Participants had a mean (range) age of 62 years (14-101), a mean follow-up of 546 days (90-1540) and the majority was in the stage 3 of CKD (59%). The most common primary diagnoses were hypertension (41.2%) and diabetes (32.4%). Mean blood pressure values at the beginning and at the end of treatment were 143 ± 26 mmHg x 87 ± 14 mmHg and 123 ± 16 mmHg x 79 ± 9 mmHg, respectively ($p < 0.001$); the eGRF decreased from 58.5 ± 31 ml/min. to 56.3 ± 23 ml/min ($p < 0.01$). Mean value of proteinuria decreased from 1.04 ± 1.44 g/day to 0.61 ± 1.12 g/day, $p < 0.001$, and the fasting glicemia decreased from 137 ± 73 mg/dl to 116 ± 42 mg/dl. One hundred and twenty-two patients (5.7%) had a CAD episode, the hospitalization rate was 6.6% (n = 143 patients), 7.3% patients died (n = 156), and 1.1% (n = 23) patients needed to start RRT. The risk of cardiovascular events, hospitalization, or death was inversely related to eGRF, and the rates of these events were low compared with the international literature. **Conclusion:** The multidisciplinary care with well defined targets is effective for the preservation of renal function and reduction in morbidity and mortality of CKD patients.

Keywords: cardiovascular diseases, hypertension, kidney failure, chronic, mortality.

INTRODUCTION

By definition, a chronic kidney disease (CKD) patient is any adult aged ≥18 years who, for a period ≥ 3 months, has shown a glomerular filtration rate (GFR) < 60 mL/(min·1.73 m²), as well as those with GFR > 60 mL/(min·1.73 m²) but with some evidence of kidney lesions (urinary abnormalities such as glomerular hematuria and/or microalbuminuria/proteinuria, or alterations on kidney imaging examination).[1]

In the USA, the prevalence of terminal-stage CKD rose from 10,000 in 1973 to 547,982 in 2008, with an annual cost of approximately \$40 billion USD and an annual mortality rate of approximately 25%.[2] A cross-sectional analysis[3] of the National Health and Nutrition Examination Survey (NHANES) conducted between 1994 and 2004 revealed that approximately 13% of the adult population in the USA has CKD in stage 1-4. Decreased renal function is linked to an increase in the risk of death, hospitalizations, and cardiovascular events, with important socioeconomic implications[4]. There are no sufficient data that can illustrate the magnitude of the incidence and prevalence of CKD in Brazil, and there are no expressive data regarding

morbidity, hospitalizations, and mortality. If we extrapolate from the actual American scenario, approximately 13% of the population has CKD, and it is estimated that approximately 16 million Brazilian individuals may be affected. According to the Brazilian Society of Nephrology, 92,000 patients were undergoing a chronic dialysis program in 2010, totaling an annual cost of more than 2 billion reais and gross annual mortality rate of 18%.[5]

The reduction in GFR occurs at an unpredictable and variable speed, oscillating between < 1 and 12 mL/(min·1.73 m^2) a year, with a typically faster decline observed in the population with diabetic nephropathy.[6] Studies confirm that hypertension, hyperglycemia, proteinuria, and cardiovascular disease are strongly linked to the speed of renal function loss. Control of these factors can avoid and minimize glomerular injury, and consequently reduce morbidity, hospitalizations, and mortality. An important component of this approach is renin-angiotensin system inhibitor therapy, with 2 objectives: reduction in proteinuria and blood pressure.[4,7]

CKD is a common, serious, treatable disease that must be prevented. In the initial stages, it can be detected with simple and extremely low-cost laboratory tests, and the treatment of underlying diseases can prevent or delay the evolution to more advanced stages of CKD, cardiovascular disease, or death.

The objective of this study was to prospectively assess the impact of multidisciplinary intervention in the progression of CKD and in outcomes such as cardiovascular events, hospitalizations, the need for renal replacement therapy (RRT), and death in CKD patients monitored in the region of the Vale do Paraíba in southeastern São Paulo (SP).

METHODS

STUDY DESIGN

The State Center for the Treatment of Kidney Disease of the Vale do Paraíba, SP (CETDRVP) was created in February 2008, and assists the population of the southeast region of the state, including primarily the metropolitan regions of Taubaté, São José dos Campos, and Aparecida, with an estimated population of 2.3 million. Individuals with suspected CKD seek the service through referral by physicians, that is, usually general physicians who work in the public network of the region. The regulating agency for appointments for the state of São Paulo is responsible for

scheduling initial visits. In the first visit, the patient is seen by a nurse, a physician, a social worker, a nutritionist, and a psychologist, who record the case history and diagnosis using a specific electronic record; then, additional examinations are scheduled. The patient returns on a monthly basis to the same physician and multidisciplinary team. Anthropometric data are noted, blood pressure (BP) is verified, and general instructions regarding CKD are provided in the nursing visit. The recorded data are stored electronically and physically at the outpatient clinic, with a copy duly signed by the healthcare professionals.

