High diagnostic performance of CT scan for analgesic nephropathy in patients with incipient to severe renal failure

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High diagnostic performance of CT scan for analgesic nephropathy in patients with incipient to severe renal failure. Recently, well performing diagnostic criteria for analgesic nephropathy in end-stage renal failure (ESRF) patients were defined by the demonstration of a bilateral decrease in renal volume combined with either bumpy contours or papillary calcifications. In this study, the diagnostic value of computed tomography (CT) scan was compared to the previously used renal imaging techniques (sonography and conventional tomography). In a first study, a cohort of 40 analgesic abusers (defined as daily use of analgesic mixtures during at least 5 years) and 40 controls, all ESRF patients without a clear renal diagnosis, were investigated with sonography, tomography and CT scan without injection of iodinated contrast material, to search for the imaging signs of analgesic nephropathy. Using CT scan, sonography and tomography, renal size could be evaluated with comparable results while CT scan was superior in the detection of papillary calcifications (sensitivity 87%, specificity 97%). In a second controlled study of 53 analgesic abusers with a serum creatinine between 1.5 to 4 mg/dl in the absence of a clear renal diagnosis, a CT scan was performed and scored for the presence of decreased renal volume, bumpy contours and papillary calcifications. It was found that the renal image of analgesic nephropathy on CT scan in an early stage of renal failure is comparable with the observations made in ESRF patients. Particularly the demonstration of papillary calcifications showed a high sensitivity of 92% with a specificity of 100% for the early diagnosis of analgesic nephropathy.

Analgesic nephropathy is underestimated in several countries, mainly due to the lack of well defined criteria for diagnosing this disease. This observation formed the basis of a study starting in Belgium in 1988 which aimed to establish diagnostic criteria for analgesic nephropathy in patients with ESRF. In a cohort of 60 analgesic abusers and 188 controls, all starting renal replacement therapy, a large number of clinical, laboratory and radiological signs reported to be associated with analgesic nephropathy were evaluated. Renal imaging investigations (sonography and tomography) demonstrating a decrease in length of both kidneys combined with either bumpy contours or signs of renal papillary necrosis showed a high sensitivity and specificity for diagnosing the disease. Other signs frequently mentioned, such as hypertension, anaemia, sterile pyuria and bacteriuria, showed insufficient sensitivity and/or specificity [1].

During the Analgesic Nephropathy Network Europe (ANNE) study, the criteria selected in Belgium, were evaluated in 23 renal units from 14 European countries and Brazil. Results, based on 82 analgesic abusers and 495 controls, all dialysis patients starting renal replacement therapy with an unclear renal diagnosis, corroborated the diagnostic performance of the renal imaging criteria [2].

Out of these studies it was learned, however, that the results of sonography were strongly operator related and that the poor spatial resolution of sonography limits its usefulness in the assessment of papillary necrosis, as was also mentioned by Davidson and Hartman [3]. Additionally, the quality of conventional tomography showed a high technical variability, and the use of the latter technique became more and more questionable due to the high dose of ionizing radiation administered to the patients. In contrast, preliminary observations with CT scan showed that this renal imaging technique has a high sensitivity particularly for the detection of papillary calcifications.

CT demonstration of papillary calcifications in analgesic nephropathy patients was reported in several publications [3–6]. The diagnostic performance of this renal imaging technique, however, was never investigated nor validated in a representative sample of analgesic abusers and controls. Furthermore, it is unknown whether the renal imaging criteria, developed for ESRF patients, are also useful in patients presenting at the outpatient clinic with incipient to moderate renal failure. Particularly, the question arises as to whether renal papillary necrosis can also be demonstrated at an early stage of renal failure.

