Isotopic renal study within diabetic nephropathy

A Benítez Segura, J Martín-Comín, Y Ricart, M T González*, M Cortés, M Roca, M C Díaz, M Ramos

Nuclear Medicine and Nephrology Departments*. Bellvitge University Hospital. L’Hospitalet (Barcelona).

Material and methods: 125 patients (IDDM:10, NIDM:115), including 62 men, ages 18-84 years, were studied. In all cases GF (Cr 51 EDTA), ERPF (131I-hippuran), kidney split function (obtained from the 99mTc-MAG3 renogram) and basal serum creatinine (SC) were evaluated at the beginning of the study and patients were clinically followed up for 5 years by SC. Ultrasound and/or intravenous digital angiography were performed in 120 patients.

Results: In patients with decreased ERPF (76 patients) the SC increased progressively during the 5 years, in both those with elevated PC (N = 54) as well as those with normal baseline (SC (n=22). In patients with normal ERPF, the SC did not change significantly during the study. An asymmetric split function (KSF < 40% in one kidney) was found in the renogram of 42 patients; in 32 of them, the ERPF was decreased. Of these, ultrasonography was normal in 9 and vascular and/or obstructive pathology was demonstrated by ultrasonography or digital angiography in only 6 patients.

Conclusion: The ERPF becomes altered earlier than serum creatinine in patients with diabetic nephropathy. ERPF and split function calculation, and GF seems to have higher prognostic value than ultrasounds in the management of diabetic nephropathy. Radionuclides seem to be an accurate test than the ultrasonography to detect renal function abnormalities in patients with diabetic and thus can be an examination of choice in these patients.

KEY WORDS: Diabetic nephropathy. ERPF. Kidney split function

EFFECTIVE RENAL PLASMA FLOW MEASUREMENT AND 99mTc-MAG3 RENOGRAPHY IN THE STUDY OF DIABETIC NEPHROPATHY

Summary – This study aimed to evaluate the prognostic value of the kidney split function (KSF), the effective renal plasma flow (ERPF) and glomerular filtration rate (GF) in the evolution of diabetic nephropathy.

INTRODUCTION

The most important systemic illness as a cause of nephropathy is diabetes mellitus. In diabetic patients, kidney disease may be due to various causes, such as atheromatosis, papillary necrosis, pyelonephritis, neurogenic obstructive uropathy and hyporeninaemic hypoaldosteronism, or type IV tubular acidosis, but the most frequent is diabetic nephropathy (DN), a term that is normally used for glomerular (Kimmelstiel-Wilson diffuse or nodular glomerulosclerosis) and arteriolar (arteriolosclerosis) disease. It is one of the most serious complications of diabetes mellitus and the primary cause of chronic renal insufficiency in our field. It presents itself after several years of development and is associated with high mortality. In fact, diabetic patients represent between 15% and 20% of patients on dialysis, and it should also be emphasised that they present a higher morbidity and mortality than other patients on dialysis (Cataluña Register of Kidney Patients). Between 30-50% of patients with type I diabetes
mellitus that has developed over 20-30 years will eventually develop renal insufficiency; by contrast, only 5% of patients with adult-onset diabetes will develop significant nephropathy at any time, although the frequency has been increasing over the past few years.

Although the pathogenesis of renal lesions associated with diabetes mellitus has been much discussed, it is accepted that this constitutes two distinct processes for the large vessels and for the glomerulus. The first of these corresponds to an accelerated form of atheromatosis, while the second may be identified with a thickening of the basement membrane of the capillaries and the mesangial matrix of the glomerular flocculus, which constitutes the basic lesion of diabetic glomerulosclerosis.

With regard to the natural development of DN, in general the following phases may be distinguished: 1) initial phase, characterised by renal hypertrophy and hyper-function; in this phase effective renal plasma flow (ERPF) and glomerular filtration (GF) are increased and may be accompanied by microalbuminuria; 2) established nephropathy phase, in which proteinuria has been detected by conventional methods and may progress until it reaches the nephrotic range. ERPF may be maintained. Hypertension is associated with the proteinuria and GF begins to decrease. This stage usually presents itself after approximately 15 years of development of diabetes mellitus; 3) Renal insufficiency phase, which has an average duration of 5 years, during which creatinine values increase progressively and ERPF and GF decrease; 4) In the final phase, the clinical picture is defined by the presence of severe renal insufficiency (creatinine clearance < 10 ml/min) and arterial hypertension that leads rapidly to the death of the patient if appropriate renal substitutive treatment is not put in place (dialysis or transplant). Diabetic retinopathy and neuropathy is frequently associated with this, as well as arteriосlorotic vascular complications.