In the initial visit at the CETDRVP, the following are conducted: clinical history, physical examination, standardized measurement of BP, body mass index (BMI) calculation, and laboratory tests, including serum creatinine and albuminuria tests. The examinations are conducted at the same laboratory of the Regional Hospital of the Vale do Paraíba (BIOFAST), making use of automated and standardized dosages.[8] Multidisciplinary care is conducted on every visit and is given by a nurse, physician, psychologist, nutritionist, and a social worker. The main interventions the patient undergoes include the following: BP control (goal: ≤ 130 × 80 mmHg), use of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), glycemic control (fasting blood glucose goal < 126 mg/dL), use of statins (low-density lipoprotein [LDL] goal ≤ 100 mg/dL), nutritional orientation with overall restriction in protein consumption between 0.8 and 1 g/(kg·day) for patients starting at stage III of CKD, and encouragement for the adoption of healthy life habits such as smoking cessation and practicing aerobic physical exercises on a daily basis.[1,9]

For demonstrably diabetic patients, nutritional orientations and optimization or initiation of hypoglycemic medication have been implemented. Once admitted to the center, the patients are prospectively monitored at outpatient visits or until there is the need for RRT (dialysis or kidney transplant), death, or transfer of residence to a different region. The last patient follow-up is confirmed with data from the record, and if necessary (when the last visit was > 3 months previous), a phone call is made to the residence to verify the current status of the patient.

In this study, 3,158 patients that visited the CETDRVP between February 2008 and March 2011 were initially assessed; among these patients, we

selected 2,151 patients who were prospectively monitored at the center for > 3 months and confirmed to have undergone multidisciplinary intervention. Using a minimum follow-up period of 3 months with the team as the only criteria, 1,007 patients were excluded. All of the patients signed a free and informed consent form in the beginning of the follow-up period. The study was submitted and approved by the Ethics and Research Committee of the institution.

The GFR was estimated (eGFR) using the abbreviated Modification of Diet in Renal Disease (MDRD) formula.[10] We used the modified classification of the National Kidney Foundation for CKD[1] with stages based upon the eGFR: stage 1, $\geq$ 90 mL/(min·1.73 m^2); stage 2, 89-60 mL/(min·1.73 m^2); stage 3a, (59-45 mL/(min·1.73 m^2); stage 3b, 44-30 mL/(min·1.73 m^2); stage 4, (29-15 mL/(min·1.73 m^2); and stage 5, < 15 mL/(min·1.73 m^2).

A cardiovascular event (CVE) was defined as the following: new or aggravated acute coronary syndrome, new or aggravated congestive heart failure (CHF), new encephalic vascular accident (EVA), and new obstructive arterial disease (OAD). Acute coronary syndrome was defined as the occurrence of acute myocardial infarction or unstable angina. EVA was defined as an ischemic or hemorrhagic lesion diagnosed by a neurologist after adequate imaging exam. CHF was defined as left ventricle deficit confirmed by echocardiograms. OAD was defined as acute arterial thrombosis of the extremities confirmed by a vascular surgeon.

Statistical analysis

The continuous variables have been expressed as mean and standard deviation, and the categorical variables have been described as n (%). Comparisons between the continuous variables at the beginning and at the last follow-up were conducted using the paired Student's t test. The comparisons between the mean values of variables in groups with or without clinical outcomes of interest were conducted using the unpaired Student's t test. The tests were 2-tailed and the value of $p < 0.05$ was defined as statistically significant. Risk calculations were conducted using odds ratios and respective 95% confidence intervals (CI) for the occurrence of death, CVE, and hospitalizations in relation to the stages of CKD, with the combined stage 1 and 2 values considered as a reference.

The survival analyses were conducted using the Kaplan-Meier method, with 3 types of outcomes considered: 1) death, with patients being censured on the starting date of the RRT or at the end of the follow-up period, whichever came first; 2) need for RRT, with patients being censured on the date of death, or at the end of the follow-up period; and 3) a combination of death or need for RRT, with patients being censured at the end of the follow-up period. Statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS) software version 14.0 (SPSS Inc., Chicago, IL, USA).

