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# Deterioration of GFR in IgA nephropathy as measured by $^{51}$Cr-EDTA clearance

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**Deterioration of GFR in IgA nephropathy as measured by $^{51}$Cr-EDTA clearance.** In 191 patients with mesangial IgA nephropathy, GFR was determined as clearance of $^{51}$Cr-EDTA. 86 (45%) of them had subnormal renal function 7.3 ± 4.6 years after renal biopsy. The change in GFR was followed in 153 patients with repeated determinations of $^{51}$Cr-EDTA clearance. 50.3% of the patients had a loss of more than 1.1 ml/min/year, which we regard as pathological. The markers of progressive disease were: male sex, high output of urinary protein, severe histological lesions and presence of hypertension. Even patients lacking these markers had a significantly increased incidence of progressive disease. Of 93 patients, with initially normal GFR, 32% will have a subnormal GFR within five years and 25% will develop end-stage renal failure within 20 years. In 38 patients with six or more determinations of $^{51}$Cr-EDTA clearance, the predictive value of the first four determinations was calculated. Of 26 with a decrease of more than 1.1 ml/min/year, 13 (50%) developed subnormal GFR during follow-up, while 11 of 12 (91.7%) with a decrease of less than 1.1 ml/min/year ($P < 0.05$) remained normal. This shows that repeated determinations of GFR with an accurate method will predict the final outcome early in the disease. We also confirmed that single or repeated determinations of clearance of creatinine are of little value in separating a normal GFR from a slightly decreased one, but more reliable in detecting a markedly reduced GFR.

It has been clearly established that the initial opinion that IgA nephropathy (IgAN) is a disease with an unvariable good prognosis [1–3] no longer holds true. Prolonged studies have shown that 10 to 30% of the patients will develop end-stage renal failure (ESRF) within 10 to 20 years [4–11]. Ten percent of the patients treated for ESRF are estimated to have IgAN as the cause of their renal failure [12].

In our own study of 176 patients [13], with a mean follow-up time of 4.6 years after renal biopsy, 17 patients developed end-stage renal failure (ESRF) during the study. This gives a 10-year renal survival of 79%.

The progress of the disease is often very slow and the patients are young at the time of presentation. Therefore the progression rate of these patients must be regularly followed for a considerable period of time.

Severe histological lesions, proteinuria >1 g/24 hr and hypertension are symptoms that require special attention. The prognosis is also worse in males. Careful control of the blood pressure is the only way to influence the progression rate of the renal disease. The blood pressure should probably be kept below the limits regarded as normal for others [14, 15].

In 1983, we decided to study our patients diagnosed with IgAN regularly with $^{51}$Cr-EDTA clearance as an accurate method of GFR determination. As serum creatinine is a rough method for determination of renal function, it is of no value in differing between normal and slightly decreased GFR. An extensive survey of this subject has been presented by Brod [16]. The GFR may show a significant decline, with a serum creatinine within normal limits.

Determination of creatinine clearance is the most common method for evaluation of renal function in clinical practice. It is often carried out as a 24 hour clearance. However, this method is open to many uncertain factors, requires the active cooperation of the patient, and varies in accuracy depending on the level of GFR.

Clearances of inulin, DTPA and $^{51}$Cr-EDTA are the only accurate methods for measurement of GFR. However, clearances of inulin and DTPA are too complicated and expensive for repeated determinations in a large number of patients.

The aim of the present study has been to detect early changes of GFR with repeated determinations of $^{51}$Cr-EDTA clearance in IgA nephropathy, which is a well defined group of patients. These changes have been correlated to other clinical and laboratory findings. A comparison has also been made between the clearances of $^{51}$Cr-EDTA and creatinine, and the serum creatinine as measures of renal function.

## Methods

The definition of IgAN is that commonly accepted [1, 2]. All 191 patients included in this study have been investigated at our outpatient department one or several times between the years 1980 and 1989. Routine examinations included blood pressure, serum creatinine, serum immunoglobulins, 24-hour urinary protein excretion, protein selectivity and 24 hour clearance of creatinine. The GFR has been calculated from the plasma disappearance of $^{51}$Cr-EDTA in patients with a GFR of more than 30 ml/min, and from conventional clearance in patients with a GFR of less than 30 ml/min [17]. The investigations were performed at the Department of Clinical Physiology at Huddinge Hospital. GFR in the text is synonymous with clearance of $^{51}$Cr-EDTA. Subnormal GFR was defined as a GFR lower than mean −2 SD according to the nomogram of Granerus and Aurell [18]. These were (mean ± 2 SD): 30 years 105 ± 26, 50

