

Renal Disease as a Cardiovascular Risk Factor

Luis Cuadrado Martin, Roberto Jorge da Silva Franco
Faculdade de Medicina de Botucatu – UNESP - Botucatu, SP - Brazil

An estimated 10% of the American population has some degree of renal disease, although asymptomatic. In Brazil, no data are available on the prevalence of chronic renal disease. A number of studies show a direct and close relationship between the degree of renal dysfunction and cardiovascular risk. This increased cardiovascular risk, despite being maximal in end-stage renal failure, begins to be noticed with slight declines in renal function. In addition, the presence of renal injury, even with normal renal function, evidenced by proteinuria or microalbuminuria, is also a potent cardiovascular risk factor. At present, the primary causes of renal disease are diabetic nephropathy and hypertensive nephrosclerosis, accelerated by cigarette smoking and dyslipidemia. Hence, increased cardiovascular risk in patients with chronic renal disease may be secondary to the accumulation of these classical risk factors; however, frequency of cardiovascular events in these patients is higher than that predicted by equations that take into account such classical factors. Therefore, there may be mechanisms intrinsic to renal lesion capable of accelerating systemic atherosclerosis. Accordingly, uremic toxicity itself, increased oxidative stress, change in the coagulation cascade, changes in lipid levels and hypervolemia are involved in the genesis of early atherosclerosis in patients with chronic renal disease. It is incumbent on clinicians, nephrologists, hypertension specialists, and cardiologists to identify these patients through urinalysis, serum creatinine measurement, and microalbuminuria screening in order to reduce, through intensive treatment, to revert at least in part, the high cardiovascular risk of that diseased portion of the population.

In 1945, Langendorf and Pirani first described cardiac changes in postmortem examinations performed on patients with chronic renal failure. By gross analysis, these authors identified marked ventricular hypertrophy and, by microscopy, severe fibrosis and interstitial edema. In their study, uremia itself had been the cause of death, since routine dialysis was not available at that time.¹

In 1975, Lindner et al. described a high prevalence of cardiovascular disease with early atherosclerosis in the first longitudinal cohort study of patients in

hemodialysis.² In 1960, in Seattle, of the 39 patients who were, on average 37 years old by the time they started hemodialysis therapy, 23 (59%) died 6.5 years after joining the program. Of these 23, 14 (61%) died from cardiovascular diseases. Cardiovascular risk for this first cohort was estimated to be 30 times greater than that of the local general population. Thus, because of renal replacement therapy, life expectancy of patients with end-stage chronic renal failure increased, once the immediate cause of death from uremia was eliminated, and cardiovascular diseases became the main cause of death: at an early age and at a much higher frequency than expected for the general population

About 19.1 million Americans (11% of the US population) have some degree of renal disease, defined by the presence of albuminuria or glomerular filtration rate below 60 mL/min, that is to say, serum creatinine above 1.3 mg/dL for women or above 1.5 mg/dL for men.³ On the other hand, according to data from the American Registry of Dialysis and Transplantation, 300,000 chronic renal disease patients are under renal replacement therapy.⁴ Therefore, even taking into account both underdiagnosis and the predicted growth of the dialysis population in that country, most patients with renal dysfunction are expected to die before they require renal replacement therapy. In these patients, death is mainly due to cardiovascular causes, and cardiovascular risk for patients with renal dysfunction, although asymptomatic, is significantly higher than that predicted by the Framingham equations⁵. It should be emphasized that a patient with renal dysfunction is much more likely to die from cardiovascular disease than from actual renal failure.

Data from the Hypertension Detection and Follow-up Program (HDFP) were the first to show a correlation between serum creatinine and cardiovascular mortality among hypertensive patients. This association was independent of other cofactors evaluated: gender, race, blood pressure, diabetes or degree of obesity.^{6,7} Creatininemia thus emerged as a major predictor of cardiovascular disease.