Results

Clinical and laboratory aspects in the beginning and end of the follow-up period

Table 1 describes the epidemiological characteristics of the study population, which included a total of 2,151 patients, with an average age of 62 years (minimum age, 14 years; maximum age, 101 years); the average follow-up period was 546 days (range: 90-1,540 days), and the female sex and white race prevalence was 50.6% and 78.9%, respectively. In relation to CKD stage, stage 3 was the most prevalent, with 1,269 individuals (59%). The most frequent underlying disease of CKD was systemic hypertension (SH), with 886 patients (41.2%), followed by diabetes mellitus (DM) at 32.4%. At admission, 773 (35.9%) patients made use of renin-angiotensin-aldosterone system inhibitors (ACEI or ARB); at the end of the follow-up period, the number of patients using these medications rose to 1,937 (90.1%; $p < 0.001$).

Table 2 describes some parameters of clinical and laboratory relevance. In the beginning and at the end of the follow-up period, the average BP was 143 ± 26 mmHg × 87 ± 14 mmHg and 123 ± 16 mmHg × 79 ± 9 mmHg, respectively ($p < 0.001$); the eGFR was decreased only by 2.2 mL/min (from 58.5 ± 31 mL/min to 56.3 ± 23 mL/min, $p < 0.01$). There was a drop in the average value of proteinuria from 1.04 ± 1.44 g/day to 0.61 ± 1.12 g/day ($p < 0.001$) in the population of 634 patients studied for this parameter (Figure 1A); for fasting blood glucose level, there was a drop in average values from 137 ± 73 mg/dL to 116 ± 42 mg/dL, while the BMI remained stable at 27.8 kg/m^2 after intervention.

There were 936 (43.5%) patients with BP ≥ 140/90 mmHg in the beginning and 452 (21%) at the end of the follow-up period. In these individuals, the average BP values in the beginning and at the end of follow-up

TABLE 1	CLINICAL AND EPIDEMIOLOGICAL CHARACTERISTICS OF THE STUDY PATIENTS (N = 2,151)
Age (years)	62 ± 16 (14-101)
Follow-up time (days)	546 ± 336
Women	1,089 (50.6)
Race	
White	1,697 (78.9)
Black	274 (12.7)
Mixed	179 (8.3)
CKD Stage	
1	281 (13.1)
2	330 (15.3)
3a	741 (34.4)
3b	528 (24.6)
4	234 (10.9)
5	37 (1.7)
Underlying disease	
SH	886 (41.2)
DM II	670 (31.1)
UNSPEC	253 (11.8)
UROLOG	160 (7.4)
DM I	28 (1.3)
CGN	37 (1.7)
ADPKD	13 (0.6)
SLE	8 (0.4)
Other	96 (4.5)

Values expressed as mean ± SD (min-max) or n (%). CKD: Chronic Kidney Disease; SH: Systemic Hypertension; DM II: type 2 Diabetes Mellitus; UNSPEC: Unspecified; UROLOG: Urological; DM I: type 1 Diabetes Mellitus; CGN: Chronic Glomerulonephritis; ADPKD: Autosomal Dominant Polycystic Kidney Disease; SLE: Systemic Lupus Erythematosus.

period were 161 ± 25 mmHg × 110 ± 10 mmHg and 128 ± 17 mmHg × 82 ± 9 mmHg, respectively ($p <$ 0.001; Figure 2).

Subsequently, we analyzed the subgroup of patients with fasting blood glucose level > 126 mg/dL at the beginning of the follow-up period (n = 368). There was a significant drop in the average values of fasting blood glucose level in the beginning and at the end of the follow-up period, from 218 ± 82 mg/dL to 137 ± 53 mg/dL ($p <$ 0.001); proteinuria, from 1.6 ± 1.9 g/day to 1.0 ± 1.7 g/day ($p <$ 0.001), BP, from 143 ± 26 mmHg × 87 ± 14 mmHg to 125 ± 16 mmHg × 79 ± 9 mmHg ($p <$ 0.001); and eGFR, from 55 ± 23 mL/min to 53 ± 25 mL/min ($p =$ 0.03).

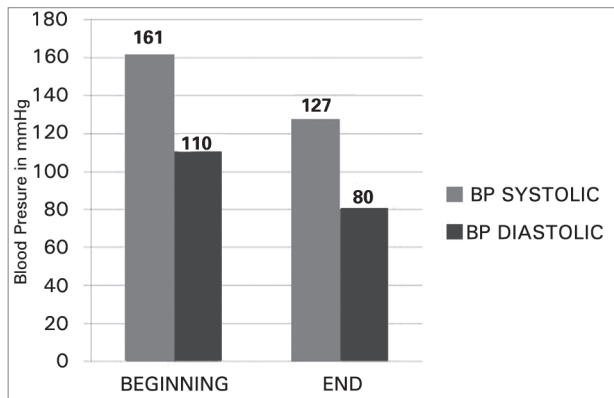| TABLE 2	CLINICAL AND LABORATORY DATA AT THE BEGINNING AND AT END OF THE FOLLOW-UP PERIOD		
	mean ± SD		
	Before	After	p
Systolic BP (mmHg)	143 ± 26	123 ± 16	0.001
Diastolic BP (mmHg)	87 ± 14	79 ± 9	0.001
eGFR (mL/min·1.73m2)	58.5 ± 31	56.3 ± 23	0.01
Proteinuria (g/day)	1.04 ± 1.44	0.61 ± 42	0.001
Fasting glycemia (mg/dL)	137 ± 73	116 ± 42	0.001
BMI (kg/m^2)	27.8 ± 5.8	27.8 ± 5.7	0.67