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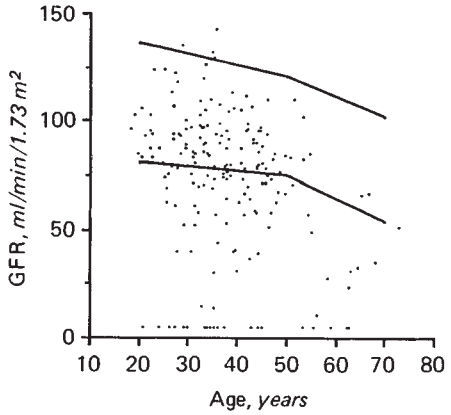


**Fig. 1.** *The latest GFR (Clearance of $^{51}$Cr-EDTA) of all patients plotted against age (N = 191).* In patients who had progressed to ESRF the GFR was defined as 5 ml/min. Subnormal GFR was present in 86 patients.

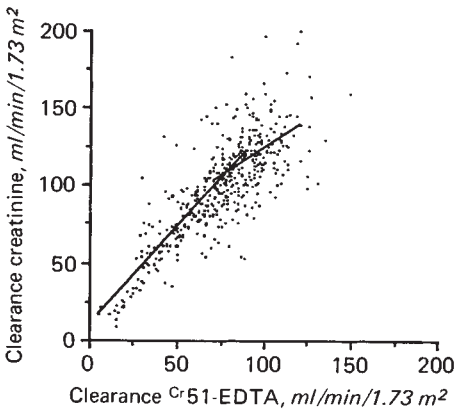


**Fig. 2.** *Simultaneous measurements (N = 477) of GFR with clearances of creatinine and of $^{51}$Cr-EDTA expressed in ml/min/1.73 m² BSA.* Regression lines are calculated for $^{51}$Cr-EDTA <80 ml/min ($N$ = 254; $R$ = 0.78) and $^{51}$Cr-EDTA >80 ml/min ($N$ = 223; $R$ = 0.36).

**Table 1.** Patients with normal or subnormal renal function related to different clinical and laboratory parameters

| | *N* | Normal GFR | Subnormal GFR |
|---|---|---|---|
| All | 191 | 105 | 86 |
| Mean age *years* | | 35.9 ± 9.5 | 40.4 ± 11.3 |
| Males | 130 | 57 (43.8%) | 73 (56.2%) |
| Females | 61 | 48 (78.7%) | 13 (21.3%) |
| Proteinuria >1 g/24 hr | 97 | 30 (30.9%) | 67 (69.1%) |
| Proteinuria <1 g/24 hr | 94 | 75 (79.8%) | 19 (20.2%) |
| Hypertension | 89 | 19 (21.3%) | 70 (78.7%) |
| Normal BP | 102 | 86 (84.3%) | 16 (15.7%) |
| Histology 3 + 4 | 60 | 17 (28.3%) | 43 (71.7%) |
| Histology 1 + 2 | 115 | 81 (69.8%) | 35 (30.2%) |

years 98 ± 23 and 70 years 78 ± 24 ml/min/1.73 m$^2$. GFR determinations were made with an interval of 6 to 18 months. All clearance values were corrected to a body surface area of 1.73 m$^2$ according to Dubois and Dubois [19].

The slope of the regression line of $^{51}$Cr-EDTA clearances was calculated in 153 patients with two or more GFR determinations and an interval between the first and the latest determination of at least one year. This gives the annual change of GFR in ml/min/year. The GFR, when the patients begun to receive active treatment of end-stage renal failure (ESRF) was defined as 5 ml/min/1.73 m$^2$. Calculated from the work of Granerus and Aurell [18] the lower limit of normal GFR (=mean − 2 SD) decreases by 0.2 ml/year in controls <50 years of age and by 1.1 ml/min in controls >50 years of age. We have defined a decline of >1.1 ml/year as a pathological decrease in GFR in all patients.

In 38 patients, with six or more determinations of GFR, the slope of the regression line for the first four investigations was calculated. Only patients having a GFR within normal limits during this period were included. The patients were divided into two groups according to an annual change of GFR of more or less than −1.1 ml/min. The time of deterioration to subnormal renal function was calculated from all GFR determinations. The difference between the two groups was calculated by survival statistics and the Log-Rank test.