Mailing Address: Roberto Jorge da Silva Franco • Rua Carlos Guadanini, 1805 - 18610-120 – Botucatu, SP - Brazil
E-mail: rjfranco@fmb.unesp.br

The Hypertension Optimal Treatment (HOT) trial results have corroborated the relationship between creatinemia and cardiovascular risk among hypertensive patients under drug therapy. In that study, serum creatinine was the most powerful risk predictor of the assessed factors.⁷ Data from many other cohorts consistently point to renal dysfunction as an important cardiovascular risk factor.⁸⁻¹³

With further regard to the HOT trial, the difference in mortality between groups treated with and without aspirin was more significant in patients with renal dysfunction. Only among patients with baseline serum creatinine above 1.3 mg/dl was there a significant reduction of cardiovascular events in which aspirin was used. This result was associated especially to the high cardiovascular risk showed by these patients with more potential benefit.¹⁴ On the other hand, as far as optimal blood pressure is concerned, intensive blood pressure control was found to be more likely to reduce cardiovascular risk in the subgroup of patients with renal dysfunction than in the subgroup of patients with normal renal function, although this trend was not statistically significant.¹⁰ Additionally, the analysis of interaction between anti-hypertensive therapy and renal function in the Systolic Hypertension Elderly Program (SHEP) trial revealed that treatment of isolated systolic blood pressure was more effective in preventing cardiac events in older patients with renal dysfunction than in those with normal renal function.¹⁵ Both in the Hypertension Detection and Follow-up Program (HDFP)⁶ and in the Modification of Diet in Renal Disease (MDRD)¹⁶ trial, renal protection was found to be enhanced in patients with more effective blood pressure control. Thus, it seems that patients with renal dysfunction should be managed with tight blood pressure control and aspirin, not only to provide renal protection, but also to optimize cardioprotection.

Prognostic significance of increased serum creatinine levels is not consistent in all population strata. Decline in glomerular filtration rate has been proven to be a moderate risk factor in patients with low risk for cardiovascular disease,¹⁷ with greater predictive value in subgroups at higher risk, such as elderly and hypertensive subjects,⁶ and even greater in patients at extremely high risk, that is, patients with peripheral vascular disease or diabetes,¹¹ acute coronary syndromes,²¹ heart failure,²¹ CABG¹⁹ or percutaneous angioplasty post-operatives.²⁰ In other words, decline in glomerular filtration rate has deleterious consequences in these specific situations.

The mechanisms by which renal dysfunction may lead to cardiovascular disease are multiple. Traditional and non-traditional risk factors alike play a role in the pathogenesis of cardiovascular disease in patients with chronic renal disease. Primary traditional risk factors include arterial hypertension, diabetes, hyperuricemia, dyslipidemia (particularly increased triglyceride levels and decreased HDL-cholesterol levels, secondary to peripheral resistance to insulin action, caused by uremic toxicity itself). Non-traditional risk factors include variables

routinely assessed in patients with chronic renal disease, such as: hyperparathyroidism and altered divalent ion metabolism,²³ anemia,²⁴ and hydrosaline overload,^{25,26} together with variables not routinely assessed in clinical practice: hyperhomocystinemia,²⁷ increased oxidative stress, endothelial dysfunction, changes in lipid levels not frequently assessed, such as apolipoprotein(a),²⁸ build-up of asymmetric dimethyl arginine,²⁸ inflammatory procoagulant activity,³⁰ and abnormal behavior of blood pressure during sleep.³¹

Left ventricular hypertrophy is an independent cardiovascular risk factor that, in the arterial hypertension setting, portends an ominous prognosis. A higher prevalence of left ventricular hypertrophy is found among patients with chronic renal failure, even in early stages, greater than would be expected for the degree of hypertension.²⁵ This prevalence becomes even higher as renal dysfunction progresses.³² A number of mechanisms contribute to the pathogenesis of this disproportionate ventricular enlargement, beyond that expected for the degree of arterial hypertension, such as anemia³³ and hyperparathyroidism.³⁴

Our group showed the important role played by sodium retention, regardless of its hypertensive effect, in the development of this cardiac abnormality in patients with chronic renal disease.²⁶

Conversely, it should be noted that recent years have witnessed a sharp increase in chronic degenerative diseases (hypertension and diabetes mellitus) as cause of chronic renal failure, the same conditions that usually produce cardiovascular lesion.^{4,35} Therefore, by the time diabetes or hypertension renal lesion develops, a corresponding heart lesion usually already exists. Thus, a question rises as to whether mild renal dysfunction is only a marker of more extensive vascular damage or the very renal failure may be involved in the pathophysiology of cardiovascular lesions.