BMI: Body Mass Index; BP: Blood Pressure; eGFR: estimated Glomerular Filtration Rate; SD: Standard Deviation.

Figure 1. Average values of proteinuria at the beginning and at the end of the follow-up period. (A) average values of proteinuria (g/day) at the beginning and at the end of the follow-up period for the entire group (n = 634), (B) average values of proteinuria at the beginning and at the end of the follow-up period in patients with initial proteinuria > 1 g/day (n = 207).
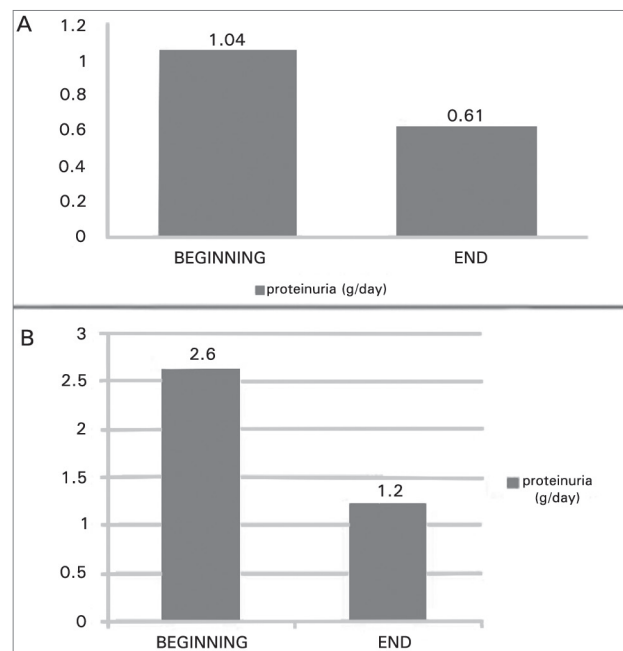
In the patients with initial proteinuria higher than 1 g/day, we noticed a significant drop of the average proteinuria level at the end of the intervention, from 2.7 ± 1.7 g/day to 1.2 ± 1.6 g/day ($p <$ 0.001; Figure 1B).

Figure 2. Average values of Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) at the beginning and at the end of the follow-up period (n = 2151). BP in mmHg.

TABLE 3	HOSPITALIZATION ACCORDING TO CHRONIC KIDNEY DISEASE (CKD) STAGE AND UNDERLYING DISEASE IN THE 360-DAY FOLLOW-UP PERIOD (N = 2,151)
Hospitalization overall rate	143 (6.6%)
CKD stage	
1	3 (1.0%)
2	17 (5.1%)
3a	46 (6.2%)
3b	39 (7.4%)
4	32 (13.7%)
5	6 (16.2%)
CKD etiology	
Hypertension	45 (31.5%)
Diabetes mellitus	61 (42.7%)
Urological	16 (11.2%)
Chronic glomerulonephritis	8 (5.6%)
Graft loss	1 (0.7%)
Unspecified	11 (7.7%)
Polycystic kidneys	1 (0.7%)

CLINICAL OUTCOMES

During the follow-up period, 122 patients (5.7%) showed CVE, of which 66 (3.1%) had ACS, 17 showed (0.8%) CVA, 21 (1%) showed CHF, and 18 (0.8%) showed OAD. The odds ratio (95% CI) for CVE was 1.2 (1.0-1.4), 1.8 (1.3-2.6), 1.8 (1.2-2.5), and 2.3 (2.0-6.4) for stages 3a, 3b, 4, and 5, respectively. The overall rate of hospitalizations was 6.6% (n = 143 patients), which increased substantially with the progression of the CKD (Table 3 and Figure 3). The odds ratio (95% CI) of all-cause hospitalization was 1.4 (1.1-1.8), 1.6 (1.3-1.9), 1.8 (1.7-2.3), and 1.9 (1.8-2.3) for stages 3a, 3b, 4, and 5, respectively. One hundred fifty-six (7.3%) deaths and 23 (1.1%) patients requiring RRT were observed. The odds ratio (95% CI) for deaths was 2.9 (1.8-3.1), 2.9 (1.6-3.1), 3.6 (2.1-4.2), and 6.8 (3.5-13.2) for stages 3a, 3b, 4, and 5, respectively (Table 4). We observed a 1% death rate for stage 1, 5.1% for stage 2, 6.2% for stage 3a, 7.4% for stage 3b, 13.7% for stage 4, and 16.2% for stage 5.

