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Parametric clearance kidney scintigrams; diagnostic potential in diabetes

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Abstract

BACKGROUND: The diagnostic usefulness of parametric clearance kidney images was studied in the early diagnosis of diabetic nephropathy, juxtaposed with conventional dynamic urinary investigation (renoscintigraphy) combined with deconvolution procedure of renal and blood time activity curves and determination of plasma clearance of ^{99m}Tc-ethylenedicysteine (^{99m}Tc-EC).

MATERIAL AND METHODS: The investigation was performed on a group of 70 individuals (41 males, 29 females) in whom diabetes type 1 was diagnosed (age 10 to 30 y.; mean 19 y.) and on a control group of 35 healthy individuals (15 males, 20 females) in the age-bracket of 18–25 years (mean 19 y.). In all subjects studied, renoscintigraphy was performed after administration of ^{99m}Tc-EC (activity 40–120 MBq) combined with determination of urinary clearance (ERPF) of the radiopharmaceutical. The renographic curves were evaluated taking into account their shape and individual share of each kidney, and the clearance function was calculated (RClr). From analysis of the time-activity, kidney curves T_{max} and $T_{1/2}$ were assessed. In addition, the mean ^{99m}Tc-EC transport time through the complete kidney (MTT) and organ's parenchyma (PTT) were calculated from results of deconvolution of the curve. From the dynamic urinary system study, conventional images of radiopharmaceutical distribution in the kidneys in the secretion phase were obtained. The parametric clearance images were also computed on the basis of relative clearance values in all the pixels of both kidney regions of interest. The disturbances in kidney function were assessed separately by means of conventional scintigram analysis and of corresponding parametric images. A three-stage classification was used in both cases for the evaluation of abnormal findings in the kidneys

RESULTS AND CONCLUSIONS: In all studied individuals, the ^{99m}Tc-EC (ERPF) clearance values were within the normal range. When renographic time activity curves were considered the flattening of the curves (III phase) was more frequent in diabetic individuals than in the controls (39.3% *vs.* 15.7%; $p = 0.001$). The shape of the curves in phases I and II were normal in all studied individuals of both groups. There were no differences observed between mean values of T_{max}, $T_{1/2}$ and PTT in diabetics and controls. However, mean MTT values were significantly higher in diabetics than in controls ($p = 0.02$).

In conventional summation images (phase II of the renograms), there were no significant differences in frequency of defects in kidney parenchyma diabetics and controls (4.3% *vs.* 2.9%). In contrast, analysis of parametric kidney clearance images revealed that parenchyma defects were found with significantly greater frequency in diabetic individuals (35.7%) than in control subjects (8.6%; $p < 0.001$). Summarizing the findings, it appears that parametric clearance kidney images reveal local deviations of renal uptake and secretory function while conventional indicators of renal function are still in the normal range. This observation points to the fact that clearance parametric images may have potential value in the early diagnosis of diabetic nephropathy, and perhaps in other types of renal damage. Incorporation of parametric images into the dynamic study of the urinary system may be promising when early detection of kidney damage seems vital.

Key words: parametric clearance kidney image, renoscintigraphy, ^{99m}Tc-EC clearance, diabetic nephropathy

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Introduction

Dynamic scintigraphy of the urinary system belongs to the group of basic and most often performed diagnostic procedures of nuclear medicine. The investigation allows complex evaluation of renal func-

tion by assessment of the uptake of a proper radiopharmaceutical (RPh) from the blood as well as of its transport through the renal parenchyma and subsequent flow via the excretory route (pelvis, ureters, bladder). Non-imaging procedures utilizing the same radiopharmaceuticals enable quantitative assessment of plasma clearance of the labelled compounds (i.e. glomerular filtration rate — GFR — and/or effective renal plasma flow — ERPF).

Conventional renoscintigraphic study provides information on global function of each kidney in the form of a consecutive image-series representing various phases of RPh-passage. The generation of time-activity curves and presentation of semiquantitative and quantitative parameters of the curves provide additional information on the functions of the system.

A technique for digital processing of scintigraphic data in the form of so-called parametric images, developed in the seventies and eighties of the twentieth century, was introduced mainly in the assessment of the cardiac left ventricle performance [1]. The method provided the possibility of disclosing to the observer hidden functional information in the form of digital scintigraphic images. The latter present the regional distribution of the value of a quantitative parameter characterizing the organ's overall function, such as systolic-diastolic amplitude or phase of the cardiac systole or spatial distribution of the ratio of ventilation and perfusion in the lungs [2].

