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EDITORIAL

Frequent office visits of patients with chronic kidney disease: Is a prelude to prevention of dialysis

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Abstract

This study is an excerpt of broad-based office practice which is designed to treat patients with diabetes and hypertension, the two most common causes of chronic kidney disease (CKD), as well as CKD of unknown etiology. This model of office practice is dedicated to evaluating patients with CKD for their complete well-being; blood pressure control, fluid control and maintenance of acid-base status and hemoglobin. Frequent office visits, every four to six weeks, confer a healthy life style year after year associated with a feeling of good well-being and a positive outlook. Having gained that, such patients remain compliant to their medication and diet, and scheduled laboratory and office visits which are determinant of a dialysis-free life.

Key words: Diabetes; Hypertension; Chronic kidney disease; End stage renal disease; Preventative care; Small kidneys; Serum bicarbonate; Non-dialysis

Core tip: Diabetes and hypertension are two most common causes of chronic kidney disease (CKD). Nephrology office practice constitutes vast majority of the patients with CKD of different stages. While CKD stages 1-3 [glomerular filtration rate (GFR) (< 60 - > 30 mL/min)] produce slight or no symptoms or signs, CKD stages 4-6 (GFR < 30 - < 10 mL/min) may increase blood pressure and produce fluid electrolyte and acid-based disorders. The goal of office practice is to identify these disorders, then treat them to enable patients to live asymptomatically.

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INTRODUCTION

Experience in direct patient care reveals that frequent office visits of patients encompassing chronic illnesses such as hypertension, diabetes, or chronic kidney disease (CKD) is a form of salutary care. This model of direct patient care is advantageous for the patients; it is educational and economical. This model of patient care is advantageous because of continuity of care which permits the patients to gain confidence in their physicians and allows them to feel comfortable in addressing their issues freely.

Similarly, continuity of care permits the physicians to identify and resolve the issues in a comfortable fashion. Other authors have reported that continuity of care has led to improved outcomes of diabetes care, delivery of preventative care and clinical satisfaction, while also decreasing the number of emergency room visits, hospitalizations, readmissions and reducing length of stay[1].

There is an interesting study which asked the question: If an outpatient repeatedly sees the same practitioner, is his care influenced? A double blind randomized trial examined the effects of outpatient health care

provider continuity on the process and outcome of the medical care for 776 men aged 55 years and older. Participants were randomized to two groups of provider care: provider discontinuity and provider continuity. During an 18 mo period, continuity group had fewer emergency admissions (20% *vs* 39%) and a shorter average length of hospital stay (15.5 d *vs* 25.5 d). The continuity group also felt that the providers were more knowledgeable, thorough and interested in patient education[2].

Giving autonomy or independence in self-care motivates patients to control their illness with prescribed medication, diet, and physical therapy uniquely in illnesses such as diabetes, hypertension or CKD. In one study, 128 patients with diabetes were tested and found to achieve significant reductions in their HbA1c values over 12 mo[3]. It is important to know that understanding of side effects of medication corresponded to compliance with any proposed regimen (87% cases *vs* 93% control: non-significant).

Despite the similarity between the two groups, 53% of cases reported that side effects of medication were explained to them, in contrast to 84% of controls. This difference is significant indicating that the side effects of therapy are often not explained to the patients[4].

Other studies have noted that a relationship exists between the way in which physicians and patients behave during an office visit and that relationship influences patients' subsequent health status. More control by the patients, less control by physicians, more negative effect expressed by both, more effective information seeking by patients, and greater overall patient conversation relative to the physician were consistently related to better control of diabetes and hypertension as measured by hemoglobin A1c and diastolic blood pressure (BP) respectively[5].

PURPOSE OF THIS COMMUNICATION

Having given that background, it is time to illustrate how chronic diseases like diabetes, hypertension or chronic kidney disease (CKD) of unknown etiology can be followed in the office setting for an indefinite period to ensure a good living for the patient. The goal of frequent office visits is to afford asymptomatic state, reduce hospitalization and prolong comfortable survival without dialysis therapy. Two patients are exemplified to that effect.

Example 1 - patient with CKD or chronic renal failure of undetermined etiology

April 2008 - first visit: A-84-year-white female referred for end stage renal disease, without history of diabetes. Patient was not aware that she was treated for hypertension and exhibited no symptoms. Physical examination revealed pulse 64/min irregular, sitting BP 140/100 mmHg, standing BP 140/90 mmHg, and chest auscultation revealed rhonchi and a questionable mass with tenderness in the left iliac fossa. Her medication included ergo/chole calciferol 2.5 mcg per oral daily, levothyroxine 75 mcg per oral daily, amlodipine 5 mg per oral daily, sodium bicarbonate 650 mg per oral three times daily, and irbesartan 75 mg per oral daily.

She brought a laboratory which was done the previous October. The findings were glucose 96 mg/dL, BUN 49 mg/dL, serum creatinine 4.3 mg/dL, estimated glomerular filtration rate (eGFR) 10 mL/min, Na^+ 143 mmol/L, K^+ 4.3 mmol/L, chloride 106 mmol/L, CO_2 25.6 mmol/L, phosphorous 4.3 mg/dL, albumin 3.9 g/dL, calcium 9.9 mg/dL hemoglobin 11.8 g/dL and hematocrit 34.9%. A urinalysis revealed protein 1+, bacteria 4+, and WBC 33/HPF. A CT scan of the abdomen done in 2001 revealed bilaterally small kidneys. Assessment was end stage renal disease. She was admitted to a local hospital for further assessment. Irbesartan was discontinued. She was treated with bicarbonate infusion and released. No dialysis was recommended. Through the years, patient has done well, remained asymptomatic but required once a year hospital admission for diarrhea and dehydration or poor appetite. Her appetite is markedly increased with initiation of megestrol. BP control was achieved with increased dose of amlodipine. Serum bicarbonate level is maintained near normal level with increased dosage of sodium bicarbonate.

Most recent visit in March of 2013, 5 years later: Symptoms: none; Appetite: good; Activity: normal; Essential medications: (1) amlodipine 10 mg per oral daily; (2) sodium bicarbonate 1300 mg per oral 4 times daily; (3) potassium chloride 20 meq per oral daily for hypokalemia. (4) appetite stimulant megestrol, 40 mg per oral daily; (5) hectoral (ergo/chole calciferol) 2.5 mcg per oral daily; (6) levothyroxine 125 mcg per oral daily; and (7) allopurinol 150 mg per oral daily. physical examination: no edema, BP 120/80 mmhg, electrocardiogram normal; Laboratory: glucose 145 mg/dL, BUN 61 mg/dL, serum creatinine 7.8 mg/dL, eGFR 5 mL/min, Na^+ 144 mmol/L, K^+ 4.3 mmol/L, chloride 109 mmol/L, CO_2 21 mmol/L, phosphorous 3.5 mg/dL, albumin 3.7 g/dL, intact parathyroid hormone 97 pg/mL; Plans: (1) continue current therapy; (2) No dialysis is recommended; and (3) Office visits are scheduled every 6 wk.