Higher values of initial systolic and diastolic BP were significant ($p < 0.01$) predictors for the need for RRT.

Subsequently, we showed the cumulative probability analyses until the occurrence of the "a priori" selected events in the 2,151 patients monitored in the study. The cumulative survival probability (± standard error) after 2 years of follow-up was 92% ± 1% and 84% ± 2% after 3 years (Figure 4A). The inexistence of renal outcome cumulative probability (need for RRT) after 2 years of follow-up was 98% ± 0.4% and 96.5% ± 0.8% after 3 years (Figure 4B).

The cumulative probability of survival or of lack of a need for RRT after 2 years of follow-up was 91% ± 1% and 82% ± 2% after 3 years (Figure 4C).

Figure 3. Hospitalization rates for 100 patients/year, according to the estimated glomerular filtration rate (eGFR), n = 2,151.
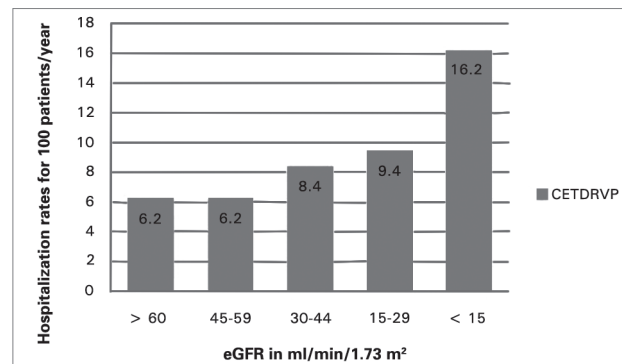
DISCUSSION

It has been suggested that CKD patients undergoing multidisciplinary follow-up in Canada showed a lower rate of hospitalization, lower rate of urgent RRT initiation, and lower treatment cost[11]. Adequate control of BP, smoking cessation, metabolic control, and decrease in proteinuria are examples of goals to be reached. They contribute to slowing the progression of CKD, and in turn reduce morbimortality[12]. Other measures are necessary, including early diagnosis, treatment of anemia, mineral and bone disorder, and metabolic acidosis, which frequently occur as CKD progresses.

TABLE 4	RELATIVE RISKS (95% CI) OF ALL-CAUSE DEATH, CARDIOVASCULAR EVENT (CVE), AND HOSPITALIZATION		
eGFR	Death	CVE	Hospitalization
		RR (CI 95%)	
≥ 60 mL/(min·1.73 m^2)*	1	1	1
45-59 mL/(min·1.73 m^2)	2.9 (1.8-3.1)	1.2 (1.0-1.4)	1.4 (1.1-1.8)
30-44 mL/(min·1.73 m^2)	2.9 (1.6-3.1)	1.8 (1.3-2.6)	1.6 (1.3-1.9)
15-29 mL/(min·1.73 m^2)	3.6 (2.1-4.2)	1.8 (1.2-2.5)	1.8 (1.7-2.3)
< 15 mL/(min·1.73 m^2)	6.8 (3.5-13.2)	2.3 (2.0-6.4)	1.9 (1.8-2.3)

* reference group (CKD stages 1 + 2). CI: Confidence Interval; RR: Relative Risk; eGFR: estimated Glomerular Filtration Rate.

The key issue is how often we are applying such information to improve the health of this population in our community. By using multidisciplinary intervention, we acted on the risk factors of CKD and analyzed the outcomes after an average 1.5 years of follow-up for patients treated in inland SP. The individuals in this study were generally hypertensive, diabetic, elderly individuals, mostly with eGFR < 60 mL/min, and only 36% were using ACEI or ARB at the beginning of the follow-up period.