Some evidence points to a direct role of uremia in the development of cardiovascular disease. A study evaluating hemodialysis therapy during about 14 years in 16 young people, ages ranging from 7 to 30, demonstrated that 14 patients showed tomographic evidence of coronary artery calcification, compared to 3 out of 60 normal controls.³⁶ Moreover, some degree of coronary atherosclerosis was found in 80% of the cases of a series of autopsies performed on children who died during hemodialysis treatment.³⁷ This prevalence is clearly higher than that of coronary atherosclerosis in the general population of the same age.

A second strong piece of epidemiological evidence supporting that uremia "per se" is implied in the acceleration of atherosclerotic process comes from a series of patients who underwent coronary angiography. Among them, patients with increased creatinine levels were twice as likely to experience a coronary event. This heightened risk was independent of other comorbidities, including

the angiographic pattern of coronary disease.¹³

Detection of renal dysfunction is of utmost importance in clinical practice, for epidemiological studies in the United States, as already stated, suggest that approximately 20 million Americans have some degree of renal injury.^{4,35} Additionally, 50% of cardiomyopathic patients show some degree of renal dysfunction, which often goes underdiagnosed.³⁸ As previously mentioned, renal dysfunction in patients with cardiomyopathy, coronary artery disease, and hypertension usually carries a worse prognosis. Patients with concomitant coronary insufficiency and renal artery atherosclerotic disease also have poor prognosis.³⁹ It has been postulated that this behavior may be due to the activation of the renin-angiotensin-aldosterone system which invariably follows this clinical condition.

It should be kept in mind that not only renal dysfunction, but also mere renal injury, identified by microalbuminuria, is associated with increased cardiovascular risk, regardless of the presence of diabetes^{40,41} or the degree of arterial hypertension.^{42,43}

In diabetics, the “non-dipper” pattern, that is, the lack of the physiological drop in nocturnal blood pressure,³¹ even among normotensive type I diabetics, is associated with microalbuminuria and often precedes its development. In cross-sectional studies^{44,45} microalbuminuria is associated with target-organ damages, and in longitudinal studies represents an indicator of adverse prognosis regarding both general and cardiovascular mortality.⁴⁰⁻⁴² In the Heart Outcomes Prevention Evaluation (HOPE) trial, microalbuminuria was associated with a 61% increase in cardiovascular risk and with a doubling of all-cause mortality.⁴⁰

Patients with microalbuminuria have an accumulation of associated risk factors, which may explain this excess mortality⁴⁴; nonetheless, as with asymptomatic renal dysfunction, these patients’ cardiovascular risk is higher than that calculated by the predictive equations.⁴⁶ In addition to reflecting increased severity of target-organ damage, this excess cardiovascular mortality is associated with endothelial dysfunction⁴⁷ and inflammatory changes,⁴⁸ as well as changes in the coagulation and fibrinolytic systems.⁴⁹

In the Life trial, not only the presence of baseline microalbuminuria, but also regression of microalbuminuria was associated with a decline in cardiovascular risk.⁴¹ Losartan was more effective than atenolol in promoting microalbuminuria regression, thus suggesting that anti-hypertensive treatment be tailored based on the presence of microalbuminuria regression. In this sense, the Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria (IRMA II) was the first trial to study⁵⁰ the class of A_{II} antagonists in secondary prevention of nephropathy. The primary endpoint was to evaluate the role of irbesartan in the progression from incipient diabetic nephropathy, defined as the presence of microalbuminuria,