Example 2 - A-70-year-white male is a five year office follow-up for hypertension and renal function control

March 2008 - first visit: Chief complaint: breathing trouble for 2-3 years. Patient gave history of hypertension for 5 years. Significant past history includes coronary angioplasty with rupture of the coronary artery followed by coronary artery bypass graft in 1992; back surgery × 4, last one in 1995. Smoked until 1990 then quit. Significant finding on physical exam was elevated BP sitting 180/110 and 170/106 mmHg standing and pulse rate 98 per minute. A questionable bruit heard left to umbilicus. Funduscopic exam reveals arterial narrowing. Disc could not be visualized. He obtained a laboratory in March 2006 which showed hemoglobin 13.5

Table 1 Characteristics of patients with advanced chronic kidney disease

	Patient 1		Patient 2	
	First visit (2008)	Recent visit (2013)	First visit (2008)	Recent visit (2013)
Age (yr)	84	89	70	75
Symptoms	None	None	None	None
Appetite	Good	Good	Good	Good
BP (mmHg)	140/100	120/80	180/110	120/70
Edema	0	0	0	0
Bun (mg/dL)	49	61	28	35
Scr (mg/dL)	4.3	7.84	2.6	2.5
eGFR (mL/min)	10	5	26	24
CO_2 (mmol/L)	26	21	29	27
Hgb (g/dL)	12	13.7	13	12
Serum potassium (mmol/L)	4.3	4.3	4.1	4.5

eGFR: Estimated glomerular filtration rate.

g/dL, hematocrit 39.5%, BUN 21 mg/dL, serum creatinine 1.9 mg/dL, eGFR 37.6 mL/min, CO_2 27 mmol/L, and albumin 3.7 g/dL. Medication at this first office visit included amlodipine 5 mg per oral daily, furosemide 40 mg per oral daily, simvastatin 10 mg per oral daily, prednisone 10 mg per oral daily and albuterol inhalation. Laboratory done in February 2008 showed BUN 28 mg/dL, serum creatinine 2.6 mg/dL, glucose 105 mg/dL, Na 145 mmol/L, K 4.1 mmol/L, eGFR 26 mL/min. One month later in March 2008, his hemoglobin was 13.1 g/dL, hematocrit 39.3%, renin 0.6 ng/mL per hour, aldosterone 3 ng/dL. Medication was adjusted to include tenormin 50 mg per oral daily, increase amlodipine 5 mg twice daily and reduce furosemide 40 mg per oral every other day and prednisone 5 mg per oral daily. Two weeks later his BP decreased to 140/90 mmHg sitting and 130/90 mmHg standing and pulse rate was reduced to 66 beats/min. Soon thereafter his BP became normal. He records his BP at home and they are all normal of average less than 130/80 mmHg. He is followed in the office every six to seven weeks with laboratory done before each visit.

Most recent visit in February of 2013, 5 years later: Symptoms: none; Shortness of breath on exertion: none; Sitting BP: 120/70 mmHg; Current medications: atenolol 50 mg per oral daily, bumetanide 1 mg per oral Mondays and Fridays, amlodipine 10 mg per oral twice daily, digoxin 0.125 mg per oral Mondays, Wednesdays, Fridays and Sundays, sodium bicarbonate 1300 mg three times daily and sodium polysterene sulfonate (Kayexalate) in 30% sorbitol 5 g in 20 mL twice daily. Laboratory (Fasting) glucose 107 mg/dL, BUN 35 mg/dL, serum creatinine 2.48 mg/dL, eGFR 24 mL/min, sodium 142 mmol/L, potassium 4.5 mmol/L, calcium 9.8 mg/dL, phosphorous 4.3 mg/dL, intact PTH 178 pg/mL, uric acid 8 mg/dL, hemoglobin 11.6 g/dL, hematocrit 34.7%; Analysis of the life style of the two examples: Patients with advanced CKD, frequent office visits are permissive of living without dialysis. These can be viewed at a glance in Table 1.

The renal function tests including serum creatinine and eGFR in patients 1 and 2 are shown in Figures 1 and 2, respectively. In five years follow up; notably both patients are asymptomatic and living good albeit active lives. In both, BP is under perfect control and potassium control is normal. eGFR is decreased in both, more so in patient 1. The latter is probably more age related decrease rather than progression of CKD. Patient 1 is much older than patient 2. Neither is anemic by definition and required erythropoietic stimulating agent any time. Hypertension which is a most important risk factor in CKD progression is under superb control in both. In both patients, BP control is achieved with dihydropyridine calcium channel blocker (CCB) alone or a combination of CCB and beta blocker. A low dose loop diuretic and digoxin is used in patient 2 for pulmonary congestion and shortness of breath sometimes during the 5-year period. Overall, neither patient manifests symptoms or signs of fluid overload. Metabolic acidosis, hence hyperkalemia is prevented in both patients with liberal use of sodium bicarbonate and potassium exchange resin. The latter is used in sorbitol solution to avoid constipation.

COLLOQUIUM OF FREQUENT OFFICE VISIT IN CKD

Frequent office visits, for example every four to 8 wk, depending on the symptoms and laboratory findings of the previous office visit, is essential for (1) detection of unwarranted symptoms and signs at an early stage (2) maintaining the current well-being and steady state of BP control and fluid-electrolyte and acid-base status. Thus during each office visit a check list is completed of the following: (2) symptoms, (2) weight, (3) BP, (4) hemoglobin/hematocrit, (5) serum glucose: fasting and 2-h postprandial for patients with existing or new-onset diabetes, (6) renal function: BUN, serum creatinine, and eGFR, (7) electrolytes: Na^+, K^+, CO_2; and calcium, phosphorous, uric acid and albumin, (8) intact PTH, (9) arterial blood gas to determine if low CO_2 is due to metabolic acidosis or respiratory alkalosis, severity of metabolic acidosis, and PO_2 in those with suspected

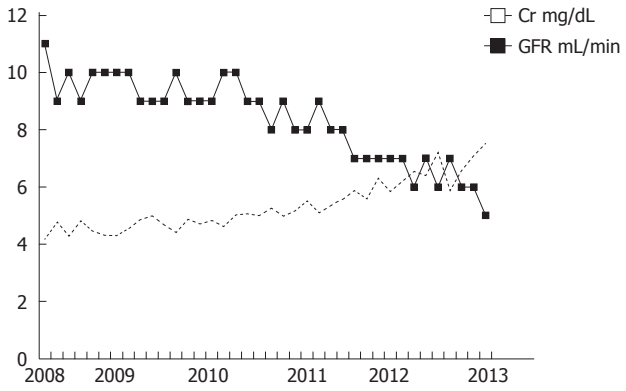

Figure 1 Serum creatinine and estimated glomerular filtration rate from patient 1 are depicted from 2008-2013. Note slow but progressive increase in creatinine (Cr) and decrease in glomerular filtration rate (GFR).

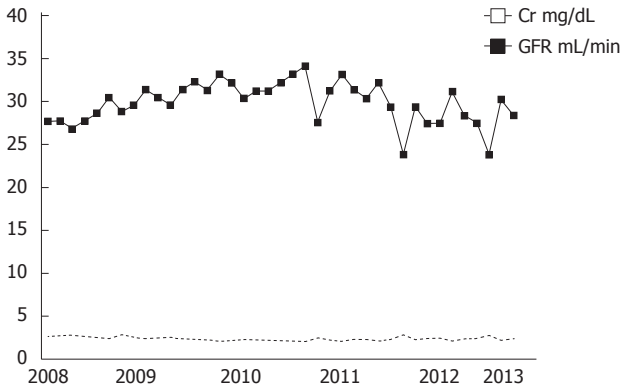

Figure 2 Elevated but essentially unchanged serum creatinin around 2.5 mg/dL yearly from 2008-2013, while estimated glomerular filtration ratevaried between 25 and 35 mL/min throughout the period from 2008-2013. Cr: Creatinine; GFR: Glomerular filtration rate.

congestive heart failure, (10) electrocardiogram in those with irregular heart rhythm, (11) review all medicines carefully. Discontinue any medicines suspected of causing renal function impairment and electrolyte imbalance.