The presence of albuminuria is one of the main risk factors for the progression of CKD and cardiovascular diseases. Its reduction is correlated with renal function stabilization.[13,14] The benefit of renin-angiotensin system inhibitor drugs was well observed in the Ramipril Efficacy In Nephropathy (REIN) Trial,[15] in which patients with non-diabetic chronic nephropathy were randomized to ramipril or placebo treatment along with another antihypertensive therapy. The study was interrupted early in patients excreting > 3 g of protein/day due to the significant benefits in the ramipril group in reducing the decline of the renal function rate (0.53 mL/min in the ramipril group vs. 0.88 mL/(min·month) in the placebo group). The decrease in BP-independent proteinuria is associated with an additional decrease in the declining rate of the GFR.[16,17]

In our study, we obtained a significant increase in the use of ACEI/ARB (from 36% to 90%), decrease in proteinuria, and slight decrease in eGFR (2 mL/min). In patients with initial proteinuria > 1 g/day, the percentage decrease of proteinuria was even higher (55%). In the subgroup of patients with blood glucose > 126 mg/dL, proteinuria decreased by approximately 40%. Our intervention was also effective in the control of systolic and diastolic BP. Patients with CKD and diastolic BP < 90 mmHg maintain better preservation of the GFR than hypertensive patients.[10,18,19] The results of the MDRD multicenter research study suggest that both the progression rate and the efficacy

of antihypertensive therapy may be linked to the basal excretion of proteins that, in turn, is a reflection of the severity of glomerular injury.[20] The Multiple Risk Factor Intervention Trial study reinforced this observation by concluding that higher BP levels were an independent risk factor for the progression of CKD.[21]

The prevalence of CVD in CKD patients, even at the pre-dialysis stage, is higher (10-20 times) than that of the overall population. Approximately 90% of CKD patients show left ventricular hypertrophy, and 35% show ischemic cardiac disease. CVD is the main cause of morbidity and mortality, and the risk of death is much higher than the risk of eventually needing dialysis.[22] In the Atherosclerosis Risk in Communities Study,[23] the presence of CKD stages 3, 4, and 5 was linked to a 30% increase in the risk of CVD in relative to stages 1 and 2. In the Kaiser Permanente of Northern California study,[4] 12.3% of the individuals with CKD showed CVD during follow-up. In spite of the short observational period, only 5.7% of our patients showed CVE, even with the majority (80%) belonging to stages 3, 4, and 5 of CKD.

We can speculate that this result may reflect the better glycemic and pressure control, the drop in proteinuria levels, and the greater use of ACEI/ARB observed in almost all of the patients. The improvement of clinical and laboratory parameters and the reduction of CVE that we obtained with our multidisciplinary intervention may likely explain the lower hospitalization rate per 100 patients/year when compared to the USA study with CKD patients monitored in California without a controlled intervention[4] (6.2% vs. 13.5%, 6.2% vs. 17.2%, 8.4% vs. 45.2%, 9.4% vs. 86.7%, and 16.2% vs. 144.6% in stages 1 and 2, 3a, 3b, 4, and 5, respectively).

We lack data in the Brazilian literature for a comparison; however, the lower number of CVE and lower hospitalization rate that we obtained with

Figure 4. Survival curves/days: (A) survival of CKD patients (n = 2,151). (B) cumulative probability of not needing renal replacement therapy (RRT; n = 2,151). (C) cumulative survival probability without the need for RRT (n = 2,151).
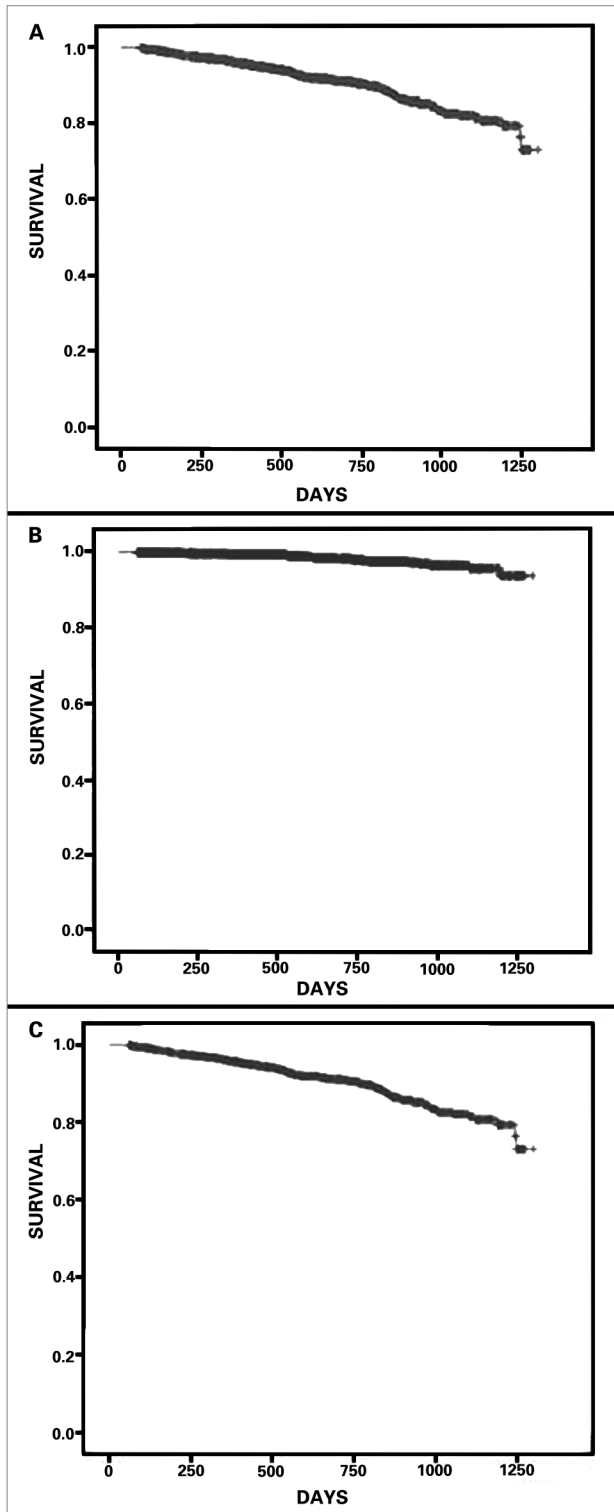
more advanced CKD patients must have an important impact in reducing healthcare costs to these patients. In 2010, in the state of SP, 2,333,179 admissions took place in the Universal Health Care