The diagnosis of DN is almost always based on the clinical parameters. The detection of microalbuminuria (30-300 mg/d) is a simple, non-invasive method of early diagnosis of incipient DN; it can predict a progressive reduction in GF and the appearance of terminal nephropathy within an average time period of 10 years. The detection in urine of renal tubule enzymes and proteins (beta-2 microglobulin, Tamm-Horsfall protein, N-acetyl-beta-D-glucosaminidase....) are markers of DN. The urinary concentration of type IV collagen is a useful marker for the initial phases of DN. The urinary detection of IgG seems to be more useful than albuminuria in the early detection of the disease. The progressive decrease in GF is an indicator of the deterioration of renal function. The use of complementary techniques such as echography is helpful when complications or other associated pathologies are suspected.

Thus nephrology has at its disposal a wide range of clinical parameters, some of which have already been mentioned, for the early diagnosis and/or detection of DN. It would also be useful to have other parameters that might enable prediction of how a given patient is going to progress and thus the establishment of appropriate measures to slow progression towards terminal renal insufficiency (TRI).

The medical examination of diabetic patients should be rigorous; a series of tests should be carried out that would enable nephropathy to be detected in its early form, and the co-existence of nephropathies of other origin to be ruled out as the cause of deterioration of renal function.

Therefore, the purpose of this work has been to analyse the usefulness of the calculation of relative renal efficiency (RRE), and the prognostic value of ERPF and GF in the development of diabetic nephropathy.

MATERIALS AND METHODS

Patients

125 patients (p) (62 males) were reviewed, with an age range of between 18 and 84 years inclusive. The majority of them, 115, were non-insulin-dependent diabetics (NIDDM) and only 10 presented insulin-dependent diabetes mellitus (IDDM), with a development time period of up to 38 years.

At the beginning of the study GF and ERPF values were assessed, together with the percentage relative renal efficiency for each kidney and plasma creatinine (PC). A 5-year follow-up of renal function using PC was carried out.

Normal values:
- Plasma creatinine: 125 µmol/L
- Glomerular filtration: 70 ml/min/m²
- Effective renal plasma flow: 350 ml/min/m²
Table I
FRANK ASYMMETRY
(1 KIDNEY < 20% ERPF): 7 PATIENTS

<table>
<thead>
<tr>
<th>Reduced ERPF in 5 patients:</th>
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<tbody>
<tr>
<td>1st patient. Echo: Kidney obstructed with dilation of the pelvis.</td>
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<tr>
<td>2nd patient. Echo: Kidney not observed. DSA*: Renal artery stenotic.</td>
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<tr>
<td>3rd patient. DSA: Renal arteries normal. Poor vascularisation.</td>
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<tr>
<td>4th patient. DSA: Renal arteries normal. Right kidney small and with low contrast concentration.</td>
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<tr>
<td>5th patient. Echo: Left kidney atrophic (vascular origin).</td>
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Normal ERPF in 2 patients:
- 1st patient. Single kidney (left), with polycystosis.
- 2nd patient: Echo: Right nephrectomy and left kidney large + cortical cyst.

* [“DSA” in the above table stands for “Digital Subtraction Angiography.”]_

Three groups were distinguished according to base PC and ERPF values by means of the t-student statistical method for matched data obtaining the mean ± standard deviation:

- Group 1: patients with high PC and reduced ERPF.
- Group 2: patients with normal PC and reduced ERPF.
- Group 3: patients with normal PC and normal ERPF.

On the renogram the RRE was calculated to be between 1 and 3 min p.i. and the presence of renal function asymmetries was assessed, considering:

- Frank asymmetry: to be where the RRE of a kidney was less than 20%.
- Moderate asymmetry: to be where the RRE of a kidney was between 20%-40%.

The morphology of the renographic trace and sequenced images was also assessed.

In 120 cases renal echography and/or angiography by digital subtraction (DSA) was carried out in order to rule out other pathologies.