GOALS OF FREQUENT OFFICE VISITS IN CKD

Keep BP under control. Generally BP less than 140/80 mmHg is acceptable. BP less than 130/70 mmHg is probably ideal. BP of less than 120/70 mmHg may be harmful. In order to maintain BP at the levels already mentioned, it is very important to review BP medication at every visit and adjust as required. In resistant hypertension, a diuretic is a choice to reduce sodium (salt) and water retention which is common in CKD patients. Chlorthalidone is the diuretic of choice which predictably reduces elevated BP associated with salt and water retention. The dose of chlorthalidone is 25-50 mg once daily. Hydrochlorothiazide 25-50 mg once daily can be used instead of chlorthalidone. Loop diuretic such as furosemide 40 mg per oral once or twice daily or bumetanide 1 mg per oral once or twice daily is preferable if patient has evidence of congestive heart failure such as shortness of breath on exertion, pulmonary congestion in a chest X-ray or low PO_2 in a blood gas analysis. Hyperkalemia and metabolic acidosis disorders are common and often severe, in those who are diet noncompliant, in particular consuming large meals or eating too many fruits. Prescription of angiotensin converting enzyme inhibitors or angiotensin receptor blockers by many prescribers with the obsessive idea of renal protection is a common cause of life threatening hyperkalemia ($\geqslant$ 7.5 mmol/L) and metabolic acidosis. Use of over the counter drugs commonly non-steroidal anti-inflammatory drugs for pain is also a common cause of hyperkalemia and metabolic acidosis.

Prevention of hyperkalemia is attainable but prevention of metabolic acidosis is more difficult to achieve. Since hyperkalemia is the result of transport of hydrogen ions, minimizing hydrogen build up is a key to prevention of both. Hydrogen ion build up can be minimized by controlling the source of hydrogen ion which is the food. A low protein diet (40-50 g) is beneficial in keeping BUN less than 50 mg/dL, reducing the risk of metabolic acidosis, hyperkalemia and hyperphosphatemia. A low protein diet supplies less sodium in the diet and is very useful in keeping BP under control and effective in minimizing fluid overload and CHF. However, low protein diet is non-palatable and adherence to this diet is uncommon. In addition, low protein diet is associated with malnutrition and low serum albumin which increase mortality. Thus protective effect of low protein diet cannot be relied upon; consequently therapeutic endeavor is essential. Protective effect of sodium bicarbonate therapy is documented by this author, and many other authors. Other authors have reported that sodium bicarbonate supplementation slows progression of CKD and improves nutritional status[6].

It should be noted that both patients in Table 1 are treated with sodium bicarbonate 650 mg tablet × 2, four times daily. Although CO_2 in patient 1 is lower than that of patient 2 which is due to severity of renal dysfunction in patient 1, but serum albumin level is near normal and comparable. For prevention and treatment of hyperkalemia, sodium polysterene sulfonate (SPS) (Kayexalate®) is a good therapy. SPS dispensed in 30% sorbitol is very effective in keeping potassium under control. The usual dose is 5 g in 20 mL sorbitol once or twice daily. It may cause diarrhea which of course is the mechanism to enhance potassium excretion through the bowel when renal excretion of potassium is low. Effectiveness of kayexalate is increased when dispensed in sorbitol rather than dispensed in powder form, however, in the long run sorbitol is likely to increase blood glucose level. 9-α fludrocortisone (Florinef®), a synthetic analog of aldosterone in doses of 0.1-1 mg per oral once daily (usual dose is 0.1-0.3 mg/d) is also effective in enhancing renal excretion of potassium, but it is fraught with a risk of hypertension and CHF. Serum sodium is a good index of fluid balance. Rapid decrease in serum sodium may be significant for fluid overload and CHF. Attention

must be paid in every office visit to hemoglobin level. Unchanged and normal or near normal hemoglobin (≥ 11 g/dL) is a good indirect evidence of stable renal function even if it is low. Rapid decrease of hemoglobin to less than 10 g/dL is a signal for rapidly deteriorating renal function, fluid overload, gastrointestinal bleeding or combination of any or all of these. Aspirin use should be avoided when hemoglobin is less than 11 g/dL and unstable. Phosphate control is a highly published item by the pharmaceutical industry. In the experience of the author, phosphate control has caused no problem to ensure well-being of the patients with CKD and maintain a dialysis free life.

CONCLUSION

Given the poor outcomes of many old, frail patients with multiple comorbid conditions on dialysis, there is a debate as to whether non-dialysis management as illustrated here would be more humane than dialysis management[7]. There are no studies done comparing survival or quality of life on conservative care and dialysis[8]. As described in the manuscript, conservative care should be given the highest priority in elderly people with advanced chronic renal failure. I believe that the evidence of the two patients shown here is important and should lead to a formal study.

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ORIGINAL ARTICLE

Silent diabetic nephropathy

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Abstract

AIM: To examine the risk of renal events in patients with biopsy-proven diabetic nephropathy (DN) and its possible associated factors.

METHODS: Clinical and histological data of 60 patients diagnosed with diabetic nephropathy were retrospectively collected. Patients with evidence or suspicion of other nephropathies were excluded from the study. The final event was defined as renal replacement therapy (RRT) initiation or progression of chronic kidney disease (CKD), according to the KDIGO 2012 definition of a decrease in CKD category and a decrease in GFR of 25% or more.

RESULTS: A total of 45 patients with a follow-up of at least 3 mo were included. Most of the patients presented type 2 DM, with a mean age of 58.3 years old. The time of evolution of DM was 9.6 ± 7.8 years, although in 13 patients, it was less than 5 years. A total of 62% of patients reached the final event in a mean period of 3.4 years (95%CI: 2.1-4.7), with 21 of them requiring dialysis. The factors that were independently associated with renal survival were estimated glomerular filtration rate (eGFR) at the time of biopsy, cardiovascular disease (CVD) history and HbA1c less than 7%. Therefore, for each 10 mL/min per 1.73 m^2 reduction in eGFR, we obtained a DN progression risk of HR = 2 (1.3-3.0) (P = 0.001); patients with CVD were at greater risk for DN progression (HR = 2.8, 1.1-7.1, P = 0.032), and CKD patients with HbA1c < 7% demonstrated greater renal risk than patients with HbA1c ⩾ 7%, with an HR of 2.9 (1.0-8.4) (P = 0.054).

CONCLUSION: A past history of CVD is a risk factor for DN progression. Levels of HbA1c less than 7% could favor an eGFR decrease in these patients.

Key words: Diabetic nephropathy; Predictors of progression; Histopathological diagnosis; Cardiovascular disease; Silent disease

Core tip: There are other forms of presentation of diabetic nephropathy (DN), in addition to progressive proteinuria, that can result in renal insufficiency. In some cases, DN is diagnosed in advanced stages, without previous suspicion of this diagnosis. The clinical course can be atypical, and the time of evolution of diabetes mellitus can be short. Not all the factors that play a role the evolution of DN have been elucidated. Our findings suggest that in patients with chronic kidney disease secondary to DN, a previous history of cardiovascular disease and HbA1c less than 7%, are negative prognostic factors for renal function.