The same basic procedure permits the evaluation of the spatial distribution of the renal clearance function in the kidneys [3].

The generation of parametric images requires the developing of mathematical models of respective functions, which have to be presented two-dimensionally. The next step involves appropriate to the model processing of scintigraphic data acquired in each pixel. Semiquantitative information on spatial distribution of the function is then presented by a colour palette. Regional disturbances of the function in question manifest themselves in the image by a change of local colour, the change from the expected function being thoroughly proportional to the change in the colour palette used for the purpose.

Renal parametric clearance images have not thus far found wider application in clinical practice. Gordon and his co-workers [4] were, however, able to demonstrate their usefulness in the detection of regional defects in the function of renal parenchyma in children with urinary tract infections.

The aim of the present study was to find out whether parametric kidney clearance images, generated in our Department [5] provide additional, clinically useful information in comparison with conventional radioisotope urinary tract dynamic studies including, in addition, deconvolution of renographic curves plus classical determination of ^{99m}Tc-EC renal clearance (which is proportional to ERPF), which has been used routinely for the assessment of renal function.

Due to the fact that extensively studied nephropathic sequelae of diabetes [6-9] are well known, in order to test the usefulness of parametric images, a clearance group of diabetic children and adolescents followed up periodically for their health status was chosen.

Material and methods

The study was conducted on 70 patients (41 males and 29 females) of the age from 10 to 30 years (mean 19 y.) in whom the diagnosis of diabetes type 1 had been made from 0.5 to 23 years ago. All these patients were treated with insulin and in the 6-month period preceding this study there were no acute incidents observed with metabolic disturbances (hypoglycaemia, metabolic acidosis).

The control group was composed of healthy volunteers: 35 individuals (15 males and 20 females) of the age between 18 and 25 years (mean 19 y.).

In all persons studied there were excluded: actual infections of the urinary system, anatomic malformation of kidneys, as well as calculosis and other diseases of the urinary system. Only in five persons from among the diabetics, a microalbuminuria was found that could be taken as an early manifestation of diabetic nephropathy.

In accord with the principles of the Helsinki Declaration, the study was performed after receiving acceptance from the Bioethical Commission of the Medical University of Lodz. There were altogether 210 kidneys studied (140 and 70 among the diabetics and controls, respectively).

In all studied individuals, a dynamic scintigraphic study of the urinary system (renoscintigraphy) was made after i.v. administration of 40–120 MBq (depending on the age) ^{99m}Tc-ethylenedicysteine (^{99m}Tc-EC). From the same administration, the renal plasma clearance of ^{99m}Tc-EC was determined by means of a multisample method as reported earlier [10].

The digital images were acquired in a matrix of 64 × 64 pixels over an interval of 20 min post *i.v.* injection, each of 10 sec. duration. The counts were recorded in the following regions of interest: kidneys, aorta, extrarenal background and urinary bladder.

The time-activity curves were analyzed, assessing their shape as normal or abnormal, with evidence of disturbed uptake-excretory function (phase I/II) and/or disturbed flow of the urine from the kidney to consecutive elements of the system (phase III).

From inspection of renographic curves, the separate uptake function of RPh of each kidney was quantitatively assessed (RClr) as well as Tmax and $T_{1/2}$ of the curve in the third phase. After matrix-type deconvolution [11], the mean transport time for the complete kidney (MTT) and mean transport of RPh through the kidney parenchyma (PTT) were computed.

After conventional processing of consecutive kidney images in the second phase, the sum of 4–5 scintigrams was formed which gave a combined image for further evaluation. From the same series, a parametric renal clearance image was generated according to the procedure described in detail by Surma and Anderson [5].

Regional defects of renal function were evaluated on the basis of summary images and separately assessed from inspection of clearance images (parametric scintigraphy). The classification in both cases was expressed in three levels (scores) of intensity:

— O° — typical shape and magnitude of the kidney, a uniform typical function distribution (uptake/secretory and/or spatial clearance distribution);
— I° — typical magnitude of the kidney; the number of focal reduced or absent uptake of the RPh, and/or reduced clearance space equal or less than 2;
— II° — size of the kidney typical or smaller, numerous (> 2) regions of smaller or absent RPh uptake and/or spatial distortions of clearance distribution.

The shape of renographic curves and evaluation of the degree and number of focal reduction uptake (conventional images) or distortion (reduction) of local clearance function was

assessed by two experienced nuclear medicine specialists; the final results for each kidney were arrived at by consensus.