In most patients, serum creatinine and clearances of creatinine and $^{51}$Cr-EDTA were performed concomitantly several times. Urine was collected for a period of 24 hours. A blood sample for serum creatinine determination was taken at the end of the period, after which then $^{51}$Cr-EDTA clearance was determined. This enabled us to compare the reliability of 1/serum creatinine and clearance of creatinine against that of $^{51}$Cr-EDTA clearance.

Hypertension was defined as a blood pressure of >140 mm Hg systolic or >90 mm Hg diastolic after 10 minutes supine rest at two separate visits. All patients on antihypertensive treatment were classified as hypertensive. The patients were divided into two groups according to their protein excretion of more or less than 1 g/24 hr. The histological scoring was based principally on the degree of mesangioproliferative changes (width and cellularity) in the glomeruli, but the degree of tubular damage and interstitial fibrosis and cellularity were evaluated as additional findings [13].

For statistical analysis, use was made of linear regression analysis, Chi$^2$ test, Students $t$-test and Actuarial Survival Method [20], and Log Rank test.

## Results

Figure 1 shows the latest value of GFR in each patient plotted against age. Of 191 patients, four have a supernormal GFR and 86 (45.0%) have a subnormal GFR for their age. Of these, 22 have progressed to ESRF. In Table 1, the patients are divided according to age, sex, degree of proteinuria, presence of hypertension and severity of histological lesions. The incidence of subnormal GFR is higher among males, patients with hypertension, a high degree of proteinuria or more severe histological lesions. The differences are significant ($P$ < 0.001) for each parameter.

Figure 2 shows the correlation between simultaneous determinations of GFR with clearances of creatinine and $^{51}$Cr-EDTA. The regression line shows that there is an over-estimation of GFR with the clearance of creatinine, especially at subnormal levels. The correlation is acceptable if GFR is <80 ml/min ($r$ = 0.78), but poor if GFR is >80 ml/min ($r$ = 0.36). The correlation is similar between $1/S_{Cr}$ and a clearance of $^{51}$Cr-EDTA ($r$ = 0.84 and 0.33, respectively).

**Table 2.** Changes in GFR in different subgroups of IgA nephropathy

| | | GFR *ml/min* | | Follow-up of GFR *years* | GFR change | *N* and % change $<-1.1$ | |
|---|---|---|---|---|---|---|---|
| | | Initial | Latest | | *ml/min/year* | | |
| All | 153 | 83 ± 21 | 76 ± 27 | 4.2 ± 1.6 | −1.4 ± 6.5 | 77 | 50.3% |
| Males | 106 | 80 ± 21 | 71 ± 27 | 4.3 ± 1.5 | −2.5 ± 6.1 | 60 | 56.6% |
| Females | 47 | 89 ± 21 | 89 ± 25 | 3.9 ± 1.8 | +1.0 ± 6.9 | 17 | 36.2% |
| Histology 3 + 4 | 48 | 72 ± 23 | 60 ± 31 | 4.2 ± 1.6 | −3.4 ± 8.6 | 32 | 66.7% |
| Histology 1 + 2 | 97 | 89 ± 17 | 85 ± 22 | 4.3 ± 1.6 | −0.4 ± 5.0 | 41 | 42.3% |
| Proteinuria >3.5 g/24 hr | 11 | 56 ± 30 | 29 ± 29 | 3.6 ± 1.7 | −8.8 ± 6.8 | 10 | 90.9% |
| Proteinuria >1 g/24 hr | 72 | 76 ± 22 | 62 ± 28 | 4.4 ± 1.7 | −3.6 ± 7.1 | 49 | 68.1% |
| Proteinuria <1 g/24 hr | 81 | 89 ± 17 | 89 ± 19 | 3.9 ± 1.5 | +0.5 ± 5.2 | 28 | 34.6% |
| Hypertension | 68 | 73 ± 22 | 57 ± 26 | 4.4 ± 1.7 | −4.0 ± 6.6 | 48 | 70.6% |
| Normal BP | 85 | 91 ± 16 | 92 ± 17 | 4.0 ± 1.5 | 0.7 ± 5.7 | 29 | 34.1% |
| Initial GFR *<80 ml/min* | 61 | 62 ± 14 | 58 ± 26 | 4.0 ± 1.7 | −1.6 ± 8.0 | 30 | 49.2% |
| Initial GFR *>80 ml/min* | 92 | 96 ± 12 | 88 ± 21 | 4.3 ± 1.6 | −1.3 ± 5.3 | 47 | 51.1% |
| Initial age *>33 years* | 76 | 78 ± 19 | 71 ± 25 | 4.1 ± 1.6 | −1.5 ± 6.3 | 34 | 44.7% |
| Initial age *<33 years* | 77 | 88 ± 22 | 81 ± 29 | 4.3 ± 1.6 | −1.3 ± 6.7 | 43 | 55.8% |
| Follow-up *>4 years* | 89 | 85 ± 20 | 75 ± 25 | 5.3 ± 1.0 | −1.8 ± 3.8 | 52 | 58.4% |
| Follow-up *<4 years* | 64 | 79 ± 22 | 78 ± 31 | 2.6 ± 0.9 | −0.9 ± 9 | 25 | 39.1% |