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INTRODUCTION

The risk factors for diabetic nephropathy (DN) include genetic predisposition[1,2], poor glycemic control[3], older age[4], male sex[5], duration of diabetes, hypertension[6] and smoking. Classically, the natural history of the disease was considered to be an evolution that began after 5-15 years after the onset of diabetes with albuminuria[7]. Albuminuria increases cardiovascular risk, but it also increases the risk of progression to proteinuria, especially in type 1 diabetes mellitus (T1DM)[8]. It is unclear what predisposes 50% of individuals with albuminuria to progress to proteinuria in a phase that lasts approximately 10 years[9]. After the development of proteinuria, 50% of patients will progress to end-stage renal disease (ESRD) in 7-10 years[10]. High risk of cardiovascular disease (CVD) further increases with deteriorating renal function. Some factors have been implicated in the increased rate of decline in kidney function, especially in type 2 diabetes mellitus (T2DM): higher baseline albuminuria; high systolic blood pressure; higher hemoglobin A1c; estimated glomerular filtration rate (eGFR); age; and coexistence of diabetic retinopathy[10,11]. However, a large inter-individual variation in the rate of decline in glomerular filtration rate (GFR) has been reported in both type 1 and type 2 DM. Recently, a nonalbuminuric renal impairment phenotype was described in T2DM, which has distinct clinical features that are not associated with HbA1c and that are correlated less strongly with retinopathy and hypertension[12]; this phenotype is associated with a higher prevalence of CVD and suggests a predominance of macroangiopathy as the underlying renal pathology, which has yet to be demonstrated. In T1DM, the development of advanced CKD relatively soon after the onset of albuminuria has also been described, and this progression was not conditional to the presence of proteinuria[13] or to a longstanding normoalbuminuric state, and it was associated with more advanced diabetic glomerular lesions and most likely with an increased risk of progression[14].

In patients with DN, there has also been described a nonlinear, abrupt and rapid progression pattern similar to that described by others[15] as rapid-onset end-stage renal disease, which some authors have related to inflammation and episodes of acute renal failure[16].

This spectrum of progression patterns highlights the need for the identification of risk factors for the loss of renal function early in the course of DN, especially in patients with histopathological confirmation of this diagnosis.

The aim of this study was to examine the risk of renal events in patients with biopsy-proven DN and its possible associated factors.

MATERIALS AND METHODS

We studied all the patients diagnosed with DN by renal biopsy at a Spanish center between December 1998 and December 2012, who had a minimum 3-mo follow-up after the biopsy. Of a total of 60 patients with histopathological diagnoses of DN (at our center), we excluded 3 patients who had less than 6 glomeruli on biopsy, 10 patients with evidence of another associated nephropathy (2 IgA nephropathies, 1 membranous nephropathy, 1 membranoproliferative glomerulonephritis associated with HVC, 2 tubulointerstitial nephritis, 2 acute tubular necrosis, 2 with amyloidosis AA) and 2 patients with acute kidney injury: 1 with a functional etiology and the other with septic shock. A total of 45 patients diagnosed with "pure" DN and a sufficient number of glomeruli for the diagnosis were included.

In all the cases, the nephrologist was the specialist who recommended the biopsy, considering all the available data. We classified the indications for renal biopsy into three groups: nephrotic proteinuria with or without nephrotic syndrome; rapidly progressive kidney injury (RPKI); and CKD. All the renal biopsies were revised by a neuropathologist to confirm the glomerular classification type, the grade of interstitial fibrosis and tubular atrophy (IFTA), interstitial inflammation, arteriolar hyalinosis and the presence of large vessel arteriosclerosis on the basis of the criteria previously described[17]. Four types are described: Glomerular Class Ⅰ, glomerular basement membrane thickening; Class Ⅱ, mesangial expansion, mild (Ⅱa) or severe (Ⅱb); Class Ⅲ, nodular sclerosis (Kimmelstiel-Wilson lesions); and class Ⅳ, advanced diabetic glomerulosclerosis.

The demographic, clinical, and laboratory data and comorbid conditions of every patient at the time of biopsy were extracted from clinical records. We recorded the date when the nephrologist began follow-up and whether the patients were receiving treatment with renin-angiotensin aldosterone system inhibitors (RAASIs), statins or antiplatelet drugs.

In 39 patients, we had available information on baseline renal function from 1.1 to 24.1 mo before renal biopsy. We recorded the last follow-up serum creatinine or the starting date of RRT for all the patients.

The glomerular filtration rate was estimated according to the CKD-EPI formula[1] at baseline, at renal biopsy and at the last follow-up visit. The GFR and albuminuria categories of CKD were classified according to the KDIGO 2012 classification[18]. In this manner, six GFR categories were recognized (mL/min per 1.73 m^2): G1 = GFR $\geqslant$ 90; G2 = 60-89; G3a = 45-59; G3b = 30-44; G4 = 15-29; and G5 < 15. Proteinuria categories were described based on protein-to-creatinine ratio (mg/g) or protein excretion rate (mg/24 h) as follows: A1 $\leqslant$ 150; A2 = 150-500; and A3 $\geqslant$ 500.

Table 1 Clinical characteristics at renal biopsy *n* (%)

Total	*n* = 45
Age (yr) (range)	58.3 ± 13.3 (28-84)
Sex (men)	32 (71.1)
Diabetes type 2	38 (84.4)
Diabetes duration (yr) (range)	9.6 ± 7.8 (0-35)
BMI (kg/m^2) (range)	29.3 ± 5.3 (27.8-47.8)
Obesity BMI > 30 kg/m^2	18 (40.9)
Hypertension (yes)	42 (93.3)
Smoker, active or past (yes)	34 (75.6)
Dyslipidemic (yes)	33 (73.3)
Ischemic heart disease (yes)	7 (15.6)
CVA (yes)	6 (13.3)
Peripheral arterial disease (yes)	8 (17.8)
Any CVD	16 (35.6)
Hematuria (yes)	18 (41.9)
Serum albumin (g/dL) (range)	3.4 ± 0.7 (2-5)
HbA1c% (range)	6.5 ± 1.4 (4.1-9.3)
Total cholesterol (mg/dL)	177.9 ± 58.7
Previous nephrology care (yr) (range)	1.21 ± 2.4 (0-12)
RAASI treatment	40 (88.9)
Statin treatment	33 (73.3)
Antiplatelet drug treatment	21 (46.7)

BMI: Body mass index; CVD: Cardiovascular disease; RAASI: Renin-angiotensin aldosterone system inhibitor; CVA: Cerebrovascular accident.

The presentation of RPKI was considered in those cases in which a decrease in eGFR greater than 25% was seen between baseline and biopsy, independent of biopsy indication. The final end-point was defined as RRT initiation or progression of CKD according to the KDIGO 2012 definition as a in CKD category and a decrease in GFR of 25% or more. The follow-up period was considered from biopsy until endpoint, death or last follow-up.

The silent diabetic nephropathy variable was defined for cases that showed an atypical disease pattern or in which DN was not suspected. This variable grouped patients with RPKI without significant proteinuria (< 0.5 g/d) and/or a duration of DM of less than 5 years and/or the need to start RRT less than 1.5 years from renal biopsy.

Statistical analysis

The statistical analysis was performed using SPSS, version 17.0 for Windows, and the STATA software, version 12. Quantitative data are described by means ± SDs or medians (interquartile ranges). Qualitative data are described by counts and percentages [*n* (%)].