This paper reports on a study of the value of the CT scan for diagnosing analgesic nephropathy in ESRF as well as in patients with incipient to moderate renal failure.
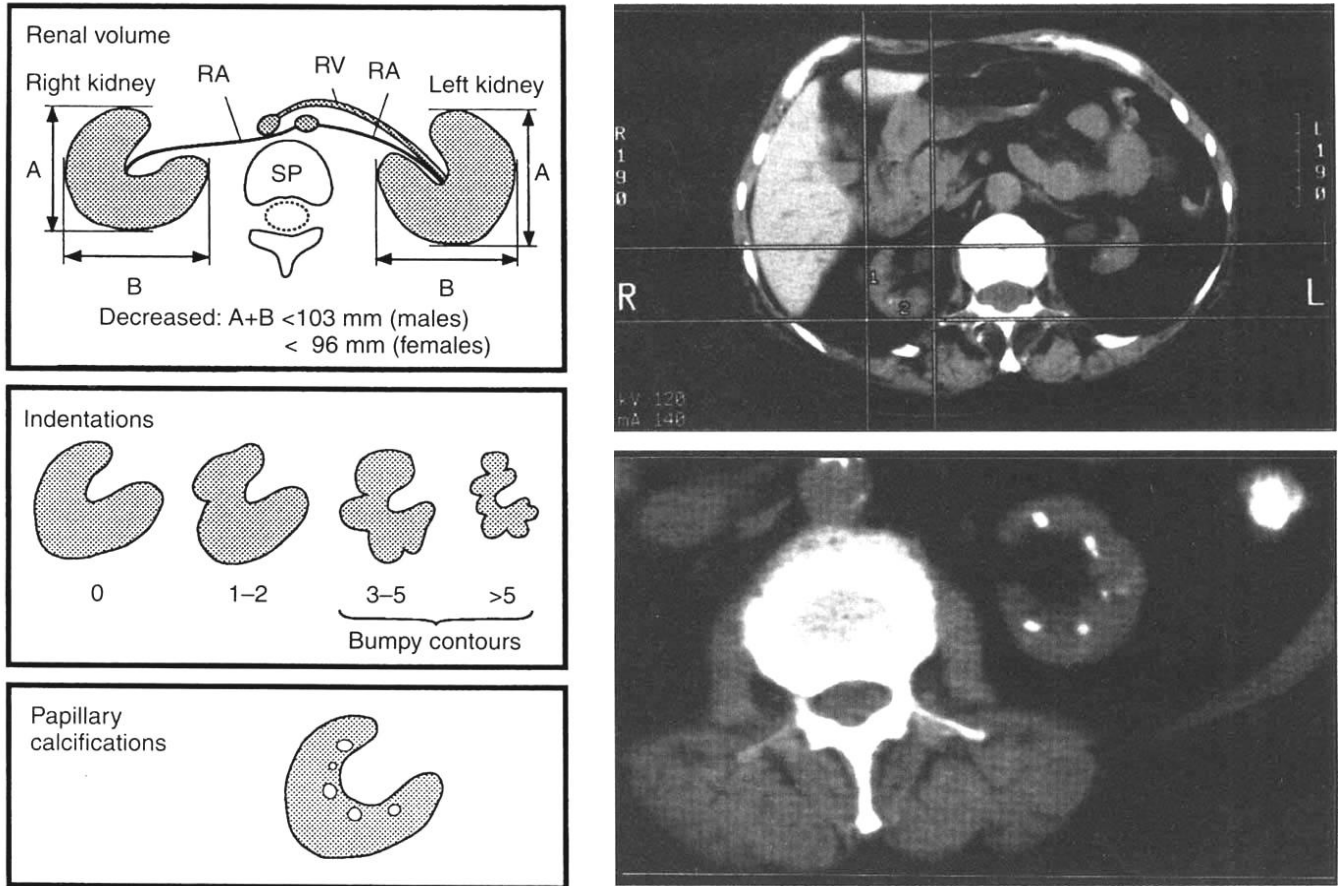
Fig. 1. *Description of the renal imaging criteria of analgesic nephropathy as observed on CT scan including a decreased renal volume, bumpy contours and papillary calcifications.* Renal size was measured by the sum of both sides of the rectangle enclosing the kidney at the level of the renal vessels. Indentations were counted at the level where most indentations were present. Triangular, ringlike or polygonic calcifications on the papillary line were considered as signs of renal papillary necrosis.

Methods

Patients with ESRF

All ESRF patients from six Belgian dialysis units, either starting renal replacement therapy or presenting at the outpatient clinic with a measured creatinine clearance below 20 ml/min, were considered for enrollment in the study. Enrollment was limited to either patients admitting the abuse of analgesics (abusers) or patients who had never consumed analgesics regularly (controls). In both groups only patients without a clear renal diagnosis were included. Patients with a clear renal diagnosis (histologically proven glomerulonephritis, polycystic disease, hereditary familial nephropathy, congenital renal hypoplasia, diabetic nephropathy and other systemic diseases) were excluded from investigation.

All patients included underwent a short interview in order to document a possible history of abuse. Analgesic abuse was investigated using three different techniques identical to the methodology used in the preceeding diagnostic criteria studies [1, 2]. First, there was a general question concerning the medication taken during the last month. Second, the regular use of medication for relief of complaints such as headache and joint pain was investigated. Third, the consumption of analgesics was tested using a picture book, containing photographs of the twelve

Table 1. Renal diagnoses in controls ($N = 40$)

EDTA code	Description	%
0	Unknown etiology	17.5
10	Glomerulonephritis (no biopsy)	17.5
20–25	Pyelonephritis	32.5
70–72	Vascular disease	25.0
99	Other	7.5

best-selling analgesics in Belgium. It was used to test the patient's knowledge of the product, if he had it at home and how frequently he was using it. Analgesic abuse was defined as a daily use of analgesic mixtures for at least five years. Analgesic mixtures were defined as products containing two analgesic components combined with potentially addictive substances (caffeine, codeine).