to the next stage, namely, overt proteinuria. While 15% of the patients in the control group receiving conventional anti-hypertensive therapy, except ACE inhibitors and A_{II} antagonists, progressed to proteinuria, only 5% of the patients receiving the highest dose of irbesartan had their condition worsened. As the secondary endpoint, microalbuminuria was normalized, reverting, therefore, to normoalbuminuria, in a significant number of patients treated with irbesartan. As microalbuminuria is both cardiovascular risk and marker of endothelial damage, the lower rate of cardiac events in the group treated with A_{II} antagonists, due to decreased rates of abnormal urinary albumin excretion, stress the role of this anti-hypertensive class on target-organ protection. Regression of microalbuminuria may, therefore, be considered a goal to be achieved in the treatment of hypertensive patients.

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) highlights renal dysfunction as a major cardiovascular risk and emphasizes the importance of identification and tighter control of blood pressure in this subgroup of patients, and thus recommend a BP goal of 130/80 mm Hg.⁵¹ The European Society of Hypertension/European Society of Cardiology guidelines recognizes mild renal dysfunction as target-organ lesion and classify these patients as being at high risk for cardiovascular disease.⁵² In 1988, the National Kidney Foundation (NKF) Task Force on Cardiovascular Disease in Chronic Renal Disease recommended that patients with chronic renal disease be considered in the highest-risk group for their treatment design.⁵³ Based on results from the MDRD, the IV Brazilian Guidelines recommend BP levels of 120/75 mm Hg in patients with diabetic nephropathy and proteinuria above 1.0 g/24h and in patients with general nephropathy and proteinuria above 3.0 g/24h⁵⁴.

In spite of these recommendations, recent epidemiological data show that patients with renal dysfunction receive cardiovascular medications and interventions less frequently than patients with preserved glomerular filtration rate, although these very studies demonstrate that the use of these medications and procedures are associated with the same benefits obtained by patients with normal glomerular filtration.

Patients with chronic renal failure require multiple drug therapy if adequate blood pressure levels are to be achieved, and the use of angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin-receptor blockers (ARBs) are mandatory owing to their renoprotective action, in addition to their anti-hypertensive effect. Diuretics are also invariably necessary, because of their anti-hypertensive effectiveness in this subgroup of patients.⁴⁹⁻⁵²

Besides greater reduction in blood pressure, other risk factors should be tightly controlled in these patients. Accordingly, hemoglobin A1c levels should be below 7%⁵⁶ and low-density lipoprotein cholesterol levels, below 100 mg/dL⁵⁷. Non-traditional risk factors should be addressed as well, by maintaining hemoglobin between 11 and 12

mg/dL⁵⁸ through meticulous iron supplementation and erythropoietin. Divalent ions should be strictly controlled with calcium chelators or calcium-free chelators, according to the case, to prevent vascular calcifications. Parathyroid hormone levels should be regulated with vitamin D used parsimoniously.⁵⁹ Low-dose aspirin proved to be safe and effective in this subgroup of patients, particularly diabetics and dyslipidemics.¹⁴ The use of non-hormonal anti-inflammatory drugs, though, should be strongly discouraged in all degrees of renal failure.⁶⁰ Finally, these patients should be considered for cardiac procedures,

which should be indicated for patients with chronic renal disease and the general population alike.⁵⁵

In sum, renal injury, even if asymptomatic, is a common condition that tends to be underdiagnosed; it carries high cardiovascular risk and should be routinely assessed in all patients with hypertension, diabetes, congestive heart failure, or coronary insufficiency. If a renal abnormality is found, appropriate measures should be taken vigorously aiming not only to preserve renal function, but also prevent cardiovascular disease progression.