Survival median was estimated by the Kaplan-Meier function. The log-rank test was used to compare survival functions. To study factors associated with renal events, univariate analysis was performed, adjusting Cox regression models. The proportionality of hazards assumption was checked graphically. Finally, a multivariate predictive model was adjusted, including statistically significant variables and clinically relevant factors. The model was adjusted by the enter method and including the least number of covariates necessary. Harrell's c-index[19] was calculated to evaluate the model's predictive ability. This index measures the ability of a predictor to separate groups with different answers and is still acceptable greater than approximately 0.85. An exploratory descriptive analysis was performed to compare the two samples, defined by the silent DN variable. Association was studied by the χ^2 test or Fisher's exact test and the Mann-Whitney *U* test. To estimate silent DN's effects on the risk of renal events, we adjusted the multivariate Cox regression model, including possible confounding factors (complete model). We defined a confusion factor as a difference of more than 10% between the adjusted hazard ratio (HR) and the complete model. HRs are presented with 95%CIs. All the tests were two-tailed, and a significance level ≤ 0.05 was considered statistically significant.

RESULTS

Data from 45 patients were included in this study. The patients' characteristics at the time of biopsy are detailed in Table 1. Most patients with biopsy-proven DN in our series had type 2 diabetes and were hypertensive, dyslipidemic and smokers. Seventy-one percent were men with a mean age of 58.3 ± 13.3 years old and a DM evolution time of 9.6 ± 7.8 years. Thirty-five percent had cardiovascular disease, 40% had retinopathy, and 40% had microhematuria. Their values of HbA1c were normal, according to international recommendations for these patients, but their cholesterol levels were not normal, although 73% of the patients were on statins. Furthermore, 89% of the subjects were on treatment with RAASIs, as well as 47% on antiplatelet drugs at the time of the biopsy.

In Table 2, we show the evolution of the renal parameters during follow-up. In 62% of the cases, the biopsy indication was a nephrotic range of proteinuria, with or without nephrotic syndrome. Nine percent of the patients presented proteinuria ≤ 0.5 g/24 h at the time of the biopsy. Although 48.8% of the patients showed baseline creatinine ≤ 1.4 mg/dL, 68% of them showed eGFRs at time of biopsy < 45 mL/min per 1.73 m^2, and 15.6% were in the grade 5 eGFR category.

Thirty-three percent of the subjects were classified with RPKI, three of them without significant proteinuria (< 0.5 g). Seven of these patients needed dialysis, two of them only for a mean time of 8 d and the others permanently.

Twenty-eight patients (62%) reached the final event, and 21 of them required RRT. The median renal survival 3.4 years (95%CI: 2.1-4.7).

In Table 3, we describe the clinical and histopathological findings, classified according to the type of glomerular lesions. Most cases (23 patients) presented glomerular class Ⅲ or nodular sclerosis, and 4 subjects (9%) had advanced diabetic glomerulosclerosis (class Ⅳ) that was not suspected when the biopsy has been recommended. The four patients whose diagnoses of DN coincided with the DM diagnosis had advanced forms of DN: 2 cases with class Ⅱ b, 1 case with class Ⅲ and

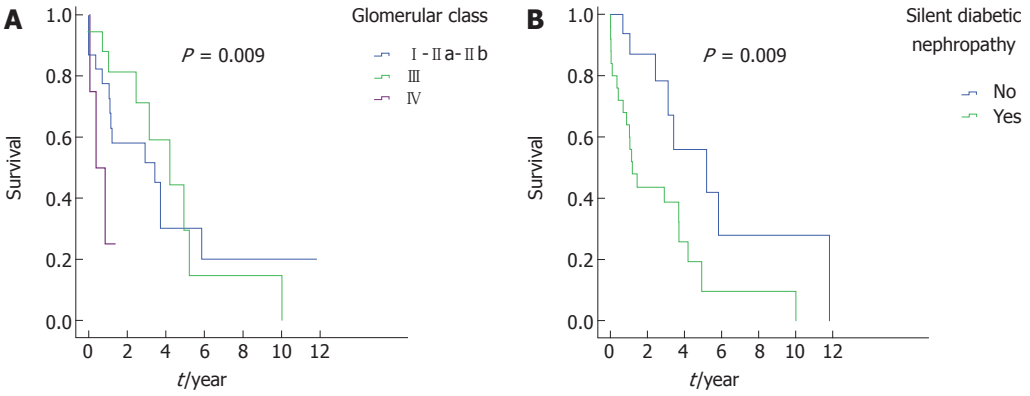

Figure 1 Renal survival. A: Depending on glomerular classification. For renal survival analysis using the Kaplan-Meier method, histopathological classes Ⅰ, Ⅱa and Ⅱb were grouped together as there were insufficient cases for separate analysis. The median renal survival in class Ⅰ/Ⅱa/Ⅱb was 4.2 years (95%CI: 1.8-6.6), in class Ⅲ, it was 3.4 (95%CI: 0.6-6.2), and in class Ⅳ, it was 0.4 (95%CI: 0-1.2). We found statistically significant differences (P = 0.009) when comparing class Ⅳ with the other classes and also when comparing class Ⅲ to classes Ⅰ and Ⅱa-Ⅱb; B: In silent and non-silent diabetic nephropathy. Renal survival of patients with silent and non-silent diabetic nephropathy (DN) was compared. The median of renal survival in patients with silent DN was 5.2 years (95%CI: 1.1-9.4) and 1.2 years (95%CI: 0.5-1.8) in cases of patients with non-silent DN (P = 0.009).

1 case with class Ⅳ.

The patients who had advanced diabetic glomerulosclerosis were younger, had more cardiovascular diseases and retinopathy, and had worse renal function and lower figures of serum albumin than other histopathological types. Additionally, this group of patients showed a higher proportion and greater severity of interstitial fibrosis and tubular atrophy but no differences in vascular lesions or inflammation scores. Renal survival was variable in the different glomerular classes, not only comparing class Ⅳ with the other classes but also comparing class Ⅲ to classes Ⅰ and Ⅱa-Ⅱb (Figure 1A); the median in class Ⅰ/Ⅱa/Ⅱb was 4.2 years (95%CI: 1.8-6.6), in class Ⅲ, the median was 3.4 (95%CI: 0.6-6.2), and in class Ⅳ, it was 0.4 (95%CI: 0-1.2; P = 0.009).

Twenty-five patients were considered to have silent DN: thirteen patients with less than 5 years of duration of DM at biopsy, 4 of them diagnosed with diabetes at the same time as renal biopsy; 1 patient with RPKI and proteinuria < 0.5 g/d; and 14 patients who began RRT before 1.5 years after biopsy (3 with less than 5 years of duration of DM). As shown in Table 4, compared to the remainder of the patients, the silent DN subjects presented with a shorter evolution time of diabetes, had worse renal function at the time of biopsy, had a higher frequency of RPKI and less HbA1c, and had more advanced histopathological forms, and they presented more renal events. They frequently had more cardiovascular disease, although this difference was not statistically significant. To estimate the risk of silent DN, we adjusted a multivariate regression model including possible bias factors: age, eGFR, proteinuria, glomerular class, CVD and HbA1c. The final model (Table 5) estimated the risk for silent DN of 2.1 (95%CI: 0.8-5.1), adjusted for cardiovascular disease and HbA1c. The remainder of the factors were discarded as they were considered confounders. Figure 1B illustrates the renal survival curves in silent DN, compared to the other subjects.

The results of univariate Cox proportional hazard analysis, according to clinical variables and histopathological variables, are shown in Tables 6 and 7, respectively. Clinical variables statistically significantly associated with renal end point were: baseline and renal biopsy eGFR and serum creatinine; BMI < 30 kg/m^2; Hb A1 < 7%; RPKI; silent DN; and coexistence of cardiovascular disease. Of the histopathological variables, only glomerular class Ⅳ and percentage of global glomerulosclerosis were statistically significantly associated with the renal end point.