System. With the goal of creating an estimate of the costs avoided with the multidisciplinary intervention that we used, we compared the prevalence of hospitalizations in our study in relation to the American study conducted in California,[4] in which there was no specific intervention during patient follow-up; we observed that there could have been a reduction of approximately 580,000 admissions/year in the state of SP. Considering the value of R$ 1,160.00 as the average cost for each hospitalization within the Universal Health Care System,[24] we would be able to save approximately R$ 670 million/year with the implementation of this type of outpatient care throughout the state of SP.

These estimates have limitations due to the lack of a national population of CKD patients to serve as a control and to the differences in social, demographic, and clinical characteristics between our population and the American population, as well as the American hospitalization patterns that have not been considered. However, these estimates serve as an example of the great economic impact that the implementation of this CKD progression prevention strategy with multidisciplinary care may have.

CKD coexists with serious diseases such as SH, DM, CVD, which partially explains the higher risk of death in relation to individuals with normal renal function. In 1 systematic review,[25] the relative risk of death was > 1 in 93% of the studies (0.94-5.0), which increased exponentially as renal function decreased. We observed 156 deaths during the 546-day follow-up (7.3%), and a risk of 2.9, 2.9, 3.6, and 6.8 for stages 3a, 3b, 4, and 5, respectively. These rates must take into consideration the 62-year average age of the patients, of which approximately 1/3 had diabetic nephropathy, and 80% were in stages 3, 4, and 5 of CKD.

In a longitudinal study with approximately 30,000 older patients,[26] the rate of RRT requirement in patients at stages 2, 3, or 4 was 1.1%, 1.3%, and 19.9%, respectively; in comparison, the mortality rate was 19.5%, 24.3%, and 45.7%, respectively. In another study with more than 12,000 elderly patients with diabetes (48% with GFR < 60 mL/min)[27] monitored for 3 years, the mortality rate was 6%, 10%, 20%, and 30% for patients at stages 2, 3, 4, and 5, respectively. In our 1.5-year follow-up study, we observed a lower rate of mortality, at 5.2%, 7.8%, 11.5%, and 21.6% for patients at stages 2, 3, 4, and

5, respectively. Our rate of RRT requirement was also lower when compared to the international literature, at 0.5% for patients with eGFR > 60 mL/(min·1.73 m²), 0.5% for stage 3a, 1.2% for stage 3b, 4.6% for stage 4, and 11.1% for stage 5.

In conclusion, our work is the first account in the national literature to prospectively assess clinical indicators and adverse events in CKD patients under multidisciplinary intervention with a large number of patients in the public health system. The present study demonstrated the effectiveness of a multidisciplinary intervention with well-defined laboratory and clinical parameter goals while monitoring CKD patients. This type of intervention may be applied to many other regions of the country, and it is expected to similarly promote a better clinical and laboratory control of the patients by decreasing CKD progression, cardiovascular morbidity, and mortality of these patients. In particular, such improvement in clinical outcomes and the lower rate of hospitalizations will also translate into a reduction of economic costs in monitoring CKD patients in our community.