Table II
MODERATE ASYMMETRY
(1 KIDNEY 20-40% ERPF): 35 PATIENTS

<table>
<thead>
<tr>
<th>Reduced ERPF in 27 patients:</th>
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<tbody>
<tr>
<td>1 patient. Echo: Kidney with hydronephrosis.</td>
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<tr>
<td>2 patients. Echo: Frank asymmetries (size).</td>
<td></td>
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<tr>
<td>9 patients. Echo: cortices reduced (1 haemodialysis).</td>
<td></td>
</tr>
<tr>
<td>9 patients. Echo: Normal.</td>
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<tr>
<td>2 patients. Echo: (In the 1st patient: large cysts in the right kidney + small ones in the contralateral one; in the 2nd patient small cysts in the left kidney).</td>
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<tr>
<td>4 patients with no Echo.</td>
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Normal ERPF in 8 patients. Echo: 4 patients normal (1 patient required haemodialysis), 1 patient DIVA [Digital Intravenous Angiography]: right renal artery small, 3 patients with no Echo.

Table III
INCREASED PLASMA CREATININE + REDUCED ERPF:
54 PATIENTS (7 HAEMODIALYSIS)

| Base creatinine: | 190 ± 51 µmol/L |
| Plasma creatinine 1st year: | 222 ± 92 µmol/L | p < 0.005 |
| Plasma creatinine 2nd year: | 290 ± 198 µmol/L | p < 0.0005 |
| Plasma creatinine 3rd year: | 361 ± 298 µmol/L | p < 0.05 |
| Plasma creatinine 4th year: | 380 ± 281 µmol/L | p < 0.05 |
| Plasma creatinine 5th year: | 397 ± 314 µmol/L | p < 0.05 |

Average reference values for GF and ERPF at the beginning of the study in this group of patients.

GF: 41 ± 14 ml/min/1.73 m²
ERPF: 279 ± 107 ml/min/1.73 m²

Exploratory protocol
A renogram with 6 µCi (222 MBq) of 99mTc-MAG3 was carried out on all patients; 174 images of 10 seconds each (64 x 64 matrix) were obtained, together with the corresponding activity/time curve (renogram).

ERPF was determined in all cases (it was calculated systematically alongside the renogram with 99mTc-MAG3 ) following the administration of 50 µCi (1.85 MBq) of 131I-HIPPURAN, carrying out extractions at 4’, 10’, 30’ and 60’ post-injection.

For the calculation of GF in 104 patients, 100 µCi (3.7 MBq) of 51Cr-EDTA was administered and extractions were carried out at 120, 180’ and 240’ post-injection.

RESULTS

Glomerular filtration
A reduction in GF was observed in 56 patients, of which 51 also had reduced ERPF. Of these 51 patients, 44 had high PC at the beginning of the study, and it was normal for only 7 of them.

In 48 patients, GF was normal; in 36 of them, ERPF and PC were normal. Twelve presented reduced ERPF, 1 of these with high PC, and in 11 of them PC was normal.

Asymmetries of function
The following were observed on the renogram:

- Frank asymmetry in 7 patients, 5 of whom presented a decrease in ERPF for various vascular or obstructive reasons. In 2 p ERPF was normal, both patients with a single kidney each, with associated pathology (table I).
• Moderate asymmetry in 35 patients. In 27 of these 35 patients ERPF was reduced; in the majority of cases a cause was found by echography or DSA that explained this, although in a third of them the echography was normal (table II).

Plasma creatinine
At the beginning of the study 71 p presented normal PC; of these, 22 (30%) had reduced ERPF.

The progression of PC in the three groups of patients was as follows:
• Group 1 (high PC and reduced ERPF): A significant increase in PC was observed in these 54 p; 7 p moved on to haemodialysis within the 5 years, 12 p died due to complications secondary to diabetes. GF at the beginning of the study was reduced in all of the patients (table III).
• Group 2 (normal PC and reduced ERPF): A progressive increase in PC was observed in the 22 p of this group, although it was slower than in the previous group. The increase in PC was only significant during the first 3 years. Two patients ended up on a haemodialysis programme within the five years, and 2 p died. At the beginning of the study GF was reduced in all of the patients (table IV).
• Group 3 (normal PC and normal ERPF): A slow and progressive, although not significant, increase in PC was observed in 49 patients. Only 1 patient ended up on haemodialysis, because he/she did not attend the annual examinations and lost control of his/her nephropathy; 1 patient died because of hepatic insufficiency due to HCV. In this group GF was maintained at the beginning of the study (table V).