The results of multivariate Cox proportional hazard models are shown in Table 8. We found that eGFR, cardiovascular disease and HbA1c at the time of biopsy were risk factors for progression of DN (initiation of renal replacement therapy or decline ⩾ 25% and change in CKD category), adjusted for age and sex. For every 10 mL/min per 1.73 m^2 decrease in eGFR, we obtained a DN progression risk of HR = 2 (1.3-3.0) (P = 0.001). Patients with cardiovascular disease were at greater risk for DN progression (HR = 2.8, 1.1-7.1; P = 0.032). Although diabetic patients with CKD and HbA1c < 7% showed greater renal progression risk than patients with HbA1c ⩾ 7%, with an HR of 2.9 (1.0-8.4), this effect was not statistically significant (P = 0.054). Harrel's c index was 0.823, indicating acceptable predictive ability.

DISCUSSION

The present study analyzed clinical and histopathological factors associated with worse renal prognosis in a cohort of patients with biopsy-proven diabetic nephropathy, mostly type 2 diabetics. Two thirds of the patients had an eGFR at the time of the biopsy < 45 mL/min per 1.73 m^2, that is, irreversible damage to renal function, and half of the patients reached ESRD in a median period of 3.4 years.

In our series, eGFR at time of biopsy was a determinative factor for CKD progression, as is already well known. In contrast, proteinuria was not associated with

Table 2 Renal parameters and evolution *n* (%)

		Previous renal data (*n* = 39)	Renal biopsy (*n* = 45)	End of follow-up (*n* = 24)
Time prior to biopsy (mo) (range)		7.3 ± 5.2 (1.1-24.1)		
Follow-up period (yr) (range)				3.4 ± 2.9 (0.2-11.8)
Renal biopsy indication	RPKI		8 (17.8)	
	Nephrotic proteinuria		28 (62.2)	
	CKD		9 (20)	
Serum creatinine (mg/dL) (range)		1.6 ± 0.8 (0.8-4.5)	2.3 ± 1.5 (0.8-6)	2.3 ± 1.8 (0.7-9.1)
eGFR (mL/min per 1.73 m^2) (range)		51.4 ± 20.9 (14.7-97.6)	39.1 ± 22.5 (8.1-101.2)	40.8 ± 25 (5.1-107.1)
[1]eGFR category	G5 < 15		7 (15.6)	24 (53.3)
	G4 15-30		8 (17.8)	6 (13.3)
	G3b 30-45		15 (33.3)	5 (11.1)
	G3a 45-60		7 (15.6)	7 (15.6)
	G2 60-90		7 (15.6)	1 (2.2)
	G1 > 90		1 (2.2)	2 (4.4)
> 25% drop in eGFR prior to biopsy		13 (33.3)		
[2]Proteinuria (range)		3.7 ± 3.4 (0-12.9)	4.5 ± 2.7 (1-8.9)	
[3]Proteinuria category	A1 < 150	3 (8.8)	0	
	A2 150-500	2 (5.9)	4 (8.9)	
	A3 > 500	29 (85.3)	41 (91.1)	
RRT		2	5	21 (46.7)
[4]CKD progression				7 (15.6)
eGFR improvement > 25%				4 (8.9)
Exitus				5 (11.1)

[1]GFR categories (mL/min per 1.73 m^2): G1 = GFR ⩾ 90; G2 = 60-89; G3a = 45-59; G3b = 30-44; G4 = 15-29; G5 < 15. [2]Baseline proteinuria was measured using protein/creatinine ratio in spot urine (mg/g). Renal biopsy proteinuria was measured using excretion rate over 24 h (g/d). [3]Proteinuria categories are described based on protein-to-creatinine ratio (mg/g) or protein excretion rate (mg/24 h) in: A1 ⩽ 150, A2 = 150-500, A3 ⩾ 500. [4]CKD progression: 25% or greater eGFR decline, accompanied by a decrease in GFR category. RPKI: Rapidly progressive kidney injury; eGFR: Estimated glomerular filtration rate; CKD: Chronic kidney disease; RRT: Renal replacement therapy.

worse renal prognosis, although the majority of patients showed proteinuria > 500 g/d, but most of patients without proteinuria also experienced renal events.

Although our study included selection bias, which was the clinical indication for renal biopsy, our series included only cases of DN in which other causes of renal damage had been excluded. Therefore, our findings, even if they cannot be extrapolated to all patients with DN, could increase understanding of why some patients with diabetes have atypical clinical courses and are diagnosed in advanced stages of renal disease, with minimal therapeutic possibilities.

Although the majority of patients had been medically followed up before biopsy, this fact did not prevent negative evolution or late diagnosis of the illness. The RPKI presentation form, predominant in 33% of the patients, was associated with a poor renal prognosis, although it behaved as a confounding factor and not as an independent risk factor.

It was shown[16] that, in DN, relatively small elevations in serum creatinine could significantly underestimate the degree of renal damage, and these elevations were unpredictable most of the time.

Without a doubt, this fact contributed to the large proportion of patients in our series that we classified with silent diabetic nephropathy, that is, cases that went unnoticed until advanced stages. These patients had shorter diabetes evolution times; they presented a higher frequency of RPKI, a major loss of renal function at the moment of the biopsy, and they had a higher proportion of renal events. Although they had more cardiovascular diseases compared to the remainder of the group, this difference was not statistically significant.

All these data support that serum creatinine is not a good parameter for monitoring renal function in diabetic patients and that even with normal serum creatinine levels, eGFR should be a routine test. It is probable that an eGFR at less than 90 mL/min per 1.73 m^2, we should recommend several tests per year in these patients to detect CKD progression and optimize their treatment.

In a study of 22 biopsy-proven diabetic nephropathy cases[16], these authors found in the majority of cases evidence of acute kidney injury in their biopsies, including tubular necrosis and interstitial inflammation, although seven subjects had similar rates of progression and yet undetectable acute events. In our series, we excluded those patients in whom we suspected renal failure secondary to another etiology. However, it is possible that some cases of functional loss might have existed, especially in nephrotic patients, because in four patients, we observed an improvement in renal function during follow-up. Other authors found that interstitial lesions, but not glomerular class, was a significant predictor of renal prognosis in diabetic nephropathy in type 2 diabetes[20],

Table 3 Clinical and histopathological findings according to glomerular classification of diabetic nephropathy *n* (%)

		Ⅰ-Ⅱa-Ⅱb (*n* = 18)	Ⅲ (*n* = 23)	Ⅳ (*n* = 4)
Age (yr)		59.9 ± 12.2	58.1 ± 14.1	52.3 ± 15.4
Years of diabetes		9.1 ± 7.4	9.3 ± 6.3	15.1 ± 18
BMI (kg/m^2)		29 ± 4.9	30.1 ± 6	26.8 ± 2.4
Serum creatinine (mg/dL)		2 ± 1.2	2.2 ± 1.4	4.4 ± 1.9
eGFR (mL/min per 1.73 m^2)		42.3 ± 21.9	40.4 ± 22.9	17.6 ± 12.3
HbA1c (%)		6.7 ± 1.4	6.3 ± 1.3	6.7 ± 2
Proteinuria (g/d)		3.1 ± 2.6	5.2 ± 4	4.7 ± 5.6
Serum albumin (g/dL)		3.6 ± 0.7	3.3 ± 0.7	2.9 ± 0.7
Serum cholesterol (mg/dL)		165.4 ± 71.6	191.5 ± 34.6	213 ± 0
Hypertension		16 (88.9)	22 (95.7)	4 (100)
Diabetic retinopathy		7 (38.9)	9 (39.1)	2 (50)
CVD		7 (38.9)	6 (26.1)	3 (75)
RPKI		0	6 (33.3)	7 (30.4)
Patients with renal events		9 (50)	15 (65.2)	4 (100)
RRT		6 (33.3)	11 (47.8)	4 (100)
[1]Years from biopsy to renal event		4.2 ± 1.2	3.4 ± 1.4	0.4 ± 0.4
% of global glomerulosclerosis		18.1 ± 12.8	18.4 ± 15.1	77.3 ± 16.9
Interstitial fibrosis	0	1 (5.6)	0	0
and tubular atrophy	1	10 (55.6)	13 (56.5)	0
	2	5 (27.8)	9 (39.1)	1 (25)
	3	2 (11.1)	1 (4.3)	3 (75)
Interstitial inflammation	0	3 (16.7)	0	0
	1	14 (77.8)	22 (95.7)	4 (100)
	2	1 (5.6)	1 (4.3)	0
Arteriolar hyalinosis	0	1 (5.6)	1 (4.3)	1 (25)
	1	3 (16.7)	2 (8.7)	0
	2	14 (77.8)	20 (87)	3 (75)
Large vessel arteriosclerosis (yes)		17 (94.4)	19 (86.4)	4 (100)