A sonography, tomography and CT scan were performed in all patients included. To increase the quality of the renal imaging investigations, local radiologists and sonographists were contacted prior to the start of the study. Per center all investigations were performed by the same experienced radiologist. Results of the renal imaging investigations were noted on appropriate forms by
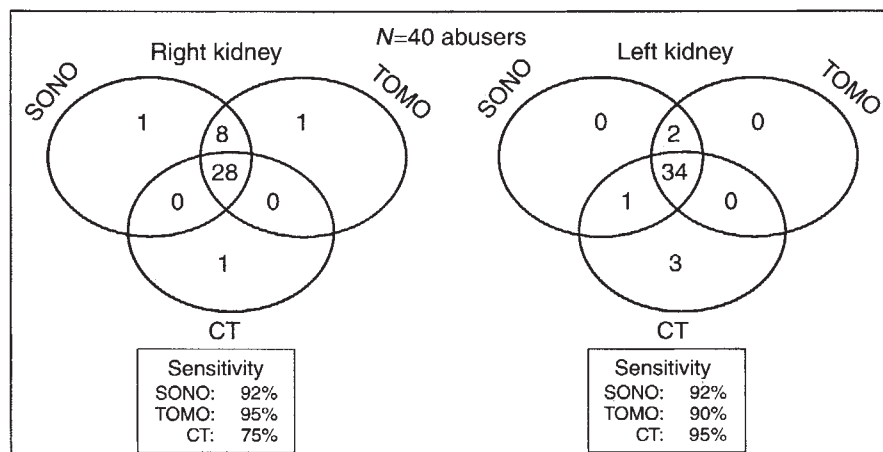
Fig. 2. *CT scan compared to sonography and tomography in their detection of a decreased renal volume (N = 40 abusers with ESRF).*

the local radiologist. For sonography and tomography, decrease in length, bumpy contours and papillary calcifications were defined as described previously [1].

CT scans were performed without injection of iodinated contrast material. Contiguous slices from the upper to the lower pole of both kidneys were made. Use of slice thickness of 10 mm, ± 120 Kv and a scan time of less than three seconds were recommended. A field of view between 30 to 38 was used with a scale bar added.

On the CT scan, the renal volume was examined by measuring both sides of the rectangle enclosing the kidney at the level of the renal vessels. To evaluate the renal contours, irregularities were evaluated at the level where most indentations could be observed and were quoted as 0, 1 to 2, 3 to 5, or more than 5 indentations. If at least 3 indentations were observed, the contour was considered to be "bumpy." Calcifications were localized as cortical, papillar or central. Triangular, ringlike or polygonic calcifications on the papillary line [5] were considered as signs of renal papillary necrosis (Fig. 1).

Normal values for the renal volume evaluation using CT scan were established investigating 183 patients without renal disease, stratified according different age and sex categories. The sum of both sides of the rectangle enclosing the kidney at the level of the vessels (Fig. 1) showed bilaterally comparable results with mean values of 112 and 114 mm for the left and the right kidney, respectively. Logistic regression, including sex, age, body length and weight in the analysis, showed that sex has to be taken into account for evaluating the renal volume as measured on CT scan. The renal volume was considered as decreased if the sum of both sides of the rectangle (A + B on Fig. 1) was less than the 5th percentile rank of the normal population. Cut-off values for males and females were respectively 103 and 96 mm.

Additionally, the diagnostic value of CT scan in the case of analgesic nephropathy in ESRF patients was validated using all CT scan documents (N = 67) performed within the framework of the ANNE study in seven other renal units [2]. The renal imaging criteria were validated by a radiologist (ADS) who was not involved in the process of data collection, and without knowledge of a possible history of abuse. His validation consisted of a blind re-examination of the CT scans, accepting or rejecting the diagnosis of analgesic nephropathy based on the observation of a
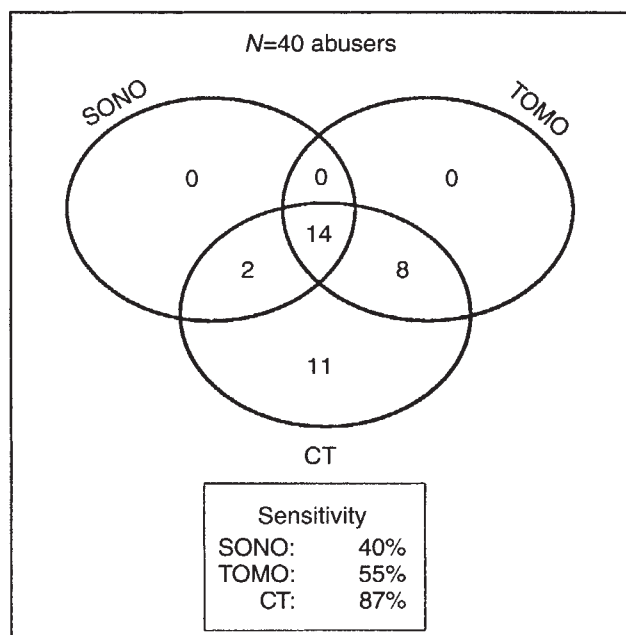