### Table IV

PROGRESSION OF NORMAL PLASMA CREATININE + REDUCED ERPF:

<table>
<thead>
<tr>
<th>Year</th>
<th>Creatinine</th>
<th>p Value</th>
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<tbody>
<tr>
<td>1st year</td>
<td>113 ± 39 μmol/L</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>2nd year</td>
<td>156 ± 118 μmol/L</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>3rd year</td>
<td>142 ± 70 μmol/L</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>4th year</td>
<td>169 ± 160 μmol/L</td>
<td>ns*</td>
</tr>
<tr>
<td>5th year</td>
<td>350 ± 366 μmol/L</td>
<td>ns</td>
</tr>
</tbody>
</table>

Average reference values for GF and ERPF at the beginning of the study in this group of patients.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>GF</td>
<td>104 ± 35 ml/min/1.73 m²</td>
</tr>
<tr>
<td>ERPF</td>
<td>607 ± 188 ml/min/1.73 m²</td>
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</tbody>
</table>

### DISCUSSION

The development of diabetic nephropathy is rapidly progressive; good control of the diabetic patient during the initial phases of renal change (microalbuminuria phase) may play a fundamental role in the progression of the nephropathy. It has been demonstrated that good control of blood sugar, lipids and blood pressure may delay the progression of the nephropathy in the early stages of the disease.

It has likewise been demonstrated that the administration of ACE inhibitors or angiotensin receptor antagonists have a beneficial effect during the onset of the disease, reducing the state of hyperfiltration that seems to be the basis for subsequent changes. By contrast, diagnosis during advanced phases does not allow for any change in the inexorable progression towards TRI.

It is therefore extremely important to diagnose kidney disease in its latter stages.

The usual parameters for measuring renal function are the determination of PC and creatinine clearance. It is well-known that some diseases, such as muscular ones, may alter these parameters. It has also been shown that creatinine levels only increase when GF has decreased, by at least 50%.

The calculation of GF is accepted as the most precise method of evaluating renal function. In our experience it behaves in a similar way to ERPF; changes in it are earlier than changes in creatinine. Likewise, it has been seen that there is a correlation between GF and ERPF values, in that both decrease in the advanced stages of DN. Its determination is an inconvenience, being somewhat more laborious than for ERPF, as extractions need to be carried out up to 240’ post-injection, while for the calculation of ERPF up to 60’ is sufficient.

The discovery of an asymmetry of function on the renogram seems a better way of detecting hypofunctionalism than echography. This is of special
interest for diabetes, where relative maintenance of, or even an increase in, overall renal size is often observed, which seems to persist in some cases, even when frank diabetic nephropathy manifests itself. Asymmetry of function (RRE < 40%) was observed within our work in 42 p, 32 of whom presented reduced ERPF, and a third of these patients had normal echography. The discovery of an asymmetry on the renogram therefore requires other explorations to be carried out in order to identify other possible causes associated with DN that explained the deterioration in renal function. In cases in which another pathology is not identified and the echography and/or angiography is normal, DN must be thought of the only cause of the deterioration, and its treatment should be proceeded with.

In relation to the follow-up of the patients using the progression of CP, the analysis of the three groups shows that the most sensitive parameter is ERPF. Within the results obtained: in all of the patients with reduced ERPF (76 p), an increase in PC was observed after 5 years whether PC was high at the beginning (no.: 54 p) or was normal (no.: 22 p). PC did not show any significant variations in the patients with normal ERPF. The number of patients moving on to haemodialysis was greater in the group with high PC + reduced ERPF, while with normal PC + normal ERPF, only 1 patient ended up on haemodialysis, and this was due to the abandonment of the follow-up on the part of the patient.

A progression towards renal insufficiency was observed in all of the patients, but in those who initially presented normal PC and ERPF the development was slower. Thus we believe that the ERPF value is indicative of the development of DN just like the GF value, as they seem to change earlier than PC in the diabetic patient.

Obtaining a radionephrogram or the determination of PC or ERPF are much simpler and less harmful methods than the administration of intravenous contrast agents, as in pyelography, as these may accelerate progression towards renal insufficiency, and less invasive than renal biopsy, which should be limited to those cases in which nephropathy of non-diabetic origin is suspected.

Our results suggest that in a diabetic patient in whom the presence of nephropathy is suspected, the observation of an echograph or some normal PC values is not sufficient. If the renogram identifies an asymmetry of function and there is also a reduction in ERPF, this patient is going to deteriorate more than one in whom these isotopic changes are not detected, and stricter control should therefore be applied.

The isotopic study described place at the disposal of the clinic a series of tests that are not only diagnostic but also prognostic, easily accessible and practically harmless, for studying how a given patient diagnosed with diabetic nephropathy is going to progress, and thus for taking appropriate measures in relation to the results of these. In our centre an isotopic renogram (with calculation of RRE) and the determination of ERPF, parameters that change early on in the development of DN, are carried out alongside each other.

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[Translation of items within the Bibliography in Spanish within the original text.]


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