REFERENCES

1. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. Am J Kidney Dis 2002;39:S1-216.
2. Bethesda MD. U.S. Renal Data System. URSD Annual Data Report National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Disease 2010. Disponivel em: www.usrds.org
3. Snyder JJ, Foley RN, Collins AJ. Prevalence of CKD in the United States: a sensitivity analysis using the National Health and Nutrition Examination Survey (NHANES) 1999-2004. Am J Kidney Dis 2009;53:218-28.
4. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004;351:1296-305.
5. Sesso RC, Lopes AA, Thomé FS, Lugon JR, Santos DR. Relatório do Censo Brasileiro de Diálise de 2010. J Bras Nefrol 2011;33:442-7.
6. Weir MR. Progressive renal and cardiovascular disease: optimal treatment strategies. Kidney Int 2002;62:1482-92.
7. The Remission Clinic Task Force; Clinical Research Center Aldo e Cele Daccó. The Remission Clinic approach to halt the progression of kidney disease. J Nephrol 2011;24:274-81.
8. Dosagem de creatinina sérica. Disponível em: www.biofast.com.br (acessado em 29/02/2012)
9. Diretrizes Brasileiras de Doença Renal Crônica. J Bras Nefrol 2004;26:1-49.
10. Sarnak, MJ, Greene, T, Wang, X, Beck G, Kusek JW, Collins AJ, et al. The effect of a lower target blood pressure on the progression of kidney disease: long-term follow-up of the modification of diet in renal disease study. Ann Intern Med 2005;142:342-51.
11. Levin A, Lewis M, Mortiboy P, Faber S, Hare I, Porter EC, et al. Multidisciplinary predialysis programs: quantification and limitations of their impact on patient outcomes in two Canadian settings. Am J Kidney Dis 1997;29:533-40.
12. Zoja C, Corna D, Camozzi D, Cattaneo D, Rottoli D, Batani C, et al. How to fully protect the kidney in a severe model of progressive nephropathy: a multidrug approach. J Am Soc Nephrol 2002;13:2898-908.
13. Russo D, Minutolo R, Pisani A, Esposito R, Signoriello G, Andreucci M, et al. Coadministration of losartan and enalapril exerts additive antiproteinuric effect in IgA nephropathy. Am J Kidney Dis 2001;38:18-25.
14. Macconi D, Abbate M, Morigi M, Angioletti S, Mister M, Buelli S, et al. Permselective dysfunction of podocyte-podocyte contact upon angiotensin II unravels the molecular target for renoprotective intervention. Am J Pathol 2006;168:1073-85.
15. Ruggenenti, P, Perna, A, Gherardi, G, Gaspari F, Benini R, Remuzzi G. Renal function and requirement for dialysis in chronic nephropathy patients on long-term ramipril: REIN follow-up trial. Gruppo Italiano di Studi Epidemiologici in Nefrologia (GISEN). Ramipril Efficacy in Nephropathy. Lancet 1998; 352:1252-3.
16. Ruggenenti P, Schieppati A, Remuzzi G. Progression, remission, regression of chronic renal diseases. Lancet 2001;357:1601-8.
17. 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 randomized trial. BMJ 2006;332:1426.
18. Brazy PC, Fitzwilliam JF. Progressive renal disease: role of race and antihypertensive medications. Kidney Int 1990;37:1113-9.
19. 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.

20. Klahr, S, Levey, AS, Beck, GJ, Caggiula AW, Hunsicker L, Kusek JW, et al. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. N Engl J Med 1994;330:877-84.

21. Klag MJ, Whelton PK, Randall BL, Neaton JD, Brancati FL, Stamler J. End-stage renal disease in African-American and white men. 16-year MRFIT findings. JAMA 1997;277:1293-8.

22. Ammirati AL, Canziani MEF. Fatores de risco cardiovascular nos pacientes com doença renal crônica. J Bras Nefrol 2009;31:43-8.

23. Manjunath G, Tighiouart H, Ibrahim H, MacLeod B, Salem DN, Griffith JL, et al. Level of kidney function as a risk factor for atherosclerotic cardiovascular outcomes in the community. J Am Coll Cardiol 2003;41:47-55.

24. Secretaria de Vigilância à Saúde, Ministério da Saúde. Sistemas de informações. http://portal.saude.gov.br/portal/svs (acessado em 20/02/2012).

25. Tonelli M, Wiebe N, Culleton B, House A, Rabbat C, Fok M, et al. Chronic kidney disease and mortality: a systematic review. J Am Soc Nephrol 2006;17:2034-47.

26. Keith DS, Nichols GA, Gullion CM, Brown JB, Smith DH. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. Arch Intern Med 2004;164:659-63.

27. Patel UD, Young EW, Ojo AO, Hayward RA. CKD progression and mortality among older patients with diabetes. Am J Kidney Dis 2005;46:406-14.