Fig. 3. *CT scan compared to sonography and tomography in their detection of papillary calcifications (N = 40 abusers with ESRF).*

decrease in renal volume plus either bumpy contours or papillary calcifications. Afterwards, these results were compared with the possible history of analgesic abuse.

Patients with incipient-moderate renal failure

In six Belgian renal units and seven ANNE centers, patients presenting at the outpatient clinic with a clear history of analgesic abuse (daily use of analgesic mixtures during at least 5 years), with a serum creatinine between 1.5 to 4 mg/dl and in the absence of a clear renal disease were selected. All patients meeting these conditions in one of the collaborating centers had to be included in the study.

Data documenting the chronic character of the renal failure (3 measurements of serum creatinine over a one year period) and the abuse of analgesics (duration and amount of abuse, kinds of
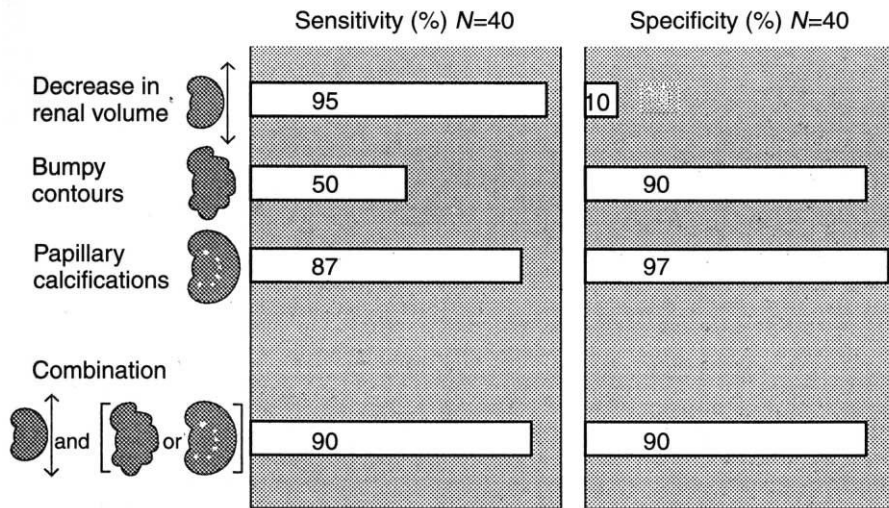
Sensitivity (%) *N*=40   Specificity (%) *N*=40

Decrease in renal volume   95   10

Bumpy contours   50   90

Papillary calcifications   87   97

Combination

and [or]   90   90

Fig. 4. *Performance of the renal imaging criteria using CT scan in patients with ESRF.* Combination can be defined as a decreased renal volume combined with either bumpy contours or papillary calcifications.

products used) were noted. All selected patients underwent a routinely performed CT scan without contrast.

Information sheets and CT scans were sent to the coordinating center where CT scans were reviewed, evaluating the renal volume and the contours, and searching for possible calcifications on the papillary line. Identical criteria as described for ESRF patients were used to quote decreased renal volume, bumpy contours and papillary calcifications.

Additionally, all available CT scans without contrast, performed in the coordinating center in patients without a history of abuse showing a serum creatinine between 1.5 to 4 mg/dl in the absence of a clear renal diagnosis, were collected. These CT scans were also reviewed for the presence or absence of a decreased renal volume, bumpy contours and papillary calcifications. In the coordinating center, analgesic consumption was routinely investigated in all new patients. Patients were selected as controls if no indication could be found suggesting a regular analgesic consumption.

Statistical methods

Data analysis was performed using the BMDP statistical package for medical sciences [7]. The group of patients with a history of analgesic abuse was compared to the group of patients without analgesic abuse regarding the renal imaging criteria of analgesic nephropathy. For all renal imaging signs with a statistical difference ($P < 0.05$) between both groups, the sensitivity and specificity was computed. Additionally, the predictive values were calculated using the Bayes' theorem [8]. Probability graphs were constructed depicting diagnostic values for pre-test probabilities ranging from 0 to 50%.