REFERENCES

- Langendorf R, Pirani CL. The heart in uremia. An electrocardiographic and pathology study. *Am Heart J* 1945; 28: 282-307.
- Lindner A, Charra B, Sherrard D et al. Accelerated atherosclerosis in prolonged maintenance hemodialysis. *N Engl J Med* 1974; 290: 697-701.
- Coresh J, Astor BC, Green T, Eknoyan G, Levey AS. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. *Am J Kidney Dis* 2003; 41: 1-12.
- National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. US Renal Data System, USRDS 2000 Annual Data Report. Bethesda, Md: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2000. Disponível em: http://www.usrds.org/atlas_2000.htm. Acessado em 13 de maio de 2005.
- Longenecker JC, Coresh J, Powe NR et al. Traditional cardiovascular disease risk factors in dialysis patients compared with the general population: the CHOICE Study. *J Am Soc Nephrol* 2002; 13: 1918-27.
- Shulman NB, Ford CE, Hall WD et al. Prognostic value of serum creatinine and effect of treatment of hypertension on renal function results from the hypertension detection and follow-up program. *Hypertension* 1989; 13 (suppl 1): 1.80-1.93.
- Zanchetti A, Hansson L, Dahlof B et al. Effects of individual risk factors on the incidence of cardiovascular events in the treated hypertensive patients of the Hypertension Optimal Treatment Study. *J Hypertens* 2001; 19: 1149-59.
- Wang JG, Staessen JA, Fagard RH, Birkenhager WH, Gong L, Liu L. Prognostic significance of serum creatinine and uric acid in older Chinese patients with isolated systolic hypertension. *Hypertension* 2001; 37: 1069-74.
- Schillaci G, Reboldi G, Verdecchia P. High-normal serum creatinine concentration is a predictor of cardiovascular risk in essential hypertension. *Arch Intern Med* 2001; 161: 886-91.
- Ruilope LM, Salvetti A, Jamerson K et al. Renal function and intensive lowering of blood pressure in hypertensive participants of the hypertension optimal treatment study. *J Am Soc Nephrol* 2001; 12: 218-25.
- Mann JFE, Gerstein HC, Pogue J, Bosch J, Yusuf S. Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: the HOPE randomized trial. *Ann Intern Med* 2001; 134: 629-36.
- De Leeuw P, Thijs L, Birkenhager WH et al. Prognostic significance of renal function in elderly patients with isolated systolic hypertension: results from Syst-Eur trial. *J Am Soc Nephrol* 2002; 13: 2213-22.
- Beddhu S, Allen-Brady K, Cheung AK et al. Impact of renal failure on the risk of myocardial infarction and death. *Kidney Int* 2002; 62: 1776-83.
- Zanchetti A, Hansson L, Dahlof B et al. HOT Study Group. Benefit and harm of low-dose aspirin in well-treated hypertensives at different baseline cardiovascular risk. *J Hypertens* 2002; 20: 2301-7.
- Pahor M, Shorr RI, Somes GW et al. Diuretic-based treatment and cardiovascular events in patients with mild renal dysfunction enrolled in the Systolic Hypertension in the Elderly Program. *Arch Intern Med* 1998; 158: 1340-5.
- Sarnak MJ, Greene T, Wang X 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. *An Int Med* 2005; 142: 342-51.
- Culleton BF, Larson MG, Wilson PW, Parfrey PS, Levy D. Cardiovascular disease and mortality in a community-based cohort with mild renal insufficiency. *Kidney Int* 1999; 56: 2214-9.
- Manjunath G, Tighiouart H, Coresh J et al. Level of Kidney function as a risk factor for cardiovascular outcomes in the elderly. *Kidney Int* 2003; 63: 1121-9.
- Lassnigg A, Schmidlin D, Mouhieddine M, Bachmann LM, Bauer P, Hiesmayr M. Minimal changes of serum creatinine predict prognosis in patients after cardiothoracic surgery: A Prospective Cohort Study. *J Am Soc Nephrol* 2004; 15: 1597-605.
- Reinecke H, Trey T, Matzkies F, Fobker M, Breithardt G, Schaefer RM. Grade of chronic renal failure, and acute and long-term outcome after percutaneous coronary interventions. *Kidney Int* 2003; 63: 696-701.
- Wilson S, Foo K, Cunningham J et al. Renal function and risk stratification in acute coronary syndromes. *Am J Cardiol* 2003; 91: 1051-4.
- Krumholz HM, Chen YT, Vaccarino V et al. Correlates and impact on outcomes of worsening renal function in patients > or = 65 years of age with heart failure. *Am J Cardiol* 2000; 85: 1110-3.
- Block GA, Hubert-Shearon TE, Lavin NW et al. Association of serum phosphorus and calcium phosphate product with mortality risk in chronic hemodialysis patients: a national study. *Am J Kidney Dis* 1998; 31: 607-17.
- Ma JZ, Ebsen J, Xia H et al. Haematocrit level and associated mortality in hemodialysis patients. *J Am Soc Nephrol* 1999; 10: 610-9.
- Martin LC. Alterações do ventrículo esquerdo e suas inter-relações com a monitorização ambulatorial da pressão arterial em pacientes tratados por hemodiálise crônica. Botucatu, 2004. Tese (Doutorado) – Faculdade de Medicina de Botucatu, Universidade Estadual Paulista.
- Martin LC, Franco RJ, Gavras I et al. Association between hypervolemia and ventricular hypertrophy in hemodialysis patients. *Am J Hypertens* 2004; 17: 1163-9.
- Moustapha A, Naso A, Nahlawi M et al. Prospective study of hyperhomocysteinemia as an adverse cardiovascular risk factor in end-stage renal disease. *Circulation* 1998; 97: 138-41.
- Longenecker JC, Klag MJ, Marcovina SM et al. Small apolipoprotein(a) size predicts mortality in end-stage renal disease: The CHOICE Study. *Circulation* 2002; 106: 2812-8.
- Kielstein JT, Boger RH, Bode-Boger SM et al. Asymmetric dimethylarginine plasma concentrations differ in patients with