Results

Values of ^{99m}Tc-EC clearance (ERPF) in all studied individuals fell in the normal range. There was no significant difference between means in the diabetics and controls.

Analysis of the shape of renographic time activity curves revealed a more frequent flattening of the IIIrd (excretory) phase in diabetics than among the controls; 39.3% *vs.* 15.7% respectively ($p < 0.001$). In the former the $T_{1/2}$ values exceeded in most cases 900 seconds; in addition, in late scintigrams there was some retention of the RPh in the urinary tracts. In contrast, the Ist and IInd phase of the curves were normal in all the studied individuals of both groups.

Division of the function between the left and right kidney was found to be normal; all the values fell in the bracket taken as normal i.e. between 42 and 58 percent. The same lack of difference between the two groups was observed when mean values of T_{max}, $T_{1/2}$ and PTT were considered.

The only significant difference found between the two groups affected the MTT; in diabetics it was 188 ± 67s *vs.* 164 ± 49 s in the controls ($p = 0.02$).

Analysis of the conventional summation images disclosed no significant difference frequency of focal defects was considered: in 2 out of 70 kidneys in controls *vs.* 6 in 140, in diabetics.

However, when parametric clearance images were considered there was a highly significant difference between the frequency of defects in the clearance function between diabetics: 50 out of 140 kidneys (35.7%), and controls: 6 out of 70 kidneys (8.6%).

The difference between the two groups was highly significant ($p < 0.001$) (Figure 1).

Figure 2 presents examples of parametric clearance kidney images in kidneys of different intensities of damage. Figure 3 gives examples of conventional and parametric images in the same kidneys.

Table 1 summarizes the distribution of defects (frequency and scores) as revealed by the conventional and parametric images in both groups of patients.

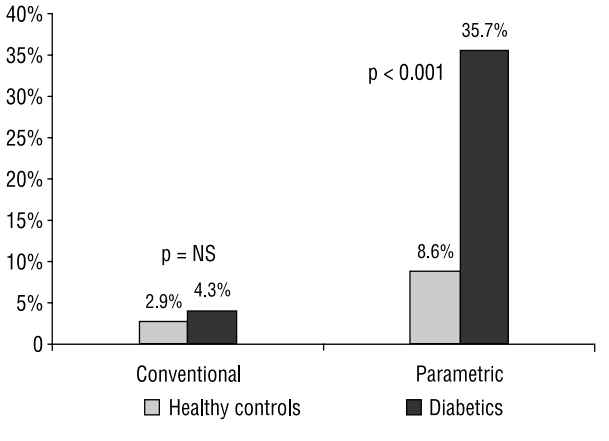

Figure 1. Frequency of defects in uptake — secretory function in healthy individuals *vs.* diabetics (conventional *vs.* parametric clearance images). NS — non significant.