Results

Patients with ESRF

Results are based on 80 new ESRF patients without a clear renal diagnosis consisting of 40 abusers (daily use of analgesic mixtures for minimum 5 years) and 40 controls (no history of abuse). Mean age was respectively 67 ($\pm$ 7) and 62 ($\pm$ 15) years. Male/female ratio was 1/9 for abusers and 5/5 for controls. Distribution of the renal diagnosis in controls is shown in Table 1.
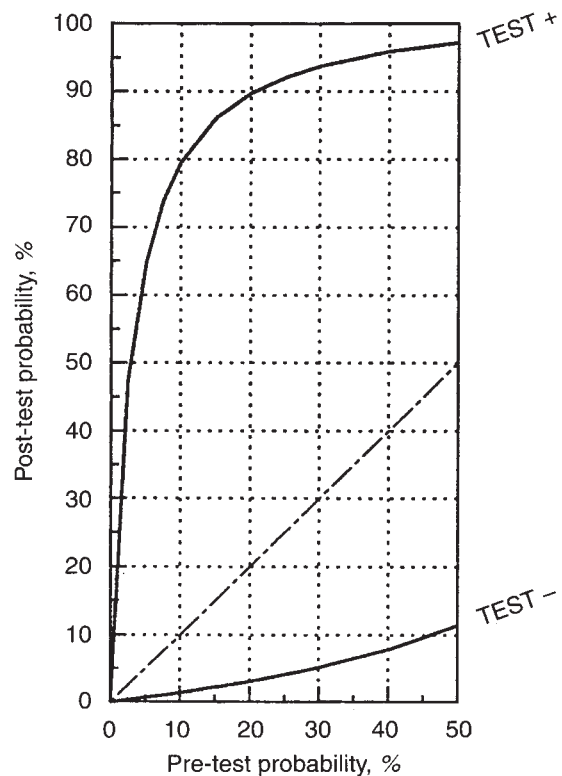
Fig. 5. *Positive and negative predictive values for diagnosing analgesic nephropathy using CT scan in patients with ESRF.* Probability graph depicting the diagnostic value of detecting papillary calcifications (given a sensitivity of 87%, a specificity of 97% and a prevalence of analgesic abuse of 50%). Curved lines indicate the predictive values (positive and negative) of diagnosing AN for different prevalences of analgesic abuse (pre-test probability) [8].

In abusers, the regular intake of analgesic mixtures, all containing two analgesic components plus caffeine/codeine, varied from 5 to 50 years (mean 21.5 $\pm$ 10.2) with a daily consumption ranging from 1 to 10 units (mean 3.5 $\pm$ 1.7; 1 unit = 1 tablet or 1 dose of powder).

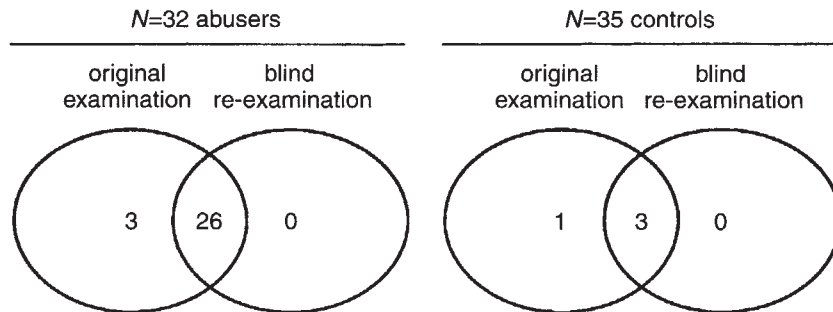Using CT scan, the mean renal sizes in abusers were 79 ($\pm$ 13)

Fig. 6. *Evaluation of the value of CT scan for diagnosing analgesic nephropathy in ESRF patients, performing a blind re-examination of 67 CT scans.* Positive diagnosis of analgesic nephropathy was based on the observation of a decrease in renal volume combined with either bumpy contours or papillary calcifications.

and 91 (± 15) mm for the left and right kidneys, respectively. Comparing CT scan to sonography and conventional tomography for evaluating the renal volume, comparable results were obtained on the left side (Fig. 2). The right kidney was found to be more susceptible to inclinations on the length axis, resulting in a false increase of the antero-posterior measurement of the right kidney (size A in Fig. 1) in one fourth of the abusers. Bumpy contours were observed in 50% of abusers using CT scan compared to 30% using sonography and 30% using tomography. The CT scan clearly was superior in the detection of papillary calcifications demonstrated bilaterally in all cases except two (Fig. 3).

Using CT scan, a sensitivity of 90% and a specificity of 90% was obtained for a combination of the renal imaging criteria (bilateral decrease in renal volume and either bumpy contours or papillary calcifications). Limiting the criteria to the detection of papillary calcifications, sensitivity and specificity remained respectively 87% and 97% (Fig. 4).