- end stage renal disease: relationship to treatment method and atherosclerotic disease. *J Am Soc Nephrol* 1999; 10: 594-600.
30. Kaysen GA. The microinflammatory state in uremia: causes and potencial consequences. *J Am Soc Nephrol* 2001; 12: 1549-57.
 31. Lurbe E, Redon J, Kesani A et al. Increase in nocturnal blood pressure and progression to microalbuminuria in type 1 diabetes. *N Engl J Med* 2002; 347: 797-805.
 32. Levin A, Thompson CR, Ethier J et al. Left ventricular mass index increase in early renal disease: impact of decline in hemoglobin. *Am J Kidney Dis* 1999; 34: 125-34.
 33. Zehnder C, Zuber M, Sulzer M et al. Influence of long-term amelioration of anemia and blood pressure control on left ventricular hypertrophy in hemodialyzed patients. *Nephron* 1992; 61: 21-5.
 34. Park CW, Oh YS, Shin YS et al. Intravenous calcitriol regresses myocardial hypertrophy in hemodialysis patients with secondary hyperparathyroidism. *Am J Kidney Dis* 1999; 33: 73-81.
 35. National Kidney Foundation. H/DOQI clinical practice guidelines for chronic kidney diseases: evaluation, classification and stratification. *Am J Kidney Dis* 2002; 39 (Suppl 1): S1-S266.
 36. Goodman WG, Goldin J, Kuizon BD et al. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. *N Engl J Med* 2000; 342: 1478-83.
 37. Portman RJ, Hawkins E, Verani R. Premature atherosclerosis in pediatric renal patients: report of the Southwest Pediatric Nephrology Study Group. *Ped Res* 1991; 29: 349.
 38. Silverberg D, Wexler D, Blum M, Schwartz D, Laina A. The association between congestive heart failure and chronic renal disease. *Current Opinion Nephrology Hypertension* 2004; 13: 163-70.
 39. Svarstad E, Urheim L, Iversen BM. Critical renal artery stenoses may cause a spectrum of cardiorenal failure and associated thromboembolic events. *Clin Nephrol* 2005; 63: 487-92.
 40. Gerstein HC, Mann JF, Yi Q et al. HOPE Study Investigators. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA* 2001; 286: 421-6.
 41. Ibsen H, Wachtell K, Olsen MH et al. Does albuminuria predict cardiovascular outcome on treatment with losartan versus atenolol in hypertension with left ventricular hypertrophy? A Life substudy. *J Hypertens* 2004; 22: 1805-11.
 42. Messent JW, Elliott TG, Hill RD, Jarrett RJ, Keen H, Viberti GC. Prognostic significance of microalbuminuria in insulin-dependent diabetes mellitus: a twenty-three year follow-up study. *Kidney Int* 1992; 41: 836-9.
 43. Nakamura S, Kawano Y, Inenaga T et al. Microalbuminuria and cardiovascular events in elderly hypertensive patients without previous cardiovascular complications. *Hypertension Research - Clinical & Experimental* 2003; 26: 603-8.