Statistical significance: sex $P < 0.02$, histology $P < 0.01$, proteinuria $P < 0.0001$, blood pressure $P < 0.0001$, initial GFR NS, initial age NS, Follow-up $P < 0.02$.

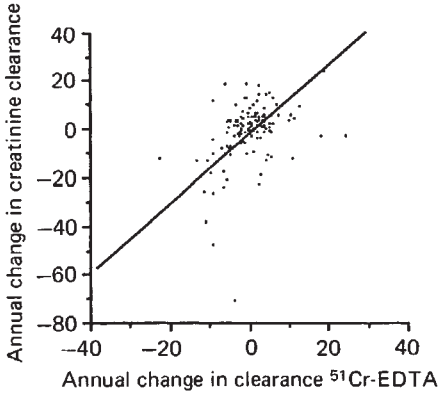


**Fig. 3.** *The annual change in GFR as measured with clearance of $^{51}$Cr-EDTA and clearance of creatinine.* The line represents the correlation between these two methods.

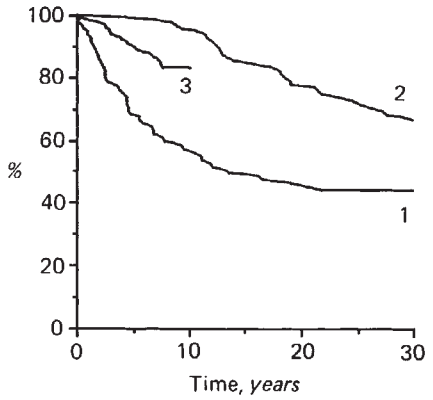


**Fig. 4.** *Calculated progression from a GFR within normal limits (1) to a subnormal GFR and (2) to ESRF with the actuarial survival method calculated from first determination of $^{51}$Cr-EDTA clearance.* The total renal survival (3) in all patients with IgA nephropathy calculated from time of renal biopsy is presented for comparison.

It was possible to calculate the slope of the GFR regression line in 153 patients (Table 2). Seventy-seven (50.3%) of them had a decrease of more than 1.1 ml/min/year and 32 (22.1%) a decrease of more than 5 ml/min/year. The incidence of pathological decrease of GFR was higher among males, patients with severe histological lesions, a high degree of proteinuria or with hypertension. But the incidence of pathological decrease of GFR was not negligible among females, patients with low proteinuria, normotensive patients or patients with slight histological changes. The level of the initial GFR or the age at first investigation did not correlate with the incidence of progressive disease. The patients who had been followed for a longer period (>4 years) had a greater incidence of pathological decrease of GFR than those with shorter observation time.

Figure 3 shows the correlation between annual changes of GFR measured by clearances of $^{51}$Cr-EDTA and 24 hour creatinine in all patients. The correlation is poor ($r = 0.40$). The correlation between clearance of $^{51}$Cr-EDTA, an $1/S_{Cr}$ (not illustrated) is also poor ($r = 0.36$). The correlation is better when GFR is decreased ($r = 0.69$).

Figure 4 presents all patients with initially normal GFR and a known annual change of GFR ($N = 93$). Assuming that the change in GFR is linear, we have calculated the time at which their GFR will theoretically decrease to a subnormal level or when they will progress to ESRF. Of these 93 patients, 32% will develop a subnormal GFR within five years and 25% of them will progress to ESRF within 20 years.

Figure 5 presents 38 patients with an initial GFR within normal limits. Eleven of 12 (91.7%) with an annual decrease of GFR of less than 1.1 ml/min, had a normal GFR at follow up. By contrast, 13 of 26 patients (50%) with an annual loss of more than 1.1 ml/min had developed subnormal GFR at follow up. The difference is significant, when calculated with survival analysis and Log Rank test ($P < 0.05$).