In Figure 5 the positive and negative predictive values of the CT scan for detecting papillary calcifications are presented. A positive predictive value of up to 97% could be reached, given a prevalence of analgesic abuse of 50% in this particular study. However, even with a prevalence of 10%, a positive predictive value of 80% can be obtained with a negative predictive value remaining above the 90% level.

For validation of the renal imaging criteria, 67 CT scans performed in other renal units were re-examined by our radiologist (ADS) who was not involved in the process of data collection. The diagnosis of analgesic nephropathy was accepted or rejected based on the observation on a CT scan of a decrease in renal volume combined with either bumpy contours or papillary calcifications. As shown in Figure 6, this blind re-examination resulted in a comparable number of patients in whom the diagnosis of analgesic nephropathy was accepted or rejected, even in the absence of any knowledge of their history of analgesic abuse. An overall accordance of 94% was obtained between the original examination and the blind re-examination.

Patients with incipient to moderate renal failure

Results are based on 53 abusers (9 males, 44 females) with a mean age of 63 years (range 37 to 80) and with a mean serum creatinine of 2.4 mg/dl (range 1.5 to 3.9). In all these patients a daily use of analgesic mixtures during a period ranging from 6 to 42 years was documented. Results were compared to CT scans of 30 controls without a history of analgesic abuse and with an unclear renal diagnosis: unknown etiology (N = 11), glomerulonephritis without biopsy (N = 4), pyelo/interstitial nephritis (N = 4), renal vascular disease (N = 8) and other renal diseases (N =

3). Mean age in controls was 58 years (range 36 to 80). They presented with a mean serum creatinine of 2.5 mg/dl (range 1.5 to 4).

As shown in Figure 7, the CT scan appearance of analgesic nephropathy in an early stage of renal failure is strikingly comparable with the observations made in ESRF patients. Indeed, even in abusers with a serum creatinine below 2 mg/dl, a decreasing renal volume, irregular contours and signs of papillary necrosis were clearly demonstrated. These criteria could be observed regardless the technical specifications of the scanner used (Fig. 8 CT scan from the Republic of Slovakia, Italy and Belgium). Renal size measurements in abusers showed a mean of 88 mm (± 13) for the left kidney and 93 mm (± 18) for the right kidney, while the mean renal size in controls was 105 (± 16) and 106 (± 18) mm, respectively. Particularly the demonstration of calcifications on the papillary line showed a high sensitivity of 92% with a specificity of 100% for the early diagnosis of analgesic nephropathy (Fig. 8). Comparing this diagnostic performance with results obtained in ESRF patients, sensitivity and specificity even slightly improved concerning the demonstration of bumpy contours and papillary calcifications. The finding of a decreased renal volume showed only a limited sensitivity while its specificity largely increased compared to ESRF.

In incipient to moderate renal failure the bilateral appearance of the lesions also has to be emphasized. Although some abusers showed a right kidney slightly larger in size compared to the left (see also ESRF patients), all patients showed a bilateral incipient shrinkage (decreased renal size and/or minimal 1 to more than 5 indentations). Papillary calcifications were observed bilaterally except in 5 out of 53 patients.

Discussion

This paper deals with the performance of renal imaging criteria for diagnosing analgesic nephropathy using a CT scan without contrast. The criteria studied (that is, a bilateral decrease in renal volume combined with bumpy contours and/or papillary calcifications) were selected during a preceeding study performed in Belgium, which investigated all new ESRF patients with sonography and tomography [1], and was corroborated in other European countries during the ANNE study [2]. In this final study, we were able to demonstrate that the use of a routinely performed CT scan further augmented the sensitivity and specificity of the renal imaging criteria, particularly for the detection of papillary calcifications. In addition, it was found that the diagnostic criteria studied are equally useful in patients with incipient to moderate renal failure.
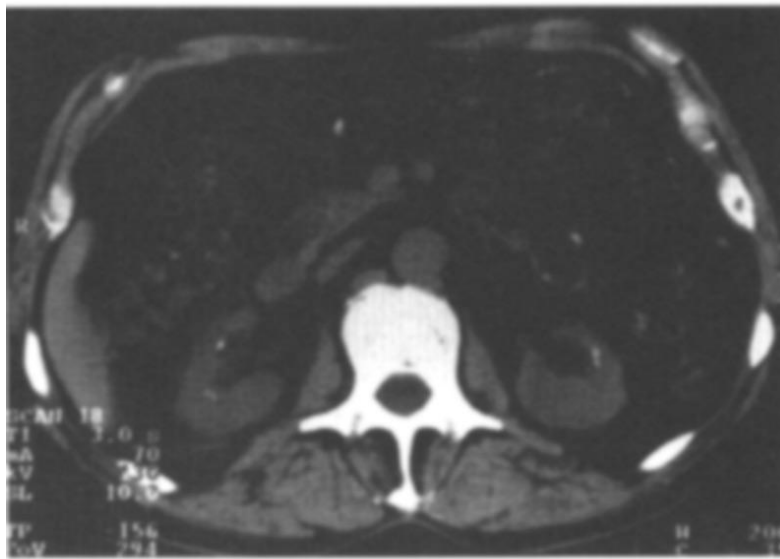
S.F.M.
Female
Italian
57 years old