 44. Torffvit O, Agardh E, Agardh CD. Albuminuria and associated medical risk factors: a cross-sectional study in 451 type II (noninsulin-dependent) diabetic patients. Part 2. *J Diab Complications* 1991; 5: 29-34.
 45. Niskanen LK, Penttila I, Parviainen M, Uusitupa MI. Evolution, risk factors, and prognostic implications of albuminuria in NIDDM. *Diab Care* 1996; 19: 486-93.
 46. Stephenson JM, Kenny S, Stevens LK, Fuller JH, Lee E. Proteinuria and mortality in diabetes: the WHO Multinational Study of Vascular Disease in Diabetes. *Diab Med* 1995; 12: 149-55.
 47. Stehouwer CD, Gall MA, Twisk JW, Knudsen E, Emeis JJ, Parving HH. Increased urinary albumin excretion, endothelial dysfunction, and chronic low-grade inflammation in type 2 diabetes: progressive, interrelated, and independently associated with risk of death. *Diabetes* 2000; 51: 1157-65.
 48. Festa A, D'Agostino R, Howard G, Mykkanen L, Tracy RP, Haffner SM. Inflammation and microalbuminuria in nondiabetic and type 2 diabetic subjects: The Insulin Resistance Atherosclerosis Study. *Kidney Int* 2000; 58: 1703-10.
 49. Tarnow L, Stehouwer CD, Emeis JJ et al. Plasminogen activator inhibitor-1 and apolipoprotein E gene polymorphisms and diabetic angiopathy. *Nephrol Dial Transplant* 2000; 15: 625-30.
 50. Parving HH, Lehnert H, Brochner-Mortensen J, Gomis R, Andersen S, Arner P for the Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study Group. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med* 2001; 345: 870-8.
 51. Chobanian AV, Bakris GL, Black HR et al. Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute. National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure 2003; 42: 1206-52.
 52. Guidelines Committee 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens* 2003; 21: 1011-53.
 53. National Kidney Foundation Task Force on Cardiovascular Disease. Controlling the epidemic of cardiovascular disease in chronic renal disease: What do we know? What do we need to know? Where do we go from here? Special report from the National Kidney Foundation Task Force on Cardiovascular Disease. *Am J Kidney Dis*. 1998; 32: S1-199.
 54. *IV Diretrizes Brasileiras de Hipertensão Arterial. Rev Bras Hip* 2002; 4: 1-40.
 55. Sarnak MJ, Levey AS, Schoolwerth AC et al. American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation* 2003; 108: 2154-69.
 56. Bregman R. Prevenção da progressão da doença renal crônica. *J Bras Nefrol* 2004; 26 (supl1): 11-4.
 57. Batista M, Rodrigues CJO. Alterações metabólicas. *J Bras Nefrol* 2004; 26 (supl.1): 15-9.
 58. Abensur H. Anemia da doença renal crônica. *J Bras Nefrol* 2004; 26 (supl.1): 26-8.
 59. Carvalho AB. Osteodistrofia renal. *J Bras Nefrol* 2004; 26 (supl.1): 29-39.
 60. Oliveira MB. Recomendações para diminuir o risco de agudização da DRC. *J Bras Nefrol* 2004; 26 (supl.1): 9-10.