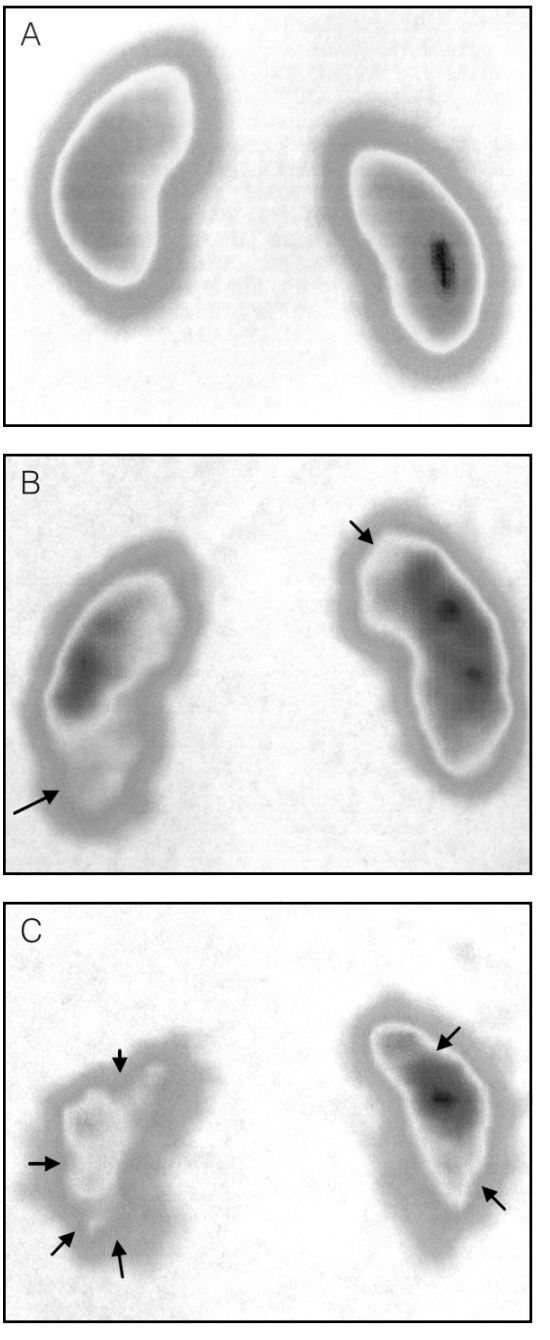

Figure 2. Parametric clearance images revealing different intensities of damage. **A.** Both normal kidneys (classification score — 0); **B.** In both kidneys, there are single defects (arrows) revealed (I degree of damage intensity); **C.** In the right kidney, there are two defects visible (I^{o}); in the left kidney, the distribution of RPh is obviously non-uniform; there are more than 2 defects in the clearance function (II degree of damage intensity).

Defects disclosed by conventional images in both studied groups revealed only abnormalities in few kidneys, and they were classified in most cases as belonging to intensity grade I.

In renal parametric clearance images in diabetics, there were more frequent disturbances, and they more advanced. Intensity of II grade of intensity dominated in this group ($p < 0.001$).

In diabetic patients with microalbuminuria (5 individuals), there

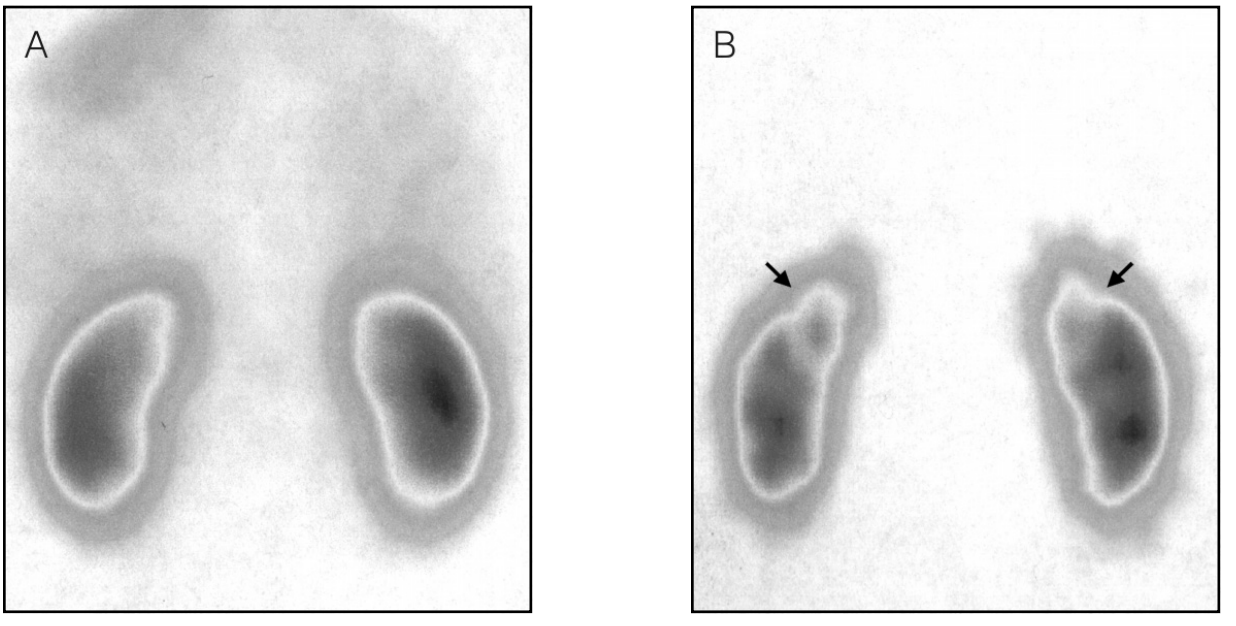

Figure 3.A. Conventional summation image — no localized damage revealed. **B.** Parametric clearance image of the same kidneys as sub A; there are single defects revealed in upper poles of the kidneys (I degree of damage intensity).