Abuse: 32 years
S_{Cr}: 1.5 mg/dl

P.C.
Male
Slovakian
60 years old

Abuse: 18 years
S_{Cr}: 1.6 mg/dl

V.G.S.
Female
Belgian
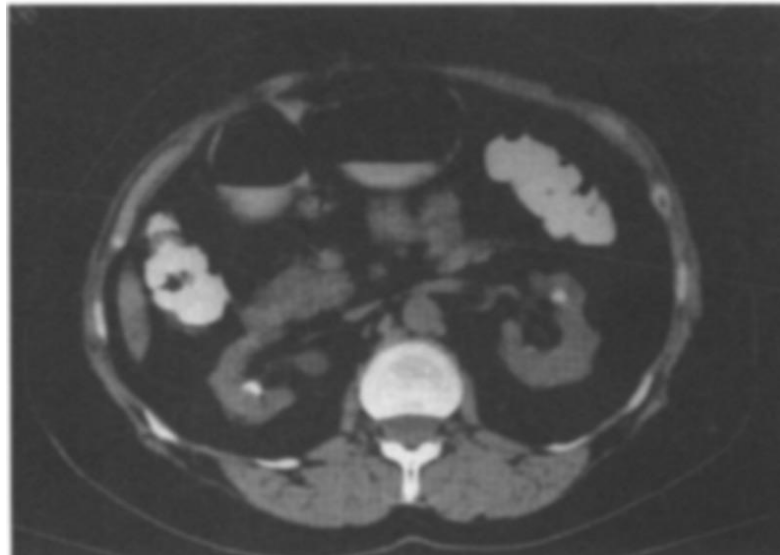62 years old

Abuse: 20 years
S_{Cr}: 1.8 mg/dl

Fig. 7. *CT scan appearance of analgesic nephropathy in an early stage of renal failure.*
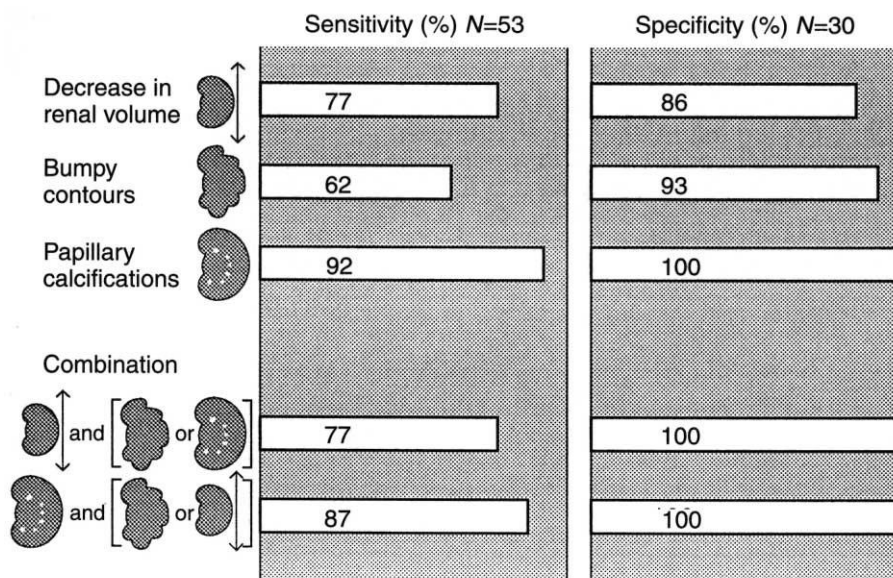
Fig. 8. *Performance of the renal imaging criteria using CT scan in patients with incipient-moderate renal failure (S_{Cr} = 1.5 to 4 mg/dl or 170 to 450 mmol/liter).* Combination 1 can be defined as a decreased renal volume combined with either bumpy contours or papillary calcifications. Combination 2 can be defined as papillary calcifications combined with either bumpy contours or decreased renal volume.