[1]Years from biopsy to renal event are expressed as medians ± SEs, estimated by Kaplan-Meier method. CVD: Cardiovascular disease; BMI: Body mass index; RPKI: Rapidly progressive kidney injury; RRT: Renal replacement therapy; eGFR: Estimated glomerular filtration rate.

Table 4 Clinical differences at the time of biopsy between silent and non-silent diabetic nephropathy *n* (%)

	Non-silent DN (*n* = 20)	Silent DN (*n* = 25)	*P* value
Age (yr)	55.8 ± 12.2	60.3 ± 14.1	
Sex (women)	5 (25)	8 (32)	
BMI (kg/m^2)	30.9 ± 6.3	28 ± 4.1	
T2 DM	17 (85)	21 (84)	
Duration of diabetes (year)	12.5 ± 5.3	7 ± 8.9	0.005
Follow-up period (year)	3.4 ± 3.5	3.5 ± 2.7	
Smoking, active or past	16 (80)	18 (72)	
Retinopathy	8 (40)	10 (40)	
CVD	6 (30)	10 (40)	
HbA1c (%)	7 ± 1.2	6.2 ± 1.5	0.03
Serum creatine at biopsy (mg/dL)	1.8 ± 1	2.7 ± 1.6	0.03
eGFR at biopsy (mL/min per 1.73 m^2)	47 ± 22.5	32.9 ± 20.8	0.04
Proteinuria (g/d)	3.5 ± 2.6	5 ± 4.3	
Hematuria	8 (44.4)	10 (40)	
RPKI	3 (15)	12 (48)	0.03
CKD progression	3 (15)	10 (50)	0.04
Renal events	8 (40)	20 (80)	0.01
Histopathological class AP Ⅲ-Ⅳ	9 (45)	18 (72)	
Glomerular sclerosis percentage	18.8 ± 14.3	27.2 ± 26.4	
IFTA 0-1	12 (60)	12 (48)	
IFTA 2	7 (35)	8 (32)	
IFTA 3	1 (5)	5 (20)	
Severe arteriolar hyalinosis	15 (75)	22 (88)	
Large vessel arteriosclerosis	18 (94.7)	22 (88)	
RAASI treatment	18 (90)	22 (88)	
Statins treatment	15 (75)	18 (72)	

IFTA: Interstitial fibrosis and tubular atrophy; CVD: Cardiovascular disease; RPKI: Rapidly progressive kidney injury; RRT: Renal replacement therapy; CKD: Chronic kidney disease; eGFR: Estimated glomerular filtration rate; BMI: Body mass index; RAASI: Renin-angiotensin aldosterone system inhibitor; DN: Diabetic nephropathy; DM: Diabetes mellitus.

Table 5 Multivariate Cox proportional model of renal end point by the variable silent diabetic nephropathy

Variables in the equation	HR	95%CI	
		Lower	Upper
CVD	3.943	1.649	9.429
HbA1c%	0.724	0.516	1.016
Silent DN	2.137	0.819	5.573

Silent DN: Histologic diagnosis of DN and RPKI without significant proteinuria (< 0.5 g/d) and/or a DM with less than 5 years of evolution and/or the need to begin RRT before 1.5 years after renal biopsy. CVD: Cardiovascular disease; DN: Diabetic nephropathy; HR: Hazard ratio; DM: Diabetes mellitus.

but it was a small series of 69 type 2 diabetic patients, all with overt proteinuria.

The only histopathological finding of our series that proved to be a risk factor for renal progression was advanced diabetic glomerulosclerosis. It is possible that if our sample had been larger, we would have been able to demonstrate prognostic values of more benign histological types, as observed by the different lengths of renal survival seen in our series, which was worse for type Ⅲ nodular sclerosis, compared to patients with types Ⅰ and Ⅱa-Ⅱb.

Another risk factor associated with poor renal prognosis was a BMI < 30 kg/m^2. Although obesity is a risk factor for CKD and ESRD[21], its effects have not been clear in patients with T2DM[22]. Although in our study, BMI seemed to have a paradoxical effect, similar to that described in the survival of patients with T2DM in TSR[23], it was not an independent risk factor for renal progression.

In the present study, HbA1c < 7% was correlated with worse renal prognosis in patients with established DN. Important large, randomized, controlled, multicenter trials have shown that intensive glycemic control in T2DM reduces the risk of albuminuria and proteinuria[24], but evidence has been lacking that intensive glycemic control reduces the risk of significant clinical renal outcomes, such as doubling of serum creatinine level, ESRD or death from renal disease[25]. In these trials, severe hypoglycemia was clearly increased among intensively treated patients[26]. In contrast, we know that the individuals with progressive renal dysfunction are at increased risk for hypoglycemia, which is multifactorial.

These trials have either failed to demonstrate a benefit of glucose lowering for CVD risk or have even suggested an increased CVD risk with very tight glycemic control, most likely explained by the adverse effects of hypoglycemia on the heart and blood vessels[27]. Acute hypoglycemia triggers a cascade of physiologic responses, including the activation of inflammatory pathways, release of counter-regulatory hormones, including epinephrine, and reduced blood flow to the myocardium.

In a recent prospective study in older adults with diabetes[28], an association between dementia and having presented hypoglycemic episodes during 12 years of follow-up was found. The authors indicated as possible etiopathogenic mechanisms hypoxia by vasoconstriction, neuronal loss, hyperinsulinemia, exacerbation of the oxidative stress and inflammatory mediators. Although this series was adjusted for cardiovascular events, small vessel vascular disease was not discharged, so it is possible that cerebral microinfarcts played some part in cerebral atrophy and cognitive deterioration.

In the present study, a past history of CVD was identified as an independent risk factor for CKD progression in DN, almost tripling the risk of progressive CKD. Although the effects that diabetic CKD has on CV risk are well known[29], the renal risk of CVD in DN has not been defined. Some authors have advocated that vascular disease of the kidney can explain nonalbuminuric progressive DN[30]. In our series, the prevalence of CVD was similar or even slightly lower than that reported by these authors (37% in patients with reduced eGFR), but we have already mentioned that this form of onset was very rare in our series. Similar degrees of intrarenal vascular disease, measured by the Doppler resistance index of the interlobar renal arteries, were found in diabetic patients with reduced GFR, regardless of their albuminuria status.