Table 1. Degree of damage intensity as revealed in both groups of patients by the conventional scintigrams and parametric images

	Controls (n = 70)	Diabetics (n = 140)
Conventional summation images		
0°	97.1% (n = 68)	95.7% (n = 134)
I°	2.9% (n = 2)	3.6% (n = 5)
II°	0% (n = 0)	0.7% (n = 1)
Parametric clearance images		
0°	91.4% (n = 64)	64.3% (n = 90)
I°	5.7% (n = 4)	13.5% (n = 19)
II°	2.9% (n = 2)	22.1% (n = 31)*

n — number of kidneys; * $p < 0.001$

were defects in renal function revealed by the parametric images: in two of them, they were classified into category I°, in the remaining three patients they belonged to category II°.

Discussion

Determination of several types of clearances and dynamic scintigraphy of the urinary system plus deconvolution procedure has been a routine practice in the radioisotope diagnostics and monitoring of renal function in the course of various diseases, also in diabetes [7–9, 12].

Toward the end of the eighties of twentieth century, methodological progress created chances to obtain additional information from the above listed procedures. Digital processing of primary renal image series and creation of parametric clearance images enlarged the scope of possible clinical investigations. The first attempt to obtain such images was presented by Fleming [3]. Thus, the author utilized the deconvolution of single-pixel renographic curves as a basic key to obtain the parametric images. The basic drawback of this method was its slowness and laboriousness, and consequently it never gained wider acceptance in clinical practise.

In the nineties, in the Nuclear Medicine Department of the Medical University of Lodz, a new method was developed for the creation of renal parametric clearance images, based on the Patlak-Ruthland theory, applied to each single-pixel time-activity curve [13]. This method obviates the requirement for deconvolution, which saves time, and the whole exercise becomes much simpler than the Flemings procedure.

The images obtained with this new procedure visualize a two-dimensional distribution of a physiological quantity which is proportional to the clearance, and which characterizes regional uptake function of the organ [5]. In contrast to the conventional summation scintigrams, the parametric images are free from the contribution of the extrarenal background and from the neighbouring, overlapping organs (liver, spleen); detection of regional functional disturbances in the renal parenchyma becomes much easier.

The above presented way of thinking created an incentive to apply the parametric clearance images in a clinical situation with the intention of testing whether this method would be able to contribute valuable information on local changes in renal function. The obvious consequence was the selection of patients in the early phase of diabetes.

As shown above, most qualitative properties and numerical values of physiologically important quantities and parameters did not differentiate renal performance in early type 1 diabetes from their healthy controls. The only positive observations applied to slightly longer MTTs and more frequent flattening of the renal time-activity curves in the IIIrd phase of renographic observation. These latter observations are most probably due to functional uropathy

(disturbed motional function of ureters) in diabetics [8].

However, when analysing the parametric clearance renal images, the functional local defects in the uptake of the RPh were significantly more frequent ($p < 0.001$) in diabetics than in healthy volunteers (controls). The local defects in the function were also more frequently seen in the parametric than in the conventional summary scintigraphic images. Moreover, in the diabetics, the semiquantitative scoring of defect intensity yielded higher values in parametric than in the conventional kidney summation scintigrams. All patients with microalbuminuria had accompanying functional defects in the parametric images.

Conversely, the frequency of focal defects seen in conventional images was very similar in both groups (3–4%), and the score representing deviation from the norm was minor.

In summary, of all the results of the dynamic scintigraphic examination, only the parametric clearance renal images provided evidence for focal functional disturbance in patients with early type 1 diabetes. The hypothesis seems plausible that focal defects in renal parenchyma could be casually linked to diabetes and may represent an early symptom of developing diabetic nephropathy. On the other hand, it is as yet impossible to exclude the possibility that the focal defects observed may represent scar formation due to clinically silent, not previously diagnosed, infections in the urinary system.

For evaluation of the method for the creation of scintigraphic parametric clearance images of the kidneys, one has to remember that is not accompanied by any additional inconvenience to the patient.

Full clinical evaluation of the regional renal clearance function on the basis of parametric images requires further studies, both in diabetics and in the course of other diseases of the urinary system. Its value should also be considered when looking for possible consequences of therapeutic methods (e.g. lithotripsy).

Conclusions

1. Parametric clearance kidney scintigraphy provides additional information on regional kidney function, which could be clinically useful in early diagnosis of low-grade nephropathy.
2. Further investigations should provide fuller evidence as to whether the inclusion of parametric clearance disturbation in kidneys contributes to the diagnostic potential of dynamic scintigraphy of the urinary system in diseases other than diabetes.

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