## Discussion

The variable course and the risk of permanent renal damage in IgA nephropathy makes an accurate and comparably simple

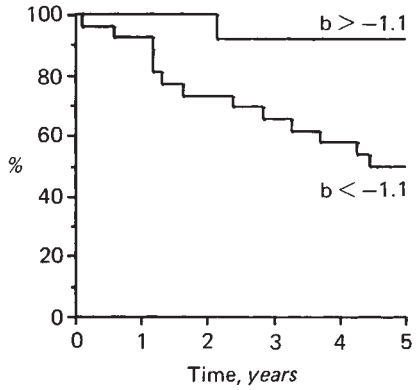


**Fig. 5.** *Survival statistics on 38 patients with six or more GFR determinations and a GFR within normal limits in the first four.* Upper line shows the patients with initial annual decrease of less than 1.1 ml/min ($N = 12$) and the lower line the patients with a decrease of more than 1.1 ml/min ($N = 26$). The calculation is presented as the percentage of patients having normal GFR at follow-up. The difference is significant ($P < 0.05$).

method for determination of renal function necessary. The $^{51}$Cr-EDTA clearance fulfills the requirements for such a method.

GFR declines with increasing age measured as clearance of inulin with 1 ml/min/year [21] and measured as clearance of creatinine 0.8 ml/min/year [22]. Our selected limit of 1.1 ml/min/year is somewhat on the high side in the younger patients.

Serum creatinine and/or clearance of creatinine are standard methods for estimating renal function in renal disease. We compared these methods with clearance of $^{51}$Cr-EDTA, with special regard to their ability to detect an early decline in GFR, in our 191 patients with IgA nephropathy.

Our conclusion is that the determinations of serum creatinine and clearance of creatinine do not discriminate between normal or slightly decreased GFR, and are useless for early detection of a progressive disease. In cases with advanced renal failure, these methods are of greater value because they are more reliable in following changes in renal function at these levels, and can easily be performed more frequently. Our results confirm those of Shemesh et al [23] who compared the clearance of inulin with clearances of DTPA and creatinine in various renal diseases. They too found an overestimation of GFR with creatinine clearance in the low range.

The positive relation (Table 1) between subnormal GFR and a high degree of proteinuria, presence of hypertension, male sex and severe histological lesions is in accordance with other investigations [4, 8, 9, 11, 24–30]. This further underlines the predictive value of these factors. The proteinuria may be highly variable, however, and hypertension is a late manifestation of the disease [15]. Early measurements of GFR are therefore more reliable for the determination of the prognosis.

The only risk factor available for intervention so far is hypertension. We have recently shown that the treatment of hypertension in these patients with an ACE inhibitor may retard the deterioration rate compared with patients treated with β-blocking agents [31].

The percentage of patients (41.6%), especially males (53.2%), with subnormal GFR is high with regard to the mean age (37.5 years) and the observation time after renal biopsy (6.5 years).

The number of patients (77 of 153) with a pathological decrease of GFR is alarming (Table 2). The markers of progressive disease are again the same: male sex, severe histological lesions, high degree of proteinuria and hypertension (Table 2). In patients with a nephrotic range proteinuria, the loss of GFR is especially high (8.8 ml/min/year) as borne out by general clinical experience. Also, a longer observation time correlates with a more rapid progression of the disease. However, this may be due to the selection of the material, that is, in patients with clinically benign disease, only one determination of GFR may have been carried out so far. There is a tendency for a higher percentage of progressive disease in the young age group. The incidence of progressive disease is independent of initial GFR.

According to actuarial survival statistics in Figure 4, 32% of 93 patients with an initial GFR within normal limits, will have a subnormal GFR after five years and 25% will progress to ESRF within 20 years.

The result shown in Figure 5 implies that the calculation of the progression rate in IgA nephropathy from several determinations of clearance of $^{51}$Cr-EDTA is valuable for early detection of progressive disease. The progression rate cannot be detected early with determinations of serum creatinine or clearance of creatinine.

It is important to define patients who are at risk at an early stage in order to plan the future examinations to be carried out on them, and the interval between the examinations. Our results indicate that repeated determinations of GFR with clearance $^{51}$Cr-EDTA are valuable in this respect.

The results of our investigation reported in this paper show that almost half our patients have a deterioration of renal function in spite of a low mean age and a short observation time. This further emphasizes our previous conclusion [13, 15] that IgA nephropathy is a severe disease in the long run.

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