Renal papillary necrosis is also described in diabetic nephropathy, obstructive uropathy and sickle-cell anemia [9]. This important differential diagnostic issue was thoroughly investigated in the two preceeding studies in which respectively 188 and 495 controls with ESRF were investigated. During the study selecting the criteria in Belgium, papillary calcifications in association with the other renal imaging features of analgesic nephropathy were only observed in two out of 33 controls with diabetic nephropathy and in one out of four controls with obstructive uropathy [1]. During the ANNE study only 3 out of 94 controls with diabetic nephropathy and 3 out of 25 controls with obstructive uropathy showed positive renal imaging criteria of analgesic nephropathy [2]. In contrast with analgesic nephropathy, the unilaterality of the lesions in a large part of cases with pyelonephritis was emphasized [10].

In patients with incipient to moderate renal failure, radiologically detectable kidney calcifications were also described in primary hyperparathyroidism and renal tubular acidosis. In these specific clinical entities, however, the accompanying kidney shrinkage was not mentioned and calcifications were not arranged on the papillary line, but showed a more diffuse distribution among the kidney tissue [3].

For the diagnosis of analgesic nephropathy, the detection of papillary calcifications has a particularly high sensitivity and specificity in ESRF patients as well as in patients with incipient to moderate renal failure. In clinical practice, however, an accompanying shrinkage of both kidneys and the bilateral occurrence of the lesions has to be observed for diagnosing analgesic nephropathy. A decreased renal volume will be based on the renal size measurement performed at the left side. In 22% of all abusers investigated renal size of the right kidney considerably exceeded that of the left kidney because of an increase in the anterioposterior measurement of the right kidney (size A in Fig. 1). This may be attributed to an increased pressure of the liver causing an inclination on the length axis of the right kidney.

In our studies, patients were selected as "case" or "control" based on their history of abuse or non-abuse. Although several authors mentioned the difficulties in detecting a history of anal-

gesic abuse [11, 12], the use of different interview techniques (noted in **Methods**), complemented by insights from the responsible nephrologist concerning the analgesic consumption of his patient, clearly improves the bias on the history of analgesic consumption.

Based on our previous observations [13], a daily consumption of analgesic mixtures for minimum five years was used as the inclusion criterium for analgesic abuse. This definition was evaluated during the analysis of the ANNE data [2]. None of the subjects with a daily use of analgesic mixtures for less than five years (N = 16), nor those with a weekly but not a daily analgesic consumption of mixtures for more than five years (N = 19) met the renal imaging criteria of analgesic nephropathy. Moreover, the diagnostic criteria studies, investigating a total cohort of 226 abusers, clearly revealed that analgesic nephropathy is associated with the abuse of different kinds of analgesic mixtures, all containing two analgesic components combined with potentially addictive substances like caffeine or codeine [13]. The nephrotoxicity of the following combinations could be documented: salicylic acid/phenacetin, phenacetin/pyrazolones, salicylic acid/paracetamol, salicylic acid/pyrazolones, paracetamol/pyrazolones and a combination of two pyrazolones.

Several authors described the characteristic appearance of analgesic nephropathy using CT scan investigations [5, 3]. Moreover, Weber et al [14] as well as Segasothy et al [6] reported on a comparative study for diagnosing analgesic nephropathy using CT scan and respectively conventional radiology plus sonography or sonography alone, searching for the presence of papillary calcifications. Although both studies describe the characteristics of analgesic nephropathy using different renal imaging techniques, the diagnostic performance and validation was not studied. Moreover, definition of analgesic abuse varied considerably in these studies, also taking into account the use of NSAID's and a less than daily consumption of analgesics.

Until now, the diagnosis of analgesic nephropathy was difficult to obtain because the disease was associated with a large number of mainly aspecific clinical symptoms. Moreover, renal papillary necrosis, considered as the hallmark of analgesic nephropathy,

could only be directly demonstrated by autopsy, after nephrectomy or in the exceptional case of a patient eliminating a papilla. In a large number of cases, the diagnosis was mainly based on a documented history of abuse after a process of exclusion of other causes of renal failure.

Particularly because in recent years a considerable number of epidemiological observations pointed to an underestimation of this renal disease [15, 16], the need for diagnostic criteria with a well defined performance became obvious. These criteria will also allow prevalence measurements to start in countries where this has never been performed before. Moreover, a clear and uniform diagnosis of analgesic nephropathy will be helpful for collecting the epidemiological data needed to identify the nephrotoxic culprits among the analgesics currently marketed. Since phenacetin has disappeared from the market but analgesic nephropathy still occurs frequently, this discussion has again gained importance [17, 18].

Based on the results of this study and the previous diagnostic criteria studies, we recommend a routinely performed CT scan in all patients with unclear renal diagnosis, in order to consider analgesic nephropathy as the possible cause of renal failure, even in the absence of reliable information on previous analgesic consumption.

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