Our data sustain that regardless of albuminuric phenotype, past history of CVD is a risk factor for progressive renal function decline in DN, as other authors have found[31]. In support of this theory, a recent study[32] linked cerebral microinfarcts, diagnosed by magnetic resonance imaging, with low eGFR and worse renal prognosis in type 2 DM, regardless albuminuria. The risk of doubling of the serum creatinine concentration or the need for dialysis was significantly greater for patients with silent cerebral infarction (HR = 4.79, 95%CI: 2.72-8.46) than for patients without silent cerebral infarction. The authors believe that this association might have been due to the similarity between renal and cerebral vascular hemodynamic behaviors.

Therefore, it is interesting that in our series, we found that cardiovascular disease and tighter glycemic control were DN progression risk factors. Although our findings cannot be extrapolated to the totality of patients with diabetic nephropathy, we can speculate that at least in diabetic patients with vascular disease, the benefits of strict glycemic control do not improve renal prognosis when kidney failure has already been established. It is possible that on an already damaged renal parenchyma, hypoglycemia could induce the release of proinflammatory mediators by means of hypoxia, which could explain the accelerated evolution of renal failure in patients with an inflamed substrate prone to cardiovascular disease.

Some studies have revealed that serum levels of various proinflammatory cytokines, chemokines and adhesion molecules, particularly TNF-α and IP-10, were associated with the severity of DN and of atherosclerosis[33]. These molecules could be useful markers for the progression of DN and atherosclerosis.

In conclusion, in our study of a cohort of patients with biopsy-proven diabetic nephropathy and kidney failure, we found that a history of CVD was an inde-

Table 6 Univariate Cox proportional hazard analysis of renal end point, according to clinical variables

	HR	95%CI		*P* value
		Lower	Upper	
Age (yr)	1.00	0.97	1.03	
Sex (men)	1.19	0.50	2.85	
Diabetes type (2/1)	0.76	0.31	1.91	
Diabetes duration (years)	1.01	0.95	1.07	
BMI < 30 (yes/no)	2.94	1.09	7.69	0.03
Smoker (yes/no)	0.92	0.34	2.50	
Hypertension (yes/no)	1.01	0.13	7.69	
CVD (yes/no)	4.56	1.94	10.69	0.000
Retinopathy (yes/no)	1.24	0.56	2.75	
Baseline Serum creatinine (mg/dL)	2.18	1.14	4.16	0.02
Baseline eGFR (mL/min per 1.73 m^2)	0.98	0.95	1.00	
[1]Baseline proteinuria (g/g)	1.12	0.98	1.27	
eGFR drop > 25% before biopsy	3.96	1.54	10.18	0.004
Serum creatinine (mg/dL) at biopsy	2.97	1.91	4.61	0.000
eGFR (mL/min per 1.73 m^2) at biopsy	0.94	0.92	0.97	0.000
RPKI	2.74	1.21	6.24	0.02
[2]Proteinuria at biopsy (g/d)	1.09	0.97	1.23	
Hematuria	1.65	0.72	3.82	
Serum albumin (g/dL)	0.75	0.41	1.35	
HbA1c % (**< 7/≥ 7**)	3.37	1.23	9.25	0.02
Total cholesterol (mg/dL)	0.98	0.96	1.01	
RAASI treatment (yes/no)	0.59	0.22	1.59	
Statin treatment	0.66	0.27	1.62	
Silent DN	3.04	1.26	7.3	0.02

[1]Baseline proteinuria was measured using protein/creatinine ratio in spot urine (g/g). [2]Renal biopsy proteinuria was measured using excretion rate in 24 h (g/d). BMI: Body mass index; CVD: Cardiovascular disease; eGFR: Estimated glomerular filtration rate; RPKI: Rapidly progressive kidney injury; RAASI: Renin-angiotensin aldosterone system inhibitor; DN: Diabetic nephropathy.

Table 7 Univariate Cox proportional hazard analysis of renal end point, according to histological variables

		HR	95%CI		*P* value
Glomerular class	Ⅲ/Ⅰ-Ⅱa-Ⅱb	1.2	0.5	2.9	
	Ⅳ/Ⅰ-Ⅱa-Ⅱb	5.6	1.6	19.7	0.007
	Ⅳ/Ⅲ	4.6	1.4	15.1	0.01
% of global glomerulosclerosis		1.0	1.0	1.0	0.01
IFTA	(> 25 ≤ 25%)	1.2	0.5	2.5	
Arteriolar hyalinosis	Severe/mild	0.7	0.2	2.2	
Large vessel arteriosclerosis (yes)	1-2/0	1.2	0.4	4.1	

HR: Hazard ratio; IFTA: Interstitial fibrosis and tubular atrophy.

Table 8 Multivariate Cox proportional hazard model of renal end point, adjusted for age and sex

	HR	95%CI for HR		*P* value
		Lower	Upper	
CVD	2.75	1.07	7.11	0.036
RPKI	1.29	0.46	3.64	0.626
eGFR (10 mL/min per 1.73 m^2)	1.96	1.28	3.00	0.001
HbA1c% (**< 7/≥ 7**)	2.88	0.98	8.44	0.054

CVD: Cardiovascular disease; HR: Hazard ratio; RPKI: Rapidly progressive kidney injury; eGFR: Estimated glomerular filtration rate.

pendent progression factor for diabetic nephropathy and that levels of HbA1c less than 7% could favor renal progression, especially in cases with associated vascular disease. Whether this accelerated progression is due to renal vascular disease or to an underlying inflammatory state could not be clarified in this study.

It is necessary to diagnose diabetic patients at risk for cardiovascular disease and kidney disease progression before these lesions become irreversible. The biochemical parameters normally used in clinical settings are not good markers of renal progression. Prospective studies should be undertaken to evaluate the usefulness more refined parameters, such as cystatine C clearance and inflammatory and early vascular damage markers, in diabetic patients to detect and treat these patients earlier.

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COMMENTS

Background

Diabetes mellitus (DM) is one of the leading causes of end-stage kidney disease. Different forms of presentation and progression of diabetic nephropathy have been described, both in DM1 and DM2.

Research frontiers

The prognostic factors of diabetic nephropathy (DN) have not been well established, nor have been the indicators for identifying patients at greater risk for progression. Further translational studies should be performed to increase knowledge of the etiopathogenic mechanisms and treatment of this type of nephropathy.

Innovations and breakthroughs

This study supports that glomerular lesions were the basic substrates responsible for renal insufficiency in a subgroup of diabetic patients. DN sometimes presents with rapid progression despite proteinuria. It is probable that glomerular lesions and cardiovascular disease in diabetic patients share a common substrate that implies a worse prognosis for these patients. Further studies are needed to support the theory of a possible negative renal effect of strict metabolic control in patients with established diabetic nephropathy.

Applications

Serum creatinine and proteinuria are not early markers to detect the risk of progression in DN. The threshold of estimated glomerular filtration rate (eGFR), less than which renal function must be monitored, should be much higher in diabetic patients than in other chronic kidney disease patients, especially if there are associated cardiovascular risk factors. Authors should be cautious in metabolic control of patients with cardiovascular disease and DN.

Terminology

Diabetic nephropathy: Renal complications of diabetes; Histopathological diagnosis: The histopathological diagnosis of DN is based on light and electron microscopic glomerular lesions. Tubulointerstitial and vascular lesions often accompany glomerular changes, but they are not specific to diabetes; Silent disease: This term describes ischemic heart disease in diabetic patients who presents as myocardial ischemia without angina. In this study, the authors have extrapolated this term to nephropathy to refer to the way it presents, with hardly any clinical renal expression until advanced stages of illness.

Peer review

This is an interesting observational study on the clinical course of DN, focusing in particular on a novel phenotype called silent DN.

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

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